Maternal Nutrition Before and During Pregnancy

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Abstract

In humans, the link between the maternal diet and the outcome of pregnancy is best illustrated by the classic study of wartime famine in Holland. During the famine it is likely that a low food intake reduced the glucose stream from the mother to fetus and gave rise to smaller size at birth. Maternal glucose production is also influenced by the type of carbohydrate in the diet. Even when famine and starvation are not issues, a low dietary glycemic index can alter maternal blood glucose production and the area under the glucose curve, and give rise to reductions in fetal growth and infant weight at birth. Reduced food intake in famine areas would also reduce the concentration of micronutrients in the maternal diet. Two micronutrients (iron and folate) have effects on pregnancy outcome that have been shown with some consistency in pregnant women. Emerging evidence now suggests that use of micronutrient-containing prenatal vitamins before and during pregnancy is associated with reductions in the risk of congenital defects, preterm delivery, low infant birthweight, and preeclampsia.

The relation between birthweight and risk of chronic disease in later life was noted by Barker et al. [1] in their study of a cohort (1915–1938) born in Hertfordshire, England; they suggested that an increased risk of early and later adverse events was linked through poor maternal nutrition during pregnancy.

In animal models maternal starvation reduces the amount of metabolic substrate produced by the mother and supplied to the fetus and diminishes intrauterine growth [2]. Likewise, a diet low is micronutrients is associated with a pregnancy complicated by congenital defects, preterm delivery and other adverse outcomes [2]. However, apart from exceptional circumstances
such as famine, the influence of the maternal diet on fetal growth and gestation duration is controversial.

**Famine and Undernutrition**

Studies in developing countries and among different ethnic groups have been virtually unanimous in showing a positive relationship between pre-gravid weight or body mass index, and gestational weight gain with birthweight and gestation duration [2]. Maternal underweight and inadequate weight gain are associated with lower birthweight, decreased gestation duration and increased risks of low birthweight reflecting fetal growth restriction and/or preterm delivery [2]. Consequently, it is widely thought that many pregnant women are underweight or gain weight poorly because they are poorly nourished. Thus, one reason that maternal pre-gravid weight and weight gain correlate to adverse pregnancy outcomes may be through diet and energy balance.

In the classic study of wartime famine well-nourished Dutch women experienced serious food shortage in the course of pregnancy [3]. It was observed that first trimester exposure at the peak of the famine, in combination with infection or another unknown factor, was linked to an excess of preterm birth and to an increase in infants weighing <2,000 g. There was also a rise in the frequency of malformations of the central nervous system including spina bifida [3] which is consistent with a deficiency in folate intake.

In ewes a short interval of food deprivation around the time of conception – from 2 months before to the first month after conception – increases the risk of preterm birth. Restriction was brief, reduced maternal weight by about 15%, and was followed by ad libitum feeding for the remainder of gestation [4]. Since the nutritional demands of the fetus early in gestation are modest, it was unclear if preterm delivery was triggered by the shortage of essential nutrient(s), a lack of calories or other factors. Likewise, in Gambia there is a fluctuating food supply between the dry and rainy seasons. This is reflected by seasonal changes in maternal weight. Pregnancies conceived in the months when women are at their lowest weights are significantly shorter (38.6 versus 39.0 weeks) than pregnancies conceived when food is more abundant [5]. Apart from food shortages, periods of extended fasting (13 h or more during the second and third trimesters) are associated with increased production of corticotropin-releasing hormone, which is related to an increased risk of preterm delivery [6].

**Glucose and the Glycemic Index**

Glucose is the main energy substrate for intrauterine growth and is transmitted in a steady stream from mother to fetus [7]. Glucose is produced by maternal metabolism principally from carbohydrate in the diet and from the
gluconeogenic amino acids. In turn, the hormone insulin regulates glucose.
Dietary restriction reduces metabolic fuels that give rise to slower fetal
growth; maternal hypoglycemia is also associated with an increased risk of
fetal growth restriction [7–9].

The Dutch famine is best known for its effects on fetal growth, and third
trimester exposure to intense famine resulted in decreased maternal postpar-
tum weight and reduced infant birthweight [3]. The largest deficits in birth-
weight, which amounted on average to 300 g, occurred with famine exposure
during the last half of pregnancy. Infants returned to their usual weight after
the famine ended. During the famine, reduced maternal intake following
small, infrequent meals would have resulted in lower circulating levels of
maternal glucose. Reductions in maternal body mass and fat stores from
famine would have altered glucose disposal and left less maternal fat to oxi-
dize as an alternative fuel. Thus, a reduced glucose stream from mother to
fetus would have given rise to slower fetal growth, smaller birth size, and an
increased risk of fetal growth restriction.

