

Maternal and Infant Nutrition and Nurture


Note

Health and social care practice and knowledge are constantly changing and developing as new research and treatments, changes in procedures, drugs and equipment become available.

The authors, editor and publishers have, as far as is possible, taken care to confirm that the information complies with the latest standards of practice and legislation.

Maternal and Infant Nutrition and Nurture

Second edition

edited by

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QUAY BOOKS
A division of MA Healthcare Ltd

Quay Books Division, MA Healthcare Ltd, St Jude's Church, Dulwich Road, London SE24 0PB

British Library Cataloguing-in-Publication Data
A catalogue record is available for this book

ISBN-10: 1 85642 435 9
ISBN-13: 978 1 85642 435 6

Printed by Mimeo, Huntingdon, Cambridgeshire

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Foreword

Fiona Dykes

The second edition of this book is very timely as we see maternal and child nutrition coming increasingly onto public health agendas across the globe, with a growing focus upon the interconnectedness of mother and child. The World Health Organization states:

> The health and nutritional status of mothers and children are intimately linked. Improved infant and young child feeding begins with ensuring the health and nutritional status of women, in their own right, throughout all stages of life and continues with women as providers for their children and families. Mothers and infants form a biological and social unit; they also share problems of malnutrition and ill-health. Whatever is done to solve these problems concerns both mothers and children together. (WHO, 2003, p. 5).

This book is particularly important, as it not only focuses upon the challenges to optimising maternal and child nutrition, but refers throughout to policy and practice related to this issue, thus bridging the gaps between rhetoric and reality. It also represents a positive move to disrupt disciplinary boundaries that have, in many cases, persisted with regard to maternal and infant nutrition, eating and feeding. It thus produces new ways of seeing within the field of maternal and child nutrition and nurture that connect the disciplines of nutrition, dietetics, midwifery, medicine and the social sciences.

In Chapter 1, Paula Williams and Hiten Mistry discuss the importance of specific antioxidant micronutrients and the crucial part that they play in the health and wellbeing of pregnant women and in early childhood. They argue that it is only by fully understanding the requirements for micronutrients during pregnancy that we will be able to evaluate the potential use of dietary antioxidant supplements as a way of preventing pathological pregnancy outcomes. They advocate that future strategies focusing upon providing nutritional guidance

specifically to pregnant women will be pivotal in helping to ensure the optimal health of both mother and baby.

In Chapter 2, Victoria Hall Moran focuses upon nutrition in pregnant and breastfeeding adolescents. She highlights the specific nutritional needs of pregnant adolescents and examines the factors that influence their eating behaviours. She emphasises that overcoming the barriers in order to achieve improved nutrition in pregnancy among adolescents requires multidisciplinary collaborations of adolescent health care providers, academics, professional organisations, policy makers, industry and service users.

In Chapter 3, Kevin Hugill discusses the enormous challenges and debates that relate to optimising nutrition and nurture for preterm infants. His discussion ranges from emphasising nutritional and immunological aspects of feeding to issues related to support and relational considerations. This is a useful guide for practitioners in their endeavour to tailor the provision of infant nutrition to address the unique needs of preterm infants.

In Chapter 4, Sally Inch discusses the crucial components of breast milk for optimal infant feeding and then explores the risks of formula feeding babies and the ways in which breastfeeding has been fundamentally undermined by the multinational marketing of breast milk substitutes. These practices have contributed to a marginalisation of breastfeeding so that, in many communities across the world, it is no longer seen or experienced as the norm. The complex socio-cultural issues related to women's choices and decision making with regard to feeding method are illuminated.

In Chapter 5, Magda Sachs discusses the reasons why breastfeeding mothers weigh their babies. She draws upon her doctoral ethnographic research on the impact of routine weight monitoring on the feeding decisions of breastfeeding women in north-west England. Magda concludes that infant health and wellbeing could benefit from a change in the assumption that health is easily measured through physical weight gain, and that weight increases will happen in a linear, mechanical way. She refers to current policy recommendations centring upon building infant social and emotional capacity in order to ensure lifelong wellbeing and achievement and argues that an understanding of wellbeing wider than physical growth needs to be facilitated.

In Chapter 6, Nicola Crossland and Gill Thomson describe health professionals' views and experiences of working alongside breastfeeding peer supporters. They refer, in particular, to the notion of 'expertise' and discuss health professionals' attitudes towards the perceived 'expert' status of the peer supporters, together with the associated facilitators and tensions of integrating a breastfeeding peer support

service in practice. They argue that suitable opportunities need to be provided for co-working between health professionals and peer supporters to encourage relationship formation, reassurance and knowledge transfer to ensure that the service is sensitively and meaningfully integrated into practice.

In Chapter 7, Katherine Ebisch-Burton reports on an analysis of discourse on breastfeeding in public in Western Europe. She concludes that the visibility of breastfeeding in the public space remains a profoundly controversial matter, with much debate revolving around its undisguised or uncensored visibility; this discourse seeks to establish relationships of responsibility between the breastfeeding mother and those around her in the public space, with the primary responsibility assigned to the former.

In Chapter 8, Tyra Gross and Alex Kojo Anderson highlight the enormous challenges and controversies for women and health practitioners in balancing the risk and benefits of breastfeeding in the context of HIV. They refer to the complex and culturally specific influences upon HIV-infected mothers' infant feeding decisions. They recommend that researchers and clinicians alike evaluate the feasibility of such guidelines in their own contexts and that WHO should continue to review their guidelines using experience from the field to ensure that HIV-infected mothers can make the best feeding decisions for their infants.

In Chapter 9, Gill Rapley focuses upon baby-led weaning; she illustrates the ways in which doctrine and cultural beliefs have led to ways of 'managing' complementary feeding that ignore the developmental readiness and needs of babies. She highlights that the best way in which to meet the WHO recommendations for exclusive breastfeeding to six months is to adopt a developmental approach to the introduction of complementary foods.

In Chapter 10, Wendy Hunt and Alexandra McManus focus upon seafood and omega-3 fatty acids for maternal and child mental health with particular emphasis on the role of maternal, gestational and childhood nutrition. They provide a review of research into mental health disorders and the positive role of seafood and marine sourced long chain polyunsaturated omega-3 fatty acid consumption. They argue that inclusion of seafood within a healthy diet, in conjunction with current best practice treatments, has the potential to significantly impact the burden of disease attributable to mental health disorders.

Understandings of maternal and child nutrition need to take account of the embodied, emotional and social nature of eating and feeding, the ways in which women negotiate these in a range of cultural contexts *and* the macro-political influences upon women in relation to their dietary and infant feeding practices. This collection of chapters provides a basis for making improvements in maternal

and child nutrition through dietary recommendations, political activity and social policy. It presents a challenge to academics and health practitioners to become more strategically engaged with government agendas to bring about fundamental changes required to ensure that women have the information, resources and support to feed themselves and their infants in ways that optimise their health outcomes.

Reference

World Health Organization (WHO) (2003) *Global Strategy on Infant and Young Child Feeding*. WHO, Geneva.

Contributors

Nicola Crossland

Nicola Crossland is a research assistant in the Maternal and Infant Nutrition and Nurture Unit at the University of Central Lancashire. Prior to her work in infant feeding, Nicola's background was in biological sciences, particularly the neurobiology of mental health disorders. Nicola's research interests relate to the sociocultural aspects of women's experiences of infant feeding and early motherhood, maternal wellbeing, infant feeding and the family, and breastfeeding peer support.

Fiona Dykes

Fiona Dykes is Professor of Maternal and Infant Health and Director of the Maternal and Infant Nutrition and Nurture Unit (MAINN), School of Health, University of Central Lancashire. She is also Adjunct Professor at University of Western Sydney. Fiona has a particular interest in the global, socio-cultural and political influences upon infant and young child feeding practices. She is a member of the editorial board for *Maternal and Child Nutrition*, the Wiley-Blackwell published international journal (editorial office in MAINN) and a Fellow of the Higher Education Academy. Fiona has worked on WHO, UNICEF, European Union (EU Framework 6), Government (DH), NHS, National Institute for Health and Clinical Excellence (NICE), TrusTECH® Service Innovation (UK), National Institute for Health Research (NIHR), Wellcome Trust, British Council and Australian Research Council (ARC) funded projects.

Katherine Ebisch-Burton

Katherine Ebisch-Burton conducts research into discourses on breastfeeding in the UK and Germany, and has collaborated with members of the Maternal and Infant Nutrition and Nurture Unit at the University of Central Lancashire. She holds a DPhil in German literature and lives in Germany, where she works as an academic translator and editor and lectures at various universities.

Tyra Gross

Tyra Gross is a doctoral candidate in the Department of Health Promotion and Behaviour at the University of Georgia in the USA. Her research interests include maternal and child health disparities, with a particular focus on breastfeeding in African-American women. Tyra Gross was a fellow for both the American Public Health Association Maternal and Child Section and the Albert Schweitzer Fellow, New Orleans chapter in 2008–2009.

Victoria Hall Moran

Victoria Hall Moran is Associate Professor in Maternal and Child Nutrition in the Maternal and Infant Nutrition and Nurture Unit (MAINN) at the University of Central Lancashire, Preston. Her research has focused on micronutrient requirements, with a particular interest in zinc, and the nutritional needs of women during pregnancy and lactation. Recent work includes a review of dietary zinc requirements and associated health outcomes within the European Commission funded 'Eurreca' Network of Excellence; whose aim is to harmonise the approach to setting European micronutrient recommendations with specific focus on vulnerable populations such as infants, pregnant and lactating women, and the elderly. Victoria is a Fellow of the Higher Education Academy and Senior Editor of *Maternal & Child Nutrition* (a Wiley-Blackwell journal).

Kevin Hugill

Kevin Hugill is a senior lecturer and neonatal courses lead at the University of Central Lancashire in Preston. His nursing background is predominantly in neonatal care and he has worked in a number of different neonatal units and higher education institutions in England. His PhD research was concerned with the emotion work of fathers after their baby's admission to a neonatal unit. He has a particular interest in preterm infant feeding and its connections with nurturance. His present research activity focuses upon parent–infant closeness in neonatal units. In addition he has served as a member of Data Monitoring Committees for randomised controlled trials and more recently a trial steering committee concerning neonatal skin care.

