How Is Maternal Nutrition Related to Preterm Birth?

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Abstract

The incidence of preterm birth in developed countries is increasing, and in some countries, including the United States, it is almost as high as in developing countries. Demographic changes in women becoming pregnant can account for only a relatively small proportion of the increase. A significant proportion of spontaneous preterm birth continues to be of unknown cause. Experimental data from animal studies suggesting that maternal undernutrition may play a role in spontaneous, noninfectious, preterm birth are supported by observational data in human populations, which support a role for maternal prepregnancy nutritional status in determining gestation length. In addition, intakes or lack of specific nutrients during pregnancy may influence gestation length and thus the risk of preterm birth. As yet, the role of paternal nutrition in contributing to gestation length is unexplored.

Contents

INTRODUCTION

Preterm birth remains a major cause of neonatal morbidity and mortality, even when it occurs only slightly before term (8, 47, 48, 89). The risks of adverse long-term neurodevelopmental outcomes following birth at extremely preterm gestations are well known (109, 192); however, it is increasingly apparent that preterm birth, including late preterm birth, also significantly increases risks of long-term chronic adult diseases including respiratory, cardiovascular, and metabolic disease (102). Preterm birth, therefore, represents a significant economic burden to society (128–130), although it should be noted that the efficiency and cost-utility of neonatal intensive care, and the quality-adjusted life years gained for survivors, are increasing over time and are greater than for many other health care interventions (42, 43).

Preterm birth: birth before 37 completed weeks, or 259 days, of gestation

Preterm birth rates in developed countries have been increasing over the past two decades, with increases of 20% reported in the United States, Japan, and elsewhere (113, 136, 171). Preterm birth now occurs in 9.6% of all pregnancies globally, with rates highest in Africa (11.9%) and North America (10.6%) and lowest in Europe (6.2%) (9). Rates in the United States are higher than in Europe in all ethnic groups, although the highest rates are seen in

non-Hispanic black people (103). Preliminary data suggest that the rates in the United States may have fallen over the past two years (52), although this remains to be confirmed. Approximately 45% of preterm birth follows spontaneous preterm labor (61). Although changes in pregnancy demographics, including increasing maternal age, use of artificial reproductive technologies, and number of multiple births, may contribute to the increased rates of preterm birth, they cannot explain the magnitude of the increase (61, 136). Increasing attention is being given to the potential role of maternal nutrition in the duration of gestation (61); undernutrition in the world's poorest countries and either a poor diet or active dieting in the world's richest countries could be factors explaining both high rates in Africa and rising rates in developed countries (9). A role for maternal nutrition in preterm birth is supported by animal experiments, which not only have demonstrated that maternal undernutrition in early pregnancy can result in preterm birth (15), but also that maternal nutritional status affects fetal developmental trajectory (69). As the fetus is largely responsible for initiating the timing of spontaneous labor (28), the effects of maternal nutritional status on fetal development, gestation length, and long-term disease may be linked (28). This review focuses on the evidence for a role of maternal nutritional status on the timing of birth.

MATERNAL NUTRITION DOES NOT EQUAL FETAL NUTRITION

When considering the impact of maternal nutrition on pregnancy outcomes such as gestation length and birthweight, it is important to appreciate that maternal nutrition is not the same as fetal nutrition. The fetus lies at the end of a nutritional supply line, with maternal nutritional intake at one end and fetal tissue uptake at the other (13). In between lie the maternal endocrine and hormonal milieu, placental blood supply, placental metabolism, umbilical blood flow, and the fetal endocrine and hormonal milieu. Various factors acting on this supply line can affect fetal nutrition. For example, a mother who is still growing will have a different endocrine and metabolic milieu, as discussed below. A significant degree of exercise in pregnancy and smoking both affect uterine blood flow and fetal size (76, 105), and placental vascular disease associated with maternal hypertension is a major cause of reduced fetal growth in developed countries (105). Nevertheless, in the absence of placental pathology, there are clear relationships between maternal circulating nutrient concentrations, placental transport of those nutrients (reviewed in 13), and thus fetal circulating nutrient concentrations. The evidence reviewed below also suggests that maternal nutrition before or in very early pregnancy, when fetal nutrition is histiotrophic rather than hemotrophic, may be a more important factor in determining gestation length than is nutrition in later pregnancy.

Histiotrophic nutrition: phagocytic/endocytic uptake of nutrients derived from the endometrium and uterine glands by the early embryo/fetus

Hemotrophic nutrition: exchange of blood-borne nutrients between mother and fetus via the placenta

Adequate Maternal Nutrition May Be Accompanied by Fetal Undernutrition: Data From Studies in Growing Animals and Adolescents

Consistent with the distinction made above between maternal and fetal nutrition, Wallace and colleagues have conducted a series of elegant experiments investigating the relationships between nutrition and pregnancy outcome in adolescent sheep (183). These studies demonstrate that overnutrition of an adolescent ewe results in accelerated maternal weight gain at the expense of nutritional supply to the fetus (180, 182). Overnourished adolescent ewes had a shorter duration of pregnancy than did control fed adolescent ewes (180); the effect was mitigated to a degree if ewes overnourished in early pregnancy were switched to a control diet for the second half of pregnancy (181), but not if the degree of overnutrition was modified while still remaining greater than maintenance requirements (184). Furthermore, maternal adiposity or body mass index (BMI) around the time of conception did not affect gestation length (184), demonstrating that it is the increased drive toward maternal growth that results in compromised fetal nutrition and preterm birth. The

compromised fetal nutrition appears to be secondary to impaired placental angiogenesis, resulting in reduced placental size and function (185).

These findings in sheep support the suggestion in human pregnancies that the nutrient requirements of a mother who is still growing may conflict with the nutritional needs of her baby. The human literature on whether growing mothers have altered pregnancy outcomes is still contradictory, with some studies showing no adverse effect of a growing mother on the outcome of a first teenage pregnancy but a significantly increased risk of preterm birth in the second (151, 160), whereas others report a significant increase in the risk of preterm birth in any pregnancy to teenage mothers even when adjustment is made for maternal weight gain and socioeconomic status [adjusted relative risk (RR), 95% confidence interval (CI), for birth before 32 weeks' gestation 1.32 (1.32–1.40) compared with birth at ≥37 completed weeks' gestation] (30). A large, well-conducted population-based study including a spread of rural and urban populations has recently been reported from the northwest of England (88). The cohort was restricted to 56,353 singleton live births between 2004 and 2006 born to women aged between 14 and 29 years in their first or second pregnancies. Outcomes were compared for women aged 14–17 years with those aged 20–29 years, and odds ratios (ORs) were adjusted for maternal BMI, social deprivation score and ethnicity, and infant sex. The OR (95% confidence intervals) for preterm birth between 33 and 36 weeks' gestation in women aged 14–17 years compared with older women was 1.21 (1.01–1.45) and for very preterm birth prior to 33 weeks' gestation was 1.71 (1.29–2.26), with birth at term (beyond 37 completed weeks' gestation) as the reference (88). ORs were slightly higher for second teenage pregnancies. These findings are consistent with other population-based studies of birth outcomes in teenage women compared with older women, which report an increased risk of all preterm birth and extremely preterm birth of between 1.5- and 2.5-fold (30, 160). It is difficult to tease out whether the increased risk of preterm birth in teenage pregnancies is due to confounding factors inherent in these pregnancies or whether nutrition of the mother and fetus may play a role. Animal experiments suggest that the latter possibility should not be excluded.

