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Placental peptides regulating islet adaptation to pregnancy: clinical potential in gestational diabetes mellitus

Sian Simpson, Lorna Smith and James Bowe



Pregnancy involves a progressive increase in insulin resistance and the β -cells must adapt to compensate and prevent gestational diabetes (GDM). In this review we discuss the evidence for placental peptides, including placental lactogen, hepatocyte growth factor, adiponectin and leptin, playing a role in the islet adaptation to pregnancy. The difficulties of translating data from rodent models into human pregnancy are covered and we summarise studies investigating associations between serum placental peptides and GDM risk. In conclusion, current data support important roles for placental peptides interacting to support β -cells during pregnancy, however mechanisms involved in humans are unclear. Further work in humans is required, but placental peptides have clinical potential from both a diagnostic and therapeutic perspective.

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Introduction

During a healthy pregnancy insulin sensitivity falls with gestational age. This physiological change prioritises the delivery of glucose across the placenta for fetal development. However, this poses a dilemma for the maternal metabolism to balance providing for the energy requirements of the growing fetus, while simultaneously maintaining maternal glucose homeostasis. In a healthy mother the insulin resistance is countered by adaptive changes in pancreatic islets to allow increased insulin secretion, including an increased β -cell mass. Failure of the insulin-releasing β -cells to sufficiently adapt and compensate for the increased metabolic demand in pregnancy leads to development

of glucose intolerance, hyperglycaemia and gestational diabetes mellitus (GDM).

Gestational diabetes

The rapid worldwide increase in the prevalence of type 2 diabetes mellitus (T2DM) is well-documented, but it is less appreciated that the incidence of GDM is also rapidly rising in parallel with the T2DM pandemic. It is currently estimated worldwide that 21.3 million pregnancies per year (16.2% of total pregnancies) are affected by some form of hyperglycaemia, with 86.4% of those cases due to GDM (IDF Diabetes Atlas: <https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html>). Maternal GDM has consequences for the mother and developing fetus, including placental insufficiency because of preeclampsia, macrosomia (birth weight >90th centile), birth injury and neonatal hyperinsulinism and hypoglycaemia. Epidemiological and experimental studies have also demonstrated that the GDM intra-uterine environment can increase susceptibility of the offspring to later life T2DM and cardiovascular disease, whilst in mothers GDM is associated with the subsequent development of T2DM.

At present GDM is diagnosed through routine oral glucose tolerance testing at 24–28 weeks of gestation, once impaired glucose tolerance has developed. Therapeutically GDM is primarily treated with either insulin injections or metformin, though the use of insulin analogs which do not cross the placenta have also been suggested [1]. Given the range of acute and potentially chronic consequences of GDM for both mother and child, there is currently great interest in developing diagnostic tools for predicting high GDM risk earlier in pregnancy, thus allowing time for intervention. Additionally, the identification of additional therapeutic targets is of keen interest for investigation.

Placental peptides

GDM is primarily the result of insufficient islet adaptation and an inability to increase insulin secretory capacity to compensate for increased insulin resistance. In normal pregnancy β -cells adapt in several respects to increase functionality. In rodent models these mechanisms include increased insulin synthesis and release, increased glucose responsiveness, increased cell–cell communication, hypertrophy, increased proliferation and reduced apoptosis, resulting in an overall increase in β -cell mass.

The β -cell adaptation in human pregnancy is more controversial, particularly concerning β -cell proliferation, but broadly speaking a similar pattern is observed with increased insulin release and increased β -cell mass. Thus, understanding the signals and mechanisms that regulate the islet adaptation to pregnancy and the reasons for these mechanisms failing in GDM warrants further investigation.

The placenta plays many essential roles during pregnancy, including supporting and protecting the fetus, and the supply of nutrients and gas exchange. The placenta also acts as an essential endocrine organ, producing and releasing hormones and mediators into the maternal circulation to maintain pregnancy. Increasing evidence suggests that several placental hormones play a role in communicating with maternal β -cells to regulate the islet adaptation necessary for a healthy pregnancy.

