Review

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Does the Physiological Acromegaly of Pregnancy Benefit the Fetus?

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Key Words
Growth hormone · Insulin-like growth factor · Placenta

Abstract
Pregnancy is accompanied by notable changes in the secretion of growth hormone (GH) and the insulin-like growth factors (IGFs). A GH variant produced by the placenta is discernible in maternal plasma from early pregnancy, rising exponentially until 37 weeks. Meanwhile, pituitary GH gradually drops to near-undetectable levels. While there might be a modest reduction in circulating IGF-I in early pregnancy, IGF-I increases 2- to 3-fold in the second half, again with a peak at around 37 weeks. Thus, placental GH is believed to replace pituitary GH as the primary stimulus for IGF-I secretion in pregnancy. Several IGF-binding proteins (IGFBPs) including IGFBP-3 are proteolyzed, leading to an elevated free (bioavailable) IGF-I fraction. IGF-II concentrations also appear to show a modest (20–25%) increase in the course of pregnancy. The possible clinical manifestations include edema of face and forearms and carpal tunnel symptoms, reminiscent of the symptoms of acromegaly and the side effects of GH/IGF-I treatment. Neither placental GH nor the maternal IGFs cross the placental barrier, yet evidence from preclinical models is accumulating that they promote trophoblast invasion, placenta growth and maturation, transplacental nutrient transport and, ultimately, fetal growth. The ensemble data strongly suggest that 'gestational acromegaly' develops in order to foster fetoplacental growth.

The Physiological Acromegaly of Pregnancy

Pregnancy is a mildly acromegalic state. As will be outlined below, pregnancy is accompanied by an exponential rise in growth hormone (GH) secretion by the placenta, as well as raised insulin-like growth factor-I (IGF-I) concentrations and bioavailability. These hormonal changes often translate into bothersome symptoms in late pregnancy [1]. Gravidas may exhibit some coarsening of their facial features owing to edema, and edema of the forearms and hands with or without paresthesia (carpal tunnel symptoms). Such symptoms are reminiscent of 'true' acromegaly – caused by GH-secreting pituitary adenomas – and the side effects incurred by recombinant GH [2] or IGF-I therapy [3]; indeed, IGF-I treatment increases forearm blood flow [4].

One would expect the maternal hypersomatotropism to help sustain a somatogenic (growth-promoting) environment for the conceptus, i.e. the placenta and fetus(es). The objective of this narrative review is to summarize the current knowledge on this topic and, in particular, to bring together maternal-endocrine and perinatal research findings.

The Growth Hormone Family

GH, chorionic somatomammotropin (CS) and prolactin (PRL) are structurally related peptide hormones with somatogenic and lactogenic properties. In humans,

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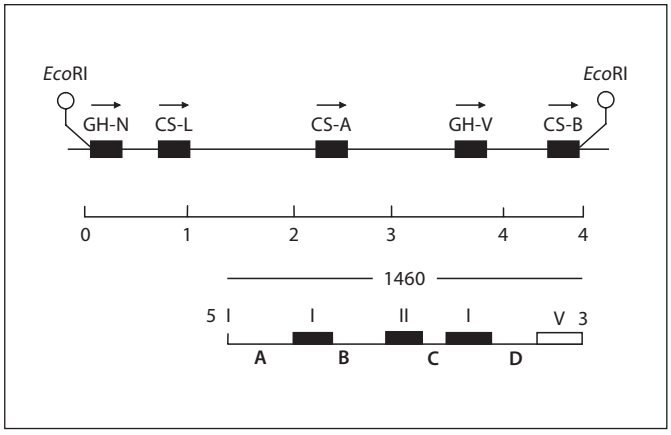

Fig. 1. Organization of the GH/CS gene family on chromosome 17q22–24.

