Nutritional Regulation of Fetal Growth

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Abstract

Fetal growth is largely regulated by nutritional supply. The placenta is responsible for fetal nutrient supply for much of pregnancy, but in early pregnancy nutrition is histiotrophic. Both placental size and efficiency, and fetal growth, may be affected by maternal nutritional state before and during very early pregnancy. In contrast, manipulating maternal nutrition during later stages of pregnancy has a smaller than expected effect on fetal growth. Maternal nutrition before and during early pregnancy also has a greater effect on gestation length than maternal nutrition later in pregnancy, suggesting that nutritional status may regulate both fetal growth trajectory and gestation length and that these two outcomes may be linked. Thus, determination of the nutritional factors regulating fetal growth, and potentially postnatal growth and body phenotype, may lie with the maternal nutritional status even before conception.

Postnatal growth is largely determined by genetic factors if nutrition is sufficient. In contrast, fetal growth is largely determined by the maternal uterine environment. For example, experimental studies of either cross-breeding or embryo transfer between breeds of different maternal body size have demonstrated that fetal growth is determined largely by factors related to maternal body size [1, 2]. In humans, the paternal genome has a relatively small role in determining birthweight, with the intraclass correlation coefficient for birthweight for maternal half-sibs substantially greater than that for paternal half-sibs (0.58 vs. 0.10) [3]. The maternal influence on fetal growth is termed maternal constraint and is thought predominantly to reflect maternal uterine size and capacity to supply...
nutrients to the developing fetus. Thus, this concept implies that fetal growth is largely determined by fetal nutritional status, a concept supported by the fact that the major hormonal mediators of fetal growth, the insulin-like growth factors, are also regulated by fetal nutrient supply [4, 5], again in contrast to their postnatal regulation. Although the fetus is dependent upon the mother for nutrient supply, fetal nutrition is quite distinct from maternal nutrition as will be discussed below. In addition, there also is increasing evidence for the role of nutrition in the very early pregnancy period in determining fetal growth, fetal developmental trajectory and the developmental origins of disease.

**Fetal Nutrition in Early and Late Gestation – Role of the Placenta**

For much of the first trimester, fetal nutrition is histiotrophic rather than hemotrophic, with the conceptus receiving nutrients secreted from uterine glands [6]. Nutrition of the early conceptus is much less well understood than transplacental nutrition and, although the nutrient requirements of the early embryo are tiny, alterations in this environment, probably largely regulated by hormonal signals, do affect fetal development [reviewed in 6]. Maternal placental blood flow, and therefore presumably hemotrophic nutrition, is present towards the end of the first trimester, initially in the periphery of the placenta and later centrally [7]. The placenta then forms the interface between maternal nutrition and fetal nutrition, and a variety of factors affect the transfer of maternal nutrients to the fetus, including placental blood supply on both maternal and fetal sides, placental size and morphology, and nutrient transporter abundance and function. Thus, fetal nutrition is determined not only by maternal nutrition but also by this supply line connecting the mother and fetus [8]. Maternal factors such as maternal disease (e.g. diabetes, pre-existing hypertension) or excessive exercise, and placental factors such as impaired placental development, may have a profound effect on this supply line and thus on fetal nutrient supply.