The effects of steroid hormones released from the placenta, including oestrogens, progestogens and glucocorticoids, on glucose homeostasis are complex and still controversial. Oestrogens have been implicated in the islet adaptation to pregnancy, through both direct and indirect protective effects on β -cells [2]. Effects of progestogens appear to vary with concentration and the presence of other hormones [2], and further work is required to understand their role. The placenta also releases a much wider range of peptide hormones into the maternal circulation that may influence the islet adaptation to pregnancy. Despite β -cells expressing cognate receptors for many of these ligands, only a few have been investigated for possible effects during pregnancy. Thus, this review will summarise the placental peptides currently thought to play a role in the islet adaptation to pregnancy and discuss whether these peptides may represent useful biomarkers for early determination of GDM risk.

Lactogenic hormones

The lactogenic hormones, prolactin (PRL) and placental lactogen (PL), are the most extensively studied hormones involved in the islet adaptation to pregnancy. During early pregnancy PRL is released from the maternal anterior pituitary, but following placentation maternal circulating levels of PRL fall and PL released from the placenta becomes the dominant lactogenic signal during peak β -cell adaptation. Both PRL and PL exert effects through the prolactin receptor (PRLR), which is expressed specifically on the β -cell of rodent islets [3].

The role of PL in the islet adaptation to pregnancy was initially implicated largely through studies demonstrating that lactogens increased glucose-induced insulin secretion, β -cell proliferation and survival in isolated rodent

islets [4–6]. Global homozygous *Prlr* knockout mice exhibit reproductive dysfunction [7], so are unsuitable for pregnant studies. However, heterozygous *Prlr*+/- mice are fertile and have impaired glucose tolerance and reduced β -cell mass during pregnancy [8], but also adipose tissue effects that influence glucose homeostasis. The recently established β -cell specific *Prlr* knockout mouse (β PRLR-KO) provides the best evidence for the role of lactogenic hormones in β -cell adaptation. Although β PRLR-KO mice have normal glucose tolerance outside of pregnancy, they become progressively glucose intolerant during gestation, with corresponding failure of β -cell proliferation [9**].

The intracellular mechanisms activated by lactogenic hormones *in vitro* closely reflect pregnant changes, including glucokinase upregulation [10] and pro-proliferative and anti-apoptotic signalling pathways [11,12]. The lactogenic hormones also stimulate β -cell production of serotonin during pregnancy [13], which appears to play a critical local role in regulating β -cell mass [14], mediating the effects of prolactin (Table 1).

Given the role for lactogenic hormones in rodent pregnancy, there is ongoing research to determine whether similar mechanisms are also relevant in human β -cells. Human PLs are derived from duplications of the *hGH* gene, whilst rodent PLs are evolved from the prolactin gene [15], and the *Prlr* gene is significantly enriched in mouse β -cells compared to human, perhaps indicating a lesser role in human β -cell adaptation [16,17]. Treatment of human islets with lactogenic hormones potentiates glucose-stimulated insulin secretion [18], but the effects on β -cell proliferation are more controversial. Increased proliferation, as assessed by BrdU incorporation, has been reported in human islets in response to PL and PRL [18], but more recent studies have been unable to replicate this effect [19].

It is also unclear whether serum PRL or PL associates with GDM pathophysiology. Several studies have investigated possible links, but the majority found no significant correlation between maternal PRL or PL and GDM [20], although counter-intuitively an association between high maternal prolactin and reduced glucose tolerance has recently been reported [21**]. Despite the apparent lack of association to GDM risk, low PRL or PL levels have been associated with reduced glucose tolerance post-partum and an increased risk of subsequent pre-diabetes/diabetes [22*], suggesting that the lactogenic hormones do play some role in human pregnancy.

Hepatocyte growth factor

Hepatocyte growth factor (HGF), acting via the c-Met receptor, has also been implicated in the islet adaptation to pregnancy. Normally HGF is released from endothelial cells in the islet vasculature to exert local effects on the β -cells [23], however during pregnancy high levels of

Table 1

Effects of placental peptides investigated in rodent and human islets that may potentially play a role in the islet adaptation to pregnancy and the development of GDM