Relative risk (RR): the probability of the outcome occurring in the exposed group compared to the probability of the outcome in the nonexposed group

CI: confidence interval

Odds ratio (OR): the odds of an occurrence in one group compared with the odds of the occurrence in a second group

MATERNAL PAN-UNDERNUTRITION AND GESTATION LENGTH

Evidence from Wartime Famine

Data from the Dutch Famine and the Siege of Leningrad during the Second World War provide some information on the effect of a severe nutritional insult on gestation length, although the shortcomings of these datasets must be acknowledged. The Dutch Famine was a short, severe famine that has been reported in detail elsewhere (98, 100). The nature of the famine, with a sudden onset and sudden relief after a duration of five months, allowed investigators to compare pregnancy outcomes among women who conceived before the onset of famine but who were exposed to famine in either the second or third trimesters and who delivered during or shortly after the famine, with those who conceived during the famine and gave birth after its relief. Preterm birth rates increased sharply in the cohort who conceived during the famine, and the effect appeared to be most marked in women who registered for antenatal care with a body mass <60 Kg (100, 163, 170). Exposure to famine during the third trimester resulted in a small reduction in gestation length; in contrast, this period of exposure had the greatest effect on birthweight (99, 164). The authors point out that preterm birth rates in the north of the Netherlands, where nutritional conditions were less severe, also were increased at this time, and suggest caution in ascribing causality.

The Siege of Leningrad was of much greater duration. A sharp increase in the incidence of preterm birth was noted in the first half of 1942 following the onset of the siege in September

1941 (2). After this, rates dropped to be similar to those before the onset of the siege. These data could suggest that the change in the plane of nutrition around the time of conception was important, but there are insufficient data to be certain.

Maternal Nutrition in Africa and Gestation Length

Preterm birth rates are highest in Africa (9), where nutritional status is generally poor and may fluctuate throughout the year. Relatively recent data from the Gambia suggest that the rate of change in maternal weight in the periconceptional period may affect gestation length. In the Gambia, there are annual rainy seasons associated with hunger and weight loss and harvest periods associated with relatively plentiful food. During the hungry season, women lose, on average, approximately 2.6 Kg or 5% of body weight, equating to a daily energy deficit of 10% to 15% (140). The incidence of preterm birth, less than 37 completed weeks gestation, in Gambian women also varies throughout the year, and in a retrospective study of approximately 2,000 women in a geographically defined area where researchers have been studying the relationships between nutrition and health for decades, the peak incidence of preterm birth followed approximately nine months after the peak period of maternal weight loss and occurred in women with the lowest weight around the time of conception (140, 141).

In this study, gestational age was assessed by trained researchers or nurses using the Ballard Score (5), a validated tool for determining gestation length to within one week in late preterm and term babies. However, the tool was not developed in an African setting and, together with the retrospective nature of this study, caution needs to be taken in ascribing causality to the association between maternal nutrition and gestation length. However, both experimental data in animals (discussed below) and novel data demonstrating significantly increased DNA methylation in candidate metastable epialleles, but not genomewide, in peripheral blood leucocytes from 25 children conceived during the rainy season compared with 25 conceived during the dry season (186) do suggest that further investigation into the effect of variations in nutrition in the periconceptional period on fetal development and pregnancy outcomes are warranted.

There are also some data on the associations between nutrition during pregnancy, rather than only around the time of conception, and risk of preterm birth in an African population. In Zimbabwe, a prospective case control study of more than 3,000 women collected data on a variety of parental factors, including proxies for maternal nutritional status such as weight, BMI, mid-arm circumference (a validated indicator of nutritional status; 12), and intakes of alcohol and mahewu, a local nonalcoholic nutritious beverage made from corn meal, rapoko or sorghum, beans, and sugar. This study found that for each one-centimeter increase in maternal mid-arm circumference, the incidence of birth before 37 completed weeks' gestation fell by 5%. However, the impact of mahewu intake was much greater, with a 25% reduction in the risk of preterm birth in women who drank this home brew compared with those who did not (55). Once again, gestational age was assessed using the Ballard Score.

Voluntary Fasting During Pregnancy

The Islamic practice of fasting during Ramadan, during which pregnant women may fast for up to 16 hours a day for 30 days, has not been associated with shorter gestation length or with adverse neonatal outcomes, although data are sparse and of relatively poor quality (87, 150). There are no data on the effects of voluntary fasting at particular time periods of pregnancy and gestation length. One small cohort study of 236 women from the United States found that women who fast for more than 13 hours per day between

HPA: hypothalamic-pituitary-adrenal

28–30 weeks' gestation have elevated plasma concentrations of corticotrophin-releasing hormone (CRH) compared with women who do not fast, and that CRH concentrations were linearly related to gestation length (75). However, women with the highest CRH concentrations also had other risk factors for preterm birth, including lowest socioeconomic status and a lower daily energy intake; the relative risk for preterm birth did not change after adjusting for these variables, although the effect was of borderline statistical significance. The same group of investigators (156) has also reported an increased risk of preterm delivery after preterm rupture of the membranes [adjusted OR 1.89 (95% CI 1.02–3.43)] in the almost 30% of a cohort of more than 2,000 American women who did not meet the Institute of Medicine's recommendations for meal frequency (three meals plus up to two snacks per day) during pregnancy (80, 81).

Hyperemesis Gravidarum

There are substantially more data on the pregnancy outcomes of hyperemesis gravidarum, a condition of severe nausea and vomiting affecting 0.3% to 1.5% of pregnancies (4, 7, 175). Hyperemesis gravidarum characteristically has its onset between four and ten weeks of gestation and typically resolves by the twentieth week (62); it is characterized by weight loss, ketonuria, and limited nutritional intake (53). Most of the studies on hyperemesis have focused on attempting to identify underlying risk factors and were not designed to address pregnancy outcomes; almost all are retrospective studies. Thus, the data on hyperemesis gravidarum and gestation length are contradictory, with some studies finding an increased incidence of preterm birth (4, 37, 125) and others, including those focusing on pregnancy outcomes, finding no effect (34, 66, 173). Although it is an early pregnancy nutritional insult, hyperemesis is not a periconceptional insult, as onset is usually from four weeks of gestation onward.

Pan-Undernutrition and Preterm Birth in Animal Experiments

There is an extensive literature on maternal undernutrition in experimental animal studies. These studies have investigated the effects of both pan-undernutrition and of diets restricted in particular macronutrients, most commonly protein, on fetal growth and development, but few have studied the effect on gestation length. Those that have investigated gestation length have studied pan-undernutrition rather than the effect of a deficit in a particular macro- or micronutrient. In both sheep and horses, a brief (24- to 48-hour) fast in late gestation has been reported to result in increased uterine prostaglandin production and preterm delivery (58, 158). These studies were performed in chronically catheterized preparations of the fetus and mother, a paradigm that has recently been reported to result in a significant incidence of preterm birth, defined as gestation length less than two standard deviations from the mean, in sheep (10).

