Regulation of Fetal Growth by the Somatotrophic Axis

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ABSTRACT Suboptimal fetal growth is associated with higher fetal mortality and with higher neonatal morbidity and mortality. It increases the likelihood of premature birth that in turn further compounds perinatal health risks. Moreover, an abnormal fetal environment, as reflected in an altered birth size phenotype, increases the propensity for disease in childhood and adulthood. Fetal growth represents the culmination of interaction between the fetal genome and the intrauterine environment determined by maternal-placental function. The role of endocrine and metabolic factors in mediating this interaction will be reviewed. There is also evidence that fetal growth, as measured in late gestation, is dependent not only on the maternal environment but on events that occurred during the periconceptual period. Thus, fetal growth not only reflects the immediate fetal environment but events surrounding conception and embryonic life.


KEY WORDS: growth hormone (GH) • insulin-like growth factor–1 (IGF–1) • fetal • nutrient • growth

Traditionally, intrauterine growth retardation (IUGR) has been defined in terms of absolute birth weight (<2500 g), which ignores gestational age and factors that may need to be considered across different populations. Over the past few years the term small for gestational age (SGA) has been introduced to correct for gestational age, and various criteria based on centiles or standard deviations have been developed to define this group. However, many standards used are population specific, and standards such as those of Usher and McLean (1), which are over 30 y old, are still in use. Since that time there has been far greater survival of premature infants, but growth curves for such infants have not been completely defined. Normality for a delivered pre-term infant may only occur rarely because these infants should still be in utero and there is a close relationship between prematurity and IUGR. Normal growth charts may have to be redefined for the 24–36-wk infant by in utero ultrasonographic measurements (2).

The work of Barker and colleagues has stressed the importance of taking into account not only birth weight but also body proportions (symmetrical or asymmetrical growth), head circumference and some measure of relative adiposity, such as ponderal index. Such considerations may reflect the nature of environmental cues the fetus has been exposed to and may also have prognostic value (3).

Barker (3) has shown that the relationship between birth size phenotype and long-term consequences extends across the normal range of birth weights and is not a function of the extreme ends of the birth-weight spectrum. For example, an infant with a normal birth weight of 3.4 kg may be physiologically growth retarded with the same long-terms risks if under optimal intrauterine conditions it was destined to be 3.8 kg. This raises the possibility that many fetuses may be growing less than their optimal potential because of a limited intrauterine environment but are not growth retarded in terms of classical definitions.

A general model for birth size

In the human fetus, little absolute variation in fetal growth occurs up to about 16 wk gestation, after which the variance increases considerably. This pattern is a result of increasing environmental influences superimposed onto the genetically determined developmental program (4). Chromosomal and genetic disorders often will present with fetal growth retardation, but excluding these, the dominant cause of growth retardation in mid- and late gestation relates to a diminished supply of nutrients, including oxygen. The genetic influence is almost entirely maternal in origin, with low paternal genetic correlation (5,6). The genetic factors are likely to be those that determine maternal habitus and physiology. For example, maternal height is an important determinant of birth size and increases considerably. This pattern is a result of increasing environmental influences superimposed onto the genetically determined developmental program (4). Chromosomal and genetic disorders often will present with fetal growth retardation, but excluding these, the dominant cause of growth retardation in mid- and late gestation relates to a diminished supply of nutrients, including oxygen. The genetic influence is almost entirely maternal in origin, with low paternal genetic correlation (5,6). The genetic factors are likely to be those that determine maternal habitus and physiology. For example, maternal height is an important determinant of birth size and increases considerably. This pattern is a result of increasing environmental influences superimposed onto the genetically determined developmental program (4). Chromosomal and genetic disorders often will present with fetal growth retardation, but excluding these, the dominant cause of growth retardation in mid- and late gestation relates to a diminished supply of nutrients, including oxygen. The genetic influence is almost entirely maternal in origin, with low paternal genetic correlation (5,6). The genetic factors are likely to be those that determine maternal habitus and physiology. For example, maternal height is an important determinant of birth size and increases considerably. This pattern is a result of increasing environmental influences superimposed onto the genetically determined developmental program (4).
mother is unlikely in view of data from embryo transfer experiments (7).

