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Fetal nutrition: A review

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Abstract
Knowledge of fetal nutrient supply has greatly increased in the last decade due to the availability of fetal blood samples obtained under relatively steady-state conditions. These studies, together with studies utilizing stable isotope methodologies, have clarified some aspects of the supply of the major nutrients for the fetus such as glucose, amino acids and fatty acids. At the same time, the relevance of intrauterine growth has been recognized not only for the well-being of the neonate and child, but also for later health in adulthood. The major determinants of fetal nutrient availability are maternal nutrition and metabolism together with placental function and metabolism. The regulation of the rate of intrauterine growth is the result of complex interactions between genetic inheritance, endocrine environment and availability of nutrients to the fetus.

Key Words: *Fatty acids, fetus, metabolism, nutrition, placental transport*

Introduction

Nutrition is one of the main factors that can affect fetal development, growth and health. During intrauterine life, determinants of fetal nutrition are quite different from those involved in postnatal nutrition. In fact, in developed countries nowadays people can choose what to eat based on personal taste, commercial influence, and also medical advice. Therefore, we consider nutrition to be one of the habits that we can modify in order to improve our quality of life.

However, fetuses themselves cannot choose what to eat. Fetal nutrition is conditioned by different processes that are not easily controlled and modified. The fetus is nourished through the umbilical cord; this "mix" is the result of maternal nutrition, metabolism, endocrinology and of placental perfusion and function [1].

Moreover, many factors influence fetal growth throughout pregnancy: during this critical period the nutritional and hormonal milieu may alter the expression of the fetal genome and this may have lifelong consequences. These factors are able to induce long-term adaptations in an individual through a process that has been defined as "fetal programming" [2]. Based on this hypothesis, some critical periods are thought to exist during fetal life, when the altered expression of a number of genes would have lifelong consequences [3]: perinatal growth, especially in the case of intrauterine growth restriction (IUGR), has pronounced effects on neonatal and adult health. For this reason, the identification of factors playing a role in normal and altered fetal growth can be useful for preventive measures.

Fetal nutrition is one of these factors: the complex interaction between genetic growth potential, the ability of the maternal–placental system to transfer nutrients to the fetus and the endocrine environment determine whether the fetus will follow its growth potential during intrauterine life (Figure 1).

This review presents firstly an overview of the major determinants of intrauterine growth together with fetal nutrition, i.e. genetic inheritance and hormonal regulation, and then deals with the maternal and placental factors determining fetal nutrition. Throughout the review, data refer to human pregnancies studied *in vivo*, although in some cases *in vitro* data are also discussed.

Determinants of intrauterine growth

Genetic inheritance

Genetic inheritance is obviously one of the major determinants of intrauterine growth. Recently, increasing evidence supports that some genes, called imprinted genes, are involved in promoting fetal growth and that alterations in their expression are

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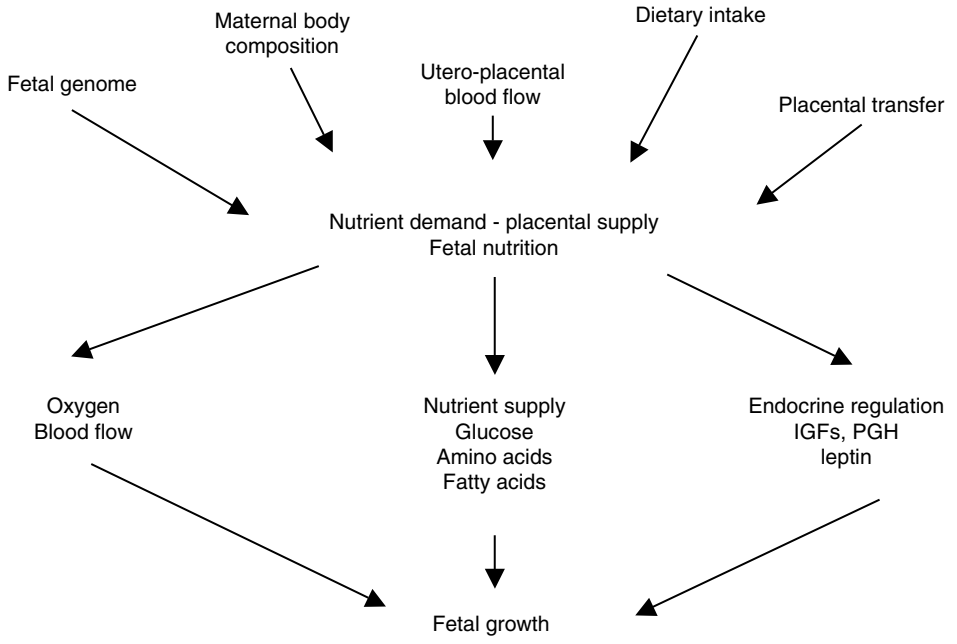

