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Early Influences of Nutrition on Fetal Growth

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Abstract

During pregnancy, the metabolic requirements of the mother are increased; however, the relationship between maternal intake of key nutrients and optimal fetal growth is not always clear. In this chapter, we have reviewed randomized controlled trials of nutritional interventions during pregnancy, with a particular focus on birthweight and infants who are small for gestational age (SGA). Of the trials that have investigated changing macronutrient and energy intakes during pregnancy, supplements in which <25% of the energy is provided by protein yielded the most promising results, producing a 31–32% reduction in the risk of SGA infants and an increase in birthweight (38–60 g) compared with control. Single-nutrient intervention trials using n-3 long-chain polyunsaturated fatty acid (LCPUFA) supplements demonstrated small increases in birthweight (≈50 g) and birth length (≈0.5 cm), which may be explained by small increases in gestation length (approximately 2.5 days). n-3 LCPUFA supplementation in pregnancy did not however decrease the proportion of SGA infants. Multiple-micronutrient supplementation trials in developing countries have resulted in increased mean birthweight (22–44 g) and reduced the risk SGA by 9–15%. Further nutritional intervention studies which are rigorously designed and implemented are needed particularly to delineate differential effects in developed and developing countries.

Infants with restricted intrauterine growth are more likely to have poor cognitive development during childhood, and later in life are also at increased risk of cardiovascular, pulmonary and renal disease. Prevention of low birthweight and growth restriction in utero is therefore an important target with the potential to improve the long-term outcome of children. It is therefore not surprising that many studies have focused their attention on improving the quality of the maternal diet during pregnancy in order to promote the growth of the fetus. However, it is evident that the relationship between maternal nutrition and fetal growth is not a simple one. Apart from maternal nutrition, there are many factors that influence the size of the infant at birth including genetic potential, the size of the mother, the success of placentation and delivery of nutrients to the fetus, pregnancy and metabolic adaptation to protect the fetus, other environmental stresses such as cigarette smoking and alcohol. In fact, some of these factors may play a greater role in influencing the size of the baby at birth, and it may be for this reason that it has been challenging to decipher the true effect of maternal diet during pregnancy on fetal growth. The scope of this chapter is to review the effects of maternal dietary intakes on the growth of the fetus with a particular focus on birthweight and the proportion of infants born who are growth restricted or small for gestational age (SGA). As we are interested in deciphering cause and effect relationships between maternal dietary intakes during pregnancy and birth size, the review is limited to randomized controlled trials that have been designed to assess the effects of specific nutritional interventions during pregnancy and have included birth size as an outcome.

The published intervention trials can be grouped into four categories: (1) macronutrient interventions that have increased energy, (2) macronutrient interventions that have decreased energy, (3) single-nutrient interventions that have not altered energy intake and (4) multiple nutrient, generally micronutrient, interventions that also have not altered energy intake.

Macronutrient Interventions That Have Varied Energy

Observational studies have consistently reported that gestational energy intake is strongly and positively associated with fetal growth. The most commonly cited example is the Dutch Famine Study that found a clear association between the forced restriction of energy intake in the third trimester and reduced fetal growth [1]. It therefore logically follows that macronutrient intervention to increase energy intake during pregnancy will increase fetal growth, while macronutrient interventions to decrease energy will decrease fetal growth.

Macronutrient Interventions That Increase Energy

The majority of trials that have investigated the effect of dietary macronutrient manipulation have focused on the protein energy balance and these are often split into supplements which provide <25% of the energy content as protein (protein energy ratio of <0.25) and supplements which provide >25% of the energy content as protein (protein energy ratio >0.25) [2]. To put this into context, many foods contain <25% energy as protein including whole milk and nuts, while lean meat and cheese are among the relatively few foods to contain >25% energy as protein.

