This chapter of the Yearbook on Nutrition and Growth reviews important articles published between July 2012 and July 2013 concerning the impact of maternal nutrition during pregnancy on intrauterine fetal growth. Along with human studies, several animal studies dealing with the effect of nutrition on the placenta are also included since this field is not sufficiently studied in humans. Finally, we included future studies that hopefully will help in understanding the goals and interventional options for healthier offspring.

**Human Studies**

**Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial**

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*BMJ 2012; 345: e5605*

**Background:** Pregnancies associated with large for gestational age and macrosomia fetuses are at increased risk for adverse maternal and neonatal outcome such as birth complications and obesity later in the offspring’s life compared to those with appropriate for gestational age fetuses. The objective of the current study was to determine whether a low glycaemic index diet in pregnancy could reduce the incidence of macrosomia in an at-risk group.

**Methods:** Between January 2007 and January 2011, 800 non-diabetic pregnant women in their second pregnancy prior to 18 weeks of gestation with previous newborns weighing >4 kg were randomized to either no dietary intervention or low glycaemic index diet. The primary outcome measure was difference in birth weight. The secondary outcome measure was difference in maternal gestational weight gain.
Results: Regarding the primary outcome, no significant difference was seen between the two groups in absolute birth weight, birth weight centile, or ponderal index. However, regarding the secondary outcome, significantly less gestational weight gain occurred in women in the intervention arm. The rate of glucose intolerance was also lower in the intervention arm: 21% compared with 28% of controls had a fasting glucose $\geq 5.1 \text{ mmol/l}$ or a 1-hour glucose challenge test result $\geq 7.8 \text{ mmol/l}$.

Conclusion: In a risk group for macrosomia, a low glycaemic index diet in pregnancy did not reduce the incidence of large for gestational age infants. It did, however, have a significant positive effect on gestational weight gain and maternal glucose intolerance.

Comments: According to the World Health Organization (WHO), over 600 million adults worldwide are clinically obese. With the growing knowledge of the association between large for gestational age and obesity later in life, effective strategies in order to halt this problem are needed. The current study is a sufficiently powered randomized control trial. Several interventional studies in the past reported that a low glycemic index diet is useful in reducing birth weight and the prevalence of large for gestational age infants. Those studies, however, had a small sample size compared to the current study. Moreover, in previous studies a much more intense regimen of intervention was used, whereas in the current study there were only a few reinforcing meetings throughout pregnancy. Women in the intervention group had gained in average 1.5 kg less than those in the control group. This relatively minor reduction of weight gain was successful in reducing the rate of glucose intolerance. Perhaps a diet that could accomplish even less weight gain during pregnancy would help in reducing birth weight infants as well.

The Mediterranean diet and fetal size parameters: the Generation R Study

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Br J Nutr 2012; 108: 1399–1409

Background: Developmental adaptations due to early nutritional exposures may have permanent health consequences. Up to date, most studies exploring the association between maternal nutrition and fetal size have mainly focused on individual nutrients. The current study focused on the pattern of food consumption and its significance.

Methods: A prospective observational study was conducted between 2001 and 2006. The present analysis was restricted to 3,207 prenatally enrolled Dutch women with a spontaneously conceived, live-born singleton pregnancy. Participants completed a semiquantitative questionnaire during early (gestational age <18 weeks) pregnancy evaluating their diet habits. Logistic regression analysis was used to predict the occurrence of intrauterine growth retardation at birth as a function of food intake. The derived solution was considered as the dietary pattern. A combination of higher
intakes of fruit, vegetables, vegetable oil, fish, pasta and rice, and lower intakes of meat, potatoes and fatty sauces was labeled the ‘Mediterranean’ diet. The study evaluated the association of dietary habits with fetal size, uteroplacental vascular resistance, placental weight and birth weight. 

**Results:** Fetal size and placental parameters were associated with the degree of adherence to Mediterranean diet. Women with low adherence to the diet had a 72 g lower birth weight and a 15 g lower placental weight compared to women with high adherence to the diet. No difference regarding uteroplacental vascular resistance was observed between the studied groups.