Walton and Hammond’s (8) cross-breeding studies and those that have followed suggest that normal fetal growth in late gestation is constrained by uteroplacental factors and that it is the maternal phenotype that determines the birth size of the fetus. A fetus of same genotype will grow larger if allowed to gestate in the uterus of a large-breed animal than in that of a small breed animal. These studies have been interpreted to show that it is the delivery of nutrients to the fetus that is actively constrained (9). This constraint prevents fetal overgrowth and resulting dystocia: the latter would be a risk for both mother and fetus and lead to evolutionary failure. The nature of this constraint, which is reflected both in the lower birth weight of twins and in the relationship between maternal stature and birth size, is poorly understood. Placental transport capacity and diffusion area (which is presumably linked to uterine size and vasculature) are primary contributors. Another element may be the demonstrated capacity of the placenta to clear insulin-like growth factor (IGF)-1 from the fetal circulation when levels are high, thus putting a ceiling on the endocrine drive for fetal growth (10; Iwamoto, H. S., Chernausek, S. D. & Murray, M. A., unpublished data, 1991).

The endocrine regulation of fetal growth in late gestation is now well understood. Whereas IGF-2 is the primary growth factor underpinning embryonic growth, the dominant fetal growth regulator in late gestation is IGF-1 produced by the fetal liver and other tissues (11). Direct fetal infusion of IGF-1 promotes fetal substrate uptake, inhibits fetal catabolism and influences placental metabolism by inhibiting placental lactate production, presumably allowing more substrate to cross the placenta (12). There has been a report of one human patient with an IGF-1 gene deletion who presented with severe IUGR (13). In contrast to the postnatal situation, the dominant regulator of IGF-1 production in the fetus is not growth hormone (GH), as GH receptors are generally expressed only at low levels in fetal tissues and appear to be induced by the peripartum glucocorticoid surge (4,14–16). Instead, fetal insulin, which in turn is predominantly under regulation by fetal glucose availability, is the primary driver of circulating fetal IGF-1 (17).

There remains debate as to the relative importance of systemic versus paracrine IGF-1 production. Generally, manipulations that affect fetal systemic IGF-1 also affect tissue levels, which limits the ability to distinguish these relationships. Additionally, evidence of interactions between endocrine and paracrine IGF production is increasing (18). In experimental IUGR induced in sheep, it was recently shown that IGF-1 of amniotic origin is present at decreased levels and that amniotic IGF-1 administration enhances fetal gut maturation, is systematically absorbed and influences systemic IGF-1 levels (19). Thus, the role of the membranes, the presumed source of amniotic IGF-1, also needs to be considered.

The fetal IGF-1 system is sensitive to maternal nutrition. In fetal sheep, short-term maternal undernutrition leads to cessation of fetal growth associated with reduced fetal IGF-1 levels and altered IGF binding proteins (20). Glucose or insulin infusion but not an amino acid infusion restores fetal IGF-1 to control levels (21). Similarly, in acute asphyxia induced by umbilical cord occlusion there is a transient fall in IGF-1 and elevation of the inhibitory IGF binding protein-1 for several hours (22). The sensitivity of fetal tissues and the placenta to IGF-1 appears to be disturbed in IUGR; IGF-1 resistance has been reported in the sheep placenta (23) and in neonatal rat muscle (24,25).

Insulin itself has long been suggested as the dominant fetal-growth-promoting hormone, but evidence suggests that its somatogenic actions are mediated through stimulating IGF-1 release (26,27) whereas its direct effects are on adipogenesis leading to the obesity typical of infants of diabetic mothers (28). In humans, growth hormone and thyroid hormone have little significant role in the regulation of fetal growth due to receptor immaturity but begin to exert a limited influence after 36 wk gestation (14–16).