**Nutritional Determinants of Placental Development**

The placenta develops from the trophectoderm, which initially forms villi surrounding the whole of the chorionic sac. Villi over the superficial pole then regress, forming the discoid placenta [6]. Maternal undernutrition throughout pregnancy has been reported to impact on placental development [9]. When the nutritional deprivation is in the second half of pregnancy, both placental and fetal weight appear to be affected. In contrast, maternal undernutrition in early
pregnancy appears to have a greater effect on placental size and efficiency than on fetal growth, perhaps indicating an adaptive response of the placenta to nutritional signals. Practice in sheep farmers has long been to place ewes on poorer pasture in early pregnancy to increase placental size and, therefore, lamb birthweight [10]. Experimental manipulation of maternal nutrition in sheep, with a period of undernutrition from around the time of placental attachment to mid-pregnancy (28–77 days’ gestation), has been shown to result in increased placental size and placental:fetal weight ratio, indicating increased placental efficiency [11]. Elegant studies in rats have demonstrated that a maternal low protein diet (9 vs. 18% casein) only in the peri-implantation period leads to reduced blastocyst cell number, due to decreased proliferation, and alterations in fetal growth [12]. This change in cell number was initially found in the inner cell mass (which forms the embryo) and then in the trophectoderm (which forms the extraembryonic tissues), and was associated with reduced H19 mRNA expression in male embryos [13]. Embryo transfer experiments between dams fed low protein and normal protein diets confirmed that these changes are inherent to the blastocyst rather than the ongoing maternal environment, indicating that the altered maternal nutrition resulted in developmental changes in the embryo [14]. Further investigation of the visceral yolk sac endoderm (VYSE), which is responsible for histiotrophic nutrition of the rat embryo from before placental development but which also makes a nutritional contribution through to term, demonstrated increased VYSE endocytic capacity and upregulated megalin protein expression, a transmembrane protein involved in endocytosis of plasma proteins for fetal growth [14]. Taken together, these experiments suggest that in both small and large mammals, maternal nutritional status in early pregnancy influences placental development, efficiency and fetal growth.

Observational studies suggest that the same is probably true in humans. Women exposed to severe undernutrition in late gestation due to the Dutch Famine of 1944–1945 had babies and placentae of reduced weight, but the placental:birthweight ratio, a measure of placental efficiency, was unaltered [15]. In contrast, women exposed to famine in early pregnancy had increased placental weights without an effect on fetal size, suggesting increased placental efficiency and indicating an adaptation of the placenta in response to early nutritional signals to maintain nutritional supply in late gestation. Data from a cohort of women in India suggest that even longer term indicators of maternal nutrition may affect placental development [16]. In this study, relationships between placental morphometry and markers of various phases of maternal growth (mother’s own fetal/early infant growth represented by adult head circumference; mother’s own childhood growth represented by adult height, and mother’s current nutritional status represented by fat mass) were assessed. Maternal head
circumference and maternal fat mass, but not maternal height, were both related to placental size and efficiency (assessed by ratios of various placental measurements to birthweight), suggesting that the mother’s nutritional experience as a fetus and also her prepregnancy nutritional status affect placental development [16]. The effects of mothers’ nutrition as fetuses may be explained by the fact that a mother’s own oocytes develop in early gestation before entering a period of quiescence until puberty implying an intergenerational effect of maternal nutrition on grand-offspring fetal nutrition. Indeed, this appears to be the case, with intergenerational studies from the Dutch Famine reporting effects on birthweight of babies born to mothers who were in utero during the Famine; effects were greatest in women exposed as fetuses to famine in the first trimester of pregnancy [17]. It has been estimated that maternal factors at the time of the pregnancy account for not more than 15% of the variability in fetal growth, whereas the parents’ own fetal growth can account for up to 50% in unadjusted analyses and 33% in adjusted analyses [18].

**Maternal Nutritional Determinants of Fetal Growth**

The concept of the fetal nutrient supply line, the central role of the placenta in fetal nutrient supply and the evidence suggesting that placental size and efficiency may be affected more by maternal nutritional status in early pregnancy help explain the relatively small effect that maternal nutritional status during pregnancy appears to have on fetal size at birth. Meta-analyses of maternal nutritional supplementation during pregnancy have found only small effects on size at birth [weighted mean difference (95% confidence intervals, CI): +37.6 (–0.2 to 75.5) g], even when only trials involving supplementation of undernourished women are considered [weighted mean difference +49.4 (–2.0 to 100.8) g] [19]. Similarly, although documented periods of significant nutritional deprivation, such as the Dutch Famine [17] and seasonal famine in the Gambia [20], do result in reduced birthweight, the effect size is relatively modest.