Placental signal	Effects on rodent islets	Effects on human islets	Correlation with GDM
Placental lactogen	Increased glucose stimulated insulin secretion, increased proliferation and pro-survival effects, upregulation of islet serotonin	Controversial, but some studies report increased glucose-stimulated insulin secretion and proliferation	No significant correlation/high PL associated with increased GDM risk
HGF	Pro-proliferative and anti-apoptotic effects	Anti-apoptotic effects in human fetal islets and transplanted human islet grafts	High HGF associated with increased GDM risk in obese women
Leptin	Reduced glucose-induced insulin secretion and potentially β -cell atrophy	Reduced glucose-induced insulin secretion, effects on β -cell mass unknown	High leptin associated with increased GDM risk
Adiponectin	Increased glucose-stimulated insulin secretion and β -cell mass	No effect on insulin secretion, effects on β -cell mass unknown	Low adiponectin associated with GDM risk
Kisspeptin	Increased glucose-induced insulin secretion, effects on β -cell mass unknown	Increased glucose-induced insulin secretion, effects on β -cell mass unknown	Low kisspeptin associated with GDM risk

circulating HGF are also released from the placenta [24]. Loss of pancreatic c-Met signalling has no significant effect on glucose homeostasis outside of pregnancy [25], but results in reduced β -cell proliferation and increased apoptosis during pregnancy, with consequently reduced plasma insulin and impaired glucose tolerance [26]. Interestingly, pancreatic c-Met knockout mice also lack the increase in islet *Prlr* levels seen in normal pregnancy, suggesting that HGF may represent an upstream factor regulating PRLR signalling [26].

Whilst few studies have examined effects of HGF on human islet function in relation to pregnancy, HGF does stimulate proliferation in human fetal β -cells [27] and improves graft survival of human islets through anti-apoptotic effects in islet transplantation models [28,29]. Despite these effects of HGF in human β -cells, there does not appear to be any correlation between serum HGF levels and GDM progression across the whole population [30]. However, obese women generally have significantly higher placental HGF levels when compared to control women [31], and specifically among obese women high serum HGF is associated with a 4.5-fold higher risk of developing GDM [30].

Given the proliferative and pro-survival effects of HGF on β -cells it is surprising that high HGF appears to be deleterious. The relative contributions of placental and endothelial HGF on β -cell adaptation are unclear. As placental HGF rises through gestation, islet endothelial cells also proliferate, increasing local HGF. This has been identified as a possible mechanism for coordinating vascular and β -cell function in pregnancy [23]. Given that raised placental HGF associates with increased GDM risk in obese women, local endothelial cell-derived HGF could be the primary driver of β -cell responses. High

HGF does associate with GDM risk in obese women and as such may be a useful biomarker for GDM generally, but it is unlikely to be an indicator of β -cell adaptation.

Adipokines

The adipokines are signalling molecules secreted by the adipocytes that regulate processes including atherosclerosis, inflammation, appetite and glucose homeostasis. The adipokines are present at increasing levels as adipose tissue expands in obesity and several adipokines, including leptin, adiponectin, visfatin, chemerin and omentin-1 have been implicated in the development of T2DM [32]. Leptin and adiponectin are also released at high levels from the placenta into the maternal circulation and, although they are more commonly linked to effects on food intake or insulin sensitivity, they have additional direct effects on β -cells.

Adiponectin has primarily been studied as a regulator of insulin sensitivity, but both human and rodent β -cells express the adiponectin receptors AdipoR1 and AdipoR2 [33]. Adiponectin has been shown to stimulate insulin secretion from mouse islets both *in vitro* and *in vivo* [34,35], although the same effect is not observed in human islets [36]. Pregnant adiponectin knockout mice have reduced β -cell mass and insulin deficiency, though despite this they are able to maintain normal plasma insulin levels [37**]. However, these mice also display increased triglyceride production, hyperlipidaemia and increased hepatic glucose, which makes assessing the relative importance of β -cell-specific adiponectin signalling on glucose tolerance difficult [37**].

Clinical studies have found decreased serum adiponectin in women with GDM compared to women with healthy pregnancies [38–41]. Placental adiponectin expression is also downregulated in GDM, suggesting that reduced

serum adiponectin in GDM is at least partly due to low placental, as opposed to adipocyte, secretion [42]. Whilst adiponectin clearly regulates β -cell adaptation to pregnancy, it also has a well-established role in increasing insulin sensitivity. Whether the link between circulating adiponectin and GDM risk is the consequence of one or both of these mechanisms is currently unclear, but first trimester adiponectin has been suggested as a potentially useful biomarker for predicting GDM [43**].