Wendy Hunt

Doctor Wendy Hunt is the Senior Food Scientist at the Centre of Excellence for Science Seafood and Health, Curtin University. She holds a Bachelor of Science (Health Science), an advanced Master of Business Administration (Marketing) and a Doctor of Philosophy (Food Science) and is a professional member of The

Australian Institute of Food Science and Technology, The Australian Society of Microbiology and The Australian Institute of Management. Wendy has expertise in food science and food microbiology across a range of industry sectors and specialises in science communication. Her research interests have centred on new product development, food safety and the importance of seafood to human health.

Sally Inch

Since 1997 Sally Inch has been employed by the Oxford University Hospitals Trust as their Infant Feeding Specialist and as Baby Friendly Initiative (BFI) and Human Milk Bank coordinator. As the Infant Feeding Specialist she runs a hospital-based drop-in breastfeeding clinic. As BFI coordinator Sally led the three midwife-led units in the Trust to obtain the Global Baby Friendly award in 2001. For the last 20 years Sally has written widely on aspects of birth and breastfeeding, and was both a contributor to and Editor of *Successful Breastfeeding*, the RCM Handbook, now in its third edition (Harcourt 2001) and published in 11 languages. She also authored the chapter on Infant Feeding in the last three editions of *Myles Textbook for Midwives*. From 2001–2003 Sally worked with the University of Coventry (on a Department of Health funded multi-centred randomised controlled trial – the Best Start Breastfeeding Project), where she is now a visiting Research Fellow.

Alex Kojo Anderson

Alex Kojo Anderson is an Associate Professor of Foods and Nutrition at the University of Georgia in the USA, with a research interest in maternal and child nutrition, and a particular interest in health promotion related to breastfeeding, child feeding and maternal health. He also teaches courses on Optimal Nutrition for the Life Span, Public Health Dietetics, and Nutrition Epidemiology.

Alexandra McManus

Professor Alexandra McManus is Director of Centre of Excellence for Science Seafood and Health, Curtin University. She is also Deputy Director of the International Institute Agrifood Security and Professor with the Curtin Health Innovation Research Institute. Alexandra has a Bachelor of Science (Health Promotion/Human Biology), Master of Public Health and a Doctor of Philosophy (Sports Medicine). Additionally, she holds several Executive Committee and Board Memberships including those for Research Australia and Kidsafe WA. Alexandra's research expertise encompasses many aspects of public health and sports medicine with specific emphasis on the management and evaluation of health interventions. Alexandra's commitment to public health is demonstrated in

her research outputs of: 133 national and international conference presentations, 54 peer reviewed journal articles, 48 major research reports, 47 invited presentations, 15 education and training resources and 12 book chapters/online training courses between 2000 and 2012.

Hiten D. Mistry

Hiten D. Mistry is a Postdoctoral Associate in the Division of Women's Health, Women's Health Academic Centre, KHP, King's College London, UK. Dr. Mistry received a first class BSc (Hons) in Biochemistry with Industrial Experience from University of Manchester Institute of Science and Technology (UMIST). He then went on to complete a PhD entitled 'Selenium, selenoproteins and factors which might interact with them relating to oxidative stress, in normal and pre-eclamptic pregnancies'. Dr. Mistry's primary research interests are focussed on the influences of antioxidant micronutrients in relation to the pathophysiology of the hypertensive diseases of pregnancy and intrauterine growth restriction. He has published widely in the field, including peer reviewed scientific articles, expert reviews, book chapters and abstracts.

Gill Rapley

Over a 35-year career Gill Rapley has practised as a health visitor, midwife and voluntary breastfeeding counsellor, and has been a certified lactation consultant (IBCLC). Latterly, she worked for 14 years with the UNICEF UK Baby Friendly Initiative, while pursuing her interest in infant development as it relates to infant feeding as the basis of a Masters degree. She is currently studying further the process and means by which infants are introduced to solid foods, with the aim of gaining a PhD. She is credited with pioneering the concept of 'baby-led weaning', although she does not claim to have invented it – rather, with the help of her co-author, Tracey Murkett, she has 'brought it out of the closet'.

Magda Sachs

Magda Sachs qualified as a volunteer breastfeeding counsellor in 1988, and is currently a Breastfeeding Supporter with The Breastfeeding Network. Magda was awarded her PhD in 2005: this examined the impact of routine weighing of babies on breastfeeding mothers' feeding decisions. In 2008 she joined the Growth Chart Working Group convened by the Royal College of Paediatrics and Child Health, which developed the UK–World Health Organization 0–4 growth charts. Magda conducted parent focus groups and staff consultation workshops which informed the design of these charts, wording of chart instructions, and parental information

for the Personal Child Health Record (red book). She took up the position of public health manager with NHS Salford in 2009, and continues in that capacity at Salford City Council.

Gill Thomson

Gill Thomson is currently working as a Research Fellow within the Maternal and Infant Nutrition and Nurture Unit (MAINN), University of Central Lancashire (UCLan). Gill is a social scientist with a psychology academic background and has worked within the public, private and voluntary sectors. Since completing her Masters in the Psychology of Child Development in 1998, she has been employed on a number of consultation projects, the majority of which involved engaging with vulnerable population groups. Following successful completion of her PhD at the end of 2007 she has been employed by UCLan and has been involved in a number of research/evaluation based projects to explore biopsychosocial influences and experiences towards maternity services and infant feeding issues. Gill's research interests relate to maternal wellbeing across the perinatal period. She also has a particular specialism in the interpretive phenomenological based research.

Paula J. Williams

Paula J. Williams studied for her PhD in reproductive immunology at the University of Newcastle working under the supervision of Professor Stephen Robson, Dr Judith Bulmer and Dr Roger Searle. After completing her PhD in 2005 she continued her research moving into the field of the role of nutrition in successful pregnancy working at the University of Nottingham. She has published a number of papers looking at the novel roles of folic acid in placental development and is interested in the role of nutrition in preventing the obstetric disorder pre-eclampsia.





CHAPTER 1

Antioxidant micronutrients in pregnancy and early childhood

Paula J. Williams and Hiten D. Mistry

Introduction

Pregnancy is a period of increased metabolic demands due to the changes occurring within the woman's physiology and the requirements of her growing fetus. During this time, insufficient stores or intake of vitamins or minerals, referred to as micronutrients, can have adverse effects on the pregnant mother, including complications such as anaemia, hypertensive disorders of pregnancy, complications of labour and even death. The fetus can also be affected, leading to stillbirth, preterm delivery, fetal growth restriction, congenital malformations, abnormal organ development, childhood disorders and even effects that do not become apparent until later in life, including obesity.

The essential nature of micronutrients has been recognised through the identification of clinical conditions associated with severe deficiencies of particular micronutrients, and through subsequent animal experiments. While the importance of deficiencies of iodine and folate during pregnancy is now well recognised, the role of many other micronutrient deficiencies during this crucial phase has only more recently become appreciated. Gaining an understanding of the importance of micronutrients is complicated by the finding that micronutrient deficiencies often coexist, and that deficiencies of specific vitamins and minerals vary by stage of life, season, year, ethnic group and economic status, and among individuals within the same community. Variability in micronutrient status can be attributed to consumption of diets with differing content and bioavailability of micronutrients and differing losses and requirements for micronutrients at different stages, with enhanced levels being required to support pregnancy. It is also important to note that micronutrients can have either positive or negative interactions, and that these interactions may not be the same for all possible consequences of deficiencies.

The possible occurrence of multiple micronutrient deficiencies in pregnant women, particularly in developing countries, and the presence of numerous confounding factors (Ramakrishnan *et al*., 1999), have meant that observational studies related to micronutrients and pregnancy outcomes are of only limited value. The best causal evidence for micronutrients and adverse outcomes of pregnancy comes from randomised controlled trials, and to date these have largely been carried out for individual vitamins or minerals. Although these results can be very informative, it is also possible that correction of a single micronutrient deficiency, when one or more other limiting deficiencies are present, may not demonstrate the effects of that micronutrient. There are also issues surrounding interpretation of results when correction of multiple micronutrient deficiencies has been demonstrated in pregnancy whilst continuing to consume a diet that is inadequate in macronutrients, such as calories and protein, therefore leading to poor outcome results, such as fetal growth restriction.

What are antioxidants?

Antioxidants are substances that either have inherent antioxidant activity or are part of antioxidant enzyme systems involved in the disposal of potentially harmful free radicals. Oxidative stress is defined as a disturbance in the balance between antioxidants and (pro)oxidants (free radical species) in favour of the latter. Oxidative stress occurs when levels of free radicals exceed the capacity of antioxidant defences due to an inadequate dietary intake of antioxidants or by an increase of cellular oxidants, which can be defined as substances with one or more unpaired electrons (Davidge, 1998). Free radicals take the form of reactive oxygen species (ROS, such as oxygen ions and peroxides), reactive nitrogen species (RNS) and reactive chlorine species (RCS) and are produced during normal metabolism. Physiological ROS/RNS/RCS production is, in fact, necessary for proper health; for example, it helps the body's immune system to kill microorganisms. Optimal health is therefore a balance between the two: antioxidants serve to regulate the levels of free radicals, permitting them to perform useful biological functions without too much damage (Halliwell and Gutteridge, 2006).

