NUTRITION & LIFESTYLE FOR PREGNANCY & BREASTFEEDING

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Nutrition and Lifestyle for Pregnancy and Breastfeeding

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Preface

A healthy life depends on a healthy start to life

Over the last few years there has been exciting progress in our understanding of what creates a healthy start to life. We now know that many aspects of embryonic, fetal, and infant development are affected by somewhat subtle aspects of parental health and behaviour. In this way, health—or conversely the risk of disease—is passed from one generation to the next, via processes operating independently of inherited genetic effects. This is important, because it means that parents, supported by their families and health care professionals (HCPs), can take many positive steps to promote the health of their children, even before those children are born.

As our scientific knowledge in this area has developed, it has become clear that the impact of parental lifestyle and behavioural choices extends beyond fetal development to influence the whole future life of the offspring. Small changes in the developmental environment created by parental health and behaviour before birth, and the circumstances of life over the first few years after birth, leave persistent echoes on the child's biology, operating both through what are called *epigenetic* processes and through learning.

The implications of new discoveries in this 'life-course biology' and the importance of the concepts of developmental plasticity are both exciting and profound for many clinical specialties, including obstetrics, midwifery, and paediatrics, and also for child psychology and the social sciences. These disciplines now have a critical role to play in future health promotion and preventative medicine. This also means that the content and nature of the information exchanged between HCPs and parents-to-be needs to change.

While the general principles of ensuring a healthy start to life may seem obvious, much of the emerging knowledge from the scientific community has not been disseminated widely or reliably. Moreover, it is important to consider a broader period of development than many of us realize—extending from well before conception though into late childhood and adolescence—and that both the mother and father can do things that make a healthy start to life more likely. But what advice should be given to parents-to-be? They want specific, clear information, but the confusion of messages available to both them and HCPs presents a real challenge.

We wrote this book in response to the frequent requests we receive from HCPs for clear guidance on what to recommend to young couples or parents-to-be about the nutritional and lifestyle choices likely to lead to the best pregnancy outcome and healthy growth and development of their child. These requests arise whenever we interact with such HCPs, whether informally, in response to our papers and books, or at scientific meetings. The precise questions vary, often relating to diet before pregnancy or in lactation, physical activity, stress, environmental toxin exposure, etc., but underlying them all is the same problem: while there is universal recognition of the importance of giving clear advice, there is no single, simple resource to which HCPs can turn to get the information upon which such advice depends.

While we hope that this book will help HCPs to advise prospective parents, we are well aware that there are many other sources of information to which such parents-to-be will turn. In fact, there are *too* many sources, especially on the internet and through a variety of media, as well from peers, formal and informal support groups, or clubs. These are often accessed before, or instead of, resorting to a HCP for advice.

All too often these disparate sources do not agree, even on fundamental issues with important health consequences. Sometimes the advice from informal sources is based more on folklore than science, but most prospective parents have no way of assessing its accuracy or quality. Faced with this overload of conflicting information, it is not surprising that some parents do not make the best choices about lifestyle. With this in mind, we have tried to make this book as user-friendly as possible while providing in-depth sources to support our conclusions, recognizing that it will provide a source of information for some parents as well as for their HCPs.

So what makes us so sure that we know the answers? To be honest, sometimes we don't. Throughout the book, we have therefore tried to be clear about our level of confidence in the information we present. In some cases, the data are unambiguous and a clear consensus exists, so there is no problem in being prescriptive. In others, when there is no such consensus, we have tried to be transparent about giving our view on the weight to be placed on what is sometimes confusing evidence. In still other situations, the evidence must be interpreted in context—for example, what might be appropriate weight gain in pregnancy for a woman of average BMI in the USA may not be appropriate for a woman of average BMI in India. Finally, there are situations where, frankly, we do not know the answers: the underlying issues can be explained and considered, but action may not be appropriate until further research is completed.

We also need to be clear at the outset in stating what this book is **not** about. It is not a self-help guide to pregnancy; it is not a textbook on the biology of human development; and it is not a guide to the complications or diseases associated with pregnancy and their management. There are many other books that serve those purposes.

What this book is intended to provide is a manual for a wide range of HCPs—from community health workers, hospital doctors, and midwives, to public health practitioners—about the importance of a healthy lifestyle for prospective parents. It sets out the essentials of current knowledge about this issue in a form that we hope can be easily accessed and can serve as a resource for informed discussion with the public and parents-to-be. We hope that this book will empower the HCP to take a major role in health promotion and disease prevention at this critical period in the life course, a time when parents are anxious to do the best for their family but are confused about the steps to take. In addition, we make no apologies for the extensive referencing. Given the confusion in the popular and technical literature, and the complications arising because of commercial claims, we think it necessary to provide access to the evidence to make clear the basis on which statements or recommendations are being made and to indicate further reading.

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Abbreviations

%DV	per cent daily value
25(OH)D	25-hydroxyvitamin D
AA	arachidonic acid
AAP	American Academy of Pediatrics
ACOG	American Congress of Obstetricians and Gynecologists
AI	adequate intake
ALA	alpha-linolenic acid
alpha-TE	alpha-tocopherol equivalents
BMC	bone mineral content
BMD	bone mineral density
BPA	bisphenol A
CpG	cytosine–guanine dinucleotide
DDT	dichloro-diphenyl-trichloroethane
DFE	dietary folate equivalent
DHA	docosahexaenoic acid
EAR	estimated average requirement
EPA	eicosapentaenoic acid
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide
GDA	guideline daily amounts
GDM	gestational diabetes mellitus
GI	glycaemic index
Gla	gamma-carboxyglutamate
HCP	health care professional
IF	intrinsic factor
IOM	Institute of Medicine
LA	linoleic acid
LRNI	lowest recommended nutrient intake
MTHFR	methylenetetrahydrofolate reductase
NAD	nicotinamide adenine dinucleotide
NCD	non-communicable disease
NICE	National Institute for Health and Clinical Excellence
NIP	nutrition information panel
NSAID	nonsteroidal anti-inflammatory drug
NTD	neural tube defects
PAH	polycyclic aromatic hydrocarbons
PIH	pregnancy-induced hypertension
PL	pyridoxal
PLP	pyridoxal-5′-phosphate
PROM	premature rupture of membranes
PTH	parathyroid hormone
PUFA	polyunsaturated fatty acid
RA	retinoic acid
RAE	retinol activity equivalent
RBC	red blood cell
RCOG	Royal College of Obstetricians and Gynaecologists
RDA	recommended dietary allowance
RNI	reference nutrient intake
ROS	reactive oxygen species
sTfR	soluble transferrin receptor
T4	thyroxine
THF	tetrahydrofolate
THR	thyroid hormone receptors
THS	thyroid stimulating hormone
UIC	urinary iodine concentration
UL	tolerable upper intake level
UTI	urinary tract infection
VAD	vitamin A deficiency

How to use this book

The book is written in four sections.

Section 1 provides a general introduction to the science underpinning the impact of parental behaviour and particularly the effects of nutrition on pregnancy and offspring health.

Section 2 details our knowledge of macro- and micronutrients on the mother and her fetus. It provides a reference manual for advice on specific nutrient intakes before and during pregnancy and lactation.

Section 3 reviews aspects of parental lifestyle that might impact on the fetus and pregnancy outcomes. This includes safe and unsafe foods, exercise, and exposure to potential toxins. It also reviews weight guidelines for pregnancy.

Section 4 takes the information in the prior sections and presents the health care professional with a checklist of advice according to the stage of pregnancy.

Section 1

Fundamentals of healthy nutrition and lifestyle

Although most prospective parents focus efforts during pregnancy on trying to make the right decisions about what to eat, what not to eat, and what else to do or not do, their sources of information are largely informal and often inconsistent, furthering their confusion and anxiety. Moreover, these questions often arise only after pregnancy is diagnosed, despite increasing evidence that nutrition and lifestyle matter not only during an established pregnancy, but also prior to and soon after conception. This section reviews the concepts and emergent science to explain how relatively subtle changes in parental behaviour can affect the outcomes of pregnancy, and why there are echoes of such influences across the whole of life of the offspring.

Chapter 1

The importance of nutrition and lifestyle to healthy development

Developmental origins of health and disease

No one would be surprised by the statement that the healthy growth of the fetus and infant depends on the mother's nutrition, and can be influenced by her lifestyle. Clearly, the components that will form the growing body of the baby must come from the food that the mother consumes or, if from her own body, they will probably have to be replaced. Just as maternal nutrient intake has a positive impact on fetal growth and development, excessive alcohol consumption, smoking, or exposure to environmental toxins, infectious agents, or drugs may have detrimental effects: well-known examples include fetal alcohol syndrome, deafness of the child resulting from measles infection during the first half of pregnancy, and the limb deformities from thalidomide.

What is less well known is that such effects are extreme examples of a spectrum of processes that operate in all pregnancies and during infancy. This concept has evolved over the last few decades, as a result of very extensive research in many settings around the world. It has been conceptualized in several ways, one of which has become particularly influential—the 'developmental origins of health and disease' paradigm. This is the concept that the early development of each individual, starting from the time of conception, sets the scene for their future health and the risk of certain diseases from which they may suffer later. This topic has been the subject of many reviews and books [1–7].

There are two important aspects of this concept which should be explained at the outset, because they have implications for understanding and applying much of the information in this book. The first is that the development of the embryo (up until about 12 weeks of gestation), fetus, and infant is far from automatic. At a previous time when scientists believed that development was simply a process of assembling biological components sequentially on the basis of a genetic programme, there seemed little scope for the developing individual to play much of a role in the process any more than a car on the assembly line of a factory can control its manufacture. However, this is now known to be incorrect; while it is true that there are genetic programmes for the assembly of tissues, organs, and the layout of the body's components, the developing organism's own biology has very significant control over how those processes operate. For example, it can alter the number of filtering units it will form in its kidneys, the number of muscle cells in its heart, and the number of fat cells in its body and, once formed, these numbers will essentially be set for life.

The 'decisions' that the developing fetus makes about these numbers are embedded in its biology and are based on information it receives from its mother and, through her, about the wider environment, in terms of nutrition and physical activity, but also about stress and other aspects of lifestyle. These biological decisions are to a large degree final, so they have long-term consequences for health and disease. Research has begun to reveal how these processes operate physiologically, highlighting the importance of this period in our lives when our innate biology exerts far more control over our destiny than was previously thought.

The second aspect is related to the first. It used to be thought that, because of an apparently fixed genetic programme of development, the fetus would take whatever it needed from its mother and would be seriously underdeveloped if for some reason this was not available. However, just as it is now clear that the developing fetus can make 'decisions' about its development, so the mother is involved in a 'dialogue' with it about such decisions. Greater demand for a particular nutrient, for example, may be met by physiological changes in the mother and the placenta to supply it; or by a signal to the fetus that these demands are excessive in terms of the mother's nutrition, body composition, etc., and so the demand should be tempered and development altered accordingly. There is far more active cooperation between the mother and her fetus or infant than we used to think—and sometimes there is competition between them too if their conflicting demands cannot be met. When there are twins or triplets, the plot thickens still further.

We emphasize that these processes are completely natural or physiological and that they operate in all pregnancies, not just in those with particular problems. The processes are part of normal human biology and operate across a wide spectrum of development. This is reassuring, but it also presents both parents and health care professionals with some problems. For example, it is not always possible to give a fixed recommendation about the daily intake of a micronutrient. It should be possible to suggest a *range*, but the precise level will depend on many other factors that may interact and probably cannot be measured. The best advice is by necessity only an approximation; it is nonetheless valuable and important for future health.

Nutrition: providing the building blocks of development and the fuel for metabolism

From an ecological perspective, humans are a generalist species; that is, humans can live in a wide range of environments across the globe rather than being confined to a relatively small niche environment, as are many other species. It is therefore perhaps not surprising that we are omnivorous and both can and want to consume a wide range of dietary components. Good fetal and infant nutrition, whether derived from the mother via the placenta before birth or ingested by mouth after birth, consists of the macronutrients protein, carbohydrates, and fats needed for building the fundamental components of the body, and micronutrients such as vitamins and trace elements that are essential structural components and cofactors in metabolic processes.

During development the need for nutrients is correspondingly increased in order to provide for growth, but the role of energetic macronutrients and micronutrients in providing the key factors to support basal metabolic processes must not be ignored. Examples would include the need for adequate trans-placental flow of glucose to support the energetic demands of the fetal brain, heart, and other organs, and the provision of thiamine (vitamin B_1) as a cofactor for oxidative decarboxylation of pyruvic acid and alpha-ketoglutaric acid as part of the energetic pathway. The daily nutrient requirements of the fetus are the subject of section 2 of this book.

Essential vs non-essential components of nutrition

Essential nutrients are those that cannot be endogenously synthesized. Inadequate intake of these nutrients will lead in the longer term to deficiencies that will be associated with ill health or disease. A well-known example is vitamin C, a deficiency of which causes scurvy. Humans and our relatives the great apes must ingest vitamin C from the diet (primarily from fruit and vegetables), although interestingly this is not true of other primates, which can synthesize vitamin C endogenously. It appears that at some point in our evolutionary past, when abundant fruit and vegetable intake was a feature of our diets, the ability to synthesize vitamin C was lost due to a loss-of-function mutation in a synthetic enzyme [8].

Similar considerations apply to 9 of the 21 amino acids, which are therefore essential dietary components in humans. However during development, when nutrient requirements for growth are large, some nutrients become conditionally essential. This is the case for the amino acid glycine, an important component of one-carbon metabolism, for which fetal requirements in late gestation

Table 1.1 Essential and conditionally essential amino acids in fetal development

Essential	Conditionally essential	Non-essential
Histidine	Arginine	Alanine
Isoleucine	Cysteine	Aspartate
Leucine	Glutamine	Serine
Lysine	Glycine	
Methionine	Proline	
Phenylalanine	Taurine	
Threonine	Tyrosine	
Tryptophan		
Valine		

are large enough for it to become an essential nutritional component. Table 1.1 lists the essential and conditionally essential amino acids for the human fetus. Similarly there are essential polyunsaturated fatty acids, alpha-linolenic acid (an omega-3 fatty acid), and linoleic acid (an omega-6 fatty acid), but other fatty acids become conditionally essential during development; this includes docosahexaenoic acid, which is also an omega-3 fatty acid.

What is a 'balanced' diet?

One of the challenges of nutritional science is that food is not just the composite of nutrients within it. The availability of nutrients is dependent on the food chemistry, its digestibility, the action of the gut microbiota, and gastrointestinal physiology. Thus, while it is easy to consider the post-absorptive requirements of the body in physiological terms, it is more complex to consider the nutritional requirements of the individual. Even where micronutrients are given as supplements, it is important to be aware of the potential interplay between those supplements and food. For example, phytates that are found in whole grains or unleavened bread can interfere with the absorption of calcium and other micronutrients.

It is important to note that diet and nutrition are not synonymous. A balanced diet means that all the nutritional requirements of metabolism, growth, immune function, etc. are being met. While variations in dietary intake in the short term can be tolerated through the use of body stores, in the longer term an unbalanced diet will lead to poor health and disease. For vitamin C, the half-life for levels in the body is about 20 days, so the effects of severe deficiency will be expected to appear after about 2–3 months if intake is zero, as found in sailors on long-distance voyages in the past.

A diet may be unbalanced either because of a deficiency or excess of macro- or micronutrients. Many micronutrients have complex dose/response relations. Too little can lead to a deficiency disease, but too much can lead to toxic effects. In some cases, such as for vitamin A, there is a relatively narrow safe band of exposure during development. Folic acid provides a good example, as low folate status in a pregnant woman during early gestation is associated with neural tube defects and other congenital anomalies in her fetus. However, sustained intake of very high levels of folic acid in adults is associated with greater risk of some forms of cancer (e.g. colon cancer) [9]. There is thus a healthy range for folate status. In other cases, such as for vitamin D, recent research suggests that previous recommendations for pregnancy may have been set at too low a level. These issues are discussed at length in section 2, where we analyse the specific micro- and macronutrient needs of pregnant and breastfeeding women and dissect a complex and sometimes confusing literature and a confusion of guidelines.

Similar considerations apply to macronutrients. Consumption of fat is needed for the provision of the essential polyunsaturated fatty acids, but excessive fatty food intake is associated with obesity and cardiometabolic disease. Both excess and deficient carbohydrate intakes during pregnancy can impact the mother and fetus. Very high protein intakes during pregnancy are associated with fetal growth restriction [10] (see chapter 4).

Fundamentals of metabolic control

The body's metabolic processes are generally tightly regulated so that supply meets demand, and this control operates at several points along the metabolic pathway. For example, lower levels of blood glucose lead to hepatic gluconeogenesis to meet demand; when blood glucose levels rise following a meal, the rise in insulin secretion by the beta cells of the pancreas and the fall in glucagon secretion by the alpha cells lead to increased glucose uptake by tissues such as skeletal muscle, thereby providing a stimulus to carbohydrate metabolism or deposition, such as storage as glycogen. Carbohydrate metabolism interacts with other aspects of metabolism, such as the effects of fatty acids on the Krebs cycle, and these processes in turn interact with other body homeostatic mechanisms. Often this involves endocrine processes, for example, the regulation of appetite by leptin and GLP1 or the control of body fat stores.

Contrast this with the fetus, which cannot undertake gluconeogenesis until very late in pregnancy when liver enzymes mature and therefore depends on the supply of glucose across the placenta. When this is inadequate, fetal growth is restricted to conserve energy for cardiac, brain, and adrenal gland function. When it is excessive the excess glucose is stored as fat—hence the macrosomia seen in infants of diabetic mothers.

Despite small fluctuations on a day-to-day basis, it is clear that metabolic control is finely tuned, as body weight remains remarkably constant over long periods of time. Recent work investigating the underlying mechanisms has demonstrated how we, and indeed many other animal species, defend our protein requirement target more vigorously than we do other nutrient requirement targets. As Fig. 1.1 shows, if humans consume a diet of low protein content for a period of time, they increase their total food intake to achieve their preset protein target at the expense of ingesting excess carbohydrate and fat. This so-called protein leverage process [11] may explain why certain diets predispose to obesity. There is also increasing evidence that appetite control and food and taste preference is set early in life for life. This can be influenced by the flavours in the foods that mothers eat in pregnancy and during lactation and by the nature of weaning [12, 13].

Aspects of metabolism change across the life course, as does body composition. A key component of the metabolic adaptation to pregnancy is the development of mild insulin resistance and changes in appetite control in the mother [14, 15]. Both are induced by placental hormones including placental lactogen and growth hormone [15]. This mild insulin resistance is postulated to ensure enhanced and reliable transfer of glucose to the fetus while the mother's metabolism becomes more dependent on lipids [16]. Thus, as pregnancy progresses, insulin sensitivity decreases in the maternal peripheral tissues, which results in

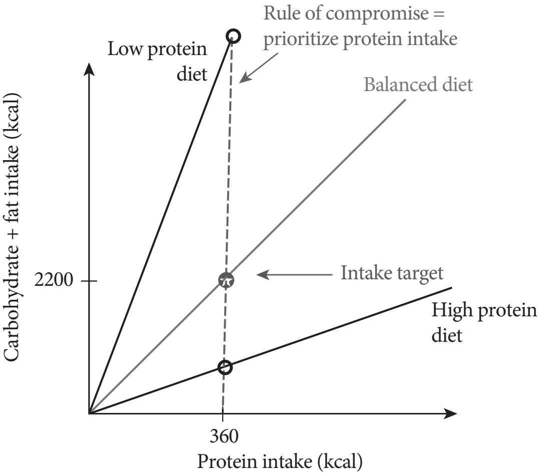

Fig. 1.1 The protein leverage hypothesis. The diagram illustrates human dietary patterns, wherein protein intake is prioritised over intake of carbohydrates and fat. If the diet contains a low proportion of protein, the total food intake will increase (i.e. excess carbohydrate and fat will be consumed) in order to reach a target protein intake. Adapted from S. J. Simpson and D. Raubenheimer, Obesity: the protein leverage hypothesis, *Obesity Reviews*, Volume 6, Issue 2, pp.133–142, Copyright © 2005 with permission from John Wiley and Sons, DOI: 10.1111/j.1467–789X.2005.00178.x

the mild hyperglycaemia and insulin resistance associated with normal pregnancy. However, in women who are already prone to insulin resistance because of obesity or developmental factors, this physiological tendency to insulin resistance becomes exaggerated and the result is gestational diabetes mellitus (GDM).

GDM has been reported to affect 4–7 per cent of pregnancies in Caucasian women, and the incidence is somewhat higher (8–15%) and rising rapidly in Asian women, to over 25 per cent in some urban populations [17–19]. This is a particular concern because women who develop GDM are at a high risk of subsequently developing type 2 diabetes mellitus. Furthermore, their offspring have a high risk of developing obesity, impaired glucose tolerance, hypertension, and dyslipidaemia [20]. Uncontrolled hyperglycaemia in pregnancy is associated with some fetal abnormalities, for example, abnormalities of the heart [21], and carries a risk for the newborn of neurological damage from neonatal hypoglycaemia [22]. Maternal glucose intolerance that is milder than that in overt diabetes mellitus can also lead to adverse outcomes; [23] indeed, maternal glucose control has been shown to correlate with maternal, perinatal, and neonatal outcomes in a continuous linear association across both normal and pathological ranges [24]. New guidelines published by the International Association of the Diabetes and Pregnancy Study Groups therefore suggest a lower threshold for diagnosis of GDM [25].

Human metabolism even changes as we develop in early life. For example, the fetal heart depends on the supply of glucose for its metabolism, but within a short period after birth, it switches to the utilization of fatty acids [26]. There are long-term functional implications for this switch, as it occurs at the point at which the number of cardiomyocytes is effectively set for life as they undergo terminal differentiation. Moreover, the switch can have later consequences in diabetes, when the exposure of the heart to high glucose levels leads to the deposition of fat in the heart rather than metabolic consumption of glucose.

The importance of energy balance

Over-nutrition

Over-nutrition before and during pregnancy is common in developed countries, where there is an increasing prevalence of overweight and obesity and excessive weight gain among pregnant women [27, 28]. It is also becoming clear that obesity is rising rapidly and can coexist with under-nutrition in low- and middle-income countries undergoing nutritional transition [29]. Deposition of some fat in a woman during pregnancy is a natural process to provide energy stores to support lactation. This fat deposition results in part from the insulin resistance that develops in pregnancy in response to the secretion of placental hormones, as discussed above. However, excessive weight gain should be avoided, as over-nutrition leads to metabolic imbalances in both mother and fetus, with long-term adverse health consequences. For instance, overweight women or those who gain too much weight during pregnancy have higher risks of developing GDM and possibly pre-eclampsia, and of their infants being large for gestational age (LGA) [30]. A positive association has been observed between excessive weight gain in pregnancy (>12.5 kg) and the risk of later childhood overweight, especially when the weight gain exceeds 20 kg [31]. Chapter 28 covers the impact of maternal body weight composition before and during pregnancy in more detail.

Under-nutrition

Poor dietary intake during pregnancy remains a challenge in low- and middle-income countries. Due in part to low socioeconomic status, low diet quality, high intensity of agricultural labour, and frequent reproductive cycles, pregnant women in developing countries are particularly at risk for malnutrition. As with over-nutrition, inadequate nutrition during pregnancy has lifelong health impacts on the offspring. During the Dutch Hunger Winter of 1944–1945, food supply to the western part of the Netherlands was cut dramatically (with daily caloric intake restricted to 400–800 calories). Babies born to mothers who experienced this famine in late gestation were frequently of low birthweight and had decreased glucose tolerance at the age of 50 compared with individuals born the year before or after the famine [32]. Similarly, fetal and/or early postnatal life exposure to war-inflicted famine in Nigeria (1967–1970) or the Great Famine in China (1959–1961) was associated with an increased risk of adult hypertension [33, 34].

Lesser degrees of under-nutrition may also have effects. In the Gambia, where there is a marked seasonal variation in caloric intake, women who conceive during the ‘hungry’ season give birth to babies who are slightly preterm and weigh less on average than those conceived during the ‘harvest’ season [35, 36]. Those born during the hungry season have markedly shorter life expectancies, although this mortality difference, which is related primarily to infection, does not appear until adulthood [37, 38].

The importance of physical activity

Adequate levels of physical activity are necessary for both cardiovascular fitness and for maintaining a healthy body composition. In non-pregnant adults 30 minutes of vigorous exercise, five days a week, is recommended [39]. In chapter 29 we discuss the recommendations for pregnancy. Even lower levels of physical activity and reduction of sedentary lifestyle have beneficial effects on cardiovascular function and reduce the risk of cardiovascular disease [40]. In addition, exercise has beneficial effects on the skeletal muscle groups used, altering their metabolism and increasing the proportion of metabolically active fast twitch fibres [41]. Physical exercise is also recognized to act as a suppressor of appetite and hence can be a useful adjunct to dietary guidelines in weight loss programmes.

Individuals vary in their propensity to undertake vigorous physical exercise, and also in the extent to which it produces beneficial effects in them. In addition there is variation in metabolism not associated with exercise, sometimes termed non-exercising active thermogenesis [42]. Fidgeting and other minor body activities can be important sources of energy consumption, especially in children, and probably interact with other forms of energy consumption. The processes by which such interactions are regulated are unknown.

Avoidance of risky exposures

One of the biggest concerns that potential parents have is about the safety of their food. Unpasteurized cheeses can contain the bacterium *Listeria* that can cross the placenta and cause fetal loss or preterm labour [43]. Other foods can contain potential toxins. The most well-known toxins in foodstuffs are those thought of as poisons (e.g. the atropine from deadly-nightshade berries, botulinum toxin from some types of poorly cooked meat, or mycotoxins associated with fungal contamination of poorly stored grains). Fungal mycotoxins are thought to be a significant source of stunting in some less developed countries [44]. Identification of safe and unsafe foods can be confusing for the mother-to-be, with the internet providing a very broad range of seemingly contradictory advice. In chapter 30 we provide a coherent set of information on such issues for health care professionals (HCPs) to provide to parents.

Components of modern diets can also be toxic if consumed in excessive quantities, the most well known being alcohol. However there is now considerable concern over other toxins in the environment that may find their way into foodstuffs even though they do not immediately exert obvious harmful effects on health. There are calls for the identification, measurement, and control of such substances in the environment although, with a few exceptions, there are at present no recommendations on their intake or exposure during development [45]. This is a very complex area of science where new measurement techniques allow extremely low concentrations to be measured, and yet there is no way to assess the significance of these concentrations.

While we would advocate the adoption of the precautionary principle, it is nevertheless easy to be alarmist without scientific justification—so a more balanced pragmatic approach is necessary [46–48]. For some exposures, however, there is no debate: attention to the toxic effects of smoking should not need reinforcing, although regrettably tobacco consumption is increasing in many low- and middle-income countries, especially in women and children. Smoking produces detrimental effects on the growth of many organs and systems in the fetal and neonatal body, including the brain, lungs, and cardiovascular system and produces long-term effects on health and the risk of disease in those individuals exposed to secondary smoke.

Opportunities and challenges

Parents universally want the best for their children and hence the opportunities to reap the benefits of lifestyle and nutrition advice from HCPs are substantial. But while there is often no lack of motivation, finding a way of reinforcing the message about healthy diet and lifestyle over what may be a relatively sustained period in what can be a complex social milieu is not so easy. An important opportunity is linked to the health benefits for the parents themselves. Even relatively small changes in body mass index can produce beneficial effects on cardiovascular function. Positive messages derived from such measurements can help sustain the healthy lifestyle message.

Good maternal diet and body composition reduce the risk of pregnancy complications such as GDM, pre-eclampsia, or preterm birth. Associated problems such as fetal macrosomia, shoulder dystocia, and the adverse cerebral effects of neonatal hypoglycaemia are also important. Coupled with the effects of healthy early development on promoting healthy postnatal growth and development and reducing the later risk of non-communicable diseases in the offspring, there are clear and simple health messages to be transmitted to parents-to-be.

However, there are often barriers to changing diet and lifestyle in many at-risk groups of the population. Consumption of a healthy, balanced diet depends on access to retail outlets where healthy foods can be purchased, adequate resources to purchase the items, and knowledge of how to prepare and cook them. These three conditions are often not met and HCPs have to be aware that innovative solutions must sometimes be found to overcome these difficulties. Similar considerations can apply to exercise promotion, if it is perceived that this requires access and membership to a gym or other sporting facility that may be difficult, unacceptable, or unaffordable for some families.

The importance of cultural issues should not be underestimated. For example, in some cultures where exposure of the body is unacceptable among women, it is difficult to advocate some forms of sport or physical exercise, such as swimming. Brisk walking might be an alternative but this is sometimes challenging in hot climates and women are rightly concerned about safety issues. Another example is that covering the body and limited exposure to sunlight is responsible for the relatively high levels of vitamin D deficiency in women of reproductive age in some countries. There are also very distinct cultural attitudes to body shape.

As will be noted throughout this book, many of the benefits of diet and lifestyle result from healthy behaviours before pregnancy, and importantly this applies both to the mother and the father (see chapter 35 for information on paternal factors). However in many societies a substantial number of pregnancies are unplanned and, by the time that the couple knows that they have conceived and the women has seen a HCP, the opportunity for maximum effect of behaviour change has been lost. It is true that healthy diet and moderate exercise during pregnancy, coupled with appropriate weight gain especially during late gestation, confer benefits but sometimes these are too late for maximal effects on the health of the next generation.

A major focus in contemporary global health is therefore on adolescence, with a view to promoting healthy lifestyle before conception (see chapter 34 for specific consideration of adolescents). Adolescents have received less attention to their health in recent decades than have younger children, despite the fact that they form a substantial proportion of the world's population. Collectively, adolescents have a powerful capacity to instigate social change in their families or among their peer group. The challenge, however, is achieving a behaviour change in this group.

In many societies adolescents will not necessarily be attending school or other full-time education, and this is particularly true of girls after marriage or when they become pregnant. In addition, research has shown that health promotion initiatives in schools are relatively ineffective compared with learning outside the classroom activities. There is therefore a need to develop community-based health promotion activities outside the formal educational setting, where adolescents and young adults are more likely to engage more positively with the health promotion agenda.

The long-term goal is to promote what is termed health literacy, that is, the empowerment or self-efficacy needed to enable individuals to make choices about a healthy lifestyle for themselves, to influence their peers and their families, and to access health care and other services when appropriate. The wider issue is that even though adolescents and young parents may be currently healthy, their individual risks of later disease vary, because they lie on different trajectories of accumulating risk in their lives (see Fig. 1.2). Promoting health literacy in terms of nutrition and lifestyle is not only important for their future health but also so that they give their children the best start in life.

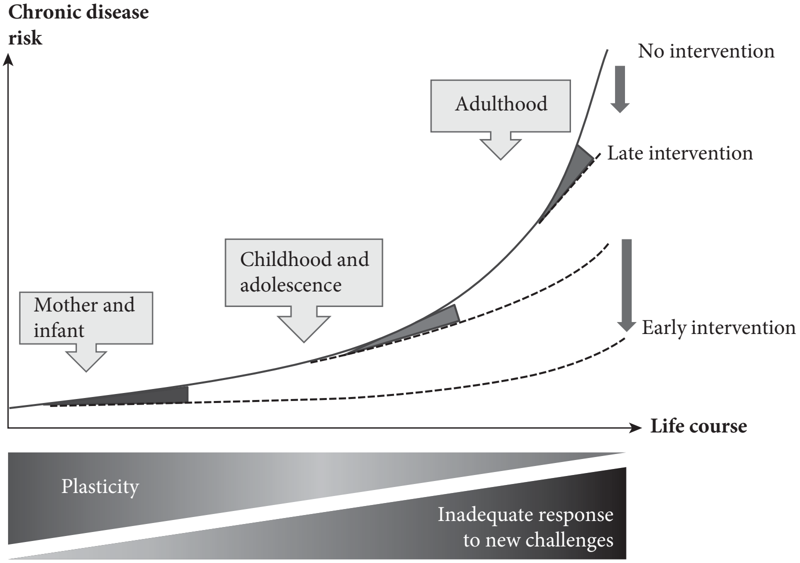

Fig. 1.2 Developmental trajectories and disease risk. Developmental trajectories established in early life influence the response of the individual to later exposures, such as adult lifestyle. Risk increases throughout the life course as a result of declining plasticity and the resulting accumulative effects of inadequate responses to new challenges. The trajectory is influenced by factors such as the mother's diet and body composition before and during pregnancy, and fetal, infant and childhood nutrition and development. Early intervention can reduce later disease risk. Adapted from *Trends in Endocrinology and Metabolism*, Volume 21, Issue 4, Keith M. Godfrey et al., Developmental origins of metabolic disease: life course and intergenerational perspectives, pp.199–205, Copyright © 2010, with permission from Elsevier, <http://www.sciencedirect.com/science/journal/10432760>

Many current initiatives employ digitally based techniques to provide information, to engage adolescents and prospective parents, and to provide the interactive learning necessary to sustain change. Even in many low- and middle-income country settings, adolescents have access to smartphones or other tools for accessing the internet and are willing to engage with virtual communities and entertainment-based information provision services. There are therefore many positive ways in which HCPs can engage with young people to promote a healthy lifestyle.

Set against this, we have to recognize the role of the food and drinks industries, which not only produce a substantial proportion of the world's food but also sometimes target advertising and marketing techniques at young people. HCPs will have to play their part in addressing this problem. In some circumstances regulatory change may be needed, as well as better cooperation between public and private sectors so that desired goals can be achieved. There may therefore have to be hopefully more truces as well as battles, but in both situations it is hoped that the information provided in this book will assist the HCP in reaching better outcomes.

Chapter 2

Conceptual background to healthy growth and development

Development is affected by early environment

Growth

Growth of the body does not occur at a constant rate throughout development—there are spurts in the relative growth rate during both fetal life and adolescence, and not all tissues and organs develop to the same pattern (see Fig. 2.1). In utero, measures of fetal growth are obtained by ultrasound and necessarily only relate to body dimensions such as abdominal circumference, head circumference, head volume, crown-rump length or femoral length. These are useful because they give an indication of growth of the liver (abdominal circumference), brain (head circumference or head volume) and skeleton (crown-rump length or femoral length). Nutritional and other lifestyle factors such as smoking can affect these growth parameters.

Fetal growth is usually assessed by means of a growth chart. It is important to realize that the usefulness of such charts depends on a range of factors. First, as they are related to gestational age, knowing this age accurately is important. Frequently, however, the time of the women's last menstrual period is not known precisely. There can be a tendency to favour the ultrasound assessment of fetal age over the women's estimate of the date of conception, but this too can be problematic: it has been shown that first trimester fetal growth varies with maternal nutrition [49] and so this diminishes the accuracy of ultrasound dating measurements. Further the growth of male vs female fetuses differs from early gestation, and discordance in growth between dichorionic twins has been observed as early as 11–14 weeks gestation [50, 51]. In addition, there can be population differences in fetal growth, for genetic and other reasons. In this respect the derivation of standardized global fetal growth charts may need to be viewed with caution.

There are a number of circumstances that can affect fetal growth but are not necessarily associated with ill health. The most obvious example is multiple conception, where twins are each smaller than singleton babies at birth, and triplets smaller still. Male fetuses grow slightly faster than do female fetuses,

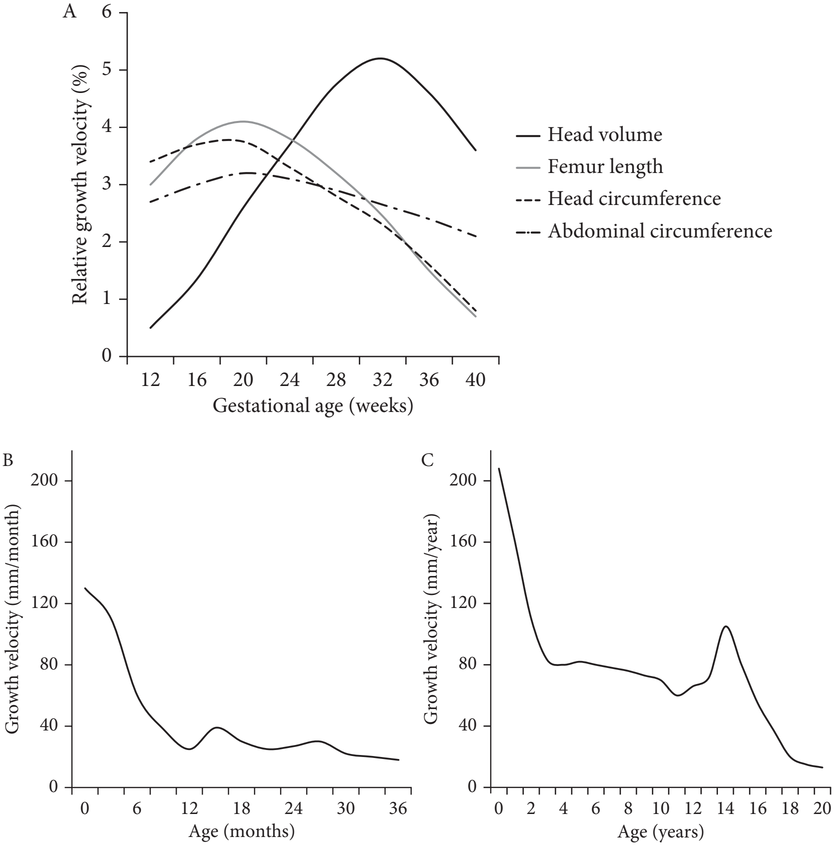

Fig. 2.1 Typical growth velocity changes over time for gestation (A), infancy/early childhood (B), and childhood/adolescence (C). Panel A adapted from *Archives of Disease in Childhood Fetal Neonatal*, E. Bertino et al., Fetal growth velocity: kinetic, clinical, and biological aspects, Volume 74, Issue 1, pp. F10–F15, Copyright © 1996, with permission from BMJ Publishing Group Ltd.

and the fetus of a woman's first pregnancy grows slightly more slowly than subsequent siblings, especially in later gestation. This latter effect can be summarized as the operation of 'maternal constraint' processes [52], by which a woman down-regulates to a degree the growth of her fetus to ensure safe passage through the pelvic canal at birth. However, maternal constraint is overridden when maternal glucose levels are high: excessive glucose crosses to the fetus, as placental glucose transport is not saturable, and sets off a chain of hormonal changes that lead to increased fetal adiposity. Hence, offspring of women with gestational diabetes tend to be adipose.

In adopting a bipedal posture during our evolutionary past, and also evolving to have large brains, humans have a much tighter fit of the fetal head through the pelvis at delivery than our nearest cousins, the chimpanzees. For this reason the fetal head must turn during vertex delivery, and humans are the only mammalian species in which a birth attendant is usually present to assist the delivery. Even so, the risk of obstructed labour remains significant and, in the absence of advanced health care, is associated with a higher risk of maternal and fetal death and other complications such as fistulation of the genito-urinary tracts.

While these issues remain a major health problem in some low-income settings, they are also important to remember in other situations. Many women still fear the delivery process, with good reason. It remains associated with a high risk of haemorrhage, puerperal fever, and death of the woman in low- and middle-income countries. Some women attempt to reduce fetal growth by dieting (e.g. in some countries by avoiding milk as a source of calcium) or smoking in the hope of having an easier delivery. This is not only ineffective but can have longer-term detrimental effects on the health of the child.

Most parents are concerned about whether the postnatal growth of their infant is adequate. Usually this is thought of purely in terms of weight, but the weight-to-length ponderal index (weight/length^3) in the infant, and BMI (weight/height^2) in older children are more important. Infants lose weight (largely from water and some fat loss) in the first few days after birth and then gain weight subsequently. Patterns of body composition change in children in the first years of life, with an overall trend for fat mass to decline followed by its return—the so-called 'adiposity rebound'—by about age 4 to 6 years. There is much debate about the importance of these patterns to later adiposity and risk of non-communicable disease (NCD); for example, crossing two or more major growth centiles in the first six months is associated with a later risk of obesity [53]. The concept of the 'fat baby as a healthy baby' is now less appropriate for this reason, at least in developed countries, as it dates from the time when under-nutrition and infection were prevalent and the energetic stores present in fat were critical to survival.

Body composition

Body composition is more important than simply a measure of size. Humans are the fattest mammals at birth—it is thought that this is to provide a metabolic buffer for the energetically expensive processes of thermoregulation and brain growth against the detrimental effects of malnutrition in infancy [54]. During prenatal life, inadequate nutrition or oxygen supply to the fetus can result from diseases such as pre-eclampsia, infections such as malaria, and poor placental function, and these problems are often interlinked.

In the face of such a challenge, the fetus reduces growth. In early gestation, this is usually manifest as a reduction in the growth of most organs but, in later gestation when the fetus is larger and its demands are correspondingly greater, the growth of specific organs including the brain, heart, and adrenal glands (the latter being important for cortisol production and organ maturation) is preserved at the expense of others. These changes in growth are usually preceded by changes in organ blood flow, measurable by ultrasound as a reduction in perfusion of muscle, kidneys, the lower body, and gut and either maintenance or an increase in flow to the head, neck, and heart. Placental blood flow is usually preserved under these conditions: in extreme conditions it may be reduced but this is likely to be an indication of a problem (i.e. placental dysfunction) rather than part of a coordinated response by the fetus. Unbalanced maternal nutrition leads to changes in the relative flow of blood to the fetal liver and blood which bypasses the liver through the ductus venosus, even at the expense of blood flow to the heart and brain [55]. This is thought to affect long-term metabolic physiology through effects on liver metabolism.

Function

Cellular differentiation, tissue deposition, organ size, and higher-level neuroendocrine control systems are all affected by developmental factors, such as nutrition. Some organs show an ability to regenerate after damage or the effects of daily wear and tear. While this is a feature of the gut and skin, for example, it is not true of the heart and brain. Newer evidence suggests that these organs do possess stem cells that may under some conditions be induced to form new neurons or cardiomyocytes, respectively, although the extent of such repair appears to be limited.

Once a critical period for organ growth has occurred, or the set point of its control has been established, it is difficult or even impossible to change the outcome. For example, aspects of appetite are set very early in life, as are the levels of many neuroendocrine feedback loops such as that regulating cortisol production. These two concepts—that functional control systems are set early in response to cues received in early life, and that there is a critical period after which the setting can be difficult or impossible to change—are critical to the new approach to preventative developmental health, which is the context in which this book is written. This is not to say that opportunities for later preventative intervention do not exist, but these may be viewed as secondary interventions. Primary interventions to promote healthy early development have potentially greater impact.

Developmental plasticity

Developmental plasticity refers to that set of changes in the development of an individual during early life in response to variation in the environment, especially the maternal state or conditions in infancy. Developmental plasticity can be considered normative and physiological, and evolved to allow the fetus and infant to tune its development to the environment in which it will live.

It is important to appreciate that these processes of developmental plasticity are ubiquitous. Evolved processes can only be adapted to the environment in which evolution occurred. Thus, because of the dramatic change in the way we now live our lives, our evolved biology is now almost inevitably mismatched to some extent to the world in which we now live [56]. But because this biology is also affected by the developmental experience affecting normative plasticity, the degree of mismatch can be enhanced, and this too can have consequences. Thus, how we start our lives can influence our relative risk of later developing various diseases (see Fig. 1.2). This is not to say that the disease process starts during development; rather, it is the developmental environment that sets the adequacy, or otherwise, of our responses to later challenges, and thus disease risk.

There are many developmental contexts which can affect the propensity for later disease risk, but which we would not normally view as 'abnormal'. For example, it appears that the later risk of obesity, diabetes, and heart disease is greater in first-born infants than in their subsequent siblings, in twins, in infants born slightly preterm or post-term, and in both infants of teenage mothers and older women. The increasing use of assisted reproductive technology is also revealing that children conceived by this method have a greater risk of these health problems either because of the technology itself or the associated context of greater maternal age and other factors. The effects may not be large, but it is important to be aware of them because it may influence the advice given to parents postnatally regarding the optimal growth patterns for their children.

Developmental plasticity can be understood from the perspective of evolutionary biology, which is driven by the need to reproduce so as to pass our genes to the next generation. However, what is best for survival to reproduce may not be best for health. It is clear from much theoretical and practical research that aspects of life-course biology set up during early development have important effects on the ability of the individual to respond to challenges in their adult life [57–59]. For example, the metabolic control processes established during development alter the amount of fat an adult individual will lay down in response to consuming a high glycaemic index diet, and thus their risk of obesity, diabetes, and the metabolic syndrome. Similar considerations apply to aspects of appetite control and perhaps even the propensity to exercise.

Experimental and clinical research has revealed some of the processes by which the environment of the embryo and fetus affects the characteristics of the individual. These characteristics are collectively called the *phenotype*. It is important to distinguish the phenotype from the *genotype*, which refers to the pattern of genes in the DNA inherited from the mother and father. There has been a tendency to view the role of genes and the environment as effectively independent. This is reflected in the rather trite but frequently used 'nature–nurture' dichotomy. What has become clear in recent years is that the concept of separating the genetic from the environmental, while a useful heuristic, is actually flawed. It turns out that the developmental environment can affect gene function in effectively fixed ways, and in ways that may cross generations [57, 60].

While we have tended to only think of two kinds of inheritance—that which is fixed in the genes through polymorphisms and other fixed genetic variation, and that which is culturally inherited (what we learn from our families and societies and pass on to the next generation; e.g. religion, language)—it is now clear that inheritance can occur in other ways. As we have already indicated, what the mother does can influence her offspring's biology, and because the oocyte formed when mother herself was a fetus, this environmental can affect her grandchildren. We term these phenomena *parental effects*. There are intriguing hints that this may even pass to more distant generations.

Underlying mechanisms—the science of epigenetics

The term epigenetics refers to a number of biological mechanisms by which gene expression is altered in a stable manner without changing the underlying DNA sequence of the organism. This may involve methylation, acetylation, ubiquination, and other modifications at specific amino acid residues, or modifications to histones, around which the DNA is coiled. Epigenetics is central to understanding both developmental plasticity and why parental and intrauterine experience can have both short- and long-term effects.

Developmental plasticity allows the fetus and infant to take information from its mother and adjust its development in response to that information. Signals from the mother such as nutrients, hormones, and metabolites reach the developing embryo or fetus across the placenta, or the infant through the milk, and induce specific epigenetic changes which in turn drive developmental processes that are reflected in structure or function. Epigenetic processes allow one genotype to produce multiple phenotypes; thus, the physical and functional differences between identical (homozygous) twins can be explained by differences in their epigenetic profiles.

Genes are often thought of as discrete entities within the genome—particulate structures that are passed from parents to offspring. The definition of a gene has, however, become more complex. A gene can be considered as a functional segment of DNA, but whereas in the past genes were defined by their coding for messenger RNA (mRNA), which in turn was translated into proteins, we now know that many genes code for mRNAs that do not function as templates for protein production but as active molecules in their own right as regulators of gene action by interaction with DNA or other RNAs. These are called microRNAs or non-coding RNAs. Thus the simplistic model of gene to mRNA to protein has been replaced by an increasingly complex one involving molecular mechanisms by which gene expression is regulated (see Fig. 2.2). While 80 per cent of the human genome does not code for protein sequences, this is not 'junk DNA', as it was once termed, but contains many active DNA sequences that operate to regulate varied aspects of gene expression through the production of these microRNAs.

The most well-known epigenetic process is DNA methylation, in which a methyl group is attached by specific enzymes primarily to the cytosine of a cytosine–guanine dinucleotide (CpG) site. CpGs lie along the gene in particular patterns, and it is this patterning that provides multiple forms of epigenetic control. Some CpGs lie in clusters called CpG islands. Their function is important in determining whether a gene is turned on or off in a particular cell type. Other CpGs are more solitary and lie at a site where a transcription factor binds—these sites appear to be particularly important in developmental plasticity. Parental imprinting is a particular form of epigenetic change where a gene is silenced by methylation if it is derived from one parent but not if it comes from the other parent. Imprinted genes appear to be particularly important for placental function and some aspects of brain function. Loss of imprinting is

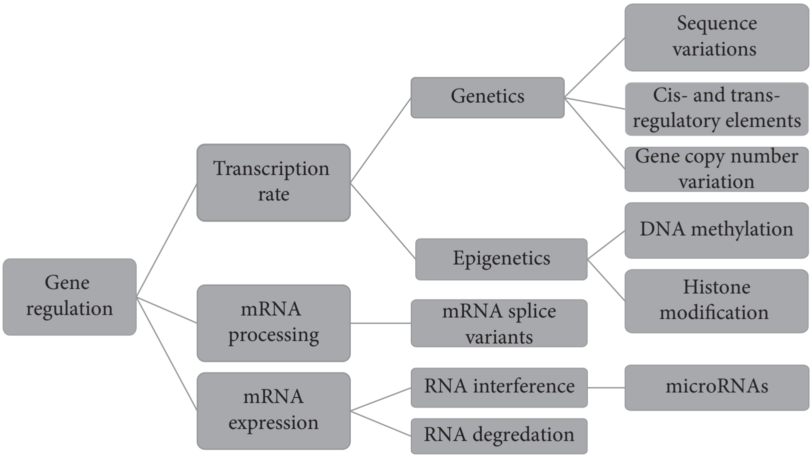
Gene regulation
Transcription rate
mRNA processing
mRNA expression
Genetics
Epigenetics
mRNA splice variants
RNA interference
RNA degradation
Sequence variations
Cis- and trans-regulatory elements
Gene copy number variation
DNA methylation
Histone modification
microRNAs

Fig. 2.2 Gene regulatory mechanisms. Variations in gene expression occur via multiple mechanisms at the DNA level to control transcription rate, or at the RNA level to control mRNA expression, stability, or processing.

associated with some diseases such as Beckwith–Wiedemann syndrome. More recently it has been shown that DNA methylation has a higher level of complexity (e.g. some CpGs are hydroxy-methylated rather than simply methylated), and cytosines outside of CpGs may also be methylated.

DNA itself is coiled around protein cores which are termed histones, and the pattern of coiling makes the DNA either very tightly packed or more open. When it is more open, it is easier for transcriptional factors to bind and so for gene expression to occur. The pattern of coiling is very complex, and chemical modifications to histones affect the coiling and thus the function of DNA. This represents a second major type of epigenetic modification. DNA methylation and histone modifications are biochemically linked because they both have the effect of changing the conformation of the coiled DNA and thus its functionality. These complicated processes involve multiple enzymatic controls, and specificity appears to be conferred in part by the action of the small, non-coding RNAs. In turn, some of these can bind directly to DNA and thus affect coiling, giving another level of epigenetic control.

Epigenetic processes serve multiple functions, from X-chromosome inactivation in the female, to mediating cell differentiation and the induction of specific features of the cell. The specific details differ between these processes and those of plasticity. X-chromosome inactivation is clearly irreversible, and it has generally been assumed that this is also the case for epigenetic change associated with developmental plasticity. However, experimental studies suggest that this may not be completely correct [61].

The critical point to appreciate is that the developing organism is particularly sensitive to epigenetic modifications—indeed, some are essential for development because it is epigenetic change that allows the omnipotent zygote to differentiate into hundreds of distinct cell types as organogenesis proceeds. Moreover, epigenetic processes can be influenced by aspects of maternal lifestyle, such as diet and stress levels, and these more subtle maternally mediated epigenetic effects can have significant outcomes on offspring health and disease risk [62]. It is also clear that paternal lifestyle factors such as smoking can have epigenetic effects via the sperm.

Critical periods and plasticity

The concept of critical periods is well known to the obstetrician and paediatrician—they are periods when the developing individual is particularly sensitive in some respect to external stimuli because a particular organ or system is developing at that time. It seems likely that epigenetic processes are central to mediating such plasticity. It may therefore be that, during such periods, the possibility exists of reversing undesirable changes, for example, if inappropriate epigenetic changes have occurred in some developing fetal tissues as a result of unbalanced maternal nutrition during pregnancy. Indeed in animals, proof-of-principle reversal of epigenetic changes in offspring has been produced by neonatal hormone treatment [63, 64]. We stress that this is purely experimental, and such studies should not be taken to provide evidence that such interventions should be tested in humans. However they do provide strong support for the concept that epigenetic changes can be measured at birth to indicate responses of the fetus to prenatal environment such as nutrition, and raise the possibility of appropriate interventions to reduce disease risk later.

Because a woman's oocytes are formed only during her fetal life, and only one generally matures per ovulatory cycle, it is possible for egg quality to be affected by what happens at any time during the mother's life from her conception to her offspring's conception. It seems probable that one way egg quality can be affected is via epigenetic modification. Similarly, the testis is formed when the father is also a fetus, and the germ cells from which sperm ultimately differentiate are sequestered in fetal life. Thus, it is possible that epigenetic changes can also occur in the father's sperm from his conception through to the production of mature sperm much later. As spermatogenesis is an ongoing process, with sperm production taking 2–3 months, then what the father does during the days and weeks before conception can affect his sperm and thus his offspring. There is growing evidence that obese fathers pass biological information to their offspring via the sperm that leads to a greater risk of obesity in the offspring [65].

These points are highlighted because there is growing evidence that parental behaviour prior to conception has influences on the embryo and fetus. This aspect will be discussed throughout the book. As every parent wishes the best for their offspring, it is important that health care professionals (HCPs) give information to prospective parents about what they can do, even prior to pregnancy as well as during pregnancy, to reduce the risk of a less than optimal pregnancy outcome.

Once conception has occurred, certain features of development are relatively consistent; for example, implantation occurs by about day 9, the fetal heart starts beating by the sixth week, fetal breathing movements start about week 10, etc. This does not, however, mean that every aspect of development is fixed; indeed, there is considerable variation. This developmental plasticity reflects the subtle changes in development as a result of variation in the information reaching the embryo and fetus from the mother and via the placenta. Many of these signals are hormonal, nutritional, or metabolic, and they can have both short-term consequences, such as altered fetal growth, and longer-term consequences, such as disease risk.

After birth, learning and experience are critical to brain development, leading to reinforcement of some pathways and pruning of excess neurons and synapses in others. Indeed, it may be that epigenetic mechanisms are involved in these neurodevelopmental processes. There is increasing evidence that brain development is subject to environmental influences, especially in the first years after birth, and this provides another stage when parental behaviour can have long-term consequences. For example, it is now clear that what a baby is weaned onto influences food preference for life through changes in neural pathways.

Much of this book will focus on the effects of maternal lifestyle on developmental plasticity. It is important to emphasize that developmental plasticity is a normative component of biology, and it is therefore inevitable that the fetus and infant will respond to changes in their environment. But there are situations that make a less than optimal outcome more likely. Similarly, plasticity for some organs, such as the brain, continues through life; but plasticity is obviously greatest in early life and, for many of the systems we are most interested in, remains apparent through infancy.

Plasticity and mismatch

The major outcome of evolutionary processes is a life-course strategy that allows the lineage to pass its genes by reproduction successfully to the next generation in such a way that each generation is fit in turn to pass them to the next. Having the capacity to adjust the phenotype through environmentally sensitive plastic processes makes it more likely that the individual is better matched to its environment after birth and thus more likely to reproduce successfully [4, 56]. But plasticity is a complex process, and at some point for some systems it ceases—for example, once the kidney is fully formed, no more nephrons can be created. So, there may be an advantage in varying the number of nephrons that develop during the plastic phase, depending on environmental signals, to suit the phenotype of the individual. Indeed, there is considerable variation in nephron number between humans, being less in those who were born smaller [5, 66]. In animals, fetuses that were undernourished or exposed to elevated levels of glucocorticoids prenatally develop fewer nephrons [67, 68].

Such processes can be understood as an evolved mechanism to try and *match* the phenotype of the individual to the environment in which he or she lives. Developmental plasticity has the challenge, however, of predicting the environment in which the adult form of the organism will live during its reproductive phase. Thus, the risk of *developmental mismatch* is significant. If the embryo, fetus, or infant detects misleading signals about the world ahead, then it may adopt a less than optimal developmental plan. For example if a mother has placental dysfunction, her fetus will receive less nutrition, which could be interpreted as signalling a future environment of low nutrition; however, the baby may in fact be born into a world of nutritional excess, in which case it may have inappropriate settings of its metabolic physiology and be at greater risk of obesity and diabetes. There is now considerable evidence for the roles of these mismatch pathways in explaining much of metabolic and cardiovascular disease and aspects of human behavioural problems.

Striking examples of the health consequences of mismatch occur in developing countries that have gone through a socio-economic transition rapidly over one or two generations, and in the children of migrants from poor to richer conditions. Under these conditions the prevalence of obesity, diabetes, and heart disease is rising dramatically. That they are on a higher trajectory of risk is made clear by the fact that they are occurring in people whose lifestyles, by Western standards, are still not affluent; moreover, these diseases are becoming apparent at younger ages.

The mismatch phenomenon can however operate even in stable populations in a developed country. Many women and their partners consume an unbalanced or inadequate diet even though food is plentiful. Very often this is linked to low educational attainment, low socio-economic status, and a lack of empowerment, also termed low *health literacy*. Their children may benefit from social mobility, have a very different diet, and so a different risk trajectory.

Other forms of developmental response

Sometimes the signals to the fetus are such that it must make immediately adaptive responses to survive. It must trade-off aspects of its development now in order to survive and cope with the consequences later. Fetal growth restriction may be the most appropriate response to under-nutrition even if it is associated with greater postnatal morbidity and mortality. Similarly, stunting as a result of prenatal or infant under-nutrition may be immediately adaptive even if it also carries later risks of ill health.

Both the plastic and immediate responses we have discussed represent physiologically appropriate adaptive responses of the developing individual in the attempt to preserve viability and reproductive potential. Sometimes, however, the normative programme of development is grossly disrupted by a teratogen, which can produce both immediate and later detrimental effects. Not all teratogens need involve novel agents—for example very high levels of maternal glucose associated with uncontrolled maternal diabetes can lead to cardiac malformations, and severe iodine deficiency can lead to thyroid agenesis.

Taking a 'life-course' approach

These insights into our fundamental biology help to provide mechanistic explanations for the large body of epidemiological data that link measures of the developmental environment, such as birthweight, to the risk of diseases, such as diabetes, in adults. This is a major reason why there is a growing focus on a life-course approach to disease prevention, which must ideally start before conception. Indeed that is a major theme of this book. The key challenge is to take these conceptual ideas and reduce them to a practical guide for HCPs to use in advising parents.

Explaining the importance of these concepts to parents can be difficult. This is partly because many people do not really appreciate the concept of risk, especially the continuity of increasing risk that is associated with the life-course model of NCDs. It is often necessary to explain that the developmental processes that lead to such risk are inevitable and occur in every pregnancy, but to distinguish between this early origin of risk and a truly pathological disruption of development such as that resulting from exposure to a teratogen. The task of explaining why it is important to act to reduce risk of health problems such as NCDs in the next generation is made doubly difficult by the fact that pregnancy and early development are inherently very variable processes, which cannot be perfectly controlled or optimized and where the outcome is always uncertain to a degree. So, on the one hand the HCP has to explain to parents who have clearly an unhealthy lifestyle the greater risk of NCDs to which they are exposing their child as well as themselves, and on the other to manage the expectations of the parents who want a 'perfect' pregnancy outcome.

It is not possible to separate fully strands of advice that focus on the short term from those that address the longer-term issues. In general it is more helpful to provide advice by stage in the life course rather than by functional pathway. This is the purpose of section 4, which provides a checklist for HCPs and a guide for parents. However the following chapters of the book give the detailed information necessary to understand the basis for such nutritional and lifestyle guidance.

Section 2

Nutritional requirements of pregnancy and breastfeeding

Recommendations for nutrient intakes and the need for supplementation before and during pregnancy continues to be a source of confusion for parents. This section outlines our current knowledge of the effects of specific macro- and micronutrients on maternal and fetal health, and provides a reference manual to equip the health care professional (HCP) with sound advice on macronutrient balance and specific nutrient intakes for preconception, pregnancy, and lactation.

Chapter 3

Practicalities: understanding nutrient recommendations

Nutritional advice and caveats

There has been much research in recent years on the nutritional requirements of mothers during pregnancy, as well as an increasing focus on the nutrition of women before conception. Because there has been much confusion with regards to some nutrients such as vitamin D, iron, and polyunsaturated fatty acids, we provide here an in-depth assessment of the evidence. While this may give more detail than some HCPs require, as an increasing number of mothers turn to the internet for information of variable quality, we present sufficient evidence to give HCPs confidence in providing advice. This is particularly important, as there is much inconsistency in the rationale for supplementation with specific micronutrients. It is also important to note that the requirements for an individual woman may vary considerably depending on her context and/or health. We have also tried to provide sufficient guidance for HCPs to be able to adjust their advice to take account of such variation.

Dietary reference intakes

There are a number of terms used by various agencies to describe nutrient requirements. The US Institute of Medicine (IOM), which sets these standards for the US, utilizes dietary reference intake (DRI) as a term encompassing the average, recommended, and upper limit reference intakes for various nutrients. The UK uses the term dietary reference value (DRV) for this purpose.

A key term is the RDA, or recommended dietary allowance, which is the daily intake amount of a nutrient that is expected to meet the needs of the majority (97.5%) of the population. The UK National Institute for Clinical Excellence and the WHO use the equivalent term RNI, or reference nutrient intake. The RDA (or RNI) is higher than the estimated average requirement (EAR) for the nutrient. The EAR is the intake level expected to meet the

Table 3.1 Dietary reference intake terminology [69]

Abbreviation	Term	Definition
US/Canada		
RDA[a]	Recommended dietary allowance	Daily intake level to meet requirement for 97.5% of the population.
EAR	Estimated average requirement	Intake level expected to meet the needs of ~50% of the population.
AI	Adequate intake	Estimated average intake level—used when data are insufficient to set an RDA.
UL	Tolerable upper intake level	Highest level of daily intake at which no adverse effects have been observed.
LRNI[b]	Lower reference nutrient intake	Intake amount sufficient for a small proportion of the population with low needs. Intakes below this are likely to be inadequate.

[a] Alternative term: RNI = reference nutrient intake. Used in the UK and by WHO; formerly used in Canada

[b] Used in the UK

Source: Institute of Medicine, *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*, The National Academies Press, Washington, D.C., US, Copyright © 2006.

needs of ~50 per cent of the population. In cases where data are insufficient to establish an RDA, the IOM sets a level considered to be an adequate intake (AI) for a specific group (by age or life stage). AI levels are generally used for infants and are based on an estimated average intake level of a specific nutrient in healthy breastfed infants.

The IOM also sets a tolerable upper intake level (UL) for most dietary nutrients. The UL is the highest level of daily consumption for which data indicate no adverse effects in humans when the nutrient is consumed indefinitely without medical supervision. In the UK, there is also a recommendation term for the lowest recommended nutrient intake (LRNI). For individuals, habitual intakes below the LRNI are likely to be inadequate, as the majority of people need more than the LRNI level. These terms are summarized in Table 3.1.

Food labelling

Nutritional information provided on food labels is intended to guide the consumer in food selection. Standardized labelling formats, based on dietary recommendations, have been applied in different countries in order to assist consumers in comparing foods in terms of nutrients that are considered to be of nutritional importance. Nutrition labels are intended to help consumers make more healthful food choices, and to understand how a particular food product fits into their overall daily diet.

Food labelling in the US and Canada

Food labels in the US and Canada (the 'Nutrition Facts' panel) show a per cent daily value (%DV) for each important nutrient [70]. The %DV is the proportion of the nutrient's recommended daily intake (based on a 2,000 kcal/day diet) that is provided in one serving of the food. This information is meant to enable consumers to determine the contribution a food would make to their total daily requirement or allowance. A %DV of 5 or less is considered low, and a %DV of 20 or more is high for all nutrients.

The Nutrition Facts panel includes information on serving size and servings per container, calories (kcal) per serving, and calories from fat. The labels first list nutrients that should be limited (e.g. total fat, cholesterol, and sodium), followed by nutrients that should be optimized (e.g., dietary fibre, vitamins, such as vitamin A and C, and minerals, such as calcium and iron). Other countries including the Philippines and Thailand have adopted strategies similar to those used in the US.

Food labelling in the UK, Australia, and NZ

A 'nutrition information panel' (NIP) is used in the UK, Australia, and NZ. The labelling is based on typical values per serving, and per 100 g or 100 mL of the

Table 3.2 UK guideline daily amounts (GDA) nutrition system advice on dietary components in food

Dietary component	High vs low levels in foods
Total fat	High: more than 17.5 g of fat per 100 g
	Low: 3 g of fat or less per 100 g
Saturated fat	High: more than 5 g of saturated fat per 100 g
	Low: 1.5 g of saturated fat or less per 100 g
Sugars	High: more than 22.5 g of total sugars per 100 g
	Low: 5 g of total sugars or less per 100 g
Salt	High: more than 1.5 g of salt per 100 g (or 0.6 g sodium)
	Low: 0.3 g of salt or less per 100 g (or 0.1 g sodium)

Note: ranges differ for drinks—all limits are half those for foods (e.g. 'high' for sugar in a drink is more than 11.25 g/100 mL).

Source: Reproduced from NHS Choices, *Nutrition labels on the back or side of packaging*, © Crown Copyright 2014, licenced under the Open Government Licence v.2.0, available from <http://www.nhs.uk/Livewell/Goodfood/Pages/food-labelling.aspx#Nutrition>.

food. The latter allows comparison of percentages between foods. Labels show a percentage of a reference intake, which is similar to %DV in the US.

The UK also uses a system based on ‘guideline daily amounts’ (GDA) to show food content percentages of the daily value for energy, macronutrients, fibre, and salt (sodium) [71]. The ‘traffic light’ system has been designed to indicate the content of food components that should be limited (e.g., fat, sugar, and salt), with ranges designated as high, medium, and low for each nutritional category. Other components of the GDA system are calories, protein, carbohydrates, and fibre. Guideline advice for high vs low levels of fats, sugars, and salt are shown in Table 3.2.

Chapter 4

Macronutrients and fibre requirements during pregnancy

Macronutrient transfer to the fetus

Complex relationships exist between maternal macronutrient intake, energy expenditure, weight gain, and fetal growth and development [72, 73]. The placenta mediates the transfer of nutrients to the fetus and secretes hormone mediators of maternal and fetal physiology, maternal adaptation to pregnancy, and fetal maturation. The maternal metabolism adapts to the fetal requirements for nutrients as gestation progresses, transporting macronutrients by a number of mechanisms that can be affected by the maternal nutritional state.

Amino acids are actively and selectively transported from the maternal to fetal plasma, and impaired transport caused by poor maternal protein nutrition can result in intrauterine growth restriction [74]. Carbohydrates are transported to the fetus as glucose, which is taken up from the maternal plasma and transported in a concentration-dependent manner into the fetal plasma; thus, maternal plasma glucose levels directly affect those of the fetus [75]. Lipid transfer involves transport proteins, and the fetal supply is regulated by an interaction between maternal diet, which determines maternal lipid concentrations, and the placental capacity to produce, modify, and transport essential fatty acids and long-chain polyunsaturated fatty acids (PUFAs). This capacity is impaired in pregnancies affected by gestational diabetes mellitus (GDM) [76].

Macronutrient balance during pregnancy

The maternal macronutrient profile can influence embryonic and fetal development. Energy balance was discussed in chapter 1. Here we consider the impact of varying intakes of protein, carbohydrates, and lipids, which are the key nutrients that contribute to calorie intake. Fibre is also an important food component that needs to be considered. Because these are always consumed as foods and not in the form of supplements, we do not take a biochemical perspective and consider them in isolation but focus on the issue of macronutrient balance as a proportion of energy intake. The exceptions are the long-chain PUFAs such as docosahexaenoic acid, which, while found in foods such as fish, have also been promoted as a specific supplement for pregnancy. PUFAs will be reviewed in more detail in chapter 5.

The proportions of macronutrients required for pregnancy are generally the same as for non-pregnant women, although macronutrient ratios in the diets of pregnant women can be quite variable. Daily dietary reference values for macronutrient intakes vary somewhat by geographical region. For the majority of women in developed countries, dietary intakes are not well aligned with country-specific recommendations [77]. Energy and fibre intakes tend to be lower than the recommendations, while the intakes of total fat and saturated fats are consistently above the recommendations. Mean energy intakes differ by socioeconomic status, with reported energy intakes increasing as status decreased [77].

A study in the UK found that maternal dietary intakes of protein, fat, and carbohydrates during pregnancy correlate with later child dietary intakes of the same nutrients. This association was stronger than the influence of either parent's postnatal diet, suggesting some effect of in utero programming on offspring dietary habits [78]. Getting the balance right in pregnancy may therefore be important not only for the immediate growth and development of the fetus, but also for its long-term health and well-being.

Protein in the maternal diet

The ratio of protein to non-protein energy in the maternal diet has been shown to influence the offspring's body composition [79], and animal studies suggest it impacts the risk of metabolic disease in adult life [80, 81]. Both low and excessively high-protein intakes during pregnancy are associated with restricted growth [82–84], increased adiposity and elevated cholesterol, triglyceride, and leptin levels [82, 85], as well as impaired glucose tolerance and insulin resistance [81, 82, 85]. The percentage of protein in the maternal diet appears to be inversely associated with fetal abdominal subcutaneous fat, regardless of whether fats or carbohydrates are the diluents of the protein [79].

The source of protein may also matter to fetal growth. In a UK survey, differences in the both placental and fetal growth were observed between mothers consuming different balances of dairy protein and meat protein. In late pregnancy, low intakes of dairy protein were associated with low placental weight, and low intakes of meat protein were associated with lower birthweight. Overall, birthweight fell by 3.1 g for each gram decrease in meat protein intake in late pregnancy [86].

Studies have shown that early-pregnancy diets that are high in protein as a percentage of energy intake are associated with higher birthweight and placental weight [87], whereas high carbohydrate intakes in early pregnancy tend to produce lower placental and birthweights [86]. However, a follow-up study in Motherwell, Scotland, of adults whose mothers had been advised to consume a high-protein (red meat), low-carbohydrate diet in pregnancy exhibited higher blood pressure in adulthood than those whose mothers did not follow such dietary advice [88]. High-protein supplementation is not recommended for pregnant women; rather, balanced protein/energy supplementation (where proteins provide less than 25% of the total energy intake) appears to be beneficial, particularly for undernourished women [89].

Fats in the maternal diet

Animal studies have shown that high-fat maternal diets can significantly increase susceptibility to diet-induced obesity and percentage total body fat in offspring [90]. Diets high in fat have been demonstrated to increase the risk for GDM recurrence in future pregnancies [91]. Early-pregnancy diets with increasingly higher fractional caloric intakes from carbohydrates relative to fats were found to decrease the risk of both glucose intolerance and GDM [92]. High intakes of saturated fat and trans-fat as a percentage of energy, and low intakes of vegetable and fruit fibre were individually associated with increased fasting glucose levels in the second trimester [93]. However, increased PUFA intake has been associated with a reduction in incidence of glucose intolerance during first pregnancies in Chinese women, highlighting the need to consider the type of fat ingested and to consider PUFAs separately from total fat [94]. Specific requirements for fatty acids are discussed in chapter 5.

Carbohydrates in the maternal diet

Glucose during pregnancy

Glucose is the main energy substrate for the fetus, and its concentration in the maternal bloodstream has a direct effect on the fetus. The type and content of carbohydrate (high- vs low-glycaemic sources) in the maternal diet influences blood glucose concentration [95]. Glycaemic index (GI) refers to the grouping of carbohydrate sources by the magnitude of their induced glucose response. Low-GI sources include whole grains, unprocessed rice, beans, most fruits, nontuberous vegetables, nuts, and dairy products; high-GI sources include processed grains (flour, bread, cereals), tuberous vegetables (potatoes, carrots), baked goods, soft drinks, snack foods, ripe bananas, and some tropical fruit. Recent data suggest that exposure to a high-GI diet in pregnancy is associated with markers of the metabolic syndrome (e.g. fasting glucose levels, triglycerides, cholesterol, blood pressure) in offspring at 20 years of age [96].

Fructose during pregnancy

Fructose is one of the natural sugars found in fruits but until recently was a small component of diets. It has been widely used as a sweetener in canned foods, baked goods, processed foods, dairy products, and carbonated drinks, predominantly in North America and Japan [97, 98] and is thought to be contributing to the rapid rise in the prevalence of obesity and metabolic syndrome [99]. The main sources of fructose are table sugar (sucrose, a disaccharide composed of glucose and fructose), high-fructose corn syrup (a sweetener containing up to 55% fructose, the remainder being glucose), fruits, and honey. Fructose consumption in the US has increased to about 80 g/day [100], and its consumption accounts for 10–20 per cent of the daily caloric intake [99, 101].

Studies have demonstrated that dietary fructose disrupts lipid metabolism and decreases insulin sensitivity [102–105]. Evidence from both animal and human studies have also shown that excessive fructose consumption is associated with various adverse metabolic outcomes such as insulin resistance, increased adiposity, hypertriacylglycerolaemia, hyperleptinaemia, hyperglycaemia, hyperinsulinaemia, impaired glucose tolerance, and hepatic steatosis [106–110]. Epidemiological studies have also reported a correlation between fructose intake and cardiovascular disease, type 2 diabetes, and obesity [108, 109] A study of 13,475 women found a 22 per cent increased risk of GDM associated with consumption of 5 servings/week of sugar (fructose) sweetened beverages [111].

Gallbladder disease is a significant cause of maternal morbidity during pregnancy [112]. Studies have shown an association between high intake of carbohydrates and gallstone disease [113–117], and in a recent, large, prospective study [112], high intakes of fructose were associated with increased risk beyond the effect of total carbohydrate intake. Gallstones are associated with metabolic syndrome [118], and excessive fructose intake might also contribute to its development [119–122].

Fibre in the maternal diet

Increased dietary intakes of fibre-rich fruits, vegetables, and whole grains are often recommended as part of a healthy dietary guideline. Fibre-rich ingredients such as wheat bran, beta-glucans from oats and barley, and soluble fibre from prebiotics are also recommended to ensure an adequate intake of dietary fibre [123]. High-fibre diets have been associated with reduced risks of cardiovascular disease, stroke, and diabetes [124–126]. Supplementary dietary fibre has also been shown to improve insulin sensitivity and plasma lipid profiles, and to reduce blood pressure [127–130].

Changes in physiological state during pregnancy may increase the risk of several gut disorders and metabolic diseases [123]. Thus, a pregnant mother's need for dietary fibre may be higher than that of the general population. Pregnant mothers have been recommended to consume between 25 and 30 g of total dietary fibre from various food sources such as fruits, vegetables, and whole grain cereals [131]. Consumption of dietary fibre during pregnancy has been reported to reduce the risk of GDM, pre-eclampsia, and postpartum weight retention [132–134].

The beneficial effects of dietary fibre on GDM seem to depend on foods such as whole grains, cereals, and fruits [135]. In the US Nurses' Health Study II cohort (>11,600 women), pre-pregnancy dietary fibre intake had a strong negative association with GDM risk, which decreased by 26 per cent with each 10 g/day increment in total fibre intake [134]. Lower intakes of vegetable and fruit fibre during the second trimester have been linked to increased fasting glucose, and in women with family histories of type 2 diabetes, a higher vegetable and fruit fibre intake has been associated with reduced insulin resistance and increased insulin sensitivity [93].