Glucocorticoids have important effects on both fetal growth and maturation (29). There are ample experimental and some clinical data to suggest that repeat exposure to maternal glucocorticoids can lead to fetal growth retardation. The fetus is normally protected to some degree from maternal glucocorticoids by the presence of the barrier enzyme, 11 β-hydroxysteroid type 2; however, this enzyme is down-regulated by maternal undernutrition, thus potentially exposing the fetus to increased glucocorticoids. The growth-retarded fetus often has elevated cortisol levels, which explains the accelerated maturation of some organs, such as the lung, in IUGR infants. Teleologically, this can be seen as an attempt to mature precociously the compromised fetus in expectation of premature delivery that frequently accompanies IUGR. Premature delivery may occur because acute undernutrition in late gestation can stimulate progesterandin release, which promotes cervical ripening and uterine contractility (30,31), or it may originate much earlier in gestation.

Early fetal growth

The regulation of embryonic and fetal development cannot be separated from the processes of tissue differentiation and organogenesis (including trophoblast development). There is a consensus that IGF-2 is an important systemic/paracrine coordinating factor in embryonic growth (32,33). In mice and humans, the IGF-2 gene is imprinted and expressed from the paternal allele whereas the IGF-2 receptor is imprinted in mice only and expressed from the maternal allele. IGF-2 exerts its biological action by binding to the IGF-1 receptor whereas binding to IGF-2 receptor, which mainly acts as a clearance receptor, reduces the circulating levels of IGF-2. In cases of isopaternal disomy in humans, IGF-2 is overexpressed leading to the Beckwith-Weidemann overgrowth syndrome. Experimental knockout of IGF-2 receptor also leads to embryonic overgrowth by impairing IGF-2 clearance. Conversely, knockout of IGF-2 leads to poor fetal embryonic growth.

Recent studies of the large offspring syndrome in ruminants caused by prolonged culture of the embryo before implantation shows that it is associated with altered imprinting of IGF-2 (34). Because folate status has been shown to influence imprinting efficiency in other genes (35) and imprinting involves gene methylation, it is reasonable to speculate that folate status at the earliest stages of development, before the imprint is established, may grossly affect fetal development and growth. This is an area where there are easily testable hypotheses.

Periconceptual events

Focus on periconceptual determinants of fetal size and development in late gestation is increasing. In sheep that were periconceptually undernourished but then restored to normal nutrition for the remainder of pregnancy, there is slower growth in late gestation (36) associated with insulin resistance, altered placental lactogen (PL) production and altered metabolism as reflected in lactate and urea responses to acute undernutrition. This might suggest irreversibly altered placental metabolism or endocrinology. In midgestation these animals have reduced fetal IGF-1 levels and altered IGF binding protein levels (37).
Persistent changes in maternal metabolism occur throughout pregnancy, even after maternal nutrition has returned to normal, with maternal taurine levels staying elevated (38). We recently observed that these animals deliver significantly prematurely as a result of premature activation of the fetal hypothalamic pituitary adrenal axes (Bloomfield et al., unpublished data, 2002). Interestingly, Fall et al. (39) showed that gestational length is reduced in women of rural India with presumed inadequate periconceptual nutrition.

The underlying molecular mechanisms that give rise to the above are not definitively understood but emerging evidence suggests that nutritional influences may alter gene imprinting. Wolff et al. (35) showed that methyl-supplemented diets fed to pregnant mice alters the expression of an imprinted gene specific to coat color in their offspring. This forms an interesting possibility with regard to the somatotrophic axis; the GH/IGF-1 axis is subject to nutritional regulation and IGF-1 promotes the conversion of the amino acid serine to glycine, giving rise to methylenetetrahydrofolate, a source of 1-carbon units that may be used for DNA methylation or imprinting (23). Hence, it is attractive to propose that the diminished IGF-1 levels after nutritional insult may affect epigenetic mechanisms, but other mechanisms cannot be ruled out. Such important but preliminary observations suggest the need for a greater research focus on events surrounding conception in determining pregnancy outcomes. Given the relatively small absolute energetic and anabolic demands of the conceptus at the earlier stages of gestation, this might suggest a focus on key micronutrients.