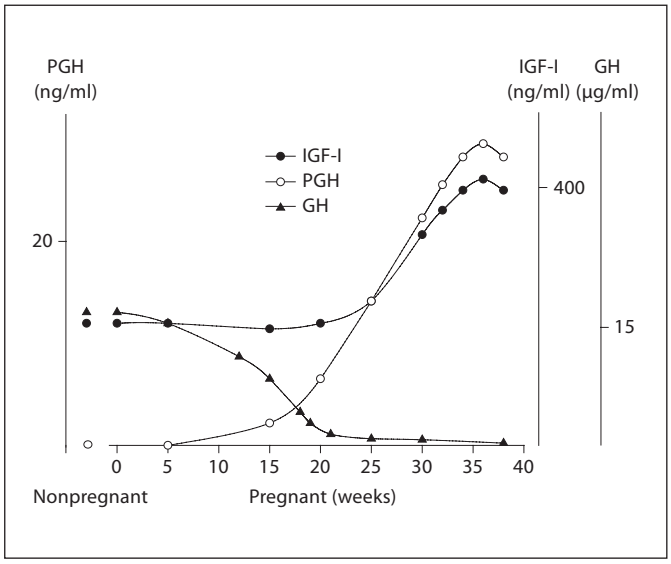

Fig. 2. Typical changes in PGH, IGF-I and GH during pregnancy [modified from refs. 6, 13–15, 47]. In some studies, a modest reduction (about 30%) was observed in IGF-I levels in the first half of pregnancy [43, 44].

a cluster of five *GH/CS* genes is located on chromosome 17q22–24 (fig. 1): *GH-N* (N for normal), *CS-L* (like), *CS-A*, *GH-V* (variant) and *CS-B*. These genes share 91–99% of their DNA sequences. *GH-N* produces GH which is secreted by the somatotrope cells of the anterior pituitary gland, whereas *GH-V* produces a GH variant secreted by the placenta. The *CS* genes are also expressed in the placenta; *CS-A* and *CS-B* produce CS which is better known as placental lactogen, while *CS-L* is considered a pseudogene. The *PRL* gene is located on chromosome 6.

The Placental Growth Hormone Variant

The *GH-V* product is a 191 aminoacids (AA)-containing protein with a molecular weight (MW) of 22.3 kDa. This protein differs by 13 AA from pituitary GH, is more basic and contains an N-linked glycosylation site at asparagine[140]; a recombinant version has been generated [5]. A second 25-kDa *GH-V* product represents a glycosylated isoform [6]. These products are referred to as placental growth hormone (PGH), because of their exclusive expression in the multinucleate syncytiotrophoblast [7].

PGH is somatogenic. The placental variant binds to the hepatic GH receptor at least as potently as pituitary GH does [8]. Also, GH and PGH comparably stimulate tibial growth plate expansion [8] and weight gain [9] in hypophysectomized rats, and have comparable metabolic effects in adipose tissue [10]. Transgenic mice have been generated that express human PGH and show plasma levels comparable to those observed in late pregnancy; these mice weigh 85% more than do normal mice, apparently by an increase in their fat-free mass [11]. By contrast, PGH binds poorly to the PRL receptor, and its lactogenic bioactivity (assessed in the NB_2 lymphoma cell line) is 20-fold lower than that of GH [8, 9].

The introduction of a sensitive monoclonal antibody-based assay by Hennen's group (Liège, Belgium) has disclosed the dynamics of PGH output [6]. Unlike the pulsatile nature of GH secretion, PGH secretion is tonic [12]. PGH is detectable in maternal plasma as early as 5 weeks gestational age (GA), and its concentration rises exponentially, attaining peak levels at 35–37 weeks [13–15] (fig. 2). But individual PGH values vary considerably at any stage, with peak levels ranging between 4.6 and 69.2 ng/ml in one study [14]. Circulating PGH is partly bound to the GH-binding protein (GHBP), which is secreted by the liver and adipose tissue and represents a truncated form of the hepatic GH receptor (i.e. its extracellular domain). The binding affinities of GH and PGH to GHBP are similarly high (affinity constant: 0.91 liters/nmol) [1]. GHBP levels drop gradually in the course of human pregnancy, approximately 40% between the first or early second trimester and term [15–17]. Thus, an even larger increment is expected in free compared to total PGH in the circulation. But the calculated free fraction also varies widely, e.g. 28–82% at delivery in one study [18].

As would be predicted for an exclusively placental product, plasma PGH concentrations plummet after delivery. The elimination of circulating PGH can be described as the sum of two exponential curves: a rapid elimination phase with a median half-life of 5–6 min, and a slower elimination phase (half-life of 63.4 min) [19]; thus, 65–89% of plasma PGH is cleared by 30 min after delivery [13, 19].

