Physiology of Pregnancy: Interaction between Mother and Child

Overview of the Nutritional Interaction between the Mother and Fetus

Irene Cetin    Manuela Cardellicchio

Department of Mother and Child, Hospital Luigi Sacco, and Centre for Fetal Research Giorgio Pardi, University of Milan, Milan, Italy

Introduction

Not too long ago, pregnancy was considered a 9-month period during which the mothers were free to eat ‘for two’ in order to have a healthy and strong baby. In recent years, after countless studies, this point of view has changed and it has become clearer that beyond a balanced maternal diet, other factors strongly influence fetal development. Pregnancy can actually be considered as a 3-compartment model where mother, placenta and fetus interact to guarantee fetal growth and development (fig. 1).

This chapter aims to elucidate the mechanisms at the basis of this interaction and how perturbations of this equilibrium may compromise the pregnancy outcome.

The Mother

Together with genes, the main determinant of fetal growth is the availability of nutrients reaching the fetus through the umbilical vein. These nutrients are transferred from the mother through the placenta but the nutrient composition in maternal blood is dependent on...
various maternal factors: diet, body composition, endocrine status and metabolism.

**Maternal Diet**

Diet is recognized as one of the major environmental factors influencing the development of the embryo and the fetus as well as maternal health. Each stage in embryonic and fetal development is influenced by maternal nutrients and the timing of a nutritional insult impacts differently on the nature of adult diseases by programming the postnatal pathophysiology, thus indicating that the early environment modifies the expression of the genome. On the whole, early programming is an established concept in biology: prenatal sex hormone exposure determines gender development (i.e. endocrine programming), perinatal exposure to allergens may induce tolerance (i.e. immunological programming), and monoallelic expression regulated by differential DNA methylation induces Prader-Willi syndrome, Angelman syndrome and others (i.e. epigenetic programming).

Therefore, programming of human adult functions and diseases seems to be influenced by hormones, metabolites and neurotransmitters during critical developmental periods as well as the early nutrition [1]. In fact, undernutrition of animals at early but not at later ages determines adult body size [2], and the developmental origins of adult disease seem to be related to poor fetal nutrition and low birth weight [3]. Evidence of the relationship between nutrition in early life and lifelong health exists for cardiovascular risk, infection and allergy risk, autoimmune diseases (e.g. diabetes type 1, inflammatory bowel disease, celiac disease), bone health, neural and brain function, as well as obesity.

Pregnancy leads to a modest increase in energy requirements compared to the nonpregnant status: 375, 1,200 and 1,950 kJ/day in the first, second and third trimester, respectively [4]. These additional calories can be met by a modest increase in consumption of a balanced diet (20–35% of fats, 15–20% of proteins, 40–50% of carbohydrates). A balanced maternal diet is fundamental
not only to fetal development during pregnancy but also to the offspring’s long-term health.

In recent years, it has become clear that maternal diet is relevant not only during pregnancy but already before conception. In particular, the periconceptional period is a critical step in determining fetal development and health. The onset of several malformations and pregnancy-related disorders (i.e., congenital abnormalities, fetal loss, miscarriage, insufficient fetal growth, premature birth, preeclampsia) may indeed occur during this period, in particular when micronutrient imbalances occur [5, 6] (table 1).

While in developed countries pregnant women can choose any kind of food based on their personal taste, in poor countries women may be exposed to undernutrition, but in both cases, an unbalanced diet may have dramatic consequences. Animal studies have shown that an excessive consumption of saturated fatty acids during pregnancy may permanently alter the fetal lipid metabolism in adult life, increasing the risk for cardiovascular disease [7, 8]. Recently, Howie et al. [9] reported that offspring born by rat dams fed with a high-fat diet are smaller and are predisposed to developing obesity independently of postnatal diet.

The Dutch famine that occurred during the Second World War allowed the study of maternal undernutrition showing that when severe maternal undernutrition occurs in the second and third trimester, it affects the birth weight, whereas compensatory placental growth was able to maintain a normal birth weight when undernutrition occurred in the first trimester [10]. Similarly to what occurs with overnutrition, individuals exposed to undernutrition in utero have an increased prevalence of cardiovascular disease [11], diabetes [12, 13] and obesity [14].

Therefore, it is fundamental that women of reproductive age and pregnant women are counseled to consume wholesome foods as well as a diversified range of foods in the right quantities, to avoid under- and overnutrition as well as micronutrient imbalances.