Moderate maternal undernutrition only in the periconceptional period has also been reported to lead to preterm birth in sheep (15). In this study, multiparous ewes were randomized to either maintenance feed or reduced nutrition from 60 days prior to mating until 30 days after mating, when placental attachment is complete in the sheep. The nutritional restriction was designed to reduce maternal weight by 10% to 15% compared with controls. This initially involved a significant reduction in food intake, but by the time of mating, undernourished ewes were receiving 80% of the intake of controls (148). Term in the sheep is approximately 145 to 150 days. Thus, the nutritional restriction ended approximately four months before full term, yet ewes exposed to the nutrient restriction in the periconceptional period still went on to deliver earlier than control ewes (10). Preterm birth was associated with an early precocious activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis (16), which is an essential prerequisite for the onset of parturition in the sheep. In addition to the accelerated

maturation of the fetal HPA axis, fetal lambs of ewes exposed to periconceptional undernutrition also demonstrated accelerated maturation of the glucose-insulin axis (118), suggesting that the signals in the periconceptional period may have altered the overall developmental trajectory of the conceptus (14).

Taken together, these data from human observational studies and animal experimental studies indicate that maternal pan-undernutrition in early pregnancy, around the time of conception, may increase the risk of preterm birth. The data for an effect of fasting or significant undernutrition later in pregnancy are less strong. Pregnancies in teenagers may represent a situation where there is fetal, but not necessarily maternal, undernutrition. There is a need for more research to clarify the relationships, and causal mechanisms, between maternal undernutrition in early pregnancy and preterm birth.

Does Supplementation with Macronutrients Decrease the Risk of Preterm Birth?

The literature on macronutrient supplementation on pregnancy outcome, mostly in women with a lower baseline nutritional status, has recently been reviewed with the conclusion that there is little effect of macronutrient supplementation on pregnancy outcome (1). However, the data from the Central American study of supplementation of pregnant women from four villages with either a gruel containing protein and energy (atole) or a low-energy drink containing no protein (fresco) are intriguing (138). Women receiving both drinks consumed similar amounts of energy, although atole has an energy concentration almost three times that of fresco, suggesting that the drinks were consumed to an energy target rather than a protein target as proposed in the protein leverage hypothesis (159). In both the atole and fresco villages, women in the highest tertile of supplement intake consumed 138 Kcal/d more than those in the lowest tertile and had a duration of pregnancy that was 1.4 weeks longer (138). The incidence of preterm birth was also lower in consumers in the highest tertile. Further posthoc analysis of these data led the authors to conclude that the supplement with no protein (fresco) resulted in a higher risk of preterm birth and that maternal malnutrition was an independent risk factor for preterm birth (176).

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

Effects of Carbohydrate Intake on Preterm Birth

The intake of sugar-sweetened and artificially sweetened soft drinks in the Danish National Birth Cohort, a prospective study of 59,334 women between 1996 and 2002, has recently been analyzed in relation to preterm birth (67). Women who ingested ≥1 serving of an artificially sweetened soft drink per day, but not those who ingested similar quantities of sugar-sweetened soft drinks, had an increased risk of preterm birth [adjusted OR 1.38 (1.15–1.65) compared with birth after 37 completed weeks' gestation]. The relationship held when stratified for maternal BMI, and there appeared to be a dose-response effect, with women who ingested more than four servings of artificially sweetened carbonated soft drinks per day having an OR for preterm birth of 1.78 (1.19–2.66) compared with those who never ingested these drinks. The authors speculate that the metabolism of the artificial sweeteners to methanol, which has been shown to decrease gestation length in nonhuman primates, even in very low doses (25), may play a role.

n-3 Fatty Acids

Prostaglandins are known to play a key role in parturition (124), and it has been hypothesized that an increased maternal intake of long-chain *n*-3 fatty acids, which are abundant in the fat of fish, may be able to influence the prostaglandin pathway and thereby decrease the risk of preterm birth. Several randomized controlled trials have compared supplementation with docosahexaenoic acid (DHA) with or without eicosapentaenoic acid (EPA), given in a variety of forms in either the second or third trimesters, or both, with a control vegetable

fat or a low-DHA diet. A meta-analysis of six randomized controlled trials (RCTs) including 1,278 women found an increase in gestation length (95% CI) of 1.6 (0.4–2.8) days with fish oil supplementation (76). The relative risk (95% CI) of preterm birth before 37 weeks' gestation in three of these studies (861 infants) was 0.67 (0.41–1.10).

Further randomized controlled trials have recently been published and are not included in this meta-analysis. In the DOMInO trial carried out in Australia, 2,399 women with singleton pregnancies were randomized prior to 21 weeks' gestation to three 500 mg capsules of DHA-rich fish oil capsules per day, providing 800 mg/d of DHA and 100 mg/d of EPA, or three 500 mg capsules of a vegetable oil per day (101). The primary outcome was postnatal depression, the incidence of which was not statistically different between groups. However, women in the fish-oil capsule group tended to have a longer gestation (282 versus 281 days; $P = 0.05$) and a reduced relative risk (RR) of preterm birth before 34 weeks' gestation [RR compared with birth after 37 completed weeks' gestation 0.49 (0.25–0.94)]. Of note was that this was offset by an increased risk of post-term induction of labor or post-term prelabor cesarean delivery (101), a finding that has also been reported in another RCT and in a large cohort study from Denmark (121, 123).

Women enrolled in the DOMInO trial were representative of all women giving birth in Australia. In contrast, a recent RCT in the United States randomized women with at least one prior preterm delivery, and who were receiving 17α-hydroxyprogesterone acetate to prevent a repeat preterm delivery, to a fish-oil supplement (1,200 mg EPA and 800 mg DHA) or a matching placebo containing mineral oil (70). Only women who passed a one-week "compliance run" were allowed to continue in the trial, which had a primary outcome of preterm birth prior to 37 weeks' gestation. The supplement was taken from 16–22 weeks' gestation until 36 weeks' gestation in 852 women of 994 who were initially randomized and placed on compliance. There was no difference in the relative risk of delivery prior to 37 weeks' gestation [RR for supplemented group versus control 0.91 (0.77–1.07)] or for preterm delivery prior to 32 weeks' gestation. Similarly, a trial of 1,040 women in Mexico who were randomized to either 400 mg algal DHA per day or an olive oil placebo from 18–22 weeks' gestation until delivery did not find any effect on gestation length [mean (SD) gestation in intervention group 39.0 (1.9) versus 39.1 (1.7) weeks in the control group] or the incidence of preterm birth prior to 37 weeks' gestation (10.1% versus 8.3%) (137).