**Conclusion:** Low adherence to a Mediterranean diet in early pregnancy seems to be associated with a lower placental mass and a lower birth weight.

**Comments**

Over the past years, the Mediterranean diet has gained popularity for its positive health effects. While no single Mediterranean diet exists, dietary patterns that prevail in the Mediterranean region share common characteristics including high intakes of vegetables and vegetables oil, moderate amounts of fish and a relatively low consumption of meat. Although showing only a modest effect on infant and placental weight, the current study is important as being one of the first studies to examine the relationship between dietary habits in early pregnancy (as opposed to a specific micronutrient) and fetal and placental growth during intrauterine life. The result of the current study supports previous reports of a reduced rate of intrauterine growth restriction fetuses associated with a dietary pattern rich in fruits and vegetables compared with one rich in meat, snacks and potatoes.

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**Dietary balance during pregnancy is associated with fetal adiposity and fat distribution**

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Am J Clin Nutr 2012; 96: 1032–1041

**Background:** The in utero environment could affect the offspring phenotype. Lean body composition at birth is associated with an increased risk for subsequent cardiac and metabolic illness in adulthood.

**Methods:** The study prospectively assessed 179 Australian women with singleton pregnancies from the Women and Their Children’s Health (WATCH) Study. Maternal diet was quantified by a validated food-frequency questionnaire at 18–24 and 36–40 weeks of gestation. Fetal body composition measurements were ascertained from abdominal and midthigh sites by ultrasound performed at 19, 25, 30, and 36 weeks.

**Results:** Maternal intakes of protein and starch and the protein:carbohydrate ratio was associated with the percentage of abdominal fat, whereas saturated fatty acids (SFA) and polyunsaturated fatty acid (PUFA) were associated with the percentage of midthigh fat. Fetal adiposity was maximized at different macronutrient intakes. Abdominal fat was highest with low protein intakes and midthigh fat was highest at intermediate protein, high fat (>40% of energy) and low carbohydrate (<40% of energy) intakes.

**Conclusion:** Fetal body fat composition may be modifiable via nutritional intervention in the mother.
In contrast to the previous studies presented above addressing infant weight, the current study deals with the association between maternal nutrition during pregnancy and fetal body composition. It was suggested in the past that fetal small abdominal viscera and low muscle mass but a preserved proportion of body fat is associated with insulin resistance later in life. However, the ideal neonatal body composition, which would be associated with optimal short- and long-term outcome, is yet to be determined, and also whether this ‘idealism’ is related to the infant total weight. It is interesting that the effect of maternal macronutrient profile was different between fetal abdominal and midthigh sites. Unfortunately, direct measurement of neonatal adiposity at birth was not performed; thus, a correlation between the sonographic and the actual measurement could not be established.

Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes

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Arch Gynecol Obstet 2013 (E-pub ahead of print)

**Background:** During pregnancy, complex changes occur in lipid metabolism. Increased lipid synthesis and maternal hyperphagia lead to fat accumulation especially in the first and second trimesters. This process is reversed during the third trimester due to increased lipolytic activity in the adipose tissue. The aim of the current study was to explore the association between maternal changes in lipid profile with pregnancy outcome.

**Methods:** In a prospective study, 1,000 pregnant women were recruited in the years 2010–2011. Lipid profile tests including triglyceride (TG), total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were established in the first antenatal visit (<14 weeks) and repeated in the third trimester (>28 weeks). The maternal nutritional as well as medical and social-demographic status was recorded. Primary outcome measures were defined as the association of the pregnancy-related lipid profile change to neonatal weight, the weight of the infant in the third month and pregnancy complications.

**Results:** The levels of TG, total cholesterol, HDL and LDL increased significantly as pregnancy progressed. Patients with good nutritional parameters had the higher percentage of change in the TG levels. An increased percentage of change in the TG levels had a positive effect on neonatal weight, but not on the placental weight and the third month weight of the infant. An inverse relation was observed between the percent change in TG levels and the risk of the preterm birth.