Energy Supplementation in Which Protein Contributes <25% Energy

Two systematic reviews and meta-analyses of intervention studies have investigated the effects of supplements with a protein energy ratio of <0.25 during pregnancy on birth outcomes [2, 3]. The included studies tested various supplements, and where documented the protein content ranged from 6 to 40 g per day and provided 322–1,017 kcal of extra energy per day. The supplements were either beverages or solid foods, and were generally administered after 20 weeks' gestation. Blackwell et al. [4] started supplementation after a prior birth and continued during the index pregnancy, while Elwood et al. [5] began supplementation at the time of first reporting the pregnancy. These intervention trials were generally not well controlled as the vitamin and mineral levels in the control supplements did not match those in the energy supplement, but in many cases the control intervention was no treatment. Additionally, concealment of randomization was not always clearly reported, and because of the nature of the interventions blinding of participants was not always possible. Blinding of the assessors was also not always reported.

Despite these limitations, both meta-analyses revealed that supplements with a protein energy ratio of <0.25 during pregnancy resulted in a 31–32% reduction in the risk of SGA infants (relative risk, RR, 0.68–0.69; 95% confidence interval, CI: 0.56–0.84/0.85) [2, 3]. Participants in 5 of the 6 trials were undernourished. When the trial relating to adequately nourished women was excluded from the analysis, the RR became 0.66 (95% CI: 0.53–0.82) [3].

Pooled results in both systematic reviews, from 11–12 trials, showed that supplementation with a protein energy ratio of <0.25 also resulted in an increase in birthweight of approximately 38–60 g. Discrepancies in the magnitude of the increase reflect differences in inclusion criteria and weighting of the trials in the meta-analyses. Both reviews demonstrated a greater effect of supplementation on mean birthweight in undernourished women; however, the magnitude and significance of the increase (approximately 50–75 g) was again dependent on the criteria established in the reviews. No significant differences were found in birth length, head circumference or gestational age (GA) [2].

A 37–38% reduction in the risk of neonatal mortality, based on results of 3–4 trials, was also detected in both reviews (RR, 0.62–0.63; 95% CI: 0.37–1.05/1.06) [2, 3]; however, the results did not reach significance in either review.

Energy Supplementation in Which Protein Contributes >25% Energy

Few studies have addressed the effect of protein energy supplements that provide >25% energy as protein during pregnancy on birth size. Such supplements are challenging to construct and are unlikely to be palatable. However, two trials have intervened with high protein supplements based on beverages containing dried skimmed milk. Supplementation was associated with a nonsignificant reduction in birthweight (mean difference, MD, –58 g; 95% CI: –146 to 29 g) [2]. One of these trials [6] also reported a nonsignificant increased risk of neonatal death, mainly in pregnancies where infants were born prior to 37 weeks' GA with the protein supplement providing >25% of energy.

Macronutrient Interventions That Decrease Energy

The increased prevalence of obesity in many industrialized countries naturally implies that many more women who are overweight or obese are entering pregnancy. These women are at increased risk of pregnancy complications and poor pregnancy outcomes. With this rationale, several trials with small numbers of women (20–90 per group) have investigated the effect of energy restriction during pregnancy on birth size. The target energy intakes in the intervention groups were variable, and some were relatively severe and required women to reduce their energy intakes by at least 1,000 kcal per day. Although the interventions were uniformly successful at reducing weekly gestational weight gain, the meta-analysis indicated significant heterogeneity which could have been related to the differing interventions and/or the differing population groups [2]. The effect of energy restriction during pregnancy on birthweight in overweight women also exhibited significant heterogeneity with the three included trials showing either no effect of intervention, a large negative effect (MD –450 g; 95% CI: –625 to –275 g) or a nonsignificant negative effect (MD –138 g; 95% CI: –450 to 174 g).

