# Hormonal Regulation of Fetal Growth

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The regulation of fetal growth is complex and still very poorly understood. It involves genetic factors, maternal nutrition and cardiovascular adaptations, placental growth and function, and to a lesser extent fetal factors, including fetal hormones. The influence of genetic, maternal, and placental factors on fetal growth has been reviewed recently (1) and will not be discussed. The purpose of this chapter is to analyze the specific role of endocrine factors in the determination of fetal growth, assuming that the nutritional supply to the placenta and to the fetus remains unaltered.

The major endocrine factors involved in postnatal growth are: (a) growth hormone (GH) via the secretion of somatomedin; (b) thyroid hormones; (c) cortisol; and (d) sex steroids at puberty (2,3). Insulin is considered to have a merely permissive role in postnatal growth (2,3). In recent years, a body of evidence has accumulated to indicate that the fetus may be less dependent on pituitary and thyroid hormones for growth than the older organism, and more dependent on insulin and tissue growth factors. Studies on the endocrine regulation of fetal growth have involved several major approaches: ablation of fetal endocrine glands; examination of newborns with congenital endocrine deficiencies; treatment of fetuses with hormones; measurement of plasma hormone concentrations and tissue receptor levels during normal or abnormal growth; and *in vitro* studies of hormone effects on fetal tissues. We shall consider principally the changes in fetal body weight in response to variations of fetal endocrine environment. However, it must be remembered that fetal growth also involves changes in body length and in body composition. This is particularly important for the human fetus which accumulates a large amount of fat in the last trimester of pregnancy. In contrast, the fetus from most other species does not accumulate fat before birth (4) (Table 1).

## FETAL PITUITARY HORMONES

As maternal growth hormone is not transferred across the placenta, the fetus is entirely dependent on its pituitary gland for GH production. The possible role of GH in fetal growth has been studied in several species by depriving the fetus of its pitu-

TABLE 1. *Body fat content in the newborn of different species*

| Species | Body fat (g/100 g body weight) |
|---|---|
| Human | 16 |
| Monkey | 2 |
| Pig | 1 |
| Sheep | 3 |
| Guinea pig | 10 |
| Rabbit | 6 |
| Rat | 2 |

itary gland *in utero*. The first experiments of this kind were performed on rabbit fetuses by Jost in 1947 (reviewed in 5,6). He deprived rabbit fetuses of their pituitary glands by decapitation *in utero* on day 19 to 23 of gestation (normal term in this species is 32 days) and found that growth of the remaining body was not affected by the lack of pituitary until 28 to 29 days of gestation (Fig. 1). This was confirmed in other species, for example, the rat, mouse, and pig (6,7). In the fetal lamb and monkey, hypophysectomy causes growth retardation (8,9), but pituitary stalk section or encephalectomy is not associated with growth retardation (10,11). As fetal hypophysectomy induces both GH and thyroid hormone deficiency, whereas encephalectomy or pituitary stalk section causes only GH deficiency (12), it has been concluded that growth retardation due to fetal hypophysectomy resulted from thyroid hormone deficiency. In the human, anencephaly and congenital absence of the pituitary, conditions resulting in GH deficiency, are not associated with reduced size and weight at birth (reviewed in 6). Fetal decapitation in the rabbit does not decrease
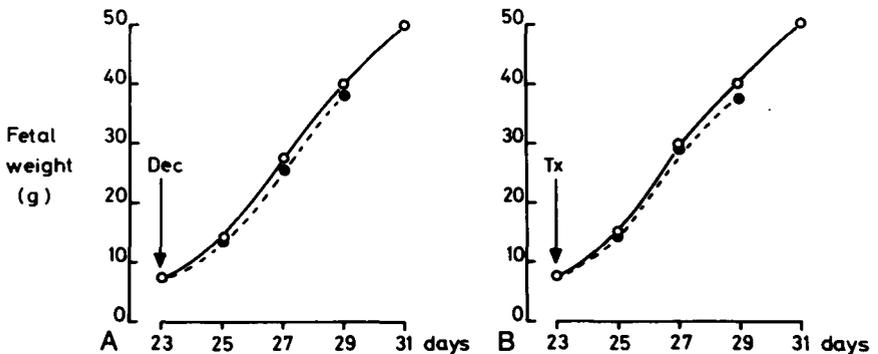