### Body Composition

Pregravidic weight is an important factor influencing the fetal and pregnancy outcome. In particular, the maternal body mass index (BMI) is one of the best markers of nutritional status. The World Health Organization guidelines define overweight as BMI 25–29.9, obesity as BMI ≥30 and underweight as BMI <19.8.

Today, obesity is a major burden in developed countries. Its incidence ranges from 18.5 to 38.3% among pregnant women in the USA [15]. Maternal obesity is associated with increased maternal and neonatal risks for pregnancy diseases such as preeclampsia, gestational diabetes, cesarean section, low Apgar scores, macrosomia and neural tube defects [15, 16]. Obese women have higher blood concentrations of nutrients due to lower insulin sensitivity [17]; increased substrates are then available for placental transfer to the fetus and contribute to fetal overgrowth (fig. 2).

On the other hand, maternal underweight is associated with increased risks of preterm labor, intrauterine growth restriction (IUGR), low birth weight and maternal anemia, this last probably due to deficiencies of micronutrients like iron and folic acid [18, 19].

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**Table 1. Animal and human studies about nutrient impact on pregnancy outcome**

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<thead>
<tr>
<th>Nutrient Abundance</th>
<th>Impact</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Elevated glucose levels in diabetic mothers</td>
<td>Altered blastocyst development and implantation</td>
<td>Leunda-Casi et al. [74], 2001, [75], 2002</td>
</tr>
<tr>
<td>High dietary intake of saturated fatty acid</td>
<td>Elevated risk of fetal outflow tract defects</td>
<td>Smedts et al. [76], 2008</td>
</tr>
<tr>
<td>High intake of western diet</td>
<td>Elevated risk of cardiovascular disease in adult life</td>
<td>Chechi et al. [7], 2006, [8], 2009</td>
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<tr>
<td>Depletion of maternal folate intake</td>
<td>Elevated risk of IUGR and fetal malformations</td>
<td>Van Eijsden et al. [78], 2008</td>
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<tr>
<td>Inadequate maternal iron intake</td>
<td>Elevated risk of preterm delivery</td>
<td>Zhou et al. [81], 1998</td>
</tr>
<tr>
<td>Reduced maternal dietary intake of B vitamins</td>
<td>Elevated risk of congenital heart defects</td>
<td>Verkleij-Hagoort et al. [82], 2006</td>
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Therefore, both underweight and obese mothers are at increased risk of adverse perinatal outcome. Major efforts should be made to reduce these risks by encouraging a nutritional education program for women of childbearing age and for pregnant women of different social and educational levels.

**Endocrinology and Metabolism**

From the beginning of pregnancy, maternal metabolism undergoes a number of changes to adapt to fetal and placental needs. In the first trimester these needs are mainly qualitative for organ development, since embryonic growth is still limited. In this period, hyperphagia and rise in insulin sensitivity allow the mother to store fats in the adipose tissue and to increase her net body weight [20]. This anabolic status occurs even in conditions of malnutrition [21, 22].

In the third trimester fetal growth becomes exponential and at the same time fetal nutritional demands increase. In order to adapt to this new condition, the maternal metabolism switches to a catabolic status: progesterone, cortisol, prolactin and leptin lead to a decrease in insulin responsiveness [23, 24] with a consequent increase in free fatty acids and glycerol plasma levels. Increased concentrations of maternal substrates are now available to cross the placenta and reach the fetus.

This physiologic adaptation is enhanced in pregnancies complicated by gestational diabetes where insulin sensitivity is significantly reduced, leading to higher maternal concentrations of glucose and free fatty acids. Obesity is an independent risk factor for developing gestational diabetes mellitus (GDM). Obese mothers have a 3 times higher risk of developing GDM compared to non-obese mothers [25, 26]. Today, the prevalence of obesity and consequently of GDM is rising worldwide together with maternal and fetal complications [25]. GDM as well as obesity predispose both mother and child to develop the metabolic syndrome and to a higher risk of cardiovascular disease [27].

![Fig. 2. Effects of obesity on pregnancy, fetus and offspring.](image-url)
The Placenta

Placental function is one of the major factors able to determine fetal nutrition and growth. This organ is not an inert membrane, since it regulates nutrients and oxygen flow to the fetus both quantitatively and qualitatively through its transport systems and its metabolism [20, 28]. The role of the placenta is shown in pathologic conditions of altered fetal growth like IUGR and GDM, both characterized by specific placenta phenotypes [29].