Higher dietary fibre intake during pregnancy has also been associated with reduced risks of pre-eclampsia [133, 136]. During pregnancy, maternal plasma lipids are significantly elevated, and pre-eclampsia exacerbates this situation [137, 138]. Pregnant women with higher intakes of dietary fibre tend to have lower levels of total triglycerides and higher levels of HDL cholesterol compared with those consuming diets low in fibre [133]. High-fibre diets have been associated with weight control and obesity prevention [139–141]. A daily intake of around 8.5 g fibre per day was found to have a protective effect against postpartum weight retention [132]; conversely, inadequate postpartum fibre intake has been reported to increase the risk of obesity [142].

Recommended macronutrient and fibre intakes during pregnancy

The US Insitute of Medicine (IOM) recommends no increase in caloric intake during the first trimester, an additional 340 calories per day (1,423 kilojoules) during the second trimester, and an additional 452 calories per day during the third trimester. In general, it is recommended that pregnant women should consume 175 g/day of carbohydrates, 60–70 g/day of protein, 28 g/day of fibre, 10–13 g/day of omega-6 PUFAs, and 1–1.4 g/day of omega-3 PUFAs [131]. During pregnancy, a balanced protein–energy diet, where protein provides less

Table 4.1 Australian National Health and Medical Research Council recommendations for macronutrient and fibre intakes for pregnant women [143]

Nutrient class	**Maternal age**		
	14–18 yrs	**19–30 yrs**	**31–50 yrs**
Protein[a]	58 g/day	60 g/day	60 g/day
Fat			
Linoleic acid (omega-6)	10 g/day	10 g/day	10 g/day
Alpha-linolenic acid (omega-3)	1.0 g/day	1.0 g/day	1.0 g/day
Carbohydrate[b]	No recommendation		
Fibre	25 g/day	28 g/day	28 g/day

[a] As there is little additional weight gain during the first trimester, no additional protein is needed. The recommendations listed are for additional protein in the second and third trimesters

[b] Data were considered insufficient to make a recommendation.

Source: National Health and Medical Research Council, *Nutrient Reference Values for Australia and New Zealand, Including Recommended Dietary Intakes*, Department of Health and Ageing, Australian Government, Canberra, Australia, copyright © 2006.

than 25 per cent of the total energy content, has been recommended as an ideal dietary pattern that may help mothers to achieve appropriate weight gain, as well as to help reduce the risk of infants being small for gestational age. The recommended percentage of energy sources are 10–15 per cent from protein, 15–30 per cent from fat, and 55–75 per cent from carbohydrates. During the second and third trimesters, it is recommended that pregnant women should consume an additional ~25 g/day of protein, ~35 g/day of carbohydrates, and ~3 g/day of fibre [131]. The Australian National Health and Medical Research Council provides recommendations for pregnant women that are slightly lower than those of the IOM [143], as shown in Table 4.1.

Our recommendations for macronutrient and fibre intake during pregnancy

The macronutrient profile of a woman's diet during pregnancy is clearly important to her own health and that of her fetus. The increased metabolic rate that occurs in pregnancy results in an increased fuel requirement in mid- and late pregnancy, as the energy and nutrient requirements of the fetus increase. By late pregnancy women require an extra ~35 g/day of dietary carbohydrates. This amount is supplied in portions of carbohydrate-rich foods such as one bagel, two slices of bread, a small baked potato, one average-sized tortilla, or four tablespoons of cooked rice. Refined sugars, in particular fructose, should be limited—low-GI carbohydrate sources should make up the majority of carbohydrate intake. With regard to protein, a single serving of meat (steak, hamburger, turkey, chicken) provides between 25 and 30 g of protein, which is sufficient for the daily needs of pregnant women. Good non-animal protein sources include legumes (e.g. 1 cup cooked chickpeas or lentils provides 12–18 g protein), tofu (9 g protein/4 oz serving), oats (7 g protein/cup), and soy milk (5 g protein/cup).

The requirement for fats in pregnancy can be met by typical Western diets, but the quality of the diet with respect to types of fats is a concern. Fats should represent 15–30 per cent of a woman's overall energy intake, although intake of saturated fats should be limited (reducing consumption of fried fast foods and processed snacks) and PUFA intake should be maintained or increased by consuming 1–2 meals/week of oily fish. However, women should be aware of fish species to limit or avoid because of possible contamination with industrial toxins (see chapter 5 and chapter 30). Fibre is important for pregnant women, and requirements for pregnancy should be achievable in a diet that includes a variety of whole grains, vegetables, fruit, and legumes. Overweight and obese women do not need to increase their energy intake during pregnancy but should focus on achieving a balanced diet in accordance with the above recommendations. Undernourished women require a balanced protein energy diet, which can be achieved via supplementation when the food components of a sufficient and balanced diet are not readily available.

Chapter 5

Polyunsaturated fatty acids in pregnancy and breastfeeding

Polyunsaturated fatty acids are essential for fetal and infant development

There is increasing interest in the role of the omega-3 fatty acids in fetal and infant development and thus in the use of dietary supplements for pregnant women and/or infants, and in promoting intakes of oily fish as a source of omega-3 long-chain polyunsaturated fatty acids (PUFAs). The evidence for supplementation over and above promoting a healthy diet during pregnancy and breastfeeding is still uncertain, but this is a rapidly evolving area of nutritional research. Given the potential beneficial effects of greater omega-3 PUFA levels on fetal brain development and on reducing the risk of allergy and the likely detrimental effects on metabolic health of a high omega-6/omega-3 ratio, this is a subject in which objective evidence can be drowned by considerable pressure to act on anecdotal observations.

The omega-3 and omega-6 fatty acids represent the two major forms of PUFAs. [144]. The simplest omega-3 PUFA is alpha-linolenic acid (ALA), and the simplest omega-6 PUFA is linoleic acid (LA). ALA can be metabolized into the longer and more unsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while LA can be synthesized into long-chain arachidonic acid (AA). However, the conversion rates from ALA to EPA and especially to DHA, and from LA to AA are usually low in humans, with estimates ranging from 1 to 10 per cent [145–147]. The conversion also varies depending on common single nucleotide polymorphisms in the fatty acid desaturase gene cluster, as these polymorphisms can result in different amounts of EPA, DHA, and AA being formed in different individuals [148, 149]. Conversion rates are lower in infants than adults, and insufficient conversion of ALA to EPA—and further to DHA—will have adverse effects on visual and neural development, particularly in premature infants [150, 151].

Dietary sources of polyunsaturated fatty acids

Significant amounts of the omega-6 PUFA LA are found in vegetable oils such as corn, sunflower, soybean, and peanut oils as well as in products made from these oils, such as margarines; the omega-6 fatty acid AA is found in animal sources only (e.g. meat, eggs) [144, 152]. Sources for the omega-3 fatty acid ALA are green plant tissues, flaxseed, walnuts, beechnuts, butternuts, chia seeds, canola, and soy [144]. The omega-3 long-chain PUFAs EPA and DHA are found in cold-water fatty fish, such as salmon. In most Western diets, up to 98 per cent of dietary fatty acid intake is made up of LA and ALA, with LA intake being in excess of that of ALA. The intake of LA in the Western diet has increased markedly over the second half of the twentieth century, following the introduction and increased consumption of vegetable cooking oils and margarines, whereas ALA intake did not change much over this time [152].

The changed pattern of LA consumption has resulted in a marked increase in the ratio of omega-6 to omega-3 fatty acids in the diets of most Western populations [153]. For example, in men the LA:ALA ratio ranges from 5.5:1 in Denmark to 13.8:1 in France; a similar pattern is seen in women. However, the LA:ALA ratio for both Spanish men and women is 27:1. This ratio is important because high LA inhibits the synthesis of DHA as a result of competition for common converting enzymes. However, while increasing the intake of ALA provides more substrate for synthesis of EPA, the final step conversion to DHA (the desaturation of 24:5omega-3) is actually inhibited at high levels of dietary ALA. Therefore diets low in ALA may be preferred so long as the level of LA is also low [154].

Polyunsaturated fatty acid status in pregnancy and lactation

Maternal transfer of long-chain PUFAs to the fetus is influenced by maternal fatty acid status, placental function, and the placental levels of fatty acid transporters and binding proteins that are involved in the selectivity of DHA for mobilization [155, 156]. Maternal PUFA status decreases progressively during pregnancy, especially in multiple pregnancies and in each subsequent pregnancy [157]. DHA status declines further after parturition, particularly in breastfeeding women, although other long-chain fatty acids increase [158].

Breast milk is sensitive to changes in fatty acid composition in the maternal diet. For a typical Western diet, the mean LA composition in breast milk has increased from 6 to 15 per cent of total fatty acids in the US from 1944 to 1990, and from 10 to 14 per cent in Australia from 1981 to 2000; while during the same period, the DHA content has decreased [159–161]. DHA levels in breast milk reflect dietary changes in the mother, although there is some selective transfer of DHA to breast milk at the expense of the maternal supply if the latter is low. The DHA levels in infant blood correlate significantly with the DHA levels in both maternal blood and milk [162]. Infants consuming human milk have higher levels of cerebral cortex DHA than do those fed with formula milk without DHA [163–165].

Effects of polyunsaturated fatty acids on health

Polyunsaturated fatty acids and maternal mental health

The prevalence rates for antenatal and post-partum depression range from 10 to 40 per cent worldwide [166]. Aside from genetic predisposition, environmental, social, and psychological factors, inadequate nutrition may also play a role in maternal depression. Intake of long-chain PUFAs, in particular the omega-3 fatty acids DHA and EPA, has been associated with mental health outcomes, and greater intake may improve maternal mental health. The omega-3 fatty acids play a role in serotonin functioning and thus may produce antidepressant effects [166].

PUFA status (especially omega-3 fatty acid status) declines during pregnancy and can be improved by supplementation [167]. The decline of maternal DHA status during pregnancy and/or lactation has been associated with post-partum depression, especially in women with a low intake of DHA. Analyses of data in published reports from 23 countries showed that higher concentrations of DHA in mothers' milk and greater seafood consumption predicted lower prevalence rates of post-partum depression [168, 169]. Nonetheless, intervention studies performed to evaluate the potential protective effects of omega-3 fatty acids in maternal depression have shown mixed, but generally negative, results [170–173].

The effect of polyunsaturated fatty acids on offspring growth and development

Maternal intake of omega-3 fatty acids and AA during pregnancy has been shown to correlate positively with fetal growth and birthweight, whereas maternal LA intake correlated negatively with birth size [174–176]. In preterm infants, AA levels at birth are associated with both birth size and growth during the first year of life [177, 178]. A large cohort study in the US reported that higher omega-3 fatty acid concentrations in the maternal diet and umbilical cord plasma were associated with a lower obesity rate in 3-year-old children

[179]. However supplementation with 1.2 g omega-3 fatty acids daily, along with dietary counselling to reduce AA intake from mid-pregnancy through 4 months of lactation had no effect on adipose tissue development during early postnatal life, despite maternal fatty acids being positively correlated with infant weight, length, and lean body mass at birth [180].

Differentiation of pre-adipocytes is promoted by omega-6 fatty acids, and exposure to these PUFAs in utero and during early infancy promotes fat cell formation and excess fat deposition in early life [181]. Increasing consumption of omega-6 fatty acids relative to omega-3 fatty acids in the Western diet has been implicated as a contributing factor to the increased incidence of childhood obesity [159, 182]. It has been hypothesised that reduction of the omega-6 to omega-3 fatty acid ratio in the maternal diet may limit the offspring's early adipose tissue development, and this may be a novel strategy to prevent childhood obesity [183].

The effect of polyunsaturated fats on cognitive/visual development

Long-chain PUFA supply during pregnancy is crucial for the optimal development of the brain and visual systems. Studies in non-human primates have reported impaired cognitive function and visual acuity in offspring of mothers who were deficient in omega-3 fatty acids, and this situation could not be salvaged by postnatal omega-3 fatty acid supplementation [184, 185]. In human observational studies, higher maternal DHA intake correlated with better motor functioning, attention, and sleep pattern development in infants and children [186–192]. The period of greatest accumulation of DHA in the developing brain is during the last trimester of pregnancy and the first year of life [162].

Observational studies suggest that consumption of oily fish (a source for omega-3 fatty acid) during pregnancy can improve the offspring's visual stereoacuity, vocabulary comprehension, receptive vocabulary and verbal intelligence quotient from infancy to 9 years of age [189, 193–196]. Pregnant mothers who consume more than the recommended amount of fish are reported to have children who show higher cognitive performance [189, 192]. These results however, have not been validated in randomized, controlled trials. A recent meta-analysis of trials of maternal omega-3 fatty acid supplementation found no differences in cognitive, language, or motor development between offspring of supplemented vs non-supplemented mothers, despite some trials showing higher cognitive scores in young children [197]. Current evidence neither supports nor refutes the hypothesis that consumption of omega-3 fatty acid during pregnancy can improve cognitive or visual development in children.

The effect of polyunsaturated fatty acids on the development of allergies and respiratory disease

The changing composition of long-chain PUFAs in human diets, with an increasing intake of omega-6 fatty acids relative to omega-3 fatty acids, has coincided with an increased prevalence of atopic diseases in children [198, 199]. This may be because the amount of omega-6 fatty acids in the diet influences the rate of formation of the inflammatory mediator prostaglandin E2 and thus the development of allergic sensitization [198]. These dietary changes are reflected in the fatty acid composition in breast milk, which has been shown to impact the susceptibility of breastfed infants to such disorders. Children who were breastfed by mothers with low levels of omega-3 fatty acids relative to omega-6 fatty acids in their milk (in particular, a high AA:EPA ratio) were found to be at increased risk of developing atopy by 18 months of age [200]. In non-atopic mothers, plasma long-chain fatty acid content was negatively correlated with the development of atopic eczema in their infants [201]. A report from the Southampton Women's Survey also provided some limited support that a low level of maternal omega-3 fatty acids relative to omega-6 fatty acids is linked to later wheeze and atopy in the offspring [202].

With the decline in the consumption of omega-3 fatty acids in favour of the more pro-inflammatory omega-6 fatty acids, numerous studies have suggested a potential protective role of omega-3 fatty acids in allergic diseases [203, 204]. Omega-3 long-chain PUFAs can be obtained from some fish and fish oils, and these fatty acids may oppose the actions of omega-6 fatty acids [203]. A study in Australia demonstrated that high-dose omega-3 long-chain fatty acid supplementation of 900 mg/day in pregnancy did not reduce the overall incidence of immunoglobulin E associated food allergy in the first 12 months of life, although it lowered the incidence of atopic eczema and egg sensitization [205].

Maternal fish intake during pregnancy has been consistently demonstrated to have protective effects on atopic or allergic diseases in infants and children, including eczema, asthma, and sensitization to dust mites or food [206–209]. However, this is not the case for fish intake during infancy or childhood, where the reported effects have been inconsistent. However, dietary supplementation of DHA and AA in infants and children is associated with delayed onset and reduced risk of upper respiratory infection and asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis up to 3 years of age [210], and a lower incidence of bronchiolitis in the first year [211], as well as fewer episodes and a lower incidence of respiratory illness [212].

Agency guidelines on polyunsaturated fatty acid intake

Based on a joint expert consultation on fats and fatty acids in human nutrition, the FAO and WHO have formulated guidelines for dietary intakes of essential fatty acids for pregnant and lactating women [213]. These guidelines suggest that PUFAs should represent 6–11 per cent of total energy intake. The recommended minimum intake of omega-3 fatty acids for optimal maternal health and fetal and infant development is 0.3 g/day EPA + DHA, of which at least 0.2 g/day should be DHA. The European Food Safety Authority has also set an adequate intake (AI) value for ALA for all population groups, including pregnant and lactating women, as 0.5 per cent of the total energy intake. According to this set of recommendations, the AI value for total EPA + DHA is 250 mg/day for adults, which should be supplemented by 100–200 mg/day DHA during pregnancy and lactation [214].

Our recommendations for polyunsaturated fatty acid intake during pregnancy and lactation

Transfer of long-chain PUFAs from a mother to her offspring during pregnancy and lactation relies on adequate maternal status, which correlates with her dietary intake and can be influenced by common genetic variants in fatty acid processing enzymes. There are large differences worldwide in dietary intake of long-chain PUFAs, particularly DHA. Although the main source is fish/fish oil and seafood, vegetable oils and cereals are other important sources of polyunsaturated fatty acids, especially for those who consume a mostly vegetarian diet.

It should also be noted that high consumption of oily fish carries an increased risk of exposure to lipophilic industrial contaminants such as polychlorinated biphenyls [215] and mercury (see chapter 30). However, the proportion of polychlorinated biphenyl exposure originating from fish is low (≤26%) compared with that from other foods of animal origin. Mercury contamination is an issue mainly with large predatory fish species such as swordfish, king mackerel, Chilean sea bass, Ahi tuna, shark, and tilefish [216]. Regional differences in environmental contaminants may be important, and health care professionals should be aware of any local or regional fish consumption advisories. Consumption of a variety of fish (not just oily fish) should be encouraged.

The LA: ALA ratio is important; diets low in ALA (from canola oil, flaxseed, walnuts, etc.) are acceptable so long as the level of LA (from other vegetable oils and meat) is also low. The FAO and WHO guidelines for dietary intakes for total fat and essential fatty acids should be followed in order to maintain adequate levels during pregnancy. At present the evidence is not sufficient to support specific additional supplementation for pregnant women, although intakes of DHA up to 1,000 mg per day and EPA up to 500 mg per day are safe and may have some beneficial effects. For children under 2 years of age, the key sources of omega-3 long-chain PUFAs are breast milk and fish. Therefore, continued breastfeeding and an increased intake of fish should be promoted.

Chapter 6

Vitamin A in pregnancy and breastfeeding

Vitamin A functions

Vitamin A refers to a group of fat-soluble compounds (retinoids) that includes retinol, retinal (retinaldehyde), retinoic acid (RA), and retinyl esters. Retinoids are required for visual function and modulate the expression of many genes involved in embryonic development, tissue growth, epithelial tissue integrity, metabolism, reproduction, and immune function. The biologically active retinoid form is RA, except in the visual system, where retinal is also required. The pleiotropic effects of RA are mediated through two types of receptors: the RA receptors and the retinoid X receptors [217].

Retinol is known as 'preformed' vitamin A and is obtained from animal sources primarily in the form of retinyl esters stored in fats (see Fig. 6.1) The provitamin A carotenoids (beta-carotene, alpha-carotene, and beta-cryptoxanthin) are dietary precursors of retinol derived from plants and are converted in the body by the retinaldehyde dehydrogenase enzymes to retinol and then to two active retinoids, all-*trans*-RA and 9-*cis*-RA. All-*trans*-RA binds to RA receptors, and 9-*cis*-RA binds to retinoid X receptors, forming heterodimers that regulate gene transcription by binding chromosomal RA response elements. RA receptors and retinoid X receptors also form heterodimers with thyroid hormone receptors and vitamin D receptors, mediating the interaction between vitamin D and thyroid hormones with their receptors [218].

Retinol is absorbed in the small intestine via a carrier-mediated and saturable process, with high absorption efficiency (70–90%). Carotenoids are absorbed passively in the small intestine; the efficiency of absorption is 9–22 per cent, decreasing with increasing carotenoid intake. Most vitamin A reserves are stored in the liver as retinyl esters, but carotenoids are also deposited throughout the body in fatty tissues [219]. The release of vitamin A from the liver and vitamin A transport in plasma is dependent on retinol binding protein. Carotenoids are fat soluble and are transported in plasma via lipoproteins [217, 220]. The maintenance of RA levels in cells and tissues is regulated by positive and negative feedback controlled by the cytochrome P450 enzymes CYP26A1, CYP26B1, and CYP26C1, which are expressed in different tissues [221].

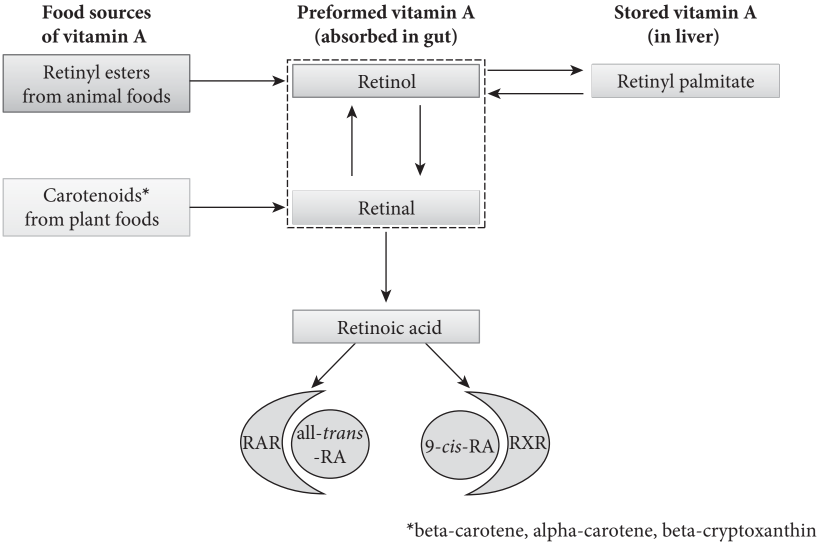
Food sources of vitamin A
Preformed vitamin A (absorbed in gut)
Stored vitamin A (in liver)
Retinyl esters from animal foods
Retinol
Retinyl palmitate
Carotenoids* from plant foods
Retinal
Retinoic acid
RAR
all-*trans* -RA
9-*cis*-RA
RXR
*beta-carotene, alpha-carotene, beta-cryptoxanthin

Fig. 6.1 Vitamin A precursor forms, sources, and conversion pathways; 9-*cis*-RA, 9-*cis*-retinoic acid; all-*trans*-RA, all-*trans*-retinoic acid; RAR, retinoic acid receptors; RXR, retinoid X receptors.

Vitamin A deficiency

The WHO classifies individuals as being at risk for biochemical vitamin A deficiency (VAD) at a serum retinol threshold of <0.7 μmol/L [222]. However, serum retinol is not well correlated with vitamin A intake or signs of deficiency, as its levels are homeostatically controlled unless liver vitamin A stores are either very low or very high. The effect of vitamin A on the visual system is reflected in early signs of deficiency or excess. The most specific evidence of VAD is xerophthalmia (dry eyes and night blindness). Other eye symptoms include keratomalacia (ulceration of the cornea), keratin debris in the conjunctiva (Bitot spots), and photophobia [223]. The visual pigment rhodopsin, which is critical for dim-light vision, is formed from the binding of 11-*cis*-retinal (derived from isomerization of retinal) to the membrane receptor opsin in photoreceptor cells of the retina [224]. Night blindness is a precursor sign of hypovitaminosis A, whereas double vision is a sign of hypervitaminosis A.

Vitamin A is essential for proper functioning of both male and female reproductive systems; deficiency causes infertility [225]. In addition, vitamin A supports several functions that are key to resistance to infection. VAD disrupts neutrophil development [226] and reduces Th2-mediated antibody responses as well as natural killer cell activity and number, thereby impairing both innate and adaptive immune responses to infection [227]. Vitamin A is also involved in mucosal epithelial barrier function, and deficiency compromises the ability of such barriers in eye conjunctiva and the respiratory, gastrointestinal, and urogenital tracts to resist penetration by pathogenic microorganisms [228]. Infection itself can impair vitamin A status and exacerbate deficiency in several ways primarily related to malabsorption. VAD is associated with an increased risk of death from common infections in pregnant women, infants, and young children [222]. As signalling molecules in embryogenesis, in part via their effects on hormone receptor activation, retinoids are required for development and maintenance of multiple organ systems, including the heart, lungs, kidneys, and skeleton. Both excess and deficiency of vitamin A in pregnancy are associated with birth defects, most typically malformations of the eye, skull, lungs, and heart [229].

Vitamin A in pregnancy

Vitamin A homeostasis in pregnancy is altered to meet fetal demands, dependent on the mother's vitamin A status. Maternal serum retinol levels decrease prior to depletion of hepatic stores, particularly in the third trimester, because accelerated fetal growth during this period is dependent on vitamin A acquired from the maternal circulation [230]. Under conditions of moderate deficiency, accumulation of sufficient vitamin A in the fetus occurs at the expense of maternal vitamin A stores. Pregnant women are therefore most susceptible to deficiency in the third trimester, and night blindness most commonly occurs at this time in women with relative deficiency [222].

It is estimated that the growing fetus requires ~100 μg of vitamin A per day during the third trimester of pregnancy. In non-vitamin A deficient populations, maternal liver stores of vitamin A are thought to be sufficient to cover this increased requirement. The active transfer of vitamin A to the fetus from the placenta during pregnancy compensates for a wide range of maternal intakes. Nonetheless, women with low vitamin A intake or reduced liver stores should increase their intake throughout pregnancy to ensure adequate stores are available for rapid fetal growth in late gestation [231]. It is assumed that an insufficient supply of vitamin A to the fetus restricts growth, and there is some evidence for a positive association of vitamin A status in pregnancy with infant birthweight and length [232]. Low birthweight was significantly more prevalent among infants whose mothers were vitamin A deficient (affected by night blindness) in a study in rural south India [233]. However, controlled trials have tested the effect of maternal vitamin A supplementation on birth/infant size and thus far have not shown a clear benefit [234, 235].

VAD in pregnant women is highly prevalent in developing countries. In such areas of high VAD risk, an estimated 7.8 per cent of pregnant women have xerophthalmia (night blindness), and >15 per cent have low serum retinol concentrations. Over 19 million women are globally affected annually [222]. A UN/WHO report estimated that 160 million preschool children in developing countries were affected by VAD (prevalence 30%) [236]. In these countries, VAD is associated with growth failure, depressed immunity, and increased morbidity and mortality due to infectious disease.

On the other hand, a high intake of vitamin A in pregnancy also presents adverse health risks, particularly to the developing fetus. Vitamin A (as retinol) is considered to be teratogenic if present in excess in early pregnancy. Fetuses exposed to high-dose retinol between the fifth and seventh week after the last menstrual period (third to fifth week postconception) are most at risk of serious birth defects [229].

Vitamin A supplementation in pregnancy

Because of the potential teratogenic effects from exposure to excess preformed vitamin A in the first trimester of pregnancy, vitamin A supplementation in pregnant women who are not deficient is not recommended. In areas of high VAD prevalence, however, vitamin A supplementation of pregnant women has been found to reduce the risks of night blindness, anaemia, and infection [237]. On the basis of the observed association between vitamin A and infectious disease resistance, supplementation has been specifically studied in HIV-positive women living in areas of high VAD risk, as well as those in areas where malaria is endemic. Vitamin A supplementation in pregnancy enhanced maternal immunity to malaria [238] but did not did not affect perinatal HIV transmission or improve birthweight and neonatal growth [239]. Supplementation of pregnant women in Bangladesh with weekly doses of vitamin A or beta-carotene had no effect on birth size [235] or neonatal mortality [240] A lack of effect of vitamin A supplementation on stillbirth or neonatal/perinatal mortality was also reported in two large randomized trials [238, 241] and a recent meta-analysis, which concluded that data do not currently support a role for antenatal vitamin A supplementation to reduce maternal or perinatal mortality.

Increasing maternal vitamin A late in gestation may reduce complications of neonatal respiratory insufficiency, particularly if preterm delivery is anticipated [242]. Preterm infants have low vitamin A stores at birth and are at increased risk of retinopathy, lung disease, and respiratory infections. Maternal supplementation appears to reduce mortality and oxygen requirements in preterm infants, but no evidence of either benefit or harm with regard to neurodevelopmental status at 18–22 months has been observed [242].

VAD is linked to impaired iron mobilization from body stores. VAD often coexists with iron deficiency in developing countries. Vitamin A supplementation was found to improve anaemia in pregnant women when added to an iron supplementation regimen in some studies [243], but others did not observe a benefit [244, 245] Data are currently insufficient to recommend vitamin A supplementation to improve anaemia in pregnancy.

Vitamin A in lactation and infancy

Newborn infants have low liver vitamin A stores and require an intake of around 100 μg retinol daily to meet their needs for growth. The sources of vitamin A at this stage are colostrum and breast milk, which serve to increase infant stores during the first few months of life unless the breast milk vitamin A content is inadequate. Breast milk from well-nourished mothers is rich in vitamin A. Not surprisingly, the mean retinol concentration in breast milk from women in developing countries is lower than that from women in developed countries [246].

In contrast to placental vitamin A transfer during pregnancy, breast milk is more sensitive to maternal intake [247]. The amount of vitamin A transferred from mother to infant in the first 6 months of lactation is 60 times that which the fetus accumulates throughout gestation. Breastfed infants are generally protected from clinical VAD, although improving vitamin A stores during infancy is important to protect against symptoms of deficiency after weaning [248]. High-dose supplementation of breastfeeding women at risk of VAD has been suggested as a possible intervention for improving both child and maternal health [249]. However, limited benefits of vitamin A supplementation (mainly single dose) were seen in post-partum women in populations with high VAD prevalence. Although supplementation enhanced serum and breast milk retinol concentrations, this effect was not sustained [250].

In a study of very low birthweight infants, poor vitamin A status (low plasma vitamin A) in the first week of life was associated with the development of chronic lung disease and increased the risk of infant death [251]. Supplementing low birthweight infants with vitamin A reduced the incidence of death in the first month and reduced chronic lung disease. It has been suggested that vitamin A supplementation may also reduce incidence of retinopathy of prematurity [242]. In middle- and low-income countries, vitamin A supplementation in infants and children under 5 years of age is associated with significant reductions in all-cause mortality, including a 27 per cent reduction in deaths from diarrhoea [252] Infections were also reduced in supplemented infants (15% decrease in diarrhoea incidence; 50% decrease in measles).

Sources and metabolism of vitamin A

In the diet, vitamin A can be found as provitamin A carotenoids (found in darkly colored fruits and vegetables, oily fruits, and red palm oil), or preformed as retinol or retinyl esters (found in fatty acids from animal products). Retinols are found in the highest concentration in the livers and liver oils of marine animals. The potency of vitamin A activity differs markedly depending on the dietary source. Beta-carotene is less easily absorbed than retinol, and food sources have poorer absorption than beta-carotene from supplements (2 μg of beta-carotene as a supplement supplies the equivalent of 1 μg retinol, but 12 μg beta-carotene from food is required to provide 1 μg retinol). Other provitamin A carotenoids are even less easily absorbed. The different retinoid potencies can be expressed as retinol activity equivalents (RAEs), as follows: 1 μg RAE = 1 μg retinol, 12 μg beta-carotene, and 24 μg alpha-carotene or beta-cryptoxanthin.

Supplemental beta-carotene is more efficiently converted to vitamin A than dietary beta-carotene, because the food matrix affects the release of carotenoids from food for conversion. Products of fat digestion are required for solubilization of retinol and carotenoids, and this process occurs more efficiently with animal sources than with vegetable sources. Absorption of vitamin A depends on the amount of lipids in the diet. Diets very low in fat result in low absorption of retinol and carotenoids [253].

Vegetarian diets do not include preformed vitamin A, which is derived only from animal sources. Therefore the intake of deeply colored (red and yellow) vegetables should be increased, or fortified foods (e.g. some margarines, cereals) should be consumed during pregnancy. Consuming the recommended 5 servings of fruits and vegetables a day should contribute between 5 and 6 mg of provitamin A carotenoids, which equates to over 400 μg RAEs, or over half of the pregnancy recommended dietary allowance (RDA) [71].

Intestinal infections and diarrhoea can cause malabsorption of vitamin A; this is a common problem in developing countries. Because of an overlap in metabolic pathways, alcohol (ethanol) can compete with retinol for metabolism and also competitively inhibits the conversion of retinol to RA. Alcohol consumption thereby potentiates the effects of VAD by further depleting liver vitamin A stores [254]. Inhibition of RA synthesis by ethanol has been suggested as a potential mechanism for defects observed in fetal alcohol syndrome [255].

Risks of excess vitamin A during pregnancy

Vitamin A has a relatively narrow range of safe intake. Excess vitamin A is hepatotoxic, and the effect on liver function is the basis for setting the upper intake limit in non-pregnant adults. Hypervitaminosis A is caused by overconsumption of preformed vitamin A, not carotenoids. In addition to liver damage, severe cases can result in haemorrhage, coma, and death. Signs of toxicity are associated with consumption around 10 times the RDA (8,000–10,000 μg/day or 25,000–33,000 IU/day). The upper intake level (UL) for adults has been set at 3,000 μg (10,000 IU)/day of preformed vitamin A.

Excess vitamin A in pregnancy is known to cause birth defects. Pregnant women should avoid multivitamin or prenatal supplements that contain more than 1,500 μg (5,000 IU) preformed vitamin A. Synthetic derivatives of vitamin A (e.g. etretinate and isotretinoin) can cause serious birth defects and should be avoided in pregnancy or if there is a possibility of becoming pregnant [256, 257]. In populations at low nutritional risk for VAD, intake of prenatal multivitamins containing vitamin A may result in excess, and potentially dangerous, levels of serum retinol [258]. These synthetic derivatives have teratogenic effects on structures derived from the cranial neural crest, resulting in abnormal external ear (e.g. microtia and anotia), small mandible, cleft palate, and conotruncal and aortic arch defects as well as brain defects (e.g. hydrocephaly and microcephaly) and a small or absent thymus. Neuro-functional deficits are reported in children without major malformations [259].

Taken as supplements in pregnancy, vitamin A (but not beta-carotene) can have teratogenic effects at levels not far above the recommended intake levels [229]. The threshold vitamin A intake above which the risk of teratogenicity increases is still debated. Most of the human data on teratogenicity of vitamin A involve doses ≥7,800 μg/day [260]. Individuals with high alcohol intakes, liver disease, hyperlipidemia, or protein malnutrition may be particularly susceptible to adverse effects of high vitamin A intake [71].

Agency guidelines for vitamin A intake

Recommendations for vitamin A intakes are now based on RAEs. A microgram quantity of RAE is based on the activity of 1 μg of all-*trans*-retinol. Previously, the unit 'retinol equivalent' was used, which expressed vitamin A activity based on retinol equivalent weights, but this measure has since been found to overestimate the activity of the carotenoids [261]. A further complication for vitamin A nutrition is the fact that food and supplement labels usually state vitamin A levels in IUs. Vitamin A measurements expressed as IUs tend to overstate the contribution of activity provided by provitamin A carotenoids. Because the conversion of IUs to RAEs is different for retinol and carotenoids, IUs cannot be directly converted to RAEs (or vice versa) for total vitamin A unless the proportion of retinol to carotenoids in the sample is known (Box 6.1).

Box 6.1 Vitamin A conversions

One IU of retinol is equivalent to 0.3 μg of retinol (1 μg = 3.33 IU) or 0.3 μg retinol activity equivalent (RAE).

One IU of beta-carotene in supplements is equivalent to 0.5 IU of retinol or 0.15 μg RAE (0.3 × 0.5).

One IU of dietary beta-carotene is equivalent to 0.165 IU retinol or 0.05 μg RAE (0.3 × 0.165).

One IU of other dietary provitamin A carotenoids is equivalent to 0.025 μg RAE.

Source: Institute of Medicine, *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*, The National Academies Press, Washington, DC, copyright © 2006. [71]

For some food groups the conversion to RAEs is simple. If vitamin A activity is being contributed by only provitamin A carotenoids, the IU value can be divided by 20 or the retinol equivalent value divided by 2 to get the RAE value. These food groups include plant foods such as fruits, vegetables, spices, nuts, seeds, and legumes. For food groups such as meats, where all of the vitamin A is being contributed by retinol, the IU value can be divided by 3.33, and the retinol equivalent value and RAE value are the same. Dietary intake recommendations for vitamin A are based on intake levels needed to ensure adequate vitamin A stores in the liver. The tolerable UL for the general population is based on the lowest intake level reported to be associated with liver abnormalities; for pregnancy (or women of childbearing age), the UL is based on the lowest level reported to induce teratogenicity [71].

According to the US Institute of Medicine, pregnant women have an estimated average requirement of 550 μg RAE per day (530 μg/day for women 18 years and younger), with a maximum dose (tolerable upper limit; UL) of 3,000 μg/day (2,800 for ≤18 years; Box 6.2). The RDA is 770 μg/day (750 μg/day for ≤ 18 years) [71, 260]. The RDA represents an increase of 50 μg/day for pregnant adolescents, and 70 μg/day for adult females, above their pre-pregnancy requirements (RDA = 700 μg RAE/day). The recommended intake for lactation is substantially higher, to account for infant requirements and losses in breast milk. The estimated average requirement for adult lactating women is 900 μg RAE/day (885 μg/day for women ≤ 18 years), and the RDA is 1,300 μg RAE/day (1,200 μg/day for ≤ 18 years). The UL for pregnancy and lactation is 2,800–3,000 μg RAE/day. The UL for vitamin A applies only to preformed vitamin A (e.g. retinol—the form of vitamin A found in animal foods, most fortified foods, and supplements). It does not apply to vitamin A derived from carotenoids.

Box 6.2 US Institute of Medicine recommended dietary allowances for vitamin A

Infants 0–6 months (adequate intake (AI)) = 400 μg retinol activity equivalent (RAE)/day
Infants 7–12 months (AI) = 500 μg RAE/day
Children 1–3 years = 300 μg RAE/day
Females 14+ years = 700 μg RAE/day
Pregnancy 14–18 years = 750 μg RAE/day
Pregnancy 19+ years = 770 μg RAE/day
Lactation 14–18 years = 1,200 μg RAE/day
Lactation 19+ years = 1,300 μg RAE/day
Tolerable upper intake level (pregnancy) = 3,000 μg RAE/day (10,000 IU/day)

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

In light of new knowledge about the potency of provitamin A carotenoids in foods, WHO/FAO guidelines have suggested that previously recommended number of servings of green leafy vegetables needed to meet vitamin A requirements should be at least doubled, particularly during the third trimester of pregnancy [231]. The most recent WHO guidelines (2011) do not recommend routine vitamin A supplementation during pregnancy or lactation for the prevention of maternal and infant morbidity and mortality, and state that high-dose vitamin A should be avoided in pregnancy, particularly between day 15 and day 60 after conception [262, 263]. However, the WHO recommends supplementation for at least 12 weeks in late pregnancy and during lactation in areas with endemic VAD, for the prevention of night blindness (populations at risk are those where the prevalence of night blindness is ≥5% in pregnant women or ≥5% in children 24–59 months of age). Specifically, pregnant women should receive up to 10,000 IU vitamin A daily or up to 25,000 IU vitamin A weekly as an oral, liquid, oil-based preparation of retinyl palmitate or retinyl acetate, beginning after day 60 of gestation. Supplementation should be continued for a minimum of 12 weeks during pregnancy until delivery [262]. The WHO previously issued guidelines on safe supplementation in light of the potential adverse effects of excess vitamin A exposure in early pregnancy [264].

UK and Australian guidelines acknowledge that there is little evidence to support routine supplementation with vitamin A and that excessive quantities of fat-soluble vitamins may be harmful. Pregnant women should be informed to avoid supplement intake above 10,000 IU of retinol (>700 μg), as this level of intake may cause birth defects [265, 266]. These guidelines recommend that pregnant women avoid consuming liver and liver products, which contain high levels of vitamin A. There is wide variation in recommendations for vitamin A throughout Europe. The individual European recommendations range from 700 to 1,100 μg and from 850 to 1,500 μg for pregnant and lactating females, respectively [267]. The government of India recommends that children should be given vitamin A supplements every 6 months from the age of 9 months until the age of 3 [268].

Our recommendations for vitamin A intake during pregnancy and lactation

Clinical deficiency for vitamin A still affects significant numbers of pregnant women in developing countries. Low intake during the nutritionally demanding periods of pregnancy, lactation, infancy, and childhood increases the risk of serious health problems in both mothers and children. These risks include growth failure, depressed immunity, and increased morbidity and mortality due to infectious disease.

Most women who are at low nutritional risk can meet their early pregnancy vitamin A requirement from food sources. An increased intake from food sources is recommended during the third trimester and throughout lactation. Although supplementation in pregnancy may be warranted in a subset of the population, both pregnant and lactating women should be encouraged to receive adequate vitamin A nutrition by consuming at least five servings a day of darkly colored fruits and vegetables (e.g. carrots, pumpkin, sweet potato, butternut squash, dried apricots, cantaloupe, red pepper, and spinach), and animal sources of retinol, although liver products should be avoided during pregnancy. In deficient areas, the WHO recommendation of vitamin A supplementation (10,000 IU/day or 25,000 IU/week) for 12 or more weeks prior to delivery should be followed.

Chapter 7

Vitamin B_1 (thiamine) in pregnancy and breastfeeding

Thiamine functions

Vitamin B_1 (thiamine) is a water-soluble vitamin involved in nervous system and muscle function, acting by multiple enzymatic processes via the enzyme cofactor thiamine pyrophosphate. Thiamine pyrophosphate catalyses the production of acetyl coenzyme A, which provides a link between carbohydrate, fat, and protein metabolism. Thiamine is essential for carbohydrate metabolism, via the enzyme transketolase, and for intermediary metabolism [269]. Thiamine at low concentrations is mainly transported from the gastrointestinal tract by a saturable, energy-dependent mechanism [270]. At higher concentrations thiamine appears to be absorbed by passive diffusion. Blood and tissue concentrations of thiamine are not subject to physiological regulation but are dependent on dietary intake. The total body thiamine content in an adult is approximately 30 mg, and the biological half-life is in the range of 9–18 days [271].

Indicators of thiamine status

Biochemical alterations reflecting poor thiamine status occur before overt signs of deficiency. The urinary excretion rate of thiamine reflects its intake and is used to assess intake. Urinary thiamine excretion of <40 μg/day is indicative of thiamine deficiency, and excretion of <100 μg/day reflects marginal deficiency [269]. A widely used measure to detect thiamine deficiency is the indirect, functional measurement of thiamine diphosphate in erythrocytes with either the transketolase activation test or the transketolase activity assay. This assay is not particularly sensitive to recent thiamine intake [272], and there are inter-individual and genetic factors that can affect transketolase activity. The measurement of thiamine pyrophosphate effect is an assay for transketolase that is performed in the absence and presence of added thiamine, expressed as an activity coefficient. The normal range is 0–14 per cent; 15–24 per cent reflects marginal thiamine deficiency, and ≥25 per cent signifies clinical deficiency.

Table 7.1 Thiamine status indicators [269]

Indicator	Marginal deficiency	Deficiency
Erythrocyte transketolase activity[a]	1.2–1.25	>1.25
Erythrocyte thiamine (nmol/L)	70–90	<70
Thiamine pyrophosphate effect (%)[a]	15–24	≥25
Urinary thiamine		
(nmol [μg]/g creatinine)	90–220 [27–66]	<27 μg/day
(nmol [μg]/day)	133–333 [40–100]	<40 μg/day

[a] Activity coefficient representing fold-stimulation above baseline following addition of thiamine pyrophosphate

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Erythrocyte thiamine pyrophosphate level has also been used to provide an indication of thiamine status [273]. The direct measurement of erythrocyte thiamine by high-performance liquid chromatography has also been used to assess thiamine status, with comparable results [274]. Indicators of thiamine status are summarized in Table 7.1.

Thiamine deficiency

Thiamine deficiency can be caused by inadequate intake, typically in populations that consume diets that are high in milled or polished rice and low in other food sources of thiamine. Severe thiamine deficiency causes beriberi, which is still endemic in Asia and occurs frequently in refugee and displaced populations [275]. Symptoms include severe lethargy/fatigue, weight loss, impaired sensory perception, emotional disturbances, and irregular heart rate. Beriberi is also seen in alcoholics, who often have poor nutrition and low intakes of thiamine-containing foods. In addition to poor dietary intake in alcoholics, thiamine deficiency is exacerbated by the interference of alcohol with thiamine absorption [276]. Thiamine deficiency associated with alcoholism is known as Wernicke–Korsakoff syndrome (or Wernicke's encephalopathy) [277]. Deficiency for thiamine is associated with HIV infection and AIDS and may result from low intake, increased metabolic rate (catabolic state characteristic of AIDS), and gastrointestinal disturbances [278]. Thiamine deficiency impairs cardiac function and can lead to congestive heart failure. Low thiamine intakes are associated with increased risks of cataracts [279] and age-related lens opacification [280].

Thiamine in pregnancy

In pregnancy, thiamine is important for fetal growth and development, and production of ATP from glucose in the brain. Deficiency in pregnancy can lead to widespread metabolic disturbances affecting the placenta and fetus. Pregnancy imposes an increasing requirement for thiamine over the course of gestation, and the increased utilization of thiamine is reflected in decreased thiamine excretion or by the erythrocyte transketolase activation test [281, 282]. Women with marginal thiamine status are at risk for developing symptomatic thiamine deficiency in pregnancy, which is associated with anorexia, maternal weight loss, neurological symptoms, muscle degeneration, and intrauterine growth restriction. Women of low socioeconomic status may be particularly vulnerable because of poor pre-conception nutritional status and an inadequate diet in pregnancy [281].

Prolonged vomiting in pregnancy results in thiamine depletion. Thiamine deficiency is thus evident in approximately 60 per cent of women with hyperemesis gravidarum [283] and can result in ketonuria. Thiamine replacement therapy has been shown to prevent or reverse maternal neurological complications of hyperemesis gravidarum [284, 285].

Free thiamine crosses the placenta, and its concentration is higher in cord blood than in maternal blood [281]. It appears that the fetus is able to sequester thiamine at the expense of the mother and has an enhanced metabolism which further stimulates the extraction of thiamine from the maternal circulation There is no evidence that thiamine deficiency causes fetal malformations, even in cases of overt maternal beriberi [282]. Nonetheless, prenatal supplementation may protect newborns from deficiency.

Thiamine in lactation and infancy

Thiamine deficiency in infants is very rare in developed countries. However, if a breastfeeding mother has low thiamine status, her infant will be vulnerable to developing symptoms of deficiency (infantile beriberi). The thiamine concentration is low in colostrum, at around 0.01 μg/L. Mature milk contains around 0.21 μg/L. Lactating women secrete approximately 0.16 mg thiamine into breast milk each day and therefore require an increase in intake to compensate for this loss. Thiamine concentrations in blood decrease over the first 12–18 months of life [286].

The essentiality of thiamine in infant nutrition was made very clear in 2003, when a number of infants in Israel developed life-threatening thiamine deficiency after being fed a defective infant formula lacking thiamine [287]. Symptoms included cardiac failure, and seizures that progressed to epilepsy in some children [288]. At 8 years of age, all of the children displayed developmental delay, and varying degrees of speech impairment [289]. Overall, the thiamine deficient formula resulted in the deaths of four children [290]. The European Community has since established specific standard requirements for infant formulae [291].

Thiamine sources

Thiamine is found in a wide variety of foods, including meats, legumes (beans, lentils), milk, nuts, oats, oranges, rice, seeds, wheat, and wholegrain cereals. The outer layer of seeds and grains are rich in thiamine, and excessive refining and polishing of cereal grains depletes them of the vitamin. Yeast and yeast extract are particularly high in thiamine.

Effects of excess thiamine

Thiamine is rapidly cleared by the kidneys, and excess intake is not associated with known adverse effects. The US Institute of Medicine (IOM) has not set a tolerable upper intake level because of a lack of data on which to base such a recommendation. Supplements containing up to 50 mg/day of thiamine are available in the US without a prescription, but the possible adverse effects of chronic high intake have not been extensively studied [269]. Thiamine is administered intravenously to treat malnourished patients with suspected Wernicke's encephalopathy.

Agency guidelines for thiamine intake

The amount of thiamine needed in the body is proportional to caloric intake (~0.5 mg thiamine required per 1,000 kcal). Larger body builds appear to require more thiamine than smaller individuals, as signs of deficiency during starvation occur earlier in larger people [292]. The IOM and the WHO recommendations for thiamine are in agreement for infants in the first year of life (see Box 7.1 for IOM recommendations). The WHO recommended nutrient intake [231] and the IOM adequate intake (AI) recommendation [269] for babies from birth to 6 months of age is 0.2 mg/day, which is approximately 0.03 mg/kg bodyweight. For infants between 1 and 3 years of age, the reference nutrient intake is 0.5 mg/day and the IOM AI is 0.4 mg/day. Similarly, the WHO recommendation is slightly higher for adolescents, at 1.1 mg/day for girls from the age of 10 years, whereas the IOM recommended dietary allowance (RDA) is 0.9 mg/day for 9–13-year-old adolescents (girls and boys). For girls aged 14–18 years, the RDA is 1.0 mg/day [269].

Box 7.1 US Institute of Medicine recommended dietary allowances for thiamine

Infants 0–6 months (adequate intake (AI)) = 0.2 mg/day
Infants 7–12 months (AI) = 0.3 mg/day
Children 1–3 years = 0.3 mg/day
Females 14–18 years = 1.0 mg/day
Females 19+ = 1.1 mg/day
Pregnancy = 1.4 mg/day
Lactation = 1.4 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin* B_6*, Folate, Vitamin* B_{12}*, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

The WHO recommended nutrient intake and the IOM RDA recommendations for adults are 1.1 mg/day for women and 1.2 mg/day for men. Both agencies recommend an increase in thiamine intake of at least 10 per cent to cover increased energy utilization in pregnancy. This is reflected in a reference nutrient intake/RDA for pregnancy of 1.4 mg/day. The WHO recommends a further increase to 1.5 mg/day during lactation to account for the energy cost of milk production [231]. The RDA for lactation remains at the pregnancy level of 1.4 mg/day of thiamine [269].

Our recommendations for thiamine intake during pregnancy and lactation

Nutritional deficiency for thiamine and other B vitamins rarely occurs in people consuming a moderately varied diet. However, the body does not store thiamine, so a continuous supply is needed. The consequences of thiamine deficiency are potentially severe, and insufficient maternal and/or infant thiamine intake may have long-lasting negative effects on child development. We recommend a varied diet during pregnancy and lactation, preferably substituting wholegrain (unpolished) rice for the more highly refined varieties, if rice is a staple of the diet. Supplementation with thiamine and other B vitamins as found in typical antenatal vitamin supplements may be beneficial for women who experience excessive vomiting in pregnancy or who otherwise find it difficult to consume a varied diet containing thiamine-rich foods.

Chapter 8

Vitamin B_2 (riboflavin) in pregnancy and breastfeeding

Riboflavin functions

Riboflavin is a water-soluble B vitamin (also known as vitamin B_2) that acts as a cofactor for an array of flavocoenzymes involved in energy-producing, biosynthetic, detoxifying, and electron-scavenging pathways. Riboflavin exerts minimal intrinsic enzymatic activity until it is converted to flavin mononucleotide (FMN) by riboflavin kinase, and from FMN to flavin adenine dinucleotide (FAD) by FAD synthetase. These active flavins form complexes with flavoprotein dehydrogenases and oxidases that participate in oxidation–reduction reactions in metabolic pathways [293]. FAD and FMN act as electron acceptors in oxidative metabolism of proteins, fatty acids, and carbohydrates. They also donate electrons to the electron transport chain and are critical for mitochondrial function and energy generation in aerobic cells.

Several human disorders are caused by mutations in flavoprotein genes. Many are mitochondrial disorders, as most flavoproteins are localized to mitochondria (e.g. Leigh syndrome) [293]. Flavocoenzymes also catalyse reactions in biosynthetic pathways of cell-signalling molecules, including steroid hormones [294].

Riboflavin is involved in the metabolism of other B vitamins. For example, synthesis of niacin (vitamin B_3) from tryptophan requires FAD as a cofactor of kynurenine mono-oxygenase. Conversion of naturally occurring vitamin B_6 (pyridoxine) to its active form, pyridoxal 5′-phosphate, requires the FMN-dependent enzyme pyridoxine 5′-phosphate oxidase. The interconversion of the folate metabolites tetrahydrofolate (THF) and 5-methyl-THF requires the action of the FAD-dependent enzyme methylenetetrahydrofolate reductase (MTHFR) [295].

The active folate and vitamin B_6 metabolites generated by flavocoenzymes link riboflavin to both the trans-sulphuration and remethylation pathways in homocysteine metabolism, and the methyl cycle. FMN-dependent generation of pyridoxal 5′-phosphate is necessary for trans-sulphuration of homocysteine to cysteine, and FAD-dependent MTHFR is required for remethylation of homocysteine to produce methionine.

Riboflavin is involved in heme biosynthesis via the FAD-dependent enzyme protoporphyrinogen IX oxidase (PPOX). Reduction in PPOX activity leads to porphyria. Deficiency for riboflavin also alters iron metabolism; correction of the deficiency improves the response to iron therapy in people with iron-deficiency anaemia [296,297].

Riboflavin is present in all tissues, although tissue depletion and repletion can occur rapidly, as very little excess riboflavin is stored. Tissue riboflavin is mainly in the liver as FAD, although it is also present in spleen, kidney, and cardiac muscle, and these organs are initially spared from riboflavin deficiency. Circulating plasma contains riboflavin in three forms: free riboflavin (50%), FAD (40%), FMN (10%) [298].

Indicators of riboflavin status

Assessment of the activity of the FAD-dependent enzyme erythrocyte glutathione reductase provides an indicator of functional riboflavin status using an activity coefficient expressing the ratio of activities in the presence and absence of added FAD. An erythrocyte glutathione reductase activity coefficient of less than 1.2 indicates adequate activity; 1.2–1.4 indicates low riboflavin status, and above 1.4 indicates deficiency [231,299].

Urinary riboflavin excretion reflects intake in excess of tissue requirements but is not considered an accurate measure of riboflavin status. Erythrocyte flavin level is primarily a measure of FMN. Values greater than 40 nmol/L are considered adequate [231,299].

Riboflavin deficiency

Riboflavin deficiency is rare in developed countries; it is encountered almost invariably in combination with deficit of other water-soluble (B) vitamins in areas of poor overall nutrition. Deficiency is endemic in populations whose staple diet consists of rice and wheat, with low or no consumption of meat and dairy products [231]. Disorders causing abnormal digestion, such as lactose intolerance or celiac disease, may result in decreased assimilation of riboflavin. The high prevalence of lactose intolerance in Asian and African populations coincides with a lower intake of milk, and poor riboflavin absorption. Hypothyroidism may be a predisposing factor in riboflavin deficiency, because thyroid hormones are involved in riboflavin metabolism [300].

Because of its interactions with other B vitamins, a severe deficiency of riboflavin affects a large number of enzyme systems, and symptoms of deficiency overlap with those associated with other B vitamin deficiencies. Signs of riboflavin deficiency are sore throat, pharyngeal and oral oedema, cracks/splits at corners of mouth (cheilosis), inflammation of the tongue (glossitis), dermatitis, and normochromic–normocytic anaemia [269]. When faced with an inadequate intake of riboflavin, the activity of flavin-dependent enzymes is hierarchically reduced. Enzymes involved in the core electron transfer chain required for ATP synthesis are preserved, while those required for the first step of fatty acid beta-oxidation are decreased. Most flavocoenzymes are FAD dependent; therefore concentrations of FAD are maintained at the expense of FMN [301].

Riboflavin deficiency ultimately leads to the depression of mitochondrial beta-oxidation, and an altered fatty acid profile of triacylglycerols and phospholipids. Diets high in lipids increase the requirement for riboflavin for growth. Deleterious effects of high-fat intake have been reported in riboflavin-deficient animals, including the development of fatty liver [302,303].

Riboflavin in pregnancy

Placental transfer of riboflavin involves binding proteins that are specific to pregnancy [304,305]. Free riboflavin accumulates in the fetal circulation, ultimately resulting in a concentration that is fourfold higher than that in maternal plasma [306]. Flavin-binding proteins are also present in the fetus at higher levels than in the mother [307]. Preterm birth is a risk for riboflavin deficiency, as most transport and fetal accumulation occurs in late pregnancy.

Infants of riboflavin-deficient mothers tend to be deficient themselves at birth and remain deficient through breastfeeding and weaning. This was noted in a study in Gambia, where the local diet was deficient in riboflavin, consisting of very little meat or dairy products [308]. Yet in two separate small studies, no correlation was found between the riboflavin status of the mother and the outcome of pregnancy, even when riboflavin deficiency was present [309,310]. This may be because riboflavin status improves transiently in the neonatal period, even when maternal status is poor, but declines again at weaning if the diet is nutritionally lacking [308].

Riboflavin in lactation

During lactation, the maternal requirement for riboflavin is almost 50 per cent higher than prior to pregnancy. Riboflavin is secreted in breast milk, and the concentration in milk is somewhat sensitive to increased maternal intake if the mother’s status is low [311]. However, supplementation of well-nourished mothers does not significantly alter the amount of riboflavin present in milk [312]. A small increase in intake of dairy products may be sufficient to meet the riboflavin need in lactating women consuming a varied diet.

Women in some regions may require different interventions or dietary changes. A recent study found that, prior to vitamin fortification of foods, >80 per cent of lactating women in South Africa did not meet the estimated average requirement for most B vitamins, including riboflavin, as well as vitamins A, C, and D, folate, zinc, iodine, and calcium. After fortification for these nutrients, >70 per cent still did not meet the estimated average requirement for riboflavin, in addition to zinc, vitamin A, and vitamin B_6 [313]. Even in developed countries, a substantial proportion of pregnant and lactating women may be lacking in riboflavin and will have breast milk concentrations below the level considered adequate (800 nmol/L) [314]. Infants receiving phototherapy for neonatal jaundice are at risk for riboflavin deficiency, because riboflavin is photosensitive and is degraded by this treatment [231,315].

Riboflavin sources

A balanced diet with a variety of foods should contain ample amounts of riboflavin, which is obtained from the diet as free riboflavin or as FAD or FMN. Dairy products and milk are the most significant sources of riboflavin in Western diets, although meats (particularly organ meats) eggs, dark/leafy green vegetables (spinach, asparagus, and broccoli), legumes, and nuts are also sources. Nutritional yeast is a good source of riboflavin for vegetarians and vegans. Breads and cereals are often fortified with riboflavin and other B vitamins [269].

Absorption is better from animal sources than from vegetable sources; vegetarians and vegans are therefore at higher risk for deficiency. Because riboflavin degrades in light, foods containing riboflavin should be stored in lightproof containers. The riboflavin content of grains and vegetables can be leached away by boiling/cooking, unless the liquid is reused as soup or in sauces [269].

Risks of excess riboflavin

Toxicity from excessive intake of riboflavin has not been observed in humans. This is assumed to be because riboflavin exhibits low solubility, which limits its absorption from the gastrointestinal tract and prevents exposure to amounts sufficient to produce toxic effects. Because of a lack of evidence on adverse effects, a tolerable upper intake level has not been set for riboflavin.

Agency guidelines for riboflavin intake

According to the US Institute of Medicine (IOM), the daily requirement for riboflavin is 1.1 mg for adult females (1.3 mg/day for males), increasing to 1.4 mg/day during pregnancy, and to 1.6 mg/day during breastfeeding (Box 8.1) Intake requirements vary somewhat depending on metabolic challenges and

Box 8.1 US Institute of Medicine recommended dietary allowances for riboflavin

Infants 0–6 months (adequate intake) = 0.3 mg/day; 7–12 months = 0.4 mg/day
Children 1–3 years 0.5 mg/day
Females 14–18y = 1.0 mg/day
Females 19+ years = 1.1 mg/day
Pregnancy = 1.4 mg/day
Lactation = 1.6 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

the efficiency of uptake. In the US, the normal intake for an adult is slightly above the recommended dietary allowance (RDA), at an estimated 1.6–2.6 mg/day [269]. There is evidence of tissue saturation with intakes above 1.1 mg/day [316,317]. The IOM AI level for infants aged 0–6 months is 0.3 mg/day, and from 7–12 months it is 0.4 mg/day [269].

The American Association of Pediatrics advises that maternal riboflavin supplementation poses minimal risk in pregnancy and lactation [318].

Our recommendations for riboflavin intake during pregnancy and lactation

A varied diet including dairy products and meat is the best way to achieve a sufficient riboflavin status in pregnant and lactating women and ensure adequate riboflavin supplies in both mother and infant. An increase in dairy products and/or meat consumption, particularly during lactation, may be necessary in some women. Vegans and vegetarians should consider nutritional yeast in addition to legumes, nuts, and dark green vegetables as a source of this nutrient.

Riboflavin deficiency rarely occurs in isolation in human populations but is seen in conjunction with other nutritional deficiencies in those whose intake of dairy products and meat is limited. An increase in consumption of milk/dairy products is recommended in areas where lactose intolerance is not an issue. In such cases, supplementation at least to the level of the RDA is recommended. Supplementation with riboflavin is generally unnecessary in individuals with a varied diet and healthy lifestyle.

Chapter 9

Vitamin B_3 (niacin) in pregnancy and breastfeeding

Niacin functions

Niacin, a term encompassing nicotinamide and nicotinic acid (and their biologically active derivatives), is one of the water-soluble B-complex vitamins and is also known as vitamin B_3. Nicotinamide is a component of the pyridine nucleotide coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate and acts as an electron donor or acceptor in redox reactions. NAD is involved in the oxidative degradation of fuel molecules (carbohydrates, proteins, fats, and alcohol), and NAD phosphate functions in the reductive biosynthesis of fatty acids and steroids, including cholesterol. Niacin is an accepted treatment for the correction of low levels of HDL cholesterol and high levels of LDL cholesterol and triglycerides. Doses of 1–3 g/day of nicotinic acid are used for this purpose.

NAD is also involved in DNA repair and replication as the substrate for poly-ADP–ribose polymerase enzymes. These enzymes catalyse the transfer of ADP–ribose pairs from NAD to arginine, lysine, or asparagine residues of proteins that are involved in these processes [319]. Niacin deficiency can therefore lead to DNA instability. NAD is also the substrate for mono-ADP-ribosyltransferases, which play a role in G protein-mediated cell signalling [320].

Niacin is rapidly absorbed from the stomach and small intestine, and supplemental niacin absorption does not appear to be significantly inhibited by food [321]. Doses of up to 3–4 g niacin can be almost completely absorbed [269]. Excess niacin is excreted in urine. All body tissues synthesize NAD and NAD phosphate from nicotinic acid and nicotinamide, and nicotinamide can also be synthesized from tryptophan, so proteins containing tryptophan are an important dietary source. The conversion of tryptophan to niacin requires riboflavin (vitamin B_2) and pyridoxine (vitamin B_6).

Indicators of niacin status

The most reliable and sensitive measures of niacin status are urinary excretion of the two major methylated metabolites, *N*1-methyl-nicotinamide and its

2-pyridone derivative (*N*1-methyl-2-pyridone-5-carboxamide) [322]. Excretion rates of less than 5.8 µmol/day indicate deficient niacin status, and those of 5.8 to 17.5 µmol/day indicate low niacin status. Erythrocyte NAD concentration is sensitive to changes in niacin intake and is therefore a reasonable functional blood measure of niacin status [323].

Niacin deficiency

Niacin deficiency is uncommon in developed countries, although it is still present in developing countries and during famines, and marginal deficiency can occur with low dietary protein intakes. Deficiency has been observed in populations for whom the chief dietary staple is corn or sorghum (including poor communities in the southern US in the early 1900s) [324]. The late stage of severe niacin deficiency is known as pellagra, a chronic wasting disease characterized by erythematous dermatitis, diarrhoea, and dementia. If untreated, pellagra can be fatal. Some sequelae of niacin deficiency reflect roles played by riboflavin or pyridoxine (vitamin B_6), as both are essential for conversion of tryptophan to niacin. Alcoholism is a significant cause of niacin deficiency [269]. Malabsorption disorders such as Crohn's disease, hepatic dysfunction, and diabetes [269], as well as the use of oral contraceptives, also affect niacin status [325].

Niacin in pregnancy and lactation

There is an increased conversion of tryptophan to niacin during pregnancy [326], possibly controlled by the altered hormonal environment [327, 328]. This increased capacity for tryptophan metabolism is reflected in an increased urinary output of *N*1-methyl-nicotinamide in pregnancy [325]. Nicotinamide is actively transported across the placenta such that fetal plasma levels are higher than maternal plasma levels. Additional energy and growth requirements in pregnancy and lactation are reflected in an increase in niacin requirement of 2–4 mg/day above the pre-pregnancy recommendation [269].

Lactating women secrete approximately 1.4 mg of niacin per day into breast milk, and an additional 3 mg/day above pre-pregnancy requirements is recommended. Breast milk provides approximately 1.5 mg (12.3 µmol) of niacin per litre [231], or the equivalent of 9.9 mg niacin per 1,000 kcal (derived from tryptophan at ratio of 60:1) [329]. Infants who are exclusively breast fed would consume twice the level necessary to prevent deficiency.

Niacin sources

The daily requirement for niacin can be met by food sources, and also via synthesis from tryptophan, which is present in dietary proteins. Niacin equivalents from tryptophan are based on the ratio of 60:1; i.e. 60 mg of tryptophan provides 1 mg of niacin, or 1 mg of niacin equivalents [329]. Food sources of niacin include dairy products, eggs, fish, lean meats, liver, poultry, legumes (peanuts), brewer's yeast, beets, nuts, and seeds. Bread and cereals are usually fortified with niacin. Grains naturally contain niacin, but in complexed forms with low bioavailability [330]. As mentioned, the prevalence of niacin deficiency is higher in populations consuming mainly corn or sorghum as a dietary staple. Corn contains niacin, but only in a bound form that is nutritionally unavailable. Heating or soaking corn in an alkaline solution (e.g. lime (calcium oxide)) releases bound niacin and improves its bioavailability [331]. Infant formulas are usually fortified with niacin and other B vitamins.

Risks of excess niacin

Long-term administration of high-dose nicotinic acid (as a therapy for lowering serum cholesterol) can lead to dermatological manifestations and hepatotoxicity. There is no evidence of adverse effects from the consumption of niacin as it occurs naturally in foods. The advised upper limit for niacin intake is 35 mg/day, which applies to synthetic forms obtained from supplements and/or fortified foods [269].

Agency guidelines for niacin intake

The US Institute of Medicine recommends 2 mg/day as an adequate intake of niacin for infants aged 0–6 months, increasing to 4 mg/day between 7 and 12 months, and 5 mg/day up to the age of 3 years (Box 9.1) [269]. For females aged 14 and older, the recommended dietary allowance (RDA) is 14 mg/day [269],

Box 9.1 US Institute of Medicine recommended dietary allowances for niacin

Infants 0–6 months (adequate intake) = 2 mg/day; 7–12 months = 4 mg/day
Children 1–3 years = 5 mg/day
Females 14+ years = 14 mg/day
Pregnancy = 18 mg/day
Lactation = 17 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

although the WHO recommended nutrient intake is 16 mg/day for adolescents up to 18 years of age [231]. The RDA for pregnant women is 18 mg/day, and 17 mg/day for lactation. In the US and Canada, intakes of niacin often exceed the RDA [269]. Although there are no reports of adverse effects of niacin or nicotinamide on the human fetus, niacin supplementation in doses above the RDA for the treatment of high cholesterol is not recommended in pregnancy (FDA category C).

Our recommendations for niacin intake during pregnancy and lactation

Diets deficient in niacin are likely to be deficient in other B vitamins. Consumption of a balanced, mixed diet is generally sufficient to meet niacin requirements. The additional needs for niacin during pregnancy are mirrored by the increased energy intake needs, and dietary supplementation is only necessary in cases of overall poor nutritional intake.

Chapter 10

Vitamin B_6 (pyridoxine) in pregnancy and breastfeeding

Vitamin B_6 functions

Vitamin B_6 is a water-soluble vitamin required for the activity of around 100 enzymes, with key roles in amino acid and carbohydrate metabolism, lipid biosynthesis, hormone function, synthesis of neurotransmitters and nucleic acids, red blood cell formation, and immune system function. The term vitamin B_6 refers to six related compounds: pyridoxal (PL), pyridoxine, pyridoxamine, and their respective active forms, pyridoxal-5′-phosphate (PLP), pyridoxine-5′-phosphate, and pyridoxamine-5′-phosphate. The main forms in animal tissues (and animal-derived foods) are PL and PLP, while pyridoxine and pyridoxine-5′-phosphate predominate in plants. All forms of vitamin B_6 can be converted to the key coenzymatic form, PLP [332].

Although they display catalytic diversity, most PLP-dependent enzymes, including oxidoreductases, transferases, hydrolases, lyases, and isomerases, act on amino acids. PLP covalently binds its substrate, acting as an electrophilic catalyst that stabilizes reaction intermediates [333–335]. In this way, vitamin B_6 is involved in basic metabolic pathways rather than in specialized regulatory functions.

Enzymes involved in the metabolism (trans-sulphuration) of homocysteine to cysteine depend on vitamin B_6 (PLP) as a cofactor. Disruption of this reaction leads to elevated blood homocysteine, which is associated with cardiovascular disease, neuropsychiatric problems, and other adverse effects. Adequate levels of vitamin B_6, along with vitamin B_{12} and folate, are required to keep homocysteine levels low [336].

Vitamin B_6 is also involved in synthesis and metabolism of neurotransmitters, which are formed by PLP-dependent decarboxylation of amino acids, and production of polyamines necessary for cell growth [337]. Lipid metabolism depends on vitamin B_6 as a cofactor in decarboxylation of phosphatidylserine. Because of its role in the synthesis of sphingosine [338], vitamin B_6 also affects the development of brain lipids and myelination. PLP and PL accumulate in erythrocytes, where they modulate the oxygen-binding affinity of haemoglobin [339,340].

Indicators of vitamin B_6 status

Plasma PLP is used as an indicator of vitamin B_6 status, also reflecting the status of liver stores [341]. Plasma levels change slowly in response to vitamin B_6 intake, plateauing around 7–10 days after a change in intake. The suggested value for adequate vitamin B_6 status is PLP >30 nmol/L, although this varies somewhat with age, sex, and protein intake [342]. The US Institute of Medicine (IOM) recommendations are based on achieving a PLP level of ≥20 nmol/L [269].

Vitamin B_6 deficiency

Although vitamin B_6 is widely available in foods, mild to moderate deficiency is still common, even in developed countries such as the US [343]. In addition to poor dietary intake, various conditions including malabsorptive disorders, inflammatory bowel disease, and diabetes, can decrease plasma vitamin B_6 levels. Classic symptoms relate to vitamin B_6 functions in neurotransmitter and haemoglobin biosynthesis, and include epileptic convulsions, depression and confusion, microcytic anaemia, and dermatitis.

Low levels of vitamin B_6 (PLP) have been linked to inflammatory disorders such as rheumatoid arthritis [344] and inflammatory bowel disease [345]. Plasma PLP concentrations are inversely correlated with cardiovascular disease risk, independent of major atherosclerotic risk factors including high homocysteine [346]. Drugs such as isoniazid (for tuberculosis) and L-DOPA interfere with vitamin B_6, reducing its plasma concentration and increasing the risk for deficiency [269].

Vitamin B_6 in pregnancy

PLP levels decline during pregnancy, beyond the effects of haemodilution. In fact, the most significant drop occurs in the third trimester, when blood volume plateaus. The fetus sequesters vitamin B_6 throughout pregnancy, and after the first trimester, the fetal concentration is higher than the maternal concentration. Low maternal intakes during pregnancy can lead to compromised vitamin B_6 status in the infant, as the vitamin B_6 status of cord blood correlates with maternal B_6 status [347].

As noted previously, vitamin B_6 deficiency can lead to hyper-homocysteinaemia, which in pregnancy is associated with pre-eclampsia, preterm birth, low birthweight, and small-for-gestational-age infants [348–350]. However, currently there is no evidence that vitamin B_6 supplementation in pregnancy reduces the risk of these adverse pregnancy outcomes. Specific other effects of vitamin B_6 in pregnancy are noted below.

Vitamin B_6 in conception

Vitamin B_6 has been implicated in regulating the length of the luteal phase in the menstrual cycle, and deficiency for the nutrient has been shown to reduce the likelihood of conception [351]. A pre-conception 'Mediterranean diet' (high in vegetables and vegetable oils, legumes, and fish, and low in saturated fats, meats, and refined carbohydrates), was shown to produce healthy levels of vitamin B_6 both in blood and follicular fluid. Couples undergoing in vitro fertilization who were following such a diet were more likely to achieve pregnancy than those following a diet that was higher in whole grains, meat, fruits, fatty dressings (e.g. mayonnaise), and snacks, despite the latter diet being low in processed foods and considered 'health conscious'. Both diets increased folate concentrations, but the Mediterranean diet led to an additional rise in vitamin B_6 [352].

The effect of vitamin B_6 supplementation on nausea and vomiting in pregnancy

Vitamin B_6 supplementation has long been considered as a remedy for morning sickness. Doses between 10 and 40 mg/day were shown to reduce the severity of symptoms of nausea and vomiting in pregnancy in two small randomized trials [353,354]. However, a recent systematic review found no strong evidence that vitamin B_6 supplementation reduces vomiting more than placebo or other interventions, including ginger and acupressure [355]. Nonetheless, the American Congress of Obstetricians and Gynecologists continues to recommend taking vitamin B_6 supplements for nausea and vomiting in pregnancy [356].

Vitamin B_6 and anaemia

Vitamin B_6 deficiency can contribute to anaemia in pregnancy. Some pregnant women with anaemia are nonresponsive to iron, but anaemia improves with administration of vitamin B_6 [357]. Deficiency for vitamin B_6 should be considered in cases of anaemia that do not respond to supplemental iron.

Vitamin B_6 and fetal brain development

Vitamin B_6 deficiency during pregnancy alters the concentrations of the neuroactive amino acids glutamate and glycine, which are endogenous ligands of the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptors are involved in synaptic plasticity during development and are important for learning and memory. Abnormalities in brain NMDA receptor function have been observed in rats postnatally following vitamin B_6 restriction during gestation [358].

In addition to glutamate and glycine, synthesis of the neurotransmitters gamma-aminobutyric acid (GABA), serotonin, epinephrine, norepinephrine, histamine, and dopamine requires PLP-dependent enzymes. Seizures can occur in utero, when GABA neurotransmission is disrupted by mutations in genes involved in vitamin B_6 metabolism [359], and in infants, when vitamin B_6 intake is deficient.

Vitamin B_6 in lactation and infancy

Gestationally accumulated stores of vitamin B_6 are important to maintain adequate levels for the breastfed neonate in the first weeks of life [360,361]. Weight gain and linear growth in early infancy have been correlated with infant vitamin B_6 intake [362]. Breast milk vitamin B_6 concentrations are influenced by maternal vitamin B_6 status and respond rapidly to changes in dietary intake. Milk from mothers receiving 2.5 mg/day of vitamin B_6 as a supplement had average vitamin B_6 concentrations that ranged from 0.15 to 0.21 mg/L [360]. However, there is significant inter-individual variation in breast milk levels despite similar intakes. Some women receiving supplements of 2.5 mg/day had breast milk vitamin B_6 concentrations well below the goal of 0.13 mg/L in milk [360], the concentration deemed adequate for infant needs [269]. A more recent study found that only infants of mothers supplemented with 10 mg/day met or exceeded the vitamin B_6 recommended dietary allowance (RDA) of 0.3 mg/day [363].