FIG. 1. Effects of fetal decapitation (**A**) or fetal thyroidectomy (**B**) on day 23 of gestation on fetal growth in the rabbit. (Data from refs. 5 and 6.) Dec, decapitation; Tx, thyroidectomy.

fetal weight but increases fetal body lipids (5). Similar observations have been made in the hypophysectomized fetal lamb (8) and in human anencephaly (6).

These studies show that normal fetal growth is possible when GH is lacking or is markedly reduced. GH-dependent growth is not observed until well after birth in most species: 6 months in the human, 3 months in the rabbit, 1 month in the rat, and 1 week in the sheep. The basis for the lack of an effect of GH on fetal growth is not entirely explained, but appears to be due to a lack of GH receptors in fetal tissues as these are important for the production of insulin-like growth factors. In the lamb, hepatic GH receptors are only demonstrated 3 to 6 days after birth (13). In the rat, liver GH receptors are also markedly reduced in early life when compared to adults (14,15).

## THYROID HORMONES

Thyroid hormones are not transferred from the mother to the fetus and the fetus is dependent on its own thyroid gland for thyroid hormone production. Fetal thyroidectomy of the rabbit fetus on day 22 or 23 of gestation does not impair normal fetal growth (5,6) (Fig. 1) but results in a 30% increase in body lipids, which are maintained at normal levels by thyroxine injection at the time of thyroidectomy (5).

Thyroidectomy in sheep and monkey fetuses causes a significant inhibition (10% to 30%) of their growth (16,17). In contrast, human newborns suffering of congenital hypothyroidism, or radiothyroidectomized *in utero* by radioactive iodine given inadvisedly to the mother, have a normal size and weight at birth (6,18–21). Thus, thyroid hormones appear to have little effect on fetal growth in most species, but they are essential for normal neural and osseous maturation in sheep and man (20,21).

## INSULIN

The concept that insulin might be an important hormone for fetal growth arose primarily from clinical observations associated with insulin excess or insulin deficiency. The infants of diabetic mothers are larger (on average 500 g) and somewhat longer (on average 1.5 cm) than control infants (22), though most of the overweight is due to lipid deposition (23,24). Since the excessive growth becomes obvious after the 28th week (25), at a time where fetal pancreas becomes sensitive to glucose (reviewed in 26), it has been suggested that maternal hyperglycemia is attended by fetal hyperglycemia which in turn stimulates insulin secretion by the fetal pancreas and induces fetal macrosomia (reviewed in 22). In contrast, newborns with pancreatic agenesis have profound intrauterine growth retardation (birthweight: 1.2 to 1.5 kg at term) associated with deficient adipose tissue and a decrease in muscle mass (27,28). Infants with transient neonatal diabetes also have a defect in insulin secretion which is associated with a low birthweight (27,29). These infants have reduced adipose tissue and a stunted muscle mass which undergoes rapid development with

postnatal insulin treatment (30). The birth size of infants born with marked fetal hy-
poinsulinemia suggests that the human fetus can reach the size of a 30 to 32 week
gestation fetus independently of insulin. This is compatible with the fact that fat de-
position in the fetus occurs in the third trimester of pregnancy and is clearly insulin-
dependent.