Thus antioxidants are essential to maintain homeostasis. An imbalance in the equilibrium between anti- and pro-oxidants can result in oxidative stress, which is a key pathophysiological mechanism involved in a number of diseases (Agarwal, 2008). Harmful effects of ROS can be bought about through their ability to oxidise DNA, lipids and proteins, causing cellular injury and cell death. Many antioxidants are obtained from dietary sources, including vitamins C and E and beta-carotene and a number of dietary micronutrients are essential co-factors of

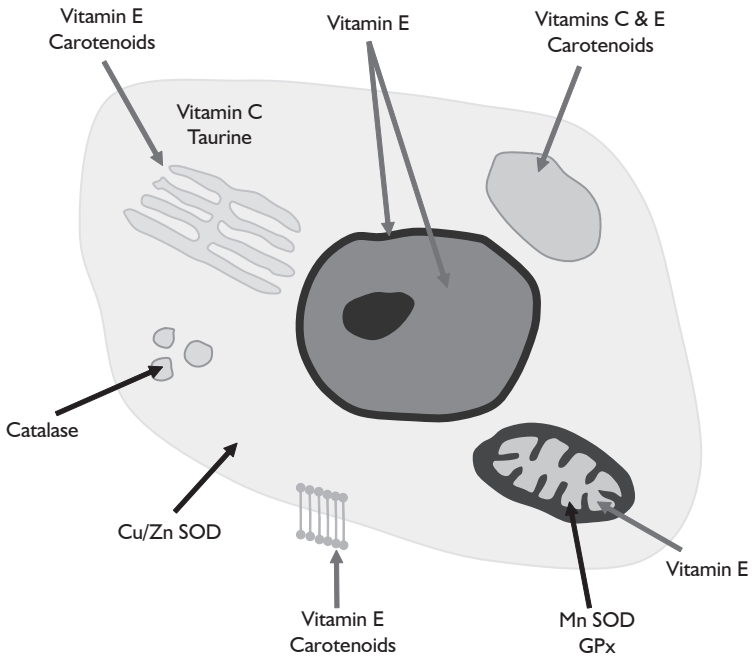

Figure 1.1 Endogenous (black) and exogenous (grey) sources of antioxidants and their places of action within the cell.

antioxidant enzymes; these include selenium (which is a co-factor for glutathione peroxidases; GPxs) and copper, zinc and manganese (which are co-factors for superoxide dismutase; Cu/Zn/Mg-SOD). Zinc is also an essential co-factor for metallothionein and copper is needed for the enzyme ceruloplasmin. Figure 1.1 shows the endogenous and exogenous sources of antioxidants and their places of action within the cell.

How antioxidants work: prevention, inception and repair

ROS are oxidants, being atoms of oxygen that can oxidise a substrate; they are reduced during this reaction. They are able to damage several key cellular components such as membrane lipids, nucleic acids, carbohydrates and proteins, thereby severely disturbing major cellular and organic physiological functions. This type of damage occurs when the host's antioxidants are quantitatively and/or qualitatively unable to counteract the production and effects of oxidants themselves. The antioxidant defence system provides protection against oxidative reactions and is organised at the levels of prevention, interception and repair.

Prevention comprises strategies that avoid the generation of ROS, RNS and RCS, for example diminished light exposure to lower photo-oxidative reactions or caloric restriction to decrease side reactions in the sequence of the respiratory chain. Proteins that tightly bind metal ions which otherwise catalyse pro-oxidant reactions are also involved in prevention.

Interception involves a network of antioxidant enzymes (i.e. exogenous and endogenous molecules) that are available to scavenge ROS, RNS and RCS once they are generated. Superoxide dismutase, catalase, glutathione and glutathione-dependent enzymes, as well as sulphur- or selenium-containing proteins and low molecular weight compounds, are produced for defence. Small molecular weight compounds with antioxidant properties such as ascorbate (vitamin C), alpha-tocopherol (vitamin E) and carotenoids, instead, are provided through the diet, particularly fruit and vegetables, and are therefore called antioxidant micronutrients. These dietary factors are an essential component of the antioxidant defence network; an inadequate supply within the diet has been epidemiologically correlated with increased risk of a number of oxidative stress related diseases.

Repair is the domain of enzymes, which recognise oxidatively damaged molecules and initiate repair, degradation or removal. The interplay of all processes and compounds in the network provides optimal protection.

Antioxidant micronutrients

It is often difficult to correlate a dietary deficiency with clinical symptoms that may arise, because many vitamins and minerals have multiple roles in metabolism (Stahl *et al*., 2002). For example, vitamin metabolites exhibit both antioxidant and pro-oxidative activity (Yeum and Russell, 2002). Further illustrating this is the observation that in general, at low ascorbate concentrations ascorbate is prone to be a pro-oxidant, yet at high concentrations it will tend to be an antioxidant.

Antioxidant micronutrients are able to exert non-antioxidant biological activities in addition to their free radical-scavenging capacity. For example, vitamin C, due to its participation in hydroxylation reactions and involvement in collagen synthesis, has been suggested to be important in the prevention of pressure sores in the elderly (Selvaag *et al*., 2002), and vitamin E exerts regulation on cell proliferation and shows a beneficial effect in improving glucose transport and insulin sensitivity (Yu *et al*., 1998).

The fact that there are a multitude of oxidants and antioxidants which have overlapping reactivity renders a biochemically rigorous assessment of the implications of oxidative stress difficult. Moreover, helpful as epidemiological studies can be, sometimes there is a confounding of associations with cause–

effect relationships, leading to erroneous conclusions. The results of observational studies, be these ecological or based on comparisons between individuals, might therefore be difficult to interpret because there is usually an abundance of possible confounding factors, such as diet, lifestyle and physical activity. Inter-individual variations should also be taken into account; similar mean intakes of vitamin E, for instance, do not relate to similar mean plasma alpha-tocopherol concentrations (Stahl *et al*., 2002). Geographical issues may also be extremely relevant, as the consumption and processing of antioxidant-rich foods vary considerably from country to country (de Lorgeril *et al*., 2002).

Even when attempts are made to carefully and rigorously control as many variables as possible in a randomised controlled trial, a statistically significant relationship between two parameters (such as a biological compound and a clinical marker of disease) does not always allow a cause–effect relationship to be elucidated. There may be several explanations for the conflicting results obtained in such trials, such as inappropriate design, lack of control of confounding factors, insufficient treatment duration, type of antioxidant used (synthetic versus natural), and the absence of evaluation of markers of oxidative stress as intermediate end-points. With respect to this latter point, it is essential to measure biomarkers of lipid peroxidation or DNA oxidation in nutritional studies (Halliwell, 2000; Mayne 2003) to confirm that antioxidant vitamins are materially able to decrease disease-related oxidative damage (McCall and Frei, 1999).

Oxidative stress and pregnancy

In the non-pregnant state endometrial stromal cells produce ROS as part of normal cellular metabolism. Antioxidant protection is provided by expression of both manganese superoxide dismutase (Mn-SOD) and copper/zinc superoxide dismutase (Cu/Zn-SOD). During formation of the maternal–fetal boundary and consequently fetal growth, O_2 tension, a function of uterine blood flow, plays an important role. Increased lipid peroxidation is a normal phenomenon of pregnancy (Hubel, 1999). The early embryo, however, is particularly vulnerable to the damaging effects that ROS can have on its DNA and proteins and therefore it is imperative that adequate antioxidant protection is provided. This protection is afforded by the embryonic supply of enzymatic antioxidant systems including Cu/Zn and Mn-SOD, catalase, GPx and peroxiredoxins (Donnay and Knoops, 2007), as well as non-enzymatic systems including vitamin E and beta-carotene (Yu, 1994), which all serve to directly protect from ROS-mediated damage (Guerin et al., 2001). Placental expression of all the major antioxidant systems, including Mn and Cu/Zn-SOD, catalase, GPx and vitamins C and E, further serves to provide

long-term protection from the damaging effects of locally produced and circulating ROS (Myatt and Cui, 2004).

Oxidative stress is increased as a part of normal pregnancy due to the increase in both placental and maternal metabolism. This increased metabolism is essential for the continued growth and development of the fetus, but it also leads to increased oxidative stress, which is associated with an increase in lipid peroxidation (Myatt and Cui, 2004). Early stages of placental (and embryonic) development take place in a hypoxic environment relative to the uterus (Red-Horse *et al*., 2004); thus the placenta limits rather than facilitates O_2 supply to the fetus during organogenesis (Jauniaux *et al*., 2003). The onset of uteroplacental blood flow at around 10 weeks of pregnancy into the intervillous space further adds to the generation of oxidative stress during normal pregnancy when the cytotrophoblast cells of the placenta come into direct contact with maternal blood. This causes the mean local O_2 pressure to rise as high as 90–100 mm Hg (Jauniaux *et al*., 2000).

Although often considered to be harmful, the generation of all of these ROS is important in regulating placental function, including trophoblast differentiation, proliferation and vascular reactivity (Figure 1.2) (Harris *et al*., 2008). In addition to their effects on the trophoblast cells of the placenta, ROS are important vasoactive factors which are essential for the vascular remodelling that occurs during placentation. RCS are also generated by macrophages within the placenta and decidua. Decidual macrophages are important in regulating trophoblast cell apoptosis, which is essential for the successful invasion and establishment of the placenta (Abrahams *et al*., 2004). Decidual macrophages are also important in

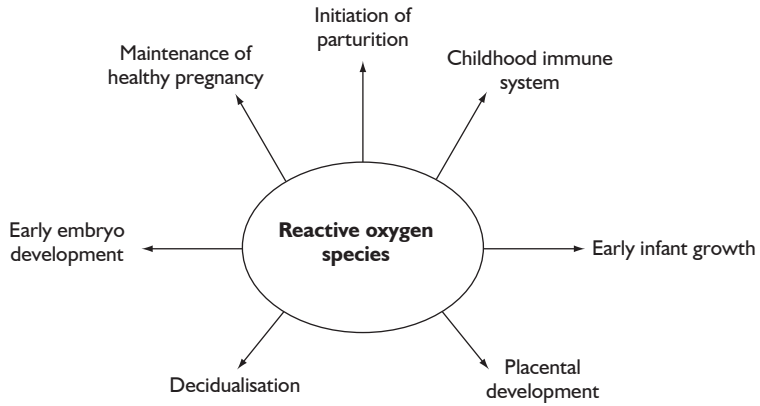

Figure 1.2 The role of reactive oxygen species in normal pregnancy and early childhood.

protecting the developing fetus from intrauterine infection via the production of oxide ions and the proinflammatory cytokine tumour necrosis factor alpha (Singh *et al*., 2005). Increased expression of antioxidant enzymes has also been shown in sheep placentomes during early pregnancy, again indicating that this is an important protective mechanism against oxidative stress-mediated damage during placental development and early fetal growth, reinforcing the critical importance of early pregnancy for both maternal and fetal health (Garrel *et al*., 2010).

The placenta is thus placed in the middle of the materno-fetal oxygen gradient and is exposed to major changes in O_2 concentration from conception to delivery (Jauniaux *et al*., 2003). It has been suggested that it has a real protective role against the damaging effects of ROS (Lista *et al*., 2010). Antioxidant regulation of ROS is crucial for successful embryogenesis and placentation to occur, as it has been shown that ROS-induced oxidative stress can alter embryonic development (Dennery, 2007).