Seizures have been observed in infants consuming milk formula with low vitamin B_6 content. The seizures respond to vitamin B_6 supplementation [364,365]. Breast milk vitamin B_6 concentrations of <0.1 mg/L are thought to place infants at risk for the development of seizures [365].

Maternal vitamin B_6 nutritional status may influence infant behaviour. A study of a cohort of Egyptian mothers and their breastfed infants found that aspects of infant behaviour (mother–infant interactions, consolability, and irritability) were better in infants whose mothers had the highest vitamin B_6 status. In addition, in these mothers, vitamin B_6 was the only nutrient present in insufficient levels in breast milk (compared with breast milk from a group of well-nourished Western women). There was also a significant positive association between maternal vitamin B_6 and birthweight in this cohort [366].

Vitamin B_6 sources and metabolism

Plants, fungi, and single-celled organisms can synthesize vitamin B_6, but animals must ingest it from external sources. Vitamin B_6 is widely distributed in foods, particularly poultry, fish (especially tuna), and meats, legumes (e.g. chickpeas), potatoes and other starchy vegetables, non-citrus fruits, and nuts and seeds (e.g. pistachios, sunflower seeds, and sesame seeds). Fortified cereals and fortified soy-based meat substitutes also provide vitamin B_6 and may be important food sources for individuals consuming vegan diets [269].

The availability of vitamin B_6 from foods is approximately 75 per cent. Food of plant origin contains mostly pyridoxine and pyridoxine-5′-phosphate, which have lower bioavailability than PL and PLP from animal-source foods. Non-phosphorylated vitamin B_6 absorbed from the diet is stored in the liver. At high intakes, the capacity for protein binding of PLP limits its accumulation in tissues [367]. However, the high PLP-binding capacity of proteins in muscle and plasma, and haemoglobin in erythrocytes allows high accumulation when other tissues are saturated.

Risks of excess vitamin B_6

There are no reported adverse effects of vitamin B_6 derived from food sources. The tolerable upper level of intake from supplements is based on sensory neuropathy as the critical adverse event. Levels below 100 mg/day are considered not to be associated with adverse effects, so this amount is set as the tolerable upper intake level [269].

Agency guidelines for vitamin B_6 intake

Both the IOM and the WHO guidelines advise intakes of 1.3 mg/day for females aged 19–50 years (1.5 for over 50 years), with reference nutrient intakes/RDAs for pregnancy and lactation of 1.9 and 2.0 mg/day, respectively [231,269]. Most people in the US and other developed countries have access to foods that offer adequate amounts of vitamin B_6 in their diets. Diets lacking B_6 would be nutritionally poor overall and would lack other B vitamins, so primary deficiency of vitamin B_6 is rarely encountered [269]. However, vitamin B_6 levels were found to be low in ~11 per cent of people who take supplements, and in ~24 per cent of people who do not take supplements, in a 2008 report of the National Health and Nutrition Examination Survey [368]. The findings suggested that the current vitamin B_6 RDAs did not guarantee adequate nutritional status for the whole population and that intakes between 3 and 4.9 mg/day would still leave some subgroups (the elderly, people of African descent, smokers, and current and former users of oral contraceptives) with inadequate vitamin B_6 status.

The CDC also considers vitamin B_6 deficiency to be a fairly common occurrence in the US [343]. Nonetheless, a study of middle–high income pregnant women in the US found that the usual intake of vitamin B_6 exceeded the estimated average requirement of 1.6 mg/day, and generally met the RDA (1.9 mg/day). The probability of intake less than the estimated average requirement was 21 per cent [369].

Box 10.1 US Institute of Medicine recommended dietary allowances for vitamin B_6

Infants 0–6 months (adequate intake (AI)) = 0.1 mg/day (≈0.014 mg/kg)
Infants 7–12 months (AI) = 0.3 mg/day (≈0.033 mg/kg)
Children 1–3 years = 0.5 mg/day
Females 14–18 years = 1.2 mg/day
Females 19–50 years = 1.3 mg/day
Pregnancy = 1.9 mg/day
Lactation = 2.0 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

There is an additional requirement of 0.6–0.7 mg/day during pregnancy and lactation. Some degree of deficiency may be present in infants whose sole source of nutrition is breast milk, and whose mothers have marginal vitamin B_6 intake and/or are not supplemented (Box 10.1).

According to European Commission recommendations, supplements of 2.5–4 mg/day are required to maintain the plasma concentration of vitamin B_6 at pre-pregnancy levels [370]. This is to account for the drop in plasma concentrations during pregnancy that are a consequence of preferential uptake by the fetus. The view of this board is that there is no evidence that vitamin B_6 metabolism changes during lactation, so unlike the IOM RDA, the recommendation is the same as for non-lactating women (15 µg/g dietary protein or 1.1 mg vitamin B_6/day) [370].

Our recommendations for vitamin B_6 intake during pregnancy and lactation

Although increased amounts of vitamin B_6 are recommended for pregnant and breastfeeding women, supplementation is usually not required if the diet is adequate and nutritionally balanced. A diet similar to the Mediterranean diet is recommended during pregnancy and lactation to provide a variety of sources for vitamin B_6 and other B complex vitamins. Most prenatal vitamins contain vitamin B_6 in adequate daily amounts. Additional vitamin B_6 supplements for alleviating nausea and vomiting in pregnancy should only be taken under the advice of a physician and should not be combined with prenatal vitamins that also contain vitamin B_6.

Chapter 11

Vitamin B_7 (biotin) in pregnancy and breastfeeding

Biotin functions

Biotin is a water-soluble B vitamin (vitamin B_7) that acts as a coenzyme for carboxylases, with roles in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Reduced activity of biotin-dependent enzymes (acetyl-CoA carboxylase I and II, and propionyl-CoA carboxylase) alters lipid metabolism and may impair synthesis of polyunsaturated fatty acids and prostaglandins [371]. Impaired hepatic gluconeogenesis results in fatty liver and kidney syndrome in animals (chickens) and is responsive to biotin supplementation [372]. Biotin has effects on gene expression by binding covalently to histones [373].

Indicators of biotin status

Biotin is a cofactor for beta-methylcrotonyl-CoA carboxylase, which is required for the degradation of leucine. Biotin deficiency causes inactivation of this enzyme and accumulation of the leucine metabolite 3-hydroxyisovalerate, which is formed via an alternate pathway. Urinary excretion of biotin and/or 3-hydroxyisovalerate, assessed via an avidin-based immunoassay, is used to determine biotin status [374]. Overt cases of biotin deficiency show decreased excretion of biotin and/or abnormally increased excretion of 3-hydroxyisovalerate (>195 μg/day) [375]. The normal range for biotin excretion is 19–62 nmol/day. Excretion decreases rapidly during biotin depletion. Low plasma biotin is not a sensitive indicator of biotin deficiency or inadequate intake [374].

Biotin deficiency

Prolonged consumption of egg whites can lead to biotin deficiency, as egg whites contain the biotin-binding protein avidin. Otherwise, dietary deficiency is rare. Clinical signs of deficiency include erythematous or seborrhoeic dermatitis, conjunctivitis, hair loss, and CNS abnormalities including lethargy, hypotonia, hallucinations, depression, paraesthesia, and developmental delay in infants [269]. Biotin deficiency has adverse effects on immune function, including reduced antibody synthesis and a lower percentage of B lymphocytes in spleen [376]. Animal studies suggest biotin deficiency can cause birth defects, primarily manifesting as cleft lip and palate, and impaired skeletal long bone growth [377]. Even marginally deficient biotin status that does not confer symptoms in the mother appears to increase the risk of these defects in various animal species. Smoking accelerates the degradation of biotin, resulting in marginal biotin deficiency [378].

Biotin in pregnancy

Placental transport of biotin is not rapid and does not generate a substantial fetal-to-maternal gradient, despite the presence of a biotin transporter in the trophoblastic villus membrane. As in other tissues, carrier-mediated biotin transport in the placenta is saturable and sodium dependent [379]. Pregnancy increases biotin breakdown and may impair absorption of biotin, resulting in maternal biotin depletion. In a small study, biotin status was abnormally low in ~75 per cent of women in late pregnancy [380]. This may reduce fetal histone biotinylation, causing altered gene expression with the potential for teratogenesis. The effects of biotin deficiency on lipid metabolism are also potentially teratogenic [381]. Yet, despite evidence that marginal biotin deficiency in human pregnancy is common, there is currently no direct evidence of teratogenicity in humans.

Biotin in lactation

The biotin content of human milk is estimated to be approximately 6 μg (24 nmol)/L [382,383]. Based on this, the estimated intake for breastfed infants is 5 μg/day (assuming consumption of ~0.75 L/day). Symptomatic biotin deficiency has not been reported in breastfed infants.

Biotin sources

Biotin is synthesized by intestinal bacteria and is present in a wide variety of foods at low concentrations. In some foods, such as wheat bran, biotin is present in reasonable quantities but is not bioavailable. Liver and egg yolks are the most significant natural sources of biotin. Egg whites contain avidin, which binds and sequesters biotin. Raw egg whites should be avoided, and cooked egg whites should be consumed in moderation to prevent biotin depletion. Other sources include legumes (particularly soybeans and lentils), sunflower seeds, milk, cheese, chicken, pork, beef, and some fruits and vegetables. The availability of biotin from cereals is low.

Risks of excess biotin

The intestinal absorption of biotin is limited, so the risk of excess is considered minimal. Biotin has been shown to be relatively non-toxic at high doses in mice (>60 mg/day) [384]. Although some individuals taking biotin supplements may experience mild nausea, stomach cramps, or diarrhoea, these effects are relatively rare. Toxicity from food sources is considered unlikely.

Agency guidelines for biotin intake

The WHO reference nutrient intakes [231] and the US Institute of Medicine (IOM) recommended dietary allowances (RDAs) [269] are in agreement with regard to biotin requirements (see Box 11.1 for the IOM recommendations). The adequate intake recommendation for infants 0–6 months is 5 μg/day and then increasing to 6 μg/day until the age of 1. Children 1–3 years of age require 8 μg/day. The RDA/reference nutrient intake for adolescents aged 13–18 years is 25 μg/day. For females 19+ years (including pregnancy), the RDA/reference nutrient intake is 30 μg/day (123 nmol/day), rising to 35 μg/day (143 nmol/day) during lactation. Despite some questions about the potential teratogenicity of biotin deficiency, and the impact of pregnancy on reducing biotin levels, the IOM does not consider the evidence strong enough to warrant an increase in the RDA for pregnancy, except in pregnant adolescents, for whom the RDA increases to 30 μg/day from 25 μg/day pre-pregnancy. However, an additional 5 μg/day is recommended during lactation to account for losses due to excretion into breast milk (Box 11.1) [269].

Box 11.1 US Institute of Medicine recommended dietary allowances for biotin

Infants 0–6 months (adequate intake (AI)) = 5 μg/day
Infants 7–12 months (AI) = 6 μg/day
Children 1–3 years = 8 μg/day
Females 14–18 years = 25 μg/day
Females 19+ = 30 μg/day
Pregnancy = 30 μg/day
Lactation = 35 μg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

Our recommendations for biotin intake during pregnancy and lactation

Deficiency is unlikely unless a biotin antagonist (e.g. avidin) is present in the diet. Currently available evidence suggests that supplemental biotin is generally not required in pregnancy, although high consumption of egg whites should be avoided. Women who smoke have a greater risk of biotin deficiency resulting from accelerated biotin metabolism.

Chapter 12

Vitamin B_9 (folate) in pregnancy and breastfeeding

Folate functions

Folate is an essential B-group vitamin (sometimes called vitamin B_9) that is synthesized by microorganisms and higher plants but not by mammals. It is a coenzyme in multiple biochemical pathways involving one-carbon metabolism, including amino acid metabolism, purine and pyrimidine nucleotide biosynthesis, the methylation cycle, and homocysteine–methionine metabolism.

Homocysteine, an amino acid that is not found in proteins, serves as an intermediate in methionine metabolism. It is formed by removal of a methyl group from methionine and can be remethylated back to methionine or converted to cysteine via the action of folate, vitamin B_{12}, and vitamin B_6 (see Fig. 12.1). Folate serves as a methyl donor, and homocysteine status is therefore influenced by the supply of folate [385]. Low folate intake results in elevated serum homocysteine, which has been implicated as a risk factor for vascular disease, especially stroke [386]. Folate supplementation has been shown to decrease homocysteine levels, improve endothelial function, and reduce the risk of stroke [387, 388].

Folate also serves as the principal source of the one-carbon group used for DNA methylation, which is central to epigenetic processes. Methylation patterns can be transmitted through mitosis, perpetuating the epigenetic pattern through subsequent cell generations. Folate deficiency may influence the ability to maintain DNA methylation patterns in replicating cells and thus may induce lasting phenotypic changes [389, 390]. Altered methylation has been associated with some cancers [391].

The key role of folate in nucleotide biosynthesis, and thus in DNA and RNA synthesis, means that folate requirements increase during periods of rapid cell division. The most overt consequence of folate deficiency is megaloblastic (pernicious) anaemia, which is caused by the inhibition of DNA synthesis in red blood cell (RBC) production [392, 393]. Embryogenesis and fetal growth also require higher levels of folate.

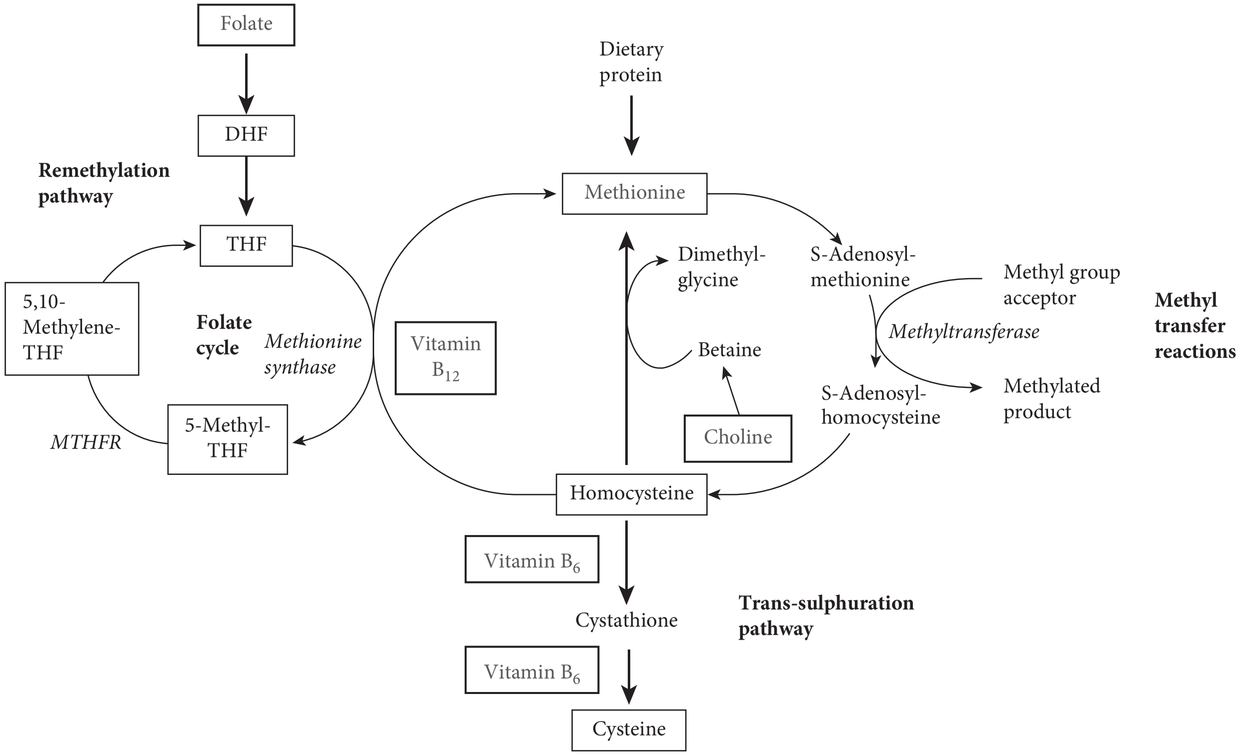
Folate
DHF
Remethylation pathway
THF
5,10-Methylene-THF
Folate cycle
Methionine synthase
MTHFR
5-Methyl-THF
Vitamin B_{12}
Dietary protein
Methionine
Dimethyl-glycine
Betaine
Choline
S-Adenosyl-methionine
Methyl group acceptor
Methyltransferase
Methylated product
S-Adenosyl-homocysteine
Methyl transfer reactions
Homocysteine
Vitamin B_6
Cystathione
Trans-sulphuration pathway
Vitamin B_6
Cysteine

Fig. 12.1 Homocysteine metabolism and the actions of dietary folate, vitamin B6, vitamin B12, and choline. The enzymes involved in the conversions are shown in italics. DHF, dihydrofolate; MTHFR, methylenetetrahydrofolate reductase; THF, tetrahydrofolate

Fetal requirements for folate must be supplied maternally during pregnancy. A link between low maternal folate levels and the occurrence of neural tube defects (NTDs, e.g. spina bifida, anencephaly, and encephalocele), has long been recognized [394, 395]. Low folate may induce NTDs by either inhibiting DNA synthesis or through the disruption of DNA methylation [396]. Maternal folate requirements increase by 50 per cent during pregnancy, and even if the daily diet consists of food rich in folates, the high requirement usually cannot be met through the consumption of unfortified foods alone. It is for this reason that peri-conceptional supplementation with folic acid is recommended internationally for the prevention of NTDs. 'Folic acid' specifically refers to the fully oxidized monoglutamate form that is used in supplements and fortified foods, and rarely occurs in nature. Randomized clinical trials have shown that folic acid taken in very early pregnancy can markedly reduce the risk that an infant will be born with a NTD [397–399].

Indicators of folate status

Clinical folate deficiency is usually defined as a serum folate concentration <7 nmol/L (~3 ng/mL) or an RBC folate concentration that is <315 nmol/L (~140 ng/mL) [269]. Low serum folate is inversely correlated with serum homocysteine. Although plasma homocysteine is very sensitive to changes in folate level, the concentration of homocysteine in plasma can also be influenced by vitamin B_{12} status [400] and is therefore not a specific indicator.

Folate deficiency

Irrespective of the clinical definition of folate deficiency, NTD-affected pregnancies may yet occur among women who are not classified as deficient. A dose–response study which aimed to determine if supplementation to increase folic acid levels beyond the threshold of 'deficient' status would further reduce NTD risk found that maximal risk reduction occurred at RBC folate levels >906 nmol/L [401]. Earlier studies showed that peri-conceptional supplementation of 800 μg folic acid/day together with multivitamins achieved a near 100 per cent reduction of NTDs as well as marked reductions of congenital heart defects [398, 399]. Folate deficiency can also occur as a result of alcohol abuse, malabsorption, liver disease, certain anaemias, and because of concomitant intake of medications that interfere with folate utilization (e.g. anticonvulsants, metformin, sulfasalazine, triamterene (a diuretic), methotrexate, and barbiturates) [402].

Obese women have a significantly higher risk of having a NTD-affected pregnancy than do normal-weight women [403, 404]. This increased risk is independent of their use of supplements containing folic acid [405], or consumption of flour fortified with folic acid [406]. Adequate folate intake thus appears to protect against NTDs in lean but not overweight women [407].

Folate levels are not specifically modified by BMI, although obesity may affect body distribution, resulting in a lower plasma folate level and a higher RBC folate level. It is not yet clear whether obese women require higher doses of folate supplements [408]. A recent pharmacokinetic study has provided evidence that obesity affects the pharmacokinetic response to supplemental folic acid and its tissue distribution, resulting in lower circulating levels of folate [409]. However other data suggest that folate deficiency may not be the primary cause of the elevated NTD risk in this population [410].

Achieving effective folate concentrations (≥906 nmol/L) is challenging. A Canadian study found that in 2006, 40 per cent of women of childbearing age and 36 per cent of pregnant women had RBC folate below the recommended level, despite nationwide flour fortification [411]. In Canada, a high (5 mg/day) dosage is recommended for pregnant women with a family history of NTDs and those trying to conceive. The relationship between folic acid intake and RBC concentration is non-linear; a study of 1.1 mg vs 5 mg folic acid per day for 30 days observed a twofold increase in RBC folate concentration from a fivefold increase in folic acid intake [412].

Folate in pregnancy

Folate in pre-eclampsia, placental vascular disorders, and gestational hypertension

Maternal folate deficiency and elevated homocysteine may increase the risk of placental vascular disorders. Folate deficiency was observed as a prominent risk factor for placental abruption/infarction in a systematic review of four early studies [413]. A study using data from the Medical Birth Registry of Norway found that women who used folic acid and/or multivitamin supplements containing folic acid had a significantly lower risk of placental abruption, particularly preterm abruption, than did women who did not use supplements [414]. The recent Generation R Study in the Netherlands, using a prospective cohort of >5,800 women, reported an association between low maternal folate concentrations and vascular-related pregnancy complications [349]. Homocysteine concentrations are higher in pre-eclamptic pregnancies than in normal pregnancies [415, 416], and levels may associate with the severity of pre-eclampsia [417]. Folic acid supplement use was reported to be associated with a lower risk of gestational hypertension in a retrospective study [418].

The effect of folate on preterm birth

A study of >34,000 low-risk singleton pregnancies found that pre-conceptional folic acid supplementation for one year or longer, compared with no supplementation, was associated with a 70 per cent decrease in the risk of spontaneous preterm delivery between 20 and 28 weeks, and a 50 per cent decrease between 28 and 32 weeks. The risk of early spontaneous preterm birth was inversely proportional to the duration of pre-conceptional folate supplementation. Pre-conceptional folate supplementation was specifically related to early spontaneous preterm birth and not associated with other complications of pregnancy [419]. Low folate levels were also associated with preterm birth in the Generation R Study [349].

The effect of folate on birthweight

Maternal folate status is thought to have a role in promoting normal fetal growth and placental function. Folate requirements peak in the third trimester to account for rapid fetal growth and fetal accumulation of folate stores. Low folate (and high homocysteine) concentrations were associated with lower birthweight and a higher risk of having a small-for-gestational-age infant in the Generation R Study [349]. Other studies report a positive association between birthweight and maternal RBC folate status or intake [420, 421].

Folate in the prevention of birth defects

Supplemental folic acid and NTD prevention

Multiple case–control and epidemiological studies have demonstrated a positive effect of folic acid supplementation or dietary intake of folate on reducing the risk of NTD-affected pregnancies [394, 422–424]. Epidemiological findings were strengthened by the results of a non-randomized intervention study in China that included 130,142 women who took folic acid before pregnancy, and 117,689 who did not. The study concluded that pre-conceptional intake of 400 μg/day folic acid could reduce risk of NTDs in areas with both high and low rates of defects [425].

The first randomized controlled trial of pre-conceptional folic acid treatment involved 112 women with a prior NTD pregnancy and showed a statistically significant effect [426]. The UK's Medical Research Council Vitamin Study was an international, multicentre, double-blind randomized controlled trial in women with a previous NTD pregnancy (from the UK, Hungary, Israel, Australia, Canada, the USSR, and France). The study found that folic acid alone can reduce NTD recurrence by 71 per cent [397]. To determine if folic acid could prevent the first occurrence of NTDs, a randomized trial was conducted using what was considered a physiological folic acid dose (800 µg/day), along with minerals and trace elements (copper, manganese, zinc, low-dose vitamin C), and compared with results obtained from supplementation with the trace elements alone [398]. The study included >4,800 women and observed no NTDs in the folic acid group, as compared with six NTDs in the group that received trace elements alone ($p = 0.01$). A meta-analysis of five trials in >6,100 women has confirmed that folic acid supplementation helps prevent both first occurrence and reoccurrences of NTD [427].

Folic acid and orofacial clefts

In a large prospective cohort study of over 240,000 pregnancies, daily maternal consumption of 400 µg of folic acid without other vitamins, started before the mother's last menstrual period, was associated with a reduced risk of cleft lip (with or without cleft palate) in babies born in a high-prevalence region of China [428]. However, an earlier Hungarian study suggested that higher doses (6 mg/day) were required in the critical period of primary and secondary palate development to reduce the incidence of isolated orofacial clefts [429]. A 2010 meta-analysis found insufficient evidence to support folic acid use for the prevention of orofacial clefts [427], but a more recent population-based cohort study of >11,000 infants in Ireland indicated that folic acid use (generally 400 µg/day) by mothers during the first trimester of pregnancy was associated with a more than fourfold lower incidence of cleft lip (with or without cleft palate) in their infants [430].

Folic acid and neurodevelopment

An increase in folic acid intake resulting from fortification and/or supplementation may increase folate levels sufficiently to avoid NTDs but not to eliminate more subtle neurodevelopmental effects of marginal folate status on the offspring. Low folate concentrations in the brain have been proposed to be a causative factor in some forms of developmental delay and autism [431, 432]. Higher peri-conceptional maternal folic acid intake was shown to correlate with a decreased risk of autism in the developing child when the mother and/or child possessed the *MTHFR* 677 C>T variant (see 'Folic acid genetics') [433]. A recent population-based analysis within the Generation R Study found that low maternal folate status in early pregnancy was associated with an increased risk of emotional and behavioural problems in offspring at 18 months ($n = 4{,}214$ children) [434] and 3 years of age ($n = 3{,}209$ children) [435]. The data suggest that folic acid supplementation in early pregnancy can help reduce the risk of later behavioural problems in children.

Folic acid genetics

There appears to be a genetic component to the causation of NTDs, as suggested by results of twin and family studies, and the higher prevalence in some ethnic groups such as Celts [436], Sikhs [437], and Northern Chinese [438]. Folate status is modified by activity of the enzyme methylenetetrahydrofolate reductase (MTHFR), which controls a rate-limiting step in the methylation cycle (remethylation of homocysteine to methionine—see Fig. 12.1). MTHFR diverts one-carbon units towards methylation reactions at the expense of nucleotide synthesis [439]. Inactivating mutations in the *MTHFR* gene, which encodes this enzyme, and particularly the 677C>T polymorphism, result in lower plasma folate, and elevated plasma homocysteine levels. The TT genotype renders individuals more susceptible to epigenetic alterations in response to low folate status; the combination of such *MTHFR* mutations in the presence of low folate intake can increase the risk of NTDs [440]. An examination of international variation in the distribution of the TT genotype in ~7,000 newborns from 16 geographic regions found that trends in frequencies of NTDs follow the genotype distribution to some extent [441, 442].

Folate interactions with vitamin B_{12} and choline

Folate and vitamin B_{12} interact in common biochemical reactions (see Chapter 11 on vitamin B_{12}), and when either is in deficit, a very similar picture of megaloblastic anaemia emerges, reflecting a derangement of DNA synthesis in erythropoietic cells [443]. Supplementation with folic acid in the presence of low vitamin B_{12} can correct the anaemia but allows the neurological pathologies associated with vitamin B_{12} deficiency to progress. These manifestations result from inactivation of vitamin B_{12}-dependent methylmalonyl-CoA mutase, correction of which cannot be addressed by increasing folate [443].

Low levels of either vitamin B_{12} or folate leads to an elevation in plasma homocysteine, and its associated adverse effects. The vitamin B_{12}-dependent enzyme methionine synthase is inactive when this nutrient is in deficit, causing folate to be trapped in the form of 5-methyl-tetrahydrofolate, compounding folate deficiency [444]. Supplementation with folate can lower homocysteine levels in the presence of vitamin B_{12} deficiency, although other consequences of this nutritional imbalance are becoming evident. Children born to women with high erythrocyte folate but low vitamin B_{12} status appear to be at high risk for developing insulin resistance [445].

There is also an intersection of the pathways of choline and folate in the formation of methionine from homocysteine. Betaine, the primary oxidative product of choline, can act as an alternate methyl donor to 5-methyl-tetrahydrofolate in this conversion. Choline becomes a limiting nutrient during folate deficiency [446].

Food folate sources

The most concentrated food sources of folates are liver (320 µg/100 g), yeast extract, green leafy vegetables, legumes, citrus fruits, and fortified breakfast cereals. Natural food folates are heat labile and may be destroyed by storage, processing, and cooking [269]. They are also less easily absorbed than synthetic folic acid, which is the most bioavailable form. The bioavailability of food folate is likely to be less than 50 per cent [447]. A strong correlation exists between serum folate concentration and daily use of a supplement containing folic acid.

Food fortification with folic acid

Despite strong confirmation of the protective effective of folic acid supplementation, and the recommendations of many agencies that women take folic acid in supplement prior to and during pregnancy, this approach alone has not translated into population-wide declines in NTD prevalence. There are reports that consumption of enriched cereal grain products (e.g. bread, pasta, etc.), produced from flour fortified with folic acid to a level of 140 µg/100g, does not appear to significantly increase serum folate to levels that are considered protective against NTDs [448, 449].

A recent survey in the US found that 77 per cent of pregnant women were taking supplements, mostly daily prenatal vitamins containing an average of 817 µg folic acid and 48 mg iron, but fewer were taking supplements in the first trimester (55%) [450]. Evaluations of NTD trends in countries that have folic acid dietary intake and supplementation recommendations, but not mandatory food fortification programmes, found that the incidence of NTDs has not fallen significantly [451, 452]. For example, an epidemiological study in France of 202,670 births did not observe a decrease in incidence of NTDs before and after recommendations were publicized in 1991–1992 [453].

Therefore, combined strategies of fortification and supplementation are likely to be required to meet population recommendations for folic acid intake [454]. Globally, around 75 countries have initiated nationwide policies of mandatory flour fortification with folic acid and other nutrients. This is meant to ensure that the entire population receives at least a small additional amount of folic acid, regardless of access to supplements (see *Flour Fortification Initiative* (<http://www.ffinetwork.org/regional_activity/index.php>) for country and regional data). A randomized trial of several doses of folic acid (100, 200, or 400 µg/day) concluded that a fortification programme that delivered 100 μg folic acid daily to women would produce an important decrease in NTD prevalence, without the expense of unnecessarily high exposure for the general population [455]. Following the introduction of folic acid fortification of enriched cereal grain products in the US, a 19 per cent reduction in NTD birth prevalence was observed [456]. In Nova Scotia, Canada, the incidence of NTDs decreased by more than 50 per cent after mandatory fortification was implemented [457]. These reduction figures are substantially different because the US data was based only on live births and, unlike the Canadian study, did not include prenatally diagnosed cases that resulted in early termination of the pregnancy [458].

Risks of excess folate

No adverse effects have been associated with the consumption of excess folate from foods. Adverse effects are exclusively reported from use of the synthetic compound folic acid [459]. The European Scientific Committee considers the risk of progression of the neurological symptoms in vitamin B_{12}-deficient patients (as a result of masking the signs of pernicious anaemia) as the most serious potential adverse effect of folic acid supplementation. This generally occurs with folic acid dosages >5 mg/day, whereas dosages up to 1 mg of folic acid are unlikely to cause this masking effect. Therefore the tolerable upper intake level in the EC is set at 1 mg of folic acid [460]. The same tolerable upper intake level of 1 mg/day is used in the US by the Institute of Medicine (IOM) and is the same for both pregnant and lactating women [269]. The recommendation of 4 mg/day for the prevention of NTD recurrence is well above the tolerable upper intake level and should be monitored by a physician.

It has been suggested that high folic acid intake could overwhelm the liver's metabolic capacity, leading to exposure to unmetabolized folic acid. Although no adverse effects have been observed at high doses (5 mg) [461], another study found that excess unmetabolized folic acid correlated with decreased activity of natural killer cells, which are important for antiviral and anticancer immunity [462]. There has been some debate over whether folic acid supplementation and/or fortification is responsible for an increasing incidence of colorectal cancer in areas where this has been implemented [463]. However, a recent meta-analysis of studies involving 50,000 individuals on the effect of folic acid supplementation on cancer incidence suggested that consuming supplements for five years has no substantial effect on this outcome [464]. As food fortification generally involves much lower doses than supplementation trials, it seems unlikely that cancer risk would be affected by the consumption of fortified foods in moderate quantities.

There is evidence from animal studies (in mice) that a maternal diet supplemented with methyl donors (folic acid, vitamin B_{12}, choline, L-methionine, zinc, and betaine) leads to decreased transcriptional activity and increased severity of allergic airway disease in offspring (via excessive methylation of the *RUNX3* transcription factor gene, a negative regulator of allergic airway disease) [465]. A few human studies have supported this idea, reporting that folic acid supplementation in early pregnancy was associated with a small increase in risk of infant wheezing (up to 18 months) [466], or with an increased risk of asthma at 3 years of age [467]. High maternal folate levels (>17.84 nmol/L) in the second trimester were also associated with an increased risk of asthma at 3 years [468]. However, results from the recent KOALA Birth Cohort Study (n = 2,834) in the Netherlands found no association between either maternal folic acid supplement use in pregnancy, or maternal intracellular folic acid levels, and impaired lung function or the development of atopic manifestations in offspring at 6 to 7 years of age. On the contrary, there was a dose-dependent correlation between high maternal folic acid levels in late pregnancy and decreased childhood asthma risk [469]. This is in agreement with a study in adults and children ≥2 years of age, in whom serum folate levels were inversely correlated with IgE levels and the presence of atopy and wheeze [470]. A recent systematic review and meta-analysis did not support a causal link between the use of antenatal folic acid supplements and increased risk of asthma in children [471]. However, to date no randomized controlled trials have been performed to assess allergic outcomes of folic acid supplementation.

Excess folate during late pregnancy may affect other aspects of the developmental course in the offspring. Recent animal studies suggest that the trajectory to peak bone mass may be sensitive to nutritional folate exposure in utero. High folate diets (equivalent to 10× recommended levels) fed to pregnant rats resulted in lower weight and reduced bone mass in female offspring [472]. If this holds true in humans, it may be of concern in light of the number of pregnant women who take folic acid well above the generally recommended amounts.

Agency guidelines for folate intake

The general recommendation prior to conception and throughout pregnancy is for supplementation with 400 μg of folic acid in tablet form, in addition to dietary sources, which can reduce the risk of NTD by approximately 50 per cent [473, 474]. Fortification of flour in some countries (providing ~25–100 μg/serving of breads or cereals) has also contributed to a marked reduction in the incidence of NTDs, as has been seen, for example, in Canada [475] and South Africa [476]. Whether fortification of flour is independently correlated with

Box 12.1 Conversions for dietary folate equivalents

1 dietary folate equivalent = 1 μg food folate = 0.6 μg folic acid from supplements and fortified food

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

decreasing incidence of NTDs is not clear [477], and supplementation is still recommended even for women consuming diets including fortified grain products in order to further reduce the risk of NTDs [478].

The recommendations for folate intake set by the IOM express the units of intake as dietary folate equivalents (DFEs) in order to account for differences in absorption of food folate (<50% absorbed) compared with synthetic folic acid (85% absorbed) [269]. DFE conversions are shown in Box 12.1

The IOM advises an intake of 400 μg DFE/day as the recommended dietary allowance (RDA) for individuals (both male and female) above the age of 14 years (estimated average requirement = 330 μg/day). Prior to and during pregnancy, the RDA increases to 600 μg DFE/day; it is recommended that 400 μg/day is taken as a folic acid supplement, in addition to a varied diet providing natural food folate. The RDA drops to 500 μg DFE/day during lactation (Box 12.2). Women with a prior NTD-affected pregnancy are advised to take 4 mg

Box 12.2 US Institute of Medicine recommended dietary allowances for folate

Infants 0–6 months (adequate intake (AI)) = 65 μg dietary folate equivalents (DFE)/day
Infants 7–12 months (AI) = 80 μg DFE/day
Children 1–3 years = 150 μg DFE/day
Females 14+ years = 400 μg DFE/day
Pregnancy = 600 μg DFE/day
Lactation = 500 μg DFE/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

DFE/day at least 1 month before conception and throughout the first trimester [269]. The adequate intake level for infants is 65 μg DFE/day up to 6 months of age, and 80 μg DFE/day from 7 to 12 months. These intakes are based on amount consumed by healthy breastfed infants [269].

In agreement with the IOM, CDC guidance states that all women of childbearing age should consume 400 μg of folic acid daily in supplement form [479, 480]. For prevention of recurrence in women who previously had an NTD-affected pregnancy, supplementation with 4 mg/day is suggested, beginning 1 month before trying to conceive and continuing through the first 3 months of pregnancy. This higher dosage should be supervised by a health care professional.

The US Preventive Services Task Force recommends that all women capable of becoming pregnant take folic acid supplements of 400–800 μg/day. Their most recent review of potential harms of this preventive measure found no evidence of significant drug interactions, allergic reactions, or carcinogenic effects associated with intake of the recommended dosages [481]. Canadian Clinical Practice Guidelines [482] advise that women who have not had a prior NTD-affected pregnancy should consume a multivitamin supplement delivering 0.4–1 mg folic acid/day from at least 2 months before conception and continuing through to the end of lactation. For women with a family history of NTDs, as well as for those in high-risk ethnic groups (e.g. Sikh) or who take anticonvulsant medications, a daily dose of 5 mg folic for 3 months both before and throughout the first 12 weeks of pregnancy is recommended as the standard of care. From 12 weeks until the end of gestation and throughout breastfeeding, these women should take a daily multivitamin supplement containing between 0.4 and 1 mg folic acid. Although the peri-conceptional use of 5 mg folic acid/day is uncommon outside this specific group of women, the Society of Obstetricians and Gynaecologists of Canada also recommends 5 mg folic acid under a broader list of indications, including for women with histories of poor medication compliance, poor or variable diets, or inconsistent/non-use of birth control.

The UK National Institute for Clincal Excellence guidelines recommend that pregnant women supplement with 400 μg folic acid/day from pre-conception through the first 12 weeks of pregnancy [266]. Regarding folic acid supplementation in obese women, the UK Centre for Maternal and Child Enquiries and the Royal College of Obstetricians and Gynaecologists have issued a joint guideline which advises women with a BMI ≥30 who are contemplating pregnancy to supplement with 5 mg folic acid daily, starting at least 1 month before conception and continuing during the first trimester of pregnancy [483]. However, there is some debate about this recommendation, as peri-conceptional hyperglycaemia may be an independent risk factor, not modifiable by folic acid intake, which contributes to the higher prevalence of NTDs in offspring of obese women [484]. The European Scientific Committee on Food advises women who are contemplating pregnancy to use a daily supplement containing 400–500 µg folic acid from 4 weeks before conception to 8 weeks postconception to reduce NTD risk [370, 460].

Our recommendations for folate intake during pregnancy and lactation

Most data are consistent with the recommendation that women who are contemplating pregnancy should consume a multivitamin supplement containing 400 µg folic acid/day, from 2 months prior to conception and through the first 12 weeks of pregnancy. This advice is in addition to consuming a varied diet containing natural food folate. Although liver is a rich source of folate, it is not recommended during pregnancy because of its high content of preformed vitamin A. A diet rich in fruits and vegetables, including legumes, is recommended, along, where available, with moderate amounts of foods fortified with folic acid. We recognize that women who have had a previous NTD-affected pregnancy require higher-dose folic acid supplementation prior to and throughout the first part of pregnancy. A dosage of 4 mg/day should be considered, under the guidance of a physician.

Translating the known protective effect of folic acid into population-wide reductions in NTD prevalence has not been straightforward. Maternal lifestyle factors such as smoking, alcohol consumption, bodyweight/BMI, and folic acid supplement use can be viewed as a proxy of nutrition and lifestyle, all of which can affect a woman's folate and homocysteine status and have important repercussions for her pregnancy. Recent data support the idea that BMI has a significant impact on folate metabolism, and recommendations based on BMI may be warranted. The current recommendations were based largely on data from several decades ago, when obesity was not as prevalent and the average BMI was in the normal range [485, 486]. It may be prudent to suggest higher folic acid supplementation for overweight or obese women.

Chapter 13

Vitamin B_{12} (cobalamin) in pregnancy and breastfeeding

Vitamin B_{12} functions

Vitamin B_{12} (cobalamin) has multiple functions in human physiology. It is required for the synthesis of fatty acids and myelin, and so is crucial for normal neurological function and maintenance of the CNS. In conjunction with folate, vitamin B_{12} is involved in red blood cell formation and DNA synthesis. In embryogenesis, vitamin B_{12}, like folate, is important for proper neural tube formation and brain development.

The terms cobalamin and vitamin B_{12} refer to a group of cobalt-containing compounds composed of ribose, phosphate, and a base attached to a corrin ring structure. Vitamin B_{12} can be converted to either of two metabolically active cobalamin enzyme cofactors. One of these, methylcobalamin, is a cofactor for methionine synthase, which catalyses the conversion of homocysteine to methionine. The second cofactor is 5-deoxyadenosylcobalamin, which is required by methylmalonyl coenzyme A mutase for the metabolism of odd-chain-length fatty acids and some branched-chain amino acids [487]. Methylcobalamin may serve as a direct methyl donor in the DNA methylase reaction [488]. Because of its role in one-carbon metabolism, vitamin B_{12} interacts metabolically with folate, and these micronutrients are nutritionally interdependent (see 'Interaction with folate').

Three soluble vitamin B_{12}-binding proteins are known to be involved in the uptake and transport of cobalamins in humans: intrinsic factor, transcobalamin, and haptocorrin. Following ingestion, dietary vitamin B_{12} enters the stomach bound to proteins and is released by pepsin and hydrochloric acid to bind to haptocorrin. In the small intestine, haptocorrin is degraded by pancreatic enzymes, and the released vitamin B_{12} is taken up by intrinsic factor. Absorption of vitamin B_{12} occurs via an active process whereby the complexes of B_{12} and intrinsic factor attach to receptors in the ileal mucosa and are internalized. Vitamin B_{12} later enters the circulation bound to transcobalamin I, II, or III. Lack of intrinsic factor results in vitamin B_{12} malabsorption [489].

Indicators of vitamin B_{12} status

Serum cobalamin concentration has limited specificity as a marker of vitamin B_{12} deficiency, as there are other causes of abnormal levels, including pregnancy, folate deficiency, transcobalamin deficiency, and some diseases such as HIV infection and myeloma [490]. Nonetheless, measurement of vitamin B_{12} in blood is the current routine procedure for determining deficiency [491]. The WHO suggests a plasma vitamin B_{12} concentration of <150 pmol/L (203 pg/mL) for defining vitamin B_{12} deficiency [492].

Methylmalonic acid and homocysteine are metabolites that accumulate in serum when vitamin B_{12}-dependent reactions are impaired. Serum levels of methylmalonic acid and homocysteine have been used to establish diagnosis of vitamin B_{12} deficiency. However, these tests are more expensive than ones that rely on the measurement of serum B_{12}, and the results can be affected by poor renal function [493]. Holotranscobalamin is considered the active form of vitamin B_{12}; it is a complex of vitamin B_{12} bound to transcobalamin that is available to cells. Measurement of holotranscobalamin may be more suitable than serum vitamin B_{12} measurement for the diagnosis of vitamin B_{12} deficiency in populations, but to date this test has not achieved wide clinical acceptance [494, 495]. The US National Health and Nutrition Examination Survey reviewed biomarkers for vitamin B_{12} deficiency and concluded that at least one biomarker of circulating concentrations of vitamin B_{12} (vitamin B_{12} itself or holotranscobalamin) and one biomarker of functional vitamin B_{12} status (methylmalonic acid or homocysteine) should be measured to determine subclinical vitamin B_{12} deficiency, as these have shown associations with anaemia and cognitive decline in various studies [496, 497].

Vitamin B_{12} deficiency

Under normal circumstances, dietary vitamin B_{12} is accumulated and stored in the liver. Relative to daily needs, the body stores large amounts of vitamin B_{12}; therefore signs of deficiency appear only after 2–5 years of insufficient intake [498]. Some gastric dysfunctions, such as hypochlorhydria or atrophic gastritis, can cause malabsorption of food-bound vitamin B_{12}, lowering serum levels and eventually resulting in deficiency [499]. Long-term use of drugs that affect gastric acid production (e.g. proton pump inhibitors) can worsen deficiency because gastric acid is needed to release vitamin B_{12} bound to proteins in food. However, such drugs have not been shown to cause deficiency [500]. Vitamin B_{12} levels are reduced among alcoholics [501] and in smokers due to increased excretion [502]. Dietary deficiency is common in vegans and those who have very low meat intakes. This is a particular issue in Asia, where vitamin B_{12} deficiency has a high prevalence.

Interaction with folate

Deficiency for either vitamin B_{12} or folate impairs the production of tetrahydrofolate, preventing DNA synthesis and cell division in blood cells. This disruption of cell division produces the enlarged erythrocytes characteristic of megaloblastic or pernicious anaemia. The megaloblastic process affects all rapidly dividing bone marrow cells and so can also lead to neutropenia and thrombocytopenia [503]. Pernicious anaemia can be caused by a lack of intrinsic factor, triggered by an autoimmune response whereby antibodies attack intrinsic factor-producing parietal cells in the gut. This results in impaired absorption of vitamin B_{12}, and subsequent signs of deficiency.

The haematological consequence of vitamin B_{12} deficiency is indistinguishable from folate deficiency, and the effects can be reversed by treatment with either vitamin B_{12} or folic acid [495]. However, folic acid treatment does not correct the neurological complications of vitamin B_{12} deficiency, which include sensory disturbances in the extremities (tingling and numbness), motor disturbances, and demyelinating degeneration of the spinal cord and peripheral nerves. Cognitive impairment (loss of concentration, memory loss, disorientation, mood changes, and dementia), visual disturbances, insomnia, and impotency, and impaired bladder and bowel control may also occur. Thus, large amounts of folic acid can temporarily mask vitamin B_{12} deficiency by correcting the megaloblastic anaemia, while allowing the neurological disease to progress [504, 505]. This is considered to be the biggest risk associated with high-dose folic acid supplementation (see 'Interaction with folate'].

The interdependence of these two nutrients means that both are ultimately required for proper homocysteine metabolism (see Fig. 12.1 in chapter 12). Even in the presence of adequate folate, a functional folate deficiency can develop if vitamin B_{12} is lacking. This is because once 5,10-methylene-tetrahydrofolate is reduced by methylenetetrahydrofolate reductase to form 5-methyltetrahydrofolate, it requires the vitamin B_{12}-dependent enzyme methionine synthase in order to be recycled to tetrahydrofolate and therefore to participate in DNA biosynthesis and cell division. Thus, in vitamin B_{12} deficiency, cellular folate becomes trapped as 5-methyl-tetrahydrofolate, and the availability of other folate coenzymes is ultimately reduced.

Women with low vitamin B_{12} status in a background of high folate are also at risk for intrauterine growth restriction and having small-for-gestational-age infants, as seen in a study in South India, where many women are supplemented with 5 mg/day of folic acid but are deficient in vitamin B_{12} [506]. Thus, high plasma folate resulting from the enthusiastic promotion of pre- and early pregnancy folic acid supplementation may, in some women, exacerbate the effects of existing vitamin B_{12} deficiency.

Vitamin B_{12} in pregnancy and lactation

Vitamin B_{12} crosses the placenta and is present in breast milk. There is some evidence, mainly from animal studies, that the absorption of vitamin B_{12} may increase during pregnancy, coincident with a lactogen-dependent recruitment of intrinsic factor receptors that allows increased intestinal uptake [507, 508]. Nonetheless, serum total vitamin B_{12} concentrations begin to decline early in the first trimester, to about half of non-pregnancy concentrations by the sixth month of gestation [509]. The decrease is greater than could be accounted for by haemodilution. The decrease does not reflect a tissue depletion of vitamin B_{12} [510].

Fetal and maternal vitamin B_{12} serum concentrations are correlated, in that lower maternal levels are associated with lower fetal levels [511]. Maternal intake during pregnancy is important, as only newly absorbed vitamin B_{12}, and not that acquired from maternal liver stores, is concentrated in the placenta. Vitamin B_{12} is transferred from the placenta to the fetus by active transport against a concentration gradient. During the last two trimesters of pregnancy, it is estimated that 0.1–0.2 μg/day of vitamin B_{12} is transferred to the fetus if the mother's diet is adequate [512, 513]. By the end of pregnancy, the serum vitamin B_{12} concentration of the newborn is approximately twice that of the mother [514].

Deficiency in pregnancy

Vitamin B_{12} status has been considered as a modifiable risk factor for neural tube defects (NTDs) and other adverse pregnancy outcomes, given the close metabolic association between vitamin B_{12} and folate and the importance of vitamin B_{12} status as a determinant of plasma homocysteine. Elevated homocysteine, which can arise from a suboptimal intake of vitamin B_{12}, is associated with pre-eclampsia, preterm birth, low birthweight, and small-for-gestational-age infants [348–350]. Early observations on the relationship between maternal vitamin status and birth defects suggested that the primary cause of some cases of anencephaly (a severe NTD) could be a deficiency of vitamin B_{12}, with accompanying depletion of folate [515]. Low maternal vitamin B_{12} was later reported as an NTD risk factor that is independent of maternal folate status [516].

Low vitamin B_{12} levels, but high vitamin B_{12}-carrier protein levels, were detected in amniotic fluid from pregnancies affected by either NTDs or the abdominal-wall birth defect omphalocele, suggesting abnormal vitamin B_{12} production, transport, or metabolism was associated with these defects [517]. Mothers of infants with spina bifida had vitamin B_{12} levels that were 20 per cent lower than controls in a small case–control study wherein a vitamin B_{12} serum concentration of ≤185 pmol/L (~250 ng/L) conferred a 3.5-fold increased risk of this NTD [518]. Similarly, a population-based case–control study in Canada reported a nearly threefold increase in NTD risk in women with low vitamin B_{12} status, despite folic acid fortification of flour [519]. A study in a population at high risk for NTDs prior to folic acid fortification found a highly significant, dose-dependent correlation between increasing vitamin B_{12} level and decreasing NTD risk [520]. The addition of vitamin B_{12} to prenatal folic acid tablets and to foods fortified with folic acid has been suggested.

Vitamin B_{12} in the neonate

Despite the active transfer during pregnancy, the vitamin B_{12} content in the newborn is low, and the infant is dependent on breast milk for ongoing needs. Lactating women with adequate vitamin B_{12} status are estimated to secrete 0.4 μg/day of vitamin B_{12} in breast milk and therefore require an extra intake of 0.4 μg vitamin B_{12} per day while they are breastfeeding. This is in addition to the recommended dietary allowances (RDAs) for adults of 2.4 μg/day, giving a total RDA of 2.8 μg/day during lactation [269]. Breast milk can have insufficient concentrations of vitamin B_{12} if the mother consumes a strict vegetarian or vegan diet, or in developing countries where the usual consumption of animal products is low. Signs of vitamin B_{12} deficiency develop by 4 to 6 months of age in breastfed infants of mothers consuming strict vegetarian diets [521].

Infants who are exclusively breastfed by women who consume no animal products may have very limited reserves of vitamin B_{12} and can develop vitamin B_{12} deficiency within months of birth. Undetected and untreated vitamin B_{12} deficiency in infants can result in severe and permanent neurological damage [522]. Clinical, biochemical, and metabolic monitoring is required for infants within strict vegetarian families. Vitamin B_{12} deficiency after birth manifests in anaemia, failure to thrive, recurrent infections, and later psychiatric and neurological symptoms [523].

Vitamin B_{12} sources

Most microorganisms (including bacteria and algae) synthesize vitamin B_{12}, which enters the human food chain through animal ingestion. In herbivorous animals, gastric fermentation supports growth of microorganisms that synthesize B_{12}, which is subsequently absorbed and incorporated into animal-origin foods. Animal products including milk/dairy products, meat (especially liver), poultry, fish, and eggs are therefore the primary sources of vitamin B_{12} in the human diet. The vitamin B_{12} intake of individuals consuming strict vegetarian or vegan diets is thus very low, unless fortified foods or supplements are added to the diet.

Foods that are fortified with vitamin B_{12} in some areas include breakfast cereals, soy-based beverages, and vegetarian burgers [269]. Vitamin B_{12} from algae preparations (e.g. spirulina) does not appear to be bioavailable in humans, and should not be considered as a vegan/vegetarian source of the vitamin [524]. Some foods of animal origin, particularly beef and some types of fish, contain amounts of vitamin B_{12} that exceed the RDA in a single serving (see <http://www.dietitians.ca/Nutrition-Resources-A-Z/Factsheets/Vitamins/Food-Sources-of-Vitamin-B12.aspx>). Areas of cobalt deficiency produce animal products that are low in vitamin B_{12} [231]. The most commonly available synthetic form of vitamin B_{12} in supplements is cyanocobalamin.

Risks of excess vitamin B_{12}

According to the US Institute of Medicine (IOM), there is insufficient evidence on which to base the tolerable upper intake level for vitamin B_{12}. Absorption is limited by the binding capacity of intrinsic factor (1.2–2.0 µg vitamin B_{12} per meal), with an additional 1–3 per cent absorbed by passive diffusion. There are no reports of adverse effects from intake of supplements of 1 mg/day. However, there are no established benefits associated with high doses, so these should be avoided in individuals who do not have conditions conferring vitamin B_{12} malabsorption [269].

Agency guidelines for vitamin B_{12} intake

The IOM RDA for vitamin B_{12} is based on the amount needed for the maintenance of haematological status and normal serum vitamin B_{12} values. An assumed absorption of 50 per cent is included in the recommended intake. The RDA for adolescents and adults (≥14 years) is 2.4 µg/day of vitamin B_{12}, which does not change with age (Box 13.1). The estimated average requirement is 2.0 µg/day. The increased demands of the fetus during gestation, and the infant during breastfeeding, mean that an additional 0.2µg/day of vitamin B_{12} is required during pregnancy, and an additional 0.4 µg/day is needed during lactation, such that the RDA for pregnancy is 2.6 µg/day (estimated average requirement, 2.2 µg/day), and the RDA for lactation is 2.8 µg/day (estimated average requirement, 2.4 µg/day) [269].

Box 13.1 US Institute of Medicine recommended dietary allowances for vitamin B_{12}

Infants 0–6 months (adequate intake (AI)) = 0.4 μg/day
Infants 7–12 months (AI) = 0.5 μg/day
Children 1–3 years = 0.9 μg/day
Females 14+ years = 2.4 μg/day
Pregnancy = 2.6 μg/day
Lactation = 2.8 μg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

The recommendation for infants in the first 6 months of life is 0.4 μg/day (~0.05 μg/kg/day), which is based on the adequate intake level (AI) that is obtained from breast milk of well-nourished mothers. For infants aged 7–12 months, AI is 0.5 μg/day (~0.05 μg/kg/day). Children 1–3 years of age have an RDA of 0.9 μg/day (estimated average requirement, 0.7 μg/day). The IOM recommends that infants of vegan mothers be supplemented with vitamin B_{12} at 0.4 μg/day from birth [269].

Vitamin B_{12} deficiency is not common in industrialized countries, except in individuals who do not consume animal-derived foods (particularly vegans) or in those who have conditions affecting vitamin B_{12} absorption. Women and children in developing countries who have limited access to animal food products are considered to be at risk for deficiency [231, 492] and supplementation should be considered, to the level of the RDA for women and the AI for infants. There is little variation from these recommendations across other agencies [143, 492].

Our recommendations for vitamin B_{12} intake during pregnancy and lactation

Maternal intake and absorption of vitamin B_{12} during pregnancy have a more important influence on the vitamin B_{12} status of the infant than do maternal vitamin B_{12} stores. As the vitamin B_{12} concentration in breast milk is also correlated with maternal intake, it is important for pregnant and lactating women to ensure that their diet contains sufficient sources of the vitamin, or supplements should be taken such that intake is 2.4 µg/day during pregnancy, and 2.8 µg/day during lactation. Pregnant women consuming vegan or strict vegetarian diets should either take vitamin B_{12} supplements of this dosage, or seek foods that have been fortified with vitamin B_{12}. Given the interplay of folate and vitamin B_{12}, the status of both should be assessed in parallel, particularly if high doses of folate are considered.

Chapter 14

Choline in pregnancy and breastfeeding

Choline functions

Choline is an essential nutrient, sometimes classified with the B-group vitamins, that is required for the structural integrity of cell membranes and is involved in methyl-group metabolism, neurotransmission, transmembrane signalling, and lipid and cholesterol transport and metabolism. It is a component of the phospholipids phosphatidylcholine and sphingomyelin, which are key building blocks of cell membranes and the myelin sheath, and precursors for the intracellular signalling molecules diacylglycerol and ceramide. Platelet activating factor and shingophosphorylcholine are choline metabolites that also act as cell-signalling molecules. The provision of choline is critical during fetal and neonatal life to ensure optimal brain and cognitive development [525].

Pathways involving choline, folate, and vitamin B_{12} intersect in the formation of methionine from homocysteine (see Fig. 12.1 in chapter 12). Betaine, the primary oxidative product of choline, can act as an alternate methyl donor to 5-methyl-tetrahydofolate in this conversion. Choline becomes a limiting nutrient during folate deficiency [446], and conversely, when choline supply is low, the demand for folate is increased. Folate metabolism is disturbed during choline deficiency, and vice versa [526].

Choline is mainly provided in the diet, although it is also synthesized in the liver in small amounts via the enzyme phosphatidylethanolamine *N*-methyltransferase. The rate of de novo synthesis is not adequate to meet the demands for choline, especially under circumstances of increased need, such as pregnancy and lactation. All tissues accumulate choline by diffusion or by mediated transport, and choline is actively transported across the blood–brain barrier.

Indicators of choline status

Plasma choline concentration is sensitive to changes in dietary choline intake; it can increase twofold after a meal containing high amounts of choline, and three- to fourfold after a supplemental choline dose [269]. Choline concentrations average around 10 μmol/L. Plasma phosphotidylcholine also declines in choline deficiency but is influenced by other factors that affect plasma lipoproteins [527].

Choline deficiency

Food sources of choline are plentiful, and deficiency is unlikely in individuals who consume a variety of foods including eggs, meat, legumes, and cruciferous vegetables [528,529]. However, certain population groups are at risk for choline deficiency, including pregnant and lactating women and infants. Liver damage and fatty infiltration of the liver can result from choline deficiency in an otherwise adequate diet [527,530]. This occurs because a lack of phosphatidylcholine limits the export of excess triglyceride from the liver.

Choline in pregnancy

Choline, as a precursor of membrane phosphatides, is needed for the growth and development of the fetus and is particularly important for the developing brain. The placenta transports choline to the fetus, resulting in a choline concentration in amniotic fluid that is ten times higher than in maternal blood. Plasma concentrations in neonates at birth are much higher than those in adults [525,531]. The placental transport depletes maternal stores, so mothers must consume substantial amounts of choline during pregnancy to ensure an adequate supply to the fetus. Recent studies suggest that choline intake above the current agency recommendations (see 'Agency guidelines for choline intake') may be beneficial to improve placental function [532] and lower circulating cortisol levels in cord blood [533]. Because of altered choline metabolism in pregnancy, intake of 930 mg choline/day was found to elevate plasma betaine concentrations to levels closer to those of non-pregnant women, compared with intakes in the recommended range (480 mg/day) [534].

Choline–folate–homocysteine interactions in pregnancy

There is a positive association between maternal choline and homocysteine levels during pregnancy. Homocysteine is an indirect product of the phosphatidylethanolamine *N*-methyltransferase enzymatic pathway, which synthesizes choline in the liver. The high fetal demand for choline appears to stimulate the de novo synthesis pathway, and this reaction also causes a rise in homocysteine concentrations [535]. Thus, it may be appropriate to advise intake of choline supplements during pregnancy to prevent activation of the de novo pathway and the resulting elevation of homocysteine, which is detrimental to cardiovascular health and has other adverse effects in pregnancy, including increased risks of pre-eclampsia, preterm birth, and low birthweight [536,537].

Choline and neural development

Maternal peri-conceptional deficiency for choline, like folate, is associated with an increased risk of neural tube defects in the offspring [538]. A linear relationship between increasing serum choline concentration and decreasing risk of neural tube defects was found in a recent large prospective study using data from over 180,000 pregnant women [539]. In animal studies, maternal choline supplementation could reverse some but not all of the effects of folate deficiency on brain development [540].

Choline is a precursor of the neurotransmitter acetylcholine and is needed for the formation of cholinergic neurons. Choline availability from 8 weeks gestation through 3 months postpartum modulates the development of the hippocampal cholinergic system over this period [541]. The formation of synapses between these neurons also requires choline; this process occurs at a high rate from fetal life through the fourth year of life [542]. Although in animal studies maternal choline supplementation during pregnancy has been shown to be neuroprotective to the fetus [543], supplementation of pregnant women with 750 mg choline/day in the form of phosphatidylcholine (in addition to dietary choline intake) did not enhance the cognitive development in the offspring (assessed at 10–12 months of age), compared with women who received a placebo [544].

Choline in lactation

During lactation, choline is secreted in relatively large amounts and is concentrated in breast milk. Choline and choline esters in human milk can be derived from the maternal circulation or by de novo synthesis within the mammary gland [545]. The concentration of phosphocholine in human milk is significantly higher than in cow's milk and in infant formulas, but other choline forms, including glycerophosphocholine, phosphotidylcholine, and sphingomyelin, are similar in human milk and cow's milk-derived formulas [546]. The average choline content of human milk is around 116 μmol/L.

Common polymorphisms in the *MTHFR* gene appear to attenuate the response to dietary choline intake and the concentration of choline in breast milk and may explain some of the variation in choline concentrations observed between women with similar dietary intakes [547]. These gene variants also affect folate and vitamin B_{12} status. Further study is required in order to incorporate genotype information into individualized recommendations for intake of these nutrients.

Choline and epigenetic mechanisms

As a methyl donor, choline affects DNA and histone methylation and is therefore involved in epigenetic regulation of gene expression. High choline intake during gestation in animals has been shown to influence the expression of cortical and hippocampal genes involved in learning and memory [548]. Other body systems will also be affected by appropriate maintenance or inappropriate epigenetic modification induced by the presence or absence of dietary methyl donors such as choline [549].

Choline sources

Choline is available in many foods as free choline or in a number of esterified forms including sphingomyelin and phosphatidylcholine. A phosphatidylcholine-enriched fraction produced through commercial purification, termed lecithin, is often added to foods as an emulsifying agent. Free choline is found in highest quantities in beef liver, eggs, peanuts, soybeans, and some vegetables (iceberg lettuce, cauliflower, broccoli). In some countries, eggs enriched with choline through feeding of hens are available. Beef liver and eggs also have a very high content of phosphatidylcholine [528]. The dietary intake of phosphatidylcholine is approximately 6–10 g/day [527].

Agency guidelines for choline intake

Few countries include choline in their nutrient intake recommendations, because the information on intake requirements in humans in sparse. In the US and Canada, the US Institute of Medicine recommends a choline intake (adequate intake (AI)) of 450 mg/day for pregnant women and 550 mg/day for lactating women [269] (Box 14.1). The pregnancy AI represents an increase over the non-pregnant AI (425 mg/day) to cover the needs of both the fetus and the placenta, based on body organ weight estimates. The main criteria for setting the AI is the level necessary to avoid liver damage from choline deficit. The AI for infants aged 0–6 months is 125 mg/day of choline, or approximately 18 mg/kg. For infants aged 7–12 months, the AI is 150 mg/day or ~17 mg/kg. This intake level should be obtainable from breast milk, which is rich in choline in well-nourished mothers.

Box 14.1 US Institute of Medicine recommended adequate intakes for choline

Infants 0–6 months = 125 mg/day
Infants 7–12 months = 150 mg/day
Children 1–3 years = 200 mg/day
Females 14–18 years = 400 mg/day
Females 19+ years = 425 mg/day
Pregnancy = 450 mg/day
Lactation = 550 mg/day
Tolerable upper intake level for 14–18 years = 3.0 g/day; 19+ years = 3.5 g/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin* B_6*, Folate, Vitamin* B_{12}*, Pantothenic Acid, Biotin, and Choline*, Dietary Reference Intakes, National Academy Press, Washington, DC, copyright © 1998. [269]

Our recommendations for choline intake during pregnancy and lactation

We recommend that pregnant women eat a variety of foods and do not restrict fat severely from their diets, as choline is derived from the lipid content of food. Eggs are a good source of choline and should not be restricted. Although liver is also a rich choline source, we do not recommend its excessive consumption during pregnancy because of the potential risk of excess vitamin A intake. Strict vegetarian or vegan diets may be low in choline. The high secretion rate of choline into breast milk means that lactating women have a high demand for this nutrient. Multivitamins containing choline at around the AI levels (450 mg/day) may be helpful for maintaining adequate choline levels in pregnant and lactating women.

Chapter 15

Vitamin D in pregnancy and breastfeeding

Vitamin D functions

Of all the micronutrients considered essential in pregnancy, recommendations regarding vitamin D have been arguably the most controversial, and the requirement for and dosage of vitamin D in pregnancy has undergone substantial recent reconsideration and redefinition. That vitamin D is essential to health is undisputed, but how much is needed, and how it should be acquired (not only for pregnant women, but for the general population), is the subject of both intensive research and some difference of opinion. Vitamin D is a fat-soluble steroid best known for its key role in maintaining bone integrity via the regulation of calcium and phosphorus homeostasis. However, vitamin D influences a number of other extra-skeletal processes, including immune function and blood glucose homeostasis. Additionally, it has been suggested to have anti-proliferative and pro-differentiation actions that may explain its reported beneficial effects on cancer risk [550].

There are two major forms of vitamin D (vitamins D_2 and D_3); the term calciferol refers to both of these forms. Vitamin D_2 (or ergocalciferol) is synthesized by plants, while vitamin D_3 (or cholecalciferol) is produced in humans from an endogenously synthesized cholesterol metabolite (7-dehydrocholesterol) upon exposure of skin to UVB radiation. Vitamins D_2 and D_3 are hydroxylated in the liver to the primary inactive vitamin D storage form, 25-hydroxyvitamin D (25(OH)D; also known as calcidiol) [551]. As the main circulating vitamin D metabolite, the concentration of 25(OH)D in serum reflects total body stores derived from food, supplements, and endogenous cutaneous synthesis and is the generally accepted measure of an individual's overall vitamin D status. Vitamin D metabolism and sources of vitamin D are illustrated in Fig. 15.1.

In response to parathyroid hormone (PTH), 25(OH)D is hydroxylated in the kidney to the active hormonal form, 1,25-dihydroxyl vitamin D (also known as calcitriol) [551]. It is now apparent that 1,25-dihydroxyl vitamin D can also be synthesized in many tissues that express the enzyme 1-alpha-hydroxylase (including the placenta and maternal decidua [552]), dependent

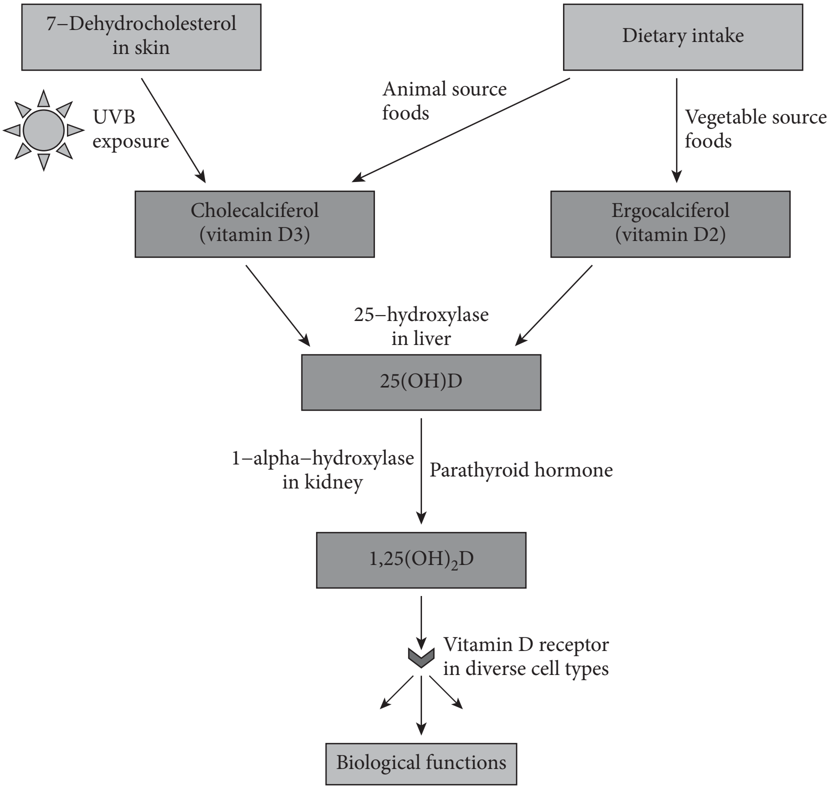
7–Dehydrocholesterol in skin
Dietary intake
UVB exposure
Animal source foods
Vegetable source foods
Cholecalciferol (vitamin D3)
Ergocalciferol (vitamin D2)
25–hydroxylase in liver
25(OH)D
1–alpha–hydroxylase in kidney
Parathyroid hormone
1,25(OH)2D
Vitamin D receptor in diverse cell types
Biological functions

Fig. 15.1 Vitamin D metabolism and sources of vitamin D. Vitamin D can be synthesised in the skin from 7-dehydrocholesterol in response to ultraviolet B (UVB) radiation, or can be ingested from animal and vegetable food sources (e.g. salmon, liver, eggs for cholecalciferol; mushrooms, yeast for ergocalciferol). These inactive forms are hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D) and then in the kidney to the active form, 1,25 dihydroxyvitamin D (1,25(OH)2D).

on the availability of its precursor 25(OH)D [553]. 1,25-Dihydroxyl vitamin D binds to the vitamin D receptor and acts as a transcription factor, its primary target tissues being bone, intestine, and kidney. Vitamin D receptor expression is widespread, however, accounting for the pleiotropic activities of vitamin D. One IU of vitamin D is defined as the activity of 0.025 μg of vitamin D_3, so the biological activity of 1 μg of a vitamin D supplement is 40 IU.

Vitamin D deficiency

The active form of vitamin D promotes intestinal calcium absorption. When vitamin D levels are low, the absorption of calcium and phosphorous becomes less efficient, triggering an increase in the production of PTH. The consequent secondary hyperparathyroidism causes calcium to be resorbed from bone and stimulates increased renal clearance of inorganic phosphate, resulting in lower serum phosphate levels. Severe vitamin D deficiency manifests as rickets in children and osteomalacia in adults.

In addition to skeletal defects associated with low vitamin D and consequent elevated PTH levels, there may also be effects on the nervous system and the immune system, [550] leading to peripheral neuropathy and an impaired response to infection, respectively, and on glucose metabolism and insulin sensitivity [554, 555]. Vitamin D may also have a direct positive effect on insulin sensitivity and beta-cell function, as low levels have been associated with reduced beta-cell response [556]. Low vitamin D intakes in childhood have been associated with increased risk of type 1 diabetes [557]. Other consequences of mild to moderate vitamin D deficiency include possible increased risks of various cancers, infections, autoimmune disorders, asthma, hypertension, and cardiovascular disease [550, 558, 559]. Some of these increased risks are thought have their initial induction in early life and possibly in utero [560, 561].

Definition of vitamin D deficiency

With the development of better assays for the various forms of vitamin D in serum, a number of studies have suggested that subclinical vitamin D deficiency is much more common than previously considered. In turn this has led to a flurry of research and not inconsiderable controversy. No consensus has been reached regarding what level of 25(OH)D renders a person vitamin D replete.

The US Institute of Medicine (IOM), which sets nutrient dietary reference intakes, recently issued new recommendations [562]. These guidelines state that individuals are at risk of vitamin D deficiency when their serum 25(OH)D levels are <30 nmol/L (<12 ng/mL) and that some are at risk with serum 25(OH)D levels between 30 and 50 nmol/L (12–20 ng/mL). The IOM considers that most people are vitamin D replete when their levels are >50 nmol/L, citing concern that treating individuals with serum 25(OH)D levels above this value with high doses of vitamin D might have unknown long-term effects. The IOM recommendations of 25(OH)D reference levels for vitamin D deficiency and insufficiency were based primarily on considering the role of vitamin D in bone health. The IOM deficiency reference threshold is disputed, however, with many experts calling for an upward revision, considering 75 nmol/L (30 ng/mL) as the minimum circulating level needed to maintain bone health [563, 564].

There are a number of factors to consider in relation to optimal circulating 25(OH)D levels. The efficiency of calcium absorption is said to be maximized and serum PTH levels maximally suppressed when 25(OH)D levels reach approximately 80 nmol/L, above which regulation of absorption is no longer limited by vitamin D status [553, 565, 566]. Yet, a meta-analysis of studies of vitamin D supplementation for fracture prevention considering over 83,000 subjects found that fracture risk continued to decline linearly with 25(OH)D levels up to 112 nmol/L (45 ng/mL) [567], far higher than the IOM report's view of a beneficial level.

Some studies of extra-skeletal effects of vitamin D suggest that the threshold for adequacy might be even higher. There have been reports of beneficial effects of vitamin D on reducing cancer risk at serum 25(OH)D levels around 125 nmol/L (50 ng/mL) [568]—effects not seen at levels below 100 nmol/L. However there are concerns about the potential for vitamin D toxicity at very high chronic exposures.

While these analyses are informative, it is important to consider the specific evidence for what vitamin D levels are required to optimize outcomes in pregnancy and in neonates. Evidence is mounting that women should attempt to maintain a level around 75 nmol/L of circulating 25(OH)D to ensure optimal pregnancy outcomes for both themselves and their offspring. The evidence in our view supports a higher (75 nmol/L or 30 ng/mL) rather than a lower (50 nmol/L) cut-off when assessing adequate supplementation.

Vitamin D in pregnancy

The importance of vitamin D for both fetal and childhood skeletal development is well recognized. During gestation, the fetal skeleton accumulates a total of approximately 30g of calcium from maternal stores, most of which crosses from the placenta in the third trimester. The fetal requirement for calcium in late pregnancy is mostly met by an increase in the efficiency of intestinal calcium absorption and enhanced transport across the placenta, rather than by increased maternal calcium intake [569]. This increase in absorption is mediated by maternal 1,25-dihydroxyl vitamin D, which also increases during the third trimester as a result of the enhanced placental metabolism of 25(OH)D [570]. The change in absorption efficiency and calcium transfer to the fetus does not appear to result in a net loss in maternal bone mineral content in well-nourished women [569].

It is, however, well known that maternal vitamin D deficiency leads to poor fetal skeletal mineralization in utero that can manifest as rickets, craniotabes (soft skull bones), and osteopenia in newborns. Deficient maternal serum 25(OH)D levels are associated with classic, severe vitamin D deficiency rickets in the offspring [571]. Beyond classical rickets, several studies have demonstrated impaired bone mass accrual in otherwise healthy newborns associated with maternal vitamin D status <50 nmol/L [572] or <37.5 nmol/L [573].

There has been some reported evidence to suggest that the environment in utero, and in particular the mother's vitamin D status, may have a long-term impact on bone health later in life. Cord blood 25(OH)D levels are closely correlated to maternal levels in late pregnancy and at birth. Studies of the long-term effects of low maternal concentrations of serum 25(OH)D in pregnancy on offspring bone development have thus far produced inconsistent results [574].