Several studies have recently been performed in animals to analyze the effects of
insulin on fetal growth (Table 2). Injection of large amounts of insulin into the rat
fetus during the last 3 days of gestation increases body weight, total lipids and nitro-
gen, and the ratio lipids to protein (31). Infusion of insulin (19 U/day) for 28 days
into the fetal rhesus monkey produces a 20% to 30% increase in fetal body weight
(32,33). Infusion of insulin for 14 days in fetal pigs has no effect on fetal weight but
has been shown to cause a significant increase in liver and muscle glycogen levels
and in body fat (34, Table 2). Insulin infusion for 18 days, but at a relatively low
rate, in the fetal lamb has no effect on fetal body weight (35). Thus, most of these
studies suggest that chronic hyperinsulinemia can produce a modest increase in fetal
body weight, mainly due to increase in body fat. However, all these studies have
been performed in species in which fat deposition does not occur before birth (4)
(Table 1). It is obvious that the fetal guinea pig or rabbit, which normally accumu-
late body fat in late pregnancy (Table 1), should be better experimental models than
the fetal monkey, sheep, pig, or rat to study the effects of insulin on fetal growth
and adiposity.

Experimental fetal hypoinsulinemia has been induced in some studies by the ad-
ministration of streptozotocin in the fetal rabbit, lamb, or monkey (36–38). Strepto-
zotocin produces fetal growth retardation in those species (36–38) but the data were
difficult to interpret as this drug may have direct toxic effects on tissues other than
the endocrine pancreas. The demonstration that the pancreas is necessary for normal
growth has been made recently in the lamb. Fetal surgical pancreatectomy in the
lamb at 113 to 121 days of gestation is associated with a 25% decrease in body
weight at 139 days gestation (39).

TABLE 2. *Effects of chronic fetal hyperinsulinemia on fetal weight at term*

|  | Species | Plasma insulin ($\mu$U/ml) | Body weight (g) | Body fat (g/100 g body wt) | Reference number |
|---|---|---|---|---|---|
| Rat | Control | — | 5.83 ± 0.48 | 2.47 ± 0.27 | 31 |
|  | Insulin | — | 6.67 ± 0.30* | 2.94 ± 0.07* |  |
| Monkey | Control | 28 ± 12 | 372 ± 54 | — | 33 |
|  | Insulin | 340 ± 208* | 459 ± 53* | — |  |
| Pig | Control | 285 ± 82 | 829 ± 36 | 1.05 ± 0.09 | 34 |
|  | Insulin | 2,376 ± 576* | 855 ± 42 | 1.25 ± 0.05* |  |
| Sheep | Control | 7 ± 1 | 3,451 ± 194 | — | 35 |
|  | Insulin | 31 ± 7* | 3,544 ± 203 | — |  |

*$p < 0.05$ when compared with control.

In addition, a positive correlation between fetal plasma insulin level and fetal body weight at term has been reported in the rat, rabbit, and guinea pig (40–42). This suggests that insulin could not only have a permissive role but also a regulatory role in normal fetal growth.

## THE INSULIN-LIKE GROWTH FACTORS

The terms somatomedin (SM) and insulin-like growth factors (IGF) are synonymous. Somatomedin A and C are analogous to IGF-I, i.e., a 70 amino acid peptide encoded by a gene on human chromosome 12, whereas multiplication stimulating activity (MSA) discovered in the rat is equivalent to IGF-II, a 67 amino acid peptide encoded by a gene on human chromosome 11. The IGFs share a large structural homology with proinsulin (reviewed in 43).

### Plasma Concentrations

IGFs do not cross the placenta (44) and the IGF-I and IGF-II found in fetal plasma in various species are produced by fetal tissues. The concentration of IGF-I is low in fetal plasma in early pregnancy in the sheep, mouse, rat, and human and it increases during gestation (Fig. 2), though it is lower at term than the levels found in the adult (reviewed in 26,45–50). In human infants, the plasma IGF-I concentration is positively correlated with birthweight (51). In the sheep and rat, the concentration of MSA or IGF-II in fetal plasma is higher than during the postnatal period (52,53). In human infants, plasma IGF-II concentration increases during gestation (Fig. 2) and is also positively correlated with birthweight (54).