Data from RCTs are therefore inconsistent, despite high-quality trials, perhaps consequent upon different trial designs with different doses and ratios of DHA and EPA and different populations of women. Overall, there appears to be minimal or no protective effect of fish oil supplementation during pregnancy on preterm birth.

Observational cohort studies are similarly conflicting, with a role for *n*-3 fatty acid intake in gestation length supported by data from a large prospective cohort study of 8,729 women in Denmark, which assessed fish intake during gestation through food questionnaires conducted around 16 and 30 weeks' gestation (121, 122), but not by U.K. and U.S. cohort studies (117, 146). In the Danish study, women were categorized as having eaten fish not at all, less than once per month, each month, or each week. The structure of the questionnaire was such that at 16 weeks' gestation women were asked to recall fish intake from the time they knew they were pregnant until the time of the questionnaire, and at 30 weeks' gestation to recall fish intake from 18 to 30 weeks' gestation. Women who did not eat any fish during the first trimester had a pregnancy duration that was 3.9 (2.2–5.6) days shorter than those who ate fish weekly, with an OR (95% CI) for preterm birth (<259 d or 37 weeks' gestation) of 2.4 (1.2–4.6) and for early preterm birth (<238 d or 34 weeks' gestation) of 7.1 (1.5–34), both relative to birth after 37 completed weeks' gestation. For women who did not eat any fish in the second trimester, the reduction in pregnancy

duration and the OR for preterm birth were similar, although the OR for early preterm birth was no longer statistically significant. However, in women who did not eat fish in either the first or second trimester, the reduction in pregnancy duration compared with women who ate fish at least weekly was 8.6 (5.5–11.7) days, with OR for preterm birth compared with birth after 37 completed weeks' gestation of 20 (2.3–165) (121).

It has been proposed that the Danish cohort study may have identified an association because it was the only cohort study that was able clearly to identify a group with zero baseline intake (121). It may be that the potential benefit of a fish oil supplement depends, in part, on prior *n*-3 consumption levels and baseline *n*-3 fatty acid status and also on whether the pregnancy has a prior high risk of preterm birth. One randomized trial has attempted to address this question by stratifying women into three groups after 16 weeks' gestation: those with a prior problematic pregnancy [preterm delivery, intrauterine growth restriction (IUGR), or pregnancy-induced hypertension] but currently experiencing an uncomplicated pregnancy, those with a twin pregnancy, and those experiencing problems (threatened pre-eclampsia with or without IUGR, or IUGR alone) in the current pregnancy (123). In the first two categories, women in the intervention groups received 2.7 g *n*-3 fatty acids per day (EPA:DHA = 1.4:1), whereas in the last category, women in the intervention group received 6.3 g *n*-3 fatty acids per day in the same ratio. In all three categories, women in the control group received olive oil. The main trial was a European multicentre trial of 1,619 women. Supplementation with *n*-3 fatty acids resulted in a significant reduction in the risk of preterm [<37 weeks' gestation; OR 0.54 (0.30–0.98)] and early preterm [<34 weeks' gestation; OR 0.32 (0.1–0.89)] delivery in the women who had had a previous preterm delivery, but not in either twin pregnancies or in those with current problems (123). In a subset of women who were enrolled in the Danish, Swedish, Norwegian, Scottish, and Dutch centers, detailed dietary histories were also available. When women were stratified according to their baseline habitual fish intake prior to pregnancy, women with problems in a prior pregnancy and who had low and middle, but not high, baseline fish intakes had decreased risks of preterm birth [hazard ratios for any preterm birth compared with term birth: low prior fish consumption, 0.56 (0.36–0.86); middle levels of prior fish consumption, 0.61 (0.44–0.84)].

IUGR: intrauterine growth restriction

Although the interaction between baseline fish intake and supplementation was not a primary outcome of this study, the data do suggest that *n*-3 fatty acid supplementation for the prevention of preterm birth may need to be a targeted intervention. This is supported by the observations that maternal dietary intake in mid-pregnancy is moderately well correlated with maternal erythrocyte and umbilical cord polyunsaturated fatty acid concentrations, with the strongest correlations for DHA+EPA (41), and that the ratio of maternal erythrocyte *n*-3 fatty acid to arachidonic acid concentrations at the time of delivery is associated with gestation length in women with moderate, but not high, fish oil intakes (120).

A small randomized trial of 290 low-risk women in Norway investigated the effect of a cholesterol-lowering diet from the second trimester on pregnancy outcome and found a 90% reduction in the risk of preterm birth [risk ratio (95% CI) 0.1 (0.01–0.77)] (90). However, women in the intervention group increased their fish intake, and a prospective cohort study, also from Norway, found that a Mediterranean diet (fish ≥2 times a week, fruit and vegetables ≥5 times a day, use of olive/canola oil, red meat intake ≤2 times a week, and ≤2 cups of coffee a day, a diet not dissimilar to the cholesterol-lowering diet in the RCT) was not associated with a reduced risk of preterm birth, but that intake of fish twice or more per week was associated with reduced risk [adjusted OR 0.84 (0.74–0.95)] (72), suggesting that the effect in the RCT may have been mediated via increased *n*-3 fatty acid intake.

In contrast to the effects of global nutrition and folate status, most of the trials of fish oil

supplementation have addressed intake in the second half of pregnancy. If the role of *n*-3 fatty acids is via the prostaglandin parturient pathway, then targeting intake in the latter half of pregnancy may be a reasonable approach. However, it is not yet clear whether there are both acute and chronic effects, with the latter relating to maternal body stores of *n*-3 fatty acids. The finding that maternal fish oil intake did not change much between the first and second trimesters in the Danish cohort study (121) suggests that there may also be a role for prepregnancy intervention. However, the inconsistent findings between studies, the possible increased risk of post-term induction of labor or post-term prelabor cesarean delivery with fish oil supplementation (101, 121, 123), and the concern around accumulation of toxic chemicals in fish that may affect offspring development mean that it is not possible for firm recommendations to be made regarding fish oil supplementation in pregnancy (39, 63).

Hazard ratio (HR): how often an event occurs in one group compared to how often it happens in another group, over time

MICRONUTRIENT INTAKE AND THE RISK OF PRETERM DELIVERY

Folic Acid

There have been numerous trials, mostly in developing countries, comparing various micronutrient supplementation protocols in addition to folic acid with folic acid alone. These trials have often utilized cluster or community randomization approaches and have enrolled women who are pregnant in these communities. Overall, the meta-analyses suggest that there is no protective effect for preterm birth of maternal supplementation commenced during pregnancy with any of these micronutrient protocols (31, 50, 127). This journal has recently published a detailed review of maternal micronutrient status and pregnancy outcome (32).