In addition to skeletal effects, women with very low vitamin D status face increased risks of other adverse pregnancy outcomes and possible long-term effects on their own health and that of their offspring [575]. These include greater risks of pre-eclampsia and having low-birthweight offspring, as well as possible effects on the development of allergy in offspring [576].

The relationship between serum 25(OH)D concentrations and total intake of vitamin D is non-linear [577]; further, sun exposure confounds the interpretation of dose–response data for vitamin D intake. When determining an optimal dose for an individual, it is important to consider the baseline status, as the increment of 25(OH)D response to an oral dose is inversely related to the starting level [566]. Giving additional amounts to someone who already has enough, or not giving enough to someone whose levels are too low to show a response, will not produce a positive result.

To optimize a supplemental dose of vitamin D, an individual's relative adiposity also needs to be considered. Vitamin D is fat soluble, meaning it is absorbed and sequestered in adipose tissue. As a consequence, serum 25(OH)D levels decrease with increasing BMI, reflecting decreased bioavailability rather than decreased total body stores [578]. Conversely, serum 25(OH)D levels have been shown to rise when obese individuals lose body fat [579, 580].

Obese individuals exhibit lower responses both to UV irradiation in terms of cutaneous vitamin D_3 synthesis, and to oral supplementation with vitamin D_2 [581]. The BMI should therefore be taken into account when estimating the vitamin D intake needed to raise serum 25(OH)D to an appropriate level. A dose 2–3 times higher than that required for normal-weight women may be necessary to maintain a sufficient circulating 25(OH)D level in obese individuals [582]. Interestingly, recent data suggest that even when their vitamin D levels are replete, obese women appear to transfer a lower proportion of vitamin D to their infants during pregnancy than do normal-weight women [583], suggesting they may require an even higher level of circulating 25(OH)D during pregnancy. This may be because fat sequesters vitamin D.

Vitamin D insufficiency in pregnancy

Vitamin D deficiency or insufficiency is now considered to be very common in pregnancy, especially among certain high-risk groups. Some reports indicate that African American women are eight times as likely as Hispanic women, and twenty times as likely as Caucasian women, to have vitamin D deficiency [584–586]. Ethnic groups at risk of vitamin D deficiency include those from the Indian subcontinent, South Asia, the Caribbean, and the Middle East, contributed to by the use of body-covering clothing.

A recent US study indicated that over 50 per cent of pregnant women had 25(OH)D levels below 75 nmol/L and 15 per cent had levels below 50 nmol/L (considered deficient), despite taking standard supplements (400 IU/day) for at least 180 days during their pregnancies [587]. While there may be biases in the study, it appears that for a large proportion of women, supplementing vitamin D intake with 400 IU/day is ineffective at maintaining sufficient levels during pregnancy. We are aware of a number of other as yet incompletely published studies, including some on maternal vitamin D status in Asian and UK populations, which reach not dissimilar estimates of the frequency of deficiency.

Vitamin D insufficiency and pre-eclampsia

While there is some variance in the reported data, the evidence would suggest that inadequate vitamin D status is associated with a moderate increase in the risk of pre-eclampsia. This conclusion is supported by several small case–control studies which have shown a relationship between low serum 25(OH)D levels (<50 nmol/L) and an increased risk of pre-eclampsia [588–590]. While other studies have shown no such association [591–593], there are observational data in support of this association. A recent longitudinal study [594] in ~700 women found that risk of pre-eclampsia correlated with lower vitamin D levels at 24–26 weeks but not at 12–18 weeks gestation, perhaps suggesting that vitamin D may be involved in modulating the peripheral vascular phase of pre-eclampsia. Similarly, in a large cohort analysis in ~23,000 pregnant nulliparous women [595], supplementation with 10–15 μg (400–600 IU) vitamin D/day in the first 22 weeks of gestation was associated with a 25 per cent reduction in the risk for pre-eclampsia.

Vitamin D levels and atopic disorders

It would appear that both low and very high maternal vitamin D levels are associated with risk of atopic disease in the offspring. Such U-shaped relationships are frequently found with micronutrients—with both low and high levels having adverse consequences [596]. A longitudinal study using a UK birth cohort [597] found the risk of infantile eczema to be higher in children whose mothers had been in the top quartile of the 25(OH)D concentration range (>75 nmol/L) during pregnancy, as compared with the bottom quartile. There is evidence from animal studies that vitamin D supplementation is associated with sustained proliferation of allergy-inducing Th2 cells; thus excess vitamin D could lead to an increased prevalence of allergy [598].There was a similar trend for increased risk of asthma at 9 years in the offspring of mothers with the highest 25(OH)D levels. In contrast, other studies have found that low, rather than high, 25(OH)D levels were associated with increased risk of eczema [599] and predisposed children to asthma [559–601] and allergic rhinitis [558].

Vitamin D insufficiency and risk of infection

A link between vitamin D status and infection risk in pregnant women and infants has been suggested. Low 25(OH)D levels (<30 nmol/L) are strongly associated with bacterial vaginosis during pregnancy [602], particularly among HIV-infected women [603]. In infants, low, cord blood levels <25 nmol/L were associated with a greater than twofold increase in risk for respiratory or other infections in the first 3 months of life [601]. A prospective study observed that newborns with cord blood 25(OH)D levels <50 nmol/L had a significantly greater risk of developing respiratory syncytial virus-associated lower respiratory tract infections, as compared with newborns whose cord blood 25(OH)D levels were ≥75 nmol/L.

Vitamin D and glucose regulation/gestational diabetes

Vitamin D deficiency has been linked to impaired glucose metabolism [604], and therefore the impact of vitamin D status on the risk of gestational diabetes mellitus (GDM) has been explored. The data suggest an adverse association between lower vitamin D levels and the risk of GDM [605–607], providing further support for considering closer attention to vitamin D status in pregnancy than has generally been the case. Improving vitamin D status may also be beneficial in women with established GDM. A recent small randomized controlled trial in which women with GDM received two doses of 50,000 IU vitamin D over a 6-week period in pregnancy found improvements in glycemic status and serum total and LDL cholesterol, as compared with women who received placebos [608].

Vitamin D insufficiency in low birthweight, and infant and childhood adiposity

Intrauterine growth restriction and consequent low birthweight can negatively impact neonatal health, with sequelae that may persist into adulthood. Evidence is mixed regarding the impact of maternal vitamin D status on infant birthweight, but the data generally suggest a positive association between vitamin D status and birthweight. A recent large retrospective cohort analysis of >2,100 women reported that low vitamin D status (<37.5 nmol/L) in early pregnancy was associated with a higher risk of small-for-gestational-age offspring, with a positive correlation between maternal vitamin D levels and the weight of offspring at birth [609]. Similarly a study of >4,200 pregnant women showed a significant association between vitamin D deficiency status (<30 nmol/L) in early pregnancy and a greater risk of having low-birthweight infants and a high risk of having small-for-gestational-age infants [610]. In a longitudinal follow-up study of offspring from 977 women in the Southampton Women's Survey cohort, mothers with low vitamin D levels in pregnancy more often gave birth to infants with low fat mass, although at 6 years of age these children had higher fat mass than those who were exposed to adequate vitamin D in utero and had higher fat mass at birth [611].

Vitamin D and fertility

The effect of vitamin D on fertility has not been extensively studied in humans. However, the vitamin D receptor is expressed in ovaries and testes [612, 613]. Data have been inconsistent with regard to the association of vitamin D status with IVF outcome, with some indicating higher 25(OH)D serum levels correlating with increased chance of pregnancy, and others showing an adverse effect of high vitamin D status on embryo quality and IVF success. Similarly, conflicting results have been reported for vitamin D effects on semen quality and sperm count and motility in males [614]. At this point, no specific recommendations can be made with regard to optimal vitamin D status for conception. However, the other considerations given above suggest the importance of ensuring all women of reproductive age have adequate vitamin D status and that the presumption of normality cannot be made without serum testing.

Vitamin D sources

The most potent source of vitamin D is the sun. Vitamin D_3 is produced in relatively large quantities in the skin by photochemical synthesis following exposure to UVB rays in sunlight. Some reports suggest that at tropical latitudes, 30 minutes of skin exposure per day (arms and face) in summer is sufficient to provide the body with all the vitamin D it needs [578, 615, 616]. However, several factors influence the amount of vitamin D that an individual produces. Having dark skin significantly reduces the cutaneous synthesis of vitamin D by reducing UVB penetration; a similar effect results from the use of sunscreens or protective clothing. Individuals living at latitudes that experience fewer daylight hours in winter, spring, and autumn (i.e. north or south of 33°), will not have sufficient UVB exposure to synthesize the required amount of vitamin D. Modern lifestyles and cultural factors reduce UVB exposure further, as a result of clothing styles and cultures, and in general spending more time indoors.

Excessive sunlight exposure does not cause vitamin D toxicity because UVB converts excess vitamin D_3 to biologically inert isomers. However, the dermatology community discourages UVB exposure as a means of maintaining high vitamin D status because of the risk of skin damage and cancer [617]. If an individual follows current advice regarding sun protection, he or she is unlikely to achieve a level of vitamin D that is considered sufficient (if this is taken to be a serum 25(OH)D level above 75 nmol/L) from sun exposure alone. To avoid deficiency, vitamin D must be ingested from dietary sources or supplements.

Dietary sources of vitamin D include oily fish, liver, and egg yolks for vitamin D_3, and yeast and fungi (mushrooms) for vitamin D_2. With the exception of some fish [571], the vitamin D content of unfortified food is low. These natural sources do not generally provide enough vitamin D to render the average individual replete through diet alone, and supplementation is often required.

Because natural food sources do not contain large quantities of vitamin D, some countries have chosen to fortify foods, including milk, cheeses, margarine, breakfast cereals, and orange juice, with vitamin D_2 or vitamin D_3. In the US, milk is fortified with 385 IU/L, and some breakfast cereals and fruit juices are fortified with vitamin D. Infant formula and margarine have statutory vitamin D supplementation in the UK. Individuals with high milk intake in these regions may have relatively high vitamin D intake, but based on a nutrient intake survey [618] the highest intake levels were only 688 IU (17.2 μg)/day for women [71].

Although food fortification is controversial, it seems clear that most people will not exceed the tolerable upper intake level with dietary intake unless they also consume an unusual and very large amount of a particular fish (like Atlantic herring) and/or take excess supplements. Fortified foods can, however, be a useful mode of supplementing intakes of vitamin D. For example, consumption of 1,000 IU/day of vitamin D_3 in 240 mL fortified orange juice was shown to maintain levels >90 nmol/L and was as effective as oral supplement tablets at raising 25(OH)D levels [619].

Vitamin D_3 is more potent than vitamin D_2 [620] and, as a supplement, is more effective in raising serum levels of 25(OH)D [621]. Because vitamin D is fat soluble, supplements are most efficiently absorbed when consumed with foods containing fat. A recent study showed that taking vitamin D supplements with a large meal increases absorption by up to 50 per cent [622].

Vitamin D supplementation

Vitamin D supplementation during pregnancy

Multivitamin supplements (including prenatal vitamins) have traditionally contained 400 IU of vitamin D [623], but this dosage has been increasing in view of the evidence given above. Supplements in a range of dose levels (1,000–5,000 IU vitamin D_3/dose) are now available in the US. A number of randomized trials have been performed to determine the level of vitamin D supplementation required to achieve or maintain adequate vitamin D status in pregnant women, but many of these trials have suffered from methodological problems [624–630].

Overall, women supplemented with vitamin D during pregnancy had significantly higher concentrations of 25(OH)D at the end of pregnancy. Compared with placebo or no intervention, vitamin D supplementation during pregnancy did not have significant effects on length and weight at birth, but children born to women who received vitamin D supplements during pregnancy had a larger head circumference at birth than infants born to women who did not receive supplements (however, given that only two studies reported on this outcome, this result should be interpreted cautiously). It should be noted that even with supplementation, vitamin D sufficiency (defined as 25(OH)D ≥50 nmol/L) was achieved in only 30 per cent of treated women [629].

The results suggest that a daily dose of 800 IU vitamin D_2 may be inadequate during pregnancy. A recent study [585] examined a much higher dose of 4,000 IU/day of vitamin D_3 and showed no safety concerns. This dosage level was considered by the investigators to be the minimal level for suppressing secondary hyperparathyroidism and for optimal intestinal calcium absorption and bone mineral density [631]. The study concluded that 4,000 IU/day starting at 12–16 weeks gestation was most effective in achieving vitamin D 'sufficiency', defined as 25(OH)D ≥80 nmol/L.

Vitamin D and breastfed infants

Maternal vitamin D status is an important factor for the development of rickets in newborns, particularly in breastfed infants [632]. Breast milk typically contains very little vitamin D [571, 633], unless the nursing mother is adequately supplemented or exposed to enough sunlight [634]. The level of maternal vitamin D intake required during pregnancy to ensure adequate vitamin D status in a full-term neonate may not be sufficient to satisfy the ongoing vitamin D needs of fully breastfed infants.

Most cases of rickets occur in babies who are exclusively breastfed, and who themselves are not exposed to sunlight or supplemented with vitamin D [635].

A 25(OH)D concentration below 27.5 nmol/litre (11 ng/mL) is considered to be consistent with vitamin D deficiency in infants and young children [562, 571, 636]. The adequate intake (AI) recommendation of the IOM has been raised from 200 IU to 400 IU/day and is now consistent with recommendations from the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society [562, 637].

Vitamin D supplementation for breastfeeding mothers

In general, studies evaluating the effectiveness of maternal supplementation on the vitamin D status of breast milk suggest that much higher than standard supplementation doses are needed for infants whose only source of vitamin D is breast milk [638]. The data suggest that high doses of vitamin D would be required to substantially increase the 25(OH)D content of breast milk. A supplementation dosage of 6,400 IU/day has been suggested for lactating women if breast milk is to be the source of vitamin D [639]. A study of Caucasian mother–infant pairs in South Africa showed that maternal supplementation with either 500 or 1,000 IU/day was less effective in maintaining infant 25(OH)D levels than supplementing the infants themselves with 400 IU/day [640]. Thus, although supplementing lactating women with high doses of vitamin D is a possible option to increase the vitamin D intake of breastfed infants, it is clear that direct supplementation to infants is more suitable for ensuring optimal vitamin D status.

Vitamin D supplementation for infants

Several studies indicate that a daily vitamin D dose of 400 IU, either as an oral supplement or in formula feed, maintains normal vitamin D status and activity, especially in low-birthweight infants [641, 642] and can prevent rickets in areas of high prevalence [636]. While this level of supplementation increases infant 25(OH)D levels, the effect on bone mineral content or circulating PTH is minimal in breastfed infants who had ‘optimal’ vitamin D status at birth [643]. It is clear that the effect of supplementation to infants is dependent on their initial vitamin D status, with a more pronounced effect seen in infants who have deficient or insufficient 25(OH)D levels at birth [644, 645]. Thus, low-birthweight and/or premature neonates may receive equal benefit from lower doses of ~200 IU/day [642, 646].

Risks of excess vitamin D

Part of the controversy surrounding vitamin D supplementation and fortification of food is the perceived possibility of toxicity. However, the risk of toxicity of oral vitamin D supplementation of 1,000–4,000 IU per day is negligible.

Excess vitamin D increases calcium absorption in the intestine, resulting in high blood calcium levels. This can lead to calcium deposits in soft tissues such as the heart and lungs, confusion and disorientation, kidney stones and kidney damage, nausea, vomiting, constipation, poor appetite, weakness, and weight loss.

The physiological limit for serum 25(OH)D concentrations in humans appears to be approximately 220 nmol/L (88 ng/mL) because this approximates the top of the range of values reported for humans who are well exposed to UV light [647]. Indigenous populations in East Africa have been found to have average serum 25(OH)D levels around 115 nmol/L, and levels of 150 nmol/L are normal during pregnancy [648]. The lowest 25(OH)D concentration causing toxic effects appears to be greater than 500 nmol/L (200 ng/mL) [649]

Agency guidelines for vitamin D intake

There are diverse expert recommendations regarding vitamin D supplementation of pregnant women, with a median of 400 IU (10 μg)/day [267]. The National Institute for Health and Clinical Excellence (NICE) in the UK recommends that pregnant and lactating women take a vitamin D supplement of 400 IU daily and that health professionals inform all pregnant women about the importance of this for their health and the future health of their baby. The recent IOM guidelines define the recommended dietary allowance (RDA) for vitamin D for pregnant women to be 600 IU (15 μg)/day [562]. The RDA is an intake that is intended to cover the requirements of most pregnant women (97–98%) and was set based on a target 25(OH)D level of 50 nmol/L (Box 15.1). These intakes represent an increase from the previous recommendation for an AI of 200 IU/day [571] but this recommendation still appears to many to be

Box 15.1 US Institute of Medicine recommended dietary allowances for vitamin D

Infants 0–12 months (adequate intake) = 10 μg/day (400 IU)
Children 1–3 years = 15 μg/day (600 IU)
Females 14+ years = 15 μg/day (600 IU)
Pregnancy = 15 μg/day (600 IU)
Lactation = 15 μg/day (600 IU)
Tolerable upper intake level (including pregnancy and lactation) = 100 μg/day (4,000 IU)

Source: Institute of Medicine, *Dietary Reference Intakes for Calcium and Vitamin D*, National Academy Press, Washington, DC, copyright © 2012. [562]

unduly conservative. The Endocrine Society suggests that pregnant and lactating women require a vitamin D intake of at least 600 IU/day, although they also propose that to maintain a 25(OH)D serum level above 50 nmol/L, an intake of 1,500–2,000 IU/day may be required [582].

The IOM also increased the tolerable upper intake level to 4,000 IU (100 μg/day), indicating what the board views as the highest average intake that is likely to pose no risk of adverse effects. It has also been argued that supplementation with 4,000 IU per day of vitamin D in adults is comparable to the amount of vitamin D acquired through natural sun exposure and thus should be regarded as a physiological intake [553]. A recent randomized control trial found that women receiving 4,000 IU/day achieved an average serum 25(OH)D level of 111 nmol/L [585].

The Endocrine Society recommends screening for vitamin D deficiency in individuals at risk for deficiency [582], with pregnant and lactating women being included as a risk group. The American Congress of Obstetricians and Gynecologists (ACOG) suggests that women with other risk factors, particularly those with medical conditions such as chronic kidney disease, hepatic failure, malabsorption syndromes (e.g. inflammatory bowel disease), and granulomatous disorders (e.g. sarcoidosis, tuberculosis, and histoplasmosis) should be screened, as well as dark-skinned individuals, those with veiled/covered modes of dress, or those living at latitudes above or below 33° [650]. In the UK, the NICE guidelines for antenatal care were updated in 2008 to incorporate an additional recommendation on informing women of the importance of maintaining adequate vitamin D stores in pregnancy, particularly for those at greatest risk of vitamin D deficiency (women of South Asian, African, Caribbean or Middle Eastern family origin, women who have limited exposure to sunlight, women who eat a diet particularly low in vitamin D, and women with a pre-pregnancy BMI above 30 kg/m^2). The recommendation is to take a multivitamin supplement containing 400 IU (10 μg)/day, and physicians are advised to carefully monitor women at greatest risk to ensure that they are taking the recommended supplements [651].

In contrast to these recommendations, a 2012 WHO guideline document does not recommend supplementation in pregnancy except in cases of documented vitamin D deficiency, when supplements of 200 IU (5 μg)/day (the WHO/FAO reference nutrient intake level) are advised [652]. The recommendation cited a lack of quality evidence from interventional studies for either the efficacy or safety of vitamin D supplementation of pregnant women for various outcomes, including pre-eclampsia and low birthweight. For lactating women, the recent IOM report does not propose an increase over the 600 IU/day recommendation for pregnancy but recommends an intake of 400 IU/day for infants [562]. The Endocrine Society suggests that lactating women should, at minimum, take a multivitamin containing 400 IU of vitamin D along with an additional vitamin D supplement of ≥ 1,000 IU daily [582].

Both the IOM and the AAP recommend supplementation of infants rather than relying on provision of adequate vitamin D through breast milk. The AAP recommends that infants <6 months should be kept out of direct sunlight [653] and therefore considers that all breastfed infants require supplementation, as well as formula- or mixed-fed infants consuming less than 1 L/day of infant formula. The 400 IU/day recommendation originated because this is the approximate amount of vitamin D found in a teaspoon of cod liver oil, which is known to both prevent and treat rickets. In a 1987 statement from the European Society of Paediatric Gastroenterology and Nutrition a vitamin D dosage of 800 to 1,600 IU/day, more than double the AAP/IOM level, was recommended for infants [654]. This recommendation does not appear to have been updated.

Bolus supplementation of 50,000 IU is recommended by some Australian health care providers for infants born to vitamin D deficient mothers (defined as 25(OH)D levels <75 nmol/L) [655]. This would appear to be extreme considering both their definition of deficiency and the high suggested dose. We will not further discuss treatment of severe vitamin D deficiency, but note that a position statement for Australia and New Zealand recommends 150,000 IU bolus vitamin D_2 to be given to infants <1 month of age for treatment of 'moderate to severe' vitamin D deficiency (<25 nmol/L) [656].

Our recommendations for vitamin D intake during pregnancy and lactation

Despite observational evidence that maintaining high vitamin D status (25(OH)D) >75 nmol/L) in pregnant women is desirable, the current data do not support the claim that high-dose vitamin D supplementation is necessary for all pregnant women. However, intakes of between 1,000 and 2,000 IU/day, which are in line with the Endocrine Society and ACOG recommendations, are likely to be beneficial and not harmful. Physicians should consider monitoring the vitamin D status (by measuring the 25(OH)D levels) of their pregnant patients, particularly those at risk for deficiency, including women who are dark-skinned or veiled, those who avoid the sun or regularly use sunscreens and/or protective clothing, live at high or low latitudes, eat vegan or vegetarian diets, or are obese. Women taking medications or having disorders affecting calcium and vitamin D metabolism should routinely be screened.

At a minimum, all pregnant women should take a supplement of 400 IU/day, in addition to maintaining sensible sun exposure and increasing their intake of oily fish during pregnancy, both of which will have other benefits for their own health as well as for that of their babies. However, our view is that all women should have their vitamin D status evaluated before or during pregnancy and supplemented in an individualized fashion. In general, the aim should be to maintain serum vitamin D levels between 75 and 110 nmol/L. In the absence of measurements, the data would suggest that pregnant women should receive dietary and supplementary vitamin D on the order of 1,000 to 2,000 IU/day. Fully breastfed infants should receive supplementation (400 IU/day) beginning shortly after birth.

Chapter 16

Vitamin K in pregnancy and breastfeeding

Vitamin K functions

Vitamin K is a fat-soluble micronutrient that is essential for the functioning of several proteins involved in blood clotting. The pro-coagulation proteins, factors II (prothrombin), VII, IX, and X, as well as the anticoagulation proteins C and S, are all activated by vitamin K-dependent gamma-carboxylation of specific glutamic acid residues, forming gamma-carboxyglutamate (Gla) residues. This post-translational modification confers affinity for calcium, which is required for the function of these vitamin K-dependent proteins [657, 658]. If sufficient vitamin K is not available for carboxylation, proteins lacking Gla residues are produced. These under-carboxylated (or descarboxy) proteins have reduced or no activity. After the formation of coagulation factors, the reaction product vitamin K epoxide is enzymatically converted back to active vitamin K by the enzyme vitamin K epoxide reductase [659]. Thus, a lack of vitamin K leads results in a hypocoagulable state, associated with a high risk of bleeding events. Poor vitamin K status is also associated with an increased risk of osteoporotic bone fractures [660]. Other vitamin K-dependent proteins, including activated osteocalcin and matrix Gla protein, have roles in bone and other tissues.

Indicators of vitamin K status

Functional bleeding time assays such as prothrombin time are not considered to be sensitive for detecting subclinical vitamin K deficiency, since the prothrombin time can be in the normal range even when the prothrombin concentration is 50 per cent of normal [661]. Direct measurements of vitamin K_1 (phylloquinone) in plasma, or of urinary Gla excretion, which reflects turnover of vitamin K-dependent proteins, have been considered as markers of vitamin K status [661]. However, the presence of under-carboxylated species of vitamin K-dependent proteins in blood is a more sensitive indicator of deficiency. The most commonly used of these markers is an under-carboxylated form of prothrombin known as protein induced by vitamin K absence or antagonist-II

(PIVKA-II). PIVKA-II assays can detect subclinical vitamin K deficiency before standard coagulation markers are altered or haemorrhage occurs [662]. PIVKA-II is also present in patients using warfarin for anticoagulation. The assessment of the degree of under-carboxylation of osteocalcin correlates well with PIVKA-II and plasma vitamin K_1 concentrations [661]. Osteocalcin appears to be the first Gla protein to appear in under-carboxylated form as intake of vitamin K decreases and thus may be the most sensitive marker of vitamin K status [660].

Vitamin K deficiency

Vitamin K deficiency results in impaired blood clotting. Deficiency is rare among adults, because vitamin K is widely available in foods and is conserved via recycling by vitamin K epoxide reductase. It is also produced by intestinal anaerobic bacteria [663]; thus, long-term treatment with antibiotics can lead to vitamin K deficiency and hypoprothrombinaemia, due to the elimination of such vitamin K-producing intestinal microflora [664].

Vitamin K in pregnancy and lactation

The placenta transmits lipids and vitamin K relatively poorly, leading to a general vitamin K deficiency in full-term neonates. The concentrations of vitamin K_1 in cord blood are typically too low to be accurately measured and are usually between 20- and 40-fold lower than in maternal blood. This apparent barrier to placental transfer is relatively unresponsive to maternal vitamin K supplementation [665].

The neonatal liver has immature prothrombin synthesis, rendering the newborn particularly vulnerable to the effects of low vitamin K levels. Deficiency can lead to intracranial haemorrhage following birth trauma, or classic vitamin K deficiency bleeding (also known as haemorrhagic disease of the newborn), which manifests as unexpected bleeding in the first week of life. Vitamin K deficiency may be exacerbated by prematurity, intrauterine growth restriction, or traumatic delivery [666].

Breastfeeding has been considered a ‘risk factor’ for vitamin K deficiency, because the short half-life of vitamin K means the levels in newborns can drop rapidly, as the vitamin K content of human milk is minimal (2.5 μg/L) compared with that in cow’s milk (5,000 μg/L). Infant formulas are supplemented with vitamin K, and formula-fed infants have substantially higher vitamin K status than do breastfed infants. In addition, maternal use of anticonvulsant therapy during pregnancy significantly increases the risk of vitamin K deficiency in infants [667]. Such deficiency could be prevented by supplementation with 10 mg/day of vitamin K by pregnant women on anticonvulsants from 36 weeks onward [668].

The risk of neonatal vitamin K deficiency is also increased if the mother has taken coumarin anticoagulants. Coumarin derivatives are vitamin K antagonists that are known to act as teratogens, increasing the risk of CNS defects caused by microhaemorrhages in neuronal tissues. The abnormalities are known as warfarin embryopathy, or fetal warfarin syndrome [669]. A more recent study compared the pregnancy outcomes of 666 women exposed to coumarin anticoagulants with a control group of 1,094 unexposed pregnant women and confirmed a significantly increased risk of major birth defects with exposure in the first trimester. Prenatal exposure was also related to higher rates of miscarriage, preterm birth, and low birthweight [670]. In the absence of prophylactic vitamin K administration, the prevalence of vitamin K deficiency bleeding is up to tenfold higher in South East Asia than in Europe [666].

Vitamin K sources and metabolism

Vitamin K derived from the diet is in the form of vitamin K_1. Vitamin K_2 (menaquinone) is synthesized by bacteria in the intestinal tract. The main dietary sources of vitamin K_1 are green leafy vegetables, such as kale, spinach, turnip greens, collards, Swiss chard, mustard greens, parsley, romaine, and green leaf lettuce. These sources contain >200 µg vitamin K_1 per 100 g (turnip greens contain as much as 650 µg/100 g). Soybean oil and canola oil are rich sources, containing >100 µg/100 g. Other vegetable sources are Brussels sprouts, broccoli, cauliflower, and cabbage. Fish, liver, meat, eggs, and cereals contain smaller amounts. Green tea contains >700 µg/100g, but black tea does not contain vitamin K. High concentrations of vitamin K_2 are found in yogurt, cheese, and butter, and fermented soybeans [671].

Dietary vitamin K is absorbed in the small bowel following the typical pathway of dietary lipids and is incorporated into chylomicrons for release into the lymphatic system and circulation [672]. The efficiency of absorption has been reported as 40–80 per cent [673]. Dietary fat enhances the absorption of vitamin K_1 from food, such that absorption of the vitamin from vegetable oil is significantly higher than from vegetables themselves. Consumption of spinach with butter can increase the availability of vitamin K_1 threefold [674]. The bioavailability of vitamin K_2 is higher than that of vitamin K_1 [675].

Vitamin K has a short half-life. Vitamin K_1, the most abundant dietary form, is poorly retained in the body. There is also a wide variation in response to vitamin K from the diet. Some of this variation is accounted for by polymorphisms in the apolipoprotein E gene, which is involved in lipoprotein transport of vitamin K_1, and uptake into liver and bone [676].

Risks of excess vitamin K

Natural vitamin K_1 taken orally is not toxic, even in large amounts. Because of a lack of reported adverse effects of high intake of vitamin K, no tolerable upper intake level has been set [260]. Synthetic vitamin K_3 (menadione) can be toxic in large doses and is generally not available in supplement form. Vitamin K from food sources is not toxic.

Agency guidelines for vitamin K intake

There are insufficient data available to determine recommended dietary allowances for vitamin K, so daily adequate intake (AI) recommendations are used instead. These are set based on the average intakes of healthy individuals [260]. The AI for infants 0–6 months is 2 μg/day. Infants 6–12 months require 2.5 μg/day, increasing to 30 μg/day for children 1–3 years of age (Box 16.1). There is no recommended increase in the AI for pregnancy and lactation. Adolescents 14–18 years, including those who are pregnant or breastfeeding, should consume 75 μg/day; women over 19 years should consume 90 μg/day. For men over 19 years, the AI is 120 μg/day [260].

The American Academy of Pediatrics recommends that all breastfed infants should receive 1.0 mg of vitamin K oxide intramuscularly after the first feeding is completed and within the first 6 hours of life [677]. Oral vitamin K is not recommended as sufficient. It may not provide the adequate stores of vitamin K necessary to prevent haemorrhage later in infancy in breastfed infants unless repeated doses are administered during the first 4 months of life [678].

Box 16.1 US Institute of Medicine recommended dietary allowances for vitamin K

Infants 0–6 months (adequate intake (AI)) = 2.0 μg/day
Infants 7–12 months (AI) = 2.5 μg/day
Children 1–3 years = 30 μg/day
Females 14–18 years = 75 μg/day
Females 19+ years = 90 μg/day
Pregnancy and lactation 14–18 years = 75 μg/day
Pregnancy and lactation 19+ years = 90 μg/day

Source: Institute of Medicine, *Food and Nutrition Board, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, And Zinc*, The National Academies Press, Washington DC, copyright© 2011. [260]

Our recommendations for vitamin K intake during pregnancy and lactation

It is important to maintain adequate vitamin K status throughout pregnancy in order to avoid added risk to the neonate at birth and in the first few weeks of life. Green leafy vegetables should be eaten with some dietary fats (e.g. vegetable oil, butter) during pregnancy to maintain or increase vitamin K stores. Supplementation of newborns by intramuscular injection should be universal.

Chapter 17

Vitamins C and E and other antioxidants in pregnancy and breastfeeding

Antioxidant functions

Normal metabolism produces oxidizing free radicals that can damage cellular components such as polyunsaturated fatty acids (PUFAs), proteins, and DNA. Free radicals generated by environmental pollutants (e.g. cigarette smoke, emissions) and photo-oxidants (UV and gamma irradiation, ozone) have the same effect. A complex antioxidant defence system normally protects cells from the destructive effects of free radicals, particularly reactive oxygen species (ROS), but the balance can be critical [679]. In pregnancy and other health states involving high or altered metabolic demands, endogenous antioxidants may provide insufficient protection from the persistent and inevitable challenge by ROS, leading to oxidative stress. Hence, dietary antioxidants have an important role in maintaining human health.

The most prominent representatives of dietary antioxidants are vitamin C, vitamin E, carotenoids, and polyphenols (flavonoids). Vitamin C enhances the endogenous synthesis of glutathione, a powerful antioxidant that is also present in fresh fruits and vegetables [680]. Zinc, selenium, and manganese also have antioxidant properties [681–683], as they are required for the function of endogenous antioxidant enzymes, including selenium-dependent glutathione peroxidases (for which glutathione is a substrate), thioredoxin reductases, selenoprotein-P, and copper/zinc and manganese superoxide dismutases. These trace elements are discussed in chapters 23, 25, and 26.

Antioxidants in pregnancy

The state of pregnancy can be considered one of oxidative stress, wherein high metabolic demands are accompanied by heightened oxygen requirements in tissues [684, 685]. The placenta contains endogenous antioxidant enzymes that control lipid peroxidation to some extent in normal pregnancies, but because of its high PUFA content, it is also a source of reactive lipid peroxides [686]. Several metabolic disturbances that can complicate pregnancy (in particular, placental disorders such as pre-eclampsia, but also gestational diabetes and hypertension) are characterized by enhanced oxidative stress. Antioxidant activity is attenuated in pre-eclamptic pregnancies [687, 688], and increased ROS activity has been observed in association with pregnancy-induced hypertension [689]. Plasma levels of some dietary antioxidant nutrients are also reduced in women with pre-eclampsia, possibly because these nutrients are utilized to a greater extent in such pregnancies to offset ROS-mediated disturbances, resulting in lower observed plasma antioxidant levels [690]. Interestingly, one study found that higher plasma vitamin E levels correlated with an increased rather than decreased risk of pre-eclampsia [691].

Oxidative stress and diabetes in pregnancy

Pregnant women with type 1 diabetes are at increased risk for pre-eclampsia and low antioxidant status. Diabetes in pregnancy is also associated with an increased risk of congenital malformations, and the involvement of ROS has been suggested in this teratogenicity [692]. Hyperglycaemia in pregnancy is linked to a deficit in the detoxification of reactive carbonyl compounds derived from oxidative reactions. This causes chemical modification of proteins and results in an accumulation of advanced glycation end products [693]. The binding of these proteins to cell surface receptors induces an intracellular oxidative stress response, leading to lipid peroxidation and tissue damage [694]. Animal studies suggest that fetal exposure to high glucose or a diabetic in utero environment causes enhanced ROS production and lipid peroxidation and that maternal treatment with antioxidants can prevent ROS-mediated damage [695]. In humans, however, supplementation with vitamins C and E has not been shown to reduce the complications of diabetes in pregnancy, except in women with very low antioxidant status [696].

Oxidative stress and fetal growth restriction

Disruption of fetal growth is a hallmark of maternal exposure to ROS during pregnancy, possibly caused by vasoconstriction and diminished placental blood flow [697]. Markers of oxidative stress have been observed early in pregnancies that were later affected by fetal growth restriction or that resulted in small-for-gestational-age births [698]. These markers may reflect early placental changes that affect fetal growth. Oxidative damage to DNA occurs in pregnancy as a result of low dietary antioxidant status in the face of rapid fetal growth and metabolic demands and is associated with increased risk of poor pregnancy outcome [697].

Oxidative stress and the fetal immune system

Oxidative stress has additional deleterious effects on the immune system. Inadequate intake of dietary antioxidants is believed to contribute to T-cell differentiation favouring the T-helper cell type 2 (Th2) phenotype, which is predominant in allergic disorders [699]. Various animal models support the hypothesis that maternal antioxidant status is linked to the risk of allergic disorders and asthma in offspring; however, data in human pregnancy is limited and inconsistent. The 'Westernization' of Asian diets is thought to be reducing the overall intake of antioxidants, thereby increasing the susceptibility to oxidative damage and airway inflammation and thus increasing the prevalence of asthma among Asian populations. In a recent Japanese study, low maternal intakes of foods rich in antioxidants during pregnancy, including green and yellow vegetables and citrus fruit, were associated with an increased risk of infant and childhood eczema [700]. Although dietary changes may be effective, other recent data have not supported a role for antioxidant supplementation in pregnancy to reduce the risk of asthma, rhinitis, and eczema in the offspring [701].

Dietary antioxidants

Antioxidants occur naturally in diets that are rich in fruits and vegetables, which are sources of the antioxidant vitamins C and E as well as carotenoids and polyphenols (mainly flavonoids). The antioxidant capacity of such natural compounds in foods is considered a key factor in the negative correlation between a fruit- and vegetable-rich diet and chronic illnesses, potentially through their ability to supplement cellular defence systems. A significant positive correlation exists between saturated fat intake, or diets rich in fats and poor in fruits and vegetables, and excretion of markers of oxidative stress [697].

Polyphenols (flavonoids)

Polyphenols, a group of compounds that exhibit antioxidant activity, are abundant in the human diet. The two major types of polyphenols are flavonoids and phenolic acids. Flavonoids are widely available in fruits and vegetables, legumes, tea, and red wine. Phenolic acids are also present in fruits and vegetables and are abundant in chocolate and coffee. The total dietary intake of polyphenols is much higher than the intake of vitamin C, even though their concentration in the body is lower. Although the multiple ROS-scavenging properties of flavonoids have been demonstrated in vitro [702, 703], dietary flavonoids are poorly absorbed and are functionally altered in vivo. Contrary to popular belief, there is currently little evidence that flavonoids have significant antioxidant effects in the human body [704, 705]. In fact, it is appearing equally likely that polyphenols also act as pro-oxidants [706].

There is no evidence in the scientific literature of antioxidant benefit of consumption of polyphenols during pregnancy. Animal studies suggest that high maternal intake of polyphenol-containing foods (e.g. chocolate) may negatively affect fetal bone mineralization and angiogenesis [707]. There is also some evidence of fetal ductus arteriousus constriction resulting from maternal consumption of polyphenol-rich foods, including herbal teas in late pregnancy [708, 709], which was reversible upon restriction of intake [710]. Cautionary advice regarding consumption of herbal teas can be found in chapter 30.

Carotenoids

Carotenoids are natural pigments that are synthesized by plants and are responsible for the red, orange, and yellow colours of fruits, flowers, and leaves. Some animals including birds, fish, crustaceans, and insects utilize carotenoids from their diets for their colour [711]. The most common carotenoid is beta-carotene, a precursor to vitamin A.

Carotenoids function as antioxidants, although this function is redundant and can be compensated by other antioxidant mechanisms [712]. Because of their lipid solubility and ability to scavenge singlet molecular oxygen and peroxyl radicals, carotenoids are thought to help maintain the integrity of lipid membranes. Like polyphenols, however, it has also been suggested that carotenoids, when supplemented in large amounts, can act as pro-oxidants [713]. When beta-carotene is present in excess, it loses its ability to protect against DNA damage and may even contribute to its cause [714–716]. Plasma levels or dietary intake of carotenoids have been assessed in pregnant women, along with other dietary antioxidants, in relation to pre-eclampsia and gestational hypertension, although results are somewhat inconsistent [691, 717]. The current evidence does not suggest that supplementation with carotenoids such as beta-carotene is beneficial in reducing the risk of pre-eclampsia or other pregnancy complications induced by oxidative stress.

Vitamins C and E

Vitamins C and E are powerful non-enzymatic antioxidants that are essential for optimal performance of antioxidant defences, and adequate intake of these vitamins is important in pregnancy. Because various disorders of pregnancy are characterized by a reduction in antioxidant activity, it has been hypothesized that maternal supplementation with antioxidants, particularly vitamins C and E, may be beneficial in preventing their occurrence. However, the balance of evidence indicates that supplementation with these vitamins does not reduce the rate of adverse maternal or perinatal outcomes related to oxidative stress, and taking high doses in pregnancy is not recommended.

Vitamin C

Vitamin C (ascorbic acid) is an essential water-soluble antioxidant vitamin that is required for normal metabolic functioning. Vitamin C scavenges reactive oxidants in activated leukocytes, lung, and gastric mucosa and protects against lipid peroxidation. It is a cofactor for hydroxylase and oxygenase metalloenzymes involved in the biosynthesis of collagen, carnitine, hormones, and amino acids. In the diet, vitamin C promotes absorption of non-haem iron from foods. Adequate levels of vitamin C are important for immune function and vasodilation and may play a role in the prevention of cancer and cardiovascular disease. Severe vitamin C deficiency results in the life-threatening disease scurvy [718].

The brain maintains one of the highest vitamin C concentrations in the body, suggesting an important function. In animals (guinea pigs), vitamin C has been shown to play a role in the regulation of neuronal development, and in particular, the development of the hippocampus. Maternal vitamin C deficiency results in a reduction in postnatal hippocampal volume, irrespective of vitamin C repletion in the neonate immediately after birth. This reduction is associated with diminished spatial memory ability [719].

Ascorbic acid occurs naturally in plants and most animals but is considered as a vitamin in humans because of our inability to synthesize it. This is the result of a mutation in the gene encoding L-gulono-gamma-lactone oxidase, an enzyme needed for vitamin C synthesis. Loss of activity of this enzyme was not deleterious in our ancestors, whose diets were replete in vitamin C and other antioxidants [8]. Attention to dietary vitamin C intake is therefore essential to human health and protection against oxidative damage-mediated diseases, including those brought on by the demands of pregnancy and lactation.

Requirements in pregnancy and lactation

Vitamin C deficiency in pregnancy is implicated in increased risk of infections and complications, including pre-eclampsia, premature rupture of membranes (PROM), and preterm birth [720]. However, supplementation with vitamin C has not been shown to reduce the incidence of these disorders (see ‘Supplementation trials of vitamins C and E in pregnancy’). Maternal plasma vitamin C concentration decreases over the course of pregnancy as a result of active transfer to the fetus, as well as haemodilution. As long as there are appreciable amounts of ascorbic acid in the maternal circulation, the fetus accumulates the nutrient to meet its needs, regardless of maternal requirements. To compensate for this, the calculated increased requirement for pregnancy is 10–15 mg/day higher than for non-pregnant women [718].

Breast milk supplies large quantities of vitamin C to the growing infant. In women not taking supplements, the content of vitamin C in milk is reported to vary between ~30 and 80 mg/L. With supplementation of between 45 to >1,000 mg/day, the content can be from 45 mg/L to 115 mg/L [721]. Infantile scurvy, which is characterized by haemorrhage around connective tissue and bone, impaired bone development, listlessness, loss of appetite, and weight loss, has not been observed in breastfed infants even when maternal vitamin C intake is low. However, formula-fed infants can develop infantile scurvy if the formula is lacking in vitamin C [718]. To compensate for the excretion of vitamin C into breast milk, lactating women require an additional 35 mg/day above the pregnancy requirement [718]. Consuming high doses of supplemental vitamin C does not result in higher vitamin C concentrations in breast milk; maternal vitamin C intake in excess of 200 mg/day resulted in increased urinary excretion of vitamin C but did not increase the breast milk content of the vitamin [721]. After weaning, the vitamin C intake of infants declines significantly—this is reflected in the US Institute of Medicine (IOM) adequate intake recommendations for older infants.

Sources and metabolism of vitamin C

Vitamin C is available in many fruits and vegetables. Major dietary sources of vitamin C include citrus fruits, bell peppers (capsicum), green beans, strawberries, papaya, guava, kiwi fruit, potatoes, broccoli, and tomatoes. Intestinal absorption of vitamin C occurs by a saturable and dose-dependent process, such that very high intakes from supplements are not absorbed. Ascorbic acid is absorbed and efficiently metabolized at doses up to 80 mg/day, but at higher doses the renal excretion of unmetabolized ascorbic acid increases proportionately with increasing dose. At very high doses, unabsorbed ascorbic acid is degraded in the intestine, which may account for the intestinal discomfort that sometimes accompanies ingestion of large doses [722].

Risks of excess vitamin C

The most common adverse effects associated with intake of high doses of vitamin C are gastrointestinal disturbances. Although not a common concern in pregnancy, excess vitamin C may be harmful in the presence of pathological iron overload (haemochromatosis), as it increases the mobilization of iron from the spleen and its deposition in liver, enhancing the deleterious effects of excess iron [723]. High-dose vitamin C supplementation in pregnancy may be associated with poorer pregnancy outcomes (see 'Supplementation trials of vitamins

C and E in pregnancy'). The IOM has set an upper tolerable intake level of 2,000 mg/day for pregnancy and lactation in women aged 19 years and older, and 1,800 mg/day for those aged 14–18 years.

Agency guidelines—vitamin C

The IOM recommended intakes for vitamin C are based primarily on prevention of deficiency and not chronic disease prevention or optimal health promotion. For pregnant women aged 19 years and older, the recommended dietary allowance (RDA) is 85 mg/day (80 mg/day for pregnant women under 19 years of age) [718] (see Box 17.1).

Cigarette smoke affects vitamin C metabolism, decreasing its availability in the circulation in a manner that is independent of dietary vitamin C intake. According to an analysis of data from the second US National Health and Nutrition Examination Survey, smokers have a threefold increased risk of marginally or severely deficient vitamin C status, and approximately 130 mg of additional dietary vitamin C per day would be required to overcome the adverse effect of cigarette smoking on vitamin C levels [724]. Smoking should be avoided in pregnancy; however, in individuals who smoke, the RDA is increased by 35 mg/day to account for the increased oxidative stress caused by toxins in cigarette smoke [718].

Box 17.1 US Institute of Medicine recommended dietary allowances for vitamin C

Infants 0–6 months (adequate intake (AI)) = 40 mg/day
Infants 7–12 months (AI) = 50 mg/day
Children 1–3 years = 15 mg/day
Females 14–18 years = 65 mg/day
Females 19+ years = 75 mg/day
Pregnancy 14–18 years = 80 mg/day
Pregnancy 19+ years = 85 mg/day
Lactation 14–18 years = 115 mg/day
Lactation 19+ years = 120 mg/day
Tolerable upper intake level (including pregnancy and lactation)
14–18 years = 1,800 mg/day
19+ years = 2,000 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Dietary Reference Intakes, The National Academies Press, Washington, DC, Copyright © 2000. [718]

The recommended nutrient reference values for Australia and New Zealand are notably lower than those of the IOM, except for young children, for whom they are higher (35 mg/day) [725]. The recommendation for pregnant women aged 14–18 is 55 mg/day, and for those aged 19+ years it is 65 mg/day, which is below the IOM recommendations for non-pregnant women. The Australia/New Zealand recommendations for lactating women are equivalent to the IOM recommendations for non-pregnant, non-lactating women (80–85 mg/day).

Vitamin E

The major biological role of vitamin E is to protect PUFAs, other components of cell membranes, and low-density lipoprotein from oxidation by free radicals. Vitamin E renders free radicals unreactive by donating the hydrogen from the hydroxyl group on its ring structure. Vitamin E is lipophilic, and as the major fat-soluble antioxidant, it acts synergistically with vitamin C [726]. Primarily located in cell and organelle membranes, vitamin E is transported in the blood by plasma lipoproteins and erythrocytes.

Vitamin E is involved in regulating the atherosclerotic process, both by controlling oxidative damage and via other functions not related to its antioxidant capacity. Smooth muscle cell proliferation is inhibited by a protein kinase C-dependent mechanism that requires vitamin E. Additional roles for vitamin E include inhibition of platelet aggregation, adhesion, and release [727]. Numerous studies have examined the effect of vitamin E for prevention or treatment of cardiovascular disease and have found that, although an adequate intake decreases disease risk, supplemental intake in those already at risk of cardiovascular disease does not reduce the incidence of cardiac events [728]. In general, adequate long-term dietary vitamin E intake has been found to be associated with lower risk of chronic disease [729].

Overt vitamin E deficiency generally does not occur except in cases of protein–energy malnutrition or fat malabsorption syndromes, or in individuals with genetic defects affecting the vitamin E transport protein tocopherol transfer protein alpha. The main symptom is peripheral neuropathy [730]. However, marginal vitamin E intake is common; the third National Health and Nutrition Examination Survey found that at least 30 per cent of the US population had serum levels below 20 μmol/L, a level corresponding to increased risk of cardiovascular disease [731]. The average intake of vitamin E in the US continues to be below the recommended level [732].

There are multiple forms of vitamin E, including four tocopherols and four tocotrienols. Of these, gamma-tocopherol is the most abundant form in the human diet, but alpha-tocopherol has the greatest nutritional significance and is the only form that is maintained in the body [718]. For dietary purposes, vitamin E activity is expressed as alpha-tocopherol equivalents (alpha-TEs). One alpha-TE is the activity of 1 mg *RRR*-alpha-tocopherol ((+)-alpha-tocopherol), which is the naturally occurring form. One milligram (+)-alpha-tocopherol is equivalent to ~1.49 IU (or 1 IU = 0.67 mg). The synthetic form of alpha-tocopherol, (±)-alpha-tocopherol, is less bioavailable: 1 mg = 1.1 IU (1 IU = 0.9 mg). To estimate the alpha-TE of a mixed diet containing natural forms of vitamin E, the number of milligrams of beta-tocopherol should be multiplied by 0.5, gamma-tocopherol by 0.1, and alpha-tocotrienol by 0.3.

Vitamin E in pregnancy and lactation

As serum lipids increase, so do the concentrations of lipid-soluble vitamins such as vitamin E [733]. The hyperlipidemic state of pregnancy is associated with an increase in maternal plasma vitamin E concentration [734], unlike other micronutrient levels, which tend to decrease as a result of haemodilution and placental transfer. Placental transfer of vitamin E to the fetus is constant throughout pregnancy.

It is assumed that an adequate maternal antioxidant status should protect the maternal–fetal unit from damage, allowing appropriate fetal growth. Low vitamin E status was reported to be associated with higher incidence of low-birthweight or small-for-gestational-age infants in some studies [735], although others have not found a relationship [736]. A prospective study in a group of women at high risk for adverse pregnancy outcomes found that higher circulating alpha-tocopherol levels correlated with increasing birthweight [737]. Nonetheless, supplementation studies have not reported a positive influence of vitamin E on birth outcomes, including birthweight, and in some studies showed a negative influence (see ‘Supplementation trials of vitamins C and E in pregnancy’). There is no evidence that vitamin E requirements in pregnancy or lactation should be different from those of other adults. It is generally assumed that increased energy intake during these periods can compensate for the increased needs for infant growth and milk synthesis [738].

Sources and metabolism of vitamin E

Most vitamin E is found in foods containing fat. Vegetable oils are high in vitamin E but also contain PUFAs which deplete the body of vitamin E. Palm oil has a higher vitamin E:PUFA ratio than soybean or safflower oil. Avocado oil and olive oil are considered to be good dietary sources. Nuts, seeds, fruits, vegetables, and grains also contain vitamin E.

The efficiency of vitamin E absorption is low in humans. Vitamin E is absorbed from the intestinal lumen and secreted in chylomicrons, to be distributed to circulating lipoproteins. Mechanisms of lipoprotein metabolism (e.g. uptake via the LDL receptor or HDL-mediated delivery systems) determine the delivery of vitamin E to tissues [718].

Risks of excess vitamin E

Animal studies indicate that excess vitamin E prolongs prothrombin times, thus increasing the risk of haemorrhage [739]. A meta-analysis of 19 randomized controlled human trials of high-dose vitamin E supplementation concluded that intake of ≥400 IU (~440–600 mg) vitamin E/day as supplements increased all-cause mortality and should be avoided [740]. Some research indicates that taking even less than the RDA of vitamin E as a supplement during pregnancy can increase the risk of congenital heart defects [741]. However the study had methodological flaws, and vitamin E intake was based on maternal recall of pre-conception and pregnancy diet when the child was 16 months old. A study of the use of high-dose vitamin E in early pregnancy found no association with major congenital malformations but was suggestive of an effect of vitamin E on reducing birthweight [742]. Potential negative effects of prenatal vitamin E supplementation, concomitant with vitamin C, are discussed below.

Agency guidelines—vitamin E

The IOM RDA for vitamin E is 15 mg per day, including during pregnancy [718]. In general, well-nourished pregnant women consume adequate vitamin E in the diet, and supplementation is not required. There is a slight increase in the requirement during lactation, to 16 mg/day (Box 17.2).

The IOM recommendations indicate a tolerable upper intake level for adults of 1,000 mg of supplementary alpha-TE, including for pregnant or lactating women 19 years or older. Pregnant or breastfeeding adolescents are advised to consume no more than 800 mg/day. Infants up to 12 months of age should not be supplemented; intake of vitamin E should be from breast milk, formula, or food only. Children 1–3 years should not take more than 200 mg/day of supplementary alpha-TE [718]. UK guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) recommend against supplementation with high doses of vitamin E in pregnancy [743].

As for vitamin C, the vitamin E nutrient reference values for Australia and New Zealand are lower than those of the IOM, except for infants [744]. The recommendation for pregnant women aged 14–18 is 8 mg/day, and for those aged 19+ years it is 7 mg/day (these are unchanged from the recommendation for non-pregnant women of the same ages). The Australia/New Zealand recommendations for

Box 17.2 US Institute of Medicine recommended dietary allowances for vitamin E

Infants 0–6 months (adequate intake (AI)) = 4 mg/day alpha-TE (6 IU)
Infants 7–12 months (AI) = 5 mg/day alpha-TE (7.5 IU)
Children 1–3 years = 6 mg/day alpha-TE (9 IU)
Females 14+ years = 15 mg/day alpha-TE (22.4 IU)
Pregnancy = 15 mg/day alpha-TE (22.4 IU)
Lactation = 16 mg/day alpha-TE (23.9 IU)
Tolerable upper intake level (including pregnancy and lactation)
14–18 years = 800 mg alpha-TE/day
19+ years = 1,000 mg alpha-TE/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Dietary Reference Intakes, The National Academies Press, Washington, DC, copyright © 2000. [718]

lactating women incorporate an allowance for the vitamin E secreted in milk, reflected in an increase to 12 mg/day for women aged 14–18, and 11 mg/day for those aged 19 or older. The recommended upper level of intake is much lower than that of the IOM, at 300 mg/day.

Supplementation trials of vitamins C and E in pregnancy

Vitamins C and E interact to maximize antioxidant activity. In addition, vitamin C helps recycle oxidized vitamin E [745]. The two vitamins are often used together as an antioxidant supplement, and most trials in pregnant women have used the combination of 1,000 mg/day of vitamin C and 400 IU/day of vitamin E.

Supplementation with vitamins C and E for the prevention of pre-eclampsia or gestational hypertension

In general, studies of the effect of providing supplementary vitamin C and E to improve pregnancy outcomes have been inconsistent or have shown no positive effect. Although one single-centre study showed a significant reduction in pre-eclampsia risk in women identified as being at high risk [746], larger, multicentre trials have not confirmed such results. For example, a 2009 WHO trial of supplementation with vitamins C and E for pregnant women who were considered to be at high risk for pre-eclampsia found no association of supplementation with maternal or infant outcomes [747]. In this randomized trial, 687 women received vitamin C at 1,000 mg/day and vitamin E at 400 IU/day from ~18 weeks gestation until delivery, and 678 women received placebos. No reduction of pre-eclampsia, eclampsia, gestational hypertension, or any other maternal outcome was observed. Rates of low-birthweight infants, small-for-gestational-age infants, and perinatal deaths were also unaffected.

Another randomized trial (the VIP trial) of 2,404 women identified as being at increased risk of pre-eclampsia provided the same dosages of vitamins C and E or placebo. This study also found that concomitant supplementation with vitamin C and vitamin E did not prevent pre-eclampsia in women at risk but did increase the incidence of low birthweight. The results indicate that the use of these high-dose antioxidants is not justified in pregnancy [748]. This recommendation is echoed in results of a later study conducted by the INTAPP group as a multicentre randomized controlled trial involving 2,363 women. Vitamin C and E supplementation did not reduce the rate of pre-eclampsia or gestational hypertension but increased the risk of fetal loss, perinatal death, or PROM [749]. A larger multicentre trial in nearly 10,000 nulliparous women at low risk for pre-eclampsia also observed no effect on adverse maternal or perinatal outcomes related to pregnancy-induced hypertension in the high-dose vitamin C and E supplemented group but did not report a similar increase in rates of low birthweight or still birth [750].

It is possible that no effect was seen because the women in these studies already had adequate vitamin C and E status before receiving the high-dose supplements, as most were taking prenatal multivitamins containing amounts of vitamin C that provide near maximal tissue saturation. However, the previous WHO study also showed no benefit of antioxidant vitamin supplements in women who were in developing countries and were at high risk for pregnancy complications because of their nutritionally deficient status [747]. A prospective observational study of over 57,000 women in the Danish National Birth Cohort assessed vitamin intake based on a food frequency questionnaire completed in gestational week 25, in relation to the development of pre-eclampsia. The general incidence of pre-eclampsia was not correlated with dietary vitamin C and E intake, although incidence of severe pre-eclampsia, eclampsia, or HELLP syndrome declined with increasing dietary vitamin C intake [751].

Supplementation with vitamins C and E for the prevention of PROM or preterm birth

Antioxidants have postulated benefits for fetal membrane integrity. It is suggested that antioxidants might inhibit the damage to fetal membrane integrity caused by ROS, thereby lessening the likelihood of PROM [752]. A randomized trial examined the effect of maternal supplementation with vitamin C at a dose of 100 mg/day, beginning before 20 weeks gestation, on the incidence of PROM and preterm birth compared with placebo. Plasma vitamin C decreased during pregnancy in both placebo and vitamin C groups as a consequence of haemodilution, but leukocyte vitamin C increased in the supplemented group and declined in the non-supplemented group. The incidence of both PROM and preterm birth were lower in the group receiving supplemental vitamin C [753]. However, conflicting results have also been reported. Another trial (n = 223 women) examined the effects of vitamins C and E given from midgestation to delivery on fetal membrane biomechanics, with membranes studied both in vivo and in vitro. Supplementation did not alter the normal remodelling process; in fact, incubation with vitamin C in vitro had an unexpected weakening effect on fetal membranes (vitamin C was expected to counteract the normal weakening process) [754].

A recent systematic review found convincing evidence that there is no gain from vitamin C supplementation for the prevention of preterm birth but did not suggest that it should be limited for other indications [755]. A study of a Hungarian cohort (of 38,151 newborns with congenital defects, representing 1.8 per cent of all Hungarian births between 1980 and 1996) specifically examined the effects of maternal vitamin E supplementation. The study showed a nearly 30 per cent reduction in preterm births in pregnant women who received vitamin E treatment. These results do not agree with those of other studies, and several confounding factors could have influenced the results, including the fact that vitamin E intake was recorded by retrospective recall in 37 per cent of the women [756].

Supplementation with vitamins C and E on infant/chilhood respiratory outcomes

The effect of maternal vitamin C and E supplementation on offspring respiratory outcomes has also been studied. A randomized trial of high-dose antenatal vitamin C and E (1,000 mg vitamin C + 400 IU alpha-tocopherol/day) found that supplementation did not improve infant respiratory outcome up to 2 years of age, and was associated with increased health care utilization and cost of care [757]. However, a recent assessment of the impact of maternal antioxidant intakes on infant allergic outcomes reported that maternal dietary vitamin C intake (assessed by food frequency questionnaire) was associated with a reduced risk of diagnosed allergic disease at 1 year for the highest vs the lowest quartile [758]. No relationship was observed between allergic outcomes and maternal intake of vitamin E, zinc, or beta-carotene.

Summary and recommendations for antioxidant intake

Traditionally, plant-based, antioxidant-rich foods formed the basis of the human diet. The western diet of today is relatively poor in such foods, and supplements are often considered to compensate for a low dietary intake. Although the risks of poor antioxidant status are even greater in pregnancy, the evidence for a beneficial effect of supplementation with antioxidant micronutrients is thus far unconvincing.

Recently, new avenues of evidence have suggested that, although free radicals may be dangerous in some contexts, they may actually beneficial in others, triggering a stress response that initiates repair processes. Every antioxidant is in essence an oxidation–reduction agent—protecting against ROS is some situations and promoting their generation in others. While antioxidants are clearly necessary to maintain a normal level of cellular defence against ROS, most evidence points to high-dose antioxidants as being more harmful than beneficial [759].

This has been borne out in numerous studies of antioxidant supplementation in pregnancy. Based on multiple studies showing a lack of effect of supplementation of vitamins C and E for the prevention of pre-eclampsia, gestational hypertension, PROM, and fetal growth restriction, the UK National Institute for Clincal Excellence (NICE) and RCOG recommend against supplementation with high doses of these vitamins during pregnancy [760, 761]. The NICE guideline specifically states that antioxidants (vitamins C and E) should not be recommended for the purpose of preventing hypertensive disorders of pregnancy [761].

Our recommendations for antioxidant intake during pregnancy and lactation

Vitamins C and E and other antioxidants are necessary in pregnancy and should ideally be obtained from food sources. Most prenatal multivitamin supplements contain vitamin C in the range of 50–70 mg, which can complement dietary intake of fruits and vegetables to help meet vitamin C needs. Additional intake of vitamin C-containing supplements is not necessary in most cases, and is not recommended. Despite mounting evidence that high levels of vitamin E are not beneficial (and in fact are potentially harmful) to pregnancy outcomes, women should not be concerned about vitamin E obtained from food sources. However, supplementation during pregnancy is not recommended.

Chapter 18

Calcium in pregnancy and breastfeeding

Calcium functions

Calcium is the most abundant mineral in the body, and 99 per cent of it is present in bones and teeth, where it contributes to structural integrity as a component of hydroxyapatite, a crystallizable salt compound. The average adult female skeleton contains approximately 1 kg of calcium, or ~25 per cent of the skeleton's dry weight. The skeleton serves as a reservoir for ionized calcium, storing it for use in other tissues, where it mediates signalling pathways for vascular contraction and vasodilation, muscle contraction, nerve transmission, and glandular secretion of hormones. As calcium is essential for the maintenance of healthy teeth and bones, its requirement is most critical during phases of rapid bone growth and tooth formation—that is, fetal development and infancy, early childhood, and the adolescent 'growth spurt'. While the skeleton is growing and maturing, it accumulates calcium at an average rate of 150 mg/day [762].

Calcium cannot be stored in excess in bone; increasing calcium intake beyond the amount required for optimal bone mass will not result in more bone accumulation. Below the threshold intake, bone formation is positively (and linearly) correlated with calcium intake and therefore limited by the amount of calcium ingested. Above the threshold, bone maintenance is not related to calcium intake. Hence, calcium requirements are based on levels correlating with maximal calcium retention, which differ depending on the life stage [562]. Calcium retention (with respect to intake) is generally positive during growth phases, neutral in adults, and negative in the elderly as an adaptation to reduced mechanical loading of bone. There is a consistent relationship between bone mass and calcium intake in both children [763] and adults [764], but different ethnic groups have different equilibrium levels. People of African descent generally have lower calcium intake but absorb and retain calcium more efficiently and therefore have stronger skeletons than Caucasians or Asians [765].

In addition to the key role that calcium plays in bone maintenance, ionized calcium in extracellular fluid is critical to many physiological functions, and its concentration is therefore tightly regulated (primarily by the calcium-sensing receptor, parathyroid hormone, and the active form of vitamin D—1,25-dihydroxyvitamin D (calcitriol)) [766]. When calcium levels decrease, the calcium-sensing receptor triggers parathyroid hormone secretion from the parathyroid glands to stimulate the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which raises serum calcium levels via mobilization from bone stores and increases smooth muscle contraction. Low calcium also triggers the release of renin from kidneys, leading to vasoconstriction and fluid/sodium retention, and is associated with hypertension [767]. Serum concentrations of free ionized calcium vary above or below a very narrow 'normal' range only in extreme circumstances such as severe malnutrition or hyperparathyroidism.

Indicators of calcium status

Total calcium measured in blood is the common test used to screen for, diagnose, and monitor conditions relating to calcium status. The normal reference range for adults is 8.6–10.2 mg/dL (2.15–2.55 mmol/L). Total blood calcium does not provide an indication of bone calcium status and is primarily a measure of free, rather than bound calcium. Ionized calcium concentration is the preferred indicator in individuals with blood protein abnormalities such as low albumin, which can affect the ratio of free to bound calcium. Measurement of urine calcium is used to determine whether renal calcium excretion is adequate [768].

Calcium in pregnancy

The fetal skeleton accumulates ~30 g of calcium by the end of gestation. Most of this uptake occurs during the third trimester, when fetal bone growth is at its peak. The extra demand for calcium by the fetus during pregnancy is balanced by increased intestinal calcium absorption in the mother, such that additional dietary calcium is usually not required if pre-pregnancy intake is adequate.

Calcium and bone turnover in pregnancy

Correlating with this peak in maternal-fetal calcium transfer, the rate of maternal bone turnover doubles in late pregnancy, observed as changes in markers of bone resorption and formation [769, 770]. Despite this increase, compensatory changes in endogenous hormone levels occur to prevent extreme calcium loss from the maternal skeleton. Specifically, serum calcitonin levels increase, opposing the effects of parathyroid hormone, and synthesis of 1,25-dihydroxyvitamin D increases, enhancing intestinal absorption and limiting the mobilization of calcium from bone. Although total serum calcium declines as a result of a haemodilution-induced reduction in serum albumin (which binds calcium), the physiologically relevant fraction—free ionized calcium—remains constant throughout pregnancy [771]. Bone loss is minimized if calcium intake is maintained at 1,000–1,200 mg/day during pregnancy. This intake level builds up calcium stores in early pregnancy for increased fetal transfer in the third trimester.

There are situations in which bone loss may increase during pregnancy. In pregnant adolescents whose bones are still growing, bone mineral density (BMD) declines by ~10 per cent during gestation [772]. Women carrying multiple fetuses also experience negative calcium balance during pregnancy, as do those taking heparin (for prevention of deep vein thrombosis), as it inhibits the synthesis of 1,25-dihydroxyvitamin D [772].

Some of the compensatory mechanisms that come into play to maximize calcium absorption during pregnancy also operate in individuals on calcium-deficient diets. The effect of low calcium intake is accentuated in pregnant women and is manifested in higher rates of calcium absorption, and reduced excretion [569, 773]. Even with this apparent intestinal and renal adaptation to low calcium consumption, chronically low dietary intakes (<500 mg/day) may still not meet maternal and fetal needs during pregnancy. Low calcium intake during pregnancy has been associated with reduced bone mineral content (BMC) in newborns [774].

Because active (vitamin D-dependent) calcium absorption is increased under calcium-deficient diets, the requirement for vitamin D is also likely to be greater. Vitamin D regulates not only calcium absorption but also plasma calcium homeostasis, and deficiency or inadequacy of this vitamin limits the body's adaptive responses to low calcium intake. Thus, calcium intake may need to be adjusted for certain dietary factors, including vitamin D intake, and for sun exposure, since both can affect calcium absorption and retention [231] (see chapter 15 for details on vitamin D).

Bone outcomes—trials of calcium supplementation during pregnancy

Maternal outcomes of calcium supplementation during pregnancy

Although resorption of calcium from the maternal skeleton into the circulation is known to increase during pregnancy, particularly in women with low calcium intakes, few randomized studies have evaluated the effect of supplemental calcium on bone mass and density in pregnant women. Short-term studies of calcium supplementation of 1–1.2 g/day for 7–10 days in late pregnancy resulted in a reduction in the expression of markers of bone turnover in women consuming low-calcium diets [775, 776]. In China, supplementation with milk or milk plus calcium (600 mg/day) increased calcium in the diet of women with habitually low intakes from ~530 mg/day to ~880 mg/day with milk alone, and to ~1,360 mg/day with milk plus calcium. A dose-dependent increase in maternal BMD was observed with increasing calcium intake [777].

Interestingly, in Gambian women with very low calcium intakes (<355 mg/day), supplementation with 1,500 mg calcium/day from 20 weeks gestation until delivery did not result in significant differences in total-body BMC, BMD, or bone area at 2 weeks postpartum, as compared with placebo. In fact, in the supplemented women, the decreases seen in these bone measures at specific sites (lumbar spine, distal radius, and hip) were significantly greater than those in unsupplemented mothers, up to 52 weeks postpartum. It is possible that this increase in calcium intake during pregnancy disrupted the adaptive mechanisms established in these women who were accustomed to very low levels of calcium in their normal diets [778].

Infant outcomes of calcium supplementation during pregnancy

Data are relatively scarce regarding the effect of maternal calcium supplementation during pregnancy on bone mineralization in the fetus. Studies have mainly evaluated growth parameters such as birthweight and length, and intrauterine growth restriction (small for gestational age at birth), and often these were studied as secondary end points to the effect of supplemental calcium on hypertensive disorders in pregnancy (see 'Calcium intake and pre-eclampsia/high blood pressure'). An early supplementation trial in India using 300 or 600 mg calcium lactate/day (from between 18 and 22 weeks gestation until delivery) found an increase in BMD in neonates born to supplemented mothers in both groups, compared with those born to unsupplemented mothers [779]. Another trial found that, overall, total calcium intake was positively associated with total-body BMC in infants [774].

A recent study of women consuming a low-calcium diet (<600 mg/day) in Argentina reported no effect of supplementation on fetal somatic or skeletal growth [780]. This is consistent with the results seen in the offspring of Gambian women who were similarly supplemented. The Gambian diets were lower in calcium, and, similar to the effect seen in the women themselves, the infants of supplemented mothers exhibited a slower rate of bone accretion (slower increase in bone area and BMC) in the first year of life compared with those born to women who had not received supplements during pregnancy [781]. The effect of maternal calcium intake on infant bone outcomes during breastfeeding has been more extensively studied and is discussed in 'Calcium in lactation'.

Calcium intake and pre-eclampsia/high blood pressure

Pre-eclampsia is characterized by vascular endothelial dysfunction and placental insufficiency during pregnancy. Epidemiological evidence has shown an inverse relationship between calcium intake and hypertensive disorders of pregnancy, and the consequent higher risk of preterm birth. Populations with high-calcium diets have low incidence of pre-eclampsia and eclampsia (e.g. historically in Ethiopia and in the Mayan Indians of Guatemala) [782].

Numerous studies have evaluated the relationship between calcium intake and the risk of pregnancy-induced hypertension and pre-eclampsia, and the effect of calcium supplementation in reducing this risk. Meta-analyses indicate an overall protective effect of supplemental calcium on pre-eclampsia in populations with low calcium intake [783, 784]. A systematic review and meta-analysis of 13 studies concluded that, with calcium supplementation of at least 1 g/day, the average risk of gestational hypertensive disorders was reduced by 35 per cent, and the average risk of pre-eclampsia was reduced by 55 per cent. The effects of calcium supplementation on the risk of pre-eclampsia were greatest for 'high-risk' women and those with low calcium intake [783]. Focusing on developing countries, a meta-analysis of ten randomized controlled trials found that calcium supplementation (1,500–2,000 mg/day) during pregnancy reduced the risk of all gestational hypertensive disorders in women with low baseline calcium intakes [784]. The reduction in risk was greatest in the subgroup of women whose pre-pregnancy risk of developing hypertensive disorders was highest.

Calcium supplementation to women with low dietary intakes (<600 mg/day) was found to reduce the risk of severe pre-eclamptic complications by 25 per cent in a WHO multicentre trial, although no effect on gestational hypertension was observed [785]. However a 2007 US FDA review considered the evidence to be insufficient to support the use of calcium supplements for the purpose of reducing gestational hypertensive disorders in the US, where baseline calcium intake is relatively high [786].

Calcium intake and preterm delivery

Preterm delivery is commonly associated with hypertensive disorders in pregnancy. Calcium supplementation was found to reduce the average risk of preterm birth in a meta-analysis of clinical trials on the prevention of hypertensive disorders in pregnancy [783]. In a WHO-sponsored randomized trial in 8,325 women with calcium intakes <600 mg/day, the risk of early preterm delivery (<32 weeks of gestation) was statistically significantly lower in the calcium group (2.6%) than in the placebo group (3.2%) [785]. Supplementation of pregnant adolescent women (≤17 years; n = 94) in the US with 2 g/day elemental calcium resulted in a significant reduction in the incidence of preterm delivery compared with placebo (7.4% vs 21.1% for the placebo group) [787]. A pooled analysis of data from five trials in developing countries (where baseline calcium intake was low) reported a significant reduction in preterm births in women who received 1,500–2,000 mg supplemental calcium from around 20 weeks gestation [784].

The effect of maternal calcium intake on childhood blood pressure

As calcium appears to have an influence on blood pressure in pregnant women, the effect of maternal calcium intake on blood pressure in infants and children has also been analysed. A systematic review of studies of maternal calcium intake and offspring blood pressure reported that higher maternal calcium was associated with a reduction in offspring systolic blood pressure up to 9 years of age [788]. However, the benefit of maternal supplementation is most evident in offspring of mothers who had high blood pressure during pregnancy, which is an independent risk factor for high blood pressure in children.

Calcium intake and lead exposure

Calcium intake may modify the impact of maternal lead exposure during pregnancy, protecting the fetus from toxic exposure. High calcium intake during pregnancy and lactation helps to minimize bone demineralization, and consequently, slows the release of lead from bone into the maternal circulation. The impact of lead exposure in pregnancy is discussed in detail in chapter 30.

Calcium in lactation

Because the concentration of calcium is tightly regulated (referred to as 'calcium economy'), maternal calcium intake has little effect on the amount that is secreted in breast milk. This appears to apply even in women consuming very little dietary calcium, such as those in Gambia, where supplementation had little effect on the amount of calcium present in breast milk [789]. The mean concentration of calcium in breast milk is approximately 260 mg/L. Based on an observed average breast milk consumption of ~780 mL/day, and using a conservative estimate of absorption, the estimated calcium intake by fully breastfed infants is around 200 mg/day [562]. This level is considered adequate for most infants, assuming that vitamin D is also present in sufficient quantity.

The absorption of calcium from breast milk is high compared with calcium absorption from solid foods. Infants who were fed a mixed diet of breast milk and solid food in a study using stable calcium isotopes retained more of the calcium derived from breast milk than from solids [790]. Calcium absorption from infant formula is also lower than from breast milk, but formula-fed infants absorb more calcium overall because of the higher calcium content of formula [791].

BMC and bone mass accretion was significantly higher during the first 6 months of life in infants fed formula containing 510 mg/L calcium and 390 mg/L phosphorous, compared with infants fed breast milk containing 300 mg/L calcium and 150 mg/L phosphorous (calcium:phosphate ratios of 1.3:1 for formula vs 2.0:1 for breast milk). This high-phosphate, high-calcium formula resulted in low serum calcium levels in the first few weeks of life. Despite the early faster accretion in formula-fed infants, breastfed infants who began consuming formula at 6 months of age had a greater increase in bone mass during the second 6 months of life than those who had been fed formula from birth [792].

A number of studies conducted in women with relatively high calcium intakes found no association between maternal calcium intake and changes in either bone mineral status or biochemical indicators of calcium metabolism in women during lactation [793, 794]. Yet, as indicated by markers of bone turnover and bone mass in breastfeeding women and after weaning, BMD decreases in the first 6 months postpartum and returns to normal 6 months after weaning in women with an average daily intake of ~1,200 mg/day [795]. It appears that, in general, calcium supplementation has little effect on lactation-induced changes in the calcium economy.