Furthermore, by both direct and indirect mechanisms, antioxidants are able to modulate aspects of the immune system and the cytokine-mediated response to pregnancy. Under normal conditions, the placental antioxidant defence systems, which have the capacity to induce conversion of ROS to water and molecular oxygen, prevent ROS overproduction as a consequence of increased metabolic activity of placental mitochondria throughout gestation.

In summary, as described above, a level of controlled oxidative stress in pregnancy, particularly during placental development, is required. Antioxidants provide regulation to ensure that the levels of oxidative stress are not raised to harmful levels.

Oxidative stress and parturition

Parturition is an inflammatory event. During term pregnancy, a massive influx of neutrophils and monocytes into the uterine myometrium and cervix is thought to be essential for the stimulation of labour (Golightly *et al*., 2007). An increased expression of cervical and myometrial cytokines triggers leucocyte migration at labour and these pro-inflammatory cytokines also serve to trigger myometrial contractility and cervical ripening (Romero *et al*., 2006).

The increase in ROS concentrations around parturition seems to be involved in prostaglandin and cytokine release. Thus labour can be considered an event during which a positive feedback and a synergism of action occur between ROS and mediators of inflammation (Jenkin and Young, 2004). Therefore the increase in ROS generation during labour is a predictable event, because ROS levels are known to increase markedly, especially in conditions of high metabolic demand.

It has also been suggested that the increased expression of Mn-SOD mRNA by fetal membranes at term labour may represent a fetal mechanism of antioxidant defence during this inflammatory process (Than *et al*., 2009). Furthermore, the marked increase in enzymatic antioxidants in the last phase of pregnancy has been suggested to serve as preparation for life in an environment rich in oxygen (O'Donovan and Fernandes, 2004). There is some controversy in studies investigating oxidative stress in women delivering vaginally versus caesarean section, with some studies reporting higher oxidative stress parameters in caesarean section in both the maternal and fetal circulation (Paamoni-Keren *et al*., 2007; Nabhan *et al*., 2009; Mutlu *et al*., 2011), while others show no differences (Mehmetoglu *et al*., 2002). Although such studies indicate that both the mother and her baby may be exposed to increased levels of oxidative stress during caesarean section, the consequences of this exposure on their health has not been examined in detail.

Antioxidants and asthma in early childhood

In the field of paediatrics, allergic disease represents the largest category of chronic disease and its prevalence has increased since the mid-20th century (Jonsson, 2010). Several recent reviews have suggested that maternal diet during pregnancy is one of the main contributing factors that may influence specific immune maturation events, allergic sensitisation and incidence of childhood allergic disease (Ramankrishnan and Huffman, 2008; Allen *et al*., 2009; Ramakrishnan *et al*., 2009). Airway development occurs predominantly antenatally, commencing approximately 24 days after fertilisation with the pre-acinar airway branching pattern being completed by about 17 weeks' gestation (Devereux, 2007).

There is growing recognition that, in addition to genetic factors, environmental elements during pregnancy and the first years of life are also implicated in alterations to the likelihood of disease development (Bhutta *et al*., 2008), and particularly strong associations have been found to exist between nutritional adequacy, immune maturation and the onset of paediatric allergies (Gera *et al*., 2009; Eilander *et al*., 2010). More specifically, suboptimal fetal nutrient status antenatally adversely affects respiratory epithelial and mesenchymal development, resulting in suboptimal early-life airway function, which is associated with an increased risk of wheezing and asthma in later childhood (Menon *et al*., 2007).

In 1994 Seaton *et al*. hypothesised that the increased prevalence of asthma had resulted from increasing population susceptibility rather than the air becoming more toxic or allergenic (Seaton *et al*., 1994). This hypothesis arose from the parallel changes in the UK diet, particularly by them becoming more deficient in

antioxidants, potentially resulting in a decline in lung antioxidant defences and thus increased oxidant-induced airway damage, airway inflammation and asthma (Seaton *et al*., 1994). Associations between several antioxidant micronutrients during pregnancy with asthma, wheezing and eczema during early childhood have been shown in a recent systematic review (Patelarou *et al*., 2011). In addition, studies have revealed that consuming a Mediterranean diet, which has a high antioxidant content (fruit, vegetables, legumes, nuts and whole-grain cereals) has been linked with a reduced likelihood of asthma, wheezing and allergic rhinitis (Bjorksten, 2008).

Antioxidant micronutrients and outcomes in pregnancy and childhood

Selenium

Selenium was first discovered in 1817 by Jöns Jacob Berzelius when investigating the chemicals responsible for outbreaks of ill health among workers in a Swedish sulphuric acid plant, which had switched from expensive, imported sulphur to a local product (Oldfield, 1987). The local product contained a contaminant which he named Selēnē, after the Greek goddess of the Moon (McKenzie *et al*., 1998). In 1957, Klaus Schwarz proved that selenium is an essential nutrient necessary for both normal growth and reproduction through experiments demonstrating that minute amounts of selenium were protective against a form of liver necrosis in laboratory rats fed diets containing torula yeast as a protein source (Schwarz and Foltz, 1957). Today, selenium is recognised as an essential trace element of importance to human biology and health, and supplementation is now recommended as part of public health policy in geographical areas with severe selenium deficiency in soil.

Plant foods are the major dietary sources of selenium in most countries (Combs, 2001). Surveys suggest that wheat is the most efficient selenium accumulator of the common cereals, and is one of the most important selenium sources for humans (Lyons *et al*., 2003). The content in food depends on the selenium content of the soil where plants are grown or animals are raised (Mistry *et al*., 2012a). There appears to be no homeostatic control of selenium absorption, which is unusual in contrast, for example, to the complex regulation of iodine absorption (Kohrle, 2005). Selenium is stored in the tissues in varying density: 30% in the liver, 30% in muscle, 15% in the kidney, 10% in the plasma and the remaining 15% throughout other organs (Levander, 1987). Concentrations of free selenium are greatest in the renal cortex and pituitary gland, followed by the thyroid gland, adrenals, testes, ovaries, liver, spleen and cerebral cortex (Drasch *et al*., 2000). The main foods

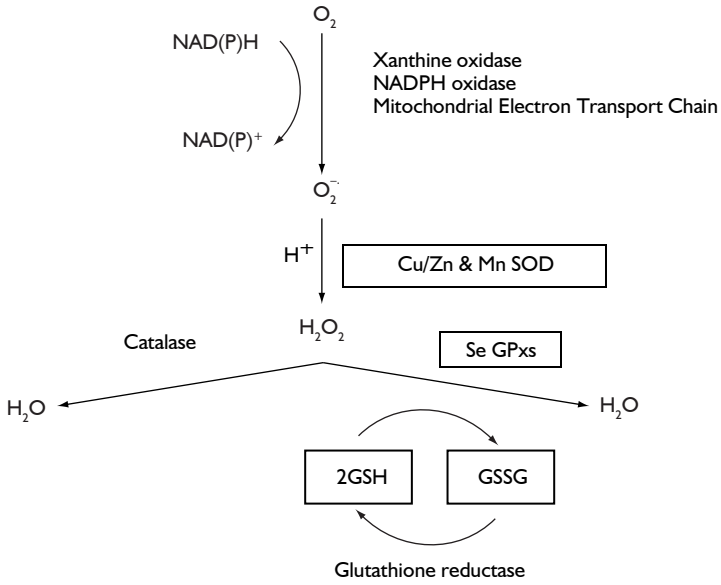

Figure 1.3 Major pathways of reactive oxygen species generation and metabolism. Superoxide can be generated by specialised enzymes, such as the xanthine or NADPH oxidases, or as a byproduct of cellular metabolism, particularly the mitochondrial electron transport chain. Superoxide dismutase (SOD) (both Cu/Zn and Mn SOD) then converts the superoxide to hydrogen peroxide (H_2O_2), which has to be rapidly removed from the system. This is generally achieved by catalase or peroxidases, such as the selenium-dependent glutathione peroxidases (GPxs) which use reduced glutathione (GSH) as the electron donor (adapted from Mistry and Williams, 2011, with permission).

that make a substantial contribution to selenium intake in northern Europe are meat, poultry, and fish (a total of about 36% in the UK) (Ministry of Agriculture, Fisheries and Food, 1997).

Of particular importance to pregnancy are the six antioxidant GPxs which play a pivotal role in reducing hydrogen peroxide (H_2O_2) and lipid peroxides to harmless products (water and alcohols; Figure 1.3), thereby dampening the propagation of damaging ROS (Brigelius-Flohe *et al*., 2003). This pathway may also offer protection against development of several chronic diseases in which oxidative damage has been implicated, including atherosclerosis and certain cancers (Rayman, 2002; Brigelius-Flohe, 2008).

The optimal range of selenium intake to ensure biological benefit appears to be narrow and has still not been determined with certainty. Assessments of requirements, adequacy and intakes of selenium have been reviewed previously in detail (Thomson, 2004; Rayman, 2008) and summarised in Table 1.1. The USA recommended dietary allowance/UK reference nutrient intake (RDA/RNI) values have been determined from the intake believed necessary to maximise the activity of the antioxidant GPx in plasma, whereas the NR is based on selenium intake needed to achieve two-thirds of maximum activity of erythrocyte GPx (Thomson, 2004).

Normal pregnancy

During normal pregnancy, the selenium requirement is increased as a result of demands from the growing fetus (Mistry *et al*., 2012a) and both inorganic and organic forms of selenium cross the placenta in humans and experimental animals (Shennan, 1988; Nandakumaran *et al*., 2003). The RDA of selenium in pregnancy in the USA, calculated based on a fetal deposition of 4 μg/day throughout pregnancy, is 60 μg/day (Institute of Medicine, 2000). It has been observed that infants on average have lower selenium concentrations compared to the mother (maternal selenium: 58.4 μg/L; umbilical cord selenium: 42.1 μg/L) (Gathwala *et al*., 2000, Mistry *et al*., 2008), which is expected, as selenium is transported via the placenta across a concentration gradient via an anion exchange pathway, shared with sulphate (Shennan, 1988).

