

Human placental growth hormone in normal and abnormal fetal growth (Review)

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Abstract. Human placental growth hormone (PGH), encoded by the growth hormone (GH) variant gene on chromosome 17, is expressed in the syncytiotrophoblast and extravillous cytotrophoblast layers of the human placenta. Its maternal serum levels increase throughout pregnancy, and gradually replaces the pulsatile secreted pituitary GH. PGH is also detectable in cord blood and in the amniotic fluid. This placental-origin hormone stimulates glyconeogenesis, lipolysis and anabolism in maternal organs, and influences fetal growth, placental development and maternal adaptation to pregnancy. The majority of these actions are performed indirectly by regulating maternal insulin-like growth factor-I levels, while the extravillous trophoblast involvement indicates a direct effect on placental development, as it stimulates trophoblast invasiveness and function via a potential combination of autocrine and paracrine mechanisms. The current review focuses on the role of PGH in fetal growth. In addition, the association of PGH alterations in maternal circulation and placental expression in pregnancy complications associated with abnormal fetal growth is briefly reviewed.

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1. Introduction

Human placental growth hormone (PGH) is produced by the growth hormone (GH) variant gene on chromosome 17 (1). PGH is expressed in the syncytiotrophoblast and extravillous cytotrophoblast (EVCT) layers of the human placenta. PGH is detectable in the fetal compartment, in cord blood and amniotic fluid (2). Its level increases in maternal circulation throughout pregnancy from gestational weeks 5 to 7 until term (3), and gradually after the fifteenth to twentieth week of pregnancy, replacing the pulsatile secreted pituitary GH (4).

PGH is considered as key in the regulation of maternal insulin-like growth factor-I (IGF-I) (5-7). Furthermore, PGH stimulates gluconeogenesis, lipolysis, and anabolism in maternal tissues and influences fetal growth, placental development (8) and maternal adaptation to pregnancy (9-11). The majority of these actions are exerted indirectly by regulating the maternal IGF-I expression levels (3,6,12), while the extravillous trophoblast expression of PGH indicates a direct impact upon the physiological development of the placenta, as it stimulates trophoblast invasiveness and function via a potential combination of autocrine and paracrine mechanisms (13). The aim of the current review was to elucidate the role of PGH in fetal growth.

2. Origin of PGH

Human GHs are the products of five genes, members of the GH gene-family, located on the long arm of chromosome 17 (q22 to q24) (14); encoding pituitary GH (GH-N gene), PGH (GH-V gene), and three chorionic somatomammotropins/placental lactogens (hCS-A, hCS-B and hCS-L genes) (15). PGH binds to the GH receptors in maternal tissues (3,16-19). Furthermore, PGH is the protein product of the GH-V gene and consists of 191 amino acid residues (20-23). It consists of glycosylated variants, hGH-V2, GH-V3 protein and various isoforms of PGH (24-29).

The presence of GH and PGH receptors in the syncytiotrophoblast indicates that this hormone contributes to the development and function of the placenta via an autocrine mechanism. Various studies have reported a significant decrease in maternal serum PGH concentrations in pregnancies complicated by fetal growth restriction (FGR) (12,30),

while increased maternal serum levels have been correlated with the presence of fetal chromosomal abnormalities (31-33).

3. PGH in pregnancy and fetal growth

The placenta delivers maternal blood (containing oxygen and nutrients) to the fetus, thus controlling its growth. Placental hormones, along with maternal pituitary gland hormones, interact and mediate the metabolic adaptations and changes during pregnancy (34-36); however, these hormones undergo changes throughout gestation.

Prolactin (PRL) produced by the pituitary gland of the mother and human chorionic somatomammotropin hormone [CSH; or human placental lactogen (hPL)], increase markedly in maternal circulation in normal pregnancy (37,38). During early and mid-pregnancy, there is a sharp decrease in the expression levels of GH (GH1), and after the twenty-fourth week of gestation GH1 is no longer detected in the maternal serum (39). GH1 is replaced by GH2 or syncytiotrophoblast-produced PGH (39). There is a tonical secretion of the variant GH, which increases from the twentieth week of gestation until term, reaching levels of 20-40 ng/ml (39). PGH binds with high and low affinity to GH and to PRL receptors, respectively (39). Thus, during mid and late gestation, the mother exhibits high levels of PRL, peaking at 150-180 ng/ml. The hPL production rate near term is ~1 g/day, which is the greatest known of any human hormone, and PGH levels reach 14 ng/ml after 28 weeks. In addition, hPL and PRL are secreted directly into the fetal circulation, while PGH is detected primarily in the maternal blood (39-41).