On the basis of the trials reviewed so far, supplements with a protein energy ratio <0.25 during pregnancy may be worthy of consideration as a public health intervention to reduce the risk of SGA infants. The positive effects of supplements with a protein energy ratio <0.25 were more pronounced in populations that were not adequately nourished, but this finding should be interpreted with some caution as the trials did not use standardized maternal body mass index cutoffs to assess undernutrition [3]. Further carefully controlled RCTs would be beneficial, in both developed and developing countries, to ascertain with more certainty the optimum amounts of supplementation and best timing of the intervention. Conversely, the limited data available from RCTs indicate that energy restriction during pregnancy appears to have negative consequences on fetal growth even for women who are overweight or obese. A recent retrospective cohort study [7] has investigated associations of gestational weight loss (GWL) and birth outcomes. Although GWL was associated with a decreased risk of pregnancy complications in obese and overweight women, it was also associated with increased risks of SGA infants (OR, 1.68; 95% CI: 1.37–2.06) in all maternal BMI groups, except for underweight women. Large-scale RCTs currently in progress will be important to determine the metabolic and health consequences for both mother and child.

Nutrient Interventions That Do Not Vary Energy

Single-Nutrient Interventions

As the deficiency of specific nutrients such as zinc is known to be associated with growth failure in early life, it is interesting to consider whether supplementation of specific nutrients during pregnancy has a role on fetal growth. However, intervention trials involving single-nutrient interventions, including iron, zinc or calcium, have not yielded consistent or promising results that would indicate that maternal intervention with these single nutrients would change fetal growth [8–10].

Of specific interest are the n-3 long-chain polyunsaturated fatty acids (LCPUFA). n-3 LCPUFA are actively incorporated into all cellular membranes, and are postulated to have an important role in delaying parturition. It is hypothesized that n-3 LCPUFA can delay initiation of labor and cervical ripening by inhibiting the production of prostaglandins $F_2\alpha$ and E_2. These mechanisms together with observational studies suggesting that women consuming high n-3 LCPUFA from marine sources have longer gestations and babies with higher birthweights than women who consume low levels of n-3 LCPUFA led to a number of intervention trials that have been summarized in three separate systematic reviews [11–13]. The meta-analyses showed remarkably consistent results despite the fact that these reviews had differing inclusion criteria based on women's risk of adverse pregnancy outcomes. In brief, supplementation with marine oil (usually 3 g n-3 LCPUFA) in the second half of pregnancy resulted in higher mean birthweights (approximately 50 g) and higher mean birth lengths (0.48 cm) in the marine oil groups compared with control [11–13]. However, it is important to note that there was also a modest increase in the length of gestation (approximately 2.5 days) with marine oil treatment. The small increases in birthweight and length with n-3 LCPUFA treatment could probably be explained by the small increase in length of gestation. Furthermore, there were no overall differences between the groups in the proportion of SGA babies [11]. It is therefore entirely feasible to suggest that the observed increases in birthweight and birth length with n-3 LCPUFA supplementation are a function of the increased duration of gestation.

Two recent large intervention trials have investigated the effect of two different doses of n-3 LCPUFA, namely, an Australian study in which 2,399 women were allocated 1 g/day of n-3 LCPUFA mostly as docosahexaenoic acid (DHA; 800 mg/day) or control [14] and a trial conducted in Mexico in which 1,094 women were allocated to 400 mg DHA/day or control [15]. In both trials, supplementation was from mid-gestation until birth. Consistent with the systematic reviews, the Australian study [14] reported a small increase in the median duration of gestation, a significant reduction in early preterm birth <34 weeks (RR, 0.49; 95% CI: 0.25–0.94), no clear effect on preterm birth <37 weeks (RR, 0.77; 95% CI: 0.56–1.05) and increased obstetric intervention (inductions and elective caesarean sections) because of post-term dates (RR, 1.28; 95% CI: 1.06–1.54). This increase in pregnancy duration was reflected in higher mean birthweight with n-3 LCPUFA treatment (MD 68 g; 95% CI: 23–114 g) and a reduction in the frequency of birthweight less than 2,500 g (RR, 0.65; 95% CI 0.44–0.96). However, the birthweight z score did not differ between groups, indicating that there was no difference with correction for GA and sex using z scores [14]. Conversely, Ramakrishnan et al. [15] reported that mean GA at birth did not differ between groups (39.1 weeks, standard deviation, SD, 1.7 weeks vs. 39.0, SD 1.9 weeks) nor did birthweight (3.20 kg, SD 0.47, vs. 3.21 kg, SD 0.45), birth length or birth head circumference. However, the babies of women experiencing their first pregnancy were heavier (MD 99 g; 95% CI: 5–193) and had larger head circumferences (MD 0.5 cm; 95% CI: 0.1–0.9) at birth compared with controls [15]. There were no differences in birth size for the offspring of multigravida women [15]. The disparity between the two studies may relate to the different doses of n-3 LCPUFA tested as most trials included in the systematic reviews assessed the effect of 3 g n-3 LCPUFA per day, and it may be that at least 1 g n-3 LCPUFA per day is required to see the effect on pregnancy duration. Clearly, further work is required to clearly delineate whether there is any effect of n-3 LCPUFA supplementation on fetal growth independent of pregnancy duration.