Figure 1. Main determinants of fetal nutrition and growth.

associated with impaired fetal growth [4]. An adequate balance of maternal and paternal imprinted genes has been shown to be required for placental implant and fetal growth [5], and a genetic conflict hypothesis has been advanced by Moore and Haig [6] to explain these requirements. This hypothesis is based on the evidence that most maternal expressed genes act as growth suppressors whereas paternal expressed genes are growth promoters, so that the father tends to promote growth, while the mother controls the fetal demand for nutrients. It is obvious that an imbalance in these attitudes would alter fetal growth in, for example, uniparental disomies (UPD), i.e. a chromosome pair originating from one parent only. UPDs of a number of chromosomes have been associated with specific phenotypes, as is the case of maternal UPD7, which is reported in 7% of cases of Silver-Russell syndrome, with pre- and postnatal growth impairment [4].

Hormonal regulation

Hormones regulate intrauterine growth by acting on the maternal compartment, placental development and fetal metabolism. The hormonal regulation of fetal growth during intrauterine life has not been completely understood, but it seems pretty clear that the main hormones involved are produced within the placenta.

Insulin-like growth factors (IGFs) are involved in fetal growth, as they are genetically old peptides that induce cell proliferation and differentiation together with DNA synthesis. Moreover, they increase glucose and amino acid uptake, while simultaneously inhibiting protein breakdown [7]. Although growth hormone (GH) is the main regulator of IGF-I synthesis postnatally, fetal tissues are relatively deficient in GH receptors, suggesting that this hormone is of minor importance during intrauterine development.

The endocrine unit of the placenta also produces a specific growth hormone, placental growth hormone (PGH), which has been characterized in the last 15 y [8] and is the product of the GH-V gene expressed in the syncytiotrophoblast. The secretion of PGH is important in the control of maternal IGF-I levels. Placental growth hormone secretion in the maternal circulation has been shown to be significantly reduced in pregnancies with fetal growth restriction, and this is concomitant with the changes in IGF-I, thus supporting a critical role for placental GH and IGF-I in determining fetal growth [9].

Leptin has raised great attention in recent years. Leptin is a circulating polypeptide hormone, the product of the *ob* gene which is expressed by adipocytes [10]. Leptin levels have been measured in blood from the umbilical cord of newborns, and a significant relationship has been reported with fetal weight [11], fetal BMI [12,13] and fetal fat mass [14]. Placental production has also been demonstrated *in vitro* by the detection of *ob* gene expression in placental tissues [15]. Moreover, a study in the dually perfused placenta produced evidence that most of the leptin produced by the placenta is released into the maternal circulation, but compared with other placental hormones, such as chorionic gonadotropin and placental lactogen, a considerably higher proportion of leptin is released into the fetal circulation [16].