Regulation of PGH Secretion

PGH is not regulated by the same mechanisms that modulate pituitary GH secretion. The administration of a GH-releasing factor (GRF) analogue to term gravidas does not alter circulating PGH [20]; neither does GRF_{1-44} addition alter the secretion of PGH by trophoblastic cells in vitro [21]. We found a normal gestational increase in PGH and IGF-I concentrations in a woman with absent GH and undetectable IGF-I before pregnancy, owing to deficiency of *Pit-1* [22]; *Pit-1* is a transcription factor necessary for the expression of GH, PRL and thyroid-stimulating hormone (TSH) in the anterior pituitary gland. The same was true in a gravida with isolated childhood-onset GH-deficiency [13]. Nor does PGH appear to be regulated by ghrelin, as will be discussed below [15, 18].

Rather, the tonic PGH secretion is dependent on the placental mass [23] and thus on gestational age (GA) [14, 24]. PGH concentrations at delivery are reduced by 33% in smoking gravidas who typically have smaller placentas [23]. In addition, both the placental expression of PGH [25] and the circulating levels of PGH [26–28] are reduced in pregnancies complicated by in utero growth restriction (IUGR) of the fetus and smaller placentas.

Interestingly, PGH concentrations in late pregnancy are inversely related to maternal body weight or BMI [14, 24, 29], but the underlying mechanism is unexplained. Of note, nonpregnant obese individuals show lower GH concentrations, owing to both reduced pituitary secretory bursts and faster metabolic clearance [30–32]. Because overweight women tend to produce larger babies and placentas [33], repressed placental PGH output is not a likely explanation. Faster metabolic clearance of PGH might be attributed to decreased plasma-binding capacity; however, overweight or obese gravidas actually show higher levels of GHBP than lean gravidas [17, 19]. A larger distribution volume is another possibility: preliminary data show that plasma volume expands to a higher degree in overweight pregnant women [34].

The Somatogenic Effects of the IGFs

Briefly, the IGF system consists of: (1) two ligands, IGF-I (formerly called somatomedin-C) and IGF-II; (2) six IGF-binding proteins (IGFBP-1 to IGFBP-6), mainly produced in the liver, which bind the IGFs in the circulation with high affinity; (3) several IGFBP endoproteases (proteolytic enzymes) which can break down the IGFBPs; (4) two IGF receptors (type 1 and type 2 IGF receptor) in target cells.

IGF-I and IGF-II are peptides of 70 and 67 AA, respectively, and a MW of ~7.5 kDa. The IGFs are secreted by virtually all tissues [35], but the liver is the primary source of circulating IGF-I postnatally – perhaps, from late intrauterine life onward. The postnatal hepatic IGF-I output is stimulated by pituitary GH, insulin, and nutritional factors such as protein intake. Hepatic IGF-I mediates part of somatogenic effects of GH via a classic endocrine mode of action; yet, IGF-I produced in other tissues (e.g. bone and muscles) also governs postnatal growth, likely acting locally [35, 36]. Unlike GH, IGF-I is essential for in utero growth: rare cases of genetic IGF-I deficiency in humans and *IGF1* gene deletion in mice are accompanied by IUGR [reviewed in 37, 38]. Circulating IGF-I concentrations in the fetus at birth are determined by both genetic [39] and environmental (uteroplacental blood flow, oxygenation) factors [37, 38]. Parental imprinting regulates the expression of IGF-II in the fetus, and deletion of the paternal allele in mice causes IUGR; but the postnatal role of IGF-II remains unclear. The IGFs are also expressed in the placenta, although IGF-II far more abundantly than IGF-I [40]; IGF-II (but not IGF-I) deficiency in mice impairs placental growth. Both IGF-I and IGF-II act primarily through the type 1 IGF receptor [37].

The core function of the IGFBPs is to bind and sequester the IGF ligands, thus modulating their bioavailability and metabolic clearance. Only ~1% of the IGF ligands circulates in the free form. Postnatally, IGFBP-3 is by far the most abundant IGFBP, binding 80–90% of circulating IGF-I in a trimeric high-molecular-weight complex (140 kDa) that also includes the acid-labile subunit (ALS); IGF-I, IGFBP-3 and ALS are all GH-regulated. IGFBP-1, by contrast, binds only ~2% of circulating IGF-I and is upregulated by signals such as fasting, hypoinsulinemia (diabetes), and hypoxemia. Nonetheless, metabolic signals allow a minute-to-minute control of the IGF-I bioavailability: e.g., nighttime fasting turns on IGFBP-1 secretion, thereby reducing the free IGF-I fraction [41] and abrogating inappropriate somatogenic and metabolic (hypoglycemic) effects [35]. During intrauterine life,

IGFBP-1 is probably the most important IGFBP, stimulated by maternal fasting, impaired uteroplacental blood flow, fetal hypoxemia and fetal hypoinsulinemia [38]. Increased sequestering of IGF-I by IGFBP-1 may explain why IUGR ovine fetuses are partially resistant to the anabolic effects of exogenous IGF-I [42].