In plasma, somatomedins (7.5 Kd) are bound to larger carrier proteins (40 and
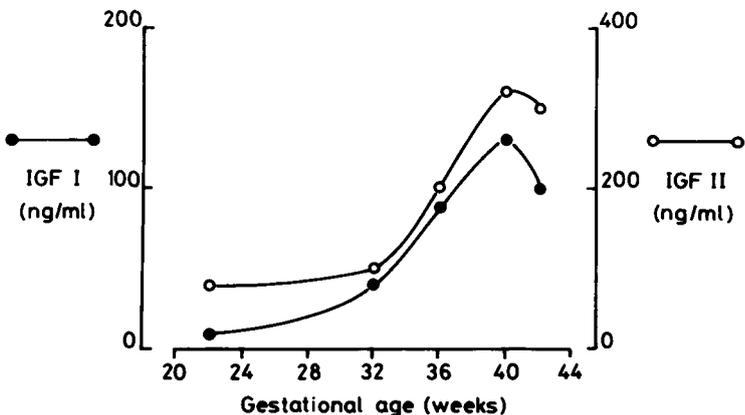


**FIG. 2.** IGF-I and IGF-II concentrations in cord blood of the human fetuses. (From ref. 54.)

150 Kd) that prevent rapid fluctuations in somatomedin concentrations by prolonging their half-life in plasma. This provides a mechanism whereby somatomedin could be delivered continuously to fetal tissues. In the fetus, IGFs circulate primarily bound to the 40 Kd carrier protein, whereas in the adult, IGFs circulate bound to the 150 Kd carrier protein. This larger protein is GH-dependent and appears in late gestation or in the postnatal period.

### Endocrine Control of IGF Secretion

After birth, the liver is the principal site for IGF-I production and this is under GH control (2,3). In the fetus, IGF-I production is not controlled by GH. Indeed, fetal decapitation, hypophysectomy, or electrocoagulation of the hypothalamus of the lamb or rabbit abolishes GH from the fetal circulation but has no effect on circulating somatomedin or IGF levels (55–58). Moreover, GH fails to stimulate IGF secretion by the rat fetus (15) or by cultured fetal rat myoblasts (59). In addition, human anencephalic infants have normal somatomedin levels in cord blood (46,49).

In the fetal lamb, plasma IGF-I concentration is reduced, whereas IGF-II is increased after pancreatectomy (60) or streptozotocin administration (37). Infants with transient neonatal diabetes have low levels of IGF-I in cord blood but normal IGF-II levels (61). Insulin infusion in rabbit, pig, or monkey fetuses is associated with increased plasma somatomedin levels (62–64). Moreover, insulin increases IGF-I production by cultured fetal rat myoblasts (65) but is without effect on IGF-II release by cultured fetal rat hepatocytes (66).

Placental lactogen (PL) is produced by the placental trophoblast in some species (human, sheep, rat) and is secreted into the fetal circulation, but at a much lower rate than into the maternal circulation (67). The major physiological role of PL was thought to be the mobilization of maternal energy stores, through its action as an insulin antagonist (67), but it is also thought to stimulate maternal IGF secretion (68). More recently, it has been reported that ovine PL stimulates amino acid uptake by fetal rat muscles, glycogen synthesis by fetal rat liver, and IGF-II release by rat fibroblasts (69–71). Human PL has been shown to stimulate somatomedin release in cultured human fetal myoblasts and fibroblasts (72). However, although the evidence that PL has a role in prenatal growth is strong, this hormone is not essential. Indeed, PL is not secreted by the placenta of several species (rabbit, pig, etc.) and infusion of an antiserum to PL for 3 and 6 days in the fetal lamb did not decrease IGF-I or -II concentrations (49). In addition, newborn infants delivered to women devoid of PL are of normal size and weight at birth, even though plasma IGF-I in maternal plasma was very low (73,74).