In contrast, following mandatory fortification of flour in many U.S. states there was a reduction in the incidence of preterm birth in California (152). This effect was not as large as expected, but this was attributed to attained folate concentrations that were lower than desired. Recent evidence from a large cohort study also suggests that folic acid status before conception or in early pregnancy may be associated with a decreased risk of preterm birth (20). Bukowski et al. prospectively recorded preconceptional folate supplementation in a cohort of nearly 35,000 women enrolled in a study of aneuploidy risk. Data were recorded in the first trimester of pregnancy. The study was carried out in the United States on a background of mandatory fortification of grain, so that all women who consumed products containing flour would have received some folic acid. Women were divided into those who had taken no additional preconceptional folic acid (44%) and those who had taken additional folic acid for either less (36%) or more (20%) than one year before conceiving. The risk of preterm birth was lowest in those women who had taken preconceptional folate supplementation for greater than one year, and there was a relationship between duration of supplementation and risk of preterm birth. Compared with women who took no preconceptional folate supplementation, the adjusted hazard ratio (HR) (95% CI) for preterm birth between 20 and 28 weeks' gestation compared with birth after 37 completed weeks' gestation in women who took folate supplementation for greater than one year was 0.31 (0.11–0.90); for birth between 28 and 32 weeks' gestation the adjusted HR was 0.53 (0.28–0.99). There was no effect of preconceptional folate supplementation on preterm birth between 32 and 37 weeks' gestation compared with term birth [adjusted HR 0.99 (0.85–1.15)] (20). This was a secondary analysis in this cohort, and the numbers of women delivering before 32 weeks' gestation on long-term supplements were small. These women were also different in many demographic features from women who did not take any preconceptional folate supplementation, meaning that the results of this study must be treated with caution. Nevertheless, the size of the effect, which was still statistically significant after adjusting for many confounders, is intriguing. These findings are also consistent

with a report on the association between maternal first trimester plasma concentrations of folate species and the risk of preterm birth (17). This study also was carried out on the background of mandatory fortification of grain, and no women were folate deficient. Women who had total serum folate concentrations in the first trimester that were in the highest tertile had an 80% reduction in the risk of spontaneous preterm birth before 37 completed weeks' gestation compared with women with serum folate concentrations in the lowest tertile [adjusted RR (95% CI) 0.2 (0.1–0.8)]. Furthermore, the authors report a linear relationship between total serum folate concentrations and preterm birth, with an increase of one standard deviation in first trimester folate concentrations associated with a 40% decrease in the risk of preterm birth (17). This study also investigated other folate species, namely 5-methyl tetrahydrofolate (THF) and 5 formyl THF, and found an interaction between the serum concentrations of these two species and preterm birth. When 5-methyl THF concentrations were high, there was a strong negative correlation between 5-formyl THF concentrations and preterm birth; in contrast, when 5-methyl THF concentrations were low, there was a positive correlation between 5-formyl THF concentrations and preterm birth. 5-methyl THF is involved in methyl donation to form methionine, which is involved in protein synthesis and, through s-adenosyl methionine, DNA methylation. 5-formyl THF is involved in nucleotide biosynthesis.

Single-nucleotide polymorphisms in genes coding for enzymes involved in folate metabolism also have been associated with an increased risk of preterm birth. A twofold-increased risk in preterm birth has been reported in white women carrying a mutation in the serine hydroxymethyltransferase (SHMT) gene (45); in black women, a similar effect size was seen in those with the lowest folate intake. Women with a deletion polymorphism in the dihydrofolate reductase (DHFR) gene have been reported to have a threefold increased risk of preterm birth [adjusted OR 3.0 (1.0–8.8)] compared with women without the polymorphism. A low folate intake (<400 μg/d) on the background of a DHFR deletion polymorphism increased the OR for preterm birth to 5.5 (1.5–20.4) compared with women without the polymorphism (84). DHFR is essential for the conversion of folic acid in its ingested form into THF, which enters the folate metabolic pathway. SHMT converts THF into the next step in the pathway, 5, 10 methyleneTHF, which can either be used for the synthesis of pyrimidines or methionine.

Thus, data on the role of folate and gestation length appear to mimic those of nutrition in general: There is little evidence for a role in mid-late gestation, but emerging evidence suggests that maternal folate status prior to conception or in early pregnancy may well be important in protecting against preterm birth. Although more than 50 countries have introduced mandatory fortification of flour, studies from the Americas suggest that, in the absence of additional folate supplementation, this only provides 25% of the recommended daily intake (179, 193). Data from Bukowski et al. (20) suggest that only about 20% of women in that selected cohort followed recommendations for additional folate; in the United Kingdom, where there is no mandatory fortification, only about 5% of women achieve the recommended daily intake of folate prior to conception (78).

THF: tetrahydrofolate

Other Micronutrients and Vitamins

The roles of maternal micronutrient status on pregnancy outcome, including preterm birth, and of maternal micronutrient supplementation have recently been extensively reviewed and therefore are not covered in detail here (32, 177). There are very few data supporting a significant role for micronutrients other than folate on the incidence of preterm birth, with none of the meta-analyses of micronutrient supplementation suggesting a beneficial effect.

Iron is a key micronutrient in pregnancy, with good evidence for benefit of

11β-HSD-2: 11 beta hydroxysteroid dehydrogenase type 2

supplementation for several pregnancy outcomes (59). However, the evidence for benefit in reducing preterm birth is less convincing. In an RCT of iron supplementation in 867 women in North Carolina, the 429 women who were iron replete at randomization were assigned to either 30 mg ferrous sulfate per day or placebo from prior to 20 weeks' gestation until 26–29 weeks' gestation (155). The incidence of preterm birth in the group that received iron was 7.5% compared with 13.9% in the control group ($P = 0.05$). In contrast, a very similar trial in Cleveland did not find a significant reduction in preterm birth with iron supplementation, although the authors remark that the curve for cumulative distribution for gestational age was shifted to the right, indicating a trend for later delivery in supplemented women (35).

One observational study reported an increased risk of preterm birth in women with a preconceptional vitamin C intake below the tenth centile (157). Two large RCTs, each of approximately 1,200 women, addressed the role of supplementation with vitamins C and E on preeclampsia, with preterm birth reported as a secondary outcome (133, 178). One of these was conducted in the United Kingdom (133); the other was a large multicentre World Health Organization (WHO) trial in developing countries and in women of poorer prepregnancy nutritional status (178). Neither trial found a significant effect of vitamin C and E supplementation on the risk of preterm birth, although there was a strong trend toward less preterm birth in supplemented women in the WHO trial [birth before 37 weeks' gestation 27.9% versus 31.8%, respectively; birth before 34 weeks' gestation 10.8% versus 13.9%. RR for birth before 37 and 34 weeks' gestation compared with term birth 0.9 (0.7–1.0) and 0.8 (0.6–1.0), respectively]. However, the very high rate of preterm birth in the control group must be acknowledged, meaning that even if this trend is confirmed it may only apply to women with a poor basal nutritional status. It is also important to note that these trials all target pregnant women and not the prepregnancy period. If prepregnancy nutritional status is indeed an important factor in determining gestation length, then more data on preconceptional micronutrient status and the risk of preterm birth are urgently needed.