Prevalence of calcium deficiency

The incidence of calcium deficiency is high in regions such as Africa and Asia, where the prevailing diets consist of few or no dairy products and grains are dietary staples. Low calcium exacerbates the effects of vitamin D deficiency and increases the risk of rickets [796], and there are also reports of rickets occurring in children with adequate levels of vitamin D [797, 798]. Low calcium intake combined with high protein intake also results in calcium deficiency, manifesting in increased rates of bone fracture [799]. Clinical signs of vitamin D deficiency—rickets and osteomalacia—are still common in tropical and subtropical countries, where people are exposed to abundant sunlight. It is suggested that the low-calcium/high-cereal diets typical of some of these regions (where susceptibility to rickets remains high) might alter the efficiency of vitamin D utilization. Calcium deficiency has been shown to enhance the degradative metabolism of 25-hydroxyvitamin D [800]. Absorption of calcium from the gut in people with minimal calcium intake cannot be enhanced if vitamin D status is also deficient. It is important to bear in mind that vitamin D deficiency aggravates the consequences of low calcium, and vice versa.

In Canada, the prevalence of inadequate calcium intake in adult women ranges from 48–87 per cent, depending on the age group [801]. In the US, the average dietary intakes of calcium are well below the recommended dietary allowance (RDA; 1,000–1,300 mg/day; see 'Agency guidelines for calcium intake'), especially for adolescent females, as a result of replacing the main source of calcium—milk—with soft drinks [571]. A survey of 250 pregnant women in the UK in 2006 indicated that 40 per cent failed to meet the UK guidelines for calcium intake [802]. In India, in both rural and urban populations, dietary intake is low relative to the Indian Council of Medical Research RDA of 400 mg/day [803] (a low RDA compared with US recommendations). Urban women in India have an average daily calcium intake of 306 mg/day, and rural women average 262 mg/day.

Calcium sources

In Western countries, milk and milk products are the major source of dietary calcium, with cereal products (where flour is fortified) and fruits and vegetables making a smaller contribution. Milk contains ~115 mg calcium/100 g, and cheeses range between 60 and 1,200 mg/100 g. Raw spinach contains ~170 mg calcium/100 g but also contains oxalic acid, which inhibits calcium absorption. Asian diets provide calcium in the form of leafy green vegetables such as bok choy, chinese cabbage, broccoli, spinach, kale, and mustard greens, as well as fish that are eaten whole, such as anchovies (or *ikan bilis*—dried anchovies), sardines, and canned salmon. Soy products (e.g. tofu and soy milk) are also good sources of calcium, containing 500–1,400 mg/100 g.

A number of dietary factors influence calcium balance. Oxalic acid present in spinach, beetroot, sweet potatoes, and other vegetables (as well as some fruits, nuts, grains, and legumes) also limits the bioavailability of calcium present in the same foods. Sodium intake affects calcium excretion; it is estimated that for every 2,300 mg of sodium excreted, there is an approximate calcium loss in urine of 40 mg [804]. A diet high in processed food will therefore provide less useable calcium than a diet that is lower in sodium but contains equal amounts of calcium. A high intake of animal protein also increases urinary calcium excretion [805]. Phytate, the storage form of phosphorus founds in grain fibre, inhibits the absorption of calcium in the gut [806]. Consumption of a high-fibre diet was associated with calcium deficit in lactating women in rural Mexico (who consumed 32 g fibre/day and 750 mg calcium/day) as a result of impaired intestinal absorption [807], although another report indicated that chronic wheat dextrin consumption did not inhibit calcium absorption in the gastrointestinal tract in women [808].

Sufficient calcium can be obtained by eating four servings of dairy products or other calcium-rich foods (e.g. sardines, dark green vegetables, or tofu) per day. Taking calcium together with iron (either in the diet or as a supplement) is not recommended, since calcium inhibits iron absorption [809]. It should be noted that diets high in animal protein and/or phytates would possibly render an individual more calcium deficient than their calcium intake alone would indicate.

Risks of excess calcium

It is unlikely that ingestion of calcium from foods would result in excess serum calcium; however, high use of supplements and medications containing calcium (e.g. antacids) has been known to cause hypercalcaemia and/or hypercalciuria in some cases. Serum calcium levels of 10.5 mg/dL (2.63 mmol/L) or higher signify hypercalcaemia, with clinical signs varying depending on the rapidity and magnitude of the elevation. Symptoms of hypercalcaemia include weight loss, anorexia, fatigue, polyuria, heart arrhythmia, and soft tissue calcification. Ultimately, hypercalcaemia can lead to renal failure.

The tolerable upper intake level set by the US Institute of Medicine (IOM) for pregnant women is 3,000 mg/day for adolescents and 2,500 mg/day for women over 18 years of age. Infants should not consume more than 1,000 mg/day for the first 6 months of life, and more than 1,500 mg/day between 6 and 12 months [562]. These levels are relatively close to the intake levels corresponding to nutritional adequacy, so care should be taken when advising the use of calcium supplements such that the upper limit is not exceeded. A recent meta-analysis suggested that calcium supplementation modestly increased the risk of cardiovascular events in middle aged women taking supplements for the prevention of osteoporosis [810, 811], but many experts disagree with the data analysis and conclusions and continue to recommend calcium supplementation in postmenopausal women [812–814].

Agency guidelines for calcium intake

The IOM Food and Nutrition Board in the US based their calcium intake recommendations on the criteria of 'maximal calcium retention'—threshold values above which the calcium balance does not further improve as intake increases [562]. The dietary reference intakes put forth by the IOM are also endorsed by Health Canada. The recommendations for pregnant women and infants are shown in Box 18.1.

Box 18.1 Institute of Medicine recommended dietary allowances for calcium

Infants 0–6 months (adequate intake (AI)) = 200 mg/day
Infants 7–12 months (AI) = 260 mg/day
Children 1–3 years = 700 mg/day
Females 14–18 years = 1,300 mg/day
Females 19–50 years = 1,000 mg/day
Pregnancy 14–18 years = 1,300 mg/day
Pregnancy 19+ years = 1,000 mg/day
Lactation 14–18 years = 1,300 mg/day
Lactation 19+ years = 1,000 mg/day
Tolerable upper intake levels
Pregnancy and lactation 14–18 years = 3,000 mg/day
Pregnancy and lactation 19+ years = 2,500 mg/day

Source: Institute of Medicine, *Dietary Reference Intakes for Calcium and Vitamin D*, The National Academies Press, Washington, DC, copyright © 2011. [562]

The recommendations for pregnant and lactating women over the age of 18 do not differ from those for non-pregnant women, because the body adapts to the increased calcium demand by increasing calcium absorption and retention. Pregnant adolescents require a higher calcium intake to compensate for the dual demands of the fetus and their own continued bone growth. These RDAs reflect the view that no additional health benefits are achieved at intakes above these levels. The IOM recommendations are endorsed by the American Pregnancy Association [815]. According to WHO guidelines, in regions where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially those at high risk of developing pre-eclampsia [816].

Our recommendations for calcium intake during pregnancy and lactation

Pregnant and lactating women consuming a diet including sufficient amounts of dairy products and vegetable calcium sources do not require supplemental calcium during pregnancy. All women should be encouraged to achieve or maintain a dietary calcium intake between 1,000 and 1,300 mg/day by increasing their intake of calcium-rich foods. Women consuming low amounts of calcium (<600 mg/day), and those at risk for hypertensive disorders, should be encouraged to increase their intake by an additional 1 g of calcium per day throughout pregnancy in order to reduce their risk of pre-eclampsia and related adverse pregnancy outcomes. Increasing dietary calcium is preferable to supplementation, but if there is a possibility of inadequate dietary intake, supplements should be taken at a dosage of 1–1.5 g/day.

Because vitamin D is essential for the adaptive calcium homeostatic mechanisms that occur during pregnancy and lactation, it is important to ensure that vitamin D is also present in sufficient amounts (see chapter 15). Calcium supplementation is also recommended for pregnant and lactating women with a history of environmental or occupational lead exposure, to reduce both circulating lead levels in the mother and lead exposure to the developing fetus and nursing infant. Infants can obtain their full calcium requirement (200 mg/day) through breast milk in the first 6 months of life, or from calcium-fortified infant formula.

Chapter 19

Iodine in pregnancy and breastfeeding

Iodine functions

Iodine is a key component of the thyroid hormones, thyroxine (also known as T4) and triiodothyronine (also known as T3), which regulate a number of physiological processes, including growth, development, and reproductive function, the maintenance of metabolic rate, cellular metabolism, and the integrity of connective tissue. All biological actions of iodine are attributed to thyroid hormones, although there may be a role for elemental iodine in early brain development [817]. Development of the fetal brain and nervous system are dependent on thyroid hormones supplied by the mother during gestation [818]. The requirement for thyroid hormone production is substantially increased in the first trimester. Thyroid hormones are important for myelination of the CNS, which is most active late in pregnancy and shortly after birth. Because the fetal thyroid system does not mature until the late third trimester, the increased demand for thyroid hormones, and therefore for iodine, is sustained throughout the full term of pregnancy. There is also a significant increase in renal iodide clearance during pregnancy reflecting increased thyroid hormone production. This results in a shortfall of ~20 μg iodine per day [819]. Women with adequate iodine intake before conception (~150 μg/day) can adapt to the increased demand for thyroid hormones during pregnancy, because the thyroid gland adjusts its hormonal output [820], but this depends on sufficient availability of dietary iodine, and the integrity of the thyroid gland.

Indicators of iodine status

Almost all iodine is excreted in urine, so urinary iodine concentration (UIC) is often used as a surrogate measure of iodine intake in populations [821]. Iodine sufficiency in pregnant women is defined as UIC >150 μg/L. Iodine nutrition status is considered optimal in a population at urinary levels between 150–249 μg/L; levels ≥500 μg/L are reflective of excessive iodine intake. For lactating women, a median UIC of ≥100 μg/L indicates adequate intake and optimal iodine status. However, the UIC test is not appropriate to diagnose iodine deficiency in individuals. Urine iodine levels are variable from day to day in a given individual, because they reflect only recent intake, whereas the thyroid can store relatively large amounts of iodine. The body of a healthy adult contains 15–20 mg of iodine, of which 70–80 per cent is found in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid might fall to less than 20 μg. Measurement of UIC therefore has a low predictive value for iodine deficiency [822].

Blood levels of free T4 or thyroid stimulating hormone (TSH) have also been used to estimate iodine status. In the first trimester of a normal pregnancy, serum TSH levels are lower than before conception, but during the second half of gestation, TSH levels return progressively to pre-pregnancy values and remain stable. Because of the normal changes in thyroid hormone levels and TSH during pregnancy, measurements of free T4 and free T3 are used to assess thyroid status in early gestation. In later gestation (from 16 weeks), a low TSH is a sensitive measure of adequate thyroid status [823].

Iodine deficiency in pregnancy

In women with suboptimal pre-pregnancy iodine stores, thyroid adaptation in pregnancy is impaired. If iodine intake continues to be inadequate in pregnancy, it triggers a progressive increase in serum TSH that enhances thyroid gland stimulation and increases thyroid volume, leading to goitre [824, 825]. Typically, plasma levels of the biochemically active thyroid hormones T4 and T3 fall, while TSH increases, sometimes to very high levels.

The effects of iodine deficiency on preterm delivery, placental abruption, miscarriage, and fetal/infant mortality

Approximately 2–5 per cent of pregnant women are affected by subclinical hypothyroidism (defined as normal circulating free T4 and elevated TSH), which can result from inadequate iodine intake. In a large prospective analysis of pregnant women who were screened for abnormal thyroid function in the first half of pregnancy, there was a twofold higher incidence of preterm delivery at or before 34 weeks gestation, and a threefold higher incidence of placental abruption among women diagnosed with subclinical hypothyroidism [826]. High maternal TSH has also been associated with miscarriage [827] and an increased risk of fetal death [828].

Maternal iodine supplementation in areas of severe iodine deficiency has been shown to decrease the rates of stillbirth and neonatal and infant mortality. Oral administration of iodized oil to mothers before or during pregnancy reduced the rate of prematurity, stillbirth, and spontaneous abortion compared with that for untreated mothers in an area of endemic goitre in Algeria [829]. In addition, iodination of irrigation water reduced infant mortality in an area of severe iodine deficiency in China [830].

The effects of iodine deficiency on birthweight and fetal/infant growth

In iodine-deficient areas, repletion of iodine in pregnancy resulted in higher birthweights and increased head circumference in newborns [831]. Children born to mothers treated with iodized oil in pregnancy had a 200 g higher mean birthweight than those born to untreated mothers [829]. Birthweight and infant growth were positively correlated with maternal use of iodized salt in an analysis of iodine intakes in several Asian countries [832].

The effects of iodine deficiency on neurodevelopment

The brain is particularly vulnerable to deficiencies of iodine and thyroid hormones during development. A lack of maternal iodine disrupts the development of the brain and myelination of the CNS. In infants, an elevated concentration of TSH reflects an insufficient supply of maternal and/or fetal thyroid hormones to the developing brain and indicates a risk of irreversible brain damage [833]. In severe form, congenital hypothyroidism resulting from iodine deficiency can manifest in major neurocognitive deficits and cretinism, which can have multiple forms, including deaf–mutism, motor abnormalities, and myxoedematous cretinism. Moderate iodine deficiency in pregnancy is associated with lower learning capacity, reduced IQ, hearing impairment, and increased risk of attention deficit hyperactivity disorder [834]. Two meta-analyses of observational studies of the effect of iodine deficiency on cognitive development found that the IQs of children from areas with moderate to severe iodine deficiency were on average 12–13.5 points lower than those of children from non-iodine-deficient areas [835, 836]. Undiagnosed hypothyroidism in pregnant women may have the same effects, which suggests that screening for thyroid deficiency in pregnant women is warranted [837].

The severity of neurodevelopmental damage depends on the timing and severity of iodine deficiency during gestation. In the first trimester, the cerebral vesicles, from which the cerebral cortex will form, begin developing. Even mild iodine deficiency during this period of neocortical proliferation can affect neurological development. If iodine supplementation is delayed until after the first 12–14 weeks of gestation in women with mild dietary iodine deficiency, their offspring are at increased risk for poor gross and fine motor coordination, and socialization problems. These adverse effects are amplified if women are not supplemented with iodine at all, as compared with being supplemented later in pregnancy [838]. Iodine supplementation before the third trimester predicted higher psychomotor test scores for children than did iodine supplementation later in pregnancy or postnatally. Women and children in iodine-deficient regions may be given iodinated oil as depot injections [831].

In Europe only 15–30 per cent of women receive iodine supplements, and consumption of iodized salt varies. A study conducted in Spain, where iodine intake is below recommended levels, evaluated neurocognitive function in infants aged 3–18 months whose mothers received 300 μg potassium iodide in pregnancy or no supplement. Children whose mothers received iodine daily from the first trimester performed better on psychomotor evaluation than those from unsupplemented mothers, suggesting benefits can be gained by maternal iodine supplementation in areas of mild to moderate deficiency [839].

Iodine in lactation

Iodine continues to be vital for brain development in the newborn infant through to 3 years of age. Maternal iodine is the only source of iodine for infants after birth, unless they receive formula or supplements. The iodine demand of newborns is partly supported by iodine accumulated in the fetal thyroid gland during gestation [840]. The recommended intake for infants in the first 6 months is 110 μg/day and between 7 and 12 months is 130 μg/day.

The concentration of iodine in breast milk is 20–50 times higher than that in plasma [841]. The sodium iodide symporter mediates iodide uptake by the mammary gland, and its expression increases during lactation [842]. Iodine in breast milk varies in response to short-term changes in dietary iodine intake. A study in which healthy pregnant women ingested 600 μg of potassium iodide showed a measurable rise in breast milk iodine concentrations, peaking 6 hours after ingestion [843]. The iodine concentration in colostrum following delivery is approximately 200–400 μg/L, but decreases to between 75 and 200 μg/L in breast milk [841]. Breastfeeding women require increased dietary iodine intake to compensate for this iodine loss.

Iodine supplementation in pregnancy

Although universal iodine supplementation during pregnancy remains controversial, the benefits of correcting iodine deficiency are generally considered to outweigh the risks of supplemental iodine. This is particularly true in areas known to have iodine-deficient soils and a moderate to high risk of deficiency.

A large number of studies have examined the effects of iodine supplementation on pregnancy outcomes.

Interventional studies—severe iodine deficiency in pregnancy

Five randomized controlled trials in low-income countries have shown that iodine supplementation before or during pregnancy reduces the incidence of cretinism in areas of high prevalence [844]. An early trial of intramuscular iodinated oil supplementation (vs saline injection) in a region of endemic cretinism in Papua New Guinea found that cretinism did not occur in offspring from women who received iodinated oil before conception [845]. In addition, studies on cognitive development showed that iodine treatment before or during pregnancy improved development scores in the offspring by 10–20 per cent [844]. In an area of severe iodine deficiency (4% cretinism rate) in Zaire, pregnant women were randomized to receive injections of either iodized oil or vitamins at around 28 weeks gestation. Psychomotor development scores at 6 years of age of the offspring from women in the iodine group were significantly higher than those of offspring from the group that did not receive iodine [846]. Other studies conducted in Zaire, Peru, and Ecuador have shown similar results [847].

Interventional studies—mild/moderate iodine deficiency in pregnancy

Multiple studies in areas of mild to moderate iodine deficiency have examined measures of maternal (and sometimes infant) thyroid function following iodine supplementation in pregnancy. Healthy pregnant women in Italy were given 120–180 μg iodine as iodized salt or a placebo daily, beginning in the first trimester. Thyroid volume increased in placebo recipients but not in those receiving iodine (n = 35; median UIC: 31–37 μg/L) [848]. Similarly, in a randomized trial of pregnant women in Denmark (n = 54) in which women received either 200 μg iodine/day as a potassium iodide solution or no supplement from 17 weeks to term, maternal thyroid volume increased by 16 per cent in the treated group and by 30 per cent in the control subjects [849]. Other studies also indicate that supplementation of women with low iodine intakes resulted in smaller thyroid volumes and improvement in both maternal and infant thyroid parameters, as compared with unsupplemented controls [850, 851].

However, data are limited with regard to the effect of iodine supplementation to mildly iodine-deficient mothers on the developmental outcomes of their offspring. Despite many agencies recommending routine iodine supplementation for pregnant women, a recent systematic review of randomized controlled trials has suggested this may not be without risk to the fetus in women with adequate iodine status [852]. As there is some disagreement on safe levels of supplementation, further investigation is necessary in areas of mild to moderate iodine deficiency as well as in areas of iodine sufficiency, to assess the benefits and risks according to background iodine status.

A possible side effect of iodine supplementation is aggravation of subclinical autoimmune thyroid disease, which is common in pregnant women and can develop into postpartum thyroid dysfunction. Subclinical autoimmune thyroid disease is diagnosed by the detection of antibodies against thyroid peroxidase. A placebo-controlled, randomized, double-blind trial of women positive for antibodies against thyroid peroxidase examined whether supplementation increased the risk of autoimmune thyroid disease but found no significant increase in postpartum thyroid dysfunction in women given 150 μg iodine per day during pregnancy and postpartum, or during pregnancy only, as compared with unsupplemented controls [853].

Iodine sources

The total body iodine requirement must be derived exogenously. Iodine is present in seawater, igneous rocks, and some soils. Food sources of iodine can vary greatly in their iodine content, depending mainly on the natural or supplemented (fertilizer) iodine content of the soil they are grown in, or the content of the food eaten by animal sources. The amount of iodine in soils varies considerably around the world, translating to a wide variation in iodine content of similar crops grown in different regions [260]. The soil in many regions is very low in iodine, and deficiency is a risk if locally grown foods are primarily consumed.

Seaweed (e.g. kelp, nori, kombu, and wakame) is an excellent source of iodine, although the content can vary from 16 μg to nearly 3,000 μg iodine per 1 g serving [260]. Many seafoods are also high in iodine. Dairy products in some areas (including the US) may have relatively high iodine content due to the use of iodine feed supplements, and contamination from iodine-containing disinfectants in milk tankers and milking equipment (although this is declining in some countries). The transfer of iodine from feed into milk from dairy cows is approximately 30–40 per cent, compared to transfer from feed into meat from pork or beef, which are both less that 1 per cent. Iodine transfer from feed into eggs is also much higher (10–20%) than from feed into meat [854]. Some bread has high iodine content because of the use of iodate conditioners in the baking process. Iodine for infants is supplied by breast milk for the first six months, or iodine-fortified formulas. However, there is a wide variation in iodine content in infant formulas.

Areas of concern for iodine availability

According the WHO, over half the population of Europe lives in areas of iodine deficiency [855]. The Eastern Mediterranean, Africa, Himalayas, Andes and the Western Pacific are also regions of concern, although many other areas also have suboptimal iodine nutrition. Inland, mountainous regions are generally most affected, as iodine leaches from the soils due to snow, water movement, and heavy rain. The reasons for iodine deficiency in different regions is therefore primarily geological rather than socioeconomic. Correction of deficiency in a region has to be achieved by supplying iodine from an external source.

Salt iodization programmes have been instituted in various countries to combat this problem and have had some success in reducing the prevalence of iodine deficiency. A 2009 report by the UN Standing Committee on Nutrition indicated that, at that point, control of iodine deficiency via fortification of salt covered an estimated 70 per cent of households worldwide, and it was calculated that ~2 billion people would have shown signs of iodine deficiency without this intervention [236]. However, iodized salt as a source of iodine may not be sufficient or appropriate for pregnant women. Even in iodine-sufficient regions (based on salt iodization), significant numbers of pregnant women still have insufficient iodine intake (e.g. Iran [856], China [857], Italy [858], and Turkey [859]). The ten most iodine-deficient countries in 2011 (assessed as those with the greatest numbers of school-aged children with insufficient intake) were Ethiopia, Sudan, Russian Federation, Afghanistan, Algeria, Angola, the UK, Mozambique, Ghana, and Morocco [860].

Risks of excess iodine

It is important to monitor the risk of thyroid disease due to an excessive consumption of iodine, as well as that due to deficiency. The range between the required amounts of iodine and the tolerable upper intake level (UL) is only about 1:3, depending on the life stage. According to the WHO, the UL for pregnancy (500 μg/day) is only twice the required intake (250 μg/day). Iodine is therefore categorized as a trace element with a high risk of deficiency, but also with high risk of excess. Symptoms of acute iodine toxicity include diarrhoea, with alternating periods of hyperactivity, weakness, convulsions, and death. Sub-chronic toxicity symptoms include reduced weight gain and haemolysis, in addition to specific inhibitory effects on thyroid function [861]. A recent cross-sectional study in China (n = 384 pregnant women) found that women with excessive iodine intake were more likely to have thyroid disease, particularly subclinical hypothyroidism [862].

Iodine readily crosses the placenta and is secreted in breast milk. Fetal exposure to excess iodine in utero via placental transfer, or infant overexposure via breast milk, can cause neonatal hypothyroidism. This has been reported in Japan, where dietary iodine intake is very high from consumption of seaweed (kombu) [863], and in the US in cases of maternal consumption of tablets containing 12.5 mg iodine per day during pregnancy [864]. Women in some Asian cultures (particularly Korea and North China) consume seaweed soup to promote breast milk supply, and this practice has been linked to iodine-induced neonatal hypothyroidism [865].

Agency guidelines for iodine intake

The US Institute of Medicine (IOM)'s recommended dietary allowance (RDA) for iodine in pregnancy is 220 μg/day, and during lactation the RDA is 290 μg/day. This is an increase from 150 μg/day for non-pregnant, non-lactating women [260]. The IOM UL is 1,100 μg/day for all adults, and 900 μg/day for adolescents 14–18 years of age. No UL has been established for infants or children. According to the IOM, the adequate intake (AI) level for infants aged 0–6 months is 110 μg/day of iodine, which can be acquired through breast milk if the mother's iodine intake is sufficient. Between 7 and 12 months of age, infants require 130 μg/day of iodine; complementary foods and/or iodine-fortified formula should be added to the diet at this point. For children between the ages of 1 and 8 years, the RDA is 90 μg/day, increasing to 120 μg/day for children 9–13 years of age [260]. Other government agencies, including the Australian National Health and Medical Research Council [866] and the New Zealand Ministry of Health, have made similar recommendations, that is, iodine intakes of 220 μg/day in pregnancy and 270 μg/day during lactation, to be achieved by consuming iodine supplements of 150 μg/day in addition to dietary sources [143]. The recommendations of the IOM are in general agreement with those of the International Council for the Control of Iodine Deficiency Disorders and UNICEF, and are shown in Box 19.1.

The WHO, UNICEF, and the International Council for the Control of Iodine Deficiency Disorders, all of which focus on the developing world, all advise women who are pregnant or breastfeeding to take a daily oral iodine supplement, so that the total daily intake is 250 μg [867]. A daily intake greater than 500 μg/day is considered unnecessary, as it would not provide any additional benefit for health and may be associated with impaired thyroid function. The WHO recommends fortification of salt at 20–40 mg iodine/kg salt. This level assumes no iodine in the usual diet pre-fortification and that salt is consumed at 10 g/day, and it is designed to provide an intake that is adequate

Box 19.1 US Institute of Medicine recommended dietary allowances for iodine

Infants 0–6 months (adequate intake (AI)) = 110 μg/day
Infants 7–12 months (AI) = 130 μg/day
Children 1–3 years = 90 μg/day
Females 14+ years = 150 μg/day
Pregnancy = 220 μg/day
Lactation = 290 μg/day
Tolerable upper intake level during pregnancy and lactation, 14–18 years = 900 μg/day
Tolerable upper intake level during pregnancy and lactation, 19+ years = 900 μg/day

Source: Institute of Medicine, *Food and Nutrition Board, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

for non-pregnant adults (150 μg/day). Pregnant and lactating women would need to consume approximately 6–15 g per day of iodized salt to receive the recommended 250 μg iodine. However, the WHO also recommends a salt intake of <5 g/day to reduce the risk of cardiovascular diseases—this may be insufficient during pregnancy in terms of iodine intake.

The Endocrine Society recommends an intake of 150 μg/day for women of childbearing age, with an increase to 250 μg/day as soon as possible before or during pregnancy. This level of intake should be maintained through breastfeeding—breast milk should provide 100 μg/day to the infant. The Society's view is that iodine intake during pregnancy and breastfeeding should not exceed twice the daily recommended nutrient intake for iodine, that is, 500 μg iodine per day [868]. The Endocrine Society recommends iodine supplementation beginning prior to conception if possible, and continuing through pregnancy and lactation. Once-daily prenatal vitamins should contain 150–200 μg iodine in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. The American Thyroid Association supports the recommendation of 250 μg/day for pregnant and lactating women [869]. To meet this daily intake requirement, supplements containing 150 μg iodine are recommended. Prenatal multivitamins should include iodine (in the form of potassium iodide—at least 197 μg), which will ensure that these vitamins contain 150 µg of supplemental daily iodine (potassium iodide contains ~76% iodine) [870]. However only about half of the prenatal vitamins available in the US contain iodine [871].

The WHO recommendation for infants is 15 µg/kg/day for those born full term, and 30 µg/kg/day for preterm infants. Based on the assumption of an average body weight of 6 kg for a child of 6 months, 15 µg/kg/day corresponds approximately to an iodine intake and requirement of 90 µg/day. The iodine requirement of preterm infants is twice that of term infants because of a much lower retention of iodine by preterm infants [231]. The WHO,UNICEF, and the International Council for the Control of Iodine Deficiency Disorders advise an increase in the iodine content of infant formulas to 100 µg/L from the former recommendation of 50 µg/L for term infants, and to 200 µg/L for preterm infants.

Our recommendations for iodine intake during pregnancy and lactation

Throughout gestation, the fetus is dependent on the maternal supply of iodine, and a lack of iodine in pregnancy is the most common cause of preventable brain damage in infants. Pregnant and breastfeeding women therefore need to increase their dietary iodine intake (from 150 µg/day before conception to 250 µg/day in early pregnancy and throughout lactation) because of the increased requirements during pregnancy and breastfeeding. We recommend that women have an adequate iodine intake of 150 µg/day before conception to avoid triggering thyroid hypertrophy during pregnancy. If pre-pregnancy iodine intake or stores are suboptimal, iodine supply should be increased as soon as possible during pregnancy, continuing through gestation and breastfeeding. The goal is to restore and maintain balanced iodine status.

It is likely that the use of iodized salt will still not meet the needs of most pregnant women, if they follow advice on sodium reduction. We therefore recommend that pregnant women take a daily multivitamin that contains 150 µg of iodine, unless they regularly consume concentrated food sources of iodine. Because of the narrow therapeutic window for iodine, care should be taken when ingesting iodine from seaweed or kelp supplements during pregnancy, to avoid excess iodine intake. The risk of iodine deficiency needs to be assessed locally and monitored over time, because of regional differences in iodine intake.

Chapter 20

Iron in pregnancy and breastfeeding

Iron functions

Most iron in the body is present as haemoglobin in red blood cells, where it serves as a carrier of oxygen from the lungs to tissues. Iron-containing enzymes in mitochondria, the cytochromes, play key roles in energy transfer during oxidative metabolism. Iron in myoglobin facilitates oxygen use and storage in muscle. Disruption of these functions because of lack of iron leads to anaemia and other serious adverse health consequences. Iron deficiency affects physical working capacity (especially endurance activities), brain function, and behaviour. Conversely, excess iron accumulation produces reactive oxygen species that can cause multiple organ dysfunction [71, 872]. Because of the negative impact of both high and low iron levels, the systemic availability of iron is tightly regulated [873].

Iron homeostasis

Iron is reversibly stored in ferritin complexes in the liver, and to a lesser extent in insoluble complexes with phosphate and hydroxide (haemosiderin). Absorption of iron in the intestine, and transfer into the circulation, is mediated by the export protein ferroportin. Hepcidin, a peptide produced in the liver, binds ferroportin and down-regulates its function by targeting ferroportin for degradation [874]. Overproduction of hepcidin decreases iron absorption and results in iron deficiency, whereas underproduction results in increased iron absorption and iron overload. Hepcidin is thus considered to be the main hormone regulating iron metabolism, and mutations in genes encoding hepcidin or its regulators are responsible for the iron-overload disorder hereditary haemochromatosis [875].

Under normal circumstances, extracellular iron is sequestered and maintained in a redox-inert state by the protein transferrin, which transports iron between body compartments when it is needed. As such, plasma transferrin is the key physiological source of iron. The soluble transferrin receptor (sTfR) mediates cellular uptake of iron by binding transferrin for internalization in endosomes, where iron is released and sTfR is recirculated. Unlike other metals, iron is not eliminated through the kidneys or liver; rather, it is lost through bleeding and exfoliation of skin and mucosal cells.

Indicators of iron status and deficiency

Measurement of sTfR in serum by various immunoassay methods provides an indication of bone marrow iron stores and is useful in the clinical diagnosis of iron-deficiency anaemia [876]. Elevated serum sTfR (≥2.0 mg/L) is indicative of iron-deficient erythropoiesis. The fractional saturation of transferrin by iron is often used as a measure of functional iron status, representative of the iron-binding capacity of serum [877]. Serum ferritin levels, on the other hand, are indicative of the status of iron stores, which become exhausted before serum iron levels are affected. Serum ferritin is therefore a more sensitive index of early iron deficiency than assays based on transferrin [878]. Measurement of hepcidin level is being considered as an additional marker of iron status [879]. The diagnosis of anaemia is generally based on haemoglobin levels or haematocrit [880], although the sensitivity and specificity of these measurements are low [881].

A serum ferritin level of <12 μg/L is indicative of depleted iron stores, and when transferrin saturation is <16 per cent in the presence of depleted stores, the individual is considered to be iron deficient. Pregnant women are considered anaemic if their haemoglobin concentration (at sea level) is lower than 110 g/L. Iron deficiency as the cause of the anaemia is confirmed by low ferritin levels, because anaemia can also be caused by deficiencies in folate, vitamin B_{12}, or vitamin A [882]. The severity of iron deficiency can thus be separated into three stages: (1) depletion of iron stores (serum ferritin <12 μg/L); (2) iron deficiency without anaemia (serum ferritin <12 μg/L, transferrin saturation <16%); and (3) iron-deficiency anaemia (serum ferritin <12 μg/L, transferrin saturation <16%, and haemoglobin <110 g/L).

Iron in pregnancy

Iron requirements increase approximately 2.5-fold by the end of pregnancy. This is the largest relative increase in nutrient requirements for pregnant women. During pregnancy there is a rise in plasma volume, red blood cell mass, and haemoglobin mass, resulting from an increased need for oxygen transport. This requires an increased iron intake of ~450 mg over the course of pregnancy (for a 55 kg woman). In addition, the growing fetus requires ~270–300 mg, and more is required for the placenta and to compensate for maternal blood losses at birth. Thus the total additional requirement during gestation is ~1,000–1,240 mg [883–885], equating to an additional 9–12 mg of iron per day above pre-pregnancy needs in the third trimester, when the majority of the iron stores in the fetus are accumulated. Even with this additional iron intake, women need to enter pregnancy with iron stores of approximately 500 mg to be able to fully meet the demands of pregnancy.

Homeostatic regulatory mechanisms operate during pregnancy to partially protect the fetus from deficiency, such that maternal and neonatal stores are correlated only if maternal iron status is very low [886]. Maternal iron absorption decreases in the first trimester, when needs are lower because of the respite from menstrual losses, but absorption increases during the second trimester and continues to rise until the end of term. Maternal iron absorption remains elevated for the first few months after delivery, to restore body iron levels [883].

Despite these regulatory mechanisms, the prevalence of iron deficiency and iron-deficiency anaemia is very high among pregnant women. The WHO estimates that 42 per cent of pregnant women worldwide are anaemic, the majority from iron deficiency [887]. The prevalence is highest in Africa, where it is estimated that 57 per cent of pregnant women have iron-deficiency anaemia. Chronic parasitic worm infections, common in South East Asia, contribute to iron-deficiency anaemia [888]. Iron deficiency and anaemia in pregnancy is still common in the US, particularly in low-income and minority groups [889].

Iron deficiency in pregnancy and infancy

Most maternal iron deficiency is caused by inadequate intake, poor iron absorption, or blood loss. When maternal iron status is suboptimal, fetal iron needs are also compromised [890]. Other conditions can influence fetal iron status, such as maternal hypertension or cigarette smoking, both of which restrict placental nutrient flow and can result in fetal iron deficiency. Vasculopathy associated with gestational diabetes impairs iron acquisition by the fetus [891]. Low pre-conception iron stores, and iron-deficiency anaemia in pregnancy, are associated with an increased risk of premature birth, low birthweight, and infant and child mortality, as well as impaired neurobehavioural development.

The effects of iron deficiency on gestational length and birthweight

Low maternal haemoglobin correlates with risk of premature birth and low birthweight. This may be due to maternal and fetal hypoxic stress associated with anaemia [892]. Pregnant women with low haemoglobin levels were found to have double the risk of premature delivery and low birthweight [893, 894].

Preterm infants themselves have low iron stores, as most iron is transferred in late pregnancy. In addition, low birthweight infants have insufficient iron stores to meet requirements for rapid catch-up growth. Maternal anaemia is also associated with increased placental weight and volume; [895] the combination of low birthweight and high placental weight are risk factors for high blood pressure in adult life [896]. A recent study of dietary iron intakes in pregnant British women found a positive correlation between intake of non-haem iron and infant birthweight [897].

The effects of iron deficiency on neurobehavioural development

There are many iron-dependent enzymes with critical functions in the CNS, including those involved in dopamine neurotransmission, which regulates motion, cognition, emotion, and hormone release [898]. Iron is supplied to the brain during an early phase of brain development, so early deficiency may lead to irreversible damage [899]. Animal studies have shown abnormal development of brain structures and altered brain myelination resulting from lack of iron in utero [900, 901]. In humans, iron deficiency in infancy is associated with poor cognitive function [902] and deficits in social–emotional behaviour [903]. Iron deficiency in early infancy has been shown to have long-term effects on auditory and visual functions that are not fully corrected by iron repletion [904]. The normal development of sleep patterns has also been shown to be disrupted in infant with iron-deficiency anaemia, with long-lasting neurofunctional effects [905].

Other effects of iron deficiency

Iron deficiency impairs thyroid metabolism and blunts the efficacy of iodine prophylaxis, which is important in pregnancy. Maternal plasma iodine declines in pregnancy and the postpartum period as it is transferred to the growing fetus via the placenta and is secreted in breast milk (see chapter 19). Further impairment of thyroid function resulting from iron deficiency is therefore of significant concern during pregnancy and breastfeeding, and iron supplementation may be warranted in women with low iodine status. Iron supplementation has been shown to improve the efficacy of iodized oil supplementation in goitrous children with iron-deficiency anaemia [906].

Groups at high risk of iron deficiency

Low body iron stores are more prevalent in pregnant adolescents than in adult pregnant women [907]. Women carrying multiple fetuses generally have lower iron stores than do those with singleton pregnancies, because of the increase fetal demand [908, 909]. A short interpartum period and high parity also increase the likelihood of low maternal iron stores. Higher rates of iron deficiency have been noted in overweight adults [910, 911], adding to the risks that overweight and obesity carry for pregnant women. Women with gestational diabetes or hypertension convey an increased risk of iron deficiency to their babies, because of poor nutrient transfer [891].

Infant iron requirements

Breast milk contains little iron, but the full-term newborn infant has iron stores of ~250–300 mg, which is sufficient for the first 4–6 months of life. Through the remainder of the first year, infants have very high iron requirements relative to body size (0.7–0.9 mg/day) [370]. From ~6 months, breastfed infants require an additional source of iron in their diets, such as lean red meat or iron-fortified infant cereal (30g cereal provides a daily requirement). Foods rich in vitamin C (fruits) enhance iron absorption from cereal. Late introduction of complementary foods was found to be the most significant risk factor for iron-deficiency anaemia in children 1–2 years of age in a study in Pakistan [912]. Iron absorption is significantly higher from human milk than from cow's milk, as casein binds iron and severely limits its absorption [260].

Iron supplementation during pregnancy

Iron supplementation in pre-pregnancy

Because of the importance of adequate pre-pregnancy iron stores, recent WHO guidelines [887] recommend intermittent supplementation (once per week) with both iron (60 mg elemental) and folic acid (2.8 mg) as a public health intervention in all non-pregnant women of reproductive age living in regions with a high prevalence of anaemia (≥ 20%, as in most developing countries). Intermittent dosing may improve iron absorption efficiency and minimize interference with absorption of other minerals (e.g. zinc), as well as minimizing the adverse effects of daily iron and improving compliance. These recommendations are based on a systematic review of 21 randomized controlled trials in Latin America, Asia, Africa, and Europe involving over 10,200 menstruating women who received weekly iron supplementation (alone or in combination with folic acid or other micronutrients) or placebo. Supplemented women had higher haemoglobin and ferritin concentrations and were less likely to develop anaemia than non-supplemented women [913].

Iron deficiency is exacerbated in malaria-endemic areas, as malaria causes iron to be shifted from haemoglobin to storage forms, resulting in anaemia. However, iron deficiency may also be protective against infection, by limiting critical nutrients to the infectious agent. Iron deficiency associated with malaria is due to iron delocalization rather than an overt lack of iron, so supplementation may not be helpful [914]. In malaria-endemic areas, supplementation with iron needs to be administered in conjunction with appropriate malaria prevention, diagnosis, and treatment measures.

Iron supplementation during pregnancy

Daily or weekly iron supplementation during pregnancy decreases the prevalence of maternal anaemia at term [915]. Meta-analyses of multiple trials could not detect any significant effect on other adverse outcomes including low birthweight, delayed development, preterm birth, infection, or postpartum haemorrhage [915, 916], although some individual studies have reported a positive effect of iron supplementation on infant birthweight. The effect of iron supplementation appears to be dependent on the degree of baseline anaemia in the population. In well-nourished women who are not anaemic, iron supplementation does not appear to affect outcomes. Nonetheless, a modelling study sponsored by Health Canada concluded that a supplement of 16 mg/day throughout pregnancy would be effective and safe for pregnant women who are in good health. When added to the iron obtained from a mixed (non-vegetarian) diet, women taking such a supplement would have sufficient iron needed for pregnancy [917, 918]. However, some studies have found that supplementation with low-dose iron (18 mg/day) could not prevent depletion of maternal stores at term [919].

In women with multiple micronutrient deficiencies, supplementation with iron alone may adversely impact the absorption of other nutrients. The prenatal supplement UNIMAP (for UN Multiple Micronutrient Preparation), formulated by WHO and UNICEF for trials in developing countries, contains 14 additional micronutrients in addition to 30 mg iron (folic acid; vitamins A, C, D, E, B_1, B_2, B_6, B_{12}, and niacin; zinc; iodine; selenium; and copper) [920]. Additional micronutrients have not been found to have a significant impact on the prevalence of anaemia, but a meta-analysis of 13 trials in developing countries found that multi-micronutrient supplementation reduced the risk of low birthweight compared with iron plus folic acid supplementation [921]. Long-term follow-up of controlled iron intervention trials in Nepal reported a 31 per cent decrease in mortality in the first 7 years of life in children born to supplemented mothers [922].

Iron supplementation in preterm infants

Because preterm infants miss the critical period in late pregnancy when the bulk of fetal iron is supplied, supplementation is generally recommended. Iron supplementation of preterm infants improves haemoglobin levels and iron stores and lowers the risk of developing iron deficiency anaemia. However, supplementation does not have clear long-term benefits on neurodevelopmental outcomes in preterm infants [923]. There appears to be no benefit in exceeding the 'standard' dose to infants (2–3 mg/kg/day) for those born preterm. Supplementation of low birthweight infants from 6 weeks to 6 months of age did not affect cognitive functions at 3.5 years but did reduce behavioural problems [924].

Iron sources and metabolism

Iron is present in the diet in two forms—haem and non-haem iron. Haem iron is a component of haemoglobin and myoglobin, and its main dietary sources are meat, poultry, and fish. Non-haem iron is obtained from cereals, pulses, legumes, fruits, and vegetables. The iron content of vegetables, fruits, breads, and pastas ranges from 0.1–1.4 mg/serving. Some fortified breakfast cereals contain up to 24 mg iron per cup. The haem iron content of meat is between 1.5 and 3 mg/serving, with pork, fish, and chicken ranging between 0.5 and 2 mg haem iron per serving. Haem iron is degraded to non-haem iron if food is cooked at high temperatures for long periods of time [260].

Although non-haem iron makes up a greater portion of iron content in most diets, it is not absorbed as efficiently as haem iron, and its absorption is inhibited by phytates present in some of the same foods. Iron absorption is also inhibited by calcium, and polyphenols from tea and coffee. However, diet modification can improve the absorption of non-haem iron. When consumed with foods containing phytates or calcium, vitamin C (ascorbic acid) improves iron absorption by releasing iron that is bound to these inhibitors. For example, a glass of orange juice can help minimize the effect of phytate in breakfast cereal and calcium in milk. Meat, fish, and poultry can also improve non-haem absorption. Even modest amounts of these foods can improve the absorption of non-haem iron in a meal [71, 925].

The recommended iron intake for pregnant women (recommended dietary allowance (RDA) 27 mg/day; see 'Agency guidelines for iron intake') is difficult to achieve even with the most optimal diets. Typical Western diets provide approximately 5–7 mg iron per 1,000 kilocalories; consuming 2,500 kcal/day would provide 12.5–17.5 mg iron/day. Analyses of intakes of middle- and upper-income pregnant women in the US found that 90 per cent had intakes below the estimated average requirement (EAR) of 22 mg/day, which is a level that is deemed to be satisfactory for around 50 per cent of the population [369, 926]. An even higher percentage would fail to meet the RDA, which was exceeded in one study only by women who regularly consumed high iron-fortified breakfast cereals [369].

In order to meet iron requirements for the latter half of pregnancy, iron usually needs to be mobilized from iron stores, or absorbed from supplemental iron. Absorption of iron is significantly lower with vegetarian diets because of a lack of meat and fish that provide haem iron and enhance non-haem iron absorption [927]. It is estimated that 10 per cent of iron is absorbed from a lacto–ovo–vegetarian diet, compared with 18 per cent from Western diet, so the iron requirement is 1.8 times higher for vegetarians [260].

Risks of excess iron

Iron supplementation is associated with adverse effects including heartburn, constipation, diarrhoea, nausea, and vomiting [928]. In various clinical studies, iron supplements of 50–60 mg/day resulted in moderate to severe gastrointestinal adverse effects in a substantial proportion of participants [929, 930]. Lower dose supplements had fewer side effects [930]. Data from studies in Canada suggested that avoidance or discontinuation of iron-containing prenatal multivitamins (and switching to folic acid + multivitamins without iron) improved symptoms of nausea and vomiting in pregnancy [931] and that adherence to and tolerability of prenatal vitamins for women with pre-existing gastrointestinal conditions was better using small tablets with low-dose iron [932]. Some of the negative gastrointestinal effects of iron supplementation may be due to increased intestinal permeability. [933]

High levels of iron in blood may have harmful effects on pregnant women. Iron overload leads to metabolic alterations that contribute to insulin resistance and increased risk of type 2 diabetes [934]. According to a recent prospective study in a cohort of 3,158 pregnant women in the US and Sweden, dietary intake of high levels of haem iron (but not total iron or non-haem iron) prior to conception and in early pregnancy were associated with an increased risk of gestational diabetes [935]. However, daily iron supplementation (60 mg/day of non-haem iron) during pregnancy was not found to affect the prevalence of gestational diabetes in a cohort of 1,164 women in China [936].

Haem iron intake was positively associated with development of type 2 diabetes in the Nurses' Health Study, which followed over 85,000 healthy women for 20 years. Women who regularly consumed >2.25 mg/day of haem iron had a significantly higher risk of developing diabetes than did women who consumed <0.75 mg/day [937]. Iron supplementation also increases the risk of zinc and copper deficiency, by competing for absorption of these minerals.

In non-anaemic women, iron supplementation can increase risk of maternal hypertension and of newborns being small for gestational age [938].

Excess free iron can generate reactive oxygen species that cause oxidative damage to tissues. Epidemiological studies support this link, showing a correlation between excess iron and increased risk of cardiovascular disease [939] and various cancers [940]. Preterm infants are particularly susceptible to the effects of reactive oxygen species because their antioxidant defence systems are immature. They are therefore at increased risk of oxidative injury from excess iron [941].

In infants who are iron replete, provision of iron-fortified formula may not be beneficial. In a small recent study, children who had high haemoglobin levels at 6 months of age and were fed iron-fortified infant formula (12.7 mg iron/L formula) had lower cognitive and visual–motor test scores at 10 years of age than children who had similar haemoglobin levels in infancy but did not receive additional iron. Those with lower baseline haemoglobin levels in the fortified group had higher scores. In other words, children who were lacking iron and received it did well, but those who received iron that they did not need did worse [942]. Although this small study needs to be replicated, the results suggest that haemoglobin levels should be tested before iron supplementation and that benefits of additional iron are dependent on baseline iron status.

Excess iron supplementation to newborns may also increase the risk of infection. Intramuscular iron dextran given prophylactically to infants in the 1970s in New Zealand (2 injections containing 50 mg each in the first week of life) resulted in a substantial increase in the incidence of *E. coli* septicaemia and meningitis until this practice of prophylactic treatment was stopped [943]. In extreme cases, excess iron can be fatal in children. Before the introduction of safety measures such as childproof caps and unit-dose blister packaging, iron supplements were the single most frequent cause of accidental ingestion fatalities in children in the US [944]. All iron-containing supplements in the US now carry the warning: 'Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6' [945].

Agency guidelines for iron intake

Iron requirements typically exceed intake during infancy, and in adolescent girls and pregnant women. The US Institute of Medicine (IOM) RDAs for iron intake are shown in Box 20.1. Recommendations differ somewhat between agencies and countries, reflecting the typical status of women and children and the prevalence of iron deficiency within their target audiences.

Box 20.1 US Institute of Medicine recommended dietary allowances for iron

Infants 0–6 months (adequate intake (AI)) = 0.27 mg/day
Infants 7–12 months (AI) = 11 mg/day
Children 1–3 years = 7 mg/day
Females 14–18 years = 15 mg/day
Females 19–50 years = 18 mg/day
Pregnancy = 27 mg/day
Lactation 14–18 years = 10 mg/day
Lactation 19+ years = 9 mg/day
Tolerable upper intake level (including pregnancy and lactation) = 45 mg/day

Source: Institute of Medicine, *Food and Nutrition Board*, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

Iron intake guidelines for pregnant women

The IOM advises pregnant women of all ages to consume 27 mg iron/day, an increase from pre-pregnancy of 15 mg/day for adolescents and 8 mg/day for adults [260]. If this intake is not achieved in the diet, iron is mobilized from maternal stores. In many women in developing countries iron stores are insufficient or do not exist. The WHO recommends that these women should be given 60 mg/day of supplemental iron (between meals) from 16 weeks gestation. Larger doses (~100 mg/day) are advised in cases of anaemia [946]. The IOM recommends supplementation for iron deficiency in pregnant women whose serum ferritin level is <12 μg/L [260].

In the US, the CDC has recommended screening for anaemia in all women of childbearing age, and low-dose iron supplementation for pregnant women [947]. The American Congress of Obstetricians and Gynecologists Practice Bulletin also recommends that all pregnant women take prenatal supplements containing iron, and advocates universal screening for anaemia, with additional iron supplementation to anaemic pregnant women [948]. The most recent publication of the Dietary Guidelines for Americans recommends that pregnant women consume dietary iron from haem sources (meat) in addition to taking an iron supplement [949]. The IOM considers a supplement of 30 mg iron/day in the second half of pregnancy to be appropriate for women consuming a diet with reasonable levels of bioavailable iron [883]. For women who consume a strictly vegetarian diet, the RDA of 27 mg iron/day (EAR 14.5 mg/day) applies even for non-pregnant women. Because of this higher requirement, the iron supplementation recommendation is even stronger for pregnant vegetarian women [260].

The UK guidelines differ from those in the US and Canada, in that routine supplementation of all pregnant women is not recommended [266, 738]. The guidelines indicate that pregnant women should screened for anaemia by full blood count in early pregnancy and at 28 weeks gestation and supplemented only following diagnosis of anaemia (defined as haemoglobin <110 g/L in the first trimester, <105 g/L in the second and third trimesters, and <100 g/L post-partum). All women should be given dietary advice to maximize iron intake and absorption [950].

Iron intake guidelines for lactating women

For lactation, the requirement drops 10 mg/day for mothers 18 years and younger, and 9 mg/day for those over 19 years. The same advice is given by the Australian National Health and Medical Research Council (<http://www.nrv.gov.au/nutrients/iron.htm>). The lower postpartum recommendation reflects the fact that secretion of iron into breast milk is not affected by maternal iron intake, unless maternal stores during pregnancy are very low. Supplementation is not generally recommended.

Iron intake guidelines for infants

The IOM has set an adequate intake level of 0.27 mg/day of iron for infants up to 6 months of age, an amount that is obtainable from breast milk and is sufficient for full-term infants born with replete iron stores. No supplementation is required for such breastfeeding infants in the first 6 months, although iron-fortified formula is recommended for those receiving formula [260]. However, after 6 months, sufficient intake of iron-rich foods (meat products or iron-fortified foods) should be ensured.

The American Academy of Pediatrics (AAP) recommends supplementation of breastfed infants from 4 months of age with 1 mg/kg oral iron supplement until iron-rich complementary foods are introduced [951]. The RDA for infants 7–12 months of age is 11 mg/day (EAR 6.9 mg/day). This is much higher (in mg/kg bodyweight terms) than other stages; after 1 year the iron requirement drops to an RDA of 7 mg/day (EAR of 3 mg/day) for children up to 3 years of age. The European Community Committee on Food guidelines state that full-term infants require an intake of 6 mg iron/day from between 4 and 6 months, up to 12 months, which equates to 0.7–0.9 mg iron/day based on an estimated bioavailability of 15 per cent [370]. More recent recommendations supported by the EURRECA (EURopean micronutrient RECommendations Aligned) network is that infants aged 6–12 months require 0.9–1.3 mg/kg body weight per day, equivalent to 7.8–11 mg/day dietary iron intake [952].

For preterm neonates, the AAP recommends supplementation with 2 mg/kg/day of enteral iron from 1 month of age, either as an iron mixture or in the form of iron-fortified formula [951]. Infant formula in Europe is usually fortified with 4–7 mg iron/L; in the US it is 12–13 mg/L. However, agencies have called for the development of a global standard [953].

Tolerable upper intake levels for iron

It is important to avoid excess iron intake. The IOM tolerable upper intake level for pregnancy is 45 mg of iron/day, which is the same as for non-pregnant women [260]. For infants and children to 13 years of age, the tolerable upper intake level is 40 mg/day. This upper limit may not be protective against iron overload in individuals with hereditary haemochromatosis, chronic alcoholism, alcoholic cirrhosis, other liver diseases, or iron-loading abnormalities (e.g. thalassaemias), in whom a lower intake is required.

Our recommendations for iron intake during pregnancy and lactation

Iron deficiency is the most common nutritional deficiency worldwide, and its prevalence is particularly high among pregnant women. Deficiency is more common in populations where malaria is endemic. Maternal iron deficiency may result in cognitive and motor deficits in the infant that may be irreversible. Prevention of deficiency is therefore critical.

Women should be advised to build or maintain sufficient iron stores prior to conception if possible. There is no international consensus on iron prophylaxis for pregnant women. During pregnancy, iron needs increase from an EAR of 8.1 mg/day for non-pregnant women to 22 mg/day, and the RDA increases from 15–18 mg/day to 27 mg/day. Pregnant women cannot normally obtain adequate iron from diet alone to meet the very high demands of the second half of pregnancy; therefore, supplementation should be considered, particularly if dietary intake of meat is low. Vegetarian women should be offered iron supplements at a recommended dosage of 30 mg/day.

In vulnerable populations, iron supplementation should be started in early pregnancy or pre-conceptionally in order to prevent preterm birth and low birthweight. Infants born to well-nourished mothers do not require iron supplementation in the first 4–6 months of life. Their first introduced complementary foods should be iron rich, for example, lean meat, lean poultry, fish, or iron-fortified cereals.

Chapter 21

Magnesium in pregnancy and breastfeeding

Magnesium functions

Approximately 50–60 per cent of magnesium in the body is present in bone; most of the rest is intracellular, with less than 1 per cent present in extracellular fluid [954]. All enzymes utilizing ATP require magnesium for substrate formation, and thus magnesium is critical to the activity of over 300 enzymes, including those involved in energy metabolism and neuromuscular signalling [955]. Magnesium acts as an allosteric activator for enzymes such as phospholipase C and adenylate cyclase, and of Na/K-ATPase, which regulates sodium and potassium transport in and out of cells. Magnesium also regulates ion channels for calcium transport, and, in addition to regulating calcium channel activity, magnesium is involved in several steps of calcium homeostasis. It is necessary for the calcium-triggered release of parathyroid hormone and for the action of parathyroid hormone on bone, kidney, and gut.

Magnesium deficiency is often accompanied by calcium deficiency, because impaired parathyroid hormone secretion caused by a lack of magnesium perpetuates low serum calcium levels. The expected rise in serum 1,25-dihydroxyvitamin D (the active form of vitamin D) that follows dietary calcium deprivation is attenuated under magnesium-deficient conditions, resulting in impaired intestinal calcium absorption. Individuals with hypocalcaemia and magnesium deficiency are resistant to pharmacological doses of vitamin D, and the hypocalcaemia cannot be corrected by administration of calcium—only supplementation with magnesium restores serum calcium to normal and improves calcium utilization [956].

Magnesium also affects potassium metabolism; the kidney cannot conserve potassium adequately if magnesium concentrations are low. Under magnesium-deficient conditions, potassium levels cannot be restored by supplementation with potassium alone—magnesium therapy is required [955]. Various conditions including diabetes, alcoholism, and malabsorption syndromes (e.g. Crohn's disease and coeliac disease) cause magnesium to be lost from the body.

Indicators of magnesium status

Hypomagnesaemia is generally defined as serum magnesium <0.7 mmol/L (<1.7 mg/dL or <1.4 mEq/L). However, measurements of serum magnesium may not adequately reflect total physiological magnesium stores because <1 per cent of total body magnesium is represented in serum. There is no generally accepted test for magnesium status [957].

Magnesium deficiency

Magnesium depletion results in neuromuscular hyper-excitability, and the first signs of deficiency are usually neuromuscular and neuropsychiatric disturbances. Other early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue, and weakness. This can be followed by numbness, tingling, spontaneous muscle contractions, and cramps (the latter are common in pregnancy).

Magnesium is a cofactor for enzymes involved in energy and carbohydrate metabolism, and low magnesium is associated with an increased likelihood of developing metabolic syndrome [958]. In particular, dyslipidaemia is strongly related to low serum magnesium levels. Supplemental magnesium may have beneficial effects in overweight individuals. Magnesium supplementation has been shown in some studies to improve dyslipidaemia and lower fasting glucose concentrations in overweight individuals and reduce markers of systemic and hepatic inflammation [959, 960].

Low magnesium levels are common in people with type 2 diabetes and can worsen insulin resistance. In the Nurses' Health Study/Health Professionals' Follow-up Study involving >85,000 women and >42,000 men, the risk of developing type 2 diabetes was higher in people with low dietary magnesium intake [961]. Particularly in overweight women, higher magnesium was associated with lower risk of type 2 diabetes [962]. The Atherosclerosis Risk in Communities Study, which involved >12,000 middle-aged participants, observed an inverse association between diabetes incidence and magnesium serum levels in Caucasian subjects but not subjects of African descent [963]. Magnesium supplementation (300 mg/day) has been shown to improve blood-glucose control in individuals with type 2 diabetes [964].

Magnesium status has an influence on cardiac function, and depletion is associated with various cardiac complications including arrhythmias, hypertension, cardiac ischaemia, and atherosclerosis. Among >7,700 women in the Atherosclerosis Risk in Communities Study, those who developed coronary heart disease had significantly lower serum magnesium levels than those who remained free of the disease, and there was a negative association between coronary risk factors and both serum magnesium and dietary magnesium intake [965]. Low dietary intake of magnesium (<200 mg/day) was associated with an increased incidence of hypertension in both men [966] and women [967] in large prospective nutritional survey studies.

Treatment with magnesium lowered blood pressure in women with mild to moderate hypertension [968]. Oral magnesium supplements of ~700 mg/day also improved exercise tolerance in small studies [969, 970]. Because of these associations, dietary changes are recommended to increase magnesium intake in individuals with or at risk for cardiovascular problems. A diet high in fruits and vegetables, which increased daily magnesium intakes from an average of 176 mg to 423 mg, significantly lowered blood pressure in non-hypertensive adults [971].

Magnesium depletion has been shown to cause a reduction in bone mass in animal models and is considered a risk factor for osteoporosis [972]. Observational data suggests a link between low magnesium intake [973] or low serum level [974] and osteoporosis [975]. Thus, supplementation may be helpful in preventing fractures.

Magnesium in pregnancy

During pregnancy, magnesium is actively transferred from mother to fetus at an average rate of 4.5 mg/day, creating a magnesium gradient across the placenta, with fetal plasma levels higher than maternal levels. However, the gradient is not sufficient to protect the fetus from maternal deficiency; in deficiency states magnesium is retained by the mother at the expense of the fetus [976]. In normal pregnancies, there is a physiological decrease in magnesium levels in the myometrium over the course of gestation. This may play a role in the initiation of uterine contractions and labour at full term [977]. Chronic or excessive vomiting that occurs with severe morning sickness in pregnancy can result in magnesium depletion, and magnesium deficiency itself can exacerbate nausea and vomiting [978]. Replenishment of magnesium is recommended in such cases.

The effects of magnesium on gestational diabetes and metabolic disturbances

Magnesium status is compromised in women with gestational diabetes [979], with decreased serum magnesium and increased urinary magnesium losses reported [980]. The effect of magnesium supplementation on the risk or severity of gestational diabetes has not been well studied, but the known effects of magnesium status on insulin resistance in non-pregnant individuals suggests that maintaining an adequate magnesium level during pregnancy would be helpful in women at risk, especially overweight and obese women. The negative impact of obesity on pregnancy outcomes suggests magnesium supplementation may help to reduce obesity-associated maternal and fetal pregnancy complications. A clinical trial is currently underway to test this (ClinicalTrials.gov Identifier NCT01510665).

The effects of magnesium on pregnancy-induced hypertension and pre-eclampsia

In non-pregnant women, higher dietary magnesium intakes have been shown to be associated with a lower risk of developing hypertension [981]. No published studies have assessed dietary magnesium in pregnancy and the risk of pregnancy-induced hypertension (PIH), but a small recent study reported significantly lower serum magnesium levels in women who developed PIH than in pregnant women without hypertension [982]. A small study in China suggested that supplementation with low-dose magnesium gluconate (3 g/day (~165 mg/day elemental magnesium)) during pregnancy may help prevent PIH in high-risk women [983], but a larger study (n = 400) using 365 mg/day elemental magnesium (as magnesium aspartate HCl) found no difference in blood pressure between the supplemented and placebo groups of young, normotensive, primigravid women [984]. A meta-analysis that included both these studies concluded that there was not enough evidence to recommend oral magnesium supplementation during pregnancy for the purpose of lowering blood pressure [985].

Magnesium is, however, used pharmacologically during pregnancy. Magnesium sulphate infusion is considered the treatment of choice for the acute management of pre-eclampsia in the US. In a trial of >10,000 participants, magnesium sulphate treatment of women with pre-eclampsia halved the risk of developing eclampsia and prevented eclamptic convulsions [986].

The effects of magnesium on preterm birth

Low serum magnesium correlated with a higher incidence of preterm birth and was associated with lower socio-economic class (and therefore probably poor diet) in a case–control study in India [987]. One study of magnesium supplementation (15 mmol/day (=369 mg/day)) provided to women prior to 16 weeks gestation reported a lower risk of preterm labour and delivery in women who received magnesium, compared with a placebo control group [988]. However, a review of trials of magnesium supplementation therapy after an episode of threatened preterm labour to prevent further preterm contractions did not find enough evidence to support the use of maintenance magnesium supplementation for this indication [989].

The effects of magnesium on low birthweight

An epidemiological study in Taiwan found evidence of a relationship between high levels of magnesium in drinking water and a reduced risk of very low birthweight (<1,500 g) in newborns [990]. Most other evidence suggesting an effect of magnesium on birthweight comes from studies on magnesium in reducing preterm births; cohorts with lower incidence of preterm birth would naturally have higher mean birthweight. A meta-analysis of trials of oral magnesium supplementation during pregnancy found that treatment before the 25th week of gestation reduced the number of low-birthweight and small-for-gestational-age infants, but because the methodology of most studies was poor, supplementation could not be recommended [985]. There is no unequivocal evidence at this time that magnesium has a direct effect on intrauterine growth restriction.

The effects of magnesium on neuroprotection in the fetus

Magnesium has neuroprotective effects via actions of the *N*-methyl-D-aspartate receptor (also known as the NMDA receptor). Neurodevelopmental problems including cerebral palsy are associated with preterm birth (<34 weeks) and very low birthweight (<1,500 g) as major obstetric risk factors [991]. Magnesium sulphate is administered pharmacologically to women in the US and other countries during threatened preterm labour to lower the risk of fetal neurological defects and improve neurodevelopment in preterm neonates. Multiple studies have assessed the efficacy and safety of magnesium sulphate administered antenatally to women at risk of preterm birth, and significant beneficial neuroprotective effects for preterm infants have been demonstrated [992].

Fetal hypoxic–ischaemic encephalopathy is a common obstetric problem in underdeveloped regions. A study of fetal outcomes of indigent Black women in South Africa found that daily supplementation with 256 mg elemental magnesium during pregnancy reduced the number of stillbirths compared with placebo but did not significantly reduce the incidence of hypoxic–ischaemic encephalopathy in this low socio-economic group, who are known to consume a diet deficient in magnesium. However, across the entire study cohort, women with red blood cell magnesium levels below the median (1.71 mmol/L) had a sevenfold increased risk of having a baby with hypoxic–ischaemic encephalopathy than those whose levels were above the median (red blood cell magnesium is considered a better reflection of total body magnesium than serum levels). Supplemental magnesium appeared to benefit the fetus in labour, reducing fetal distress and depressed respiration during birth, possibly by reducing or preventing the impaired uterine activity caused by low maternal magnesium [993].

The effects of magnesium on skeletal development

There are no data directly linking magnesium deficiency to fetal skeletal defects or maternal bone resorption in pregnancy, although its involvement in calcium metabolism suggests that deficiency could lead to adverse bone outcomes during fetal development. A longitudinal study into the effect of the maternal diet on bone mineral density (BMD) in children found a positive association between maternal magnesium intake during pregnancy and total body BMD in the offspring at 9 years of age [994]. Similarly, a smaller longitudinal cohort study showed femoral neck BMD at 8 years of age was related to the magnesium and phosphorus content of the maternal diet in the third trimester of pregnancy [995]. Maternal magnesium intake remained positively associated with BMD in offspring at 16 years of age [996], supporting the idea that in utero magnesium exposure contributes to long-term bone mineralization responses and influences peak bone mass.

The effects of magnesium on muscle cramps

Nocturnal leg cramps are a common occurrence during the second half of pregnancy. An early study found that supplementation with 360 mg/day (15 mmol) magnesium lactate/magnesium citrate was effective in relieving muscle cramps in pregnant women [997], but a more recent study of the same supplementation regimen did not find a significant effect on cramp frequency or intensity [998]. Another study using magnesium bisglycinate chelate at 3 daily doses of 100 mg demonstrated a 50 per cent reduction in cramp frequency [999]. The frequency and occurrence of leg cramps was found to be lower in a group of pregnant women who habitually consumed a high magnesium, plant-based diet compared with a control group consuming a standard Western diet [1000], suggesting that dietary changes may be at least as effective as supplementation in reducing leg cramps in pregnancy.

Magnesium supplementation in pregnancy

Overall, trials of oral magnesium supplementation during high-risk or normal pregnancies have not shown definitive benefit for various maternal and infant outcomes including neonatal mortality, neonatal morbidity (low birthweight, preterm birth, and related measures), maternal morbidity, blood pressure, PIH, pre-eclampsia, and length of labour. A meta-analysis of seven magnesium supplementation trials concluded that there was not enough high-quality evidence to recommend the routine use of magnesium supplements during pregnancy [985]. Other observational data suggest that routine magnesium supplementation is not needed for populations of relatively good socio-economic status [1001].

Magnesium in breast milk

Maternal serum magnesium does not change significantly during lactation, and excretion in breast milk also remains relatively constant. Despite this, magnesium concentrations in infant sera appear to increase with longer breastfeeding duration [1002]. No relationship has been found between intake of dietary magnesium supplements and the level of magnesium in breast milk. It is estimated that fully breastfed infants receive approximately 6.5 mg/kg/day of magnesium in early lactation [1003] and that the average concentration of magnesium in breast milk is approximately 31 mg/L [1004]. Mothers nursing multiple infants may require additional magnesium intake to account for the increased milk volume requirement [253]. Adolescent pregnancy is a risk factor for poor bone mineralization, and the magnesium content of breast milk from adolescent mothers is lower than that from adult mothers [1005].

Sources of magnesium

Magnesium is present in the core of the chlorophyll molecule; thus, green vegetables such as spinach are good dietary sources. A half-cup serving of cooked spinach contains 78 mg of magnesium. Other good sources are whole grains (wheat bran), nuts, and legumes (beans and peas). On a weight basis, spices, nuts, cereals, and seafood are high in magnesium; however, on a calorie basis, green leafy vegetables have the highest amount. Coffee, tea, and cocoa are also magnesium rich, although coffee and tea are diuretic and therefore result in some magnesium loss.

Drinking water can also be a major source of magnesium, although the concentrations of magnesium in drinking water are highly variable. ‘Hard’ water is characterized by the presence of minerals and has a higher magnesium content than ‘soft’ water. Consumption of tap water containing magnesium can therefore significantly influence magnesium intake, contributing up to 40–100 mg/day [571], or up to 38 per cent of daily magnesium intake in hard-water communities [1006]. Regular consumption of magnesium-rich mineral water (110 mg/L) can also make a significant contribution to magnesium requirements [1007].

The calcium, phytate, and protein content of the diet can influence magnesium absorption. When magnesium intake is low, calcium supplementation may reduce magnesium absorption and retention. Low dietary protein intake (<30 g/day) also lowers magnesium absorption [1008, 1009], but protein intakes over 94 g/day may enhance magnesium excretion [1010]. Excess protein, calcium, phosphate, and phytate therefore increase the magnesium requirement, and the magnesium balance can be negative in pregnancy under diets that provide adequate amounts of these other nutrients [1011].

Refining and cooking foods diminishes their magnesium content. In particular, the refining of flour results in the loss of ~90 per cent of its natural magnesium content. Moreover, refined foods in general have the lowest magnesium content [571]. A diet that is high in green vegetables and whole, unprocessed grains, nuts, legumes, and seafood is beneficial from a standpoint of magnesium content and is recommended generally as an ideal pregnancy diet that has a positive impact on overall health. It should be noted, however, that predatory fish and seafood containing high levels of mercury or other toxins should be avoided (see chapter 30).

Risks of excess magnesium

Magnesium intake from food does not pose a health risk. Pharmacological doses of magnesium supplements or high doses of magnesium-containing antacids and laxatives can cause diarrhoea and abdominal cramps. Single doses of elemental magnesium of 800–1,600 mg can produce a dose-limiting laxative effect. The kidney has a large capacity to excrete excess magnesium. However, people with kidney disease should not take magnesium supplements, as excretion of excess magnesium could be impaired [1012]. Hypermagnesaemia in the fetus can result from administration of magnesium sulphate to the mother for pre-eclampsia or threatened preterm labour. This can result in neuromuscular depression at birth and other possible adverse effects including anaphylaxis [976], although these effects are rare using current standard infusion protocols.

Agency guidelines for magnesium intake

According to the US Institute of Medicine (IOM), the normal requirement for non-pregnant women is between 310 and 360 mg/day of magnesium, but requirements are elevated somewhat during periods of growth, including pregnancy. The IOM recommended dietary allowances (RDA) for pregnancy and lactation vary according to maternal age, as shown in Box 21.1.

The RDA represents an increase of 40 mg/day during pregnancy, returning to non-pregnancy requirements during lactation. The calculation is based on the assumption that women gain an average of 7.5 kg lean mass during pregnancy, and that the absorption efficiency of magnesium is ~40 per cent. This increase could be achieved through the consumption of green leafy vegetables, whole grains, and nuts. Throughout lactation, bone resorption and reduced urinary excretion compensate for the extra requirements for magnesium secretion in milk. However, women who are breastfeeding multiple infants will require additional intakes of magnesium-rich foods to account for their increased milk production requirement [71, 571].

Box 21.1 US Institute of Medicine recommended dietary allowances for magnesium

Infants 0–12 months = not determined.
Children 1–3 years = 80 mg/day
Females 14–18 years = 360 mg/day
Females 19–30 years = 310 mg/day
Females 31+ years = 320 mg/day
Pregnancy 14–18 years = 400 mg/day
Lactation 14–18 years = 360 mg/day
Pregnancy 19–30 years = 350 mg/day
Lactation 19–30 years = 310 mg/day
Pregnancy 31+ years = 360 mg/day
Lactation 31+ years = 320 mg/day
Tolerable upper intake level = 350 mg/day supplemental magnesium

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*, Dietary Reference Intakes, The National Academies Press, Washington, DC, copyright © 1997. [571]

Because acute excessive intake of magnesium is possible from non-food sources, the IOM recommends a tolerable upper intake level of 350 mg/day of supplemental magnesium. Higher doses are prescribed for specific medical problems. There is no set upper level for magnesium intake from food [253, 571].

The UK National Institute for Clinical Excellence recommends against advising women to take magnesium supplements, with the aim of preventing hypertensive disorders during pregnancy [761]. The UK Royal College of Obstetricians and Gynaecologists (RCOG) recommends that pregnant women should not take supplemental magnesium unless advised to do so by their physicians following tests to identify possible deficiency. The American Pregnancy Association suggests that intake of supplemental magnesium in the form of antacids may be beneficial if taken in limited quantities, but should not be taken in high doses without the advice of a physician [1013].

Various clinical practice guidelines recommend administration of intravenous magnesium sulphate to women for fetal neuroprotection (reducing the risk of cerebral palsy) in situations of threatened preterm birth. (Australia [1014]; Canada [1015]; UK (RCOG) [1016]). The recommended adequate intake for infants up to 6 months of age is 30 mg/day, which can be acquired through breast milk in most cases. Infants 7–12 months of age require ~75 mg/day, some of which will need to come from solid food sources [71, 571].

Our recommendations for magnesium intake during pregnancy and lactation

Current evidence does not support a requirement for specific magnesium supplementation for most pregnant women, although all women should strive to increase their consumption of magnesium-rich foods, such as green leafy vegetables, relative to high-fat and processed foods in the diet. Diets high in magnesium represent positive lifestyle modifications, particularly for individuals with hypertension, as they are often also high in dietary fibre and potassium. Consuming a magnesium-rich diet throughout pregnancy is recommended. Women who are overweight, have risk factors for hypertensive or metabolic disorders or malabsorption syndromes, or who are carrying multiple fetuses should pay particular attention to their diets and should be monitored for signs of magnesium deficiency.

Chapter 22

Potassium in pregnancy and breastfeeding

Potassium functions

Potassium is an important electrolyte that is present in intracellular fluid at a concentration that is much higher than that outside cells. The ion concentration difference across the cell membrane generates a voltage gradient (membrane potential) that allows cells to transmit electrical signals important for muscle contraction, nerve impulse transmission, and cardiac function. The balance between intra- and extracellular potassium and sodium is maintained by the sodium–potassium pump Na/K-ATPase [1017].

Serum potassium less than 3.5 mmol/L is indicative of potassium deficiency (hypokalaemia), which is characterized by cardiac arrhythmias, blood pressure elevation, muscle weakness, and glucose intolerance. Blood pressure is closely associated with the sodium:potassium ratio, correlating inversely with potassium intake and directly with sodium intake [1018]. Glucose intolerance occurs in the presence of hypokalaemia because the capacity of the pancreas to secrete insulin is reduced. Thiazide diuretics used for the treatment of hypertension cause a reduction in serum potassium and have been associated with an increased risk of type 2 diabetes [1019]. Potassium bicarbonate acts as a buffer which neutralizes non-carbonic acids from the diet. When potassium is low, alkaline calcium salts are mobilized from bone matrix for acid neutralization, and bone demineralization occurs [1020].

Normal renal function protects against hyperkalaemia at high potassium intakes, but does not prevent deficiency at low intakes. High levels of potassium (hyperkalaemia) can also cause dangerous, even life-threatening arrhythmias. High serum potassium concentrations have been observed in people with sickle-cell anaemia, as deoxygenation of sickle cells induces potassium efflux, resulting in red blood cell dehydration. Potassium intake from supplements can cause gastrointestinal upset, although this is not observed with potassium intake from food [1017].