In addition to the amount of food (energy) that is eaten, maternal glucose
is influenced by the type of carbohydrate in the mother’s diet [8, 10, 11]. The
glycemic index is a relative measure of the blood glucose response to a given
amount of carbohydrate that represents the quality of the carbohydrate that
is eaten. The glycemic index is defined as the incremental area under the glu-
cose response curve following the intake of 50 g of carbohydrate from food
compared to the glucose area generated from a similar amount of white bread
or glucose [10, 11]. Some carbohydrates are absorbed more slowly than oth-
ers and thus may have a weak effect on blood glucose levels. Although there
is variation within and between individuals, on average foods with a lower
glycemic index give rise to a smaller blood glucose response than foods with a
higher glycemic index [10, 11].

During pregnancy a mother’s dietary glycemic index is positively and sig-
nificantly related to circulating levels of glucose; in urban, low-income women
from Camden there was a 2% difference in glycosylated hemoglobin and a 4%
difference in plasma glucose between gravidae at the extremes (quintiles) of
the glycemic index [12]. In the same cohort, a low dietary glycemic index was
associated with lower infant birthweight – a reduction of 116 g and a 2-fold
increased risk of bearing a small for gestational age infant [12]. These obser-
vations were in accord with the results of a small clinical trial (n = 12) where
exercising women eating a low glycemic index diet had a lower plasma glu-
cose response to a standard meal than women on a diet with a high glycemic
index diet and infants with birthweights that were substantially lower by
1,000 g [13]. A recent randomized trial in which Australian women (n ~30/group)
were randomly assigned to a low or higher glycemic index diet also showed
changes [14]. Women in the low glycemic index group again had infants with
lower birthweights (~236 g) and lower ponderal indices, and the risk of large
for gestation births was substantially reduced (3.1 vs. 33.3%), but a smaller
increase (9.4 vs. 6.7%) in the risk of fetal growth restriction was not statistically significant. Even in situations where starvation is not an issue, the mother's glycemic index can alter blood glucose production and the area under the glucose curve, reduce fetal growth and infant weight at birth (fig. 1). It should be noted that several epidemiological studies have produced inconsistent results on the influence of the glycemic index or load on risk of type 2 diabetes. However, the evidence from pregnancy, although not yet definitive, suggests that further study may be fruitful and important.

**Micronutrients**

Reduced food intake in famine areas would also reduce the concentration of micronutrients in the maternal diet. A low intake of micronutrients has the greatest potential to do harm during times of rapid tissue growth such as pregnancy. But, unlike animal models that involve experimental manipulations of single nutrients, in humans inadequate intake of a single nutrient usually does not occur in isolation.

Although there are exceptions, many studies now demonstrate that the use of micronutrient containing prenatal vitamins before and during pregnancy is associated with increases in birthweight and reductions in the risk of preterm delivery, low infant birthweight, gestational hypertension and preeclampsia [15, 16]. Two micronutrients (iron and folate) have effects that have been demonstrated with some consistency, and for a third (vitamin E) data on pregnant women are beginning to emerge.

Iron is a micronutrient that is essential for the formation of hemoglobin to transport oxygen, and for the synthesis of enzymes that use oxygen to provide cellular energy. Anemia (low hemoglobin levels) and iron deficiency anemia also serve as indicators of overall maternal nutritional status during pregnancy. When overall dietary intake is inadequate, the risk of anemia is increased [2].

![Infant birthweight with high versus low maternal dietary glycemic index (GI).](image_url)
Folic acid functions as a coenzyme in the transfer of single-carbon atoms from donors such as serine and histidine to intermediates in the synthesis of amino acids, purines, and thymidylic acid. Inadequate intake of folate leads to impaired cell division and alterations in protein synthesis.

Vitamin E is a lipid-soluble chain-breaking antioxidant that is dietary in origin. In addition to its antioxidant actions, vitamin E enhances the release of prostacyclin, a metabolite of arachidonic acid that inhibits platelet aggregation, quiets uterine contractility and increases vasodilation thus potentially improving blood flow between the fetus and placenta.