PGH and the IGF Axis during Pregnancy

A decline of ~30% between prepregnancy and first- or second-trimester IGF-I values has been observed in some studies [43, 44], which may be related to the upsurge in estrogen production [45]. However, we found the IGF-I concentration to be raised as early as 12 weeks in a GH-deficient gravida [22]. In the second half of pregnancy (from 24–25 weeks onward), IGF-I concentrations rise robustly, with a peak at ~37 weeks [14, 26, 44, 46, 47] (fig. 2). The difference between trough and peak values during pregnancy is 2- to 3-fold [14, 26, 43, 44]. A similar pattern was observed in gravidas with type 1 diabetes [48]. While the interindividual range is considerable, e.g. 215–705 μg/l at 37 weeks [14], it is smaller than for PGH. All studies concur that there is a significant correlation between PGH and IGF-I concentrations at any stage of pregnancy [22–24, 26, 27, 47, 48] as well as between the slopes of PGH and IGF-I during pregnancy [14, 47, 48]. IGF-I concentrations drop gradually in the postpartum period (by 40% in the first 48 h [18]).

The effect of pregnancy on IGF-II concentrations has been less studied, but there appears to be a modest increase between first- and second- or third-trimester values (25% change between trough and peak values [44, 46]) and again a modest drop postpartum (22% drop between delivery and 48 h postpartum [18, 46]).

Whereas IGFBP-3 concentrations are elevated during late pregnancy when measured by radioimmunoassay [44, 49], Western ligand blotting shows consistently that the characteristic doublet for IGFBP-3 (39–42 kDa) is undetectable in pregnancy serum; this observation is confirmed by Western immunoblot. The discrepancy is explained by the proteolysis of IGFBP-3 into smaller fragments (apparently still captured by immunoassay) by a pregnancy-induced circulating endoprotease [44, 50]. The protease activity is discernible as early as 6 weeks and is trophoblast-derived, perhaps corresponding to a disintegrin-metalloproteinase type enzyme [51]. Pregnancy serum is also proteolytically active against IGFBP-2, IGFBP-4 and IGFBP-5 but not IGFBP-1 [50, 51]. Whether the robust IGFBP proteolysis results in reduced IGF-binding capacity (i.e. higher free IGF ligands) and a corresponding boost in IGF bioactivity, remains controversial. Experimental arguments supporting [52] or refuting [53] this reasoning are at the center of the debate, yet I believe that some supportive arguments merit emphasis. Notwithstanding methodological limitations [54], the measurement of the free form of IGF-I reveals a free IGF-I fraction of 1.5–2.4% during pregnancy as compared with 0.9% outside pregnancy [55]. Also, suggestive evidence of increased IGF-I tissue uptake during pregnancy was obtained in rats, showing a nearly 5-fold faster clearance of radioactive IGF-I while urinary excretion is negligible and placental transport absent [56].

IGFBP-1 (formerly called placental protein-12) is not proteolyzed and is probably the most important IGFBP during pregnancy. The liver produces highly phosphorylated isoforms that bind IGF-I with high affinity; in addition, the decidualized endometrium is an abundant source of highly phosphorylated but also lesser- and non-phosphorylated isoforms [40, 57, 58]. Decidual IGFBP-1 diffuses into the amniotic fluid [59, 60]. The plasma concentrations of total IGFBP-1 as well as the nonphosphorylated isoforms increase 2- to 3-fold between the first and second trimester, and remain constant or decrease slightly thereafter [43, 44, 61–63]. Amniotic fluid concentrations rise steeply from 10 weeks onward with peak levels in midpregnancy that are 10^2 to 10^3 times higher than those in serum [61, 64, 65]. The detection of IGFBP-1 constitutes one of the biochemical tests (e.g. a rapid strip test for on-site use) to detect the presence of amniotic fluid in vaginal secretions, i.e. to diagnose preterm rupture of the fetal membranes [66, 67]. Plasma IGFBP-1 is not only regulated by GA, but there is also the expected diurnal variation with higher levels during the night [68]. IGFBP-1 concentrations are predictably higher in gravidas with type 1 diabetes [69] and lower in overweight gravidas [24, 70–72]; we confirmed an inverse relationship to insulin and IGF-I concentrations in normal pregnancies at 24–29 weeks [24]. Theoretically, a higher free IGF-I fraction is expected in obese/hyperinsulinemic gravidas [41], but this remains to be verified; in fact, both total and free IGF-I are lower in obese nonpregnant women [73]. Many studies confirm that gravidas who develop preeclampsia show decreased plasma IGFBP-1 concentrations before disease onset [74–79], probably reflecting defective decidual function or/and relative hyperinsulinemia – the latter being an independent risk factor for preeclampsia. But gravidas with clinical preeclampsia [76, 80–83] or the antiphospholipid syndrome [84] actually demonstrate higher plasma IGFBP-1, a paradox which is unexplained at this time.