Potassium in pregnancy

The fetus accumulates approximately 12 g (307 mmol) of potassium by the end of gestation. Very little information is available, however, about maternal potassium balance during pregnancy [1017]. A small study in Swedish women found that total body potassium decreased in pregnancy and was significantly lower at 6 months postpartum than in the pre-pregnant state [1021].

Conditions associated with pregnancy, such as severe vomiting or morning sickness, can cause potassium loss. Caffeine increases the renal excretion of potassium, and a high caffeine intake in pregnancy can cause a further reduction in serum potassium. Cases of hypokalaemia in pregnancy have been observed in women with heavy caffeine/cola consumption, resulting in extreme muscle fatigue [1022] and muscular paralysis [1023]. Hypokalaemia caused by excess caffeine and/or cola consumption can also manifest as myopathy [1024]. Similar hypokalaemic symptoms caused by eating clay (geophagia) during pregnancy have also been reported [1025].

Despite its role in cardiac function and blood pressure control, potassium intake has not been not associated with hypertensive disorders of pregnancy [1026]. There are no data available on the effect of potassium on bone mineralization changes during pregnancy and lactation. To date, there is insufficient evidence to suggest that the potassium requirement is increased during pregnancy, although a small increase in intake is needed for lactation. To maintain the normal potassium content of human milk (0.5 g/L (13 mmol/L)), an additional 0.4 g/day (10 mmol) is required, based on a milk output of 780 mL/day [1017].

Potassium sources

Leafy green vegetables are good sources of potassium, as are root vegetables, beans and peas, fruits from vine-based plants (e.g. tomatoes, cucumbers, zucchini, eggplant, and pumpkin), and tree fruits. Dairy products, meats, and nuts have moderate potassium contents. Salt substitutes that are sometimes used in low-sodium diets contain between 440 and 2,800 mg potassium/teaspoon. High protein, low carbohydrate diets that are also low in fruit contain adequate potassium but result in mild metabolic acidosis. Long-term consumption of cola-based soft drinks or large amounts of coffee or other caffeinated beverages can result in hypokalaemia.

Agency guidelines for potassium intake

The US Institute of Medicine recommends an adequate intake (AI) level for infants for the first 6 months of 0.4 g potassium/day (see Box 22.1), which

Box 22.1 US Institute of Medicine recommended dietary allowances for potassium

Infants 0–6 months (adequate intake (AI)) = 0.4 g/day
Infants 7–12 months (AI) = 0.7 g/day
Children 1–3 years = 3.0 g/day
Females 14+ years = 4.7 g/day
Pregnancy = 4.7 g/day
Lactation = 5.1 g/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate,* The National Academies Press, Washington, DC, copyright © 2005. [1017]

can be acquired from breast milk. Infants aged 7–12 months should consume 0.7 g/day, based on consumption of human milk and complementary foods [1017]. From the age of 14, the recommended AI level for both adolescents and adults is 4.7 g potassium/day [1017]. This is based on the protective effects of this potassium intake level on blood pressure, bone density, and risk of kidney stones. No increase in this requirement is advised for pregnant women, but lactating women need 5.1 g potassium/day.

Our recommendations for potassium intake during pregnancy and lactation

Pregnant and lactating women should ensure adequate potassium in their diets by increasing their consumption of fruits and vegetables. Consumption of cola and caffeine should be minimized to reduce the risk of hypokalaemia. Reduction of cardiovascular risk factors and bone loss may be assisted by increasing potassium intake, and/or by dietary sodium reduction.

Chapter 23

Selenium in pregnancy and breastfeeding

Selenium functions

Selenium is an essential trace mineral that is required in the diet in small amounts. It is a component of selenoproteins that act as antioxidant enzymes, preventing cell damage by neutralizing the deleterious effect of free radicals. Selenoproteins also regulate thyroid hormone metabolism [1027] and immune function [1028]. The main selenoprotein families include glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases. The iodothyronine deiodinases are required for the conversion of thyroxine (also known as T4) to the biologically active thyroid hormone, triiodothyronine (also known as T3). Thyroid metabolism is thus sensitive to selenium in the diet, and selenium deficiency can exacerbate the effects of iodine deficiency [906].

Selenium deficiency is also associated with enhanced viral virulence. For example, Keshan disease myocarditis is a selenium deficiency disorder that occurs in regions where soil selenium, and therefore selenium intake from food, is very low (e.g. China). Keshan disease appears to involve activation of a normally quiescent virus via increased oxidative stress in the presence of low selenium [1029]. Vitamins A, E, and C can modulate selenium absorption. A combined deficiency of vitamin E and selenium leads to an increase in oxidative damage.

Indicators of selenium status

Urinary selenium is used to assess selenium intake status, with a reference range of 15–50 μg/L. Daily excretion of <15 μg/L indicates insufficient selenium nutriture, and an output of >50 μg/L indicates excessive intake [1030]. Other frequently measured markers include plasma selenium, plasma selenoprotein P, and glutathione peroxidase, all of which are responsive to changes in selenium intake. However, all these markers exhibit some heterogeneity in responses to supplementation, and further research is required to optimize them as standard tests for selenium status [1031].

Selenium and fertility

Several selenium-dependent proteins are important in male fertility. The selenoprotein glutathione peroxidase 4 is essential for sperm structure and function. In addition, the sperm mitochondrial capsule selenoprotein has both structural and enzymatic roles in sperm tail motility and integrity. A study in Glasgow (an area with low selenium intakes) found enhanced sperm motility in men receiving selenium supplements [1032]. A more recent randomized controlled trial in Iran found that supplementation of infertile men with 200 µg selenium and/or *N*-acetyl cysteine increased sperm count and sperm motility after 26 weeks of treatment [1033]. However, there is no indication of a link between selenium levels and fertility in females.

Selenium in pregnancy

Selenium is important in pregnancy as an antioxidant, and low selenium status has been implicated in pregnancy complications that are associated with increased oxidative stress. During pregnancy, there is a decrease in maternal selenium concentrations in whole blood and plasma and in glutathione peroxidase activity in red blood cells, correlating with an increase in selenium concentration in cord blood, as selenium is actively transported to the fetus. An analysis of intakes of middle- and upper-income pregnant women in the US found that the usual intake in this group exceeded the estimated average requirement (49 µg/day) and generally met the recommended dietary allowance (RDA; 60 µg/day) [718]. Selenium levels are affected by alcohol consumption and tobacco smoking, both of which decrease selenium absorption.

Selenium and miscarriage

Selenium deficiency is associated with idiopathic spontaneous abortion in farm animals [1034], and several studies have investigated the possible link between low maternal selenium levels and increased risk of miscarriage in humans; however, the results are inconsistent. One study reported that serum selenium levels were lower in women who miscarried in the first trimester when compared to those in women with viable pregnancies [1035]. Others found no difference in selenium levels in whole blood or plasma between women with viable pregnancies and those who had miscarried but noted a significantly lower activity of the selenoprotein glutathione peroxidase in red blood cells and plasma of women who had miscarried [1036]. Lower levels of selenium were also found in hair samples from women with recurrent miscarriage [1037]. However, all studies were small and therefore should be interpreted with caution.

Selenium and preterm delivery

Low selenium concentrations in maternal and cord blood were observed in preterm deliveries as compared with term births in two small case–control studies [1038, 1039]. It was suggested that decreased levels of selenium may be involved in the pathogenesis of retinopathy and respiratory distress syndrome in premature infants, as oxidative stress is implicated in these preterm complications [1040]. Epidemiological evidence suggests that good maternal selenium status may be protective against the potentially toxic effect of oxidizing agents that can provoke preterm delivery.

The effects of selenium on infection and viral transmission

In animals, blood selenium levels are inversely correlated with risk of infection from various bacterial agents. Selenium deficiency may be a risk factor for mother-to-child transmission of HIV, which can occur in utero, during delivery, or through breastfeeding [1041]. It is possible that selenium deficiency accelerates HIV disease during pregnancy. There is evidence that viral shedding into the genital tract is increased in selenium-deficient women [1042].

Low selenium is also a risk factor for the progression of AIDS in children who were infected perinatally, leading to an increased risk of death by the age of 5. Children with selenium levels ≤85 μg/L died at a younger age, suggesting a more rapid disease progression [1043]. In HIV-infected pregnant women in Tanzania (n = 670), low maternal plasma selenium was not related to risk of in utero HIV transmission but did increase the risk of intrapartum transmission, and transmission through breast milk during early lactation [1041]. Selenium levels were also inversely correlated with risk of fetal death and child death in the first 24 months. This is supported by the results of a placebo-controlled intervention trial (randomized, double-blind) in 913 HIV-infected pregnant women, which showed improved child survival with maternal selenium supplementation. Selenium supplementation did not, however, delay maternal HIV disease progression or improve other pregnancy outcomes [1044]. A recent systematic review concluded that the evidence is currently insufficient to recommend selenium supplementation alone; multivitamin supplementation is recommended [1045].

Selenium in breast milk

The selenium concentration and glutathione peroxidase activity of breast milk are positively correlated with maternal plasma selenium concentrations, indicating that the selenium content in breast milk is influenced by maternal selenium nutrition [1046]. Selenium decreases in breast milk over the course of lactation and is lower in the serum of lactating mothers compared with that of non-lactating mothers [1047]. Lactating women therefore require additional selenium intake in order to produce milk that meets their infant's selenium needs.

Selenium sources

The selenium in crop foods is substantially affected by the amount of selenium in the soil in which they are grown. Brazil nuts are extremely high in selenium and should be eaten only occasionally or in small amounts. Other dietary sources include shellfish and other seafood, meat, poultry, and cereals. A recommended diet emphasizes intake of a variety of fruits, vegetables, whole grains, and reduced fat or fat-free dairy products, with a moderate intake of lean meats, poultry, fish, beans, and eggs. In the UK, cereals account for ~20 per cent of total selenium intake; 30–40 per cent comes from meat, poultry, and fish [1048].

Risks of excess selenium

Selenium overload, or selenosis, results from excess selenium in soil and consequent elevated selenium intake in localized areas. High blood selenium (≥100 μg/dL) occurs at intakes around 1.25 mg/day [1049]. Symptoms include garlic breath odour, gastrointestinal distress, hair loss and fingernail changes, fatigue, and irritability. Selenosis can also cause mild nerve damage. The Nutritional Prevention of Cancer Trial found that intake of selenium supplements of 200 μg/day in addition to usual dietary intake over a period of almost 8 years was associated with increased risk of type 2 diabetes, as compared with placebo [1050].

Agency guidelines for selenium intake

Selenium has a very narrow safe intake range. Agency recommendations in the US and UK differ slightly. The UK reference nutrient intakes [738] for selenium are slightly lower for infants and slightly higher for adults, as compared with the US Institute of Medicine (IOM) recommendations [718] (see Box 23.1 for IOM recommendations). However, these agencies' recommendations are the same for pregnancy, at 60 μg selenium/day, and lactation, at 70 μg/day. These levels are increased from the 55 μg/day RDA for the non-pregnant state. European recommendations [370] are similar to those of the IOM. For infants 0–6 months of age, the UK reference nutrient intake is 10–13 μg/day, whereas the US adequate intake (AI) level is 15 μg/day. For those aged 7–12 months, the UK reference nutrient intake is 10 μg/day, whereas the US AI level is 20 μg/day. The

Box 23.1 US Institute of Medicine recommended dietary allowances for selenium

Infants 0–6 months (adequate intake (AI)) = 15 μg/day
Infants 7–12 months (AI) = 20 μg/day
Children 1–3 years = 20 μg/day
Females 14+ years = 55 μg/day
Pregnancy = 60 μg/day
Lactation = 70 μg/day
Tolerable upper intake level = 400 μg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*, Dietary Reference Intakes, The National Academies Press, Washington, DC, copyright © 2000. [718]

tolerable upper intake level is 400 μg/day for adults, 45 μg/day for infants aged 0–6 months, and 60 μg/day for those aged 7–12 months.

A report of a joint FAO/WHO expert consultation in 2001 [884] proposed a significant decrease in the suggested need for selenium for developing countries, based on a proportionally lower weight range than for most Western and developed communities, among other factors. Their recommendations for pregnant women were 28 μg/day in the second trimester and 30 μg/day in the third; these levels are approximately half that of the IOM recommendation.

Our recommendations for selenium intake during pregnancy and lactation

Selenium supplements are usually not necessary to meet dietary needs, regardless of pregnancy or lactation status. More is not better, as excess selenium can be toxic. However, individuals with malabsorption syndromes may require supplementation, which should be supervised by a physician.

Because some foods differ widely in selenium content according to their geographical sources, a variety of foods should be eaten to ensure adequate intake and to avoid toxicity. Most pregnant women in developed countries will be able to meet selenium requirements through their usual diet. Taking selenium supplements in addition to adequate dietary intake is not recommended.

Chapter 24

Copper in pregnancy and breastfeeding

Copper functions

Copper is an essential trace mineral that readily accepts and donates electrons, which accounts for its central role in oxidation–reduction reactions. It is a component of oxidase metalloenzymes (cuproenzymes) with essential cellular functions. The copper-dependent ferroxidase enzyme ceruloplasmin, for example, plays a significant role iron transport and metabolism [1051]. Cytochrome C oxidase, another copper-dependent enzyme, catalyses the reduction of molecular oxygen to water, generating an electrical gradient involved in cellular energy production. Copper/zinc superoxide dismutase is important in antioxidant defence in cells exposed to oxygen [1052]. Other copper-dependent oxidases catalyse metabolic reactions in the formation and degradation of neurotransmitters, including norepinephrine, epinephrine, serotonin, and dopamine [260].

Copper is involved in connective tissue formation, as the cuproenzyme lysyl oxidase is required for collagen and elastin cross-linking. Reduced activity of this enzyme leads to fragility of connective tissue and blood vessels. Copper also plays a role in the disulphide bonding of keratin [1053]; one manifestation of copper deficiency is twisted, kinked hair [1054]. Most copper in the body, however, is found in bones, muscle, and liver.

Indicators of copper status

Low levels of serum or plasma copper or ceruloplasmin and decreased erythrocyte dismutase activity are all indicators of copper deficiency but not of copper intake, as they are not sensitive to marginal copper status [1055]. In deficiency conditions, these markers respond to copper supplementation. A serum copper level below 10 μmol/L or ceruloplasmin below 180 mg/L is indicative of deficiency [260].

Copper deficiency

Clinical deficiency for copper is uncommon but can result from malnutrition, a lack of trace metals in food sources, or genetic disorders. Nutritional copper deficiency has been increasing in prevalence, including in people consuming a Western diet [1056]. Genetic mutations in copper transporters or the copper-binding protein ceruloplasmin result in severe copper deficiency, with multiple serious health consequences including neurodegeneration [1057]. Marginal copper deficiency may compromise immune responses [1058]. Secondary copper deficiency can be induced by excess intake of zinc or iron and is sometimes seen in individuals taking supplements of these minerals. Conversely, alteration of the copper:zinc ratio during treatment for copper deficiency can precipitate zinc deficiency.

Copper in pregnancy, lactation, and infant feeding

Copper requirements are increased in pregnancy, and a suboptimal supply may have adverse effects on developing tissues and organ systems, including lungs, skin, bones, and the immune system [1059]. Serum copper and ceruloplasmin concentrations increase in pregnancy as copper is mobilized from the liver. This normal increase in blood copper has the potential to mask copper deficiency in tissues.

The body of a full-term fetus contains approximately 13.7 mg of copper. Manifestations of deficiency in the newborn include oedema, anaemia, bone disease, and recurrent apnoea [1060]. The requirement of the fetus for copper must be met throughout gestation from the maternal diet and maternal tissue reserves; low birthweight or premature infants are at risk of copper deficiency because of their increased need of nutrients for growth and bone formation. Infants of very low birthweight require at least 1 μmol/kg of copper per day during parenteral and enteral feeding [1061]. Premature infants fed iron-fortified formulas lacking sufficient copper may also be at increased risk for deficiency conditions [1062]. The copper content of human milk is highest during early lactation and declines as lactation progresses, averaging approximately 250 μg/L during the first 6 months [260]. The recommended intake for infants is based on this breast milk concentration and average daily milk intake and is estimated at 200 μg/day for the first 6 months.

Risks of excess copper

There is an adaptive response to high copper intake that limits absorption, although increased serum copper levels may lead to an increased risk of cardiovascular disease. Acute copper poisoning is rare, as excess copper is highly emetic, causing nausea and vomiting. Ingestion of >15 mg is toxic. Gastrointestinal irritation is seen at 5.3 mg/day. Ingestion of gram quantities is fatal [1063].

Copper sources

Foods high in copper include organ meats, grains, shellfish (oysters), nuts, seeds, and cocoa products. Foods that are relatively low in copper but are consumed in substantial amounts include tea, potatoes, milk, and chicken, and these represent significant dietary sources for many populations. Fats and oils are notably low or completely lacking in copper. A higher percentage of copper is absorbed from animal sources than from plant sources [260]. Pure drinking water contains approximately 4–10 μg copper/L water and contributes 6–13 per cent of the average daily copper intake in the US [1064].

Agency guidelines for copper intake

The US Institute of Medicine recommendation for adults (19+ years) is 900 μg/day copper, with a tolerable upper intake level of 10 mg/day from a combination of food, water, and supplements (see Box 24.1). For pregnant women of all ages, the recommended dietary allowance is 1 mg/day, increasing to 1.3 mg/day during lactation [260].

The Australian National Health and Medical Research Council and the New Zealand Ministry of Health recommend 1.3 mg/day for pregnant adults and 1.2 mg/day for pregnant adolescents (14–18 years) [1065]. The upper level of intake that is considered safe during pregnancy is 8–10 mg/day.

Box 24.1 US Institute of Medicine recommended dietary allowances for copper

Infants 0–6 months (adequate intake (AI)) = 200 μg/day
Infants 7–12 months (AI) = 220 μg/day
Children 1–3 years = 340 μg/day
Females 14–18 years = 890 μg/day
Females 19+ years = 900 μg/day
Pregnancy = 1,000 μg/day
Lactation = 1,300 μg/day
Tolerable upper intake level 14–18 years = 8,000 μg/day; 19+ years = 10,000 μg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

Our recommendations for copper intake during pregnancy and lactation

Copper is an important micronutrient that is widely available in foods and drinking water. Although copper needs are increased in pregnancy, supplementation is generally not recommended. Women consuming high doses of iron and/or zinc supplements are at risk for marginal copper deficiency, and this should be taken into account in assessing the mineral supplement needs of pregnant women. An increased intake of foods high in copper, such as nuts, and a proportionate lowering of low-copper foods (e.g. fats/oils) may be advisable in women with potentially marginal copper status.

Chapter 25

Zinc in pregnancy and breastfeeding

Zinc functions

Zinc has important structural and functional roles in a number of enzyme systems that are essential for gene expression, cell growth and division, neurotransmission, and reproductive and immune functions [1066]. Loss of zinc from plasma membranes increases their susceptibility to oxidative damage [1067]. In infants and children, zinc is necessary for physical and neurobehavioural development, and protection against infection. It is crucial for periods of growth, including pregnancy and lactation, infancy, childhood, and adolescence.

Indicators of zinc status

Although much is known about the effects of zinc and its deficiency, the ability to provide practical advice to individuals has been hampered somewhat by the lack of a sensitive marker of zinc status. The concentration of zinc in serum or plasma is used as a biomarker of zinc deficiency risk in populations, as on a population scale, it reflects dietary zinc intake and response to zinc supplementation. However, serum zinc does not consistently reflect the functional zinc status of an individual, and it is not recommended as a diagnostic indicator or to signal the need for supplementation on an individual basis [1068, 1069]. Marginal deficiency for zinc causes broad, and often non-specific, adverse effects due to its involvement in the normal function of a wide range of biochemical pathways. The diagnosis of zinc deficiency can therefore be difficult—there are no truly characteristic physical signs or appropriately sensitive laboratory indices.

Zinc deficiency

Inadequate zinc intake often accompanies general protein/calorie malnourishment but is also seen in individuals consuming poor quality diets. It is estimated that 20–30 per cent of the global population are at risk of inadequate zinc intake, and deficiency is common in regions such as sub-Saharan Africa and South Asia, where the zinc content in the food supply may be inadequate to meet nutritional needs [1070]. Diets low in animal protein [1071] and/or those high in phytates (e.g. in whole grains or unleavened bread) [1072] provide limited amounts of bioavailable zinc. In addition to inadequate dietary intake, zinc deficiency occurs under conditions of abnormal mucosal uptake (e.g. coeliac disease), abnormal intestinal loss (e.g. Crohn's disease), abnormal renal excretion, alcoholism, or treatment with diuretic drugs. It can also be caused by hereditary conditions, for example, acrodermatitis enteropathica [1073].

The effects of zinc on growth

Zinc deficiency attenuates growth factor signalling, specifically impacting the insulin-like growth factor axis [1074]. Periods of rapid growth (e.g. late pregnancy, infancy, and adolescence) are the most susceptible to the effects of dietary zinc deficiency. In childhood, zinc deficiency is associated with poor growth and delayed sexual development, and the prevalence of low zinc intake correlates with the prevalence of stunting (low height for age) in children under 5 years of age [1070]. Zinc affects appetite, and anorexia is a symptom of deficiency. This can further potentiate the negative effect of inadequate zinc on growth [1075]. Correction of low zinc intake by zinc supplementation (10 mg/day) of growth-stunted infants and children aged 4–36 months in rural Vietnam increased plasma insulin-like growth factor 1 levels and promoted growth (increased weight and height gain), as compared with placebo [1076]. Infants displaying failure-to-thrive also benefitted from supplemental zinc in a placebo-controlled study in the US [1077]. However, effects of zinc supplementation on growth have not been observed in well-nourished children [1078].

The effects of zinc on immune function

Zinc affects multiple aspects of the immune system. Inadequate zinc intake increases the risk and severity of infection. Likewise, zinc supplements can have beneficial effects in reducing the duration of infectious illness, including the common cold [1079]. In developing countries with widespread zinc deficiency, decreased resistance to infection is common in children. Preventive zinc supplementation has been shown to reduce childhood mortality from diarrhoeal diseases and pneumonia in such settings [1080]

The effects of zinc on neurological development

Deficiency of zinc in infancy and early childhood can lead to impaired cognitive development, behavioural problems, and neuronal atrophy [1081]. Low maternal zinc can result in neurobehavioural deficits in animals [1082]. There is some evidence that human maternal zinc deficiency or inadequacy affects the neurological development of the fetus, resulting in alterations in attention, activity, motor development, and neuropsychological behaviour [1083]. However, supplementation with 25 mg/day zinc during the second half of pregnancy had no effect on the neurological development of offspring up to 5 years of age [1084]

Zinc in pregnancy

Daily zinc requirements increase by up to 40 per cent during pregnancy. It has been estimated that non-pregnant women need to absorb approximately 2.0 mg zinc/day; during pregnancy the maternal/fetal unit requires 2.6 mg/day. Because absorption is only partial (estimated 25%), the calculated intake requirement is approximately 10.5 mg zinc/day in late pregnancy (this has been rounded to 11 mg/day for the recommended dietary allowance (RDA)—see 'Zinc sources and bioavailability') [1085, 1086]. Placental zinc transport is bidirectional and does not occur against a concentration gradient [1087], so if maternal zinc levels are inappropriately low, the movement of zinc to the fetus is reduced. Adequate zinc stores should be ensured prior to pregnancy so that the high requirements of the developing fetus can be met. There is an adaptive increase in zinc absorption during pregnancy and lactation to compensate for some of the increased demand [1088, 1089].

Inadequate maternal zinc intake can have adverse effects on a number of outcomes of pregnancy [1090]. Gestational zinc deficiency is known to be teratogenic in animals, causing intrauterine growth restriction and structural abnormalities [1091, 1092]. This teratogenicity appears to be potentiated by other factors such as infection, inflammatory disease, and alcohol intake, all of which are significant risk factors in pregnant women with low zinc status. These triggers increase the expression of the zinc-binding protein metallothionein in the liver, the effect of which is to decrease zinc transfer to the fetus [1086, 1087].

Low maternal zinc levels are generally thought to contribute to the risk of infants being of low birthweight or small for gestational age; however, study results are inconsistent. Most studies show no significant effect of maternal zinc supplementation with infant birthweight [1093–1096]. Two meta-analyses of 20 zinc intervention trials in over 15,000 women and their infants concluded that zinc supplementation in pregnancy had a small but significant effect on the reduction of preterm birth (–14% with zinc), but not on low birthweight or other outcomes [1097, 1098]. Babies who are born premature may miss the critical period of zinc accumulation during late gestation. It is recommended that such infants be supplemented with zinc [1099].

Because of its role in immunity, zinc supplementation has been evaluated in immunocompromised pregnancies. A study of HIV-infected pregnant women in Tanzania found that the addition of zinc (25 mg/day as zinc sulphate) to a supplemental regimen of multivitamins, iron, and folate had no significant beneficial effects on pregnancy outcomes [1100]. Other studies have shown that zinc supplementation in populations at high risk, such as those in developing countries, reduces the incidence of preterm delivery, childhood diarrhoea, and acute lower respiratory tract infections, and increases growth and weight gain in infants and children [1101, 1102]. Data do not support the use of zinc supplementation for reducing gestational hypertension or pre-eclampsia [1097].

Zinc in lactation and infant feeding

Infants require approximately 2 mg zinc per day for the first 6 months of life [260]. Breast milk from well-nourished mothers supplies all the nutritional zinc required by the infant for first few months. The zinc supply in breast milk is not particularly sensitive to changes in maternal zinc intake; instead, a homeostatic mechanism involving high fractional absorption (twofold higher during lactation) and intestinal retention ensures maintenance of the zinc supply despite potentially low zinc intake and high demands of the nursing infant [1088, 1089]. Nonetheless, malnourished women usually produce milk that lacks sufficient zinc to meet infant demands during lactation, and supplementation of mothers with zinc during lactation does not appear to increase the zinc concentration in their milk [1103].

The stage of lactation affects zinc concentrations in milk, which decline rapidly from 4 mg/L at 2 weeks, to 1.2 mg/L at 6 months postpartum. These levels provide the newborn infant with approximately 2.3 mg zinc/day for the first month, declining to approximately 1 mg/day at 6 months. Impaired growth resulting from zinc deficiency has been observed in some exclusively breastfed infants from 4–6 months of age [1104]. Such a decline in growth velocity can occur despite apparently adequate energy intake and responds to supplemental zinc, implicating zinc as a growth-limiting micronutrient. Maternal zinc supplementation has no significant effect on the decline in breast milk zinc concentration during the course of lactation [1103]. Requirements of older breastfed infants (6+ months) therefore cannot be met without the consumption of complementary foods such as meat or zinc-fortified cereals/infant foods, or by infant supplementation [1105].

Infants with the hereditary zinc deficiency disorder acrodermatitis enteropathica, which is caused by an autosomally recessive mutation in the zinc transporter gene *SLC39A4*, are protected during breastfeeding by the supply of zinc from their mothers' milk but later show signs of deficiency and require zinc supplementation. On the other hand, women with this disorder produce milk that is deficient in zinc, and their infants, if exclusively breastfed, show symptoms similar to acrodermatitis enteropathica if not supplemented with zinc [1106, 1107]. Similarly, mutations in the zinc transporter gene *SLC30A2*, which is expressed in mammary gland epithelial cells, inhibit zinc excretion into breast milk, resulting in transient zinc deficiency in exclusively breastfed infants [1108, 1109].

Zinc sources and bioavailability

Oysters are very high in zinc; other shellfish (e.g. crab) and red meat (beef) are also rich sources with high zinc bioavailability. Additional food sources include nuts and legumes, poultry, eggs, whole grains, some fruits (e.g. watermelon and blackberries), seeds (e.g. sesame seeds, pumpkin seeds, and sunflower seeds), and dairy products. The typical Western diet is considered adequate to supply zinc for pregnant and lactating women, providing an average intake of ~13 mg/day [1103]. However, in a study of middle- and upper-income pregnant women in the US (n = 63), 30 per cent did not achieve the estimated average requirement of 9.5 mg/day and more failed to meet the RDA (11 mg/day) [369]. Regular consumption of zinc-rich or zinc-fortified foods during pregnancy is necessary to meet the requirement. Fortification of flour with zinc has been recommended in some areas [1110].

The average availability of zinc from the diet is 25 per cent. Intake of phytate, which is present in most plant foods—particularly grains and legumes—has a significant effect on zinc absorption. Zinc absorption is lower in vegetarian diets because of a higher consumption of phytate-containing foods and an avoidance of zinc-rich meats and seafood. Low-income women in developing countries have low zinc intakes [1103], and the bioavailability of zinc from the diet is generally less than that from Western diets, which are higher in red meat. Diets in developing countries are typically high in unrefined, unfermented, and ungerminated cereal grain, and intake of animal protein is often negligible. Zinc bioavailability is especially low when the cereal grains are fortified with inorganic calcium salts.

Iron and calcium supplements also decrease zinc absorption, although intake of iron and calcium from food has little effect [1111, 1112]. Zinc and iron compete for intestinal absorption because they can bind the same transporter. The routine use of iron supplements during pregnancy may therefore interfere with zinc bioavailability at a time when it is in high demand [1113]. Including zinc in supplements with iron may reduce this effect, and this approach may be important in populations at risk for both deficiencies. Populations with high zinc requirements, including pregnant and lactating women, infants, and adolescents, may be more sensitive to iron-zinc interactions [1114]. Zinc interacts with other micronutrients, including copper, folic acid, and vitamin A. As a component of the copper–zinc superoxide dismutase enzyme (in which copper is catalytic and zinc is structural), high zinc intakes (≥ 50 mg/day) interfere with copper absorption.

Risks of excess zinc

Supplemental doses of zinc from 50–150 mg/day can cause gastrointestinal distress [1115]. Acute toxicity causing abdominal pain, diarrhoea, nausea, and vomiting can occur from consumption of food or beverages contaminated with zinc released from galvanized containers. Long-term excess zinc consumption (50 mg/day as supplements in addition to 10 mg/day from food) causes copper deficiency; the US Institute of Medicine (IOM) therefore recommends a tolerable upper intake level of 40 mg/day [260]. There is no evidence of toxicity from the intake of naturally occurring zinc in food.

Agency guidelines for zinc intake

The US RDA for zinc for non-pregnant women is 8 mg/day [260]. The UK recommendation for women is 4.0–7.0 mg/day (lower than that from the US), with a total intake of up to 50 mg/day considered safe [1116]. The RDA for pregnant women 14–18 years of age is 12 mg/day and is 11 mg/day for pregnant women 19 and over. During lactation, an additional 1 mg/day is recommended (13 mg/day for 14–18 years; 12 mg/day for 19+). The upper limit set by the IOM for pregnancy and lactation is 34 mg/day for adolescents, and 40 mg/day for women aged 19 years and above [260] (Box 25.1).

There are some groups that require special consideration. Absorption of zinc is lower from vegetarian diets, especially those high in calcium; this combination may result in low zinc status. The zinc requirement for vegetarians may be up to 50 per cent higher [260, 1117]. The UK Food Standards Agency guidelines indicate that persons taking iron supplements of 30 mg or more per day should also take 15 mg zinc, along with 2 mg of copper [1116]. Long-term excessive alcohol consumption leads to impaired zinc absorption, increased zinc excretion, and possibly an increased daily zinc requirement [1118].

The IOM recommendation for infants 0–6 months of age is 2.0 mg/day zinc. This level reflects the average intake of infants fed breast milk only. Absorption of zinc from human milk is higher than from cow's milk, although cow's milk formulas generally contain higher levels of zinc, so formula-fed infants achieve

Box 25.1 US Institute of Medicine recommended dietary allowances for zinc

Infants 0–6 months (adequate intake) = 2 mg/day
Infants 7–12 months = 3 mg/day
Children 1–3 years = 3 mg/day
Females 14–18 years = 9 mg/day
Females 19+ years = 8 mg/day
Pregnancy 14–18 years = 12 mg/day
Pregnancy 19+ years = 11 mg/day
Lactation 14–18 years = 13 mg/day
Lactation 19+ years = 12 mg/day
Tolerable upper intake level 14–18 years = 34 mg/day
Tolerable upper intake level 19+ years = 40 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

similar intakes to those who are breastfed. Older infants require complementary foods to meet zinc intake needs. The RDA for infants 7 months or older (up to 3 years) is 3 mg/day, which cannot be obtained from breast milk alone. Introduction of lean meats (finely minced) and/or zinc-fortified cereals is recommended from 6 months of age [260]. The tolerable upper intake level for infants is 4 mg/day up to 6 months, and 5 mg/day from 7–12 months.

The WHO is developing recommendations for zinc supplementation for susceptible children (10 mg/day for 0–6 months; 20 mg/day) for the prevention and management of diarrhoea and other health issues, which mainly affect developing countries [1119].

Our recommendations for zinc intake during pregnancy and lactation

Zinc is required for male fertility, and supplementation may improve fertility in subfertile men. Zinc supplementation in pregnancy has not been shown to improve outcomes for mothers or infants, except possibly to reduce the risk of preterm birth. Women consuming diets that are low in bioavailable zinc (i.e. those that are high in unrefined cereal grain and low in animal protein) or who have risk factors for preterm delivery should be advised to take a prenatal multivitamin containing zinc.

Most prenatal multivitamins contain between 12 and 20 mg of elemental zinc, which is at or above the IOM RDA for pregnant women. These amounts have not been found to be harmful, although they can cause stomach upset in some women. Nonetheless, since iron supplementation is widely prescribed to pregnant women and may lower zinc absorption, inclusion of zinc in multivitamins is recommended. Intake from all sources should not exceed 40 mg/day. Breastfed infants should be introduced to zinc-rich complementary foods (e.g. fortified cereals) by 6 months of age to prevent possible zinc deficiency resulting from declining zinc content in breast milk.

Chapter 26

Manganese in pregnancy and breastfeeding

Manganese functions

Manganese is both an essential element and a potent neurotoxin. It is involved in cellular metabolic processes and, as a component of antioxidant enzymes such as manganese superoxide dismutase, is protective against lipid peroxidation. Other manganese metalloenzymes include arginase, glutamine synthetase, and phosphoenolpyruvate decarboxylase.

Uptake and efflux of manganese is tightly regulated, as both deficiency and excess can result in disease states. Most manganese is located on erythrocytes [1120] and is taken up from blood by the liver and transported by transferrin. Absorption of manganese is low, and retention is affected by dietary calcium, iron, and phosphorus [1121–1123]. Women usually have lower iron status than men and have been found to absorb more manganese [1124]. Despite its low bioavailability, manganese deficiency is rare in humans, as manganese is found naturally in a number of commonly consumed foods.

Animal studies have shown that manganese is particularly critical during gestation and early infancy. In manganese deficiency, elevated concentrations of serum calcium, phosphorus, and alkaline phosphatase have been observed, suggestive of bone resorption in humans [1125] and animals [1126]. Manganese is directly involved in bone growth as a cofactor of glycosyl transferases [1127] and participates in insulin-like growth factor metabolism [1128]. Manganese deficiency interferes with normal skeletal development in animals because the manganese-dependent enzyme prolidase is needed for collagen formation and wound healing. However, in human pregnancy, manganese levels do not correlate with newborn bone growth parameters [1129].

Indicators of manganese status/exposure

Serum or plasma manganese concentrations have been reported to respond to dietary intake [1130], as has urinary manganese excretion [1125]. However, there is some disagreement on the use of these measurements as indicators of manganese status [260]. Serum manganese concentrations in combination with lymphocyte manganese superoxide dismutase activity may be the best biomarkers for monitoring manganese intake. Blood arginase activity may also be used. Brain MRI scans and neuro-functional tests are used to assess overexposure to manganese [1122]. The normal blood level of manganese is between 4 and 14 μg/ml, but there is no clear 'normal' range for young children.

Manganese in pregnancy

Manganese status and metabolism change in pregnancy. Since manganese is primarily found in association with erythrocytes, its concentration would be expected to decrease with haemodilution over the course of pregnancy. However, manganese absorption in inversely correlated with iron status [1131], which tends to decrease in pregnancy. Accordingly, manganese content in blood has been shown to increase in pregnancy [1132, 1133]. The increase is slightly lower in women who receive iron supplements [1132] and may be related to accelerated erythropoiesis. Transfer of manganese to the fetus appears to be limited by the placenta [260].

In the brain, homeostatic mechanisms operate between iron and manganese transporters. Neonatal dietary iron deficiency upregulates manganese transporters in the developing brain and results in elevated brain manganese accumulation [1134]. This has been shown in animals to influence manganese neurotoxicity [1135].

The retention rate for manganese in the neonate is high, and high levels are observed in early infancy [1136]. In infants, both low and high blood manganese levels were associated with lower scores on a standard test of cognitive development at 12 months in a longitudinal study of Mexican children [1137]. The observed U-shaped association between manganese and cognitive development might be explained by effects on oxidative stress at both high and low levels of manganese, with deficiency increasing sensitivity to oxidative injury, and excess causing manganese to act as an oxidant itself [1138].

Approximately 3 μg/day of manganese is secreted in human milk. Although this is a low level compared with other species, it is the recommended adequate intake (AI) level for infants up to 6 months of age. Although the concentration of manganese in human milk is low, infant formulas can vary widely, containing between 30 and 300 μg/L. Infants 7–12 months of age who are fed complementary foods are estimated to consume around 70–80 μg/kg manganese per day. Based on this, the AI for these infants is calculated as 0.6mg/day [260].

Manganese sources

Manganese is found in high amounts in nuts, seeds, tea, and whole grains, with levels sometimes exceeding 30 mg/kg. Only very small amounts are present in meats, dairy products, and sugary and refined foods [1139]. Manganese is also present in drinking water and may be more bioavailable from water than from food. Many dietary supplements contain manganese at levels between 5 and 20 mg [260]. The average dietary intake for adults is less than 5 mg/day. Heavy tea drinkers, and vegetarians who consume foods rich in manganese such as grains, beans, and nuts may have a higher intake of manganese than the average person [1138].

Risks of excess manganese

Over-ingestion of manganese from food sources is not likely to cause problems, except in individuals with severe iron deficiency or chronic liver disease. High intake of supplements or exposure to contaminants from occupations such as welding or steel metal work may increase the chance of excessive intake of manganese. The symptoms of manganese toxicity in adults appear slowly over months and years [1138]. The major recognized symptoms of manganese toxicity relate to the CNS. Accumulation of manganese in dopamine-rich brain regions that control muscle movement causes damage to the extrapyramidal system, leading to dyskinesias and neuropsychiatric disturbances [1140]. Liver damage has also been reported [1141].

Several factors, including higher rates of intestinal absorption and brain delivery, potentially predispose the neonate to enhanced manganese accumulation and increased toxicity [1142]. Homeostatic mechanisms control plasma manganese concentrations but can be overwhelmed at high exposure levels [1143]. The developing striatum may be particularly vulnerable to damage from excess manganese in utero and during early neonatal development [1144].

Agency guidelines for manganese intake

No recommended dietary allowance has been established for manganese intake, although AI recommendations have been made (Box 26.1). The AI for pregnancy and lactation represent an increase based on average intake above that of the non-pregnant state, at 2 mg/day of manganese for pregnant women of all ages and 2.6 mg/day for lactation [260].

Guidelines from Australia and New Zealand for manganese intake by adults differ somewhat from those of the US Institute of Medicine, being 5.0 mg/day for women, regardless of pregnancy or lactation status. The advised intake for non-pregnant adolescents (14–18 years) is 3.0 mg/day, although

Box 26.1 US Institute of Medicine recommended adequate intake levels for manganese

Infants 0–6 months = 3 μg/day
Infants 7–12 months = 0.6 mg/day
Children 1–3 years = 1.2 mg/day
Females 14–18 years = 1.6 mg/day
Females 19+ = 1.8 mg/day
Pregnancy = 2.0 mg/day
Lactation = 2.6 mg/day
Tolerable upper intake level 14–18 years = 9 mg/day
Tolerable upper intake level 19+ y = 11 mg/day

Source: Institute of Medicine, Food and Nutrition Board, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, The National Academies Press, Washington, DC, copyright © 2001. [260]

this age group follows the adult recommendation of 5.0 mg/day during pregnancy and lactation [1145].

The WHO evaluated manganese intakes in adult diets and found that the average daily consumption ranged from 2.0–8.8 mg/day, with higher intakes associated with diets high in wholegrain cereals, nuts, green leafy vegetables, and tea. An intake of 2–3 mg manganese per day is therefore considered adequate for adults, and intakes of 8–9 mg/day are deemed safe. Intake from drinking water is considered to make only a minor contribution to manganese intake in general [1146].

Taking into consideration the ubiquity of manganese in foods, and the limited evidence for deficiency in humans, the European Food Safety Authority recommends that exposure to manganese should remain low and should not exceed that found in the diet. Nonetheless, it states that supplemental intakes of 4 mg manganese/day are unlikely to produce adverse effects in the general population. Such supplementation would result in a total intake of 12.2 mg/day, taking into a consideration a dietary intake level of 8.2 mg/day (which may be a high estimate). Specific recommendations have not been made for pregnant and lactating women [1147].

Our recommendations for manganese intake during pregnancy and lactation

The hazard posed by overexposure to manganese must be weighed against the necessity for some minimum amount of manganese in the diet. Manganese has essential functions in maternal health and fetal development, and in healthy women adequate amounts can be obtained from a mixed diet of grains, cereals, and fruits. Supplements containing manganese should be used with caution, as excess intake can have neurotoxic effects on the developing brain. Newborn infants and young children are the most vulnerable. Maternal intake in pregnancy and lactation is not a cause for concern in most cases, as transfer of manganese to the fetus and into breast milk is limited. However, in situations of iron deficiency or chronic liver disease, excess manganese accumulation can occur and should be monitored.

Chapter 27

Prebiotics and probiotics in pregnancy and breastfeeding

Prebiotic and probiotic functions

Probiotics are live, non-pathogenic commensal microorganisms with beneficial effects on the host organism; they improve and/or maintain intestinal flora balance by suppressing and displacing harmful bacteria. Prebiotics are nondigestible food components that stimulate growth or activity of these beneficial intestinal bacteria. Probiotics are found in fermented foods such as yoghurt; prebiotics are found in whole grains, soybeans, bananas, onions, garlic, honey, and artichokes. It has been claimed that prebiotic and probiotic supplements improve the symptoms of irritable bowel syndrome, diarrhoea, intestinal infections, and vaginal yeast infections and prevent or treat eczema, colds, and flu. When prebiotics and probiotics are combined, they are referred to as synbiotics [1148].

Gut bacteria synthesize some essential vitamins (e.g. vitamin K) and breakdown indigestible polysaccharides to short-chain fatty acids. Such microorganisms form an integral part of the intestinal mucosal defence system [1149] and are important for the development and maturation of the infant's gastrointestinal tract. The infant gut is initially colonized by bacteria that it obtains from the mother during birth, with different patterns of colonization occurring dependent on the mode of delivery: with caesarean delivery, the infant does not come into contact with the mother's intestinal and vaginal microbiota, and the acquisition of some species (e.g. bifidobacteria) is delayed [1150].

Human milk contains functional oligosaccharides with prebiotic effects [1151]. These oligosaccharides modulate bacteria–host interactions and affect the composition of infant gut microbiota. They also serve as decoy receptors that prevent the attachment of pathogenic bacteria to the intestinal lining. In addition to prebiotic compounds, probiotic microbes are present in breast milk and in the gut of breastfed infants, where bifidobacteria and lactobacilli predominate [1148]. These organisms produce antimicrobial compounds and compete with other pathogens for available nutrients. They also strengthen the intestinal barrier against further pathogenic infections

[1152]. Some infant formula is supplemented with factors that mimic the prebiotic effects of human milk and produce similar effects on the gut microbial composition [1153].

Probiotics and the immune system—the 'hygiene hypothesis'

The basis of the hygiene hypothesis is that increased hygienic standards prevent the neonate from experiencing the immune stimulus of microbial infection that provides a driver for the maturation of the immune system and gut, thereby predisposing the individual to allergies [1154]. Conversely, early microbial exposure promotes B-cell maturation and reduces susceptibility to infections and sensitization to environmental antigens later in life [1155]. Infants in developing countries with poorer hygiene have more rapid colonization than infants in developed countries, where the prevalence of allergic disorders is rising [1156].

Maternal probiotic and prebiotic supplementation has been reported to enhance the development and maturation of the neonatal gastrointestinal tract [1157]. In a randomized, double-blind trial, lactobacillus supplementation to pregnant women for 2–4 weeks (1×10^{10} colony-forming units/day) before expected delivery halved the occurrence of atopic eczema in their offspring at 2 years of age, as compared with placebo [1158]. Probiotics at weaning reduced the risk of developing eczema (early manifestation of allergy) at 13 months in a double-blind, placebo-controlled study [1159]. A higher Th1/Th2 ratio was observed in the probiotic group, suggesting enhanced T cell-mediated immune responses. Feeding infants that were between 4 and 13 months of age (weaning) with cereals containing probiotics also decreased levels of monounsaturated fatty acids, which have been linked to visceral obesity, and raised levels of polyamines that are important for gut maturation and integrity [1160].

A potential role of probiotics in the prevention of gestational diabetes mellitus

Dietary interventions and lifestyle modifications, as well as medical therapies, have been recommended for the management of insulin resistance during pregnancy. Probiotics have recently been proposed to play a role in prevention of gestational diabetes. Studies in animal models have reported the beneficial effects of probiotics on fasting plasma glucose levels as well as on improved insulin resistance [1161, 1162]. Since probiotics utilize glucose as their primary energy source, they can influence blood glucose and insulin levels through their effects on decreased glucose absorption. Probiotics can also improve insulin resistance through their impact on reduced inflammatory signalling [1162], upregulated expression of proglucagons [1161], and decreased adiposity [1163].

Trials involving probiotic supplementation in pregnancy examining metabolic outcomes are limited. A study involving 256 normal weight pregnant women in Finland demonstrated that women who received probiotic supplementation that consisted of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12, along with dietary counselling, had a reduced risk of elevated maternal glucose concentration [1164] and a reduced frequency of gestational diabetes [1165], as well as a reduced frequency of having a maternal waist circumference of 80 cm or more [1166]. Both maternal fasting glucose and insulin levels in the third trimester were significantly lower in mothers who received the probiotic supplement and dietary counselling [1164]. There was no significant difference in the infant weights [1165]. A recent randomized controlled trial [1167] found that pregnant women who consumed 200 g of probiotic yoghurt for 9 weeks were more likely to maintain their insulin levels and avoid the development of insulin resistance compared with women who consumed regular yoghurt for the same period.

Our recommendations for prebiotic and probiotic intake during pregnancy and lactation

Evidence is accumulating that prebiotics and probiotics ingested during pregnancy and lactation or provided to the weaning infant are beneficial for the infant's developing gastrointestinal and immune systems. We recommend that prebiotics and probiotics be acquired from food sources as the first option, unless other circumstances such as the use of antibiotics suggest that supplementation may be necessary. A diet including yoghurt, whole grains, soybeans, bananas, onions, and garlic should provide sufficient amounts of pre- and probiotics for the health of both mother and nursing infant. Some of these foods can also be introduced to the weaning infant. Further research is needed before prebiotic or probiotic supplements should be routinely considered.

Section 3

A healthy lifestyle for a healthy pregnancy

Adopting a healthy lifestyle and reducing behaviours that have adverse effects on health is essential for ensuring the best pregnancy outcomes for both mother and child. This should ideally begin before conception, as many critical embryonic and fetal developmental processes and maternal adaptations to pregnancy occur during the first trimester. This section provides information on aspects of lifestyle that can have significant effects on pregnancy, including safe and unsafe foods, exercise, and exposure to potential toxins, as well as weight guidelines for pregnancy.

Chapter 28

Pre-conception maternal body composition and gestational weight gain

The impact of maternal pre-conception bodyweight

In addition to diet, a woman's body composition at conception is an important factor in her overall health and influences both the amount of weight she gains during pregnancy and infant growth patterns [1168]. It has been known for many years that size at birth is more related to maternal than paternal size [1169, 1170]. Shorter mothers in general give birth to children who are shorter in length, and maternal short stature (height less than 148 cm) is also strongly associated with the risk of low birthweight in term deliveries [1171]. Maternal lean body mass is positively associated with fetal growth [1172, 1173], and both obesity and underweight at the start of pregnancy are associated with birthweight [1174–1176]. Excessive or inadequate weight gain is also detrimental to fetal development.

Under-nutrition and underweight at conception

Low maternal pre-pregnancy weight, low BMI, and low attained weight throughout pregnancy are associated with impaired fetal growth [1177]. In the developing world there remain many women who have low body mass at conception [1178], although the proportion is decreasing. In developed countries, the prevalence of underweight in pre-pregnant women has also decreased with time [1179], and in the US approximately 5 per cent of women begin pregnancy underweight (BMI <18.5 kg/m^2) [1180]. Underweight mothers or those with low BMIs (<19.5 kg/m^2) are also at increased risk of both small-for-gestational-age and spontaneous preterm birth [30, 1181], particularly if their gestational weight gain is low [1182]. In studies that considered pre-pregnancy BMI as a continuous variable, an increased preterm delivery risk correlated with a decreasing BMI below 22–26 kg/m^2 [1181, 1183].

Pre-pregnancy obesity

Obesity prior to and during pregnancy has been associated with adverse outcomes for both mother and fetus. In 2004–2005, 23 per cent of women in the US began pregnancy as overweight (BMI 25.0–29.9 kg/m^2), and 19 per cent began pregnancy as obese (BMI ≥30.0 kg/m^2) [1180]. A more recent UK study showed that 50 per cent of women of childbearing age were either overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI >30 kg/m^2) [1184]. The rates of female overweight and obesity are also rising rapidly in low- and middle-income countries as they become increasingly urbanized and use different food sources [1185–1187].

Overweight and obesity increases the risks of developing gestational diabetes mellitus (GDM) [1174, 1188, 1189], with obese women having up to a fivefold higher risk compared to normal-weight women [1190]. Obese women also have a higher risk of pre-eclampsia compared to their normal-weight counterparts [30, 1191], and this increased risk may be related to an increase in inflammatory factors associated with obesity [1192, 1193]. Obesity in pregnancy also increases the risks of thromboembolism [1194, 1195], infection [1191, 1196], caesarean delivery [1197, 1198], congenital anomalies [404], labour induction [1199], stillbirth [1200, 1201], shoulder dystocia [1191], and preterm delivery [1202]. Being obese at the start of pregnancy is associated with fetal macrosomia [1203], and large-for-gestational-age infants, and the risk increases as the pre-pregnancy BMI increases [1204–1206].

Obesity, both at conception and during pregnancy, can also have long-term effects on the offspring, such as greater risks of adiposity, cardiovascular and metabolic dysfunction, and poor cognitive development [59, 1207–1209]. While these trans-generational effects may in part be cultural, reflecting intra-familial feeding behaviour, there is growing experimental evidence of the biological effects of maternal obesity leading to obesity in the offspring [1210]. These effects include induced epigenetic changes [1211, 1212]. Additionally, maternal obesity is frequently associated with mild hyperglycaemia, which leads to fetal hyperinsulinaemia and thus greater adipogenesis in utero [1213].

Gestational weight gain

Gestational weight gain has an impact on both short- and long-term pregnancy outcomes. Low weight gain in pregnant women without diabetes is associated with reduced fetal growth and increased risk of preterm birth [1204], whereas high weight gain is associated with a greater risk of excessive fetal growth [1214]. However there is a paucity of data on which to base good management guidelines. To date only the US Institute of Medicine (IOM) has produced guidelines (see ‘Agency guidelines for weight gain during pregnancy’), which are based on US data and opinion and do not extrapolate directly to other societies and across ethnicities where body habitus and healthy BMI ranges may differ. Furthermore, the IOM guidelines are seen as rather broad and in need of revision.

While adopting the IOM recommendations seems to be beneficial for underweight and normal-weight mothers, different guidelines or thresholds might be more appropriate for overweight and obese mothers in order to avoid adverse short-term pregnancy outcomes. In a large German population-based data set, overweight and obese mothers who gained weight within the IOM recommendations for gestational weight gain had a lower incidence of pre-eclampsia and fewer non-elective caesarean deliveries, but higher risks for GDM, small-for-gestational-age birth, preterm delivery, and perinatal mortality [1215]. Unfortunately, overweight and obese women are nearly twice as likely to exceed the recommended guidelines for gestational weight gain compared with normal-weight women, and underweight women are more likely to fall below IOM guidelines.

The issue of whether reducing gestational weight gain affects the risk of pre-eclampsia is controversial, and, if it has any effect, it is likely restricted to obese women [1216–1218]. Nonetheless, in some countries such as Japan, it is still considered preferable to limit weight gain, even in normal- and underweight women. This practice is of considerable concern given the consequences that the resulting lowered birthweight can have for the offspring (see ‘Active management of gestational weight gain’).

Gestational weight gain and offspring obesity

There is considerable interest in the relationship between gestational weight gain and the risk of offspring obesity. Maternal obesity and high gestational weight gain are associated with weight gain in childhood and adolescence [1189, 1219–1221]. In a study of ~3,000 singleton births to women without pregnancy complications, weight gain in all trimesters was significantly and independently associated with birthweight, although only first trimester weight gain was associated with child BMI outcomes [1222]. In analyses of 3,600 participants from the Early Childhood Longitudinal Study Birth Cohort, after adjusting for socio-demographics and family lifestyle, there was a significant overall association between gestational weight gain and child adiposity among normal and overweight mothers [1223]. In Germany, a higher risk of both overweight and abdominal adiposity at school entry has been observed in children of mothers who gained weight excessively (as defined by the IOM guidelines) during pregnancies [31].

In a study cohort of ~6,500 mother–child pairs, women who avoided excessive weight gain in the third trimester had children with a 31 per cent lower probability of being overweight [1224]. A similar reduction (27% lower probability) was also observed for women who reversed from excessive weight gain in the first or second trimester to normal weight gain in the third trimester. A meta-analysis [1225] demonstrated that at least a 21 per cent risk for childhood overweight was related to excessive gestational weight gain and that further efforts to design appropriate interventions against excessive weight gain were warranted.

Agency guidelines for weight gain during pregnancy

To date, the only generally accepted guidelines for weight gain during pregnancy are those developed by the IOM in 1990 and which provide recommendations for women of different BMIs. The guidelines were slightly revised in 2009 [1226] (see Box 28.1) The IOM intended these guidelines to be used for women in the US; however, the IOM committee suggested that these guidelines are potentially 'applicable to women in other developed countries' [1215]. Further research is needed to achieve population specific guidelines because of the very different maternal height and body shape norms between populations.

Maternal height has been considered in the design of two similar charts [1227, 1228]. The latter chart, based on a Chilean population, is now being used in several Latin American countries and could be also adopted in other developing countries where maternal height is shorter than in the US. In this chart, short and tall women are recommended to gain proportionately more and less weight, respectively, than average-height women.

Box 28.1 Gestational weight gain recommendations according to the revised US Institute of Medicine guidelines

Underweight women (BMI <18.5 kg/m^2) should gain 12.5–18.0 kg
Normal-weight women (BMI between 18.5 and 25 kg/m^2) should gain 11.5–16.0 kg
Overweight women (BMI between 25 and 30 kg/m^2) should gain 7.0–11.5 kg
Obese women (BMI ≥30 kg/m^2) should gain 5.0–9.0 kg

Source: Yaktine, A.L. and K.M. Rasmussen, eds., *Weight Gain during Pregnancy: Reexamining the Guidelines*, Institute of Medicine, Washington, DC, copyright © 2009. [1226]

Active management of gestational weight gain

The evidence presented above clearly demonstrates that it is crucial for overweight and obese mothers to gain weight within population-appropriate guidelines. Advice to restrict energy intake to between 1,800 and 2,000 kcal/day, with an intake of carbohydrates between 150 and 180 g/day, has been shown to reduce gestational weight gain by 50 per cent and to lower fasting insulin concentrations in late pregnancy [1217, 1229]. A behavioural intervention programme (including a face-to-face visit, weekly mailed materials that promoted an appropriate weight gain, healthy eating, and exercise, use of individual graphs of weight gain and telephone-based feedback) promoted adherence to IOM recommendations in normal-weight women and increased the percentages of normal and overweight/obese women who returned to their pre-conception weights or below by 6 months postpartum [1230]. Another intervention programme, named the Lifestyle in Pregnancy Study, produced significantly lower gestational weight gain by providing dietary guidance, free membership to fitness centres, and physical training, as well as personal coaching, although the obstetric outcomes were similar in both the intervention and control groups [1231]. Weight management interventions in pregnancy have been found to be effective in reducing the incidence of pre-eclampsia and shoulder dystocia and may also reduce the incidence of GDM [1184]. The interventions, however, showed no differences in the incidence of small-for-gestational-age infants between the groups.

It should also be emphasized that these studies involved only minor weight reduction. In contrast, in Japan there has been a tendency toward much more stringent dietary advice, apparently in an attempt to reduce the incidence of pre-eclampsia. This has been associated with a much more dramatic fall in gestational weight gain, on the order of 4 kg/pregnancy [1232], accompanied by a considerable fall in birthweight and a rise in the rate of small-for-gestational-age births [1233]. These very low gestational weight gains fall outside the IOM advisory range. Our own view is that this is a most unwise practice, unlikely to confer additional protection against pre-eclampsia and likely to have long-term adverse effects on the offspring. Maternal undernutrition is practised in some less developed African societies to reduce the risk of complications at delivery, and we are aware of arguments in some Asian countries to promote a marked reduction in gestational weight gain to reduce the rate of caesarean section. For similar reasons we think this unwise, particularly given that the high rates of caesarean section have a major elective component.

Our recommendations for pre-conceptional maternal body composition and gestational weight gain

Maternal weight status, lifestyles, and general health during pregnancy play important roles in the offspring's development and can contribute to the risk of non-communicable disease in the offspring in adulthood. Maternal weight in particular seems to have the most dominant effect in influencing the offspring's body composition, which can consequently affect future health outcomes. Women who are underweight at the beginning of pregnancy have a greater risk of having smaller babies and shorter gestational lengths. The offspring may have long-term sequelae of this peri-conceptual under-nutrition. Women who are overweight prior to pregnancy and those who gain more weight than the recommended guidelines during pregnancy may develop GDM and maternal obesity, both of which can have adverse effects on the fetus and child.

Currently the IOM guidelines are the only ones available for developed countries, where mean maternal height is similar to that in the US. We would recommend that attention be given to body composition before pregnancy and that the IOM guidelines be followed, but that simple measures of habitus such as maternal height are taken into account in applying them. Alternatives that include the influence of maternal height to proportionally guide weight gain may be considered for developing countries.

Chapter 29

Exercise and physical activity in pregnancy

Exercise and physiological changes in pregnancy

Regular physical exercise is known to reduce cardiovascular disease risk factors such as blood pressure and plasma lipid levels and can improve insulin sensitivity, increase lean body mass, and reduce fat mass [40]. As these factors have important consequences for pregnancy, there is an increasing focus on the role of exercise in maintaining a healthy pregnancy. At the same time, there is a need to consider whether extreme exercise or excessive physical exertion might have adverse effects on pregnant women.

Various mechanisms beyond straightforward changes in energy homeostasis have been proposed to explain how exercise can alter the physiology of pregnancy, including promotion of placental growth and vascularization, reducing oxidative stress, and improving maternal vascular endothelial function and immune and inflammatory responses [1234]. Trophoblastic, endothelial, and stromal cell proliferation is increased in active pregnant women [1235], as is functional tissue volume in the placenta [1236], resulting in an improved surface area for gas and nutrient exchange [1237]. Exercise in pregnant women has been shown to increase the circulation of pro-angiogenic factors while reducing anti-angiogenic factors [1238]. Likewise, exercise training has been shown to increase circulating anti-inflammatory cytokines such as interleukin-10 and reduce pro-inflammatory factors such as interleukin-1 beta, interleukin-6, and tumour necrosis factor alpha [1234]. An elevation in the levels of anti-angiogenic and pro-inflammatory factors may contribute to the pathophysiology of pre-eclampsia [1234, 1239].

Cultural factors influencing exercise during pregnancy

There are wide cultural and population differences in the energy expenditure of pregnant women. In many low-income countries, pregnant women continue with hard physical exertion, such as carrying heavy loads of water over long distances, well into pregnancy [1240, 1241]. Coupled with poor nutrition, this high-energy expenditure can impair fetal growth and maternal health [1242], Conversely, modern sedentary lifestyles have contributed to a greatly increased prevalence of obesity and type 2 diabetes in both developed and developing countries, where, in many areas, women of reproductive age are more likely than not to be overweight.

The benefits of exercise for expecting mothers

Compared with sedentary pregnant women, those who exercise moderately at least once a week are less likely to have low back pain and depression. In addition, more frequent exercise can help reduce pelvic girdle pain [1243]. Women who exercise in accordance with the 2002 American Congress of Obstetricians and Gynecologists (ACOG) guidelines [1244] (see 'Agency guidelines on exercise for pregnant women') exhibit significantly improved fitness levels and muscular strength, and recover faster post-delivery [1243].

The effects of exercise on gestational weight gain

Regular physical activity is important for maintaining optimal maternal bodyweight during pregnancy. Both excessive and inadequate gestational weight gain are associated with adverse maternal and infant outcomes (see chapter 28). Many studies have shown that intervention programmes that include leisure time physical activity/exercise can be successful in preventing excessive gestational weight gain. Such activities include aqua-aerobics, supervised walking/biking, a progressive walking programme, and unsupervised free gym membership with personal coaching [1231, 1246–1248].

The effects of exercise on gestational diabetes and pre-eclampsia

Because of its potential effects on insulin resistance, angiogenesis, and blood pressure, exercise has been suggested as a means to reduce the risks of gestational diabetes mellitus (GDM) and pre-eclampsia. However, evidence for an effect of physical activity on these outcomes has been mixed [1247, 1249–1256]. Most studies that examined the impact of physical activity before conception reported a significant impact in reducing the risk of pre-eclampsia [1254, 1257], but some reported no benefit [1258]. A recent Cochrane systematic review reported no significant differences in the incidence of GDM in women who received exercise interventions compared with those who received routine antenatal care [1259]. Based on these outcomes, there was not enough conclusive evidence to recommend a prescriptive exercise programme and establish a standard guideline and practice.

The effect of exercise on preterm birth

Physical activity throughout pregnancy has been reported to have a protective effect against delivery before 37 weeks gestation [1260–1262]. In a population-based cohort study of >61,000 singleton pregnancies in Norway, women who exercised 3 to 5 times a week in mid-pregnancy had a longer gestation than those who did not exercise [1263]. Frequent vigorous recreational activity (e.g. jogging, swimming, and brisk walking) in the first trimester was associated with longer gestation and a reduced risk of preterm birth [1264].

Stress management during pregnancy through yoga

Maternal stress and anxiety can have negative consequences for the growth and development of the fetus [1265–1267]. Stress increases fetal exposure to glucocorticoids and has been suggested as a risk factor for the development of attention deficit hyperactivity disorder or lowered performance on executive function tests in the offspring [1268, 1269]. More detail on the effects of prenatal stress on pregnancy outcomes is provided in chapter 33.

Yoga has gained popularity as a method of reducing stress, anxiety, depression, and chronic pain syndromes in adults. In high-risk women, yoga performed 3 times per week from the 12th to the 28th week of gestation significantly reduced the risk of pregnancy-induced hypertension, pre-eclampsia, GDM, and intrauterine growth restriction [1270]. In addition, women who practised yoga were significantly less likely to have a baby that was small for gestational age or had a low Apgar score at birth. Two recent reviews of both controlled and observational trials reached similar conclusions regarding a reduction in the rates of preterm labour, intrauterine growth restriction, low birthweight, sleep disturbance, and stress [1271, 1272].

The effects of moderate maternal exercise on the offspring

In general, non-extreme exercise is reported to have minimal risk and potential indirect (i.e. via mother's health) benefits to the fetus [1273, 1274]. Regular aerobic exercise during pregnancy is associated with lower fetal heart rate and higher heart rate variability at rest [1275, 1276]. The exact mechanisms by which maternal exercise may affect fetal heart rate control are uncertain, but a dose-response relationship has been demonstrated [1277].

Maternal physical activity before and during pregnancy may have a beneficial impact on the timing of delivery, birthweight, and offspring health [1278]. In a study of >79,000 pregnant women from the Danish National Birth Cohort, women who exercised during pregnancy had a reduced risk of giving birth to small-for-gestational-age or large-for-gestational-age infants compared with those who did not exercise [1279]. Data from >9,000 women who were involved in the National Maternal and Infant Health Survey also demonstrated a protective effect of leisure physical activity during pregnancy against low birthweight outcomes [1280].

The long-term effects of maternal exercise on the offspring

Little is known of the long-term effects of maternal exercise on offspring health. In general, the apparent reduction in preterm delivery and the associated improvements in maternal health might be expected to improve offspring health. Whether the physiological effects on the fetus of moderate maternal exercise provide long-term benefit is not clear.

Children of mothers who exercised during pregnancy had a leaner body mass and better neurodevelopmental outcome at 5 years of age [1281]. The mechanisms of this long-term protective effect are unknown. A confounder on such studies is that the social environment of families where mothers were committed to regular exercise may be sufficiently different to impact on the child's development independently of the woman's exercise pattern.

The potential risks of exercise during pregnancy

The potential risks of exercise in swimming pools during pregnancy

It has been suggested that swimming in pools during pregnancy might be harmful for pregnant women because the chlorine disinfection by-products may be toxic to the fetus [1282]. Although several studies have suggested that exposure to such by-products may increase the risk of low birthweight, the evidence is inconclusive [1283]. There are few studies of swimming exposure per se, but these are reassuring. The Avon Longitudinal Study of Parents and Children birth cohort of >11,000 pregnant women found no apparent association between swimming and birthweight [1284]. Similarly, a more recent study in nearly 75,000 singleton pregnancies from the Danish National Birth Cohort reported that swimming in pool water was not associated with adverse reproductive outcomes [1282], and in fact women who swam in early/mid-pregnancy had a slightly reduced risk of having preterm birth. Based on the limited studies that have been conducted and reported so far, the current practice of swimming in pools for pregnant women should be safe.

Extreme exercise in pregnancy

While there is strong evidence for the benefit of moderate and regular exercise in well-nourished pregnancies, there is more debate about the wisdom of severe exercise in pregnancy, particularly in late pregnancy, because of its effects on birthweight. Studies suggest that women who perform vigorous exercise (e.g. running, aerobic dance, and cross-country skiing) throughout pregnancy give birth to infants with reduced birthweight (~300–500 g lighter), compared with those who do not exercise or exercise moderately [1241, 1279, 1286–1288]. A randomized controlled trial in healthy women in the second half of pregnancy showed that vigorous aerobic exercise was associated with lower birthweight and BMI, as well as lowered cord serum insulin-like growth factor 1 and insulin-like growth factor 2 [1289].

Because of this association with reduced birthweight, caution is indicated with respect to extreme exercise in late pregnancy. Whether such reduction in birthweight has long-term consequences for the offspring is not certain but, given that the mechanism of the reduction in birthweight is likely to be analogous to the effects of poor late gestational maternal nutrition, we would suspect that the offspring of mothers undertaking extreme exercise may be at greater risk for the development of obesity, insulin resistance, and other non-communicable diseases. Further studies are needed to address this question.

Agency guidelines on exercise for pregnant women

The ACOG recommends that healthy pregnant women should engage in 30 minutes or more of moderate physical activity per day on most, if not all, days of the week. ACOG also states that physically active woman with a history of or risk for preterm labour or fetal growth restriction should reduce their activity in the second and third trimesters [1244]. The Canadian guidelines [1290] recommend that healthy pregnant women should perform aerobic exercise regularly for at least 15 minutes, 3 days per week at the target intensity. The exercise duration can be increased from a minimum of 3 days per week to 4 or 5 days per week over time. Healthy pregnant women who were previously inactive can gradually increase the duration of exercise from 15 to 30 minutes per session during the second trimester. In addition, women should avoid exercising in the supine position after the fourth month as well as performing the Valsalva manoeuvre during resistance exercise (which is easy to do without being aware of it in activities such as weightlifting).

The Royal College of Obstetricians and Gynaecologists suggests that all women be encouraged to participate in aerobic and strength-conditioning exercise as part of a healthy lifestyle during their pregnancy [1291]. Reasonable goals of aerobic conditioning in pregnancy should be to maintain a good fitness level throughout pregnancy without trying to reach peak fitness level or train for athletic competition. Women should choose activities that will minimize the risk of loss of balance and fetal trauma.

Our recommendations on exercise for pregnant women

Moderate and regular exercise and/or physical activity benefits both mothers and offspring. Although some studies have reported the benefits of exercise in reducing the risks of GDM, pre-eclampsia, and caesarean delivery, others have not been able to demonstrate these benefits. Exercise/physical activity also been reported to reduce the risks of large-for-gestational-age/small-for-gestational-age babies and of preterm birth.

Although there are various exercise guidelines for women during pregnancy, the consensus is that 30 minutes or more of moderate physical activity per day on most, if not all, days of the week is desirable. However extreme exercise in late gestation is associated with lower birthweight and the possibility of long-term adverse consequences on the offspring. We therefore would counsel, at this stage of our knowledge, against such extreme forms exercise during the later stages of pregnancy and suggest a more moderate approach.

Chapter 30

Foods, exposures, and lifestyle risk factors in pregnancy and breastfeeding

Deciphering the messages about foods and exposures to avoid during pregnancy

Pregnant women can feel bombarded with messages from various sources regarding foods and exposures to avoid during pregnancy. Some of this guidance is sound and should be followed. However, other commonly propagated advice is not based on scientific evidence and may in fact be disadvantageous in some situations. For example, despite common belief, avoidance of certain foods in pregnancy has not been shown to reduce the risk of childhood allergies. In a large population-based UK birth cohort, some dietary patterns were associated with eczema, IgE, lung function, and asthma; however, none had any effect after allowing for other environmental confounders [1292].

Previous advice on food avoidance has included peanut consumption in pregnancy as a potential risk factor for development of peanut allergy in the offspring of women with familial risk factors. A study of the effect of this advice in the UK found that the prevalence of peanut sensitization more than doubled in the ten-year period after the advice on peanut avoidance was publicized [1293]. A recent systematic review of available evidence concluded allergen avoidance in the maternal diet during pregnancy is unlikely to reduce offspring susceptibility to atopic disease, even in high-risk women [1294]. In fact, recent studies have shown that in utero allergen exposure (peanuts and tree nuts) may increase offspring tolerance and reduce the risk of childhood food allergy [1295, 1296]. Hence, avoidance diets in pregnancy, including peanut avoidance, are no longer advocated for the prevention of allergy.

There are, however, various natural substances and toxic contaminants present in our environment and in common foods and drinks that may be harmful to the developing fetus, and consumption of or contact with these substances should be restricted or avoided during pregnancy. There are also a number of known occupational, behavioural, or environmental factors that can affect pregnancy outcomes. Women need to know the possible impact of these so that precautions can be taken and harmful contacts can be minimized.

Foods to avoid during pregnancy and lactation

Teratogens are substances that have been found to interfere with fetal development and cause birth defects, either in animal studies or from reports of human exposure. Some foods and drinks have been identified as containing teratogens, usually when consumed in high amounts early in pregnancy. There are specific vulnerable periods at different stages of fetal development.

Organogenesis begins around day 16 and continues up to the 8th week post conception. Major malformation of the brain, eyes, ears, limbs, lungs, heart, and kidneys can be caused by the ingestion of teratogens during this critical period. Neural tube defects and some craniofacial malformations stem from disruptions or toxic insults during this window of fetal development. Cleft palate, micro-opthalmia, and hydrocephalus can occur as a result of exposures between days 40 and 60 of gestation. Sexual differentiation starts in this period, and from that point on, exposure to endocrine disruptors can affect male genital development. From the 8th to the 15th week, interference with neuronal proliferation, differentiation, and migration can occur, disrupting brain growth and cognitive development. CNS maturation is also vulnerable throughout the remainder of pregnancy [1297].

Liver consumption during pregnancy and the risk of excess vitamin A

High maternal exposure to vitamin A or retinoic acid early in pregnancy has been shown to be teratogenic in rodents and humans [229, 1298], causing craniofacial, CNS, thymic, and heart defects. Avoidance of foods and supplements containing high concentrations of preformed vitamin A is strongly recommended (see chapter 6). As vitamin A is stored in the liver of animals, eating liver, especially during early pregnancy, should be avoided.

Herbal tea consumption during pregnancy and potential risks from polyphenols and phytotoxins

Herbal teas are widely consumed around the world and are rich in polyphenolic compounds with antioxidant and anti-inflammatory properties [1299, 1300]. While these may seem beneficial for pregnant women, overconsumption may have adverse effects. Oral administration of polyphenols extracted from green tea can inhibit the activity of cyclo-oxygenase 2, which mediates the transformation of arachidonic acid into prostaglandins. Substances with the capacity to inhibit maternal circulating prostaglandins in pregnancy can have a constricting effect on the fetal ductus arteriosus, altering fetal haemodynamics and potentially resulting in neonatal pulmonary hypertension. Indeed, maternal consumption of large quantities of polyphenol-rich foods in late pregnancy is reported to be associated with fetal arterial ductal constriction [708]. Among other types of herbal teas, chamomile tea consumption in pregnancy has been associated with constriction of the ductus arteriosus in case reports [1301].

Pyrrolizidine alkaloids are phytoxins found in plants used in Chinese and Indian (Ayurvedic) herbal remedies and teas, and are contraindicated in pregnancy as they are potentially teratogenic. Comfrey tea preparations can contain pyrrolizidine alkaloids, and cases of fetal hepatic veno-occlusive disease have been reported from high maternal consumption [1302]. This fatal birth defect was also observed following daily consumption of an herbal cooking mixture containing pyrrolizidine alkaloids [1303]. Honey made from plants of genera that produce pyrrolizidine alkaloids, particularly *Senecio*, *Borago*, and *Echium* spp., is another source of ingestion. These plants are significant contributors to honey production in many countries [1304, 1305]. However, most women would not consume enough honey for this to be a problem, and honey is not currently contraindicated in pregnancy.

Avoidance of contaminated grains during pregnancy and lactation

Mycotoxins are produced by fungi that can contaminate grains such as rice, corn, and wheat. Peanuts, almonds, walnuts, sunflower seeds, and spices, including black pepper and coriander, are also potential sources of contamination. Food can be contaminated during processing, storage, or transport in conditions favourable for mould growth.

Aflatoxins are the most prevalent of the mycotoxin food contaminants, and exposure is common in sub-Saharan Africa and East and South East Asia [1306], where aflatoxins are known to contribute to increased risk of hepatocellular carcinoma [1307, 1308]. Aflatoxin exposure in utero can occur via placental transfer following maternal intake of contaminated foods [1309] or during lactation via contaminated breast milk and has been shown to increase the risk for growth faltering [1310]. Exposure to aflatoxins can cause growth impairment in children [44].