Implantation and placentation begin in the first days of pregnancy and continue throughout gestation. During this long period, the structure and function of the placenta undergo important changes to meet fetal demands: progressive increases in surface area, decreases in thickness [30, 20] and modification of nutrient transport systems.

The transfer capacity of the placenta is dependent on its size, morphology, blood flow and abundance of transporters [31]. Moreover, the placenta also influences the rate of fetal growth with its capacity to synthesize hormones and metabolize nutrients [32].

Size, Morphology and Metabolism

At midpregnancy, the placenta uses half of the oxygen and glucose received from maternal circulation for its own growth and metabolism, whereas in the second half of pregnancy it transfers the majority of nutrients to the fetus [33]. Its efficiency is defined as grams of fetus produced per gram of placenta [34] and in human beings this value is approximately 5:1 near term gestation [35]. The fetal/placental weight ratio is genetically determined, but it can be modified by environmental conditions during pregnancy [36]. Experimental animal studies have demonstrated that placental efficiency is reduced by decreases in uterine blood flow or by hypoxemia, while dietary calorie or protein deprivation leads to an increased efficiency in the first part of gestation and to a decreased efficiency closer to term [37, 38]. Generally, in normal oxygenation conditions lighter placentae are more efficient than heavier ones in humans [36].

In early stages of placental development branches of uterine arteries are converted into low-resistance vessels by placental extravillous trophoblast [39]. IUGR pregnancy is characterized by an incomplete spiral artery invasion and consequently by a condition of hypoxia and hypoperfusion. However, placentae of IUGR are characterized by a decreased coefficient of oxygen extraction and by increased uterine venous O₂ content, suggesting an inability of fetal villi to extract oxygen independently of blood flow [40]. Actually, IUGR placentae are characterized by an abnormal pattern of villous morphology and by increased thickness of the exchange barrier and both of these abnormalities seem to reduce oxygen and nutrient permeability [29]. Recent data show that the mitochondrial DNA content is significantly increased in IUGR placentae and that this increase is inversely related to umbilical venous oxygen [41]. Increased placental mitochondrial DNA may either represent a compensatory mechanism to hypoxia or a placental metabolic adaptation to the reduced nutrient availability.

An increased placental/fetal weight ratio has been reported in pregnancies complicated by GDM even with an optimal maternal glycemic control [42]. The increased placental mass could augment nutrient exchange by extending the surface area available for substrate transfer.

Transport Systems

Glucose, the most important and essential nutrient for fetal growth, is transported from mother to fetus by a facilitated diffusion system and its fetal concentration is constantly lower and dependent on maternal concentration and gestational age [43].

Amino acids are transported by active carriers, in particular neutral amino acids, by a sodium-dependent transport system, while branched amino acids, phenylalanine and lysine are carried by a sodium-independent transporter [44]. During pregnancy, the fetal amino acid concentrations are constantly higher than in the mother [45]. Stable isotope studies have shown that fetal nonessential amino acids (i.e. glycine and proline) mainly derive from placental production from metabolically related amino acids. In particular, for glycine and serine and for glutamate and glutamine an interorgan cycle between placenta and fetal liver has been hypothesized [46, 47], while maternal essential amino acids are taken up by the placenta and reach the fetus quite rapidly in bolus studies [46, 47].

Recently Jansson et al. [48] have suggested that the placenta is a ‘nutrient sensor’ able to modify its transport function according to maternal nutrient supply and fetal needs.

Fatty acids can cross the placenta as free fatty acids by simple diffusion or as lipoproteins connecting specific binding proteins and are then released by way of specific placenta lipoprotein lipases [49]. Simple diffusion is allowed by the presence of a maternal-fetal concentration gradient. The fetal concentration is constantly lower than in the mother but also qualitatively different: long-chain polyunsaturated fatty acids (LCPUFA) like arachidonic...
acid and docosahexaenoic acid are present in higher proportions compared to their precursors linoleic acid and α-linolenic acid [50]. This phenomenon, called ‘biomagnification’, is due to the ability of the placenta to transfer preferentially LCPUFA to guarantee a correct fetal neurodevelopment, but the underlying mechanism is still not clear [51].

IUGR, a condition characterized by the inability of the fetus to achieve its full growth potential [28], is an important cause of perinatal mortality and morbidity, and it increases the risk of developing cardiovascular diseases in adult life (fig. 3) [52]. Placental metabolism and nutrient transport systems are altered in IUGR placentae [29]: the fetal amino acid concentrations are reduced in IUGR fetuses [53] and a reduction in the activity of a number of amino acid transport systems has been demonstrated by some studies [54]. The total plasma levels of fatty acids are the same in IUGR fetuses [55], but the relative composition is different, with a significantly lower fetal/maternal ratio for the LCPUFA docosahexaenoic acid and arachidonic acid [56]. These changes may explain the high susceptibility of IUGR fetuses to vascular brain damage.