Numerous reports implicate selenium deficiency in several reproductive and obstetric complications including male and female fertility, miscarriage, pre-eclampsia, fetal growth restriction, preterm labour, gestational diabetes and obstetric cholestasis (intrahepatic cholestasis of pregnancy) (Mariath *et al*., 2011; Mistry *et al*., 2012a). Recurrent early pregnancy loss has been associated with reduced serum selenium concentrations compared to healthy controls in two observational studies from the UK (Barrington *et al*., 1997) and Turkey (Kocak *et al*., 1999). It has therefore been suggested that reduced selenium concentration results in reduced GPx activity, culminating in reduced antioxidant protection of biological membranes and DNA during the early stages of embryonic development (Barrington *et al*., 1997; Zachara *et al*., 2001). Although speculative and requiring larger placebo-controlled randomised trials, women with recurrent early pregnancy loss may benefit from optimisation of selenium status.

Table 1.1 Requirement of micronutrient intakes for selenium, copper, zinc, manganese, vitamin C, vitamin E and folate.

		Selenium (μg/d)	Copper (μg/d)	Zinc (mg/d)	Manganese (mg/d)	Vitamin C (mg/d)	Vitamin E (μg/d)	Folate (μg/d)
RDA	Male adult	55	900	11	2.3	90	15	400
	Female adult	55	900	8	1.8	75	15	400
	Pregnancy	60	1,000	11	2	85	15	600–800
	Infants 0–6 months	15	200	2	0.003	40	4	65
	Infants 7 months–3 years old	20	340	3	1.2	15	6	150
	Children 4–8 years old	30	440	5	1.5	25	7	200
	Upper limit	400	10,000	40	11	2,000	1,000	1,000
RNI	Male adult	75	1,200	9.5	1.4	40	–	400
	Female adult	60	1,200	7	1.4	40	–	400
	Pregnancy	75	1,500	7	–	50	–	600
	Infants 0–6 months	10	200	4	–	25	–	50
	Infants 7 months–3 years old	15	400	5	–	30	–	70
	Children 4–8 years old	20	600	6.5	–	30	–	100
NR	Male adult	40	1,350	1.4	–	–	–	400
	Female adult	30	1,350	1	–	–	–	400

Table 1.1 (*continued*)

	Selenium (μg/d)	Copper (μg/d)	Zinc (mg/d)	Manganese (mg/d)	Vitamin C (mg/d)	Vitamin E (μg/d)	Folate (μg/d)
Pregnancy	–	1,150	2	–	–	–	800
Infants 0–6 months	9	370	4	–	–	–	–
Infants 7 months–3 years old	20	560	5	–	–	–	–
Children 4–8 years old	25	750	5	–	–	–	–

RDA: Recommended Dietary Allowance, USA; RNI: Reference Nutrient Intakes, UK and NR: Normative Requirement Estimate, World Health Organization.
Values taken from Institute of Medicine (2000, 2001), Department of Health (1991) and WHO/FAO/IAEA (1996).
– indicates no recommended values at present.

Pre-eclampsia

Recently, retrospective studies have demonstrated associations between low serum selenium concentrations and reduced antioxidant function of the associated antioxidant GPx enzymes in women with pre-eclampsia (defined as de novo proteinuric hypertension) (Mistry *et al*., 2008, 2010; Maleki *et al*., 2011; Katz *et al*., 2012). It has been suggested that adequate selenium status is important for antioxidant defence and may be a potential factor in women at risk of pre-eclampsia; this hypothesis has been further supported by the reduced expression and activities of GPx found in maternal, fetal and placental samples taken from 25 pre-eclamptic pregnancies when compared to 27 normal controls in our recent cross-sectional retrospective study (Mistry *et al*., 2008). Dawson *et al*. also completed a retrospective study in the USA and reported lower amniotic fluid selenium concentrations in 29 pre-eclamptics delivering between 33 and 36 weeks' gestation compared to 48 gestation-matched controls (10 ± 1 vs. 7 ± 0.7 μg/L respectively) (Dawson *et al*., 1999). A study of data from around the world found that increasing serum/plasma selenium concentration correlated with a reduction in pre-eclampsia incidence; the authors also noted that countries with serum/plasma selenium concentration ≥ 95 μg/L (selenium sufficient) had a significant reduction in incidence (Vanderlelie and Perkins, 2011). This study also highlighted that the reduction in pre-eclampsia incidence coincided with an increase in serum/plasma selenium concentrations following government interventions to increase selenium intakes in countries such as New Zealand and Finland (Vanderlelie and Perkins, 2011), contributing to the evidence that supplementation of selenium may be beneficial in reducing oxidative stress in women at risk of pre-eclampsia.

To date there have been a limited number of small placebo-controlled randomised controlled trials on selenium supplementation, reporting lower rates of pre-eclampsia and/or pregnancy-induced hypertension in the supplemented groups (Han and Zhou, 1994; Rumiris *et al*., 2006 Tara *et al*., 2010a). It must be noted that none of these studies adequately addressed the role of supplementation on the incidence of pre-eclampsia. Currently the 'Selenium in Pregnancy Intervention Trial' (SPRINT) is under way in the UK, run jointly by the Universities of Surrey and Oxford. This is a small randomised controlled trial of selenium supplementation (60 μg a day). While it is not powered to demonstrate clinical benefit, it will provide insight into the impact of selenium supplements on laboratory measurements of circulating factors that are relevant to the development of pre-eclampsia. If the study is successful a much larger multicentre trial will be needed to further explore clinical benefit.

Preterm labour

Among the few studies to have investigated selenium and preterm labour (delivery < 37 weeks' gestation), Dobrzynski *et al*. reported lower maternal selenium concentrations and reduced maternal and cord plasma GPx activities in 46 women who delivered preterm compared to 42 women delivering at term (Dobrzynski *et al*., 1998). In addition, a potential association with selenium and preterm premature (pre-labour) rupture of membranes has been highlighted through a small prospective double-blind placebo-controlled randomised controlled trial in which 166 primigravid pregnant women were randomised in the first trimester of pregnancy to receive 100 μg/day selenium or placebo until delivery (Tara *et al*., 2010b). The supplemented group demonstrated a significant increase in the mean serum selenium concentration and a reduction in the incidence of preterm premature (pre-labour) rupture of membranes (Tara *et al*., 2010b). Once again, reduction in oxidative stress as a result of increased selenium concentrations is likely to play an important role.

Fetal growth restriction

Fetal growth restriction or delivery of a small-for-gestational-age infant is defined as an individualised birth weight ratio below the 10th percentile (Cetin *et al*., 2004). Correlations between selenium concentrations and fetal growth restriction are inconsistent. A retrospective study reported low placental selenium concentrations in 49 mothers affected by fetal growth restriction, compared to 36 healthy normal birth weight controls (Klapec *et al*., 2008), whereas others have reported higher (Osada *et al*., 2002; Zadrozna *et al*., 2009) or unchanged concentrations (Llanos and Ronco, 2009). Another retrospective study also demonstrated that in 81 small-for-gestational-age babies, infant plasma selenium concentrations were significantly lower compared to controls (Strambi *et al*., 2004). A retrospective study on an adolescent cohort (Baker *et al*., 2009) found lower maternal plasma selenium concentrations in 28 mothers who delivered small-for-gestational-age babies compared to 143 healthy controls (Mistry *et al*., 2012a). Further studies are warranted to fully investigate the potential link between selenium deficiency and fetal growth restriction.

Obstetric cholestasis

Selenium has also been associated with obstetric cholestasis (also known as intrahepatic cholestasis of pregnancy) a serious complication of pregnancy which affects approximately 4,500 women per year in the UK (Gurung *et al*., 2009). Selenium was first linked with obstetric cholestasis in 1987 when Kauppila *et al*.

demonstrated that serum selenium concentrations were significantly lower in 12 Finnish women with obstetric cholestasis when compared to 12 normal pregnancies during the last trimester and postpartum (Kauppila *et al*., 1987). Furthermore, they also showed GPx activities to be decreased, showing a significant positive correlation with selenium concentration (Kauppila *et al*., 1987). Thus it has been hypothesised that inadequate antioxidant protection may lead to hepatocyte oxidative damage and reduce excretion of bile (Akerboom *et al*., 1984). These initial results have been confirmed and extended in a study of 21 women with obstetric cholestasis in Chile, also showing that the decrease in prevalence of obstetric cholestasis in Chile during the last decade coincided with an increase in plasma selenium concentrations (Reyes *et al*., 2000).

Gestational diabetes mellitus

Gestational diabetes mellitus, defined as a deficient insulin supply relative to the increased demands that are characteristic of pregnancy, is an increasing problem with an incidence of 7.6% (Lawrence *et al*., 2010). Animal studies have highlighted a link between selenium and glucose metabolism (McNeill *et al*., 1991; Becker *et al*., 1996). Several studies from China, Kuwait, Turkey and the USA have shown a decrease in maternal plasma selenium concentrations in women with gestational diabetes mellitus (Tan *et al*., 2001; Al-Saleh *et al*., 2004; Hawkes *et al*., 2004; Kilinc *et al*., 2008). Bo *et al*. (2005) completed a retrospective study investigating selenium intakes through dietary questionnaires in 504 pregnant women (210 with hyperglycaemia and 294 healthy controls) as well as measuring serum concentrations in a second cohort (71 hyperglycaemic and 123 controls). A lower dietary intake of selenium was observed in the hyperglycaemic group, and in the second cohort selenium concentrations were significantly lower in the women who had impaired glucose tolerance; both dietary intakes and selenium concentrations were negatively associated with gestational hyperglycaemia in a multiple regression model (odds ratios 0.97 and 0.92 respectively) (Bo *et al*., 2005).

An inverse relationship between selenium concentrations and blood glucose concentrations has also been observed (Tan *et al*., 2001; Hawkes *et al*., 2004; Kilinc *et al*., 2008), but was not accompanied by changes in insulin (Hawkes *et al*., 2004), suggesting that selenium may affect glucose metabolism downstream from insulin, or possibly through independent energy regulating pathways such as thyroid hormones (Hawkes *et al*., 2004). This relationship is unique to pregnancy; diabetes in non-pregnant subjects is associated with higher blood selenium concentrations (Laclaustra *et al*., 2009).