In contrast to this small effect of maternal nutritional status during pregnancy, maternal prepregnancy weight and body mass index are associated with impaired fetal growth. A recent large meta-analysis found a 50–60% increased risk of low birthweight in women who were underweight before pregnancy (adjusted relative risk 1.64, 95% CI: 1.38–1.94) compared with normal weight women [21]. Artificial reproductive technology (ART), which may involve altered nutrition of the early embryo in the case of in vitro fertilization and, via different hormonal and uterine environments, possibly in other modes of ART
also, is also associated with reduced size at birth in both singleton and twin pregnancies [22, 23].

Thus, it seems that maternal factors operating both well before and during very early pregnancy may be more important for determination of placental efficiency, fetal growth trajectory and birthweight than variations in maternal nutrition during pregnancy. If these factors operate solely through effects on the placenta, then one would expect effects on fetal growth only to become apparent after the onset of hemotrophic nutrition; that is, after the first trimester. Indeed, given consistent maternal phenotypes and ‘normal’ pregnancies, fetal growth does appear to be fairly uniform during the first trimester [24], forming the basis of the reliance on first trimester ultrasound dating of gestational age. However, observational data in humans and experimental data in animals indicate that fetal growth trajectory may be determined before hemotrophic nutrition is fully established. For example, a fetal size that is smaller than expected on first trimester ultrasonography in fetuses of known gestational age is linearly associated with reduced size at birth [25].

Intriguingly, all of the pre- and/or early-pregnancy factors discussed above (maternal prepregnancy weight/body mass index, discrepancy between observed and expected fetal size on first trimester ultrasonogram and ART) also increase the risk of preterm birth [26]. Babies born preterm are relatively growth restricted compared with fetuses of similar gestational age who go on to deliver at term [27], raising the intriguing possibility that the early factors leading to reduced fetal growth may also lead to preterm birth.

**Experimental Manipulation of Maternal Nutrition and Fetal Growth**

Although maternal nutrition during pregnancy in humans appears to have relatively small effects on fetal growth, in experimental animals it is relatively straightforward to induce fetal growth restriction via significant levels of maternal undernutrition throughout gestation or in late gestation in rats [28], guinea pigs [29] and sheep [30]. Direct fetal catheterization in late-gestation sheep has shown slowing of fetal growth with severe maternal undernutrition that is reversible only for a limited period of time; with ongoing undernutrition, the reduced fetal growth trajectory does not return to normal with refeeding [31].

In singleton sheep pregnancies, we also have shown that moderate maternal undernutrition only around the time of conception results in a reduced fetal growth trajectory in late gestation [32]. Intriguingly, although in this study the fetuses of periconceptionally undernourished ewes had slower growth rates in late gestation, they exhibited a lesser reduction in growth trajectory in response
to an additional, brief, maternal fast in late gestation than fetuses whose mothers had been well nourished throughout pregnancy [32, 33]. Thus, a fetus with a slower growth rate determined by a periconceptional exposure may be better able to tolerate nutritional restriction in late gestation, either due to reduced demand (although the birthweight of fetuses in the two groups was very similar) or due to altered metabolic regulation.