**Conclusion:** In pregnancy, complex alterations occur in lipid metabolism. Percent change in TG levels is positively affected by the maternal nutrition level. The neonatal weight and the risk of preterm birth are affected by the percent change in TG levels.

**Comments**

The purpose of the current study was to explore the effect of maternal lipid profile changes in pregnancy in relation to fetal growth and development, prognosis, and complications of pregnancy. The current study result joins previous reports regarding the increase in lipid levels during pregnancy. The main difference of this work in comparison to previous studies was the assessment of the percentile change in lipid profile between early and late gestation and its effect on pregnancy outcome. Therefore, lipid profile should be assessed several times during pregnancy as a single measurement could be misleading. Maternal nutritional status showed an association only to the change in TG levels and not to other parameters of the lipid profile. A possible
future implication for this finding is that the change in TG levels during pregnancy may assist in evaluating maternal nutritional status. Moreover, this parameter was associated to both neonatal weight and the risk of preterm birth.

Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation

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Paediatr Perinat Epidemiol 2012; 26: 178–190

Summary: This paper reviews the evidence on the association of maternal nutrition with birth outcome and the effect of balanced protein-energy supplementation (protein provides <25% of total energy content) in particular. Sixteen intervention studies were included in the review. Only randomized, quasi-randomized trials and before-after designs were included. Pooled analysis showed a positive impact of balanced protein-energy supplementation on birth weight compared with control. Protein-energy supplementation was associated with a reduced rate of low birth weight infants and a reduced risk for intrauterine growth restriction. The effect was more pronounced in undernourished women compared with adequately nourished women.

Comments: This is a meta-analysis regarding the association of balanced protein-energy supplementation and fetal weight. The strength of this study is the inclusion of intervention-al studies only. In any case, subgroup analyses based on the nutritional status of the mothers showed that balanced protein-energy supplementation was more effective in malnourished women than adequately nourished ones. However, there were no standardized criteria to define undernourished women. Moreover, none of the studies used body mass index (BMI) as the recruitment criteria. A similar evaluation was conducted by the Cochrane review. However, while the Cochrane review results were in accordance with the current study results, the results of the current analysis reached statistical significance (as opposed to the Cochrane review) mainly due to the inclusion of 5 more studies in the current analysis which provided its statistical magnitude.

Animal Studies

Effect of maternal dietary energy types on placenta nutrient transporter gene expressions and intrauterine fetal growth in rats

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Nutrition 2012; 28: 1037–1043

Background: The mechanism mediating the maternal nutritional effects on fetal growth is unclear. Intrauterine growth is largely determined by the capacity of the placenta to supply
nutrients from the mother to the fetus which depends primarily on the function of the placental nutrient transporter. The investigators wished to explore the effect of different maternal energy-intake types on placental nutrient transporters and whether fetal growth could be associated with different gene expressions relating to fetal DNA methylation and energy metabolism.

**Methods:** Three-month-old rats (n = 72) were allocated to one of four groups: low fat/low fiber (L-L), low fat/high fiber (L-H), high fat/low fiber (H-L), or high fat/high fiber (H-H). Rats were fed the treatment diets 4 weeks before mating and continued in pregnancy until sample collections were obtained on days 13.5 and 17.5 of pregnancy.

**Results:** The fetal weight in the L-L group was significantly lower than that in the H-L group. The placental nutrient transporter mRNA expressions of glucose transporter-3 (Slc2a3) and cationic amino acid transporter-1 (Slc7a1) in the L-L group with a decreased fetal weight were downregulated compared with that in the H-L group with an increased fetal weight. For the placental imprinted gene Igf-2 and H19 expressions, lower Igf-2 and higher H19 expressions were associated with the decreased fetal growth in the L-L group compared with the H-L group with an increased fetal weight. A different fetal growth was associated with different DNA methyltransferase-1 and methyltransferase-3a expressions and energy metabolism-related genes.