Iron and Anemia

Maternal anemia is linked to an increased risk of adverse outcomes during pregnancy [2]. During the first and second trimesters, the hemoglobin concentration declines, reaches a low point early in the third trimester, and rises thereafter. Depending on the stage of gestation when anemia is assessed, it can be difficult to separate truly anemic women from those whose anemia results from hemodilution. The best time to detect risk associated with maternal anemia may be early in pregnancy before the plasma volume is fully expanded. This was originally examined in Camden, separating maternal anemia by time, i.e. early vs. late (week 28), and etiology (iron deficiency anemia (IDA) vs. anemia from other causes) [17]. IDA at entry was associated with greater than 2-fold increases in the risks of low birthweight and preterm delivery, while anemia from other causes was associated with a small but non-significant increase in risk. In the third trimester when the effects of hemodilution are profound, the risk of preterm delivery was reduced for women with IDA, and there was no increased risk for women with other anemias [17]. The association of maternal anemia, based upon early pregnancy hemoglobin with preterm delivery extends to the time before conception. Anemic Chinese workers who later experienced a pregnancy had 5- to 6-fold increases in the risk of low birthweight infants and fetal growth restriction, and gave birth to infants weighing 140–200 g less than other women. When anemia was attributable to iron deficiency, the birthweight reduction was greater still amounting to a decrement of approximately 250 g [18].

Two clinical trials conducted among low income iron-replete women from the United States suggested that iron supplementation can reduce associated risks. Gravidae were enrolled early in pregnancy (≤20 weeks) and randomly assigned to supplemental iron (30 mg/day as ferrous sulfate) or to multivitamins with and without iron (ferrous sulfate 30 mg) [19, 20]. In both instances infant birthweight was increased and supplemented women had either significantly longer gestations or a lower risk of delivering preterm. Plausible biologic mechanisms underpinning the effects of iron during pregnancy include chronic hypoxia that initiates a stress response with the
release of placental corticotropin-releasing hormone and an increase in fetal production of cortisol, increased oxidative stress that damages the maternal–fetal unit and reduced immune function which increases the risk of maternal infection [21].

**Folic Acid**

It is recommended that pregnant women in the US consume 600 μg folic acid/day, which includes 400 μg of synthetic folic acid from supplements or fortified cereals, to reduce the risk of neural tube defects. Fortification of flour and cereal products in the US with folic acid (since 1998) has been associated with a 19% decline in the risk of live-born infants with neural tube defects, along with changes in biomarkers of folate status, including increases in serum and red cell folate and a decline in homocysteine levels [22].

An absolute deficiency of folate (from a diet inadequate to meet the needs of pregnancy) will interfere with the growth of the conceptus [2]. The influence of dietary and circulating folate on preterm delivery and low infant birthweight was studied in women from Camden, one of the poorest cities in the continental US. Low folate intake (<240 μg/day) was associated with a greater than 3-fold increase in the risk of low infant birthweight and preterm delivery. Circulating folate at week 28 was also associated with risk; the adjusted odds for low birthweight increased by 1.5%, and preterm delivery increased by 1.6% per unit decrease in concentration [23, 24]. Lower dietary folate intake (<500 μg/day) at 24–29 weeks gestation was associated with an approximately 2-fold increased risk of preterm delivery in women from North Carolina. Low levels of serum or RBC folate at the same gestation were each associated with an increased risk of preterm birth [25].

In Camden, we demonstrated an interaction between a pregnant woman’s dietary folate intake and the presence or absence of a deletion allele in a folate-metabolizing gene that codes for the production of dihydrofolate reductase (DHFR) [24]. DHFR is an enzyme that converts folic acid used in supplements, and fortifies the US food supply to the reduced folate forms used by cells. The presence of the DHFR deletion allele increased the risk of preterm delivery 3-fold and, when folate intake was also low (<400 μg/day), increased the risk of low birthweight 8-fold and the risk of preterm birth 5-fold.

A metabolic effect of folate deficiency is an elevation of homocysteine [2]. Hyperhomocysteinemia can occur when dietary folate intake is low or a nutrient–gene interaction increases the metabolic requirement for folate. Homocysteine levels measured in more than 5,800 women aged 40–42 were linked to past data on pregnancy outcome contained in Norwegian birth registries [26]. Women with high homocysteine levels were more likely to have had a past reproductive history that included preeclampsia, preterm delivery, low birthweight, or fetal growth restriction.
Two recent studies supported these adverse effects with measurements of homocysteine taken before or during pregnancy. In China, pre-conceptional levels of maternal homocysteine were associated with a 4-fold increased risk of preterm delivery [27]. An evaluation of homocysteine in 93 Spanish women before and during pregnancy showed that maternal and fetal levels were positively correlated (r = 0.5 to r = 0.7); and reduced by the use of folate-containing vitamins. The birthweights of infants exposed to high levels of maternal homocysteine before conception, at 8 weeks gestation or at delivery were approximately 200 g below the birthweights of infants born to mothers with lower homocysteine levels [28].