Fetal nutrition

When considering fetal nutrition, it is important to keep in mind that pregnancy represents a three-compartment model, with the mother, placenta and fetus each presenting their own metabolism while interacting with each other. Glucose, amino acids and fatty acids are the most important nutrients in fetal life, both for tissue deposition and as fuel for oxidative purposes.

There is considerable experimental evidence suggesting that, in the second half of gestation, fetal growth is controlled by both maternal and placental factors [17]. It is difficult to estimate the relative influence of these two compartments in determining the rate of intrauterine fetal growth. Both maternal and placental factors are involved in alterations of fetal growth rate, by changing the amount of nutrients supplied to the fetus. Intrauterine growth restriction is characterized by a reduced ability of the utero-placental unit to supply oxygen and nutrients to the fetus [18]. In gestational diabetes, on the other hand, excess fetal growth seems to be derived from the increased availability of maternal nutrients. The increased fetal fat mass in these cases results from the combined effects of this excess of nutrients and the permissive environment of fetal hyperinsulinaemia [19].

Maternal determinants

Maternal metabolism changes during pregnancy to supply the feto-placental unit with all its nutritional needs. A mother's "adaptation to pregnancy" consists of a number of changes that affect metabolism as well as the function of the fetal placental unit through haemodilution, reduction of peripheral resistances to blood flow and reduction of blood pressure, most of all within the placental district, and hormonal changes.

Maternal nutrition and metabolism vary further during the course of pregnancy. The beginning of pregnancy is characterized by storing substances mainly within the adipose tissue: this is achieved through maternal hyperphagia which, together with endocrine changes, allows an increase in maternal net body weight [20]. This is the period when the fetus is very small but developing its organs and the quality of the substrates obtained from the maternal circulation prevails over quantity.

During the second part of gestation, the fetus grows at an exponential rate and completes the structure of important systems such as the central nervous system. Nutritional needs increase: it has been estimated that, in the term fetus, 40–50 kcal/kg/d are utilized for tissue deposition, while 50 kcal/kg/d serve for oxidative purposes [1].

The mother adapts her metabolism in order to support the continuous draining of substrates by the feto-placental unit: all the stores prepared at the beginning of pregnancy are mobilized with this aim, persist in the circulation for longer periods, and accomplish a faster metabolism to make the trans-placental passage easier. There is a marked increase in blood glycerol, free fatty acids and keto acids induced by fasting, even of a moderate degree, and this phenomenon is known as "accelerated starvation of pregnancy" [21].

Many studies have sought to link maternal nutrition and metabolism to fetal growth. Some explanations may be found at the extremes of normal conditions. Maternal indices of insulin resistance, such as maternal pre-pregnancy weight and maternal weight increase, are related to fetal growth and birthweight [22]. The effect of maternal undernutrition was studied during the Dutch famine showing differences depending on whether undernutrition occurred during the first or the third trimester [23]. Birthweight was most affected in the third trimester in women starving and acutely hungry [24], whereas even moderate undernutrition in the first trimester is associated with compensatory placental growth [25].

In recent years, a number of studies have also suggested that maternal nutrition in both quantitative and qualitative terms may have long-term effects in increasing the risk of diseases in adult life, and that the effects are different depending on the gestational age of occurrence [26,27]. Moreover, pregnancy is a period of rapid growth and cell differentiation, when both the mother and the fetus are very susceptible to alterations in the dietary supply of nutrients. Maternal metabolism should offer to the fetus a precise balance of substrates, at the right time, according to different stages of development.

Placental function

The fundamental role of the placenta in ensuring normal fetal growth has been recognized both with respect to its function in the fetal–maternal transfer of nutrients, and also regarding its metabolic and endocrine effects on the regulation of maternal and fetal metabolism. The placenta is not only a passive filter, its role is active, representing the main regulator of fetal–placental metabolism.

Nutrients are transferred to the fetus by the placenta through complex mechanisms involving transport systems present on the trophoblast microvillous and basal membranes and on the endothelial membranes of fetal capillaries. Moreover, extensive placental metabolism has been demonstrated. Therefore, although the maternal concentration is the main determinant of fetal glucose, amino acid and fatty acid concentrations, the placenta acts to determine the composition of the fetal diet.