Children

Selenium deficiency has also been linked with complications in early childhood. Low selenium concentrations and GPx activities in the blood of preterm infants have been proposed to contribute to respiratory distress syndrome, retinopathy of prematurity, increased haemolysis or other prematurity-related conditions (Dobrzynski *et al*., 1998). Several studies have observed significantly low mean plasma/serum selenium concentrations in very preterm (gestational age <32 weeks, birth weight < 1500 g) compared to healthy term infants (Mask and Lane, 1993; Sievers *et al*., 2001; Iranpour *et al*., 2009). Maternal plasma selenium concentrations during pregnancy are inversely associated with wheezing in children at 2 years of age (Devereux *et al*., 2007). In addition, low selenium concentrations in umbilical cord plasma have been observed in children with wheezing compared to controls (Shaheen *et al*., 2004; Devereux *et al*., 2007). This has been further confirmed by measurements of selenium in nails from children at 12 years of age; those children with the highest quintile of nail selenium concentrations presented a five-fold decrease in the prevalence ratio of asthma, whereas those in the lowest selenium quintile presented with an almost 2.5-fold increase (Carneiro *et al*., 2011). Lower plasma selenium concentrations have also been found in children at 12 years of age with childhood asthma compared to healthy age-matched controls (Kocyigit *et al*., 2004).

Zinc

Zinc is an essential constituent of over 200 metalloenzymes participating in carbohydrate and protein metabolism, nucleic acid synthesis and antioxidant functions (through Cu/Zn-SOD; Figure 1.3) (Izquierdo Alvarez *et al*., 2007). In addition, zinc is required for cellular division and differentiation, making it essential for successful embryogenesis. Total body zinc content is estimated to be 2 g and plasma zinc has a rapid turnover, representing approximately 0.1% body zinc content (WHO/FAO/IAEA, 1996). The body does not store zinc, thus a constant dietary intake is essential. The main dietary sources of zinc include meat, seafood, pulses, legumes and whole grain cereals (FAO/WHO, 2004). It has been highlighted that in many parts of the world, including the Latin American countries, 40% of the population is at risk for inadequate zinc intake (Brown *et al*., 2004). Zinc deficiency has increased over the last decade due to a trend towards zinc-poor diets, based on processed foods and soy-based substitutes, as well as food grown in zinc-poor soil (Tahan and Karakukcu, 2006); current recommended intakes are shown in Table 1.1. In addition, mean plasma zinc concentrations are lower in African-American compared to Caucasian women, and multiparous compared to nulliparous women (Neggers *et al*., 1996).

During pregnancy, zinc assists fetal brain development. It has been estimated that the total amount of zinc retained during pregnancy is ~100 mg (Swanson and King, 1987). The requirement of zinc during the third trimester is approximately twice as high as that of non-pregnant women (WHO/FAO/IAEA, 1996). Plasma zinc concentrations decline as pregnancy progresses and increase towards delivery (Izquierdo Alvarez *et al*., 2007; Liu *et al*., 2010). Alteration in zinc homeostasis may have devastating effects on pregnancy outcome, including prolonged labour, fetal growth restriction, or embryonic or fetal death (King, 2000; Simpson *et al*., 2011).

Many zinc supplementation studies have been conducted in developing countries where the incidence of zinc deficiency is high, and these women are often selected as they are less well-nourished or have low plasma zinc levels (Goldenberg *et al*., 1995; Black, 2001). Benefits of supplementation include reduced incidence of pregnancy-induced hypertension, low birth weight (Goldenberg *et al*., 1995) and preterm birth (Mahomed *et al*., 2007). Such studies suggest benefits of zinc supplementation in developing countries where zinc deficiency is likely, although for developed countries there is conflicting data as to the benefits (Garg *et al*., 1993; Caulfield *et al*., 1999; Osendarp *et al*., 2000). However, zinc-containing multivitamins have been shown to reduce preterm birth incidence in an intervention study in the USA (Goldenberg *et al*., 1995). Moreover, a US study in a cohort of low-income urban girls and women observed a low intake of zinc early in pregnancy was associated with a greater than three-fold increased risk of preterm birth preceded by premature rupture of membranes, after controlling for other known risks (OR 3.5, 95% CI 1.0–11.5) (Scholl *et al*., 1993).

Pre-eclampsia

Zinc deficiency has been associated with pre-eclampsia since the 1980s (Kiilholma *et al*., 1984). Placental zinc concentration has been shown to be lower in pre-eclampsia in a cross-sectional retrospective study of 11 pre-eclamptic and 15 healthy pregnancies with placental zinc values positively correlating with birth weight (Diaz *et al*., 2002). More recently lower serum concentrations of zinc have been associated with pre-eclampsia in two relatively small retrospective studies from Turkey (Kumru *et al*., 2003; Kolusari *et al*., 2008). The authors suggested that this may be useful for early diagnosis, as lower plasma zinc concentrations have been associated with increased lipid peroxidation in rat studies (Yousef *et al*., 2002). Moreover, a retrospective study in India reported reduced serum zinc concentrations in mild and severe pre-eclamptic mothers compared to controls; the

authors suggested that the reduction may not only affect antioxidant protection, but could also contribute to a rise in blood pressure (Jain *et al*., 2010). The lower serum zinc concentrations in mothers who develop pre-eclampsia have been suggested to at least be partly due to reduced oestrogen and zinc binding-protein levels (Bassiouni *et al*., 1979).

Zinc is transported across the placenta via active transport from the mother to the fetus. The fetus has notably higher zinc concentrations compared to the mother, even in cases of pre-eclampsia (Kiilholma *et al*., 1984) and higher fetal arterial and venous blood zinc concentrations in severe pre-eclampsia (Katz *et al*., 2012), indicating that the fetus itself can maintain adequate zinc homeostasis. In contrast, two case-control studies in Iran (Bahadoran *et al*., 2010) and Israel (Katz *et al*., 2012), showed no differences in third trimester maternal zinc concentrations between pre-eclampsia and control women, although Bahadoran *et al*. (2010) did observe an association between lower zinc concentrations and severity of pre-eclampsia, suggesting that zinc status may still be a useful clinical marker for severity. It must be noted that, as with all these micronutrients, the concentration early in pregnancy in relation to the development of pregnancy complications remains to be established.

Allergies

As with some of the other antioxidant micronutrients, maternal zinc intake during pregnancy could also influence early life immune responses to allergens, which has been shown using human and murine experimental models (Prasad, 2000; Richter *et al*., 2003). Animal studies report that zinc deficiency results in impaired lung maturation, with the lungs of pups born to zinc-deficient rats being smaller, having reduced DNA levels, and smaller lumina of alveolar ducts (Vojnik and Hurley, 1977). Maternal zinc intake during pregnancy has been shown to be negatively associated with childhood asthma status at 5 years of age in a Scottish study (Devereux *et al*., 2006). A similar observation has been reported in a large US cohort study (Project Viva), with reduced maternal zinc intake being associated with increased likelihood of childhood wheezing and asthma at 2 years of age (Litonjua *et al*., 2006). Also, a zinc-dependent metalloprotease (ADAM33) has been identified as a putative asthma susceptibility gene (Van Eerdewegh *et al*., 2002) and has been shown to be expressed in embryonic lungs, increasing with gestation (Haitchi *et al*., 2005). Thus the associations demonstrated between maternal zinc intake and childhood asthma may potentially be mediated through ADAM33 by zinc modulating ADAM33 activity, thus influencing lung development (Devereux *et al*., 2006; Devereux, 2007).

Children

Infants and young children are particularly vulnerable to zinc deficiency because of the higher zinc requirement for rapid growth, and growth-limiting zinc deficiency can exist in otherwise healthy infants (Solomons, 1988). Lower zinc concentrations in children suffering from wheezing and asthma have been observed using both nail (Carneiro *et al*., 2011) and hair (Tahan and Karakukcu, 2006) samples compared to controls. Bahl *et al*.'s observational study provide some evidence of higher risks of infectious diseases in children with low plasma zinc concentrations (Bahl *et al*., 1998). Zinc deficiency is thought to increase infections of the respiratory tract, possibly through defects in T-cell immunity, as zinc regulates the balance between CD4+ and CD8+ T-cells and between Th1 and Th2 subsets (Soutar *et al*., 1997; Prasad, 2000). It has been suggested that zinc deficiency causes a shift towards a Th2-dependent response, which possibly promotes the production of inflammatory cytokines and mucosal IgE in asthma (Zalewski, 1996). This deficiency may also increase eicosanoid production, which could lead to promoting airway inflammation (Tahan and Karakukcu, 2006). Zinc supplementation in populations with low zinc intake, during pregnancy and for vulnerable infants may be beneficial, as it has been suggested that physiological supplementation of zinc for 1–2 months restores immune responses and reduces the incidence of infection (Ferencik and Ebringer, 2003).

Manganese

Manganese is a free element in nature (often in combination with iron) and is abundantly present in the environment. Manganese(II) ions function as cofactors for a number of enzymes; the element is thus a required trace mineral for all known living organisms. About 80% of the known world manganese resources are found in South Africa; other important manganese deposits are in Ukraine, Australia, India, China, Gabon and Brazil (Corathers, 2009). While essential to human health, overexposure to manganese is associated with devastating irreversible neurological impairment (Aschner *et al*., 2009).

The classes of enzymes that have manganese cofactors are very broad, and include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins and integrins. One of the most well-known manganese enzymes is the antioxidant Mn-SOD (Figure 1.3) which may protect the placenta from oxidative stress by detoxifying superoxide anions (Ademuyiwa *et al*., 2007). The human body contains about 12 mg of manganese, which is stored mainly in the bones; in the tissue it is mostly concentrated in the liver and kidneys (Emsley, 2001).

In the human brain, manganese is bound to manganese metalloproteins, most notably glutamine synthetase in astrocytes (Takeda, 2003). Current requirements for manganese, although less studied compared to other micronutrients, are shown in Table 1.1.

Little is known about the effects of deficiency or excess of manganese on the developing human fetus or pregnancy outcome (Wood, 2009). This is further hampered by the fact that at present sensitive biomarkers of manganese exposure and nutritional status are not available (Wood, 2009). Manganese, upon absorption, is primarily sequestered in tissue and intracellular compartments and thus blood manganese concentrations do not always provide a good estimate of manganese levels in targeted tissues (Zheng *et al*., 2011).