**Vitamin E**

In Camden, we found that plasma concentrations of α-tocopherol, the most common isomer of vitamin E, were positively related with increased fetal growth (birthweight for gestation), a reduced risk of small for gestation births and an increased risk of large for gestation births [29]. Concentrations of α-tocopherol were positively related to the use of prenatal multivitamins before and during pregnancy and to the intake of vitamin E in the maternal diet. Although vitamin E is well studied in cardiovascular disease, there is little evidence of its effectiveness during pregnancy. However, more than a decade ago von Mandach et al. [30] studied more than 300 women and their offspring and correlated lower vitamin E at delivery with low birthweight at term (n = 12), a measure of fetal growth restriction. Thus, emerging evidence suggests that circulating concentrations of vitamin E may be associated with increased fetal growth possibly via increased blood flow and nutrient supply to the fetus.

In summary, maternal nutrition and nutritional status before and during pregnancy are associated with decreased birthweight and increased risk of low birthweight, measured either as preterm delivery or restricted fetal growth. This is particularly germane in the developing world where much of the low birthweight that occurs is related to the mother's past and present nutritional status. By affecting fetal growth and gestation it is plausible that maternal nutrition may have a long-term influence on the risk of chronic disease in later life [1].

**References**

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Discussion

Dr. Cameron: Given all the work you have done with teenager pregnancies, can you give us some sense of how these deficiencies interplay with growth during that time in terms of outcome, in terms of birthweight outcome?

Dr. Scholl: The deficiencies are more prevalent in teenager mothers. About 10 years ago we demonstrated that roughly half of the teenage women from Camden were still growing during pregnancy; but that maternal growth was not demonstrable from usual clinical measurements taken in the course of pregnancy [1–4]. Growing adolescents have lower levels of micronutrients (ferritin, folate), larger gestational weight gains but smaller babies. That is, they do not show the usual relationship between weight gain and birth weight, where women who have larger gestational weight gains have babies with higher weights at birth. The maternal diet buffers the effect of the mother’s growth on the growth of the fetus that is not seen in mature women or teenagers who do not grow. When a still-growing mother has a lower caloric intake the birth weight deficit is quite large, 500 g or so. When caloric intake is higher (>2,400 kcal/day) the deficit is less, on the order of 200 g. The still-growing mother gains and retains more fat than the others, and has a 5-fold increased risk of new overweight/obesity in the postpartum. The competition for nutrients between a growing mother and her fetus has also been demonstrated in animal models including the rat dams and ewes [5, 6]

Dr. R. Bergmann: Could we overdo micronutrient supplementation? I am thinking about a study by Poston et al. [7] who gave very high, but still advisable doses of antioxidants, vitamin E and vitamin C, and in some risk groups there was a higher rate of preterm and in others of low birthweight newborns.

Dr. Scholl: The study you refer to supplemented gravidae at high risk of pre-eclampsia with higher levels of Vitamins C (1000 mg) and E (400 IU), and Poston et al. did show reduced birth weight at this level of micronutrient supplementation [7]. However, I was commenting on usual prenatal multivitamin mineral preparations. Poston et al. also demonstrated that babies in the placebo arm of their trial were larger when the mother used prenatal vitamins and minerals. Other studies [8, 9] have not demonstrated adverse effects on birth weight or gestation in supplemented women who later developed pre-eclampsia.

Dr. Bier: You showed us some data on the glycemic index of diets but the amount of carbohydrate in the mother and the fetus is not strictly based on the glycemic index, it is the glycemic load and this requires measuring the amount of the carbohydrate taken. What were the differences in glycemic load of these diets?

Dr. Scholl: The glycemic load had a weak effect on hemoglobin A1C. But in general it was the glycemic index that seemed to be associated with a stronger maternal blood glucose response, with hemoglobin A1C and with a response in fetal growth. The recent trial of the glycemic index among Australian gravidae [10] gave both groups the same amount of carbohydrate making the glycemic index and glycemic load equivalent.

Dr. Bier: If the glycemic load is no different, I don’t understand how that has an effect on insulin secretion, glucose transport or anything else. That’s what is moving, the amount of glucose.

Dr. Scholl: All of the women in the study were glucose tolerant; none of them had pre-gestational or gestational diabetes so that insulin sensitivity and beta cell function were normal; glucose homeostasis was balanced. But, I suggest that such a response might be demonstrable under experimental conditions i.e. with a hyperglycemic clamp.