Placental function varies through pregnancy so that while at mid-gestation the placenta utilizes half of its oxygen and glucose uptake and transfers the rest to the fetal circulation, the proportion transferred to the fetus increases with the progress of gestation [28,29]. In part, these changes are related to a large increase in the fetal/placental mass ratio during gestation. Moreover, functional maturation of the placenta occurs progressively through gestation, including significant increases in total placental surface area and decreased thickness [30], allowing increased nutrient transport to meet the needs of advancing fetal growth. In addition, significant changes have been observed in the activity of placental transport systems and in their regulation [31].

A facilitated diffusion system is responsible for maternal-to-fetal transfer of glucose, mediated by members of the GLUT family, which are localized in both maternal and fetal facing membranes [32]. The primary isoform involved in the transplacental movement of glucose is the GLUT1 glucose transporter, responsible for glucose transport from mother to placenta. Glucose transport from placenta to fetus seems to be mediated by the GLUT3 protein, localized on the vascular endothelium. In normal pregnancies, fetal glucose concentrations are strictly dependent on both maternal concentrations and gestational age [33], with the placenta itself consuming a considerable amount of glucose [29].

Placental amino acid transporters are protein complexes within the maternal and fetal facing plasma membranes. Amino acid placental transport is an active, carrier-mediated process. Numerous amino acid transporters have been characterized, mostly on a functional basis, and some also on a molecular basis, and each transports more than one amino acid [31]. The microvillous membrane (MVM) has several transport systems, including system A, which is sodium dependent and transports neutral amino acids such as alanine, serine, proline and glycine. There are also sodium-independent transport systems, such as system L, for the branched-chain amino acids and phenylalanine and system y^+ for lysine.

In contrast, the mechanism of transport of fatty acids across the placenta is not completely understood. The placenta preferentially transports long-chain polyunsaturated fatty acids (LC-PUFAs), indicating an important role of the placenta in handling the fatty acid supply to the fetus [34,35]. Cellular uptake and intracellular translocation of non-esterified fatty acids has been proposed as a multistep process that is facilitated by various membrane-associated and cytoplasmic proteins [36]. Although all fatty acids can cross lipid bilayers by simple diffusion, a number of fatty acid-binding proteins (FABPs) have been identified that seem to allow a bidirectional flux of fatty acids into and out of cells. Essential fatty acids are mainly transported to the placenta by non-esterified fatty acids carried by triglycerides from lipoproteins from the maternal adipose tissue and liver [20]. They are released by way of lipoprotein lipase (LPL), the activity of which was demonstrated in human placenta [37]. The placenta also contains specific binding sites for lipoproteins (VLDL, LDL, HDL) that carry esterified lipids [34]. The characteristics of placental fatty acid exchange are represented in Figure 2. The placenta could also take part in the elaboration, elongation and desaturation of fatty acids, since the fatty acid profile in fetal blood is different to that in maternal blood, with proportionally higher amounts of long-chain polyunsaturated fatty acids in fetal plasma [38]. Many questions remain to be solved, however, since the enzymes involved in these metabolic pathways have not been reported within the placenta [39].

Fetal nutrients

The most important nutrients for the fetus are represented by glucose, amino acids and fatty acids together with many micronutrients such as vitamins and ions. During the last decade, a number of studies have analysed the composition of fetal blood by *in utero* fetal blood sampling. This relatively non-invasive procedure has facilitated the study of the placental supply of nutrients and the hormonal status of the fetus during the second half of pregnancy [40].

By this means it has been possible to determine the relationship between fetal and maternal glucose concentrations from 18 wk to term [33]. In human pregnancies, fetal glucose concentration decreases during the second half of gestation depending on both maternal glucose concentration and gestational age, with fetal concentrations always lower than maternal [33]. No significant glucogenesis has been demonstrated in the fetal–placental unit, even in growth-restricted fetuses [41].