Männik *et al* (42) assessed the association between the expression levels of PGH and CSH, and the birth weight in normal, healthy pregnancies at term using a fluorescent-labeled semiquantitative RT-PCR as well as gene-specific restriction analysis. The study was conducted in a homogeneous healthy sample of Caucasian pregnant women without any metabolic or pregnancy-associated pathological conditions. Women with gestational diabetes mellitus (DM) and toxemia, as well as fetuses affected by infections, and genetic and congenital disorders were excluded. The results of the study facilitated with elucidating the physiological and pathological role of PGH and CSH in the regulation of fetal growth. Despite the fact that half of the PGH transcripts encode proteins with C termini distinct from the major GH2 product (GH2-1), their function remains unclear. The GH2-1 expression was demonstrated to be lower in the placentas from pregnancies with small for gestational age (SGA) fetuses, while it was normal in pregnancies with large for gestational age (LGA) fetuses. It was demonstrated that the expression levels of the major CSH transcript (CSH1) were greater in the placentas of LGA babies, but remained unchanged in those of SGA babies. Previous studies by Caufriez *et al* (6), McIntyre *et al* (12) and Ursell *et al* (43), observed that decreased levels of PGH in pregnancies resulted in SGA neonates and high maternal serum levels of CSH in women with gestational diabetes (6,12,43).

PGH is not regulated by placental GH-releasing hormone, but responds inversely to the levels of glucose and insulin in maternal circulation, assuring glucose disposal to the fetus, by increasing nutrient availability to the fetus either directly or indirectly via IGF-I (9,44,45). A positive correlation

between PGH and fetal and neonatal weight has been demonstrated (46-48). PGH levels decline during an oral glucose tolerance test in women with gestational diabetes (4). As the major glucose transporter (Glut 1) is expressed by syncytiotrophoblast cells and remains directly in contact with maternal blood, these cells adjust PGH secretion according to the maternal serum glucose level.

In the blood of pregnant women metabolic interdependence is observed between PGH and IGF-I. During pregnancy, the concentration of PGH and IGF-I increases proportionately and, following delivery, their concentration decreases. GH1 blockade appears to be released during labor and delivery, and its level increases three-fold, it then returns to normal postpartum (49). Pedersen *et al* (50) conducted a study to investigate whether maternal levels of PGH, IGF-I and hPL are associated with the growth rate of biparietal diameter during the first half of gestation. High maternal PGH concentrations were observed in fetuses with increased first-trimester growth rates in the unadjusted and adjusted analyses for a variety of known and potential confounders. It was concluded that PGH may contribute in the regulation of fetal growth from the first stages of the pregnancy (50).

PGH is considered to be key in the signaling pathways of maternal metabolic adaptation to pregnancy. This is a pregnancy-specific hormone that along with other hormones coordinates trophoblast invasion (8), fetal growth (3,46,51) and maternal adaptation to pregnancy (9,10). The somatotrophic, lactogenic and lipolytic action of PGH resembles that of pituitary GH. However, PGH secretion follows a non-pulsatile pattern (52), unlike the pulsatile mode of GH. PGH mRNA and protein are expressed in syncytiotrophoblast and EVCT (20,35,53,54).

PGH is detectable in maternal blood as early as at 5 weeks of gestation (3). Its level increases throughout pregnancy until term (51), when it has been observed to either plateau (5,6) or slightly decrease (55). The interaction between placental hormone expression and maternal nutritional status contributes to the regulation of fetal growth. The polymorphic or epigenetic regulation of PGH and CSH expression changes the secretion of other hormones or growth factors (insulin or IGF-I), and the circulation and disposal of maternal nutrients. Reduction in expression of PGH may reduce lipolysis and the levels of circulating IGF-I, as PGH is a potent insulin antagonist, as well as a lipolytic hormone that stimulates production of IGF-I during pregnancy (6,11,56-58). This may reduce the availability of maternal nutrient and limit placental nutrient transfer; hence, may reduce fetal weight (59). By contrast, there are theories stating that increases in expression levels of CSH may promote insulin resistance, lipolysis and IGF-I expression in maternal tissues (60,61). This may lead to increased maternal nutrient availability and placental transfer, which in turn results in promotion of fetal growth. However, these theories are controversial. Lipolysis reduction due to deficiency of PGH should be correlated with increased maternal fat levels; however, many pregnant women with SGA fetuses/neonates have low body mass index values (12).