Dr. Makrides: I want to ask your views on vitamin and mineral supplementation in pregnancy. The Cochrane Systematic Reviews bring together the relevant randomized
trials, whether they are to do with the antioxidants, vitamin E, vitamin C, magnesium, iron, and generally conclude that there is no clear beneficial effect [8, 9]. I wonder whether you could comment about specific subgroup analyses and whether we should be looking in more detail at population differences as you have some great data that suggest that some people may benefit more than others.

Dr. Scholl: I think there are large population differences. If you do a clinical trial in middle class women from the UK or the US, I would think that the results would be much more attenuated than the results of women who are poor, who eat diets that are high in fat, and who basically eat no fruits and vegetables. Certainly there must be huge differences between populations.

Dr. Makrides: Do you have any suggestion on how we might be able to group the populations across trials?

Dr. Scholl: You could stratify according to risk status of the underlying population. In other words does the population underlying the sample have a high risk of low birth weight, of pre-eclampsia, of preterm delivery? In effect, you could use the known prevalence of an adverse outcome as the gauge of an expected response.

Dr. Ogra: Thank you for a really very thoughtful presentation, Dr. Bier raised the issue about the glycemic index. Does it correlate well with the actual levels of insulin or C-peptide in the mothers?

Dr. Scholl: No, our unpublished data suggest a correlation with fetal levels of insulin and IGF-1. But, in his trial Clapp et al. [11] demonstrated differences in the area under the maternal insulin and maternal glucose curves.

Dr. Ogra: I was wondering if one might be able to reconcile the concerns voiced by Dr. Bier by looking at insulin levels? The second question is related to IGF-1. Do you think there is a change taking place at the transcriptional level; perhaps there are changes in other transcription factors beside IGF-1 and others, possibly NF-κB?

Dr. Scholl: I would not speculate. We measured only IGF-1 and insulin in the cord blood, but it's quite possible.

Dr. Ogra: Why do you think IGF-1 is in fact altered in this situation?

Dr. Scholl: The reason why I think the IGF-1 is altered is because the fetus is growing more. The women who ate a diet with a higher glycemic index had babies who grew larger, and insulin and IGF-1 are related to fetal size, but part of the stimulus came from the maternal diet.

Dr. Malka: Can you say anything about fish oil supplements in the third trimester that improve neonatal neurodevelopment?

Dr. Scholl: We have never measured fish oil consumption in Camden. I do know that there was a clinical trial done throughout Europe, a multicenter trial that showed reductions in the risk of preterm delivery but not in pre-eclampsia, that was another arm of the trial. So they seem to be very important but we haven’t worked with fish oils.

Dr. Malka: What about women who gained more than 16 kg, were they at risk of macrosomia?

Dr. Scholl: We do have some macrosomia in Camden but prevalence is low. The women with gestational diabetes and the women who are obese have an increased risk of macrosomia, but on the whole our babies are small.

Dr. Walker: Just a point of clarification, it is my understanding that when zinc and vitamin A are given to HIV-positive mothers who are transmitting the virus to their babies who developed AIDS, they are effective only under conditions in which they were insufficient. The mothers were being given quantities of these micronutrients to make them sufficient, rather than excessive amounts having an anti-HIV effect, is that right?

Dr. Scholl: That’s right, thank you for that.

Dr. Makrides: May I contribute to the discussion about glycemic index and the question that Dr. Bier raised. I understand that there was an issue with the Australian
study in that the women allocated to the high glycemic index group also happened to have a higher BMI at study entry, and that may have contributed to the results because BMI at study entry was not adjusted for in the statistical analysis [10]. I understand that this group is now planning to do a much larger study that will address this particular issue. With regard to fish oil supplementation in pregnancy, we have recently finished the Cochrane Systematic Review including all relevant trials with over 6,000 women, and the effect of fish oil supplementation in pregnancy was to increase the length of gestation by an average of 2.5 days, and have no effect on low birthweight or preeclampsia [12]. The effect on gestation length is of questionable clinical significance. There are a number of ongoing studies in Mexico, Australia and the USA trying to address the issue of neurodevelopment, but in terms of major pregnancy outcomes, such as preterm birth and preeclampsia, fish oil does not seem to play a large role.

Dr. Guinto: From the studies you cited, were the micronutrients given for the entire pregnancy or are there critical periods during pregnancy during which these micronutrients must be given?

Dr. Scholl: Women were provided with micronutrient supplements, it was an observational study. Some women used them, some did not. Some of the women used them during the first, second and third trimester, others used them erratically, and all of this was taken into account. I didn't show the data on the supplements which did have an effect on preterm delivery. They reduced the risk of preterm delivery depending upon when they were started, how often they were taken, and how often they were used.

References