### Paracrine or Autocrine Functions

It has been shown that IGF-I and -II are produced by a large number of fetal tissues in rodents (Fig. 3) and humans, and are present in these tissues far in excess of amounts that can be accounted for by contamination from blood (75–77). On the ba-
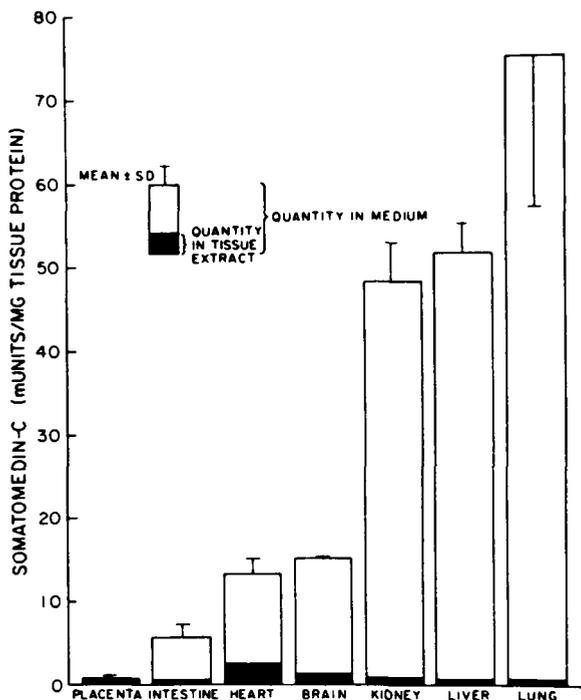
**FIG. 3.** Somatomedin-C (IGF-I) concentration in extract and in incubation medium of tissues from fetal mouse. (From ref. 76.)

sis of these findings, the classical concept that IGFs could act as endocrine factors, i.e., molecules synthesized and secreted by an organ in the body which pass via the bloodstream to exert their actions distantly, has been progressively abandoned for the concept of paracrine or autocrine function, i.e., molecules synthesized and secreted by an organ and acting at or near their site of production (Fig. 4) (78). As
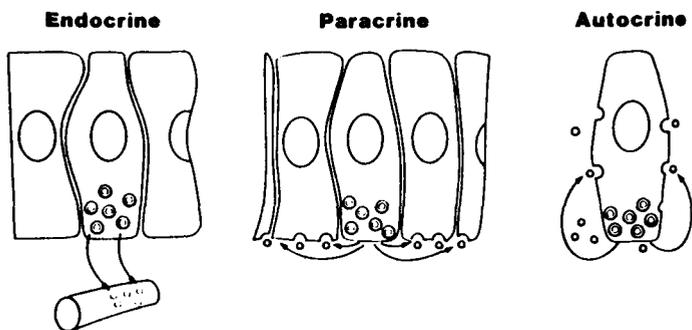


**FIG. 4.** Schematic view of endocrine, paracrine, and autocrine roles of trophic hormones. (From ref. 3.)

IGF-I and IGF-II stimulate DNA synthesis by human fetal myoblasts, fibroblasts, and chondrocytes (79–81), these locally produced mitogens would be readily available for regulating tissue growth. However, the importance of paracrine/autocrine mechanisms relative to the traditional endocrine actions of IGFs is not clear, and it is possible that IGFs act through all three mechanisms.

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# DISCUSSION

*Dr. Bracci:* What do you think of the possibility which has been suggested that insulin acts to increase the number of receptors in the tissues? If this is true, it is possible that insulin may moderate the number of receptors during fetal life, which could have important effects on their numbers after birth. This has been suggested, especially in the case of infants of diabetic mothers.