CSH is lipolytic and IGF-I-tropic is weak (16). As CSH and PGH have almost the same molecular weight, it is possible that CSH is purified from human placenta in quantities that induce lipolysis *in vivo* and *in vitro* (62,63). Alternatively, the PGH

Table I. Association between PGH and pregnancy complications.

Author, year	Condition	Outcome	Association	Refs.
Hübener <i>et al</i> , 2015	GTD	hGH-V may be detected in all types of GTD by immunohistochemistry, as well as by serum analysis and may therefore serve as a novel biomarker for the disease	Strongly associated	(107)
Ringholm <i>et al</i> , 2015	T1DM	Lower levels of placental growth hormone in early pregnancy in women with T1DM and LGA infants	Associated	(104)
Schock <i>et al</i> , 2015	EOC	Higher insulin-like growth factor -I levels in pregnancy may be associated with lower risk of invasive and endometrioid EOC	Associated	(106)
Eleftheriades <i>et al</i> , 2014	GDM	At 11-14 weeks in pregnancies that develop GDM the maternal serum levels of PlGF were increased	Associated	(101)
Higgins <i>et al</i> , 2012	T1DM	Maternal T1DM PGH correlated with antenatal fetal weight and birth weight suggesting a significant role for PGH in growth in diabetic pregnancy.	Significant Associated	(102)
Sifakis <i>et al</i> , 2011	PE	PE group serum PGH level during the first trimester was normal, indicating that it is unlikely that this hormone is involved in the pathogenesis of PE	Not associated	(2)
Männik <i>et al</i> , 2010	SGA neonate	The expression profile of placenta l hGH/chorionic somatomammotropin hormone genes in placenta is altered in pregnancies accompanied by SGA and LGA compared with appropriate for gestational age newborns	Associated	(42)
Sifakis <i>et al</i> , 2010	Trisomies	In the first trimester, maternal serum hPGH levels in trisomy 21 and trisomy 18 pregnancies are reduced	Associated	(72)
Christiansen <i>et al</i> , 2009	DS	PGH levels are early first trimester maternal serum markers for DS	Strongly Associated	(67)
Papadopoulou <i>et al</i> , 2008	DS	The PGH levels in maternal serum were found to be higher at gestation weeks 16-23 in pregnancies affected by fetal DS	Associated	(33)
Papadopoulou <i>et al</i> , 2006	IUGR associated with PE	Maternal serum and amniotic fluid PGH levels at 16-22 weeks are higher in pregnancies that will be complicated by IUGR associated with PE	Associated	(80)

PGH, placental growth hormone; GTD, gestational trophoblastic disease; T1DM, type 1 diabetes mellitus; EOC, epithelial ovarian cancer; GDM, gestational diabetes mellitus; PE, preeclampsia; SGA, small-for-gestational age; DS, Down syndrome; LGA, large for gestational age; IUGR, intrauterine growth retardation; PlGF, placental growth factor.

fall may be an indirect effect of maternal undernutrition. A decrease in pregnancy weight gain would augment the sensitivity of maternal insulin and plasma adiponectin, reducing the expression level of PGH in trophoblast cells *in vitro* (64). A decline in the expression levels of PGH may reduce maternal lipolysis, thereby somewhat recompensing the reduction of maternal fat stores. A combination of these mechanisms may result in reduction of PGH and maternal IGF-I in pregnancies associated with FGR.

The physiological role of CSH and PGH is controversial, as certain women with CSH and/or PGH gene deletions experienced a normal pregnancy outcome in terms of children birth weight (34). This may indicate that neither CSH nor PGH is required for normal fetal growth; however, it is possible that other hormones, such as pituitary GH or PRL may

counterbalance PGH or CSH deficiency. Various studies on GH-deficient mouse receptors (63,65) provide evidence that somatogens and lactogens modify metabolism and fetal growth via overlapping, but distinct actions (34). There is no clear evidence regarding maternal serum PGH concentration during labor (66); however, abrupt decrease has been reported (30).