In various animal studies, Mn-SOD has been shown to play a contributing role in hypertension. Mice lacking Mn-SOD die of cardiomyopathy within 10 days of birth and mice lacking one of the alleles (Mn-SOD$^{+/-}$ mice) develop hypertension (Rodriguez-Iturbe *et al*., 2007). In addition, overexpression of Mn-SOD improves endothelial function, as well as reducing hypertension and oxidative stress in angiotensin II-induced hypertensive mice (Dikalova *et al*., 2010). These studies highlight the importance of manganese in relation to Mn-SOD in regulating mitochondrial O_2 production and endothelial function.

Fetal growth restriction

Circulating whole blood manganese concentrations have been shown to be lower in women with fetal growth restriction compared to healthy controls indicating that this micronutrient may be important in maintaining fetal growth (Vigeh *et al*., 2008). This study also found that manganese concentrations were higher in umbilical samples from fetal growth restriction cases compared to controls, suggesting that manganese contributes different effects on birth weight in healthy mothers (Vigeh *et al*., 2008). Zota *et al*.'s (2009) retrospective study in the USA reported a non-linear relationship between manganese concentrations and birth weights in a cohort of 470 full term (delivered at > 37 weeks' gestation) infants further indicating the potential effect on fetal growth. A small retrospective study of African-American mothers reported reduced umbilical cord whole blood manganese concentrations in neonates born to mothers with pre-eclampsia compared to controls (Jones *et al*., 2010). Furthermore, this study found that, like other micronutrients, umbilical cord blood from smoking mothers had reduced manganese concentrations (Jones *et al*., 2010). Increased fetal membrane Mn-SOD mRNA expression has also been demonstrated in women with preterm labour (Than *et al*., 2009). Manganese is one of the

least studied micronutrients and at present no supplementation trial has been published, which may reflect the lack of data on manganese concentrations in pregnancy.

Children

Manganese deficiency has also been linked with an increased risk of childhood asthma. A case-control study from Turkey reported significantly lower plasma manganese concentrations in children (aged 2–13 years) suffering from asthma compared to age-matched controls (Kocyigit *et al*., 2004). Only one other study has investigated manganese concentrations in an adult population, showing that dietary manganese intake was inversely related to bronchial activity and the lowest intake of manganese (and vitamin C) was associated with a five-fold increase in risk of bronchial reactivity (Soutar *et al*., 1997). At present, an explanation for this association is unclear, but it can be speculated that, as with the other antioxidant micronutrients, reducing levels of oxidative stress may play an important contributory factor. Future studies are required to elucidate potential factors as well as whether manganese deficiency during pregnancy has any influence on the prevalence of childhood wheezing and asthma.

Copper

Copper is an essential trace element and a cofactor for a number of enzymes involved in metabolic reactions, angiogenesis, oxygen transport and antioxidant protection, including catalase, superoxide dismutase (Figure 1.3) and cytochrome oxidase (Gambling *et al*., 2008). During pregnancy, plasma copper concentrations significantly increase from the first to the third trimester, returning to normal non-pregnant values after delivery (Izquierdo Alvarez *et al*., 2007; Liu *et al*., 2010). The increase in copper with progression of pregnancy could be partly related to synthesis of ceruloplasmin, a major copper binding protein, due to altered levels of oestrogen (Liu *et al*., 2010). Approximately 96% of plasma copper is strongly bound to ceruloplasmin, a protein with antioxidant ferroxidase properties (Shakour-Shahabi *et al*., 2010). The dietary intake of copper in women aged 19–24 years is generally below the recommended levels (Table 1.1) (Institute of Medcine, 2001), which may cause problems during pregnancy when requirements increase (McArdle *et al*., 2008).

Copper is essential for embryonic development (Kambe *et al*., 2008). Maternal dietary deficiency can result in both short-term consequences (including early embryonic death and gross structural abnormalities) and long-term consequences, such as increased risk of cardiovascular disease risk and reduced fertilisation rates

(Keen *et al*., 2003; Gambling *et al*., 2008); current recommendations on intakes are summarised in Table 1.1.

Normal pregnancy

Cu/Zn-SOD is an important antioxidant known to be expressed in both maternal and fetal tissues (Ali Akbar *et al*., 1998). Copper concentration has been shown to be higher in maternal plasma than in umbilical cord plasma (Krachler *et al*., 1999). It has been suggested that the placenta acts as a blockade in the transfer of copper from the mother to the fetus (Krachler *et al*., 1999; Rossipal *et al*., 2000). An observational Turkish study on 61 placentae from healthy pregnancies between 37 and 40 weeks' gestation found that copper concentrations positively correlated with neonatal weight; the authors suggested that copper may have interactive connections in human placenta (Ozdemir *et al*., 2009), and this requires further studies to fully elucidate its role. It is known that copper is transferred across the placenta via high-affinity carriers (Ctr1) which have been shown to be expressed early in pregnancy. It is also thought that placental copper transport is related to iron transport, but the mechanism is unknown (McArdle *et al*., 2008).

Pre-eclampsia

Retrospective studies have shown elevation of maternal serum copper levels in pre-eclampsia after clinical onset of the disease (Serdar *et al*., 2006; Kolusari *et al*., 2008; Katz *et al*., 2012). It is thought that as copper is a redox-active transition metal and can participate in single electron reactions and catalyse the formation of free radicals, including undesirable hydroxyl radicals, it could contribute to the oxidative stress which is characteristic of pre-eclampsia (Serdar *et al*., 2006). This illustrates that copper itself appears to act as a pro-oxidant, but when associated in Cu/Zn-SOD it functions as an antioxidant. Furthermore, studies have reported increased levels of serum concentrations and placental expression of ceruloplasmin in women with pre-eclampsia; this is positively correlated with serum malondialdehyde, indicating an increased production of this antioxidant protein as an adaptation to increased lipid peroxidation (Aksoy *et al*., 2003; Serdar *et al*., 2006; Guller *et al*., 2008). These abnormal levels of copper may also interfere with the ascorbic acid/copper balance in pre-eclampsia, thus compromising normal nitric oxide release (Gandley *et al*., 2005). However, it must be remembered that concentrations early in pregnancy have yet to be determined and data on copper status in normal human pregnancies are sparse. This is further hampered by the fact that at present there is no reliable biomarker

for copper status, so whether deficiency is a significant public health problem remains unclear (Arredondo and Nunez, 2005).

Children

Copper nutrition in infants and children is not usually considered as an area for concern unless the infant is born prematurely. Umbilical cord blood copper (Perveen *et al*., 2002) and ceruloplasmin concentrations have been reported to be lower in preterm infants compared to full-term newborns, with a consistent rise in concentrations as gestation increases from weeks 26 to 42 (Galinier *et al*., 2005). Lower copper concentrations and Cu/Zn-SOD activities have been reported in both preterm and fetal growth restricted placentae (Sutton *et al*., 1985; Zadrozna *et al*., 2009). A study that followed preterm children up to 100 days of life noted that plasma copper concentrations and erythrocyte SOD levels were constantly and significantly lower in preterm compared to term children at all time points measured (Nassi *et al*., 2009). Newborns often exhibit reduced activities of antioxidant enzymes, which may be associated with a deficiency of their constitutive elements, the availability of which appears to be less sufficient the lower the gestational age and/or birthweight <1000 g (Nassi *et al*., 2009).

Vitamin C and E

Vitamin C (ascorbic acid and dihydroascorbic acid) is an essential water-soluble vitamin found widely in fruit and vegetables; it has important roles in collagen synthesis, wound healing and prevention of anaemia, and as an antioxidant as it can quench a variety of reactive oxygen species and reactive nitrogen species in aqueous environments (Buettner, 1993). Vitamin C is commonly included in low doses (< 200 mg/day) within multivitamin preparations for pregnancy, but has also been given in higher doses (up to 1000 mg/day) as a supplement, alone or in combination with vitamin E (Poston *et al*., 2011). Smoking has been shown to increase oxidative stress and metabolic turnover of vitamin C; thus the requirement for smokers is increased by 35 mg/day (Institute of Medicine, 2000).

Vitamin E (alpha-tocopherol) is a lipid-soluble vitamin acting with the lipid membrane and with synergistic interactions with vitamin C (Packer *et al*., 1979). Vitamin E functions primarily as a chain-breaking antioxidant that prevents propagation of lipid peroxidation, including inhibition of NAD(P)H oxidase activation and the inflammatory response (Chappell *et al*., 1999; Poston *et al*., 2011).

Pre-eclampsia

Considerable interest exists regarding prevention of maternal and perinatal morbidity with vitamins C and E given the abnormally low plasma vitamin C and E concentrations reported in women with pre-eclampsia. However, the most recent meta-analysis of ten trials (6,533 women) of antioxidant supplementation (including vitamin C and E but also other supplements such as lycopene) showed no difference in the relative risk (RR) of pre-eclampsia (RR 0.73, 95% CI 0.51–1.06), preterm birth (before 37 weeks) (RR 1.10, 95% CI 0.99–1.22), small-for-gestational-age infants (RR 0.83, 95% CI 0.62–1.11) or any baby death (RR 1.12, 95% CI 0.81–1.53) (Rumbold *et al*., 2008). Considerable heterogeneity between the trials was seen, reflecting the different supplements studied, the varying risk criteria used for entry into the studies, and the study sizes. Two subsequent multicentre double-blind randomised trials of a combination of vitamin C and E (Roberts *et al*., 2010; Xu *et al*., 2010) also found that supplementation did not reduce the rate of pre-eclampsia or gestational hypertension and, similar to the 'Vitamins In Pre-eclampsia trial' (Poston *et al*., 2006), increased the risk of fetal loss or perinatal death and preterm prelabour rupture of membranes. Another multicentre placebo-controlled trial of vitamin C and E in women with type 1 diabetes in pregnancy (DAPIT) also reported no differences in the rates of pre-eclampsia between supplemented or placebo groups (McCance *et al*., 2010).