Compartmentalization of nutrients in late gestation

Fetal growth in late gestation reflects the compartmentalization of nutrients among mother, placenta and fetus. The compartmentalization appears to be maintained by the maternal, placental and fetal somatogenic axes but the available data are rather limited.

By the end of the first trimester in human pregnancy, the placenta becomes the dominant source of an alternate form of growth hormone (GH-2, placental GH or GH-v), which suppresses pituitary GH (GH-I or GH-N) secretion (40). Whereas GH-1 is secreted in a pulsatile manner, GH-2 is secreted in a constant, pseudoacromegalic fashion and is only secreted into the maternal circulation. GH levels are reduced in IUGR but whether this is causative or solely reflects placental dysfunction is not clear. In contrast, the other placental somatogenic hormone, PL, while largely secreted into the maternal circulation is also found in the fetal circulation (41). These two hormones are believed to create a state of relative maternal insulin resistance that allows glucose to be transferred across the placenta and for the mother to undergo lipolysis more readily for her own metabolic needs.

Additionally, GH-2 may directly affect placental function or development. We (42,43) reported that maternally administered GH in the sheep enhances placental diffusion capacity and that this can be associated with enhanced fetal growth. Whether the outcome on fetal growth is primarily due to the effects on placental function or maternal metabolism is not known. These data raise the possibility that therapeutic approaches to enhance fetal growth via maternal therapy may be possible.

Pregnant women do not develop acromegalic IGF-1 levels, suggesting that the effects of GH and PL are largely on fat stores rather than on musculoskeletal tissue. This suggests that a degree of functional GH resistance is created in maternal liver and perhaps muscle during pregnancy. We speculate that the steroid profile of pregnancy creates this differential tissue sensitivity to GH. Of potential relevance, we (Blair, H. T., McCutcheon, S. N., Breier, B. H. & Gluckman, P. D., unpublished data, 2002) recently found that in sheep selected over several generations for high IGF-1 levels, fetal growth retardation ensues in the high–maternal IGF-1 line, supporting the speculation that GH sensitivity in the mother may be tissue specific.

These placental somatogenic hormones (40) are derived from a cluster of 5 genes on human chromosome 17. To date, no viable pregnancy has been reported where the entire cluster is deleted. There was one report of a pregnancy where GH-2 and two PL coding genes were deleted (44). In this case, GH-1 expression persisted albeit at low levels, which might suggest a very high degree of critical redundancy, but the data are lacking.

The placenta itself can secrete IGF-1, but its regulation is not well understood and it is presumed to largely have intraplacental roles (45). The fetal IGF-1 system can modulate placental metabolism and the placenta can modulate fetal IGF-1 levels (10,12; Iwamoto, H. S., et al., unpublished data, 1991). We (46) have proposed that fetal growth relies on optimal nutrient compartmentalization that occurs with high-to-normal levels of IGF-1 on both sides of the placenta.

The nutrient pipeline

The supply of nutrients to fetal tissues depends on a complex process involving maternal health, maternal homeostasis, uteroplacental circulation, placental transfer and metabolism, umbilical blood flow and the fetal anabolic-catabolic state. It is, thus, not surprising that interference with this pipeline is the dominant cause of impaired fetal growth. We (Gluckman, P. D., et al., unpublished data, 2001) recently showed a relationship between maternal dietary status and cord blood IGF-1 levels in the Southampton Women’s Study, suggesting that even within an unremarkable Western population, fetal growth is influenced by maternal dietary status.

Recent studies showed that severe exercise in late gestation can reduce fetal size dramatically, presumably by redistribution of maternal blood flow (47,48). Maternal health can also affect fetal growth in many ways. For example, cardiac disease can lead to fetal hypoxemia, and chronic infection can lead to maternal catabolism and, thus, to nutrient competition between mother and placenta.