**Conclusion:** Different energy-intake types could affect intrauterine fetal growth and it is regulated through placental nutrient transporter gene expressions.

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**Comments**

The placenta plays a crucial role in the growth and the survival of the fetus in utero. This study not only explored the association between different energy-intake types on the fetal growth, but also reported on the placental role in this process. Moreover, they showed that there is alternation in gene expression in both the placenta and the fetus in response to maternal diet. However, while those genomic adaptations could be important for fetal survival in utero, it is possible that this mal-programing in genes associated with fetal metabolism could be responsible for an adverse metabolic outcome later in the offspring life.

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**Maternal calorie restriction modulates placental mitochondrial biogenesis and bioenergetic efficiency: putative involvement in fetoplacental growth defects in rats**


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**Background:** Maternal undernutrition is known to be associated with decreased fetal growth. This is mainly due to placental inability to supply adequate oxygen and nutrients to the fetus. However, the mechanism by which maternal nutritional status affects the placenta is still unclear.

**Methods:** Rat term placentas from 70% food-restricted (FR30) mothers were used for a proteomic screen. Placental mitochondrial functions were evaluated using molecular and functional approaches, and ATP production was measured.

**Results:** FR30 was associated with reduced fetal and placental weight compared with controls. FR30 placentas displayed 14 proteins that were differentially expressed, including several mitochondrial proteins. FR30 induced a marked increase in placental mtDNA content and changes in mitochondrial functions, including modulation of the expression of genes implicated in biogenesis and bioenergetic pathways.
Conclusion: Maternal undernutrition is associated in reduced fetal and placental weight. Fetoplacental pathologies could be explained by placental mitochondrial defects involving biogenesis and bioenergetic pathways.

Comments: The current study explored placental adaptive proteomic processes implicated in response to maternal undernutrition. The main focus of the study was the mitochondrial physiology in the placenta since these organelles play a crucial role in maternal-fetal exchanges. This is one of the first studies demonstrating the plasticity of the mitochondria in the placenta in response to maternal nutrition. This finding suggests that placental mitochondrial defects could be related to the etiology of intrauterine growth restriction as well.

Future Studies

The objectives, design and implementation of the INTERGROWTH-21st Project

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Comments: This is a multicenter, multiethnic, population-based project, being conducted in eight geographical areas. There are 5 objectives to this project. Three sets of international growth standards for (1) fetal growth from early pregnancy, (2) postnatal growth of preterm infants and (3) birth weight, length and head circumference for gestational age. The remaining two objectives are to investigate the determinant of preterm delivery and impaired fetal growth and to develop a prediction model for the estimation of gestational age during mid-trimester based on sonographic measurements. As the project has selected healthy cohorts with no obvious risk factors for intrauterine growth restriction, these standards will describe how all fetuses and newborns should grow, as opposed to traditional charts that describe how some have grown at a given place and time and will allow the identification of at risk population needed for careful surveillance.
The Maternal Obesity Management (MOM) Trial Protocol: a lifestyle intervention during pregnancy to minimize downstream obesity

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Contemp Clin Trials 2013; 35: 87–96

Comments

Pregnancy represents a crucial period both for its effect on the offspring downstream obesity potential and the comorbidity associated with it and as an opportunity in changing maternal behavior since women are highly motivated during that period. This randomized controlled trial objective is to examine whether keeping maternal weight gain during pregnancy within the limits could affect the offspring weight even in long-term follow-up. The MOM trial begins as a pilot study randomizing a total of 60 women in order to examine feasibility and acceptability of the intervention and to provide evidence for future power calculation. Maternal nutrition affects fetal growth in several mechanisms. However, nutrition like any other medical intervention should be personalized taking into consideration the genetic, demographic, behavioral and other factors influencing the potential for fetal growth. In order to achieve that goal, more randomized, well-controlled and adequately powered trials are needed.