Licorice Consumption and Gestation Length

Licorice is a very interesting food item, coming from the rhizome of the plant *Glycyrrhiza glabra* and containing glycerrhizin, a natural substance that blocks the activity of 11 beta hydroxysteroid dehydrogenase type 2 (11β-HSD-2). 11β-HSD-2 converts active cortisol into inactive cortisone and is present in the placenta, where it is thought to act as a modulator of fetal exposure to maternal glucocorticoids (142). Various animal experiments have reported decreased 11β-HSD-2 mRNA, protein, or activity levels with maternal undernutrition, and it is suggested that this results in fetal exposure to excessive glucocorticoid concentrations with subsequent effects on fetal organ development, particularly of the HPA axis (142). Activation of the fetal HPA axis occurs prior to birth in all species studied (57) and is essential for parturition in some, such as the sheep (29). In sheep moderately undernourished only around the time of conception, placental 11β-HSD-2 activity was decreased in mid-gestation (83); fetuses of these ewes had accelerated activation of their HPA axis and were delivered preterm (15).

Finland is a country with high licorice intake, with one study of pregnant women reporting that only 2.3% of women never ate licorice in pregnancy (167). Of those who did, average weekly consumption was calculated to be 363 mg, with 11% of women consuming more than 500 mg/week (high consumers). This population, therefore, presented a unique opportunity to study the relationship between glycerrhizin intake and gestation length. Gestation length was significantly less in high consumers [mean (SD) 39.7 (1.5) weeks] compared with medium [250–499 mg/wk; gestation length 40.0 (1.3) weeks] and low consumers [<250 mg/wk; gestation length

40.1 (1.2) weeks] (167). Heavy consumption was associated with a twofold increase in the risk of preterm birth prior to 37 weeks' gestation and a threefold increase in the risk of early preterm birth prior to 34 weeks' gestation [adjusted OR 3.07 (1.17–8.05)] compared with term birth (166). Furthermore, at age 8 years, offspring of high consumers had decreased scores on the Wechsler Intelligence Scale for Children, lower narrative memory scores, and externalizing behavior with reduced attention compared with zero-low consumers (134). These findings appeared to be dose-related and independent and were not related to perinatal outcomes. Children of high licorice consumers demonstrated elevated morning salivary cortisol peaks and elevated cortisol concentrations throughout a Trier stress test (135), findings that have also been demonstrated in offspring of women exposed to psychosocial stress during pregnancy (46) or who ate an unbalanced high-protein diet in pregnancy (143).

These are small studies, but they suggest a dose-dependent effect of a food substance on placental function, resulting in altered exposure of the fetus to maternal glucocorticoids, with consequences for fetal HPA axis function that ultimately lead to reduced gestation length and postnatal consequences. Considering the critical role the placenta plays at the interface between a mother and her fetus, the study of how placental function may mediate exposure of the fetus to ingested substances, including potential toxins such as endocrine disrupters (97), is clearly an important area for research.

PREPREGNANCY NUTRITIONAL STATUS AND GESTATION LENGTH

Maternal Nutritional Status and Preterm Birth

Data from populations or cohorts that are undergoing significant nutritional deprivation, such as famine, provide an extreme example of the effect of nutrition on pregnancy outcome. Of great interest currently is the nutritional status of women in our own societies who are of childbearing age. The Southampton Women's Survey, a prospective survey of 12,500 women of childbearing age, has provided insight into nutritional intakes in a relatively affluent city in southern England (79). Only 47% of women of childbearing age ate a diet that included ≥5 portions of fruit and vegetables daily (78), thereby meeting national recommendations (107, 114). This proportion was not different between women who did ($n = 238$) and did not ($n = 12,207$) become pregnant in the three months following the food survey (78). Furthermore, a later study that included additional nutritional data in early ($n = 2,270$) and late ($n = 2,649$) pregnancy demonstrated that there were only very small changes in dietary habits from before pregnancy to early pregnancy and from early pregnancy to late pregnancy (36). Only 5.5% of women who became pregnant within three months were taking the recommended daily folic acid supplement (78). The authors went on to devise a diet score for each woman based on principle components analysis (145). Up to 60% of women with the lowest level of educational attainment fell into the lowest quartile for the diet score (145); there was little effect on a change in dietary habit from before pregnancy to during pregnancy according to whether women were eating a prudent or "imprudent" diet (36). In 381 of these women, the investigators reported on fetal hepatic blood flow at 36 weeks' gestation. The majority of fetal hepatic blood flow comes directly from the placenta via the umbilical vein (71). A proportion of this blood bypasses the liver via the ductus venosus, and this proportion can change; for example, in intrauterine growth restriction there is increased shunting of umbilical venous blood through the ductus venosus to preserve oxygen and nutrient supply to the brain. In the fetuses of these healthy, low-risk women, the proportion of blood that was delivered to the liver was increased, and thus blood shunted through the ductus venosus was decreased, in slim women with reduced subscapular skinfold thickness prior to pregnancy and in those women with an imprudent diet score prior to pregnancy (71).

Trier stress test: a method to induce psychosocial stress involving a 5-minute speech followed by 10 minutes of mental arithmetic in front of an evaluative panel

These data suggest that the late-gestation fetus is able to make cardiovascular adaptations to nutritional availability in early pregnancy, even when nutritional availability is likely to be in the normal range. The implications of this fetal "liver sparing" for postnatal metabolic health are unknown. However, preliminary data from the same study also suggest that women with reduced prepregnancy subscapular skinfold thickness and "imprudent" diet scores are twice as likely to deliver preterm (85, 86).

Similar concerns regarding the diet of young people have been expressed from Canada and in indigenous Australian peoples (64, 82, 106). This is despite the fact that in the United Kingdom, Canada, and Australia, as in most Western countries, the incidence of obesity in pregnancy is steadily increasing (127), indicating that obesity is not necessarily synonymous with good nutrition. In contrast, Japan seems to be facing an epidemic of thinness, which also may be associated with impaired nutrition, as low BMI has been reported to be a good marker of both individual and community nutritional deficit (3). Between 1976 and 2000, thinness among Japanese women between 15 and 29 years increased significantly, regardless of whether they lived in a metropolitan or rural area, so that by 2000 more than 20% had a BMI of less than 18.5 (172). BMI usually increases in teenage years; contemporary data suggest that in many Westernized countries it continues to increase through adulthood (168). However, in Japan, BMI starts to decrease again from about 18 years of age, and this trend has increased since the 1970s (168). Over a similar time frame, from 1980 to 2007, preterm birth in Japan has increased from 4.1% to 5.8%, and the incidence of low birthweight (<2,500 g) has increased from 5.2% to 9.6% (171).