Maternal and paternal age appear to have significant but poorly defined effects (49–51). Given the increasing number of Western women who have delayed first pregnancies and the continuing epidemic of teenage pregnancy, the rising statistics appear to justify both epidemiological and experimental research. Data in sheep, for example, show that pregnancy during adolescence is associated with fetal growth retardation (52). We presume this reflects continued competition for nutrients for maternal growth at the expense of the fetus. This is supported by observations we have made that high maternal IGF levels throughout pregnancy appear to compromise fetal growth (Blair et al., unpublished data, 2002). Maternal age may impair fetal growth for many reasons (e.g., altered distensibility of uterine vasculature) but few compelling data support these possibilities.

The placenta matures relatively late in pregnancy—the full chorioallantoic placenta is not developed until about 12–14 wk in humans—and transport of oxygen and nutrients from mother to conceptus may well be by less efficient trophotrophoblast diffusion before the full establishment of the placental villus system. The effectiveness of the trophoblast invasion into the maternal spiral arterioles is critical to a well-functioning
placenta, a feature disrupted in preeclampsia. Placental disease secondary to preeclampsia or maternal diabetes and other vascular episodes is common in developed nations; in the Third World, malarial infection is a critical cause of placen
tis.

The placenta itself is a metabolically active tissue. Until recently it was thought to function autonomously, but we now have some evidence that both maternal and fetal hormones may influence placental function (12,42,53). If this is the case, it may suggest therapeutic approaches. The placenta consumes about 40–60% of glucose and oxygen extracted from the maternal circulation (54). In the case of glucose and perhaps amino acids, a significant proportion transfers from the maternal to fetal circulation and then is reextracted from the fetal circulation. In IUGR the rate of fractional placental extraction rises and can lead to fetal wastage, visible on ultrasound and demonstrable experimentally, leading to loss of lean body mass from the fetus. Thus, an evolutionary hierarchy is established—the fetus may become catabolic to try and sustain the placenta and both may be compromised to try and sustain the mother.

Knowledge of intraplacental metabolism is extremely limited. Data suggest, for example, that fetal IGF-1 levels can affect amino acid metabolism and serine-glycine conversion (23). Similarly, placental function continues to evolve as the placenta ages—the villus area appears to increase well into the third trimester and in sheep, at least, may be enhanced by maternal GH administration (42). Late in pregnancy there appears to be some degree of trophoblast degeneration, as reflected in declining PL production, which presumably is part of the risk to the postterm fetus—again an area with minimal investigation (55,56).

Nutrient transport depends on specific transporters for both glucose and amino acids. Glucose transport depends on the expression of glucose transporter-1 and -3 in the placenta and is therefore independent of insulin (57). The regulation of these transporters is poorly documented. Alcohol, smoking and opiates can affect amino acid transporters. In the rat, glucose transporter-1 and -3 expression may be affected by maternal nutritional status both past and present (Bassett, N. S., Currie, M. J., Breier, B. H., Woodall, S. M. & Gluckman, P. D., unpublished data, 1997).

Fetal responses to a disturbed pipeline

The fetus responds to the asphyxia that accompanies maternoplacental disease with a redistribution of fetal blood flow to protect the brain, heart, adrenals and placenta (58–60). This leads to the so-called asymmetrical pattern of fetal growth retardation. If the supply of glucose to the fetus is limited, fetal insulin and IGF-1 (both endocrine and paracrine) levels will fall and musculoskeletal growth impairment will occur. In humans, insulin also drives the deposition of fat in the fetus in late gestation.

Although it is traditionally said that the brain is spared in IUGR, this is not meant to imply that brain function or morphology is normal (61). A summary of the available data suggests that in animals with experimentally induced IUGR, neuronal number is affected in some areas of the brain. There have been reports of disturbed myelination and that the neuropil is reduced in some areas, such as the hippocampus. Evidence also exists that the IUGR brain is more sensitive to asphyxial injury. In Western populations, it is clear that the incidence of neurological morbidity in surviving very-low-birth-weight infants is very high. However, it is not easy to separate effects of prematurity from those of growth.