4. PGH in pathological pregnancy

PGH and GH binding protein are potentially early first trimester maternal serum markers for Down syndrome (33,67-70). Higher PGH levels in amniotic fluid were reported in fetuses with Down syndrome compared with healthy pregnancies during the second trimester (71). PGH was detected in all amniotic fluid samples, indicating that it could possibly enter the fetal

compartment; until then it was proposed that PGH was present only in maternal circulation (71). Sifakis *et al* (72) investigated the maternal serum concentration of PGH in trisomy 18 and trisomy 21 pregnancies at 11 to 13 weeks of gestation, and examined the possible association between fetal nuchal translucency thickness and maternal serum free β -human chorionic gonadotrophin (β -hCG) and pregnancy associated plasma proteinA (PAPPA). Serum PGH was reduced in trisomy 21 and trisomy 18 compared with euploid pregnancies in the first trimester. There was a significant association between serum hPGH and PAPPA in the euploid ($P=0.006$) and trisomy 21 pregnancies ($P=0.030$), although not in trisomy 18 pregnancies ($P=0.445$) (72). Alldred *et al* (73), in a review of first trimester serum screening tests for trisomy 21, reported that the double test (comprising PAPP-A and free hCG in combination with maternal age) detects ~70% of the affected pregnancies for a 5% false positive rate (73).

There is differential regulation of the major placental syncytiotrophoblast protein members of the GH/CSH hormone family. Previous studies reported low maternal levels of PGH and CSH in pregnancy complications, such as hypertension, preeclampsia (PE) and intrauterine growth restriction (IUGR) (74-78). PGHs have an effect on placental trophoblast invasion and normal growth. Various studies have been conducted to investigate the correlation between maternal serum levels of PGH and IUGR (6,12,30,79). The concentration of PGH has been identified to be lower in SGA, while there are conflicting results regarding PGH in PE (55,80-83). Numerous studies have reported lower PGH levels in pregnant women with clinically established PE, following 20-22 weeks of gestation (79,84-97).

PGH maternal and amniotic fluid concentrations were increased at 16-22 weeks of gestation in women that subsequently developed PE and IUGR (80). The same authors, Sifakis *et al* (2) conducted a study to investigate the maternal serum concentration of PGH at 11-13 weeks of gestation in pregnancies that subsequently developed PE, and examined the possible association with uterine artery pulsatility index (PI) and maternal serum PAPPA. The median serum PGH concentration was not observed to be significantly different in the pregnancies that subsequently developed PE when compared with that in the unaffected group, whereas uterine artery PI was increased and serum PAPPA was decreased. No significant association was identified between serum PGH and gestational age at delivery, uterine artery PI, or serum PAPPA. PAPPA multiples of median (MoM) in the group that developed PE. The normal serum PGH level during the first trimester in the PE group indicates that it is unlikely that this hormone is involved in the underlying mechanisms or the pathogenesis of PE (2).

Mittal *et al* (55) conducted a cross sectional study to investigate the alterations of the maternal serum concentrations of PGH in women with PE, women with PE and an SGA neonate and women with SGA neonates alone. In patients with severe PE, the median serum PGH concentration was higher (23,076 pg/ml) compared with women with uncomplicated pregnancies (12,157 pg/ml), women with SGA neonates (SGA group, median 10,206 pg/ml; $P<0.05$), as well as women with PE and SGA (PE + SGA group, 1,027 pg/ml; $P<0.05$). PE was correlated with increased median values of PGH in the

maternal and fetal compartment when compared with normal pregnancies. Differences observed in the median maternal serum level of PGH among pregnant women with PE and SGA, SGA alone, and in healthy pregnancies were not statistically significant ($P>0.05$). The umbilical serum concentration of PGH (median value) was significantly higher in neonates of women with PE (356.1 vs. 128.5 pg/ml in normal pregnancies; $P<0.01$). Furthermore, PGH was detectable in all cord blood specimens. These observations indicate that PGH may be involved in the pathophysiology and the underlying mechanisms of PE and FGR.

The role of PGH and the IGF-axis in IUGR has been further investigated during a study conducted by Koutsaki *et al* (98) using in term placentas from 47 pregnancies complicated with IUGR. Decreased placental expression of PGH, IGF-I and IGF binding protein-I was observed. The authors concluded that further investigation is required to clarify whether these observations represent a causative factor of IUGR, or accompany other pathogenetic underlying mechanisms. However, Sifakis *et al* (99) demonstrated that, in early pregnancy (11-13 week of gestation), the concentrations of PGH in maternal serum is not altered in pregnancies that resulted in SGA neonates (99).