Pituitary GH in Normal and Acromegalic Pregnancies

Several studies using specific immunoassays have demonstrated that pituitary GH concentrations are very low or below the detection limit in the second half of pregnancy [6, 15, 26, 47] (fig. 2). This phenomenon occurs concomitantly with the rise in PGH and IGF-I levels, inferring that the raised hepatic IGF-I secretion suppresses GH secretion via a negative feedback mechanism (fig. 3). Thus, PGH replaces GH as the primary IGF-I releasing hormone.

Our knowledge about the effect of pregnancy on GH and IGF-I secretion in acromegalic patients is very limited and case-based. Cozzi et al. [85] reported that GH concentrations decreased by 50–90% in the course of pregnancy in 3 of 5 women with acromegaly and GH-secreting adenomas, despite discontinuing GH-suppressive treatment. The IGF-I concentrations appear to be stable or to increase during these pregnancies, while any correlation between GH and IGF-I levels in acromegalic gravidas is lacking. Suppressed GH and stable IGF-I concentrations during pregnancy were also reported in an untreated patient with GH hypersecretion caused by the McCune-Albright syndrome [86]. Estrogens likely play a role in the apparently spontaneous amelioration of the IGF-I hypersecretion [45, 87], but further research into the interaction of estrogens and PGH on hepatic IGF-I and pituitary GH secretion is mandatory. Importantly, pregnancies in acromegalic patients appear to proceed normally and produce healthy infants [85].

Ghrelin is a 28 AA-containing peptide which is secreted in the stomach and acts as a GH-releasing factor; yet ghrelin is also expressed at a low level in the placenta [88]. Fasting ghrelin concentrations do not vary substantially in the course of pregnancy [15] nor in the first 2 days postpartum [18]. Therefore, it is unlikely that ghrelin drives the gestational downturn or the postpartum restoration of GH secretion.

Maternal Plasma PGH and IGF-I: Indices of Fetoplacental Growth?

Several studies have examined whether maternal PGH and IGF-I are correlated with fetal size, as calculated from ultrasound parameters or measured at birth. It appears from the data that PGH and IGF-I do correlate with fetal size when assessed at or around the same GA, whether in the early third trimester [29, 44] or at delivery [23].

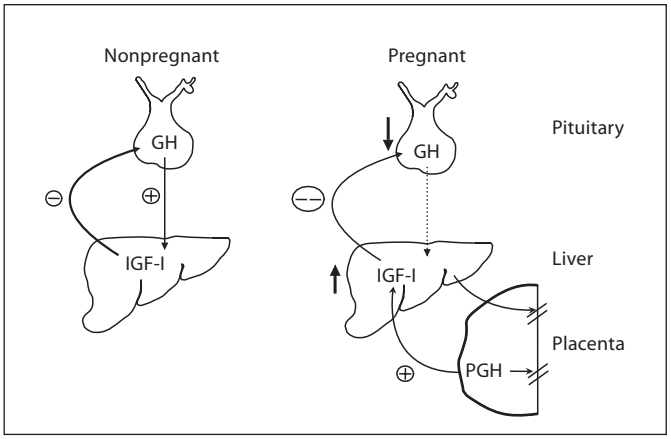

Fig. 3. Schematic view of the alterations in the GH-IGF axis during pregnancy. In the nonpregnant state, pituitary GH is the main stimulus for hepatic IGF-I secretion in the liver, which in turn regulates pituitary GH secretion by a negative feedback mechanism. During pregnancy, the placenta produces PGH, a GH variant which is equally somatogenic and stimulates hepatic IGF-I secretion from the second half of pregnancy; consequently, pituitary GH secretion is downregulated. Neither PGH nor IGF-I cross the placental barrier.