*Dr. Girard:* The effect of insulin on human fetal growth, and particularly lipid deposition, only appears after about 26 to 27 weeks gestation. Before that time it is not important. It is also clear that during fetal life there is no down-regulation of insulin and insulin-like growth factor (IGF) receptor numbers as occurs during postnatal life, when an excess of insulin results in a decrease in insulin receptor concentration. The lack of this mechanism during fetal life could certainly be an important factor in determining an increase in fetal growth. There are very few studies of IGF receptors during fetal life, but we do know that they exist in most tissues—skeletal muscle, myoblasts, fibroblasts, cartilage, and so on. But there are no studies of change in receptor numbers during maturation, especially during the fetal period, so we don't know to what extent IGF could be implicated. Another factor to consider is the extent to which competition occurs between insulin receptors and IGF receptors. It could be that the extent to which IGF receptors bind to insulin receptors is greater during fetal life, or that insulin receptors bind specifically and mainly to IGF receptors during this period. This is a new field and we do not have the answers yet, but it is a fascinating growth area.

*Dr. Bracci:* Do you think that other hormones may be important for fetal growth, such as calcitonin or parathyroid hormone (PTH)?

*Dr. Girard:* It is clear that depriving the pregnant mother of calcitonin or PTH causes a marked reduction in fetal growth, but I think this is more likely to be due to deleterious effects on the mother than to the fetus. When a thyroidectomy is performed on a pregnant rat, the marked effect on fetal growth which occurs is due to metabolic derangement in the mother and not to specific endocrine deficiency in the fetus.

*Dr. Toubas:* Your very clear presentation gave me the impression that the fetus is in charge of his growth. What is the role of the placenta? It has recently been found that the placenta contains growth factors, such as epidermal growth factor (EGF), and growth factor receptors. Does the placenta control fetal growth?

*Dr. Girard:* I cannot answer this. I have restricted my talk to the role of fetal endocrine glands in fetal growth, when all is well with the mother, the placenta, and the placental perfusion. Of the various factors influencing fetal growth, it is clear that the fetal endocrine glands are not the most important, and certainly not as important as maternal nutrition, or placental

size and blood flow. I have shown you that at worst, when you completely destroy one endo-crine gland, you have a reduction in body weight of the fetus of not more than 20% to 30%. So there are much more important factors controlling body weight at term.

*Dr. Toubas:* What about the possible role of vasoactive intestinal polypeptide (VIP)? This has recently been implicated in the secretion of prolactin. Do you think it may affect fetal growth?

*Dr. Girard:* If you perform fetal decapitation you deprive the fetus of prolactin, but you do not affect the weight of the fetus at term. Neither do you by administering drugs which inhibit prolactin secretion in the fetus.

*Dr. Robyn:* However, in 1982, Sinha and Vanderlaan (1) reported that injections of anti-prolactin serum in newborn mice were responsible for a high incidence of mortality and generalized developmental abnormalities in the survivors when compared to injections of non-immune serum.

*Dr. Girard:* The situation is not at all clear. In the rabbit there is definitely no source of prolactin other than in the pituitary, i.e., there is no placental lactogen which provides a source in, say, the sheep fetus. Nevertheless, the decapitated rabbit fetus grows perfectly normally.

*Dr. Robyn:* In the fetus, there may be sources of prolactin other than the pituitary. Immu-noreactive prolactin has been found to be produced by other cells than the lactotrophs of the anterior pituitary gland: the endometrium, the lymphoid tissue, the myometrium, hypotha-lamic neurons. Immunorective prolactin is present in B-cells of the endocrine pancreas (2). Thus, prolactin may play a significant role in fetal development. Prolactin may even exert paracrine effects.

*Dr. Hay:* You speak about differences in body weight, but could you also comment on dif-ferences in body composition? I refer specifically to fat, which reflects the major difference in body composition between species. In George Alexander's studies (3) on the sheep, he found that hypophysectomized lambs got quite fat, which normally they don't. With growth hormone replacement they did not get fat, which suggests that this hormone has a specific role in the regulation of fat deposition.