Further investigations are required, as the concentrations of these vitamins remain significantly reduced in women with pre-eclampsia, but in the absence of further evidence routine supplementation with higher dose vitamin C and E is not recommended as they can be potentially dangerous in high concentrations. Whether these trials suggest that oxidative stress is not part of the pathogenesis of pre-eclampsia, or that the dose, timing of supplementation and/or choice of antioxidant prophylaxis is inappropriate, is unknown.

Children

Epidemiological data of children and adults have reported associations between asthma and reduced intake and blood levels of dietary nutrients such as antioxidant vitamins (vitamin C and E) (Bodner *et al*., 1999; Hijazi *et al*., 2000; Gilliland *et al*., 2003; Harik-Khan *et al*., 2004). Several studies have reported reduced maternal vitamin E concentration associated with increased incidence of wheezing and asthma in children at both 2 and 5 years of age (Devereux *et al*., 2006; Litonjua *et al*., 2006; De Luca *et al*., 2010). However, supplementation with vitamin E has not been consistently associated with improved asthma outcomes (Fogarty *et al*., 2003; Pearson *et al*., 2004; Ram *et al*., 2004; Greenough *et al*., 2012). It

is thought that these inconsistencies may be due to dietary antioxidants which primarily influence the development of asthma during the critical period early in life (Devereux *et al*., 2006).

Folate

Folic acid, the synthetic form of folate, is a micronutrient found in green leafy vegetables, dairy products, poultry and meat, seafood, fruits and cereal products (Tamura and Picciano, 2006). Folate is involved in a number of important functions within the body, including synthesis of proteins required for DNA and RNA and as an essential substrate for a range of enzymatic reactions needed for amino acid synthesis and vitamin metabolism; as such, folate is essential for cell multiplication and differentiation processes (Friso and Choi, 2002; Fox and Stover, 2008). Although not a classical antioxidant, studies have highlighted the potential antioxidant capacity of folate (Joshi *et al*., 2001) and thus it is considered in this chapter.

Normal pregnancy

It is well established that there is an increased demand for folate associated with pregnancy, mainly caused by the growth of the fetus and its placenta (Jauniaux *et al*., 2007). Current knowledge suggests that nutrient transfer via the placenta from the maternal circulating pool must in most cases supply the demands of fetoplacental growth, but information on human placental transfer is limited (Jauniaux *et al*., 2007). Several studies have shown that folate levels drop slightly as pregnancy progresses (Qvist *et al*., 1986; Megahed and Taher, 2004) and have been shown to remain decreased up to six weeks after delivery (Cikot *et al*., 2001).

Neural tube defects

The importance of folate in the prevention of neural tube defects has long been known (MRC, 1991). However, folate may also have important roles in other physiological pathways needed for successful pregnancy, including angiogenesis and vasculogenesis (Sasaki *et al*., 2003), methylation of the harmful, sulphur-containing homocysteine (Ciaccio *et al*., 2008), antioxidant protection (Joshi *et al*., 2001; Gori and Munzel, 2011) and endothelial-dependent vascular relaxation (Griffith *et al*., 2005). These processes are essential for the establishment of fetoplacental circulation, enabling successful pregnancy outcome. We have recently shown folic acid to possibly play a direct role in extravillous trophoblast invasion, angiogenesis and secretion of matrix metalloproteinase (Williams *et al*., 2011).

Interest in folic acid supplementation followed observational studies linking decreased red blood cell folate (Smithells *et al*., 1976) and lower maternal dietary folate intake (Bower and Stanley, 1989) with neural tube defects. A number of randomised controlled trials of periconceptional supplementation with a variety of multivitamins followed (MRC, 1991). Due to its roles in DNA synthesis, repair and methylation, folate intake is increased five- to tenfold during pregnancy, indicating that an adequate supply of folate is important in the implantation and development of both the placenta and fetus (Williams *et al*., 2011). Folate supplementation is now recommended peri-conceptually at a dose of 400 μg/day to prevent neural tube defects (MRC, 1991). However, few studies have examined how extending folic acid supplementation may also benefit later stages of pregnancy.

Meta-analyses have reported that maternal folic acid supplementation is also associated with decreased risk of other congenital anomalies, including cardiovascular defects (OR 0.61, 95% CI 0.40–0.92) and limb defects (OR 0.57, 95% CI 0.38–0.85) (Goh *et al*., 2006) and some paediatric cancers including leukaemia, paediatric brain tumours and neuroblastoma (Goh *et al*., 2007). Concern has been expressed over an increase in twin births associated with periconceptional folic acid supplementation. The two largest studies have given discrepant findings, with one showing no association (OR 0.91, 95% CI 0.82–1.00) (Li *et al*., 2003) and the other showing tentative evidence of a possible relationship (adjusted OR 1.26, 95% CI 0.91–1.73) (Vollset *et al*., 2005).

Pre-eclampsia

Folate deficiency is associated with recurrent miscarriage, placental abruption, fetal growth restriction and pre-eclampsia (Kupferminc *et al*., 1999). Studies have shown supplementation with multivitamins containing folic acid to reduce the occurrence of pre-eclampsia (Bodnar *et al*., 2006; Wen *et al*., 2008). The exact mechanism by which folic acid supplementation leads to this reduction in pre-eclampsia remains to be elucidated; however, a number of mechanisms have been suggested, including improvement of endothelial function, direct or indirect lowering of blood homocysteine, or via antioxidant mechanisms through increasing nitric oxide bioavailability or contributing to reducing ROS-induced endothelial dysfunction (Ray and Laskin, 1999; Joshi *et al*., 2001). There is evidence to indicate that folic acid supplementation in pregnancy reduces the risk of pre-eclampsia (Ray and Laskin, 1999; Sanchez *et al*., 2001). However, there are also a number of contradictory studies in which no association has been found between folate deficiency and pre-eclampsia (Rajkovic *et al*., 1997; Powers *et al*., 1998; Makedos *et al*., 2007; Mistry *et al*., 2011). Nor was folic acid supplementation associated

with a reduction of pre-eclampsia (Ray and Mamdani, 2002). Furthermore, increasing parity has been shown to reduce folate concentrations, especially in mothers who have previously had pre-eclampsia (Mistry *et al*., 2011); this area requires further investigation. This raises the question of whether the standard recommended folic acid supplementation of 400 μg/day may be of too low a dose to be effective in pre-eclampsia.

A systematic review estimated the use of periconceptional folic acid in the UK to be 21–48%, with awareness of the health prevention message at 66–81% (Stockley and Lund, 2008), rates similar to those in Europe, the USA and Australasia. The authors highlighted a package of interventions relevant to increasing uptake, particularly for those groups with lowest use (lower income and young women), but acknowledge the considerable difficulties of any approach, particularly in the light of the significant unplanned pregnancy rate in the UK. The NICE guideline 'Antenatal care: routine care for the healthy pregnant woman' advises folic acid supplementation at a dose of 400 μg/day before conception and up to 12 weeks' gestation (NICE, 2008).

Multivitamin and multinutrient supplementation

There has been much interest in the potential benefits of antioxidant multivitamin or multinutrient supplementation, but the substantial majority of these trials have been undertaken in resource-limited countries with undernourished populations (Haider *et al*., 2011). Although the practice of multivitamin supplementation in pregnancy is widespread among women in developed countries, contemporaneous evidence for benefit is sparse. It has been suggested that there is a link between maternal diet during pregnancy, preterm birth and cardiovascular disease in offspring at least 50 years after their births (Barker, 1999, Klebanoff *et al*., 1999), but at present it remains unknown whether women who use supplements before and during pregnancy have children with fewer chronic diseases at middle age.

Accurate assessment of the prevalence of multivitamin and/or folic acid use is fraught with difficulties. The frequent use of case-control studies increases the likelihood of recall bias and the retrospective recollection of multivitamin use in early pregnancy may also lead to inaccuracies. Many preparations are available over the counter and thus use cannot easily be cross-referenced with prescription databases. The definition of multivitamin use varies, with many studies concentrating on folic acid as the main constituent. A small double-blind placebo-randomised control trial of daily antioxidant supplementation (including vitamin C and E, folic acid, copper, selenium, zinc and manganese) in pregnant women presenting with low antioxidant status at 8–12 weeks' gestation reported significant reductions in pre-eclampsia

rates in the supplementation group compared to the control group (Rumiris *et al*., 2006). The authors also commented on increased perinatal outcomes, with a reduced number of fetal growth restricted fetuses (Rumiris *et al*., 2006). Although these results are positive, caution must be exercised, as the numbers used in this study were low and the study was probably underpowered; this is further highlighted by a Cochrane review of antioxidant trials (mainly with vitamin C and E, but also including other antioxidants) that reported no significant benefit of supplementation in pregnancy in relation to relative risk of pre-eclampsia, preterm birth or fetal growth restriction (Rumbold *et al*., 2008).

Conclusions

Micronutrient status is increasingly recognised to play an important role in the health and wellbeing of pregnant women and in early childhood. Increased knowledge about the importance of these specific antioxidant micronutrients and the crucial part that they have in maintaining successful pregnancy and determining both the long- and short-term health of both mother and baby needs to be addressed and made a key focus for future health strategies in improving pregnancy outcomes. The importance of meeting and maintaining the desirable intakes of these vitamins and micronutrients is essential to sustain a balance between antioxidants and pro-oxidants. This is particularly important with regard to pre-eclampsia and fetal growth restriction during pregnancy and also for childhood asthma, where oxidative stress is an essential component of the aetiology of these conditions, and so these specific antioxidant micronutrient deficiencies may play a contributing role. Micronutrient deficiencies during pregnancy can undoubtedly have profound influences on the health of both the mother and her child; however, conflicting evidence hinders the development of robust public health guidance.

Only by fully understanding the requirements for micronutrients during pregnancy will we be able to evaluate the potential use of these dietary antioxidant supplements as a way of preventing pathological pregnancy outcomes. At present, there is a need for adequately powered, randomised controlled trials, including long follow-up periods to elucidate causality, as well as the best formulation, dose, duration and period of supplementation during pregnancy. Furthermore, the influences of these trials on the health of the child both early and later in life must also be considered. However, it must also be remembered that these antioxidant and other micronutrients can be obtained via a healthy diet, thereby negating the need for supplementation. Future strategies focusing on providing nutritional guidance specifically to pregnant women will be pivotal in helping to ensure optimal health of both mother and baby.

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