It remains unclear whether PGH is involved in the regulation of the growth of the fetus in pregnancies with pre-existing DM or in those complicated by gestational DM (GDM) (100,101). There is a higher incidence of macrosomia in the babies of diabetic women; however, there are few studies that demonstrate high concentrations of serum maternal PGH in diabetic pregnancies. In a prospective study by Higgins *et al* (102) maternal PGH was significantly associated with fetal weight estimated by ultrasonography ($P=0.02$), birth weight ($P=0.05$) and birth weight centile ($P=0.03$) in pregnancies with type 1 DM (T1DM) (102). A study by Fuglsang *et al* (103) indicated a role of PGH in the regulation of IGFs and fetal growth in T1DM. However, an increase in insulin requirements in type 1 diabetic patients during pregnancy was not associated with the levels of PGH (103,104). A more recent study by Ringholm *et al* (104) reported PGH at lower levels during early pregnancy in women with T1DM and large for gestational age (LGA) infants (104). GDM and pre-gestational diabetes pose risks to the mother and the fetus, and may associated with abnormal fetal growth. In human pregnancy, PGH appears to contribute to the mechanisms of regulation of maternal insulin resistance and may exert an influence on fetal growth by modifying nutrient availability and via paracrine activities in the developing placenta. Thus, the evidence of a clear pathophysiological role of PGH in the development of fetal macrosomia attributed to hyperglycaemia is insufficient; however, *in vitro* studies indicate a potential fetoplacental feedback as a modulator of fetal growth (105).

5. PGH in oncogenesis and in gestational trophoblastic disease

It has been demonstrated that signaling of IGF-I may promote the development of ovarian tumors by exerting proangiogenic, mitotic and antiapoptotic effects (106). Production of maternal IGF-I is regulated by PGH during pregnancy. To the best of our knowledge, there are no existing studies evaluating the

role of PGH and IGF-I in pregnancy and epithelial ovarian cancer (EOC). A study by Schock *et al* (106) provides data on PGH and IGF-I levels in pregnancy and EOC risk. A total of 1,045 EOC cases were investigated. Placental GH and IGF-I levels were analyzed in maternal serum from the last pregnancy before EOC diagnosis and served as a control. Higher levels of IGF-I were associated with a decrease in the risk for invasive [odds ratio (OR), 0.79 (0.62-1.02)] and endometrioid [OR, 0.55 (0.28-1.07)] tumors; however, these observations were not statistically significant. This protective association was stronger between higher IGF-I levels and the risk of invasive EOC in women aged <55 years at diagnosis [OR 0.74 (0.57-0.96)]. These data suggest that higher IGF-I levels during pregnancy may be associated with a decreased risk of invasive and endometrioid EOC.

Gestational trophoblastic disease (GTD) arising from the placental villous trophoblast is associated with abnormal placental trophoblast proliferation. PGH is significant in the regulation of placental growth and development, and exerts various angiogenic actions. Furthermore, hGHV is detected in the different types of GTD by immunohistochemistry and serum measurements. The value of PGH as a potential biomarker for GTD has been investigated (107); however, the available data from the literature are limited.

6. Conclusion

PGH performs an important role in the regulation of placental growth and development, as well as in fetal growth by increasing nutrient availability, either directly or indirectly, via IGF-I. As with many other hormones, PGH may be used as a biomarker for a variety of abnormal pregnancy conditions and complications. However, further investigation is required to clarify the value, if any, of PGH as a clinically useful biomarker for particular pregnancy-associated pathological conditions. It is possible that the measured levels of PGH in maternal circulation may correspond to the synthesis rate of PGH; however, larger studies simultaneously evaluating placental expression and maternal and/or fetal serum concentration are required. In addition, important aspects of the physiological actions of PGH require further clarification. The same is true for the association between PGH and the IGF-axis, and other hormones of placental or maternal origin. The majority of previous studies thus far focused upon investigating the alterations of PGH in PE, FGR, GDM, as well as the more common aneuploidies. Despite the controversial results, it has been demonstrated that evaluation of the maternal concentrations throughout pregnancy may offer ground for further investigation and establishment of a clinically useful role of PGH. Details of the underlying mechanisms of the regulation of PGH remain unknown or poorly understood, although it has been shown that PGH has an important role in placental development, fetal growth and the outcome of the pregnancy.

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