Catch-up growth

In the Western world, the incidence of those born short who fail to show catch-up growth has fallen dramatically over the past 40 y—catch-up growth is usually present by 6 mo and complete by 2 y—and it seems probable that this is related to better prenatal care. However, in undeveloped countries, catch-up growth may be much delayed or compromised. This may have an antenatal origin or reflect on the incidence of infection or other maternal situation that compromises the infant’s nutrition or endocrine status postnatally.

Mellor and Murray (62) demonstrated in sheep undernourished in late gestation and then returned to normal feed that the fetus shows catch-up growth if fetal undernutrition is brief but not if fetal undernutrition is prolonged. The basis of this switch from reversible to nonreversible growth failure is not known, but prolonged intrauterine insults may be more likely to persist in the postnatal period as short stature.

The fetal pattern of regulating IGF-1 (i.e., nutrition dependence) is generally thought to be dominant until about postnatal age 6 mo, when GH receptors have increased in number to the extent that GH-dependent growth dominates. This may be reflected in the infant and child phases of the infancy-childhood-puberty growth charts developed by Liu et al. (63). This developmental switch in growth regulation makes sense. GH-regulated growth allows one to grow to the full genetic potential (given the evolutionary significance of adult size) whereas insulin-dependent IGF-1 secretion, as present in the fetus, ensures a direct linkage between nutrient availability and growth and in turn ensures that maternal constraint can operate to avoid dystocia.

Macronutrients, micronutrients and fetal growth: the endocrine perspective

Macronutrient balance can affect the pattern of human fetal growth. For example, patterns of fetal growth in early and late pregnancy may be linked to the maternal intake of carbohydrates and low dairy intake (64). Additionally, there is an interaction with maternal folate status whereby the metabolism of folate provides substrates for regulatory processes such as imprinting mechanisms and DNA synthesis that have downstream effects on growth.

The role of micronutrients in fetal growth is of rising interest. There is ample evidence postnatally that micronutrient availability can have a major influence on the somatotropic and insulin axes (65–67). Unfortunately, data are limited on the effects of these nutrients prenatally on fetal or placental physiology. Zinc, for example, is critical for insulin packaging and secretion (68), and zinc deficiency is known to be associated with IUGR (69,70). Vitamin E is an important up-regulator of insulin sensitivity (67,71). Vitamin A and its metabolite retinoic acid enhance GH secretion postnatally (65), and although this may not be critical to fetal growth, it is not yet known whether there are similar influences on placental GH secretion.

GH and IGF-1 stimulate the induction of the active form of vitamin D through vitamin D-24-hydroxylase (72,73). Conversely, ample data suggest that high doses of vitamin D can inhibit GH secretion (74), again probably not of fundamental importance to fetal growth unless similar interactions exist within the placenta. On the other hand, polymorphisms of the vitamin D receptor are associated with insulin resistance and with reduced birth size (75,76).

Experimentally induced folic acid deficiency leads to embryonic fetal growth retardation (77). As discussed previously,
folic acid is critical to methyl group supply and, thus, to DNA methylation during early pregnancy and to protein deposition in the conceptus throughout pregnancy. Fetal IGF-1 infusion in the sheep was recently observed to regulate serine-to-glutamine conversion in the placenta—a folic acid–dependent step (23).

Final comments

Optimal fetal growth is essential for perinatal survival and reduction in morbidity in the perinatal period. However, data increasingly suggest that optimal fetal growth has longer-term consequences extending into adulthood and that it may depend on influences extending back to the periconceptual period. We thus have to revise a number of our basic tenets surrounding influences extending back to the periconceptual period. We developing understanding of imprinting sheds new light into how micronutrient status early on the regulation of fetal growth. Our increasing understanding of optimal fetal growth has longer-term disadvantage and severe short stature. Acta Paediatr. 86: 39–45.