Prepregnancy BMI and gestational weight gain have both been associated with pregnancy outcome, and there appears to be an additive effect of low prepregnancy BMI and low gestational weight gain. A recent robust systematic review and meta-analysis of 78 observational studies including 1,025,794 women found that underweight women (defined by any BMI definition of underweight with a reference group) were at significantly increased risk of delivering prior to 37 completed weeks' gestation compared with women who were not underweight [crude RR from 32 studies 1.21 (1.14–1.28); adjusted RR from 14 studies 1.29 (1.15–1.46)] (68). In retrospective cohort studies, women with a normal prepregnancy BMI but who achieve below the recommended weight gain during pregnancy have been reported to have approximately a twofold increase in the risk of preterm birth (144); in women of normal prepregnancy BMI who have gestational weight loss the risk was almost threefold (11). Women with a prepregnancy BMI in the class III range of obesity, however, appear to be protected from this effect in some (10, 144), but not all (191), studies. A large ($n = 113{,}019$) retrospective study using data from the Pregnancy Risk Assessment Monitoring System in 21 U.S. states found increased risks (95% CI) for moderately [32–36 weeks' gestation; OR 3.1 (2.0–4.9)] and very [20–31 weeks' gestation; OR 9.8 (7.0–13.8)] preterm birth compared with term birth in women with a prepregnancy BMI <19.8 kg/m^2 and who gained less than 0.12 kg/week during pregnancy (40). Underweight women who did have weight gain within or above the recommended range still had a greater incidence of preterm birth (40), and the risk of preterm birth appears to be associated with the degree of thinness (149). As BMI is known to be associated with various socioeconomic factors that may also affect the risk of preterm birth, these studies have adjusted for factors such as level of education, marital status, previous preterm birth, preterm birth of the mother, and other variables, suggesting that the association is with BMI and not other confounding factors. However, it is important to note that all of these studies are retrospective cohort studies, with the potential flaws inherent in these studies.

In overweight and obese women, RCTs are needed addressing the effect of restricted weight gain or weight loss in pregnancy on pregnancy outcome, including the risk of preterm birth. Despite a lack of high-quality

evidence in this area, a recent report from the Institute of Medicine recommends a rate of weight gain in obese pregnant women that is half that in women with a BMI in the normal range (139).

Taken together, the data above suggest that nutrition in women of childbearing age in developed countries is often suboptimal, and this may be associated with an increased risk of adverse pregnancy outcomes, including preterm birth. As approximately 45% of preterm birth is idiopathic (61), it is urgent that the potential contribution of maternal nutrition to this problem, even in developed countries, is better understood. Data from the Southampton Women's Study may shed valuable light upon this question. The burgeoning data reporting altered metabolism and physiology, potentially leading to increased risks of disease in later life following nutritional deficits during pregnancy, in both human observational and interventional studies (49) and in experimental animal studies (69, 96), further add to the importance of understanding the relationships between maternal nutrition, fetal development, and pregnancy outcome.

Eating Disorders and Risk of Preterm Birth

The literature on pregnancy outcomes in women with an eating disorder or a past history of an eating disorder is conflicting. Sollid et al. (162) undertook a retrospective register-based cohort study in Denmark and identified 302 women who had been hospitalized for an eating disorder prior to pregnancy. The risk of preterm birth in these women was 1.7 (1.1–2.6) times greater than in women without a history of an eating disorder; the odds ratio was similar even in women who had been hospitalized more than eight years prior to the index delivery and who the authors considered were, therefore, more likely to have recovered. Other cohort studies have also reported an approximate doubling in the rates of preterm birth in women with eating disorders (6, 19, 23). However, a recent prospective cohort study of pregnancy outcomes in Norway (24), a nationwide study of pregnancy outcomes in women with anorexia nervosa in Sweden (44), and a longitudinal cohort study in the United Kingdom (108) did not find an increased risk of preterm birth in women with a variety of eating disorders, suggesting that the earlier studies may have been confounded. Numerous potential confounding factors may influence the association between maternal eating disorders and pregnancy outcome. For example, it has been reported that girls born preterm (33) or small-for-gestational age (51) are at increased risk of developing anorexia nervosa. Girls born preterm also are more likely to deliver preterm themselves (132). Women who have recovered from anorexia nervosa are more likely to maintain a lower BMI than women who did not have an eating disorder (169), and women with lower prepregnancy BMI are more likely to deliver preterm (40). Overall, the evidence does not suggest a large effect of eating disorders on the risk for preterm birth.

Socioeconomic Factors, Ethnicity, and Preterm Birth

It is possible that the associations between BMI, poor pregnancy weight gain, poor nutrition, and preterm birth could be explained by socioeconomic status (112). Preterm birth has been widely reported to be associated with lower socioeconomic status in many cohorts and populations (65, 91, 92), although not in all (126), and significant risk of selection bias in cohort studies of women of low socioeconomic status has been proposed (93). A study from Finland investigated two cohorts separated by 20 years and reported an almost halving of preterm birth rates that was strongly associated with increasing socioeconomic status (119). However, the association between BMI and socioeconomic status is complex, with recent data suggesting that although a positive association remains in low- and middle-income countries (162), the burden of obesity in developing countries shifts toward lower socioeconomic status groups as the gross national product increases and that this shift occurs earlier in women than in men (111). In developed countries, obesity is more common in lower socioeconomic groups (147),

although the quality of the diet remains suboptimal (38), even in pregnancy (116). Thus, it is currently not possible to determine definitively whether the increased risk of preterm birth in lower socioeconomic status groups is related to nutritional factors, other factors associated with lower socioeconomic status, such as stress, or a combination of these.

Data from all births in the United States in 2007 clearly show that rates of preterm birth are higher in women of non-Hispanic black origin than in those of Hispanic or non-Hispanic white origin (103). This is true for all births before 37 completed weeks' gestation, but also for each category of preterm birth (between 34 and 36 weeks' gestation, between 28 and 33 weeks' gestation and before 28 completed weeks' gestation) (103). It remains true even in the 9.6% of women identified as being in pregnancies at low risk for preterm birth ($n = 18{,}815$) in the Pregnancy Risk Assessment Monitoring System database, which includes singleton births from selected U.S. states between 1988 and 2002 (189). This study found that low-risk, multiparous African-American women had a 1.3-fold (1.0–1.6) increased risk of preterm birth before 37 completed weeks' gestation compared with white women (189). Mason et al. (104) investigated the effect of ethnic density on preterm birth rates in New York, analyzing city birth records from 1995 to 2003 ($n = 1{,}052{,}576$ births). They hypothesized that high ethnic densities may restrict nonwhite ethnic groups' access to white neighborhood resources but may increase the strength of social support. Adjusted preterm birth risks were calculated for ethnic groups, comparing areas of high (>25%) and low (≤25%) ethnic density using a proximity-weighted ethnic density measure. In non-Hispanic whites, maternal residence in areas of high ethnic density was associated with an adjusted risk difference for preterm birth of −15 (−18.5, −11.4) compared with residence in areas of low ethnic density, indicating a protective effect. For non-Hispanic black women, residence in an area of high ethnic density was associated with a risk difference of 6.4 (2.8–9.9), indicating a damaging effect. For all ethnicities apart from non-Hispanic blacks, the risk difference for preterm birth associated with residence in areas with a high ethnic density was lower in poorer neighborhoods compared with richer neighborhoods; for non-Hispanic blacks the risk difference increased from 6.4 to 9.0 (4.0–14.0) (104). The authors conclude that conventional measures of deprivation cannot explain all of the differences between non-Hispanic whites and non-Hispanic blacks because data for Hispanics with a similar deprivation score tend to show a protective effect of high ethnic density, similar to that seen in whites. Others have suggested that epidemiological data suggest a life-course approach toward understanding the ethnic discrepancies in pregnancy outcomes might be helpful (27, 95). Potential life-course factors include early-life fetal developmental programming of later health and reproductive success (26, 94), and weathering (60), both of which are influenced by nutrition.