Multiple Nutrient Interventions

The concept of multiple-micronutrient supplementation for undernourished women is particularly noteworthy because in most situations of undernutrition there is insufficiency of many micronutrients, and it is in fact quite rare to have single-nutrient deficiencies. Several systematic reviews of multiple-micronutrient interventions have been conducted recently [16–18]. Many, but not all, of the trials reviewed, used a United Nations International Multiple Micronutrient Preparation supplement and most were conducted in developing countries/rural areas. Overall, multiple-micronutrient supplementation, compared with iron-folate, resulted in increased mean birthweight by 22–44 g, reduced prevalence of low birthweight by 11–14% and reduced risk of SGA by 9–15%. One review also reported an increase in the prevalence of large for gestational age births (OR 1.13; 95% CI: 1.00–1.28) and an overall upward shift in birthweight distribution [16]. There was no significant impact on duration of gestation [16], the risk of preterm birth [16], neonatal mortality [17] or perinatal mortality [18]; however, there is considerable heterogeneity in the mortality results. Maternal education, GA at commencement of supplementation and home births were thought to contribute to the heterogeneity [17, 18]. The effects of the supplements on birthweight observed by Fall et al. [16] were also reported to be greater in women with higher BMI, suggesting that perhaps micronutrients do not have a positive influence during pregnancy if there is an 'overriding' maternal energy deficiency [16]. However, in a recent study in rural China, the beneficial effects of multiple-micronutrient supplementation on birth parameters were not seen in women from the wealthiest households [19] who would be expected to have a more adequate diet, less micronutrient deficiencies and greater access to healthcare information/services during pregnancy [19].

Few trials appear to have been conducted in developed countries. Hininger et al. [20] have investigated the effects of an iron-free multiple-micronutrient supplement on a small sample of women (n = 100) in urban France. Only 65% of women remained at the end of the study, but the supplement, compared to placebo, increased birthweight by around 10% and reduced the proportion of newborns with weights <2,700 g. Brough et al. [21] also conducted a study on a socially deprived group of women in London, UK. While only 39% of women completed this study, analysis showed there were no significant differences in mean birthweight, GA at birth, or risk of SGA between placebo and supplemented groups. However, when only compliant mothers were included in the analysis, it appeared that there may have been a role of the supplements in reducing SGA [21].