In some studies, there is also a relationship between PGH or/and IGF-I sampled in the second or early-third trimester and birth weight [28, 48], but this is not the case in other studies [24, 29, 44]. A study in diabetic women confirms that the correlation between PGH and birth weight strengthens with later GA at sampling [48]. An elegant longitudinal evaluation shows that while the PGH (but not the IGF-I) slope between 24.5 and 37.5 weeks GA (peak value) modestly predicts birth weight, the overall PGH and IGF-I slopes during pregnancy are not predictive of birth weight [14].

The above findings might be explained by the assumption that circulating PGH and IGF-I reflect (regulate?) placenta growth and function, and by the well-known correlation between placenta weight and birth weight. Indeed, the correlation between PGH or IGF-I and placenta weight is better than that with birth weight in several studies [23, 43, 48], and the overall IGF-I slope during pregnancy predicts placenta but not birth weight [14, 43]. Predictably, PGH and IGF-I values in the third trimester are lower in pregnancies complicated by severe preeclampsia or IUGR with uteroplacental blood flow insufficiency [26–28, 83, 89, 90], although there is some inconsistency in the reported early or mid-pregnancy PGH and IGF-I values of women who later develop preeclampsia [77–79, 91].

Table 1. Fetoplacental effects of maternal endogenous or exogenous GH, PGH, IGF-I and IGF-II, and IGFBP-1

Effect	Maternal ligand	Research model	Reference
Stimulation of trophoblast invasion	PGH	in vitro	107
	IGF-I		108
	IGF-II		109
	IGFBP-1		109
Stimulation of placental growth	IGF-II	mouse and guinea pig	103, 111
	IGF-I?	guinea pig	103, 113
Stimulation of placental maturation	IGF-I	guinea pig	103, 113
	IGF-II	mouse and guinea pig	103, 112
Stimulation of placental diffusion capacity	GH	sheep	115
	IGF-II	mouse	111, 112
Stimulation of placental and fetal glucose uptake	IGF-I	guinea pig	104, 114
	IGF-II?	guinea pig	104
Stimulation of placental and fetal amino acid uptake	IGF-I	in vitro	116, 117
		guinea pig	114
	IGF-II	mouse	111, 118
Increase in fetal amino acid concentrations	IGF-I	guinea pig	103
	IGF-II	guinea pig	103
Stimulation of fetal lactate uptake	IGF-I	sheep	115
Stimulation of fetal growth	IGF-I	guinea pig	103, 114
	IGF-II	mouse and guinea pig	103, 111
Improved fetal survival	IGF-I	guinea pig	103
	IGF-II	guinea pig	103

The data are even more controversial for IGFBP-1. Maternal plasma total and nonphosphorylated (i.e. decidua-derived) IGFBP-1 concentrations (22–26 weeks GA) were reported to be increased in IUGR pregnancies [92], and IGFBP-1 (sampled at various GA) show a moderate inverse correlation with birth weight in some [44, 69, 70, 72] but not other [24, 63, 93] studies. It is unlikely that this correlation would persist after controlling for the major effect of maternal body size [33]. We [65] and Giudice's group [63] documented that amniotic fluid IGFBP-1, sampled at 14–20 weeks GA, does not predict birth weight; but other groups reported a negative correlation between amniotic fluid IGFBP-1 at 13–19 weeks GA and birth weight [94], or higher amniotic fluid IGFBP-1 (15–16 weeks GA) in IUGR pregnancies (<5th percentile) [93].

Collectively, the data indicate that maternal circulating PGH and IGF-I correlate with fetoplacental size at that GA. However, the measurement of IGF-I or IGFBP-1 in second-trimester amniotic fluid and the measurement of PGH, IGF-I or IGFBP-1 in maternal plasma in the second or early third trimester do not emerge as consistent, clinically useful biochemical predictors of size parameters at birth.