In contrast, for most amino acids, no significant changes have been observed at different gestational ages, with fetal concentrations higher than maternal concentrations [42]. However, studies performed in human pregnancies *in vivo* by infusing stable isotopes into the maternal circulation have demonstrated that, for non-essential amino acids, fetal concentrations are mostly obtained by production within the placenta, from metabolically related amino acids [43]. For glycine and serine and for glutamate and glutamine, this is part of an inter-organ cycle between the placenta and fetal liver [44].

Fatty acids represent a very good model of the relationship between maternal diet and fetal growth and wellness. The fetus needs mostly essential fatty acids and their derivatives, arachidonic (n-6) and docosahexaenoic (n-3) acid. Intrauterine requirements for essential fatty acids (derivatives of n-6 and n-3)

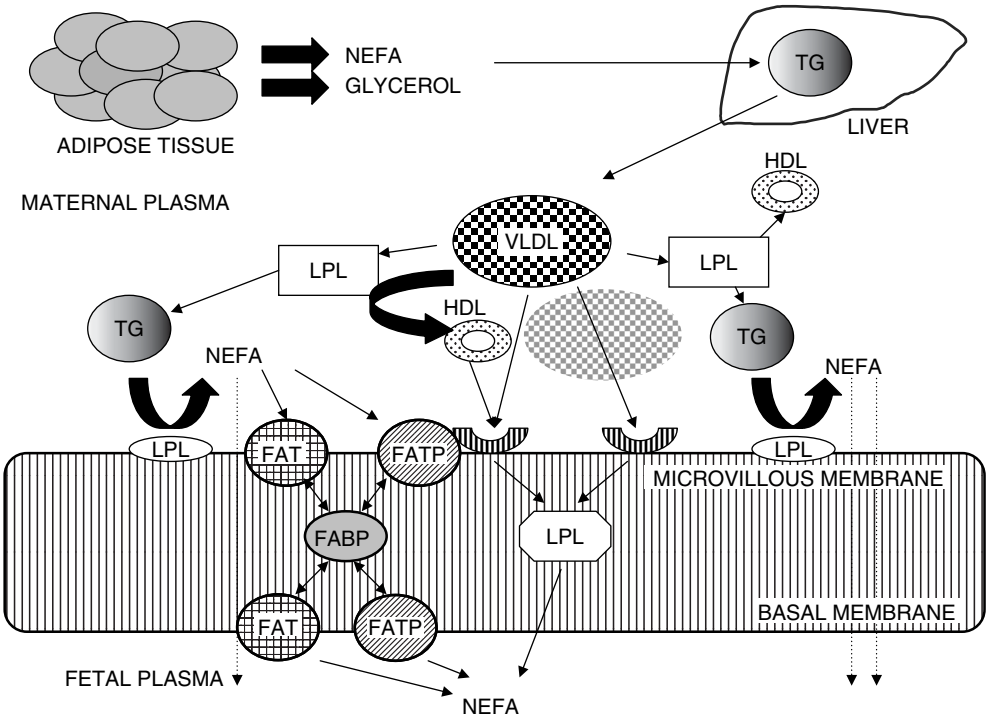

Figure 2. Fatty acids: maternal metabolism and placental handling. NEFA: non-esterified fatty acids; TG: triglycerides; LPL: lipoprotein lipase; FATP: fatty acids transport protein; FABP: fatty acid-binding protein.

during the last trimester of pregnancy through to the early weeks of life have been estimated to be 400 mg/kg/d for n-6 and 50 mg/kg/d for n-3 [45]. LC-PUFAs are rapidly incorporated into structural lipids of the brain [46] where they maintain the fluidity, the permeability and conformation of membranes and play an important functional role in brain development and visual function [47]. They are precursors of important molecules such as prostaglandins, leukotrienes and tromboxanes, and they also represent a source of energy.