The consumption of predatory fish during pregnancy

Several toxicants that can negatively affect fetal development have been identified in predatory fish from some regions. These include PCBs, hexachlorobenzene, and mercury. PCBs and hexachlorobenzene are banned industrial organochlorine chemicals that were used extensively in North America and Europe and appear as persistent environmental contaminants in fish and marine mammals living in surrounding waters [1311]. In seafood-eating populations such as Inuit Indians, in utero exposure to moderately high levels of organochlorines and mercury is associated with shortened gestational length and consequent lower birthweight and reduced length and head circumference [1312]. PCBs also interfere with thyroid function during development, resulting in learning and behavioural problems in childhood [1313].

Mercury in the aquatic environment is methylated by bacteria to methylmercury, which is accumulated through the food chain such that the bodies of predatory fish including swordfish, tuna, and shark can acquire high concentrations. All fish contain some level of methylmercury, which may act as a neurotoxicant even at low levels of exposure. The fetus is particularly vulnerable, as many developmental processes are susceptible to disruption by mercury. There are examples of congenital poisoning, for example, following environmental contamination in Japan [1314] and Iraq [1315], resulting in neurological abnormalities and severe developmental delays in children even when mothers showed little or no overt signs of toxicity. The American Pregnancy Association advises that fish containing modest levels of mercury (e.g. bass, carp, Alaskan cod, halibut, Mahi Mahi, freshwater perch, monkfish, sea trout, snapper, and canned tuna) be limited to 1–2 meals per week [216].

The beneficial effects of omega-3 long-chain polyunsaturated fatty acids from a diet high in fish may partially mask the adverse effects of prenatal methylmercury exposure [1316]. Longitudinal studies in a population of high fish consumers have shown no long-term neurological consequences in prenatally exposed offspring at 9 years of age [1317], suggesting that the beneficial influence of fish-derived polyunsaturated fatty acids may counteract the possible adverse effects of prenatal methylmercury exposure. Fish consumption is still recommended during pregnancy, but high consumption of predatory fish and marine mammals should be avoided.

Sources of foodborne infections during pregnancy

During pregnancy, hormonal changes occur that down-regulate cell-mediated immune function to accommodate the semi-allogenic fetus [1318]. A consequence of these changes is that pregnant women may be more susceptible to some types of infections, or at risk for more severe disease [1319]. For example, *Listeria monocytogenes* infection (listeriosis) occurs most frequently in people whose cellular immunity has been suppressed by drugs, disease, or pregnancy. In healthy adults, including pregnant women, listeriosis causes only minor (usually gastrointestinal) illness but can have profound effects on the developing fetus. *L. monocytogenes* is a gram-positive bacterium that can grow in aerobic or anaerobic conditions. It is a particular concern with regard to food contamination because it can grow at refrigerator temperature and is not killed by freezing [1320]. Ready-to-eat foods such as cold cuts or deli meats and cheeses or other dairy products are likely sources of contamination. In particular, it is advisable that pregnant women avoid mould-ripened soft cheeses (e.g. Camembert, Brie, and blue-veined cheese), unpasteurized milk (or products containing it), pâté (any kind, including vegetable), and uncooked or undercooked ready-prepared meals and meats.

Toxoplasmosis, caused by infection by the protozoan parasite *Toxoplasma gondii*, is another foodborne illness of significant concern for pregnant women. *T. gondii* infection is very common worldwide. Pregnant women who were previously unexposed to the parasite and who become infected during pregnancy usually transmit the infection to their fetus, with potentially serious and lasting consequences, including intellectual disability, blindness, and epilepsy [1321]. Toxoplasmosis can be acquired from eating undercooked meat (mainly pork), or salad vegetables contaminated with soil. *T. gondii* is also present in cat faeces and litter, and pregnant women are advised to avoid coming into contact with cat litter trays. There are some concerns that the increasing use of free-range farming increases the risk of exposure of pigs to grass, soil, feed, and water potentially contaminated with *T. gondii,* possibly increasing the risk of toxoplasmosis from the consumption of organically raised pork [1322]. More studies are needed before advice can be provided on organic vs traditionally farmed meat products for pregnant women at this stage.

In any case, pork and other meats should be cooked thoroughly and eaten soon after cooking to avoid the potential for infection with this parasite during pregnancy. Rare-cooked lamb is also a potential source of infection. It is advisable to cook whole cuts of lamb, pork, veal, or beef to at least 65.6°C (150°F) as measured by a food thermometer [1323]. Fruits and vegetables should be peeled or thoroughly washed before eating. Cutting boards and utensils should be washed with hot soapy water after they have been in contact with raw meat, poultry, seafood, or unwashed fruits or vegetables [1324].

The gram-negative bacteria *Salmonella enterica* can contaminate raw or partially cooked eggs (or foods that may contain them, e.g. mayonnaise and homemade Caesar salad dressing), raw or partially cooked meat (especially poultry), and raw sprouts [1324]. Although pregnant women are at no greater risk of salmonellosis than the general population, if infection occurs in pregnancy it can be transmitted to the fetus, possibly leading to preterm delivery or intrauterine death. As a general precaution, pregnant women are advised not to eat raw or partially cooked meat or eggs. Eggs should be cooked until the yolk and white are firm.

To avoid possible infection with pathogens that may cause fetal harm, all pregnant women, regardless of their diet, are advised to be vigilant about the washing, cooking, and storage of foods. The opinion of researchers from the Motherisk programme in Canada is that improved hygiene standards and surveillance have substantially lowered the risk of infection from deli meats and soft cheeses, such that these no longer need to be avoided if acquired from reputable establishments [1325]. However, most agencies continue to recommend against consumption of these foods. Foods that should be avoided in pregnancy are listed in Table 30.1

Table 30.1 Forbidden foods

Food	Risk in pregnancy	Comment/advice
Liver	Excess vitamin A—teratogenic	Best to avoid, particularly in early pregnancy.
Fish with mercury[a]	Fetal brain damage/ developmental delay	Avoid large predatory fish.
Fish exposed to pollutants (PCBs)[b]	Birth defects	Check with local health authorities whether locally caught fish is safe to eat.
Cold deli meat	Listeriosis	Reheat cold meats until steaming hot.
Cold smoked seafood[c]	Listeriosis	Reheat until steaming hot.
Soft cheeses[d]	Listeriosis	Avoid unless made from pasteurized milk.
Pâté (including vegetable)	Listeriosis	Avoid all refrigerated pâtés. Canned or shelf-safe pâtés can be eaten.
Unwashed fruits and vegetables	Toxoplasmosis	Peel or wash fruits and vegetables thoroughly before eating.
Undercooked or raw meat, poultry or seafood	Toxoplasmosis, salmonella	Cook food thoroughly and eat while hot.
Raw eggs[e]	Salmonella	Avoid .

[a] Predatory fish: swordfish, marlin, tuna, shark, orange roughy, king mackerel, bigeye or Ahi tuna, and tilefish

[b] From contaminated rivers and lakes (locally caught, not from supermarket): bluefish, striped bass, salmon, pike, trout, and walleye

[c] Deli or cold packaged. Canned or shelf-safe smoked seafood is safe to eat

[d] Cheeses made from unpasteurized milk: Brie, Camembert, Roquefort, feta, Gorgonzola, Mexican style cheeses (queso blanco and queso fresco)

[e] Includes homemade dressings made with raw eggs, e.g. Caesar and Hollandaise; also homemade ice creams or custards. Commercially available dressings, custards, and ice creams are made with pasteurized eggs and are considered safe to eat

Source: American Pregnancy Association, *Food to avoid during pregnancy*, copyright © 2014 American Pregnancy Association. <http://americanpregnancy.org/pregnancyhealth/foodstoavoid.html>; US Department of Health and Human Services, *Checklist of foods to avoid during pregnancy*. 2014, <http://www.foodsafety.gov/poisoning/risk/pregnant/chklist_pregnancy.html>; NSW Food Authority, *Foods to eat or avoid when pregnant*, copyright © State of New South Wales through the NSW Food Authority. 2014, <http://www.foodauthority.nsw.gov.au>.

Caffeine consumption during pregnancy

Approximately 70 per cent of pregnant women in the US report consumption of coffee, soft drinks, and/or tea during pregnancy, at average caffeine intakes of around 150 mg/day [1326]. The methylxanthines theophylline and caffeine found in tea and coffee, and theobromine (an active derivative of caffeine) found in chocolate, are subject to uninhibited transport through the placenta to the fetus [1327]. Caffeine also passes into milk during lactation. Metabolism of methylxanthines is impaired in pregnant women, fetuses, and neonates, allowing accumulation of these substances [1328].

Caffeine increases the levels of catecholamines, which can induce placental vasoconstriction [1329]. High maternal caffeine consumption (>300 mg/day) is mainly associated with an increased risk of fetal growth restriction [1330–1333], although there are also reports of increased risks of spontaneous abortion [1334, 1335], or stillbirth [1336]. Even in the intake range of 200–299 mg/day (3 single espressos or 4–6 cups of tea), caffeine consumption was found to be associated with a statistically significant increased risk of fetal growth restriction, with the strongest effect in women who were rapid metabolizers of caffeine [41].

A longitudinal study demonstrated that exposure to caffeine was related to poorer neuromuscular development and significant increases in breech presentation of fetuses; breech presentation was doubled with caffeine use above 444 mg/day from coffee, tea, and/or chocolate [1337]. The Food Standards Agency in the UK now recommends that women be aware of all the sources of caffeine in the diet that will contribute to their daily intake, including chocolate, energy drinks, and colas in addition to tea and coffee, and to limit their intake of caffeine to 200 mg/day [1338]. In a study in which caffeine consumption was recorded by interview, the level of intake during pregnancy did not have an effect on the sleep patterns of infants up to 3 months of age, although night-time waking was most frequent in infants of mothers with the highest intakes (≥300 mg/day) throughout pregnancy and breastfeeding [1339].

In addition to the possible risks of high caffeine intake during pregnancy, pre-pregnancy caffeine consumption may affect a couple's ability to conceive. Caffeine metabolism varies during the menstrual cycle, with reduced clearance during the luteal phase. This results in caffeine accumulation during the period of implantation and early embryonic development [1340]. High caffeine intake has been shown to reduce conception rates [1341], with a similar decline in fertility in both females and males, the latter effect possibly resulting from an impact of caffeine on semen quality.

Despite numerous reports in the literature, the risks associated with caffeine consumption are still a matter of debate. A recent comprehensive review of 17 epidemiological studies since 2000 concluded that it is not possible to verify a causal relationship between outcomes and caffeine consumption because of confounding issues such as imprecise calculation of caffeine consumption, recall bias, etc. [1342]. Common advice is to limit caffeine intake to 200 mg/day (~2 medium cups of filtered coffee) during pregnancy and breastfeeding, a recommendation that continues to be justified based on the available data.

Effects of exposure to environmental toxicants during pregnancy and lactation

Prenatal exposures to some relatively low-level environmental contaminants may have significant effects on later development. For example, prenatal lead exposure affects behavioural and cognitive development in children. Endocrine disruptors, a classification of substances that interfere with hormone action, can alter fetal hormone signalling, inappropriately modulating fetal growth and organ development. Indeed the same phenomenon of altered developmental programming that increases susceptibility to diseases later in life as a result of altered maternal nutrition can also be shown for many cases of chemicals with endocrine-disrupting activity. Some commonly encountered toxins that pregnant and lactating women should be aware of are discussed below. This is by no means comprehensive, and there is growing interest in a broader range of potential exposures [1343].

Lead exposure during pregnancy and lactation

Lead exposure remains a concern for pregnant and lactating women, despite improved policies in many countries to reduce environmental and workplace sources of exposure [1344]. Lead is non-biodegradable and accumulates in soil and dust near industries that utilize lead in manufacturing, and near electronic waste dumps, in addition to its presence in lead paints in old houses, some ceramic glazes, and even common foods and home remedies in some countries [1345, 1346]. Lead accumulates in the skeleton over time, and the increased bone demineralization that occurs during pregnancy causes the release of lead from bone into blood. This results in fetal exposure, as lead readily crosses the placenta via diffusion.

In utero lead exposure can affect the developing nervous system, and in extreme cases leads to spontaneous abortion or fetal death. Prenatal exposure of low levels of lead (less than 10 μg/dL in maternal blood) has been shown to affect indices of infant cognition at 7 months of age [1347]. Paternal employment in the lead industry or other occupations that are associated with exposure to lead (e.g. automotive painting and/or radiator repair, scrap handling, house renovation/paint stripping, demolition of ships or old buildings, etc.) is regarded as an indirect risk to the fetus, as lead dust can be brought into the home on clothing, skin, and hair [1348].

The intellectual functioning of children is affected by lead exposure from an early age, and the effects are long-lasting and irreversible. Therefore, prevention is critical. Recent studies indicate that even low lead exposure can have subtle negative effects on cognitive, behavioural, and neuropsychological development and that every 10 μg/dL increase in blood lead level in children correlates with a drop of 4.6 IQ points [1348].

There are nutritional influences on lead toxicity. Calcium, iron, and vitamin C help protect the developing fetus from the harmful effects of lead exposure. Increased intake of calcium in the diet is known to decrease the gastrointestinal absorption of lead. Women with inadequate calcium intake during pregnancy are more likely to have elevated blood lead levels [1349]. High calcium intake also reduces blood lead exposure in pregnancy by minimizing bone demineralization and the consequent release of lead from bone [1350]. A randomized trial in pregnant women who received 1.2 g calcium/day or placebo starting in the first trimester demonstrated a modest reduction in blood lead levels (with the highest reduction seen in the most compliant group) [1351]. When given during lactation, calcium supplementation (1.2 g/day) has been shown to reduce lead levels in maternal blood (by 15–20%) and breast milk (by 5–10%) [1352, 1353]. Supplementation with 1 g calcium per day during pregnancy and 6 months postpartum delayed the increase in blood lead levels until later in the postpartum period [1354].

Vitamin C has a chelating effect: higher serum ascorbic acid levels correlate with significantly lower blood lead levels [1355, 1356]. The mechanism of the interaction of iron and lead is less well understood, but it is known that iron deficiency increases susceptibility to lead toxicity. Both iron and lead affect the haem biosynthetic process; in particular, lead inhibits the enzyme ferrochelatase, which catalyses the insertion of ferrous iron into protoporphyrin, forming haem. When iron deficiency is present, ferrochelatase is more sensitive to lead effects. Because iron deficiency is common in pregnancy (see chapter 20), it serves as an additional risk factor for lead toxicity. The precautionary advice for pregnant women provided by the US CDC [1357] is outlined in Box 30.1.

Recognition and removal of lead sources is important for the prevention of maternal and neonatal morbidity. Universal screening for maternal lead exposure is recommended in some areas [1345].

Box 30.1 Advice of the US CDC: precautions for pregnant women regarding lead exposure

- Avoid dust from the renovation of older homes—paint peeling or cracking in older homes may release dangerous lead dust.
- Stay out of the house if a room with lead paint is being cleaned, painted, or remodelled.
- Discuss the use of any home remedies or supplements, some of which may contain lead, with a doctor.
- Cravings to eat dirt or clay should also be made known to the doctor.
- Avoid work that may involve lead exposure, such as auto refinishing, construction, and plumbing.
- Note that indirect maternal exposure can occur when a worker brings home lead dust on clothing.
- Household members involved in such occupations should change to clean clothing before entering the home.
- Eat foods high in calcium, iron, and vitamin C.
- Avoid candies, spices, and non-commercial food products from foreign countries, which sometimes contain lead.
- Store food properly—avoid lead-glazed pottery and pewter.

Source: CDC, *Lead: pregnant women*. <http://www.cdc.gov/nceh/lead/tips/pregnant.htm> accessed 7 May 2013. [1357]

Pesticide exposure during pregnancy and lactation

Pesticides can have neurotoxic and endocrine-disrupting effects in humans and can be harmful to the developing fetus. Several studies have suggested that maternal occupational exposure to agricultural pesticides during pregnancy is associated with increased risk of impaired reproductive development in male offspring [1358–1360]. Among these pesticides is vinclozolin, a fungicide that has been shown to alter epigenetic programming of the male germ line in animals (rats) [1361]. The principal toxic effects induced by vinclozolin and/or its metabolites are related to its anti-androgenic activity.

The organochlorine pesticide dichloro-diphenyl-trichloroethane (DDT) is an effective and relatively inexpensive means of mosquito (malarial vector) control that is still used in some regions, despite being banned in the US in 1972 and its use curtailed around the world in 2001. DDT persists as an environmental contaminant worldwide and accumulates in fatty tissues of animals and humans. Prenatal exposure to DDT was associated with neurodevelopmental delays during early childhood in a highly exposed population working on farms in California [1362]. Other studies have shown that in utero exposure to low-level, background concentrations of DDT may also decrease cognitive function, particularly in girls [1363]. Notably, there was a beneficial effect of breastfeeding, even in highly exposed women.

A longitudinal study of children born to women who were occupationally exposed to pesticides during pregnancy showed immediate and long-term effects on body composition. The exposed children had thicker skin folds and higher body fat percentage at school age than their non-exposed counterparts, with higher exposure correlating with higher adiposity [1364]. The effect was amplified if the children had also been exposed to cigarette smoke in utero. In addition, organophosphate insecticides inhibit acetylcholinesterase, thereby prolonging the action of acetylcholine. A study of an agricultural community with relatively high exposure to these chemicals indicated that in utero exposure has a detrimental impact on neurobehavioural functioning in newborns [1365].

Aside from occupational exposure, substantial exposure to pesticides that may affect the developing fetus can occur in and around the home and garden. Metabolites of indoor pesticides are frequently found in blood samples of pregnant women. Moreover, these substances are able to cross the placental barrier and are detectable in newborn blood [1366].

It is advisable to be aware of and limit occupational exposure to pesticides during pregnancy, including paternal exposure that may be tracked into the household on clothing and skin. Within the home, pesticides should be used with caution and under conditions of adequate ventilation. Protective clothing or gloves should be worn if handling is necessary.

Herbicide exposure during pregnancy

Atrazine is the herbicide most commonly used in the US and around the world for weed control and is a potent endocrine disruptor. Although monitored by the US EPA [1367], significant concentrations are occasionally found in drinking water in some areas, as a result of run-off from crops sprayed with the chemical. The use of atrazine in plant protection products was banned by the European Commission in 2003 [1368].

Gastroschisis, an increasingly common birth defect involving incomplete closure of the abdominal wall, has been attributed in part to in utero exposure to agricultural chemicals, including atrazine [1369]. A seasonal variation in incidence has been observed, relating to exposure during the peri-conceptional period [1369, 1370]. The mechanism is thought to involve oestrogen disruption. A recent study has shown that the effect is specific to offspring of women ≥25 years of age, as compared with those from younger mothers, possibly relating to the fact that older women have lower first trimester oestrogen levels than younger women, making them more sensitive to oestrogen disruption [1371].

Increased risk for intrauterine growth restriction has also been observed in communities where the municipal drinking water contained higher atrazine concentrations (2.2 μg/L vs 0.6 μg/L) [1372]. Dermal and inhalation exposure of atrazine in farming communities has also been associated with increased incidence of preterm delivery and spontaneous abortion [1373, 1374]. The latter studies involved farming couples where in most cases the fathers had direct exposure to the chemical, and mothers were mainly indirectly exposed through contact with contaminated clothing or by consuming contaminated drinking water. This emphasizes the often overlooked influence of paternal factors, in particular the contribution to potentially damaging exposures, on birth outcomes (see chapter 35 for more detail).

Exposure to polycyclic aromatic hydrocarbons during pregnancy

Polycyclic aromatic hydrocarbons (PAHs) are formed from incomplete burning of coal, oil, gas, wood, and other organic substances such as tobacco or chargrilled meat. PAHs are found throughout the environment; exposure is mainly as vapours (e.g. cigarette smoke, exhaust fumes, and wood fires) or attached to dust particles. Food grown in contaminated soils may also contain PAHs. Some PAHs, such as benzopyrene, are known to cause tumours in laboratory animals [1375] and DNA damage in humans [1376].

Cigarette smoke exposure increases PAH metabolism in human placental tissue [1377]. However, PAHs do not readily cross the placental barrier, so maternal and placental levels are higher than fetal levels [1378]. In epidemiological studies, prenatal PAH exposure was associated with impaired fetal growth, resulting in reduced birthweight, smaller head circumference, and/or small size for gestational age [1379]. as well as diminished cognitive development [1380, 1381].

The fetus has a heightened susceptibility to PAH-associated DNA damage in early development because of high cell proliferation rates. A critical window of vulnerability to exposure in the first gestational month has been identified [1382], although pre-conception parental exposure is also a factor. Paternal pre-conceptional exposure to PAHs from cigarette smoke or occupational exposure (e.g. oil and gas production, coal-fired and other power plants, and restaurants) has been reported to increase the risk of childhood brain tumours in their offspring [1383], although this assumption remains unconfirmed. Maternal occupational exposure has been linked with an increased risk of gastroschisis [1384]. Occupational exposure to PAHs should be limited if possible, particularly maternally during the first month of pregnancy. Exposure (both first-hand and second-hand) to cigarette smoke should be avoided throughout pregnancy.

Exposure to bisphenol A during pregnancy

Bisphenol A (BPA) is an endocrine-disrupting chemical present in polycarbonate plastic and epoxy resins and is ubiquitous in the environment. It is classified as a xenoestrogen, meaning it has estrogenic properties. Very small amounts of BPA (below the no-observed-adverse-effect level typical of environmental exposure) alter the development of reproductive organs in mice [1385]. In utero exposure to BPA in sheep increased the fetal expression of CYP19, which is involved in the conversion of androgens to oestrogens, and disrupts the expression of microRNAs involved in regulating oestrogen signalling and insulin homeostasis [1386]. Consequent to such exposure, puberty is accelerated and body weight is increased [1387].

Animal studies suggest that BPA might augment the allergic immune response [1388, 1389], and that prenatal exposure has more profound effects than exposure in adulthood [1390]. A recent study of allergic/asthmatic outcomes relating to prenatal and postnatal BPA exposure measured urinary BPA concentrations in pregnant women (n = 568) and their children at ages 3, 5, and 7 years and found an inverse correlation between prenatal urinary BPA levels and wheeze in children at 5 years of age but a positive association between childhood urinary levels and wheeze or asthma [1391].

BPA is detectable in urine in most people, including pregnant women, and fetal tissues accumulate BPA [1392]. BPA is used in linings of food cans, and has been shown to leach into the food products. Women who regularly eat canned vegetables had higher urinary BPA levels than those who did not. BPA is also found in cigarette filters, and women exposed to cigarette smoke had levels of BPA that were 20 per cent higher than unexposed women. Leaching of BPA from plastic products is increased with heating (microwave) or with repeated use [1393]. Exposure was found to affect childhood behaviour, with higher exposure linked to increased aggression [1394].

Research towards improved understanding of the effect of BPA on humans is ongoing, although preliminary data suggest that caution concerning BPA exposure is warranted, especially for pregnant women and infants. Recommendations for avoiding excess BPA exposure include reducing the amount of canned foods (including beverages) that are consumed, rinsing canned fruits and vegetables before eating them, decreasing the use of plastic food-storage containers, and avoiding heating foods in plastic containers in the microwave. There has been a move away from BPA-containing plasticware used for infant feeding.

Exposure to arsenic during pregnancy

Arsenic is at the top of the US Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances [1395]. Its presence in variable amounts in drinking water and some foods is a worldwide health concern. Arsenic readily crosses the placenta, and animal studies suggest it may have growth inhibiting and possibly teratogenic effects, even at low doses that are equivalent to common human exposure in drinking water [1396]. There has been widespread arsenic poisoning in Bangladesh due to groundwater contamination in the Ganges basin [1397], and a prospective cohort study of 1,578 mother–infant pairs in this region showed that arsenic exposure in utero was associated with smaller size at birth [1398]. Other studies have implicated arsenic exposure in increased stillbirth and preterm birth rates [1399].

Grape and apple juices have been reported to contain arsenic, and rice, particularly brown rice grown in the US, is also a potential source. A study found that consumption of one half-cup cooked rice provided the same arsenic exposure as drinking one litre of tap water containing arsenic at the US Environmental Protection Agency's highest allowable level [1400]. A concern has been raised that daily consumption of rice, as in some Asian cultures, may result in elevated exposure to arsenic at levels that may be of concern for the developing fetus.

Exposure to cadmium during pregnancy

Like arsenic, cadmium is a toxic metal with potential adverse effects for the developing fetus, and is among the top ten substances on the most recent Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances (2011) [1395]. Cadmium is embryotoxic and teratogenic in animals [1401], although the impact of in utero exposure in humans is not well documented. A negative correlation between maternal and cord blood cadmium levels and infant birth size has been noted [1402]. The mechanism of cadmium teratogenicity may relate to the substitution of cadmium for zinc or calcium in biological processes, and these minerals may be important in lowering the toxicity of cadmium exposure, although human data are minimal [1401]. Individuals with iron, calcium, or zinc deficiency or with protein malnutrition may absorb cadmium at an increased rate [1403].

Inhalation of tobacco smoke is a major source of human exposure to cadmium. Cadmium is used in batteries, pigments, coatings, and platings, as well as stabilizers for plastics, and can enter the food chain, resulting in exposure through foods such as cereals and seafood [1404]. Pregnant women can be exposed to cadmium through their own or their partners' work in cadmium-emitting industries such as smelting and electroplating, wherein the main route of exposure is inhalation of dust and fumes. Exposure can be controlled through the use of protective equipment and good hygiene practices such that cadmium dust is not transferred to the home from the workplace [1405].

Maternal behaviours that affect pregnancy outcomes

Alcohol consumption during pregnancy and lactation

Alcohol is considered a dietary teratogen when consumed in large quantities. Acute exposure to ethanol in early gestation compromises development of the cerebral cortex [1406]. In an Australian study of approximately 4,700 women who gave birth between 1995 and 1997, those classified as 'heavy' drinkers in the first trimester were four times more likely to have a baby with a birth defect than those who did not drink [1407]. Chronic or frequent heavy alcohol use during pregnancy confers significant risk of fetal alcohol spectrum disorders, manifestations of which include facial abnormalities, growth deficiency, and nervous system defects. Yet alcohol consumption remains common among pregnant women: a report from Australia found that around 30 per cent of women consumed some alcohol during their pregnancies [1408], and the issue of mild alcohol consumption during pregnancy remains controversial.

In 2001, the Australian National Health and Medical Research Council changed their recommendation from abstinence during pregnancy to advising that women should consume less than seven standard drinks per week, and no more than two standard drinks on any one day [1409]. This message was reversed in 2009 to advise that alcohol avoidance is the safest option for pregnant and breastfeeding women [1410]. The UK Royal College of Obstetricians and Gynaecologists (RCOG) concurs with this opinion, advising that the safest approach in pregnancy is to choose not to drink at all [1411]. Various studies have reported no effect of 'light' alcohol consumption in pregnancy with negative childhood outcomes [1412, 1413], although this is potentially confounded by the fact that light alcohol drinkers tend to be socially advantaged, which may account for some of the favourable development of their offspring.

It is important to note that women are more likely to avoid eating foods that can potentially be contaminated with *Listeria* than to avoid alcoholic beverages, even although the rate of fetal harm from infections is lower than the risk from prenatal alcohol exposure [1414]. Health care professionals need to be more proactive in informing women about the possible harm of alcohol consumption on the fetus. It remains the opinion of most researchers that avoidance of alcohol is the safest choice, as there remains no known safe level of consumption during pregnancy.

Smoking during pregnancy

Numerous studies have addressed the impact of maternal smoking during pregnancy on infant outcomes (for a review, see [1414]). Although environmental and genetic confounders may limit the interpretation of studies of maternal smoking behaviour in pregnancy and offspring outcome, maternal smoking is clearly a fetal stressor, with multiple potential toxic exposures to the fetus including nicotine, carbon monoxide, and heavy metals. There are also indirect effects resulting from alteration of placental function and umbilical artery blood flow that may impair oxygen exchange across the placenta [1415].

Infants of mothers who smoke during pregnancy are at increased risk of low birthweight and smaller head circumference [1416–1418]. Maternal smoking has also been linked to preterm birth. In an analysis of over 150,000 births in Germany [1419], the risks of preterm delivery and premature rupture of membranes were directly related to the number of cigarettes smoked per day. The incidence of intrauterine growth restriction increased from 5.7 per cent in non-smokers to 15.8 per cent in patients who smoked >10 cigarettes per day. Smoking is associated with an increased risk of intrapartum stillbirth, which is accentuated in adolescent mothers [1420].

Maternal smoking has also been linked to offspring obesity in later life. Women who were exposed to cigarette smoke in utero were at a significantly higher risk of obesity in adulthood, and gestational diabetes in their own pregnancies [1421]. A recent study of >1,600 births reported an increased risk of overweight, specifically in boys at 5 years of age [1422].

Smoking and exposure to second-hand smoke are among the most important preventable risk factors for adverse pregnancy outcomes. Smoking cessation interventions have been shown in numerous studies to reduce the risks associated with maternal smoking [1423]. Efforts should be made by health care professionals to encourage and implement cessation strategies for their patients who are pregnant or planning a pregnancy. According to National Institute for Clinical Excellence guidelines issued in 2008 [266], nicotine replacement therapy should be offered to pregnant women, with instruction that nicotine patches should be removed at night.

Pica during pregnancy

Pica is a compulsive dietary aberration that occurs worldwide and is prevalent among pregnant women. It is defined as the pathological/persistent craving and consumption of non-food matter such as clay or dirt (geophagia), purified starch (amylophagia), or other substances, including charcoal, ash, paper, chalk, coffee grounds, or egg shells. In a form of pica known as pagophagia, pregnant women consume large quantities of ice (averaging 700 g daily).

Pica is most common in, but not limited to, low socio-economic and underdeveloped populations and may have strong cultural implications. Among a group of pregnant women studied in rural Kenya in 1999, 73 per cent ate soil (mainly from the walls of houses) on a regular basis. Soil eating was considered to be related to fertility and reproduction, and although not entirely endorsed, was regarded as acceptable behaviour in pregnancy in this society [1424]. Among a US cohort of 553 African American women in an urban environment, 8.3 per cent of women said that they consumed non-food substances before they became pregnant. A larger proportion of this group (28.2%) said that they had seen other family members eat non-foods; the women themselves were most likely to practice pica if the person they had observed doing this was their mother, although the substances they consumed were often different [1425]. Pica was more common among rural, socio-economically disadvantaged African American women; 38 per cent reported pagophagia during pregnancy in a multicentre prospective study [1426].

The primary hypothesis to explain this enigmatic behaviour is that it is associated with specific nutrient deficiencies, particularly of iron, zinc, and calcium. Other proposed explanations for pica suggest that it may be motivated by hunger, psychological stress, or gastrointestinal distress [1427]. However, despite decades of study, the causes of pica remain poorly understood.

Iron supplementation has been evaluated for the treatment of pica, with mixed results [1428]. Pagophagia appears to respond most consistently to supplemental iron treatment. Zinc treatment has also been used with some success in children and mentally handicapped adults [1429], but controlled studies are lacking. Although iron deficiency is thought to be a possible cause of pica, it also appears to be a consequence in some cases, either as a result of decreased consumption of nutritional, iron-containing foods, or because the ingested substances bind (and thereby sequester) elemental iron [1430].

In pregnancy, amylophagia may be involved in precipitating gestational diabetes [1430] or pre-eclampsia [1431]. Potential complications of geophagia include helminth infection [1432] or lead toxicity [1433]. High maternal blood lead levels have been observed in women with geophagia in pregnancy [1434], and fetal lead poisoning can occur as a result of maternal ingestion of plaster [1435]. In the urban African American population described above, women with pica (mainly amylophagia and pagophagia) gave birth to infants with smaller head circumference, compared with nonpica women [1425]. In addition to traces of lead, some soils that are consumed in geophagia may contain *Bacillus* and *Clostridium* spores and should be considered harmful in pregnancy, despite providing a proportion of recommended daily intakes of iron and zinc, as well as traces of magnesium and calcium [1436].

Pica in pregnancy may be under-reported. Anecdotal evidence suggests that few health care professionals question women about pica, despite its apparently widespread prevalence. Women are unlikely to volunteer information about pica, but should be asked, in a non-judgemental manner, if they have any unusual cravings during pregnancy.

The use of over-the-counter drugs during pregnancy

The use of pain relieving/anti-inflammatory drugs is common in pregnancy. Some of these drugs are available over-the-counter, such as paracetamol (acetaminophen) and the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen, diclofenac, naproxen, and aspirin. Data are conflicting regarding the effect of prescribed or over-the-counter NSAIDs on pregnancy outcomes, with some studies linking use in early pregnancy with spontaneous abortion [1437, 1438], but others finding no such association. Most studies were not able to find associations with specific NSAIDs. A study looking specifically at over-the-counter NSAIDs found no evidence that non-prescription drugs such as ibuprofen are linked to an increased risk of spontaneous abortion [1439].

Other studies have suggested that NSAID use in late pregnancy is associated with persistent pulmonary hypertension in the newborn, a serious and sometimes fatal disorder caused by a maladaptive pulmonary vascular response during the transition at birth from fetal to neonatal circulation [1440, 1441]. This association is biologically plausible, given the inhibitory effect of NSAIDs on prostaglandin synthesis, which are involved in the regulation of pulmonary vasculature and maintenance of ductal patency [1442]. However, a recent large multicentre epidemiological study did not find evidence to support the hypothesis that NSAID use in pregnancy increases the risk of persistent pulmonary hypertension [1443].

Regular or frequent paracetamol use in late pregnancy was associated with an increased risk of childhood asthma and wheeze in a population-based longitudinal study in the UK [1444]. The increased risk was observed in the offspring followed up to 7 years of age [1445] and is supported by a recent meta-analysis of additional studies [1446]. The effect of paracetamol on asthma risk may be related to increased oxidative stress, brought on by a reduction in glutathione [1447, 1448].

The link between paracetamol use and asthma is also supported by a number of epidemiological studies in adults, and exposures in young children (for reviews and meta-analysis see [1449, 1450]). It is therefore advisable for pregnant women to limit their use of paracetamol, especially during late gestation. A recent study has also suggested that prolonged paracetamol use (≥28 days) during pregnancy may increase the risk of poor gross motor functioning and other adverse developmental outcomes, including externalizing behaviour and negative emotionality in children. There was a trend towards stronger effects following exposure during the third trimester [1451].

Skipping breakfast or maintaining a low-carbohydrate diet during pregnancy

Skipping breakfast or maintaining a very low-carbohydrate diet during pregnancy can result in amplification of maternal ketosis. Ketones are produced as by-products of fatty acid metabolism. Conditions that amplify maternal ketosis, such as diabetes and malnutrition, are associated with a less favourable fetal outcome. Hyperketonaemia can cause increased circulating levels of pro-inflammatory cytokines and markers of oxidative stress [1452]. Ketones readily cross the placenta and may impair fetal neuropsychological development if present in excess [1453].

Ketone levels rise threefold in pregnant women when breakfast is omitted, a condition that has been referred to as 'accelerated starvation' [1454]. Accelerated starvation is a mechanism occurring in pregnancy whereby carbohydrate depletion causes a rapid adaptation to metabolize fat as energy, so that less expendable fuels, such as glucose and amino acids, are spared for the growth of the fetus. It is associated with hypoglycaemia, elevated plasma levels of free fatty acids, and increased urinary excretion of nitrogen and ketones. As glucose is transferred for fetal consumption, the resulting fall in maternal circulating glucose suppresses insulin secretion, enhancing lipolysis and conversion of fatty acids to ketones. Fetal blood glucose levels also fall and ketone levels rise in response to prolonged maternal fasting [1455].

Non-diabetic pregnant women are vulnerable to enhanced ketosis during brief periods of fasting in the third trimester. Falls in insulin and glucose coincident with increased free fatty acids and ketones are factors in widespread metabolic changes [1456]. Because such conditions partially mimic the diabetic state, this is thought to be harmful in pregnancy, both for the mother and the fetus. However, several studies indicate no adverse effect of gestational Ramadan fasting in healthy pregnant women on maternal oxidative stress, fetal development, or birthweight [1457–1459], despite a higher incidence of ketonuria observed in fasting women [1460] (see also chapter 31).

The increasing popularity of low-carbohydrate diets, including the 'Palaeolithic' diet (which is known to be ketogenic), has raised questions about the effect of enhanced ketosis on pregnancy outcomes. Although there are examples of healthy women and their offspring coping with fasting and enhanced ketosis during gestation, thorough studies on the effect of this metabolic shift on fetal outcomes are lacking. Results from prospective cohort studies such as the Southampton Women's Survey and other studies show that unbalanced diets (especially a low-carbohydrate, high-protein diet) in early pregnancy are associated with alterations in cardiovascular structure, blood pressure, cortisol levels, and adiposity in the children [88, 1461–1463]. In general, such diets and fasting are currently not recommended during pregnancy. Women who choose to follow these practices should be closely monitored, although it should be recognized that educational and other socio-economic factors often contribute to the consumption of such diets, so they are not always a matter of choice.

The use of hair dyes and skincare products during pregnancy and lactation

A recent report released by the RCOG [1464] has suggested that pregnant women might wish to consider minimizing the use of various personal care products, including moisturizers, cosmetics, shower gels, and fragrances, because of the potential for harmful exposure to their fetuses. However, a review of multiple studies on the level of exposure from such products concluded that use of cosmetics and other personal care products confers minimal exposure risk [1465]. This is consistent with data from other sources as reviewed in 2005 by the Cosmetic Ingredient Review Expert Panel in the US [1466].

In general, skincare products act locally and have little systemic effect and therefore most are safe to use during pregnancy. However there are notable exceptions, including the skin-bleaching agent hydroquinone and the acne medication tretinoin/isotretinoin, both of which can cause birth defects [1467]. Acne creams containing benzoyl peroxide or salicylic acid are considered safe to use during pregnancy. Topical preparations containing glycolic acid (an alpha-hydroxy acid) are also assumed to be safe to use, as very little is expected to be absorbed systemically. Similarly, topical hair removal agents containing thioglycolic acid (<5%), and hair bleaching creams containing hydrogen peroxide are not expected to cause problems if not used excessively [1467].

Various claims have been made about the safety of hair dyes, which contain *N*-nitroso compounds that have been shown to be mutagenic and carcinogenic in animals. As with most other topical cosmetic products, ingredients in hair dyes exhibit only minimal penetration of skin. Nonetheless, there is some concern that use of hair dyes could increase the likelihood of cancers in the offspring, despite inconsistent data.

For example, although a possible connection between maternal hair dye use in pregnancy and childhood brain tumours was not confirmed [1468], one study found some association with increased risk of neuroblastoma, and, specifically, more risk with temporary dyes than with permanent dyes [1469]. The effect was seen with exposure one month before and/or during pregnancy. An increased risk of childhood germ cell tumours was also observed with exposure to hair dyes one month prior to conception [1470]. Interestingly, this effect was sex-specific, with an increased risk for male offspring. The same study noted an increased risk for germ cell tumours in female offspring of mothers exposed to hair dyes while breastfeeding [1470]. Thus, although the risk may be low, we would advise women to delay the use of hair dyes until at least the end of the first trimester, if not throughout pregnancy and breastfeeding. Occupational exposure to hair dyes does not appear to pose a risk [1471].

Our recommendations concerning foods, exposures, and lifestyle risk factors during pregnancy and lactation

The lists of food, lifestyle, and environmental risk factors to be avoided may seem dauntingly long to newly pregnant women. New advice, often based on minimal evidence, is publicized in the news media or online on a near daily basis. This can cause undue stress during a time when stress should be minimized for the wellbeing of both mother and fetus (see chapter 33 for more on maternal stress).

While certain chemical exposures can cause serious adverse effects in the developing fetus, a report from the United Nations Environment Program and the WHO concluded that most effects of endocrine-disrupting chemicals have been observed in areas where chemical contamination was high [1472]. However, occupational exposures should be minimized, and, where possible, reduction of exposures in the home is advisable. Although evidence is still accumulating, it also appears prudent to try to minimize exposure to BPA during pregnancy.

With regard to food and lifestyle factors, women with reasonably healthy lifestyles prior to pregnancy should not find the recommendations above too onerous. The most important modifiable risk factors discussed here include smoking and exposure to second-hand smoke, alcohol consumption, and avoidance of foodborne illness. Excess consumption of caffeine and herbal teas should also be avoided, along with seafood that is high in mercury. Unusual cravings (pica) should be discussed, and measures taken to curb consumption of non-food items if this occurs. We recommend that alcohol, tobacco, and illicit drugs be avoided completely during pregnancy, and we would suggest that where practical, both parents should abstain from the use of these substances in the weeks prior to conception.

Chapter 31

Cultural and traditional food practices in pregnancy and breastfeeding

Pregnancy-related diet, food practices, and 'taboos'

A woman's dietary intake before and during pregnancy and through lactation is influenced by her sociocultural environment. Some traditional health care beliefs and food practices favoured in different cultures appear to result from efforts to address specific environmental challenges. For instance, Native American populations incorporated lye, ash, or lime (which were all alkaline) into their maize cooking procedures in a manner that balances the essential amino acids and frees the otherwise unavailable niacin [1473]. Without these practices, they would face widespread malnutrition, including niacin deficiency (pellagra) and a lack of certain essential amino acids [1473]. Other examples include intricate processing techniques which would protect foraging and horticultural populations from the toxins present in otherwise valuable food sources such as acorns, cycads, and cassava [1474–1476]. The use of pathogen-killing spices in meat preparations are believed to protect people in warmer climates from foodborne illnesses [1477]. This chapter discusses the implications of some common food practices, as well as cultural practices that are specific to pregnancy and lactation, on maternal and infant health.

Cultural beliefs and practices can markedly influence a woman's pregnancy and childbirth experiences, and may shape her mothering behaviour. Immigrants to a new country often attempt to balance the values of their cultural heritage with those of the host society, which can create tension for pregnant women. Their traditional beliefs and practices may not always follow the biomedical norms of maternal nutrition for optimal fetal growth and obstetric outcomes [1478]. Yet it is important to recognize and respect these beliefs while guiding women towards optimum nutrition and away from harmful practices or prohibitions.

Food taboos exist in virtually all human societies. What may be considered unsuitable by one group may be perfectly acceptable to another. Even when

Table 31.1 'Hot' and 'cold' foods according to Indian custom[a] [1481]

Hot foods—prohibited in pregnancy[b]	Cold foods—encouraged in pregnancy
Meat, chicken	Milk, yoghurt[a], buttermilk[a]
Eggs	Butter, ghee[a]
Fish	Coconut
Ghee[c]	Green leafy vegetables
Pulses/lentils	Wheat[a]
Aubergine (eggplant)	Rice[a]
Onion, garlic	Bananas[a]
Dates	
Jaggery[d], sugar	
Alcohol	
Coffee, tea	
Most spices, including ginger and chilies	
Papaya	
Banana	
Pumpkin	
Wheat	
Rice	
Yoghurt[a], buttermilk[a]	

[a] The perception of these foods as hot or cold varies from region to region in India

[b] Hot foods are encouraged in late pregnancy to facilitate labour

[c] Clarified butter

[d] Course, dark brown sugar

Source: Choudhry, U.K., Traditional practices of women from India: pregnancy, childbirth, and newborn care, *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, Volume 26, Issue 5, pp. 533–9, copyright © 2007 John Wiley & Sons, Inc.

based on myths and misconceptions, they can serve bring a society together, maintain its identity, and create a sense of belonging for the group. In many cases the 'taboo' food is not something that would be considered essential for pregnant women, unless it is among few other sources of essential nutrients in their normal diet. Several cultures adhere to a practice of restricting certain fishes from the pregnancy diet (e.g. some populations in West Malaysia, Papua New Guinea [1479], and Fiji [1480]). If the woman has no other significant source of omega-3 fatty acids in pregnancy, this restriction may be of concern but otherwise may not be harmful. In some cases, these food taboos may even have a utilitarian origin because they selectively target the most toxic marine species, effectively reducing a woman's chances of poisoning during pregnancy and breastfeeding [1480].

In India, and for many immigrant women of Indian descent, there is a belief that pregnancy generates a 'hot' state, and foods that are considered 'cold' are desirable in order to achieve a balance. 'Hot' foods should be avoided to reduce the risk of miscarriage but are given in the last stages of pregnancy to facilitate labour. These terms do not relate to the temperature or spiciness of the food but rather to its perceived nature, although most spices are considered hot (see Table 31.1). Some of these perceptions of 'hot' and 'cold' foods vary by region in India, such that foods considered hot in one region are viewed as cold in another [1481].

Koreans have a long history of food beliefs influenced by centuries-old practices of shamanism (animism), Buddhism, Taoism, and Confucianism. Ancient cures often included the use of garlic and ginseng, among other herbs [1482]. Foods such as seaweed soup, beef, and rice are considered to have qualities that will strengthen the body during the difficult time of pregnancy [1482].

Fasting and dieting during pregnancy

In some societies in Africa and Asia, small women practice 'eating down' in pregnancy [1188, 1481, 1483, 1484]. This practice is based on the idea that a small baby is less likely to hurt or kill the mother in childbirth, and its origin is understandable in places where midwifery is non-existent. It is concerning that proposals for the promotion of 'eating down' are currently being considered in some Asian cities to reduce the rates of caesarean section, without consideration of the long-term potential harm of such behaviours for the offspring. The outcome of famine restricted to the last trimester has been well documented in the Dutch famine and includes a greater risk of obesity, glucose intolerance, and hypertension [32, 1485]. These findings are supported by studies of the Chinese famine of the Great Leap Forward era [34, 1486] and of the Biafra civil war famine [33].

Ramadan is the one-month obligatory fasting period in Islamic religion, during which no food or drink (including water) can be consumed from dawn to sunset. Although pregnant women are allowed to defer fasting until after pregnancy, many pregnant women prefer to fast in order to share the spiritual and social experiences of Ramadan with their families. Pregnant women who fast during Ramadan are reported to have symptoms of 'accelerated starvation' (as characterized by low serum levels of glucose and alanine and high levels of free fatty acids—see chapter 30, 'Maternal behaviours to limit during pregnancy and lactation') [1487, 1488]. While there have been conflicting reports, more robust studies suggest that Ramadan fasting is associated with reduced birth size and possibly placental size [1488–1490]. In general, dieting prior to and in pregnancy is not recommended except in the management of gestational diabetes and significant obesity; fad diets and diets for cosmetic reasons should be avoided.

Postpartum food practices and beliefs

In certain cultures and societies, women practice postpartum food restriction (also known as confinement diets) and behaviour following delivery. Women in several Asian countries such as China, Korea, Thailand, and Singapore are known to perform a traditional postpartum practice called 'doing the month' or 'sitting month' [1491–1493]. During this month, women lie in bed continually, with doors and windows closed [1494–1496]. These women are advised to consume plenty of eggs, meat, chicken soup, brown sugar water, and millet every day, often with large amounts of ginger and garlic, while simultaneously avoiding any raw and cold foods such as fruits and vegetables, which are believed to be unfavourable for postpartum recovery [1494–1496]. Many Chinese women who have immigrated to Western countries still believe in the importance of this traditional postpartum practice [1497–1500].

The Indian belief that the state of 'hotness' generated by pregnancy is balanced by the consumption of 'cold' foods has a postpartum counterpart. It is believed that delivery of the baby upsets the balance achieved during pregnancy and brings about weakness; so, to return a new mother to a state of balance, it is desirable to include milk, ghee, nuts, and jagerry in the diet, and to avoid consuming cold food and water. Dried ginger is eaten in the belief that it helps control postpartum bleeding and acts as a uterine cleansing agent [1481].

Many cultures, particularly the lower educated segments of the populations, maintain a practice of withholding colostrum and giving newborns prelacteal feeds that often include honey or sugar water. These practices have been reported in Africa [1501, 1502], India [1481], China, and other Asian societies [1503]. This practice continues today, for instance in Ethiopia [1492], where colostrum is considered either non-nutritive or harmful to infant health. Prelacteal feeding behaviours continue and in most cases are maladaptive, as they do not provide the immunological benefits of colostrum and may contain harmful contaminants. A 2009 study in Turkey found that newborn infants are commonly fed sugar water [1504]. Many postnatal practices which are considered harmful have been identified in Turkey [1505].

Summary and recommendations concerning cultural and traditional food practices during pregnancy and lactation

Cultural beliefs and practices play a role in the distribution of nutrition messages to the community, and those adopted by pregnant women can affect their birth outcomes. Many of these beliefs and practices have been passed down for generations without any scientific or validated health reasons behind them. Postpartum food restrictions and practices may also affect the mother's and infant's health following delivery.

It is important to examine different contributing and constraining factors (e.g. pregnancy experience, food habits, and related beliefs and practices) not only for effective health care and awareness about traditional food beliefs and habits but also to make subsequent improvements in overall health and pregnancy outcomes of women globally. Interventions and educational support are also needed in order to improve the quality of maternal diet, in particular for those who are still practising cultural traditions that may be harmful to the mother's and their offspring's health outcomes.

Chapter 32

Traditional and herbal remedies in pregnancy and breastfeeding

The use of complementary medicine during pregnancy and lactation

Women are the highest consumers of complementary and alternative medicine [1506], and the use of herbal medicine during pregnancy has become very common worldwide. Those who use these therapies tend to believe they offer safe alternatives to pharmaceuticals, allow greater choice and control over the childbearing experiences, and are compatible with their holistic health beliefs. Regarding herbal products, pregnant women tend to rely on advice from family and friends and often do not disclose their use of herbal medicine to their health care providers [1501]. However, it is important for health care providers to be aware of the effects of and precautions associated with the use of herbal medicine, bearing in mind the weak evidence base to support claims for efficacy and the lack of standards of quality and potency for many of the available products.

Herbs that are frequently used by pregnant women include ginger, chamomile, liquorice, fennel, aloe, valerian, echinacea, almond oil, propolis, and cranberry [1507]. Among Chinese populations, traditional Chinese medicine is officially recognized as a medical profession and remains an important form of medical care, including that for pregnant and breastfeeding women [1508, 1509]. In a study of ~21,000 women from the Taiwan Birth Cohort Study, at least one Chinese herbal medicine was used by 33.6 per cent and 87.7 per cent of the participants during pregnancy and the postpartum period, respectively [1510].

Indications for the use of herbal remedies during pregnancy

The use of herbal remedies for pregnancy-induced nausea and vomiting

Ginger root (*Zingiber officinale*) has been used worldwide for morning sickness, and some efficacy has been shown in a few small randomized trials [1511–1513].

However, the use of ginger during pregnancy is not without precautions. Ginger is known for its anticoagulant effect [1514], and women taking anticoagulant therapy such as heparin or warfarin, nonsteroidal anti-inflammatories, aspirin, or other drugs or herbs which have a similar action are recommended to avoid ginger completely. In addition, women prone to dizziness, which affects some expectant mothers, as well as those on anti-hypertensive medication, are recommended not to take ginger [1514].

Although there is no real evidence of adverse effects of ginger on the developing fetus, the German E Commission on herbal medicines recommends that ginger should be avoided during pregnancy [1514]. Finland has placed a warning on the labels of all ginger medicinal products as being unsafe for use in pregnancy due to the possibility of the impairment of fetal development [1515]. Denmark has also issued warnings to pregnant women about the high levels of ginger in a particular product, GraviFrisk™, which was banned in 2008 [1516].

The use of herbal remedies for urinary tract infections during pregnancy

Unsweetened cranberry juice or cranberry pills have been used as a complementary support for the treatment of urinary tract infections (UTIs) during pregnancy. Cranberries are claimed to help prevent and inhibit infections by preventing *E. coli* bacteria from sticking to the bladder wall [1517, 1518]. Daily consumption of cranberry juice in multiple doses has been reported to have a trend in reducing UTIs, with no effects on either obstetric or neonatal outcomes [1519].

Among women receiving cranberry juice, there was a reduction in the frequency of both asymptomatic bacteriuria (57%) and the prevalence of UTIs (41%) [1519]. The 2012 Cochrane review on the use of cranberry for the prevention and treatment of UTIs reported a small benefit for women with recurrent UTIs; however, there were no statistically significant differences when the results of a much larger study were included [1520]. Since UTIs can also be a precursor to preterm labour [1521], the use of herbal medicine should not be used solely in the treatment of UTIs, and it should always be monitored by the physician.

The use of herbal remedies to treat mild depression during pregnancy

St John's wort (*Hypericum perforatum*) is commonly used in both the US and Europe to treat mild depression. St John's Wort contains hypericin and hyperforin, which play a significant role in this herb's pharmacological effect in the treatment of depression [1522, 1523]. However, safety concerns regarding the use of this herb have been raised, as studies indicated that its use may potentiate other antidepressant drugs and decrease the effectiveness of oral contraceptives and the protease inhibitors used to treat HIV [1517]. Its safety in pregnancy is not known.

The use of herbal remedies to treat skin conditions during pregnancy

Aloe vera gel is one of the ten most commonly used herbs but should be used externally only. Topical use is considered safe in pregnancy. The gel is effective for the quick healing of burns [1517].

The use of herbal remedies as labour aids

Raspberry, castor oil, and blue cohosh have been administered to pregnant women for labour aid [1507]. Evidence is thus far insufficient to support claims of efficacy for raspberry leaf, in the form of tea, tablets, or tincture [1524, 1525]. The most common adverse effect is lowered blood pressure. Because of the lack of efficacy and safety data, the use of raspberry leaf extracts in pregnancy is questionable [1526].

Castor oil has also been used to initiate labour. In a prospective cohort study of 103 singleton pregnancies with intact membranes at 40 to 42 weeks gestation, participants were alternately assigned to receive either a single oral dose of castor oil (60 mL) or no treatment [1527]. The study revealed that women who received castor oil had an increased likelihood of initiation of labour within 24 hours compared to women who received no treatment. Specifically, following treatment with castor oil, 30 of 52 women (57.7%) began active labour compared to 2 of 48 (4.2%) receiving no treatment. In addition, 83.3 per cent (25/30) of the women who received castor oil delivered vaginally.

Blue cohosh however, should be avoided for labour aid. Jones and Lawson [1528] reported that a newborn infant whose mother ingested an herbal medication containing blue cohosh to promote uterine contractions experienced acute myocardial infarction associated with profound congestive heart failure and shock. Severe cases of multi-organ hypoxic injury and perinatal stroke have also been reported in neonates whose mothers consumed blue cohosh [1529, 1530].

Summary and recommendations for the use of traditional and herbal remedies during pregnancy and lactation

Women commonly look towards herbal remedies as 'natural' alternatives to promote and maintain health during pregnancy and breastfeeding. Some pregnant women believe that herbal remedies are more effective and that they have fewer side effects than prescription medications. Although the use of these products has been widely promoted by television, magazines, and the internet, the evidence for efficacy of most of the products is extremely limited.

There is some government regulation of herbal medicine in Europe. However, in the US, herbs are classified as dietary supplements. Therefore, manufacturers are not required to conduct studies of the efficacy or safety of herbs before selling them to the public, and, overall, too few studies have been conducted to permit clinical guidance. With the exception of ginger, there is currently not enough data to support the use of any other herbal supplements during pregnancy. Therefore, it is recommended that women who are interested in using herbal remedies should discuss their symptoms and wishes with their doctors. Pregnant women should not use over-the-counter herbs and supplements in pregnancy without prior consultation with their health care providers.

Chapter 33

Maternal stress in pregnancy and breastfeeding

The stress response during pregnancy

There are a number of reasons for women to avoid stress as much as possible in pregnancy. Acute stress can trigger maternal vasoconstriction, decreasing uterine blood flow [1531] and possibly resulting in the restriction of oxygen and vital nutrients to the fetus, as evidenced in studies in primates [1532, 1533]. Chronic stress can lead to chronic hypercortisolaemia, with metabolic consequences for mother and fetus. There is also growing evidence to suggest that a parent's adverse experience both pre-conceptionally and during pregnancy can affect the ability of their offspring to cope with adverse life events.

Acute stress triggers an autonomic response involving release of the catecholamines epinephrine and norepinephrine [1534]. Chronic stress is associated with increased reactivity of the hypothalamic–pituitary–adrenal axis, which mediates a sustained neuro-endocrine response. In this stress response, corticotropin-releasing hormone is synthesized in the hypothalamus, promoting the release of adrenocorticotropic hormone into the bloodstream. This hormone stimulates the adrenal cortex to release glucocorticoids, mainly cortisol, which acts both centrally and peripherally through ubiquitously distributed intracellular receptors. Glucocorticoids normally play a role in energy metabolism, growth processes, and in the functioning of the immune system and the brain. During exposure to stressful stimuli, they govern the intensity of the stress response and are key to its termination via negative feedback control [1535, 1536].

The placenta provides a barrier to natural glucocorticoids, buffering the fetus from minor changes in maternal cortisol levels. The enzyme 11-beta-hydroxysteroid dehydrogenase type 2 inactivates cortisol into the relatively inactive cortisone. However, this barrier can be saturated by high maternal levels of cortisol, and, under conditions of maternal under-nutrition and where there is placental compromise, levels of the enzyme are reduced [1537, 1538]. The consequent higher levels of cortisol in the fetal circulation may play some role in accelerating fetal maturation to make a premature birth more viable, but they are also strongly implicated in the longer term consequences as reflected in the cluster of phenomena related to the developmental origins of health and disease [1539–1541].

Stress and conception

Stressors prior to pregnancy may impact the ability to conceive, as physiological stress responses could affect ovulation, implantation, or other aspects of successful conception. A relatively high degree of anxiety and depression has been noted among infertile couples (both idiopathic and non-idiopathic), although dissecting the cause from the effect of stress in these situations is difficult [1542]. A recent meta-analysis of 14 prospective studies conveyed an assurance to women that emotional distress, which is often associated with unintended childlessness, should not significantly reduce the chances of successful conception via IVF [1543].

Stress and pregnancy outcomes

The effect of stress on preterm birth and low birthweight

High maternal antenatal stress or anxiety is predictive of poorer obstetric outcomes, most commonly preterm delivery and/or low birthweight [1544]. In a large Danish epidemiological study (n = 5,873), the experience of life events during pregnancy that were perceived by the mother as highly stressful was associated with a greater risk of preterm delivery [1545]. The effect appears to be stronger in more socio-economically deprived groups.

In poor African American and Hispanic groups, women experiencing high levels of stress (a combination of life events, anxiety, and perceived stress), were several-fold more likely to deliver preterm [1546]. Unfortunately, studies of interventions designed to provide psychosocial support for such high-risk women were not found to reduce the incidence of low birthweight among infants [1547, 1548]. A recent study showed that infants born in New York to women who were pregnant at the time of the September 11, 2001 terrorist attacks on the World Trade Center and the Pentagon were more likely to be born preterm, or to be small for gestational age or of low birthweight. It was hypothesized that environmental pollution and stress in New York at that time contributed to this trend [1549].

The effect of stress on offspring behavioural outcomes

Increases in maternal glucocorticoid levels can provide hormonal cues to the fetus about its future environment, potentially resulting in profound changes in offspring phenotype [1550]. There is growing evidence that exposure to stressful influences in prenatal life can permanently alter the biological response to stress later in life [1551]. In a controlled study, young adults whose mothers had experienced extreme social stress during pregnancy had higher corticotropin-releasing hormone neuronal activity when exposed to psychosocial stress in the Trier Social Stress Test. When exposed to this test, the prenatally stressed subjects also showed a higher increase in cortisol than control subjects, despite having lower cortisol levels prior to the test [1552].

Numerous studies have shown consistent associations between maternal stress during pregnancy and an increased risk of emotional and behavioural problems and impaired cognitive development in their offspring [1553, 1554]. Some have suggested a direct effect of maternal anxiety on fetal brain development [1555], with specific influences on the amygdala, which is involved in the generation of anxiety responses [1556]. The amygdala is activated in the presence of fear-provoking stimuli in humans, and a larger amygdala has been noted in children with generalized anxiety disorder [1557]. A recent study has linked maternal stress hormone levels in human pregnancy with subsequent volume of the amygdala and affective problems in childhood [1558]. Some large cohort studies have found an elevated incidence of autism or attention deficit hyperactivity disorder in children born to women exposed to stressful situations during pregnancy, particularly during the third trimester [1559–1561]. Other studies, however, have not found support for this association [1562].

The effect of stress on the risk of congenital malformations

There is very limited evidence that offspring of women exposed to emotional stress from severe life events (e.g. death of a child) during the first trimester are at higher risk of congenital abnormalities. The defects were predominantly cleft lip and/or palate and congenital heart malformations. The tissues involved in such abnormalities originate from the cranial neural crest and are vulnerable to disruption during early pregnancy [1563].

Stress hormones and lactation

Transmission of abnormally high levels of glucocorticoids through breast milk has been shown in animal models to modify brain development. Animals exposed to elevated levels of glucocorticoids in milk during infancy display stably altered hypothalamic–pituitary–adrenal axis regulation and altered behavioural responses to stress [1564]. In humans, glucocorticoids in breast milk, which rise in relation to stress, have been shown to influence infant behaviour and temperament, particularly among female offspring [1565, 1566].

Stress and the offspring sex ratio

The secondary sex ratio refers to the proportion of male births in a population and is usually around 0.51 (i.e. a slight excess of males). A prominent hypothesis is that the sex ratio is partially controlled by the hormone levels of both parents at the time of conception, girls being favoured by high levels of gonadotropins and low levels of testosterone [1567]. The sex ratio may also be affected by maternal stress, as it has been reported to decline after environmental or natural disasters [1568, 1569], war [1570, 1571], and periods of economic instability [1572, 1573]. In general, male fetuses appear to be more susceptible to maternal stress than female fetuses. For example, women who were pregnant during times of social stress such as the 1995 Kobe earthquake in Japan [1569] and the September 11 World Trade Center attacks [1574] produced significantly fewer male offspring than female offspring. Paternal stress could also contribute to this effect, as reduced sperm motility was observed among stressed males after the Kobe earthquake [1575].

Summary and recommendations for managing maternal stress during pregnancy and lactation

Multiple threads of evidence suggest that severe stress is detrimental to both the mother and her fetus during pregnancy, with effects that can be long-lasting for the offspring. Unfortunately this type of stress is not always easily avoided. The effects of day-to-day stress on pregnancy outcomes are difficult to measure and have not been adequately studied.

Pregnancy itself can be stressful for women in many ways. The ever-growing list of what prospective mothers should and should not do, and the potential to blame oneself for failing to do or avoid those things, are not insignificant factors in this. Yet being stressed is itself counted among the prohibited behaviours that a pregnant woman may feel guilty about—continuing the cycle of stress [1576].

We recommend that women be cautious about behaviours that are known to carry significant potential risks to their unborn child (e.g. smoking, heavy drinking, eating risky foods, and exposure to known toxins/teratogens) but not to worry too much about unknown risks or factors that cannot be controlled. Anxiety in pregnancy is a predictor of postpartum depression [1577]; for this and the other reasons outlined above, caregivers should do what they can to reduce the anxiety levels in their patients by providing sound advice that is not overly burdensome for pregnant women to follow.

Chapter 34

Effects of maternal age on pregnancy outcomes

Advanced maternal age in pregnancy and breastfeeding

Maternal age on both ends of the reproductive spectrum (teenage and 35+) is associated with increased risk of adverse pregnancy outcomes compared with the 20–34 year old age range. Pregnancy in women in their late 30s to mid -40s is becoming increasingly more common. However, advanced maternal age (≥44 years) is associated with significantly higher odds of medical complications during pregnancy and more interventions during delivery [1578].

Analysis of a large data set from the US National Center for Health Statistics (the Birth Cohort Linked Birth and Infant Death Data, 1995–2000; n > 8 million singleton pregnancies) showed a decrease in mean birthweight and an increase in the proportion of low-birthweight babies and preterm births among older mothers [1579]. Maternal age ≥45 years was associated with an increase in the risk of hypertension, diabetes, and infant death, including death due to congenital abnormalities. Older women were at higher risk for excessive bleeding and breech presentation and were more likely to have prolonged, dysfunctional labour. These factors contributed increased frequencies of labour induction, use of forceps or vacuum, and caesarean delivery with advancing maternal age [1579].

Diminishing cardiovascular reserve and a reduced ability to adapt to physical stress, both of which accompany the normal ageing process, may contribute to some of these outcomes. Additional factors such as the higher prevalence of overweight and obesity [1580] and uterine fibroids among older mothers [1581] are also likely to influence the poorer pregnancy outcomes in this group. The risk of adverse pregnancy outcomes is elevated in women who receive treatment for infertility, the majority of whom are over 30 years of age, although some of this increased risk may be related to the cause of the infertility itself.

The effects of advanced maternal age on maternal morbidity and mortality

Some of the increase in pregnancy complications in older mothers is caused by underlying age-related health issues such as hypertension and diabetes, which increase linearly with increasing age [1582]. Related diseases can also develop during pregnancy, including gestational diabetes, severe pre-eclampsia, and pregnancy-induced hypertension, for which older mothers are at increased risk, as underlying factors are exacerbated by the physiological effects of pregnancy. Among other reports, these increased risks have been confirmed by analysis of the Swedish Medical Birth Registry data on >31,000 women aged 40–45 years, and >1,200 women >45 years of age [1583].

The overall maternal mortality rate increases with increasing maternal age. Thromboembolic complications during pregnancy, labour, and puerperium together with intrapartum and postpartum haemorrhage account for a large proportion of maternal deaths and are also the strongest determinants of the age-related obstetric risk to mothers [1584]. Maternal deaths remote from the time of birth but possibly related to aggravation of thromboembolic risk factors are likely to be under-reported.

The effects of advanced maternal age on birth defects and neonatal mortality

A 7-year prospective study of over 100,000 pregnancies in the US observed increasing risk for specific non-chromosomal fetal malformations, including cardiac defects, club foot, and diaphragmatic hernia, with advancing maternal age [1585]. These data included stillborn fetuses and terminated pregnancies and therefore were at variance with some earlier studies that did not find a relationship between maternal age and congenital malformations [1586, 1587]. Maternal age 40 years and older at delivery was reported as an independent risk factor for perinatal mortality in a study cohort of over 36,000 women in the First and Second Trimester Evaluation of Risk trial, a prospective multicentre investigation of singleton pregnancies from an unselected obstetric population [1588].

Other studies have also found an increase in perinatal and neonatal death with increasing maternal age. Data from the National Infant Mortality Surveillance Project in the US in 1980 (n = 1,579,854 births and 14,591 deaths) indicated that infants born to mothers 35–39 years of age were at a slightly elevated (18% higher) risk of perinatal and neonatal death compared to those born to mothers 25–24 years of age, and those born to mothers 40–49 years of age were at a much more elevated (69% higher) risk [1589].

Trisomy 21 is a common chromosomal non-disjunction error resulting in Down's syndrome, the risk for which increases with maternal age [1590–1592]. There may be an added effect of paternal age on Down's syndrome risk, but this is yet to be definitively proven, and the relative contribution is likely to be small (see chapter 35).

The effects of advanced maternal age on lactation

Older mothers tend to experience more difficulty in establishing breastfeeding and maintaining lactation, in part because breast milk yield decreases with advancing maternal age [1593]. Colostrum of older mothers is higher in fat content, possibly because of decreased water content [1594]. However, once breastfeeding is established, the composition of milk is not significantly different between older and younger mothers.

Pregnancy and lactation during adolescence

Young maternal age also comes with risks. Pregnant adolescents are more likely than adults to consume micronutrient-poor, energy-dense diets. They are also more likely to have inadequate prenatal care, often as a result of less favourable social and economic circumstances. Statistically, teenage pregnancy is associated with increased risk of maternal complications from pregnancy and delivery, and anaemia is highly prevalent [1595].

Infant birthweight and preterm birth in adolescent pregnancy

Compared with pregnant adults, young women who are still growing more often give birth prematurely or have low-birthweight infants. In a study of >15,000 adolescent pregnancies (age 13–17 years) and >90,000 pregnancies in women aged 20–24 years, young age was found to be a significant intrinsic risk factor for low birthweight and prematurity, independent of socio-demographic factors that may also predispose adolescent mothers to poorer outcomes [1596]. The poorer fetal growth associated with adolescent pregnancy possibly results from a competition for nutrients, as the adolescent mother may still be growing herself [1597, 1598].

Pregnant adolescents are prone to having abnormal weight gain in pregnancy. In addition, teenage mothers are more likely than older, non-growing mothers to retain more weight postpartum [1598]. However, the Camden Study, which prospectively evaluated nutrition and pregnancy in teenage girls vs older mothers in one of the poorest cities in the US, found that, despite a larger total weight gain in growing teenage mothers, their infants weighed significantly less at birth than those of older, non-growing mothers [1598].

Birth defects in adolescent pregnancy

The effect of young maternal age on the incidence of birth defects was assessed in a California population of over a million births, which included 29,848 malformations. Risks were substantially increased for mothers younger than 20 years for some types of birth defects, with the highest risks observed for nervous system and abdominal wall anomalies [1599]. The risk elevation in young mothers was comparable to the oldest group (women over 40 years of age; i.e. risk showed a U-shaped pattern).

Breastfeeding in adolescence

A prospective study of breastfeeding behaviours among adolescent mothers in the US found that, while the percentage of adolescent mothers who initiated breastfeeding was high (71%), breastfeeding duration was very short as compared to that observed with older mothers [1600]. In addition, obese adolescents had significantly lower odds of breastfeeding compared with their normal weight peers. This may relate to body image issues, which may prevent them from breastfeeding outside the home.

Bone loss in adolescent pregnancy

Maternal bone loss following pregnancy and lactation is an important issue in women with low calcium and vitamin D status and intake. This is of particular concern in adolescents, whose bones are still growing and whose diets are often low in calcium [1601–1603]. Some studies have suggested that an increase in calcium intake during pregnancy and lactation may help reduce postpartum bone loss in adolescent mothers [1604]. In a recent placebo-controlled study, supplementation with 600 mg/day calcium and 200 IU/day vitamin D from 26 weeks gestation in adolescents whose normal dietary intake of calcium was below 600 mg/day resulted in higher maternal bone mass and reduced bone loss in the first 20 weeks of lactation [1605].

Summary and recommendations concerning maternal age during pregnancy and lactation

Because pregnancy at both extremes of the reproductive age spectrum comes with risks to both mother and fetus, both adolescents and older women should be closely monitored during pregnancy. Adolescents, especially those who are still growing, will often benefit from dietary advice and monitoring of nutritional status. Although calcium supplementation is not generally required for pregnant women who consume a healthy diet, young women whose bones are still growing do benefit from additional calcium in the form of supplements.

Adolescent mothers are less likely to have consumed folic acid supplements pre-conceptionally but should be encouraged to do so as soon as possible in early pregnancy. They should be made aware of the impact of excessive gestational weight gain from high-fat diets and be encouraged to select a variety of foods specifically including fruits and vegetables.

Older mothers [35–40 years] who do not have underlying risk factors for diabetes and hypertension should receive advice similar to younger mothers. However, those who are overweight, obese, or who already have hypertension or diabetes should be encouraged to reduce their risk of aggravating these disorders during pregnancy. This can include dietary improvement and moderate exercise, and gestational weight gain within recommended ranges (see chapters 28 and 29).

Chapter 35

Paternal factors that affect conception and pregnancy

Paternal pre-conception nutrition and lifestyle

The father's nutrition and lifestyle can influence pregnancy outcomes in a number of ways. In the pre-conception period, several modifiable factors can influence sperm count and quality and consequently affect fertility. For example, sperm count and quality is affected by alcohol, recreational drugs, prescription drugs, infections, tobacco, and environmental toxins. In addition, a father's BMI and metabolic status may have some impact on the metabolic trajectory of his offspring. Other aspects of a father's behaviour can indirectly affect the developing fetus through environmental exposures.

The effects of paternal obesity, BMI, and diabetes on conception and fertility

Obese males or those with poorly controlled diabetes may have difficulty conceiving. Diabetes affects the endocrine control of spermatogenesis and can lead to structural and genetic abnormalities in spermatozoa [1606, 1607]. In addition, poor glycemic control can affect sperm quality and testicular function [1608]. A prospective observational study in the Netherlands (n = 450 men) found that BMI and waist circumference had an effect on sperm quality in men of subfertile couples, independent of other lifestyle factors. Ejaculation volume, sperm concentration, and motility were reduced with increasing BMI and central adiposity [1609]. In a study of >1,500 young men in Denmark, BMI was related to sperm count, which decreased with both high and low BMI [1610].

A systematic review of 31 studies did not find evidence for a disadvantage of high BMI on sperm parameters but did note strong evidence of a negative relationship between BMI and testosterone levels. However, the heterogeneous nature of the studies meant that confounding factors could not be accounted for [1611]. A recent prospective cohort study observed a significant (84%) decrease in the odds of a live birth following the use of the assisted reproduction technique of intracytoplasmic sperm injection with sperm from an obese male partner. However, male BMI was unrelated to other IVF outcomes [1612].

Nutritional factors and male fertility

A healthy and nutritionally balanced diet is as important for male fertility as it is for females. Diets lacking sufficient quantities of certain micronutrients may affect a man's sperm count and quality, lowering his chance of conceiving a healthy infant. There is also some evidence to suggest that men who consume obesogenic diets may pass on poor metabolic attributes to their offspring.

Folate, for instance, is an important pre-conception micronutrient for men as well as women. Potential fathers require adequate folate in their diets, as low folate concentrations in seminal plasma may be detrimental to the stability of sperm DNA [1613]. Associations have also been found between folate deficiency and sperm aneuploidy [1614] and low sperm count [1615]. A recent study also links paternal folate levels with adverse pregnancy outcomes [1616].

Zinc also has a significant impact on male fertility, as it is involved in DNA synthesis and is required for spermatogenesis. Zinc levels in semen correlate positively with sperm count [1617], and poor zinc nutrition is a risk factor for low sperm quality and male infertility [1618]. An early sign of zinc deficiency in males is an arrest of spermatogenesis, manifested in a lack of elongated spermatozoa [1619].

Supplementation of subfertile men with a combination of folic acid (5 mg/day) and zinc sulphate (66 mg/day) for 26 weeks increased sperm count by 74 per cent in a randomized, placebo-controlled trial (n = 108 subfertile men and 107 fertile men). Zinc alone also increased sperm count but not to a statistically significant level [1620]. In its antioxidant capacity, zinc may protect cells, including sperm, from the negative effects of alcohol consumption and cigarette smoking. In rats, tobacco smoke-induced changes in spermatozoa were prevented by zinc treatment [1621].

Several selenium-dependent proteins are important in male fertility. The selenoprotein glutathione peroxidase 4 is essential for sperm structure and function. In addition, the sperm mitochondrial capsule selenoprotein has both structural and enzymatic roles in sperm tail motility and integrity. A study in Glasgow (an area with low selenium intakes) found enhanced sperm motility in men receiving selenium supplements (100 μg selenium or selenium plus vitamins A, C, and E daily), compared with a placebo control group [1032]. A more recent randomized, controlled trial in Iran found that supplementation of infertile men with selenium (200 μg/day) and/or *N*-acetyl cysteine increased sperm count and sperm motility after 26 weeks of treatment [1033].