POTENTIAL MECHANISMS UNDERLYING A ROLE FOR PRE- OR EARLY-PREGNANCY NUTRITION IN PRETERM BIRTH

Nutrient requirements for the embryo and early fetus are tiny and are unlikely to be compromised even in situations of significant maternal nutritional deprivation. In addition, nutrition in early pregnancy is histiotrophic rather than hemotrophic (13). Thus, it seems most likely that the developing embryo and fetus must "sense" the nutritional environment and respond accordingly, perhaps by setting a developmental trajectory that will determine the timeline for maturation and also gestation length (14). Observational data in humans and experimental data in animals lend some support to this suggestion. For example, twin pregnancies are of shorter duration than singleton pregnancies, and twins are born smaller even when the number of fetuses is reduced to a singleton in early gestation either spontaneously or by intervention (18, 131). We have

recently demonstrated the same phenomenon experimentally in sheep, in which one twin was randomly euthanized on day 42 of a 150-day pregnancy, and the twin-bearing control ewes underwent a sham procedure (S.N. Hancock & F.H. Bloomfield, unpublished data), indicating that fetal growth trajectory and gestation length in twins are determined in early pregnancy. This appears to be true in singleton pregnancies also; a large cohort study found that singleton fetuses that are smaller than expected on a first trimester ultrasound scan have a twofold increased risk of preterm delivery (161). This relationship was confirmed in a cohort with known gestational age secondary to assisted reproductive technology (21). Smaller-than-expected size at first trimester scan was also associated with an increased risk of being born small-for-gestational age, suggesting a link between early growth trajectory and gestation length, an association that has also been demonstrated in twins (73). Male fetuses are also smaller than female fetuses in the first trimester, suggesting early setting of growth trajectories according to sex (22).

Although the data on the association between assisted reproductive technologies and preterm birth are not unanimous and may be confounded, the weight of evidence suggests that the risk of preterm birth is increased following assisted reproductive technologies in both singletons and twins (153, 190). As the embryos are often developing in an artificial environment, it is likely that factors operating in this time are responsible.

Thus, many factors, in addition to maternal nutritional status, may operate around the time of conception to determine pregnancy outcome and, indeed, the long-term outcome of the offspring. Factors proposed include nutrients, oxidative stress, and metabolic stress. These factors may act via a variety of mechanisms to influence fetal growth, development, and the timing of birth, including the relative allocation of embryonic cells to the trophectoderm and inner cell mass, which will become the placenta and embryo, respectively, changes in the rate of apoptosis, and altered endocytic capacity of the early embryo, which is an early route for nutrition (56, 187, 188).

How these adaptations are brought about is still not clear, but a proposed mechanism is that of epigenetic modification of the embryonic genome. The early embryo undergoes genomewide epigenetic reprogramming between the zygote and morula stages, which involves both a loss of DNA methylation and of histone modifications (54). Studies in mice have found that embryos from superovulated dams, or that have been cultured in vitro, have a greater incidence of disturbed methylation patterns than do control embryos as early as the two-cell stage (154), suggesting that the concern around an increased incidence of imprinting disorders in human in vitro fertilization pregnancies (190) may be valid. Embryo transfer in mice, without in vitro culture, has also been demonstrated to perturb methylation at embryonic day 9.5; a period of in vitro culture increased the number of affected genes (144). Recent evidence suggests that nutritional factors also affect epigenetic modifications in the fetus (for review, see 26). The periconceptional undernutrition in sheep that led to preterm birth (15) also led to epigenetic change in the late-gestation fetus, with hypomethylation and increased H3K9 acetylation of the glucocorticoid receptor and pro-opiomelanocortin genes in the appetite-regulatory pathways in the ventral hypothalamus (165). Recent data from the offspring of the Dutch Famine suggest that epigenetic changes secondary to maternal undernutrition are both sex specific and dependent upon the time of exposure, with the periconceptional period being a critical window for these effects (74, 174). Similarly, conception during the rainy season in the Gambia, when there is poor maternal nutrition, has been found to be associated with increased methylation at putative metastable epialleles in 9-year-old offspring (186). Metastable epialleles are genomic loci that demonstrate altered epigenetic change in response to the environment independently of genotype and thus could assist in understanding the relationships between the early life environment,

epigenetic regulation of gene expression, and later disease.

Finally, epigenetic inheritance from the father may also be a factor. Female offspring from rats fed a control diet but mated with bucks chronically exposed to a high-fat diet develop impaired glucose tolerance, suggesting that the underlying mechanism is paternal epigenetic inheritance (115). This review has focused on the relationship between maternal nutrition and preterm birth; these preliminary data in rats suggest that research on the role of paternal nutrition in pregnancy outcome and offspring health should not be neglected.

CONCLUSIONS

Many women of childbearing age do not have optimum nutritional intakes. In developing countries this may be due to undernutrition, whereas in developed countries it may reflect a poor or unbalanced diet. Published recommendations around healthy eating for pregnant women focus on healthy eating while pregnant (80, 110, 114), yet maternal eating habits seem to change little during pregnancy (121). The evidence presented in this review suggests that maternal nutrition during pregnancy and a woman's underlying nutritional status even before conception may be of significant importance with respect to decreasing the risk of preterm birth. Total nutritional intake, the balance between energy and protein, and adequate intake of specific micronutrients such as folate, as well as maternal body nutrient stores, may all play a role in gestation length. Inadequate maternal nutrient stores may be reflected by low BMI, but caution must be taken in assuming that a high BMI equates to adequate nutrition. There is some evidence for a role of particular nutrients in either prolonging (*n*-3 fatty acids) or shortening (licorice) gestation length. The role of paternal nutrition in gestation length is unexplored but may also be important.

Further research is needed to identify the best nutrition for women who may become pregnant, but in the meantime there is enough evidence to suggest that targeting dietary advice that is available at women before they become pregnant may be a better approach than waiting until pregnant women book for care, which is usually toward the end of the first trimester. Data from experimental studies into mechanisms by which maternal nutrition may affect fetal development and pregnancy outcome suggest that this is too late.

SUMMARY POINTS

1. Poor maternal nutrition in the prepregnancy and periconceptional periods appears to be a risk for preterm birth.
2. An adequate intake of specific micronutrients, particularly folate, may be important in decreasing the risk of preterm birth.
3. It is not yet known whether the associations between maternal prepregnancy and periconceptional nutrition and gestation length are due to overall nutrition or deficiency of a particular nutrient.
4. Although the reductions in gestation length with poor maternal nutrition are generally not large, increasing evidence of both short- and long-term morbidity following late preterm birth indicates that this is a significant issue in population terms.

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Errata

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