The incorporation of preformed arachidonic acid (AA) and docosahexaenoic acid (DHA) into the developing brain is selective and more than 10 times faster than incorporation via the biosynthetic routes from linoleic (LA) and α-linolenic acid (αLA) [48,49].

Although fatty acids supplied to the fetus are largely determined by the fatty acid composition of the maternal blood, the placenta is able to preferentially transfer AA and DHA to the fetus, which is carried out by means of a combination of several mechanisms, as recently reviewed [34]. This has been described as a process of "biomagnification": the fetus shows higher percentages of AA and DHA compared to the mother [38], probably finalized to central nervous system enrichment.

Fetal fatty acid plasma composition could also be influenced by fatty acid metabolism in placental and fetal tissues, but human placental tissue shows no activity of either the Δ6- or Δ5-desaturases [39], and although LC-PUFA synthesis from esterified fatty acid precursors has been demonstrated to occur in preterm infants as early as 26 wk gestation [50], other reports have estimated that the contribution of endogenous synthesis to the total plasma LC-PUFA pool in term neonates is small [51].

From an energy point of view, fatty acids seem less important at the beginning of pregnancy and instead become of greater importance near delivery when they represent an energy storage in adipose tissue. By studying pregnancies at the time of *in utero* fetal blood sampling, we have observed that saturated fatty acids proportionally increase during pregnancy in fetal plasma [38].

The role of micronutrients is essential at every stage in fetal growth and development, although their study is quite complicated due to interactions between them. Retinoic acid is essential for signalling; others, like zinc, are essential for stabilizing enzymes and transcription factors or as central components of catalytic processes (like copper and iron) [52]. Iron deficiency, besides being associated with maternal anaemia and an increased risk of maternal haemorrhage, has been related to an increased placental/fetal weight ratio, a predictor of cardiovascular disease in adulthood [3]. Amongst vitamins, the fat-soluble vitamins play an important role for their antioxidant capacity, protecting cells against damage induced by free radicals. There is a complex interaction between n-3 and n-6 fatty acids and fat-soluble vitamins. An excess

intake of polyunsaturated fatty acids (PUFAs) has been shown to reduce antioxidant capacity [53]. The hyperlipidaemia characteristic of normal pregnancy during late gestation is associated with enhanced LDL oxidation rate, although this effect is counteracted by increased oxidative resistance. The latter probably occurs thanks to the enhanced levels of vitamin E, although other antioxidant vitamins, such as β-carotene and vitamin A, remain respectively stable or decreased during normal pregnancy [54]. We have recently described that, even in normal pregnancies, there is a significant relationship between levels of fatty acids and antioxidant vitamins [55]. These relationships might influence placental function by reducing placental perfusion or by altering the profile of cytokines in the placenta, shifting the equilibrium towards pro-inflammatory cytokines [56]. This imbalance at the maternal–fetal interface may directly or indirectly reduce the ability of the placenta to grow and function.

Conclusions

The adequacy of fetal nutrition is of utmost importance for fetal growth and wellness. The relative needs of different nutrients, however, are difficult to ascertain and depend mainly on calculations obtained at birth or, more recently, during the second half of pregnancy at the time of *in utero* fetal blood sampling [40]. Moreover, fetal nutrition depends on both maternal and placental factors that interact in complex ways. Alterations in these factors may lead to changes in the rate of fetal growth. For example, failure in maternal adaptation and/or in trophoblast invasion in early pregnancy can lead to intrauterine growth restriction: a model in which nutrients become deficient because of an alteration of the mechanism of the making and functioning of the feto-placental unit [18].

In summary, fetal nutrition is not comparable to adult nutrition because it is influenced by many factors including maternal diet, maternal metabolism, adaptation to pregnancy, and predisposition to pathologies that could affect normal placental development.

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