The influence of reactive oxygen species (ROS) on fertility, and the possible benefits of antioxidant nutrients, has been the subject of investigation with particular emphasis on the possible role of ROS in idiopathic male infertility. Human sperm produce ROS and are susceptible to ROS-mediated peroxidative damage. Elevated production of ROS and increased sperm membrane damage has been observed in men with reduced sperm motility (asthenozospermia) [1622]. Because of this, protective agents against ROS, including vitamins C and E, have been postulated as useful agents in the treatment of male infertility. However, an 8-week placebo-controlled trial of daily high-dose vitamin C and E (1,000 mg vitamin C and 800 mg vitamin E) did not improve semen parameters or sperm survival in men with asthenozospermia [1623]. Several systematic reviews have confirmed that while dietary antioxidants may be beneficial for sperm health, there is currently no established role for supplemental antioxidants, including high-dose vitamin C and E, in the treatment of male infertility [1624–1626].

Overall dietary patterns may impact semen quality. A typical ‘Western’ diet characterized by high intake of red and/or processed meat, refined grains, snacks, high-energy drinks, and sweets has been associated with lower sperm motility as compared to a diet including high intakes of fish, chicken, fruit, vegetables, legumes, and whole grains [1627, 1628]. A recent cross-sectional study found an inverse association between intake of full-fat dairy products and semen quality (sperm motility and morphology) [1629]. This result needs confirmation in prospective longitudinal studies but may suggest that high intake of full-fat dairy foods such as cheese be reduced in men trying to conceive a pregnancy. There was no correlation between reduced-fat dairy foods and semen quality. In addition, high caffeine intake has been shown to reduce conception rates [1341], with a similar decline in fertility in both females and males, the latter effect possibly resulting from an impact of caffeine on semen quality.

Paternal environmental and occupational exposures that can affect conception and pregnancy

Substances that induce mutations or epimutations in spermatic DNA have the potential to cause birth defects or cancers in offspring. Such mutagens include ionizing radiation, pesticides, ethylene dichloride, and vinyl chloride. Exposure to some of these agents may be occupational [1630].

Xenobiotic agents, including polycyclic aromatic hydrocarbons, PCBs, dioxins, and phthlates, have been shown to cause oxidative stress and DNA damage to the sperm and can therefore decrease fertility or result in birth defects, childhood cancers, or miscarriage of defected fetuses [1631]. Occupations that involve exposure to metals, combustion products, solvents, and pesticides (e.g. welding, painting, auto mechanics, firefighting, and agriculture) have been implicated, although various studies have failed to replicate such findings. Paternal exposure to paints, hydrocarbons or exhaust fumes, and to a lesser extent pesticides, has been consistently shown to increase risks of childhood cancers [1632]. These agents are discussed in chapter 30 with respect to their impact on the fetus. Development of immature sperm to mature sperm takes approximately 72 days and is a continual process; therefore a 3-month period of freedom from exposure is desirable to improve sperm quality prior to a planned pregnancy.

The effects of paternal cigarette smoking on conception and pregnancy

Tobacco smoke contains a large number of agents with mutagenic, aneugenic, and/or carcinogenic properties that can damage sperm. Cigarette smoking is associated with an increased concentration of leukocytes in seminal fluid, considered to be a marker of low semen quality [1633]. Among subfertile men, smokers had reduced sperm motility, poorer sperm morphology, and a higher leukocyte count in seminal fluid than non-smokers [1634]. Leukocytes are the major source of ROS in the ejaculate, and elevations in their concentration are thought to increase oxidative DNA damage in sperm and thus reduce fertility [1635]. The sperm antioxidant defence system is sensitive to disruption by cigarette smoking [1636], and there are reports of tobacco-induced oxidative damage to sperm DNA [1637, 1638].

The effects of paternal drug and alcohol use on conception and pregnancy

Most drugs to which the male has been exposed can be found in seminal fluid and transmitted to the female in the ejaculate. Some of these, such as the cancer drug cyclophosphamide, have demonstrated the potential to confer pre-implantation loss or embryopathy. There is also an increase in sperm aneuploidy during chemotherapy, and men should be advised not attempt to conceive pregnancy during such exposure or in the first cycle of spermatogenesis following termination of therapy [1639]. Toxins such as cocaine may also bind to sperm and be transported to the ovum at fertilization [1640], as has also been demonstrated with sperm exposed to viruses [1641]. In addition, the use of anabolic steroids for increasing muscle mass has been shown to decrease sperm count and alter sperm morphology, in some cases resulting in azoospermia [1642].

The effect of alcohol on sperm parameters is not yet fully understood. Although some studies have not observed significant effects of alcohol on sperm parameters [1643–1645], the balance of evidence suggests that alcohol contributes to developmental defects of sperm morphology and sperm production (reduced sperm count), the incidence of which increases with increasing alcohol consumption [1646–1650]. Alcohol withdrawal improves semen quality and has been shown to completely and rapidly reverse alcohol-associated azoospermia [1651, 1652]. The use of alcohol or marijuana is associated with elevated leukocyte levels in seminal fluid and thus with low semen quality [1653]. Marijuana also interferes with spermatogenesis, resulting in lower sperm density and motility and increased numbers of sperm with morphologic abnormalities [1653].

Paternal factors and pregnancy outcomes

The impact of paternal nutrition and lifestyle does not end at conception, although pre-conception behaviours can result in germline mutations or epigenetic changes that can be passed on to their progeny. Cigarette smoking, for example, has been linked to genetic damage in sperm, with the potential to cause developmental defects in the offspring. An epidemiological study in China found a paternally mediated effect of smoking on the risk of birth defects, including a more than twofold increased risk of anencephalus and spina bifida. Infants of fathers who smoked were also more likely to have a diaphragmatic hernia and were more than three times more likely to have skin pigmentary anomalies than infants of non-smokers [1654].

Paternal factors influencing infant birthweight and metabolic health

A father's metabolic status can have an influence on development of the fetus, as well as possible long-term effects on the offspring's metabolic development. In the international SCOPE Study cohort, paternal obesity and central adiposity were both associated with a 60 per cent increase in risk of fathering a small-for-gestational-age infant [1655]. In addition, when analysed for the influence of parental BMI on childhood obesity, the Avon Longitudinal Study of Parents and Children data revealed an equivalent relationship between either maternal or paternal BMI and the BMI of the offspring at age 7, arguing against a significant effect of the intrauterine environment [1656]. However, paternally derived epigenetic influences could be a factor that enhances paternal effects. This hypothesis has been suggested to explain the trans-generational influence of paternal smoking on offspring BMI, a pattern seen in cohorts from both the Avon study and the Swedish Överkalix study [1657].

Fathers consuming high-fat diets pre-conceptionally may be at increased risk of having offspring with diabetes. Evidence from a rodent model suggests that obese fathers are likely to have offspring with diabetes [1658]. Another recent study found that a high-fat diet causing paternal obesity and impaired glucose tolerance in the offspring also induced paternal sperm microRNA profile alterations that were transmitted to a second generation, indicating transgenerational paternal effects of obesity on glucose tolerance [1659].

The effects of paternal age on pregnancy and child outcomes

There have been a number of recent studies on the effect of advanced paternal age on pregnancy and child outcomes. Paternal age is thought to influence the accumulation of de novo germline mutations and/or methylation of paternally imprinted genes. Advanced paternal age is also associated with a reduced capacity for DNA repair, and increased mutagenesis. A recent study demonstrated an exponential increase in germline point mutations as men age, beginning at a rate of approximately 2 mutations per year and doubling every 16.5 years [1660]. This study also found that men transmit a higher number of mutations to their children than women, despite a higher rate of recombination in females, which also increases with maternal age.

Down's syndrome, which results from the non-disjunction of chromosome 21 during meiosis, is known to be influenced by the advancing age of the female gametes [1590–1592]. Whether there is an effect of paternal age on the incidence of trisomy 21 has been the subject of debate [1661], but studies in specific populations (e.g. Norway) have reported an increased risk, independent of maternal age, with paternal age >50 years [1662]. Other studies also suggest some influence of paternal age [1663, 1664], but more recent reanalyses suggest that the effect is small and unlikely to influence family-planning decisions [1661].

Epidemiological studies have shown that the risk of schizophrenia in the offspring increases significantly with increasing paternal age [1665], possibly involving a mutational hotspot in a schizophrenia-related gene, or impaired imprinting [1666]. Additionally, over 20 genetic disorders have been associated with older paternal age, including achondroplasia, cardiomyopathy, multiple endocrine neoplasia, osteogenesis imperfecta, and craniosynostosis syndromes (causing craniofacial anomalies) [1667]. On the other hand, offspring of very young fathers have an elevated risk for de novo genetic disorders—possibly because spermatids are immature and DNA repair and antioxidant activities are low [1668].

Such a U-shaped relationship between paternal age and adverse offspring outcomes has also been observed in regard to cognitive development. A significant U-shaped relationship was observed between paternal age and offspring IQ scores in a study of >44,000 births in an Israeli cohort [1669]. A similar U-shaped relationship between paternal age and the risk of type 1 diabetes was also observed in a small Taiwanese study [1670].

Paternal occupational exposures and offspring outcomes

Paternal occupation can affect birth outcomes in two ways. Occupational exposure to harmful substances can cause genetic alterations in the male germ cell line, as discussed in 'Paternal pre-conception nutrition and lifestyle'. Alternatively, such exposure can lead to exposure of the mother (through contaminated clothing or skin).

Paternal employment in the lead industry or other occupations that are associated with exposure to lead (e.g. automotive painting and/or radiator repair, scrap handling, house renovation/paint stripping of old buildings, demolition of ships or old buildings, etc.) is regarded as an indirect risk to the fetus, as lead dust can be brought into the home on clothing, skin, and hair [1345]. High or prolonged paternal occupational lead exposures (including the period from 6 months before conception to the end of pregnancy) were associated with a higher risk of low birthweight and preterm birth [1671]. In addition, the offspring of workers exposed to benzene, chromium, and other minerals have a higher risk of being small for gestational age, and offspring of men exposed to X-rays have a higher risk of preterm birth [1672].

Between 1980 and 2002, flour mill workers exposed to various fumigants in Washington State fathered fewer male offspring, and male infants had significantly reduced birthweight [1673]. The results suggest that the workers' exposure had an effect on testicular function, as seen with the now-banned fumigant dibromochlorpropane (a nematocide for worm control), which causes oligospermia or azoospermia [1674]. This chemical was used extensively in the US between 1955 and 1977 for controlling crop-damaging parasitic worms and is still found in groundwater in areas of past high use.

Our recommendations concerning paternal factors in pregnancy

Prospective fathers need to be conscious of their personal health and nutrition, as well as of environmental factors that may influence both their ability to conceive and the health of their future offspring. Poor dietary habits that contribute to obesity and type 2 diabetes have a negative impact on male fertility and, potentially, on the metabolic health of their children. Eating habits are learned and perpetuated within families, but biology also suggests that metabolic trajectories are established to some extent in utero, with the paternal status contributing to this outcome.

Nutrients including zinc and selenium are important for male fertility, but in most cases can be obtained from a balanced diet. However, subfertile men may benefit from supplementation with these minerals. Antioxidant therapy with vitamins C and/or E is not recommended to improve male fertility.

Smoking is detrimental not only to sperm and reproductive health but also to the fetus via maternal exposure to second-hand smoke. Men should be encouraged to quit smoking before trying to conceive, or, at a minimum, to restrict their smoking behaviours so that the mother (and the infant after birth) is not exposed. In addition, although evidence is still accumulating, it is prudent to advise men to limit alcohol consumption and curtail recreational drug use, as both may cause sperm damage and lead to birth defects. Men should also be made aware of the potential impact of various occupational exposures that can cause genetic damage to sperm or be transmitted to the mother and fetus through dust on clothing brought into the home.

Section 4

A management guide—from before conception to weaning

In practice, health care providers do not deal with individual nutrients or behaviours but must take a holistic approach to providing advice at each stage of pregnancy, from preconception through birth and breastfeeding. In this section, we provide a summary checklist of points to consider in interacting with parents at each pregnancy stage. The justification and sources of the recommendations made in this chapter are encompassed in sections 2 and 3 of this book and will not be again referenced here.

Chapter 36

Guidelines for the pre-conception period

Advice for a healthy pre-pregnancy state

An increasing number of parents seek pre-pregnancy counselling. That creates an opportunity to address issues of lifestyle and nutrition as well as addressing any specific medical problems. We would suggest similar advice be given where possible to both prospective parents. The central effort should be to encourage and inform about a healthy diet, install healthy exercise behaviour, and promote abstinence from harmful substances such as tobacco, alcohol, and non-medically indicated drugs.

The evidence suggests that attention to the potential mother's BMI is important; both low and high BMIs are associated with poorer pregnancy outcomes, and there is growing evidence that this may also be true for the paternal BMI. The issue becomes more complex when the mother has a very high BMI as, based on animal experiments, severe dieting at conception may have adverse epigenetic effects on the embryo. It is therefore best to try to address these issues ahead of the proposed pregnancy.

Establishing and/or maintaining optimal nutritional intakes prior to conception will help minimize adverse outcomes for both mothers and offspring. Pre-conception nutrition remains a challenge worldwide, with under-nutrition still a concerning issue in low-and middle-income countries, and poor/unbalanced diet or over-nutrition predominating in developed countries. Poor nutrition around the time of conception can influence the fetal growth trajectory and weight at birth and has been documented to increase the risk of preterm birth. A well-balanced diet consisting of fruits, vegetables, iron, and calcium-rich foods, as well as protein-containing food, should be consumed. Health care professionals should address optimal weight gain, healthy diet, eating guidelines, and the use of dietary supplements as part of pre-conception care and counselling.

Recommended nutrition and supplementation prior to conception

Ideally most aspects of nutrition can be addressed by a balanced diet, particularly one containing adequate amounts of oily fish to provide omega-3 fatty acids. Supplementation is usually only required for a few nutrients, except in certain cases as outlined below. Folic acid supplementation has been shown to have protective effects against birth defects, in particular neural tube defects (NTDs), and all women of reproductive age, especially those who are planning a pregnancy, are recommended to consume 0.4 mg (400 µg) of synthetic folic acid daily, obtained from supplements and/or fortified foods. Where possible, this should be associated with a blood test for vitamin B_{12} and folate status, and in some circumstances this will lead to different dose requirements. Vitamin D status also needs to be considered; covert deficiency is far more common that generally recognized, and low-dose supplementation (400 IU/day) may be necessary. Women residing in areas with a high prevalence of vitamin A deficiency may need pre-conception supplementation, but otherwise vitamin A should be obtained from food sources.

Depending on the context, the health care professional may need to consider other forms of supplementation, including iodine, zinc, iron, and some B group vitamins. In strict vegetarians, the status of vitamin B_{12} and iron needs particular consideration. Vegetarian diets contain low levels of alpha-linolenic acid and are devoid of omega-3 fatty acids. Zinc absorption is lower in vegetarian diets because of a higher consumption of phytate-containing foods and the avoidance of zinc-rich meats and seafood. Choline may also be low in vegetarians. A summary of daily requirements for non-pregnant women prior to conception is given in Table 36.1, along with increases for pregnancy and lactation. Details of those nutrients for which supplementation may be considered are provided in the sections that follow.

Folic acid supplementation prior to conception

Folic acid is a B-complex vitamin that is recognized to have protective effects against NTDs. Dietary sources that are rich in folic acid include legumes, green leafy vegetables, citrus fruits and juices, and breads and cereals that contain flour enriched with folic acid. Women of reproductive age are advised to consume 0.4 mg (400 µg) of synthetic folic acid daily, obtained from fortified foods and/or supplements.

Women with a prior history of NTD-affected pregnancy are advised to take a dosage of 4–5 mg folic acid per day, under the guidance of a physician, for at

Table 36.1 Recommended dietary allowances (or adequate intake levels) in the pre-conception, pregnancy, and lactation periods

Nutrient	**Maternal status**		
	Pre-pregnancy	**Pregnancy**	**Lactation**
Protein (g/day)	46	71	71
Fibre (g/day)	25	28	29
Carbohydrate (g/day)	130	175	210
n-6 PUFAs[a] (g/day)**	11–12	13	13
n-3 PUFAs[a] (g/day)**	1.1	1.4	1.3
Vitamin A (µg/day)[b]			
14–18 yrs	700	750	1200
19+ yrs	700	770	1300
Vitamin B_1 (thiamine; mg/day)	1.0	1.4	1.4
14–18 yrs	1.1	1.4	1.4
19+ yrs			
Vitamin B_2 (riboflavin; mg/day)			
14–18 yrs	1.0	1.4	1.6
19+ yrs	1.1	1.4	1.6
Vitamin B_3 (niacin; mg/day)[c]	14	18	17
Vitamin B_6 (pyridoxine; mg/day)			
14–18 yrs	1.2	1.9	2.0
19+ yrs	1.3	1.9	2.0
Folate (µg/day)[d]	400	600	500
Vitamin B_{12} (cobalamin; µg/day)	2.4	2.6	2.8
Vitamin C (mg/day)			
14–18 yrs	65	80	115
19+ yrs	75	85	120
Vitamin D (µg/day)[e]	15	15	15
Vitamin E (mg/day)[f]	15	15	19
Biotin (µg/day)**			
14–18 yrs	25	30	35
19+ yrs	30	30	35
Calcium (mg/day)			
14–18 yrs	1300	1300	1300
19+ yrs	1000	1000	1000

Table 36.1 (continued) Recommended dietary allowances (or adequate intake levels) in the pre-conception, pregnancy, and lactation periods

Nutrient	**Maternal status**		
	Pre-pregnancy	**Pregnancy**	**Lactation**
Choline (mg/day)**[g]			
14–18 yrs	400	450	550
19+ yrs	425	450	550
Copper (µg/day)			
14–18 yrs	890	1000	1000
19+ yrs	900	1300	1300
Fluoride (mg/day)**	3	3	3
Iodine (µg/day)	150	220	290
Iron (mg/day)			
14–18 yrs	15	27	10
19+ yrs	18	27	9
Magnesium (mg/day)			
14–18 yrs	360	400	360
19–30 yrs	310	350	310
31–50 yrs	320	360	320
Manganese (mg/day)**			
14–18 yrs	1.6	2.0	2.6
19+ yrs	1.8	2.0	2.6
Phosphorus (mg/day)			
14–18 yrs	1250	1250	1250
19+ yrs	700	700	700
Selenium (µg/day)	55	60	70
Zinc (mg/day)			
14–18 yrs	9	12	13
19+ yrs	8	11	12

** Adequate intake recommendations (insufficient data to establish a recommended dietary allowance)

[a] n-6 PUFAs = omega-6 polyunsaturated fatty acids (e.g. linoleic acid); n-3 PUFAs = omega-3 polyunsaturated fatty acids (e.g. alpha-linoleic acid)

[b] As retinol activity equivalents (RAEs); 1 RAE = 1 µg retinol, 12 µg beta-carotene, 24 µg alpha-carotene, or 24 µg beta-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than the retinol equivalent, whereas the RAE for preformed vitamin A is the same as the retinol equivalent

[c] As niacin equivalents; 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not niacin equivalent)

Table 36.1 (continued) Recommended dietary allowances (or adequate intake levels) in the pre-conception, pregnancy, and lactation periods

[d] As dietary folate equivalents; 1 dietary folate equivalent = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach. In view of evidence linking folate intake with the prevention of NTDs in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet

[e] As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D. Recommendations assume minimal exposure to sunlight

[f] As alpha-tocopherol

[g] Although adequate intake levels have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages

Source: Institute of Medicine, Food and Nutrition Board, *Dietary reference intakes (DRIs): estimated average requirements*, National Academies, Washington, DC, copyright © 2014. <http://www.iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/DRIs/5_Summary%20Table%20Tables%201-4.pdf>.

least 1 month prior to conception. The risk of NTDs is significantly elevated in overweight and obese women. Thus, those with BMIs ≥30 should be also be advised to take folic acid supplements in the higher dose range.

Vitamin A intake prior to conception

Vitamin A is crucial for proper visual, fetal growth, reproduction, immunity, and epithelial tissue integrity. However, excess vitamin A can result in miscarriage and birth defects that affect CNS, craniofacial, cardiovascular, and thymus development. The recommended dietary allowance of preformed vitamin A for women is 770 μg RAEs (retinol activity equivalents) per day, with a tolerable upper intake level for pregnancy of 3,000 RAEs/day or 10,000 IU/day. Supplementation is generally advised against prior to conception and in early pregnancy, though women from areas with high prevalence of vitamin A deficiency are recommended supplementation in later pregnancy. For women at low risk, vitamin A should be obtained from food sources.

Vitamin B_{12} intake prior to conception

Vitamin B_{12} is critical for neurological function. Women who follow strict vegetarian diets are at risk of vitamin B_{12} deficiency, as are their infants, who often have very limited reserves of vitamin B_{12} at birth. Pre-conceptional supplementation with vitamin B_{12} is highly recommended for vegetarian and vegan women, and others who may be at risk of low vitamin B_{12} status. Prenatal multivitamins generally contain vitamin B_{12} in varying doses; it is recommended that such multivitamins, if used, contain at least 6 μg of vitamin B_{12}.

Vitamin D supplementation prior to conception

Vitamin D can be synthesized endogenously in skin exposed to sunlight, or obtained from dietary sources that include milk, orange juice, fatty fish, egg yolks, beef liver, and cheese. A minimum of 400 IU/day is recommended by the US Institute of Medicine for women prior to conception. We would advise that intakes of between 1,000 and 2,000 IU/day, which are in line with the Endocrine Society and American Congress of Obstetricians and Gynecologists recommendations, are likely to be beneficial and not harmful, particularly for women who are at high risk of deficiency (e.g. dark-skinned or veiled individuals, vegetarians, and people living at high or low latitudes with minimal/no sun exposure).

Calcium intake prior to conception

Calcium is important for pre-conception health; inadequate calcium stores can result in some maternal bone loss during pregnancy, as the fetus draws calcium from the maternal circulation to meet its needs. If intake is adequate, no adjustment will need to be made after conception, as homeostatic mechanisms ensure that levels are appropriate for both mother and fetus. All women should be encouraged to achieve or maintain a dietary calcium intake between 1,000 and 1,300 mg/day prior to conception, by increasing their intake of calcium-rich foods such as dairy products, leafy green vegetables, sardines/anchovies, soy products, and fortified cereals. Supplements are not required in most women, although calcium is included in most prenatal vitamins. Young women (under the age of 25) may benefit from supplementation with 1.0–1.5 g calcium per day if their dietary calcium intake is low.

Iron intake prior to conception

Many women in the pre-conception period have low iron stores as a result of menstrual blood losses and/or poor diet. Aside from the fact that conception itself is compromised by iron deficiency, building iron stores prior to pregnancy is important to prepare for the high fetal requirement for iron, and the increase in maternal blood volume that occurs during gestation. It is difficult to restore a normal iron level during pregnancy if pre-conception iron status is low, let alone meet the increased fetal demands. It is recommended that, during the pre-conception visit, screening should be conducted for women with risk factors for iron deficiency for the purposes of identifying and treating anaemia. Women who consume little or no animal source foods are likely to benefit from supplementation with low-dose iron (30 mg ferrous iron per day) taken at bedtime or between meals.

Iodine intake prior to conception

Salt iodization is the recommended, preferred strategy to control and eliminate iodine deficiency. Women of reproductive age should be counselled on the risks of iodine deficiency on pregnancy outcomes, and the importance of maintaining an adequate daily dietary iodine intake of 150 μg prior to conception (increasing to at least 220 μg/day when pregnant). Maintaining this level of intake is necessary to avoid abnormal thyroid gland stimulation during pregnancy, which has negative consequences for both mother and fetus. Women whose diets may be low in iodine, either because they reside in iodine-deficient regions (e.g. inland, mountainous terrain) or because they follow salt-restriction diets or do not consume iodine-fortified bread products, should be advised to take oral iodine supplements of 150 μg/day while trying to conceive. Supplementation with seaweed or kelp tablets is not recommended, as the iodine content of such products is highly variable, and the safe range of iodine intake is narrow. Excess iodine can inhibit thyroid function.

Zinc intake prior to conception

Zinc is important in the pre-conception period for optimal reproductive health in both males and females. In women who are taking supplemental iron, zinc supplements may be required, because iron interferes with zinc absorption. Most prenatal vitamins contain zinc, though diets that include regular consumption of shellfish and red meat are likely to provide adequate levels of bioavailable zinc.

Biotin intake prior to conception

Marginal or subclinical biotin deficiency may go undetected in many women. Because of the possibility of teratogenicity (mainly cleft lip and palate) it is prudent to ensure that women are not at risk of biotin deficiency in the pre-conception period. Women who regularly consume large amounts of egg whites (without yolk) may risk deficiency, as avidin in egg whites binds biotin (present in excess in egg yolk) and renders it nutritionally unavailable. Women should be encouraged to consume whole eggs rather than egg whites, and when choosing a prenatal vitamin, to choose one containing biotin.

Essential fatty acid intake prior to conception

During the pre-conception period, women are recommended to consume a diet rich in omega-3 and omega-6 fatty acids, the major source of which is oily fish. However, there is growing concern over levels of mercury in some fish species, including swordfish, king mackerel, shark, and tilefish, and consumption of these species should be limited by women who are attempting to conceive. Consumption of canned albacore tuna should also be limited to 2 meals per week (85 g/meal). Essential fatty acids are available through other dietary sources, including nuts and vegetable oils. More studies are required in order to endorse supplementation for women prior to pregnancy.

Weight status and exercise prior to conception

Fertility in both females and males is decreased by being either overweight or underweight. Weight loss in non-pregnant overweight and obese women is associated with positive health outcomes and can also improve both fertility and pregnancy outcomes. The pre-conception period is a critical window of opportunity to establish good eating and exercise habits that will set the stage for a healthy pregnancy. Because weight loss is generally not recommended during pregnancy, it is best to have overweight women lose their excess weight prior to conception.

However, advice in this regard is often inadequate and, given that many women do not seek pre-pregnancy health checks, it is also often unheard. Many women with BMIs in the obese range do not consider themselves obese or even overweight. In some communities, obesity is now so common that it is perceived as normal. Adding to this conundrum is the fact that even when advised to lose weight prior to pregnancy, a large proportion of overweight and obese women fail to do so [1675].

Women who require modification in body weight, either loss or gain, should be advised to undertake this gradually prior to pregnancy. Regardless of BMI, women should also be encouraged to engage in regular aerobic exercise (walking, jogging, swimming, etc.) in order to achieve and maintain an acceptable level of fitness, not only for their own general health and well-being, but also to maximize their ability to cope with the demands of pregnancy, and allow the best chance of an optimal outcome for their offspring.

Pre-conception exposures

Medications and supplements that are not prescribed or approved by a physician should be discouraged in women planning a pregnancy. Some plants used in Chinese and Indian (Ayurvedic) herbal remedies and teas contain phytotoxins that are potentially teratogenic. In addition, some ethnic home remedies have been found to contain hazardous contaminants such as lead and mercury; therefore all supplement consumption should be scrutinized, and unnecessary intake should be avoided.

As mentioned in 'Vitamin A supplementation prior to conception', avoidance of supplements and foods (e.g. liver) containing high concentrations of preformed vitamin A is recommended prior to conception, as vitamin A can be teratogenic in early pregnancy if present at high levels. Fish containing high levels of methylmercury, including shark, swordfish, king mackerel, and tilefish should also be limited in women planning a pregnancy. In addition, caffeine should be limited in the pre-conception period, as excess consumption may affect a couple's ability to conceive and contribute to fetal growth restriction during pregnancy. The current advice is to limit the consumption of caffeine from all sources, including chocolate, energy drinks, and colas as well as tea and coffee, to 200 mg/day prior to conception and throughout pregnancy. Tobacco, alcohol, and illegal drugs should also be strongly discouraged in the pre-conception period, as harm from these substances can occur early, before a woman realizes that she is pregnant.

Certain occupations may expose women to relatively high levels of toxicants, including heavy metals (e.g. lead, cadmium, and arsenic) that have reproductive and developmental effects. Both the dose and duration will affect the extent of risk, and for many substances, the critical period for harm has not been clearly determined. Some types of factory work that exposed fathers pre-conceptionally to mercury vapour were found to increase the risk of spontaneous abortion in the workers' female partners [1676]. Similarly, peri-conceptional exposure of females to mercury can induce early spontaneous abortion.

With regard to congenital malformations or childhood cancers, pre-conception occupational exposures of either parent can possibly contribute to increasing the risks. Parental pre-conception exposure to low-level ionizing radiation, for example, has shown an association with NTDs in the offspring. Exposure to high concentrations of herbicides, fungicides, pesticides, and other hydrocarbons such as solvents and oil and coal products during the pre-conception period may also contribute to the development of birth defects or cancers. Factory workers, farmers, and horticulturalists are among those potentially at risk. Occupational exposures of both parents should be queried and, where possible, minimized prior to attempting to achieve a pregnancy. In addition, contact with solvents used in the home, such as paint-stripping and furniture-stripping solvents, metal cleaners, and non-latex-based paints, should be minimized.

Diabetes control prior to conception

For women with pre-existing diabetes, pre-conception care should focus on achieving and maintaining good glycemic control, which has been shown to reduce the incidence of spontaneous abortions, preterm deliveries, malformations, stillbirths, and neonatal deaths associated with poorly controlled maternal type 1 diabetes [1677]. The target for metabolic control in women with diabetes is to lower glycated haemoglobin levels to near the normal range before conception (43 mmol/mol (6.1%) or lower, according to UK National Institute for Health and Care Excellence guidelines), in order to reduce the risk of abnormal development of fetal organs in early pregnancy [1678].

Recommendations for a pre-conception diet

A woman's pre-conception diet can affect her chances of conceiving a pregnancy and will also influence the early stages of pregnancy, when the embryo is particularly sensitive to poor intrauterine conditions. A diet high in vegetables, vegetable oils, legumes, and fish and low in saturated fats, meats, and refined carbohydrates (the 'Mediterranean diet') is recommended. The diet should be low in fat, saturated fat, and cholesterol. Components of a healthy pre-conception diet are shown in Table 36.2.

Table 36.2 Dietary components of a healthy pre-conception diet

Dietary component	Number of servings/day	Serving size example
Fruit	2	1 apple, orange, banana, pear, 2 small plums, apricots
Vegetables	3	1 cup leafy vegetables
Grains*	6–11	½ cup rice, 1 slice bread
Lean meat, fish, poultry, legumes	2	½ chicken breast, ¾ cup flaked fish, ½ cup dry beans (1 cup cooked), 2 tbsp peanut butter
Low-fat dairy products	2–3	1 cup milk, ⅔ cup yogurt, ⅓ cup shredded cheese
Vegetable oils*	1–2	1 tsp olive oil used in cooking or salad dressing

* Choose whole grains whenever possible

* Choose olive oil, rapeseed oil; avocado oil

Chapter 37

Guidelines for pregnancy

Guidelines for early pregnancy

Once pregnancy is diagnosed, the health care provider has the responsibility to ensure that parents have a clear understanding of the benefit of a good parental lifestyle. This should include advice as to healthy and unhealthy eating, weight gain goals in pregnancy, and a list of unsafe foods (see Table 30.1 in chapter 30). In addition, there should be advice on healthy exercise behaviours, and the effects of alcohol and drugs.

Diet composition and micronutrient requirements in early pregnancy

If the mother has not had pre-conceptional counselling, it is important to ensure that she understands the importance of a balanced diet and what that means. Women should be advised that their energy intake needs in early pregnancy do not increase from pre-pregnancy levels; they should focus on eating well for pregnancy, and not eating more. Depending on the context, folate, vitamin B_{12}, iron (haemoglobin), and vitamin D status may need to be measured.

All women should receive vitamin D and folate supplementation; this is increasingly done in the form of multivitamin supplements that provide other micronutrients that should be present in a balanced diet in any event. Most of the required nutrients should be obtainable from food sources if, for example, women follow a diet similar to the Mediterranean diet, which is replete with fresh fruits and vegetables, fish (aside from large predatory species), legumes, and olive oil as the fat source. The recommended dietary allowances (RDAs) for micronutrients in pregnancy, as compared with the pre-conception requirements, are shown in Table 36.1 in chapter 36. In this section, we provide advice regarding specific micronutrient needs in the early pregnancy period.

Vitamin A intake in early pregnancy

Vitamin A deficiency in pregnancy confers increased risks of growth failure, depressed immunity, and increased morbidity and mortality due to infectious disease. However, high intakes of preformed vitamin A in early pregnancy are associated with an increased risk of birth defects. Most women can meet their early pregnancy needs for vitamin A from food sources of beta-carotene by consuming at least five servings of darkly coloured fruits and vegetables, or animal sources of retinol, although foods that are very high in vitamin A, such as liver, should be avoided. Supplementation with vitamin A is not recommended in early pregnancy, and even in areas of endemic vitamin A deficiency, supplements containing >10,000 IU of retinol (>700 μg)/day or >25,000 IU weekly should be avoided.

Folic acid supplementation in early pregnancy

Women should be advised to continue taking folic acid at their pre-conception recommended level (at least 400 μg/day), through the first 12 weeks of pregnancy. Low maternal folate is associated with low birthweight, small-for-gestational-age infants, and maternal pre-eclampsia, as well as an increased risk for neural tube defects. However, women taking high dosages of folic acid should ensure that their vitamin B_{12} intake is also sufficient.

Vitamin B_{12} intake in early pregnancy

Vitamin B_{12} requirements do not change drastically during pregnancy, but women at risk for deficiency, such as vegans and vegetarians, require supplementation to ensure adequate nutritional status. The requirement for vitamin B_{12} in early pregnancy is 2.6 μg/day. As noted above, vitamin B_{12} status is interlinked with folate status, and both need to be adequate in early pregnancy to ensure optimal pregnancy outcomes and to avoid maternal adverse health effects associated with deficiency for these nutrients.

Vitamin D supplementation in early pregnancy

Deficient maternal vitamin D status (<30 nmol/L) in early pregnancy is associated with reduced birthweight followed by accelerated growth after birth. This growth pattern may increase the risk of obesity, cardiovascular disease, and insulin resistance in the offspring. Supplementation with vitamin D should be continued through pregnancy, especially in high-risk women. The dose of the vitamin D supplement should be at least 400 IU/day, and the total intake should be in the range of 1,000–2,000 IU/day from dietary and supplemental sources.

Iron intake in early pregnancy

Maintaining or building optimal maternal body stores of iron in early pregnancy is important in order to prepare for the increased demands of late gestation. Iron status should be monitored, and supplementation is recommended in women with low iron stores or anaemia (haemoglobin <110 g/L in the first trimester), starting in early pregnancy if not prior to conception. All women should be given dietary advice to maximize iron intake and absorption, and should consume ~27 mg iron/day during pregnancy.

Iodine intake in early pregnancy

Adequate iodine intake should be ensured in early pregnancy. Intake should be increased from the pre-pregnancy recommended level of 150 μg/day, to around 250 μg/day in early pregnancy. In many countries it is difficult to obtain iodine in sufficient quantity purely from dietary sources and, if iodized salt is not used or is used minimally, pregnant women should be encouraged to take iodine supplements (150 μg/day) as early as possible in pregnancy.

Guidelines for middle and late pregnancy

Weight gain, exercise, and glucose monitoring in middle and late pregnancy

The rate of weight gain accelerates from mid-pregnancy, and it should be plotted against the US Institute of Medicine norms, taking into account measured or estimated pre-pregnancy BMI. Energy requirements increase from early pregnancy, with an average requirement for an additional 340 calories (~1,422 kilojoules) during the second trimester and an additional ~450 calories during the third trimester. Dieting, except under medical advice to address gestational diabetes or other conditions, should not occur unless weight gain is excessive. It should *not* be used to manage social concerns regarding the ease of labour.

Moderate exercise regimens should be maintained throughout pregnancy. As well as providing maternal health benefits in terms of cardiovascular fitness, moderate to vigorous exercise in the second trimester may reduce the risk of preterm birth by improving placental functional capacity and thus nutrient delivery to the fetus. In addition, all women should have their glucose status measured in mid-pregnancy. While there remains debate as to whether a fasting glucose or a non-fasting polycose test is sufficient unless there are clinical risk factors present, at least in Asia, where the incidence of gestational diabetes is very high, we would recommend an oral glucose tolerance test at 24–28 weeks for all women.

Diet composition and micronutrient requirements in middle and late pregnancy

Energy requirements increase in general in mid to late pregnancy, but the specific macronutrient composition of the diet may also be important. In particular, there is some evidence that adequate intakes of protein, preferably animal protein, in late pregnancy are important to protect against low birthweight. The intake of vegetable and fruit fibre should be maintained or increased in order to control fasting glucose levels and insulin resistance. Particular attention should be given to ensuring an adequate supply of polyunsaturated fatty acids and, if the diet is low in oily fish, supplementation should be considered.

The RDAs for micronutrients do not change between early and late pregnancy, despite greater energy requirements. Where supplements have been advised starting in early pregnancy, their intake should be continued. Some micronutrients are required in greater amounts in this period (e.g. iron), but the recommendation is that intakes are increased from early pregnancy in order to maintain and/or build adequate stores. Specific requirements to be aware of are discussed below.

Vitamin A intake in middle and late pregnancy

The growing fetus requires ~100 μg/day of vitamin A in the third trimester. If women have been following appropriate dietary advice for early pregnancy, consuming five or more servings per day of darkly coloured fruits and vegetables, and animal sources, including fish, eggs, and dairy products, their liver stores should be adequate to cope with the increased fetal demand in late pregnancy. In areas of endemic vitamin A deficiency (e.g. sub-Saharan Africa and southern India), supplementation is advisable beginning after day 60 of gestation and continuing for at least 12 weeks to delivery. Supplements should contain up to 10,000 IU vitamin A daily or up to 25,000 IU vitamin A weekly as an oral liquid, oil-based preparation of retinyl palmitate or retinyl acetate.

Vitamin D intake in middle and late pregnancy

Women in mid to late pregnancy should continue to take vitamin D supplements of *at least* 400 IU/day. The level of supplementation should be higher if they fall into the risk groups for deficiency (e.g. women who are dark-skinned or veiled, avoid the sun or regularly use sunscreens and/or protective clothing, live at high or low latitudes, eat vegan or vegetarian diets, or are obese). The intake should be in the range of 1,000–2,000 IU/day from diet, supplements, and/or sensible sun exposure.

Calcium intake in middle and late pregnancy

Bone turnover doubles in late pregnancy. Thus, dietary calcium intake in middle and late pregnancy should be maintained to support this. However, women with habitual low intakes of calcium should not increase their consumption markedly, as the maternal adaptative processes may be disrupted, potentially leading to worse outcomes for both mother and infant.

Iron status in middle and late pregnancy

Requirements for iron increase in the third trimester, but it is preferable that iron stores be built up from pre-conception and through gestation in order to meet the late pregnancy fetal demand. Women should be encouraged to maintain an adequate intake (two servings per day) of a mix of dietary iron sources such as meat, fish, poultry, legumes, nuts, green leafy vegetables, and iron-enriched breakfast cereals. Eating foods rich in vitamin C in the same meal as the iron source will increase the amount of iron that is absorbed. Women consuming a Western diet are likely to have iron intakes of only 12–18 mg/day and therefore may require supplementation in mid to late pregnancy to meet the RDA of 27 mg/day. Because both the intake and absorption of iron tends to be lower in vegetarian women, they are advised to take iron supplements at a dosage of 30 mg/day. Women in developing countries are recommended a supplementation dosage of 60 mg/day from 16 weeks gestation, with larger doses (~100 mg/day) advised in cases of anaemia.

Zinc intake in middle and late pregnancy

Zinc is required for the rapid fetal growth that occurs in late pregnancy to protect against low birthweight and impaired immune function. For the most part, requirements for zinc can be met through dietary sources such as seafood, red meat, poultry, leafy green vegetables, nuts, and legumes. However, the zinc content of plant-based foods tends to reflect the local soil zinc levels, and in some regions including sub-Saharan Africa and South Asia, the zinc content in the food supply may be inadequate to meet nutritional needs. In addition, diets high in phytate are associated with poor bioavailability of dietary zinc, because phytate forms insoluble complexes with zinc in the gastrointestinal tract. Iron supplementation also reduces zinc absorption, so women taking iron supplements or consuming diets low in bioavailable zinc should be advised to take a daily multivitamin containing zinc.

Exposures to avoid in middle and late pregnancy

Some substances should be specifically avoided in late pregnancy in order to reduce the potential risk of poor infant outcomes. During the third trimester, women should avoid high intakes of herbal teas and polyphenol-rich foods, which have been associated with the development of fetal ductus arteriosus brought on by inhibition of prostaglandin synthesis. For the same reasons of prostaglandin inhibition, nonsteroidal anti-inflammatory drugs should not be taken in late pregnancy. In addition, paracetamol (acetaminophen) should be avoided late in gestation, as there is some evidence to suggest that its use may increase the risk of childhood asthma. Recent data also suggest that prolonged paracetamol use in pregnancy, particularly during the third trimester, increases the risk for adverse psychomotor outcomes in children.

Chapter 38

Guidelines for breastfeeding and weaning

Benefits of breastfeeding

In the first 4–6 months of life, the infant will double its birthweight from that accumulated during its 9-month gestation. Nonetheless, provided that maternal nutrition is good, the infant requires little other than breast milk during this period. Breastfeeding is regarded as the optimal and most natural form of infant feeding. Milk from well-nourished mothers provides almost all of the nutrient requirements for the growing infant to the age of 6 months.

In developing countries with poor hygiene, breastfeeding is the safest feeding option, preventing infection both by avoiding contaminated water or foods and by provision of protective components, including secretory IgA antibodies and lactoferrin, in breast milk [1679]. Even in developed countries, breastfeeding is associated with a significant reduction of infections, including acute otitis media and gastrointestinal infection [1680]. Observational evidence suggests other positive health benefits for the breastfed infant later in life, including a reduced risk of hypertension and lower total cholesterol in adulthood [1681]. The latter may reflect long-term effects of adjustments in cholesterol metabolism in response to the higher cholesterol content of breast milk compared with infant formulas. In addition, the pattern of infant growth is quite different for breastfed and formula-fed infants [1682, 1683]. Although there are conflicting data, it is generally accepted that exclusive breastfeeding for >4 months is associated with a reduction in the risk of later obesity [1684, 1685].

In addition to its documented benefits for the growing infant, breastfeeding is also beneficial for the mother, reducing postpartum weight retention [1686] and lowering the risk of premenopausal breast cancer, particularly with extended breastfeeding [1687]. Other potential benefits include improved mother–infant bonding and maternal bone health, as well as reduced risks of postpartum depression and endometrial, ovarian, and postmenopausal breast cancer [1688, 1689]. If exclusive breastfeeding for the first 6 months is not accomplished, partial breastfeeding and/or breastfeeding for a shorter time period is also valuable and should be encouraged. Breastfeeding is contraindicated in only a few circumstances, which include cases of maternal HIV-1 or human T-cell lymphotropic virus type I or type II infection, or herpes simplex lesions on the breast [1690]. Yet in resource-poor settings, continued breastfeeding by HIV-infected women is recommended because the risk of morbidity and mortality from other infections or malnutrition outweighs the risk of HIV transmission to the infant.

Nutritional and lifestyle guidance for women during the highly demanding period of lactation is as important as that given before and during pregnancy. Although exclusive breastfeeding for the first 6 months is a desirable goal, we also acknowledge that some women either cannot or choose not to breastfeed their infants. For these women, guidance is required in terms of the optimal infant formulas for their newborns. The weaning period is equally important, and advice on complementary foods should be provided to all women, whether formula feeding or breastfeeding.

Nutrition for lactation

The need to maintain healthy eating habits into lactation is obvious. This may create some challenges, as in some cultures quite distinct confinement diets are the norm during the first month after birth (see chapter 31). In general, the nutritional needs of women during breastfeeding exceed those of pregnancy, and the micronutrient recommended dietary allowances (RDAs) for lactation are accordingly different to those of pregnancy (see Table 36.1 in chapter 36). Lactating women may need supplementation with a multivitamin.

Energy and macronutrient requirements during breastfeeding

Breastfeeding women have increased energy requirements to meet both the energy cost of milk production and the energy content of the milk they produce. On average, women who are exclusively breastfeeding their infants produce ~780 mL of milk per day during the first 6 months and ~600 mL/day between 7 and 12 months, and the average energy density of the milk is 0.67 kcal/mL [131]. Part of this energy demand can met by the mobilization of fat stores laid down during pregnancy, and this mobilization occurs at a rate of ~170 kcal/day in well-nourished women [1691].

Weight loss varies during lactation but is most steady in women who exclusively breast feed. Women who are underweight or who had low gestational weight gain require some additional caloric intake above that consumed during pregnancy in order to meet the energy demands of exclusive breastfeeding. The recommended intake is an additional 500 kcal/day during the first 6 months of lactation, in addition to the energy mobilized from fat stores. This extra intake is reduced to 400 kcal/day after 6 months because milk output is reduced as infants begin complementary feeding.

Overweight or obese women do not require additional energy during breastfeeding. On the contrary, they can safely restrict their energy intake at this time, in order to encourage weight loss. This can be accomplished without affecting the growth of their infants by reducing their overall energy consumption by 500 kcal/day [1692]. The proportions of macronutrients required in the lactation diet do not differ from those during non-lactating states [1693]. However, the breast milk composition of some macronutrients is influenced by the amount, proportion, and types of nutrients consumed by the mother.

Fatty acid requirements during breastfeeding

The type and amount of fat in the maternal diet strongly influences the composition of fatty acids present in breast milk. For example, the trans-fatty acid content of human milk correlates directly with the maternal intake of partially hydrogenated fats and oils [1694]. Long-chain polyunsaturated fatty acids such as docosahexaenoic acid (DHA) are important for infant brain and visual development, and their presence in breast milk is largely determined by the maternal diet.

In addition to its effect on the infant, a decline in maternal DHA status in lactation is associated with postpartum depression in the mother [1695]. Supplementation with 200–220 mg/day DHA from mid-pregnancy through lactation has been shown to improve maternal DHA status and the amount of DHA present in breast milk [1696, 1697]. Very premature infants miss out on third trimester accretion of DHA and may benefit from maternal supplementation to increase breast milk supply [1698]. Neurological development in preterm, low-birthweight infants is also enhanced by feeding them DHA-enriched formula to match the level of accretion missed in utero [1699].

Protein requirements during breastfeeding

The RDA for protein intake during lactation is 1.1 g per kg of body weight per day, which is the same as for pregnancy but is an additional 25 g/day above the requirement for non-pregnant, non-lactating women [131]. Body composition does not influence the amount of protein present in breast milk, but increasing dietary protein intake does modify the total amount of protein in milk [1700]. The recommended percentage of energy derived from protein in the lactation diet is 10–35 per cent, which does not differ from that for the general population. High-quality protein sources such as meat, fish, eggs, and milk provide all the essential amino acids required for lactating women. Vegetarian women need to ensure that their diet contains adequate combinations of plant proteins (legumes, nuts, fruits, starchy root vegetables, cereals) to provide all essential amino acids.

Carbohydrate requirements during breastfeeding

The carbohydrate content of human milk is mainly lactose, which at 70 g/L makes up the second largest component of milk, after water. The lactose content of milk does not appear to be influenced by the maternal diet. Lactose and oligosaccharides facilitate growth in the gut of *Bifidus* spp., which helps to protect the breastfed infant from gastrointestinal infection. Oligosaccharides differ in composition and quantity in human vs cow's milk [1695]. Infant formulas are quite heterogeneous in their oligosaccharide makeup but in general are more similar to cow's milk than human milk, despite efforts to mimic the human milk composition [1701].

Micronutrient requirements during breastfeeding

Nutrients are prioritized to breast milk during lactation, often at the expense of maternal reserves. Differences in milk composition, especially with regard to vitamins, can occur as a result of varying dietary intake. The concentrations of vitamins B_6, B_{12}, A, and D in breast milk are particularly sensitive to maternal intake [1702]. In well-nourished women, most micronutrients will be in adequate supply in their milk, with the exception of vitamins D and K. A number of other micronutrients, including folate, calcium, iodine, and zinc, may also be in short supply in lactating women if their own body stores were low at the end of gestation.

Vitamin D requirements for breastfeeding mothers and newborns

Vitamin D is one micronutrient that is likely to be present in insufficient quantity in the breast milk of lactating women. Its activity in breast milk is directly related to the vitamin D status of the mother, and recent data suggest that a large percentage of women have less than optimal vitamin D stores during pregnancy. If mothers are deficient in the nutrient, vitamin D will not be detectable in their milk.

The US Institute of Medicine (IOM) RDA for vitamin D during lactation is 600 IU (15 μg/day), the same as for pregnancy. However, as dietary sources of vitamin D are minimal and UV-avoidance behaviour is common, a large proportion of the population requires supplementation in order to obtain adequate vitamin D. The recommended supplementation level of 400 IU/day, generally taken in the form of a multivitamin, has only a modest effect on maternal blood 25-hydroxyvitamin D levels [1702]. The Endocrine Society suggests that lactating women should take a vitamin D supplement of ≥1,000 IU daily *in addition* to the 400 IU/day provided in multivitamins [582].

However, despite such results and advice, maternal high-dose supplementation remains controversial. Supplementation of infants with 400 IU/day orally is therefore increasingly recommended, because provision of adequate vitamin D through breast milk cannot be consistently assured in the absence of high-dose maternal supplementation. Recent recommendations of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition support this advice in order to achieve a 25-hydroxyvitamin D serum concentration in infants of >50 nmol/L (indicating vitamin D sufficiency according to their criteria) [1703].

Vitamin K requirements for newborns

Regardless of maternal intake or status, vitamin K is generally not deposited in sufficient quantities in breast milk to support the needs of the newborn infant in the first few days of life. Therefore infant supplementation with an initial vitamin K dose shortly after birth is recommended to prevent vitamin K deficiency bleeding. The American Academy of Pediatrics recommendation is intramuscular administration of 0.5 mg vitamin K for infants ≤1,500 g, and 1 mg for infants >1,500 g [677]. Mothers should continue to consume 90 μg/day, obtainable from green leafy vegetables such as kale, spinach, beet greens, and herbs, as well as broccoli, Brussels sprouts, and spring onions.

Vitamin A requirements during breastfeeding

Breast milk is rich in vitamin A, derived mainly from maternal fat stores and transported in the lipid fraction of milk as retinyl ester. Breast milk vitamin A content is also sensitive to maternal dietary intake, and women with low intakes may be at risk of vitamin A deficiency resulting from further depletion of their body stores, as postnatal uptake of vitamin A by the infant is much higher than during pregnancy [1704]. The provitamin A carotenoid beta-carotene remains an important source of dietary vitamin A, and women are encouraged to obtain this by increasing their intake of darkly coloured vegetables and fruits. Postpartum supplementation with vitamin A has minimal effect on maternal or infant morbidity and is therefore not generally recommended [250]

Vitamin B_6 requirements during breastfeeding

Weight gain and linear growth in early infancy have been shown to correlate with infant vitamin B_6 intake [362]. Infants with very low intake of vitamin B_6 may be at risk for the development of seizures [365]. Vitamin B_6 concentrations in human milk respond to changes in maternal intake [363], and it is therefore important to ensure that breastfeeding mothers consume adequate amounts of vitamin B_6 to supply to their infants. The IOM RDA for lactation is 2.0 mg/day.

Vitamin B_6 is widely distributed in foods, so supplementation is usually not required if the maternal diet is healthy and balanced. However, in women with low vitamin B_6 intake or status, supplementation with 2.5 mg/day pyridoxine-HCl provides adequate levels of vitamin B_6 in breast milk to support the growth of their breastfed infants [363].

Vitamin B_{12} requirements during breastfeeding

The vitamin B_{12} content of breast milk is positively correlated with meat and fish consumption [1704]. Women who consume a strict vegetarian or vegan diet should be supplemented with vitamin B_{12} during lactation to help insure adequate vitamin B_{12} levels in their milk. If the mother is not sufficiently supplemented herself, breastfed infants of vegan mothers should receive vitamin B_{12} supplementation, for the prevention of severe megaloblastic anaemia and neurological abnormalities associated with vitamin B_{12} deficiency.

Iron requirements during breastfeeding

The IOM recommendation for iron intake during lactation is lower than during pregnancy (see Table 36.1 in chapter 36). However, as many women enter pregnancy with insufficient iron stores, it is reasonable to consider the need to maintain similar iron intake to allow for recovery of iron stores after pregnancy. Despite the fact that breast milk contains little iron, full-term infants of well-nourished mothers generally have sufficient iron stores and receive enough iron from breast milk to satisfy their requirements through the first 4–6 months of life [1705]. Low-birthweight infants or those born to diabetic mothers may have reduced iron stores at birth [951]. At around 4–6 months, the infant's iron stores are depleted, and its need for iron simultaneously increases dramatically. At this point, the introduction of iron-rich complementary foods is strongly recommended (see 'Iron requirements during weaning').

Folate requirements during breastfeeding

The folate content of human milk is conserved at the expense of maternal stores. Thus, most breastfed infants receive sufficient folate, except in cases of severe maternal folate deficiency. Lactating women planning or considering a subsequent pregnancy should continue to consume 400 μg folic acid/day as a supplement, although they should also ensure adequate vitamin B_{12} intake to avoid the risk of masking deficiency for this vitamin, and possible associated neurological damage.

Calcium requirements during breastfeeding

As in pregnancy, the maternal calcium status is tightly regulated by homeostatic mechanisms during lactation and is unrelated to dietary intake of calcium or vitamin D. Lactational bone loss from the mobilization of maternal skeletal calcium stores is transient and recovers after weaning unless calcium intake is very low. Adolescent mothers tend to have lower calcium intakes than adults and, if they are still growing themselves, they risk poor recovery of bone mineral density after lactation. Young mothers should therefore be advised to maintain or increase their dietary calcium intake to recommended levels (1,300 mg/day) during lactation to ensure their own long-term bone health [562].

Zinc requirements during breastfeeding

Zinc is vital for infant development, and the demand for this trace mineral is high during lactation because zinc is preferentially concentrated in breast milk from maternal tissues. Maternal zinc status thus may be jeopardized by low intake, although dietary or supplementary zinc intake does not significantly influence the concentration of zinc in breast milk, which declines over the course of lactation irrespective of maternal consumption [1706]. Low-zinc diets are usually also poor in other nutrients, including iron and vitamin B_{12}, because they lack animal protein. Low-zinc status increases susceptibility to infections, so lactating mothers are advised to consume adequate levels of zinc in their diets or consume a multivitamin supplement containing zinc.

Iodine requirements during breastfeeding

During lactation, iodine is concentrated in the mammary gland for excretion in breast milk, a process that is influenced by maternal iodine status. To protect against maternal deficiency, lactating women should consume an additional 50–70 μg/day of iodine above the recommendation of 200–220 μg/day during pregnancy by the WHO and the IOM [260, 867]. The iodine status of women varies widely by region, depending on the iodine levels in local soil, and the availability and use of iodized table salt. Most women in regions where salt iodization programmes are in effect have acceptable iodine status.

Dieting during lactation

Postpartum weight retention is higher for women who were overweight or obese during pregnancy or whose gestational weight gain was high. For these women, breastfeeding has less of an effect on weight loss than it has in women who were normal weight in pregnancy [1686]. Overweight lactating women can safely exercise and restrict their energy intake by 500 kcal/day if they consume a well-balanced diet, decreasing the amount and proportion of fats, sweetened drinks, sweets, and snack foods that they consume. A small study of such an intervention (including exercise for 45 minutes/day, 4 days/week) showed increased maternal weight loss without obvious effects on infant well-being, although the dieting women had lower intakes of vitamin D and calcium, which consequently required supplementation [1707]. All women in the study, including those not restricting their energy intake, had low intakes of vitamins C and E. Overall, the study suggested that lactating women need to increase their consumption of fruits and vegetables as well as foods high in calcium and vitamin D; in addition, they may also need to take multivitamin supplements—particularly those women following a weight loss programme.

Exposures during lactation

Exposure to environmental contaminants during breastfeeding

Some environmental toxins accumulate in body fat, and there has been concern that they will enter the fat component of breast milk. It is advisable that breastfeeding women avoid high-level acute exposures to known toxic substances, as also advised during pregnancy (see chapter 30 for details). Although substances such as pesticides and herbicides have been detected in breast milk, their levels in most cases are lower that what is normally found in cow's milk. Thus, despite the possible contamination of breast milk from environmental chemicals, breastfeeding is still recommended, except in cases of acute high-level exposures [1690]. Some heavy metals have been detected in human milk, including lead, arsenic, mercury, and cadmium [1708]. Lead in particular remains a concern around the world, and women who are known to be exposed should consume extra iron and calcium either in their diets or via supplements in order to minimize the mobilization of lead from bone.

Alcohol, drugs, and smoking during breastfeeding

Alcohol transfers readily into human milk, but also suppresses milk production. Heavy alcohol consumption should be discouraged during lactation. Mothers who ingest alcohol in moderate amounts should be advised to wait ~2 hours for each drink consumed before resuming breastfeeding [1709]. Marijuana use should also be discouraged, as some secretion into breast milk has been reported, and exposure of the infant may risk neurodevelopmental complications [1710, 1711].

Cigarette smoking is strongly discouraged during lactation, as it exposes infants to toxic xenobiotics in addition to nicotine, which can affect sleep patterns and feeding [1712]. Maternal smoking also alters the micronutrient composition of breast milk; for example, thiocyanate in cigarette smoke interferes with the transport of iodine into milk [1713]. Environmental cigarette smoke exposure is associated with wheeze and respiratory infection in infants and children [1714]. The use of drugs such as cocaine, methamphetamine, and heroin is clearly contraindicated during breastfeeding, as these substances can be transferred to the infant in breast milk and can cause serious adverse effects [318]. Passive exposure to the smoke of crack cocaine also poses a risk for the infant [1715].

Use of prescribed drugs during breastfeeding

Women may be concerned about taking medications if they are breastfeeding. Thus, they may consider either not breastfeeding or stopping their medications in order to continue. However there are many common conditions that require drug treatment and which do not constitute a contraindication to breastfeeding, as exposure of the infant to the drugs via breast milk is minimal.

Drugs for postpartum depression

Postpartum depression is a common condition affecting women after childbirth, and drug treatment is usually recommended. Breastfeeding should not be discouraged in women taking many of the common medications such as selective serotonin reuptake inhibitors, as transfer to breast milk and uptake by the infant has been shown to be low [1716, 1717]. Fluoxetine is the least preferred because of its longer half-life and therefore higher infant exposure, but women for whom this drug is the best choice to treat their condition are not advised to change to another drug. Women for whom benzodiazepines or other drugs for sedation/anxiety are warranted should be prescribed an agent with a short half-life and at the lowest effective dose and duration, in order to minimize infant exposure [1718].

Pain medication during breastfeeding

Most nonsteroidal anti-inflammatory drugs, and acetaminophen, are suitable for use during lactation. However, the overuse of these agents should be discouraged. Opioids should be used with caution and only under the supervision of a physician [1718].

Antihypertensives during breastfeeding

Some anti-hypertensive medications in the beta-adrenergic blocker class can cause hypotension, bradycardia, and lethargy in infants when used by breastfeeding mothers. However, angiotensin-converting enzyme inhibitors and calcium channel blockers have not raised concerns. Thus, despite some indication that diuretics reduce milk volume, these drugs are not contraindicated for lactating women [1718, 1719].

Anti-infectives during breastfeeding

Many anti-infective agents are excreted into breast milk and have the potential to affect the breastfeeding infant. Most antibacterials, including penicillins, aminoglycosides, cephalosporins, and carbapenems, are suitable for use during lactation, though tetracyclines can cause tooth discolouration in infants [1720]. Of the antivirals, acyclovir has been most studied in lactating women and is considered to be compatible with breastfeeding [1721]. Because of a lack of safety data, most systemic antifungal agents, with the exception of fluconazole, are not recommended during breastfeeding [1722].

Maternal stress during breastfeeding

Glucocorticoid levels rise in response to various forms of stress. Moreover, they are secreted in breast milk, via which they can affect infant behaviour and temperament, particularly among females [1565, 1566]. As in pregnancy, women who are breastfeeding should try to avoid stress and stressful situations as much as possible.

Infant formulas

Women who wean their infants early or do not breast feed for medical or social reasons need advice from a health care professional on suitable formulas. Infant formula is devised as a breast milk substitute and can be used as such at least through the first year of life. Formula-fed infants require complementary foods at the same stage as breastfed infants (i.e. around 6 months; see ‘Weaning and complementary foods’).

Most infant formulas are based on cow’s milk or soy and are designed to match as closely as possible the nutritional composition of breast milk. Protein hydrolysate formulas contain extensively hydrolysed proteins and are meant for babies with protein allergies or who do not tolerate regular cow’s milk or soy-based formulas. Soy formula is suitable in some but not all cases of cow’s milk protein allergy; otherwise, there are no particular benefits of soy formula, and there is some concern over the presence of phytoestrogens (isoflavones), which have been shown to cause changes in sexual development in animals [1723]. While this is still a matter of some debate and ambiguity, we suggest that soy formulas should be used only for specific medical indications, under the advice of a health care professional. Lactose-free formulas are usually not necessary, as true lactose intolerance is very rare in infants.

Essential components and composition of infant formulas

An international expert group coordinated by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition published recommendations for a global standard for the composition of infant formula, based on current scientific knowledge in 2005 [953]. Formula used in the first 6 months should meet the basic guidelines proposed, some of which are outlined below. The specific micronutrient recommendations are detailed in Table 38.1.

Table 38.1 Recommended micronutrient composition of infant formula. Unless specifically stated, the amounts of vitamins, minerals, trace elements, and other components are appropriate for formulas based on either cow's milk protein or soy and are based on global standards developed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition [953]

Micronutrient	**Recommended amount in formula (per 100 kcal)**	**Comments**
Vitamin A	60–180 μg RE	Provided by retinol or retinyl esters. Carotenoid content should not be included in the calculation of vitamin A activity.
Vitamin B_1 (thiamine)	60–300 μg	
Vitamin B_2 (riboflavin)	300–400 μg	
Vitamin B_3 (niacin)	300–1500 μg	As preformed niacin.
Vitamin B_5 (pantothenic acid)	400–2000 μg	
Vitamin B_6 (pyridoxine)	35–175 μg	
Vitamin B_{12} (cobalamin)	0.1–0.5 μg	
Vitamin C	10–30 mg	High intakes may induce copper deficiency.
Vitamin D	1–2.5 μg	As vitamin D_3; data on activity of vitamin D_2 in infants is lacking.
Vitamin E	0.5–5 mg α-TE	Composition should not be less than 0.5 mg α-TE/g linoleic acid.
Vitamin K	4–25 μg	
Folate	10–50 μg	As folic acid.
Biotin	1.5–7.5 μg	No agreed reference intake range. Human milk range = 0.75–1.3 μg/100 kcal.
Calcium[a]	50–140 mg	Bioavailability is lower from cow's milk than human milk.
Chloride	50–160 mg	
Choline	7–50 mg	
Copper	35–80 μg	

Table 38.1 (continued) Recommended micronutrient composition of infant formula. Unless specifically stated, the amounts of vitamins, minerals, trace elements, and other components are appropriate for formulas based on either cow's milk protein or soy and are based on global standards developed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition [953]

Micronutrient	Recommended amount in formula (per 100 kcal)	Comments
Fluoride	≤60 µg	Infants may be exposed from other sources (e.g. water). High exposure risks dental fluorosis.
Iodine	10–50 µg	Recommended intakes range from 35 to130 µg/day.
Iron	0.3–1.3 mg (cow's milk) 0.45–2 mg (soy)	Phytic acid in soy inhibits iron absorption.
L-Carnitine	≥1.2 mg	
Magnesium	5–15 mg	
Manganese	1–50 µg	Higher manganese content may cause brain accumulation and adverse effects
Myoinositol	4–40 mg	
Phosphorus[a]	25–90 mg (cow's milk) 30–100 mg (soy)	Bioavailability is higher from cow's milk than from soy-based formula.
Potassium	60–160 mg	
Selenium	1–9 µg	Human milk content=0.8–3.3 µg/100 kcal. Very high intakes may cause adverse effects.
Sodium	20–60 mg	
Zinc	0.5–1.5 mg	

RE = retinol equivalent; α-TE = alpha-tocopherol equivalent

[a] The calcium:phosphorus ratio (weight/weight) should be between 1:1 and 2:1

Source: Koletzko, B. et al., Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group, *Journal of Pediatric Gastroenterology and Nutrition*, Volume 41, Issue 5, pp.584–99, copyright © 2005 ESPGHAN Committee on Nutrition.

Energy density of infant formulas

The energy density of infant formula should be in the range of 60–70kcal/100 mL to emulate the average energy density of human milk (65 kcal/100 mL) [953]. Formulas with substantially higher energy density will promote inappropriate weight gain, which can increase the risk of obesity later in life [1724]. Infants fed formulas with energy densities below the recommended range may exhibit low weight gain and may not be receiving some necessary dietary fats.

Fatty acids in infant formulas

Previously, infant formula did not contain preformed arachidonic acid or DHA; rather, 18-carbon precursors to these long-chain polyunsaturated fatty acids (specifically, linoleic acid and alpha-linolenic acid) were present. However, it was noted that formula-fed infants, who need to either synthesize DHA from alpha-linolenic acid or utilize body stores, did not accumulate DHA to the same level as breastfed infants, who acquire DHA in their mothers' milk [165, 1725]. Human milk DHA levels correlate positively with visual development in breastfed infants [1726]. Trials of formula compositions containing doses of DHA between 0.3 per cent and 0.5 per cent of total fatty acids, and at least equal amounts of arachidonic acid, have consistently reported significant visual and cognitive benefits for term infants [1727]. The fatty acid composition of current formulas is now between 0.15 per cent and 0.32 per cent DHA, and between 0.4 per cent and 0.64 per cent arachidonic acid. Preterm infants may require additional long-chain polyunsaturated fatty acid supplementation.

Protein content of infant formulas

Human milk has a high whey:casein ratio (70:30) as compared to cow's milk (18:82). This higher ratio promotes more rapid gastric emptying and makes human milk more digestible [1728]. Whey proteins also differ, so to match the whey:casein ratio of human milk, cow's milk formulas have a higher protein content than human milk and are supplemented with taurine, the second most abundant amino acid in human milk [1729]. The protein content of cow's milk infant formulas should be between 1.8 and 2.0 g/100 kcal and should not exceed 3.0 g/100 kcal. This includes formulas based on protein hydrolysates [953]. The protein content of soy-based formulas should be slightly higher than that of cow's milk formulas (minimum 2.25 g/100 kcal) to account for poorer digestibility but should also not exceed 3 g/100 kcal.

Carbohydrates in infant formulas

Carbohydrates are an essential energy source for infants. The carbohydrate content of formulas should consist mainly of lactose, be between 9 and 14 g/100 kcal, and represent ~56 per cent of the energy content of the formulas [953]. Formulas should not contain glucose, sucrose, or fructose.

Iron in infant formulas

Most infant formulas are fortified with iron, although the optimal amount remains a matter of debate, and fortification levels vary in different countries. The benefits of additional iron are dependent on the newborn's iron status. In infants who are iron replete, provision of iron-fortified formula may not be beneficial. Excess iron can interfere with zinc and copper absorption and may increase the risk of infection.

The suggestion of the international expert group coordinated by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition was that infant formulas based on cow's milk be fortified with 0.3–1.3 mg iron/100 kcal. For infants with adequate iron stores, there is no additional benefit of iron above the minimum level. In areas with a high prevalence of iron deficiency, iron contents at the higher end of this range are appropriate [953].

Other minerals and vitamins and additional components in infant formulas

The recommended composition of other minerals, vitamins, and additional components of infant formulas are outlined in Table 38.1.

Follow-up formulas

Follow-up formulas are intended for older infants and young children. However, they are dispensable, as infant formula can be used for the first year, and cow's milk or other milks are appropriate after that time. Follow-up formulas should not be used prior to the introduction of complementary foods [1730].

Weaning and complementary foods

Timing of weaning

The timing of the introduction of complementary foods into the infant diet is determined by the nutritional adequacy of exclusive breastfeeding at different ages. Thus, the appropriate time for weaning will depend on the nutritional status of the mother and infant. The timing will also depend on the growth and development of the infant, and the readiness of the infant to accept a different feeding mode.

The concentrations of many nutrients in breast milk decline rapidly between 6 and 12 months of lactation. For example, breast milk may not provide sufficient iron and zinc for some infants between 4 and 6 months of age. This is a period of rapid growth for the infant, who begins to require additional dietary sources of these vital nutrients for continued healthy development. On a per body weight basis, the nutrient requirements at this stage are higher than any other time during the lifespan.

The 4–6 month window also appears to be critical for the introduction of complementary foods from the standpoint of allergen exposure, as delayed introduction of new foods can hinder the normal development of immune tolerance [1731, 1732]. Despite earlier belief that a delay in the introduction of solid foods would lessen the risk of atopic disorders, food sensitization was actually found to be more frequent in children whose first experience of solid foods was after 6 months of age [1733]. To reduce the risk of developing celiac disease, it is recommended that gluten-containing cereals be introduced by the age of 6 months, while maintaining breastfeeding to help reduce the risk of food allergy [1734]. On the other hand, very early introduction of solid foods (before 16 weeks) also increases the risk of developing allergic or autoimmune diseases.

From a growth perspective, the introduction of complementary foods earlier than 4 months may increase the rate of weight gain and the later risk of obesity, type 2 diabetes, and cardiovascular disease, while later introduction (after 6 months) can decrease growth velocity [1735]. Because formula-fed infants generally consume more energy than breastfed infants, their set point for energy demand is higher at weaning [1736]. Between 6 and 12 months of age, infants should consume between 800 and 1,000 kcal/day.

Nutrient requirements during weaning

There are some nutrients, most notably iron, for which infant stores are a primary source and which are depleted over the course of extended breastfeeding. The specific nutrients must be acquired through complementary foods starting between 4 and 6 months of age. Infants also begin to require fibre in their diets, which is not present in breast milk. The specific nutrient requirements for infants beginning complementary feeding, and recommended foods and sequence, are discussed below. The British Dietetic Association recommends that infants from 6 months be given a supplement containing vitamins A, C, and D, unless they are consuming formula (500 mL/day).

Fibre requirements during weaning

Prior to the introduction of complementary foods, breastfed infants consume no dietary fibre, as it is absent from human milk. Fibre becomes important in the diet as solid foods are introduced, to balance energy density and to provide protection against immunogenic agents by modifying the composition of colonic flora [1737]. Foods such as legumes, unprocessed grains, fruits, and vegetables are sources of fibre that can be introduced to infants during the weaning process, such that by 12 months of age, the infants are consuming 5 g fibre/day [1737]. However, there is a limit to the amount of fibre-rich foods that infants should consume, as a diet too high in fibre could diminish caloric intake and reduce the bioavailability of minerals and other nutrients.

The metabolic effects of fibre-containing foods are important for the infant's developing physiology and optimum metabolic function. Supplementing the infant's diet with vegetables prior to the introduction of animal-based foods may be preferable to establish an appropriate energy balance in the diet. A suggestion for the order of introduction of complementary foods is given in Table 38.2.

Vitamin B_6 requirements during weaning

The vitamin B_6 status of breastfed infants of well-nourished mothers is generally adequate in the first 4 months, because gestationally accumulated stores supply some of the required nutrient to the infant. However, after 6 months the risk of low vitamin B_6 increases, even if the mother's status is adequate [361]. Many foods contain vitamin B_6, but infants who do not receive complementary foods after 6 months may require supplements of the vitamin.

Vitamin B_{12} requirements during weaning

The requirement for vitamin B_{12} increases slightly (from 0.4 μg/day to 0.5 μg/day) during the second half of the infant's first year of life. If the infant has been breastfed by a vegetarian mother, its stores of the nutrient will likely be depleted by around 4 months of age. Thus, for these infants, supplementation with

Table 38.2 Complementary foods and their approximate timing of introduction into the infant diet during continued breastfeeding

Food	Infant age (months)
Rice, maize	4
Potato, carrot, lettuce	4–5
Apple pear, banana	5–6
Gluten-containing cereals	5–6
Meat, fish, chicken	6
Broccoli, cabbage	7
Legumes, breakfast cereals	8
Citrus fruits	8–10
Tomato, celery	9–10
Berries, nuts	12

vitamin B_{12} or the addition to the diet of animal-derived complementary foods will be required.

Iron requirements during weaning

Once infants reach 6 months of age, their iron requirements increase substantially, to around 8–11 mg/day. At this stage, their iron stores from birth are also severely diminished or exhausted. Because of this, iron-rich foods such as meat and poultry should be introduced at around 6 months, or once the infant is eating pureed rice and vegetables.

Zinc requirements during weaning

The zinc content of human milk declines rapidly during the first 6 months, and like iron, infant zinc stores are exhausted in most infants between 4 and 6 months of age. Zinc deficiency risk increases after 6 months of age and is associated with decreased growth velocity. Complementary foods are needed to provide adequate quantities of the mineral to support development and immune function. Weaning cereals containing zinc usually also contain phytates, which limit zinc absorption, so supplementation is sometimes necessary.

Guidelines for the introduction of complementary foods during weaning

Guidelines on complementary feeding published by the WHO and the Pan American Health Organization recommend the daily or frequent consumption of meat, poultry, fish, or eggs—the main concern being the provision of adequate quantities of iron. However, the first complementary foods should be easily digestible foods such as pureed rice or maize. Continued breastfeeding throughout the period of introduction of solid foods is strongly recommended and should be encouraged in all women who are able to do so. New foods should be introduced in a gradual manner over a period of around 6 months, beginning with a small number of pureed semi-solid foods, followed by an increasingly greater range of tastes and textures as the infant begins to self-feed (see Table 38.2). From 1 year of age, a child should be capable of participating in family meals and eating at least some family foods.

Food preferences and flavour learning during breastfeeding and weaning

Flavours of foods eaten by the mother during pregnancy are detectable in amniotic fluid and are sensed by the fetus. Similarly, the infant is exposed via breast milk to flavours in the mother's diet during lactation [12, 13]. Studies with formula-fed infants indicate a sensitive period spanning the first three postnatal months for acceptance of specific flavours. Flavour acceptance is very specific to the flavours experienced in the formulas, which can vary drastically depending on the content of free amino acids (e.g. protein hydrolysate formula vs standard cow's milk formula).

Flavours in formulas impact on taste preferences for food at weaning. For example, protein hydrolysate formulas, which have been shown to induce satiety at lower intakes than standard formulas, have a bitter taste that is perceived as unpleasant in older infants who did not experience this flavour in the first 3 months. Infants fed protein hydrolysate formulas have a greater preference for savoury vs sweet foods at weaning, as compared to infants fed with standard cow's milk formulas [13].

Unlike formula feeding, breastfeeding allows for a wide variety of flavour experiences as a function of food choices of the mother. Subsequently, these experiences can influence the infant's acceptance of new flavours when complementary foods are introduced. This highlights the importance of a varied diet for both pregnant and lactating women.

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