GDM pregnancies are characterized by fetal overgrowth due to an increase in nutrient availability. However, in the last years, it has been shown that the risk of excessive fetal growth is elevated also with a strict maternal metabolic control [57]. This evidence, together with in vitro studies, suggests that even short periods of metabolic imbalance early in pregnancy may affect placenta transport systems [58]. Neutral amino acid transporters are markedly increased in the syncytiotrophoblast of GDM pregnancies, whereas the glucose transport system is upregulated only in pregnancies complicated by diabetes mellitus type 1 but not in GDM [59, 60].

Data obtained in GDM pregnancies at the time of cesarean section show that the fetal glucose levels are higher than in normal pregnancies even when the mother has glucose levels in the normal range. In these same pregnancies, the fetal oxygen levels are decreased and the lactate concentrations increased, confirming placental alterations [61]. Moreover, the fetal concentrations of most amino acids are significantly increased in GDM pregnancies [62].
The marked insulin resistance of GDM and the consequently enhanced lipolysis determines a high-fat maternal-fetal concentration gradient and then a higher transfer of fatty acids to the fetus. This transfer is favored also by an increased expression of a specific fatty-acid-binding protein (L-FABP) on microvillus membrane [63].

### The Fetus

The fetus receives a nutrient mix that is determined by the mother and the placenta. Both are able to influence the fetal diet and consequently fetal daily growth. However, the fetus is also a key player in its own development through its genes and the endocrine environment. Besides traditional mendelian genetic inheritance, some inherited genes, called imprinted genes, act differently in relation to their maternal or paternal belonging (table 2). Maternal genes act as growth suppressors, whereas paternal ones are growth promoters, so an imbalance in their expression may alter fetal and placental growth, as shown in uniparental disomy [64].

Different environmental conditions, like maternal diet or uterine blood flow, influence fetal growth and can compromise this genetic potential. The fetus’s endocrine status is changed and the placental efficiency influenced by these insults. In particular under favorable conditions, the fetus enhances anabolic hormones like insulin and insulin-like growth factors (IGFs), whereas under adverse conditions catabolic hormones like cortisol and cathecolamines increase [32].

Among the hormones, IGFs seems to have a predominant role in regulating fetal growth: they are expressed from both maternal and fetal tissues and are able to regulate placental efficiency by modifying its transfer ability. Animal and in vitro studies show that placental weight, thickness and surface area are directly related to maternal IGF-I concentrations [65, 66]. In the human placenta, maternal IGF-1 increases the amino acid uptake [67]. Fetal IGF-I instead seems to be involved in fetal but not in placental growth: mice with deletion of the Igf-I gene develop growth restriction [68].

Igf-II is also implicated in fetoplacental development: its overexpression determines fetal and placental overgrowth, whereas its deletion provokes growth restriction [69]. IGF-II production is regulated by an imprinted gene with paternal expression. In Igf-II KO mice both fetal and placental weights are strongly reduced with significant changes in placental amino acid transport systems happening already at midpregnancy [70]. The real molecular mechanisms at the basis of the ability of IGFs to influence fetal and placental growth are still not clear, but recent data suggest that they may regulate placental transporter concentrations by influencing the mTOR pathway [71].

Moreover, when the fetal nutrient exchange is altered, the fetus may also modify its own metabolism in order to try to adapt to the adverse environment. In particular, preliminary data in IUGR fetuses indicate a significantly lower umbilical oxygen uptake value on per kilogram basis, suggesting that their metabolic rate is significantly decreased [72].

On the other side of the fetal growth spectrum, fetuses of GDM mothers show reduced levels of arachidonic (20:4 n–6) and docosahexaenoic (22:6 n–3) acids. Recent data show that this difference is evident in the umbilical artery but not in the umbilical vein, therefore suggesting changes in fetal metabolism of LCPUFA rather than altered placental transfer [73].

### Conclusions

When external factors hinder the fetal genetic growth potential, both fetus and placenta start morphological and functional adaptation mechanisms to reduce the imbalance. However, when these compensatory changes are insufficient, growth restriction or overgrowth are established with consequent intruterine and adult health disorders.
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