Twins are often considered to be growth restricted [34] and, indeed, are born smaller than singletons. The growth restriction in twins has long been considered to be due to constraints of intrauterine space and limitations of placental nutrient supply, although there are few data to support this. In sheep, twin fetuses also grow more slowly than singletons in mid-late gestation and are born smaller, yet have a greater slowing of growth in response to a maternal fast in late gestation than do singletons [35], presumably reflecting the fact that the reduced maternal nutrient supply is distributed between two fetuses. However, when twin-bearing ewes are also exposed to periconceptional undernutrition, the effect of the early pregnancy influence on late gestation responses to nutritional deprivation is again apparent, with the lighter twins of periconceptionally well-nourished ewes exhibiting a greater slowing of growth than the lighter twins of periconceptionally undernourished ewes [35]. These complex interactions between periconceptional events (maternal nutrition, twin conception) and late gestation fetal growth responses to nutritional stress suggest that the periconceptional stressors themselves determine fetal growth trajectory and, perhaps, also the nutritional regulation of fetal growth. We recently have demonstrated that this is indeed the case in twins in sheep. Twin-bearing ewes were randomly assigned to either fetal reduction of one twin at the end of the first trimester, converting the twin pregnancy to a singleton, or a sham procedure [36]. Fetuses conceived as twins, but which spent the majority of pregnancy as singletons (reductions), were of very similar size to twins at birth, particularly in measures of linear growth, indicating that constraint of fetal growth in twins is largely determined in early gestation. Gestation length was also the same in reductions and twins, again suggesting that fetal growth and gestation length in twins may be linked and determined in early pregnancy. Perhaps most intriguingly, it appears that twin conception also determines the regulation of postnatal growth to some degree. Reductions had accelerated postnatal growth between birth and weaning, growing faster than both singletons and twins, despite similar milk intakes. After weaning, twins demonstrated accelerated growth such that by 2 years of age (puberty is at approximately 7–9 months) animals in all three groups were of similar size (fig. 1). However, twins and reductions had greater fat mass than singletons, suggesting that adult fat mass in twins is determined by twin conception and not by fetal number in late gestation, birthweight.
We also have shown that maternal periconceptional undernutrition, with ewes undernourished from 60 days before to 30 days after mating (approximately the time of placental attachment in sheep) and fed normally thereafter, perturbs metabolic and endocrine regulation of postnatal growth (fig. 2) [37] and alters adult fat mass [Jaquiery, unpubl. data].

Taken together, these data indicate that the intrauterine environment, including the nutritional environment, during the very earliest stages of pregnancy may impact not only on fetal and placental growth, but also on postnatal growth and its regulation.

**Fetal Nutrition and Epigenetic Modifications**

The reprogramming of epigenetic marks in the zygote that occurs up to the blastocyst stage [38] makes epigenetic modifications one possible mechanism mediating the effect of the intrauterine environment on fetal development. Imprinted genes (resulting in parent of origin gene expression) are known to affect placental function and to be associated with patterns of fetal growth, with paternally expressed genes associated with promotion of fetal growth and maternally expressed genes associated with constraint of fetal growth. However, there is less evidence for an association between environmental factors known to affect fetal growth and epi-
genetic modifications in placental genes [38, 39]. Extraembryonic tissues, derived from the trophectoderm, are globally hypomethylated compared with embryonic tissues derived from the inner cell mass from as early as the blastocyst stage, and it has been proposed that this may be important for allocation or function of the lineages [38]. In contrast, a variety of environmental factors in pregnancy, including nutritional factors, have been shown to result in epigenetic modifications in the fetus. Recent data from human cohorts have correlated epigenetic marks at birth with childhood adiposity [40] and have described epigenetic changes in metastable epialleles in offspring conceived during periods of famine [41]. Experimental data in sheep have shown that periconceptional maternal undernutrition and twin conception result in similar epigenetic modifications in the pro-opiomelanocortin and glucocorticoid receptor genes in the appetite regulatory centers of the fetal ventral hypothalamus [42], and offspring have increased adult fat mass [43]. However, the signals that are responsible for transmitting intrauterine environmental information to the embryo remain unknown.

**Conclusion**

Fetal growth is regulated largely by nutrition and the intrauterine environment. Evidence increasingly is pointing towards nutritional factors in very early pregnancy, and even before pregnancy, playing key roles in determining fetal growth trajectory. Whether these nutritional factors act directly on the embryo or act via intermediary factors is not yet known. The observations that a variety of seemingly very different periconceptional factors (maternal nutrition, ART,
twin conception) can all affect fetal growth, gestation length and epigenetic marks in the fetus suggest that research into the mechanisms underlying these effects may have wide applicability to our understanding of fetal growth and, potentially, to ways of optimizing fetal growth in pregnancies where this may be at risk of being suboptimal.

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Disclosure Statement

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