*Dr. Girard:* It is true that when we discuss fetal growth we refer largely to body weight, although growth is clearly also related to length, body composition, and so on. The most in-teresting effects of hormones on body weight are in relation to their influence on adipose tis-sue, particularly in humans. Most of the animal experiments, for example, those in the sheep, rat, or rabbit, have been performed in species in which fat accumulation does not normally occur during fetal development, and this is an important limitation. The guinea pig seems to be the only other species in which it is possible to modify body weight composition during the fetal period hormonally. However, it is also true that the decapitated rabbit fetus, while being the same weight as the intact fetus, is also fatter. So it is possible that pituitary hor-mones may play a role in determining fetal body composition, even if they have no other ef-fects on fetal growth.

*Dr. Bossart:* Does IGF influence the rate of mitosis or only the weight or size of cells? And does IGF cross the placenta?

*Dr. Girard:* There are very few experiments with IGF *in vivo.* Purified IGF injected into hypophysectomized rats can cause an increase in growth; and when injected into dwarf mice it will cause an increase in weight. *In vitro* experiments show that it has a major mitogenic effect in a number of different tissues—skeletal muscle, cartilage, fibroblasts, etc. Most of these experiments have been performed in adult tissues, so it would be very interesting to study the effect on fetal tissues as well.

*Dr. Cédard:* I believe that the fetus is less autonomous than you say. One ought to consider the feto-placental unit as a whole, since the placenta is able to secrete many things, especially EGF and other growth factors, and has receptors for them. It is quite possible that there is an interaction beween the placenta and the fetus. A new placental growth factor has recently been demonstrated in Liège, Belgium (4), which is detectable by specific monoclonal antibodies and which increases in concentration towards the end of pregnancy. This is more likely to be a fetal growth-promoting factor than is placental lactogen, which is found chiefly in the maternal circulation (maternal:fetal plasma ratio = 1,000:1) and probably plays its main role in maternal lipid or glucose metabolism. I should like to see a new concept of IGF in relation to this new growth hormone and to the feto-placental unit as a whole.

*Dr. Girard:* I restricted my talk to fetal endocrine glands and fetal growth, so I didn't discuss the placenta. It is interesting to me that the placenta contains a large number of insulin receptors, the purpose of which is not known. No one has made a good study of the hormonal controls and other factors involved in placental growth. I believe the size of the placenta to be one of the most important determinants of fetal weight, and a search for the factors which are important for the growth of the placenta would be a very useful exercise.

*Dr. Wharton:* If you look at placental size in babies with pancreatic hypoplasia or after fetal pancreatectomy, is it reduced or normal?

*Dr. Girard:* I think it is decreased.

*Dr. Wharton:* So it is decreased, and yet the primary pathology is in the fetus. That implies to me that it is the fetus that controls the growth of the placenta rather than the other way around. This is not a new concept, of course, but I suggest that the idea of the placenta being all-important may well be wrong. The placenta should be regarded as just another organ of the fetus. Thus, if the fetus does not grow for any reason, be it an endocrine defect, malnutrition, or anything else, then the placenta does not grow either. I believe that the large statistical analysis done on the Dutch famine data (5) suggested that the main determinant of placental growth was the fetus rather than a direct effect of the famine. I think we are attaching too much importance to the placenta.

*Dr. Girard:* This could be so. It is true that the placenta in diabetic pregnancies is larger, which supports the argument.

*Dr. Hay:* The other way to look at this issue is to ask whether the fetus can grow independently of the placenta. I do not know of any situation where you can have a large baby and a small placenta.

*Dr. Wharton:* If we put it the other way, you cannot grow a large placenta unless you have a large fetus, and just as he grows a large leg and a large arm, so he grows a large placenta!