Conclusions

Collectively, the available data indicate that the protein energy ratio in the maternal diet during pregnancy is important for fetal growth. Excessive energy restriction during pregnancy is likely to limit fetal growth, while energy supplements with <25% of the energy as protein appear to increase fetal growth resulting in fewer babies born SGA. Additionally, supplements with a protein energy ratio of <0.25 seem most effective in women who are undernourished. Energy supplementation with excessive protein (>25% of energy) during pregnancy does not appear to have a clear effect on fetal growth, although the data are limited. The effect sizes observed in trials of energy supplementation of <25% energy as protein appear modest (38–60 g), accounting for 1–2% of total birthweight. However, when one considers that cigarette smoking during pregnancy reduces birthweight by 140–250 g (4–8% of total birthweight), the potential importance of nutritional intervention can be put into context. Interestingly, single-nutrient interventions in isolation probably have limited effectiveness in altering fetal growth even in women who are not well nourished. Conversely, multiple-micronutrient supplementation in undernourished women could help to support fetal growth probably because women who are undernourished are insufficient in more than one nutrient. What is not clear and has not been well investigated is the relative effect of energy supplementation with a protein energy ratio of <0.25 versus multiple-micronutrient supplementation especially since the studies of protein energy ratio also inevitably included a range of micronutrients, the concentration of which was often not controlled. Further studies, which are rigorously designed and implemented, are needed to optimize the dietary prescription for pregnant women.

References

1 Stein AD, Ravelli ACJ, Lumey LH: Famine, third-trimester pregnancy weight gain, and intrauterine growth: the Dutch Famine Birth Cohort Study. Hum Biol 1995;67:135–150.

2 Kramer MS, Kakuma R: Energy and protein intake in pregnancy. Cochrane Database Syst Rev 2003;CD000032.

3 Imdad A, Bhutta ZA: Effect of balanced protein energy supplementation during pregnancy on birth outcomes. BMC Public Health 2011;11(suppl 3):S17.

4 Blackwell RQ, Chow BF, Chinn KSK, et al: Prospective maternal nutrition study in Taiwan: rationale, study design, feasibility, and preliminary findings. Nutr Rep Int 1973;7:517–532.

5 Elwood PC, Haley TJL, Hughes SJ, et al: Child growth (0–5 years), and the effect of entitlement to a milk supplement. Arch Dis Child 1981;56:831–835.

6 Rush D, Stein Z, Susser M: A randomized controlled trial of prenatal nutritional supplementation in New York City. Pediatrics 1980;65:683–697.

7 Beyerlein A, Schiessl B, Lack N, et al: Associations of gestational weight loss with birth-related outcome: a retrospective cohort study. BJOG 2011;118:55–61.

8 Mahomed K, Bhutta ZA, Middleton P: Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2007;CD000230.

9 Pena-Rosas JP, Viteri FE: Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Cochrane Database Syst Rev 2009;CD004736.

10 Hofmeyr GJ, Lawrie TA, Atallah AN, et al: Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2010;CD001059.

11 Makrides M, Duley L, Olsen SF: Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. Cochrane Database Syst Rev 2006;CD003402.

12 Szajewska H, Horvath A, Koletzko B: Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2006;83:1337–1344.

13 Horvath A, Koletzko B, Szajewska H: Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Br J Nutr 2007;98:253–259.

14 Makrides M, Gibson RA, McPhee AJ, et al: Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA 2010;304:1675–1683.

15 Ramakrishnan U, Stein AD, Parra-Cabrera S, et al: Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico. Food Nutr Bull 2010;31:S108–S116.

16 Fall CHD, Fisher DJ, Osmond C, et al: Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. Food Nutr Bull 2009;30:S533–S546.

17 Haider BA, Yakoob MY, Bhutta ZA: Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. BMC Public Health 2011;11(suppl 3):S19.

18 Kawai K, Spiegelman D, Shankar AH, et al: Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. Bull World Health Organ 2011;89:402–411B.

19 Zeng L, Yan H, Cheng Y, et al: Modifying effects of wealth on the response to nutrient supplementation in pregnancy on birth weight, duration of gestation and perinatal mortality in rural western China: double-blind cluster randomized controlled trial. Int J Epidemiol 2011;40:350–362.

20 Hininger I, Favier M, Arnaud J, et al: Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. Eur J Clin Nutr 2004;58:52–59.

21 Brough L, Rees GA, Crawford MA, et al: Effect of multiple-micronutrient supplementation on maternal nutrient status, infant birth weight and gestational age at birth in a low-income, multi-ethnic population. Br J Nutr 2010;104:437–445.