Possible Mechanisms of Action to Explain Improved Fetal Growth

Neither PGH nor the IGFs cross the placental barrier. Indeed, PGH is not detectable in the fetal circulation [6], and animal studies have confirmed the lack of transplacental passage of IGF-I [56]. Yet PGH and the IGFs might stimulate fetal growth indirectly by affecting maternal metabolism, placental development and/or the transplacental transport of nutrients.

Regarding maternal metabolism, it is hypothesized that PGH is one of the placental hormones – together with progesterone and placental lactogen – involved in the physiological insulin resistance and reduced glucose tolerance that characterizes the second half of pregnancy [10, 95]. These metabolic changes are well known to promote the nutrient flow to the fetus and fetal growth rate [96]. Certainly, acromegaly [97] and GH use by healthy [98] or GH-deficient [99] individuals all lead to insulin resistance in the liver and peripheral tissues (i.e. skeletal muscles or/and adipose tissue) and hyperinsulinemia. Also, transgenic mice with PGH expression display insulin resistance and hyperinsulinemia [11]; one possible mechanism is the disturbance of insulin receptor signaling pathways in skeletal muscles [100]. But the available

evidence in humans does not strongly support this hypothesis. We found no difference in plasma PGH in gravidas with an abnormal vs. normal response to a glucose load [24]. Also, the PGH concentrations of diabetic (type 1 or type 2) gravidas are unchanged [28], and PGH levels in type 1 diabetic pregnancies are unrelated to changes in insulin requirements [48]. Conversely, plasma PGH remains unaltered during an oral glucose tolerance test in healthy gravidas [101], while extreme hyperglycemia (25 mM) inhibits PGH secretion by the placenta in vitro [102]. Further research is needed but the conclusion that PGH is a 'diabetogenic' hormone of pregnancy is premature.

GH is a lipolytic hormone [99]. PGH may also promote lipolysis, because a correlation between PGH and FFA levels was reported at delivery [23]. In guinea pigs, the chronic infusion of IGF-I during the second half of gestation reduces maternal adipose tissue stores, suggesting increased lipolysis which in turn might lead to alterations in the 'nutrient partitioning' between mother and fetus [103, 104].

IGF-I and IGF-II, GH/PGH receptors and type 1 IGF receptors are all expressed in the placenta [40, 105–107]. It is unknown whether PGH or the IGFs modulate placental IGF-IGFBP expression by an auto-/paracrine mode of action. Yet data obtained in vitro and in animal models indicate that PGH and the IGFs have beneficial effects on trophoblast invasion and placenta function (summarized in table 1). The promotion of trophoblast invasion is likely mediated by locally produced PGH and IGFs, e.g. IGF-I in villous mesenchyme [108], IGF-II in trophoblast and IGFBP-1 in decidua [40, 109]; IGF-II and IGFBP-1 appear to act in concert [109, 110]. However, the larger placentas in mice with decidual IGFBP-1 overexpression are dysfunctional, resulting in IUGR [60]. The stimulation of placenta growth and maturation, and transplacental nutrient transport appears to be mediated by both locally produced IGF-II [111, 112] and circulating IGFs [103, 104, 113, 114]. The guinea pig is an attractive animal model for this type of research, because its hemochorial placenta closely resembles the human placenta; the ovine placenta, however, is substantially different.

Conclusion and Future Directions

Pregnancy is a hypersomatotropic state. The soaring PGH secretion stimulates hepatic IGF-I secretion which increases 2- to 3-fold in the second half of pregnancy, while pituitary GH secretion is suppressed. The tissue bioavailability of IGF-I is probably increased as well, as suggested by increased free IGF-I concentrations. Data obtained in preclinical models show that the local production of PGH and the IGFs promotes trophoblast invasion and placenta growth and function; in addition, increased circulating IGF-I promotes placenta maturation and transplacental nutrient transport. These effects should boost fetal growth rate.

Further preclinical data are required, but we also need to move on to human pregnancy. It would be interesting to know whether the considerable variation in PGH and IGF-I levels during pregnancy bears consequences for symptoms such as edema and carpal tunnel syndrome, for carbohydrate, lipid and protein metabolism in the mother, and for placental functional indices. In a next phase, pilot studies could assess whether recombinant IGF-I treatment (which does not cross the placenta) improves placental function in gravidas at risk for uteroplacental insufficiency. Surely, to investigate how PGH, the IGFs, the IGFBPs and the classic steroid hormones (estrogens and progesterone) interact at the maternal-fetal interface to promote fetal growth, represents a fascinating area for further research.

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