*Dr. Marini:* I have a couple of comments on what Drs. Hay and Wharton have said. First, Dr. Hay asked about body composition: I think this is very important because, from a clinical point of view, we have two kinds of growth retardation: asymmetrical, such as can be produced by insulin deprivation, and symmetrical, which can follow insults such as malformation syndromes. The experiments Dr. Girard described show that hormonal defects can cause a major influence on weight gain, for example, in the sheep, with little or no influence on length growth. With respect to what Dr. Wharton said about the placenta, this is the same concept as one already proposed by Warshaw (6), which is that intrauterine growth retardation is not a disease but an adaptation, and that neither the fetus nor the placenta grows any more because they do not have the right conditions to do so. There are many clinical implications in these concepts regarding the treatment of mothers with growth-retarded fetuses.

*Dr. Rosso:* IGF is apparently very important, but depends on insulin secretion, which in turn depends on the amount of glucose available. Thus the fetus is totally dependent on glu-

cose supply. If this is so, I feel that there must be some way in which the fetus can influence what comes across the placenta, by adjusting blood flow, for example. What do you think of this possibility?

*Dr. Girard:* There is one clear mechanism of control of the flux of glucose from the mother to fetus, and this is that when the blood glucose concentration in the fetus increases, fetal insulin secretion also increases, as does fetal glucose utilization, and you then create a gradient between mother and fetus, allowing an increased glucose flux across the placenta.

*Dr. Rosso:* My other question relates to IGF release. You showed that it was possible to extract IGF from the placenta but very little is released into the culture medium. The implication of this is that the placenta is not involved in IGF-mediated regulation of fetal growth, since the IGF is apparently not released from the organ. If this is so, then when we see small placentas and small fetuses, there is probably something on the fetal side preventing the placenta from growing.

*Dr. Girard:* The placenta not only synthesizes IGF-I but will also release it into the culture medium. So the placenta *is* able to secrete and release IGF-I and may well be implicated in fetal growth control. A fascinating new area to explore is the extent to which insulin or other factors may be able to modulate the synthesis and release of IGF-I by specific fetal organs, and to what extent the activity of this IGF is confined to the secreting cell or cells in the immediate neighborhood. I think the autocrine, or paracrine, role of IGF-I is likely to be much more important than its possible endocrine role as a hormone.

*Dr. Marini:* You said that insulin-like growth factors are controlled by insulin during fetal life, but that after birth they are controlled by growth hormone. What happens in preterm babies? We have recently seen how such infants may develop a lot of fat when fed on the new preterm formulas. Do these infants have an increased production of insulin-like growth factors?

*Dr. Girard:* One problem is the large amount of glucose which is commonly infused in parenteral nutrition solutions. This stimulates insulin production markedly and leads to increased fat synthesis.

*Dr. Senterre:* It is not only a question of the type of nutrient—it is a question of overall energy intake and the ratio of protein to energy. If you give too much energy you will cause an increase in fat deposition. Insulin output is increased not only by high carbohydrate but also by high protein intake, since some amino acids are potent insulin stimulants. In our experience, it is possible to mimic intrauterine weight gain composition by giving preterm infants less energy than is usually provided by preterm formulas and by increasing the ratio of protein to fat and carbohydrate (7,8). What influence these manipulations have on insulin, IGF-I, IGF-II, growth hormone, glucagon, and so on is not yet known, but I suspect that effects on all these growth factors will be shown.

*Dr. Chessex:* I should like to make a further comment on this. We have done a study with total parenteral nutrition in which we compared the effects of isocaloric quantities of glucose and fat at two different levels of intake. We found that plasma insulin was related to the energy intake and not to the composition of the infusion. This supports the view that insulin secretion is more strongly related to the overall energy intake than to the kind of substrate.

*Dr. Girard:* I do not think these results necessarily mean that insulin is mainly affected by the energy intake. When you give a different mixture of substrates the sensitivity of the tissues will change. Thus, if the plasma concentration of insulin is the same but the tissues are much more sensitive to insulin in one situation than in another, then plasma insulin is not a good indicator of the functional effect of the insulin. When you give a high fat intake the tissues are probably more resistant.

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