The hypothalamic effects of leptin to regulate food intake, with subsequent effects on adiposity, insulin resistance and glucose tolerance are well-established. However, mouse and human β -cells also express several isoforms of the leptin receptor [44]. Leptin reduces glucose-induced insulin secretion in isolated mouse islets [45,46] when administered to mice *in vivo* [47] and in isolated human islets [47,48]. Mice heterozygous for the leptin receptor (*db/+*) develop GDM during pregnancy, with associated glucose intolerance and macrosomia, though they also exhibit increased weight gain and adiposity [49]. Whether the impaired glucose tolerance is due to direct β -cell effects or secondary to hypothalamic effects of leptin is unknown. Mice with β -cell-specific leptin receptor knockout show mildly improved glucose tolerance, enhanced glucose-stimulated insulin secretion and increased β -cell mass through hypertrophy [50,51], but have not yet been studied in pregnancy.

There is a well-established association between raised serum leptin and increased GDM risk [52*,53], which has resulted in leptin having also been proposed as a first trimester biomarker for establishing GDM risk [52*,54]. Similar to adiponectin, circulating leptin in pregnancy may be derived from either the placenta or the adipocytes, but leptin expression is increased in GDM placenta [55–57]. As with adiponectin, the relative importance of the β -cell and the hypothalamic effects of leptin on GDM risk is unclear.

Novel signals

The signals described above are all placental derived hormones whose potential role in mediating the islet adaptation to pregnancy has been established to some extent. However, it is worth noting that the placenta produces and secretes a very wide range of different peptide hormones into the maternal circulation. G-protein coupled receptors (GPCRs) represent the most abundant family of cell surface receptors and mouse and human islets express 279 and 293 different GPCRs respectively [58]. Additionally the mouse placenta expresses mRNA for 79 different endogenous GPCR ligands, the majority of which have at least one cognate receptor on the islets [59**]. As yet unidentified signals may also play a significant role in the communication between placenta and β -cells.

Kisspeptin represents one placental GPCR ligand that potentially plays a role in the β -cell adaptive response to pregnancy. Under normal physiological conditions kisspeptin is primarily a hypothalamic signal involved in regulating reproductive function, but during pregnancy serum levels increase several-thousand fold due to placental release [60]. Both mouse and human islets express the kisspeptin receptor, GPR54 [61], and kisspeptin stimulates glucose-stimulated insulin secretion in isolated mouse and human islets [62,63]. Unfortunately, due to the role of kisspeptin in reproductive function, global GPR54 knockout mice are infertile and unsuitable for pregnancy studies [64]. However, upcoming studies in β -cell specific GPR54 knockout mice show impaired glucose tolerance and reduced glucose-stimulated insulin secretion during pregnancy (T. Hill, abstract in *Diabetic Medicine* 2017, 34(S1): 27–28). Furthermore, clinical studies have shown that serum kisspeptin is significantly lower in GDM [65] and can be safely administered in humans to stimulate glucose-stimulated insulin secretion [66**]. More work is required to determine whether kisspeptin represents a potentially important signal to add to the established factors described above.

Conclusions

There is a growing body of evidence linking placental peptides to rodent β -cell adaptation to pregnancy. However, the major challenge going forward is understanding how these mechanisms translate to human pregnancy. How human β -cells adapt to pregnancy is still poorly understood, particularly in terms of β -cell mass. Post-mortem studies indicate that β -cell mass increases during human pregnancy, but the mechanisms remain controversial. The limited data suggests β -cell proliferation does not increase in human pregnancy, as assessed by Ki67 staining, and neogenesis is more important in humans [67]. These conclusions are based on autopsy samples from different time-points when there may not have been active proliferation, but they demonstrate the difficulties in translating results from rodent models into humans. The core principles associated with β -cell adaptation in rodents also appear to be conserved to at least some extent in human pregnancy, though a clearer understanding of this is key for future advances.

Understanding the signals involved in regulating the human β -cell response to pregnancy is of great interest for both potential diagnostic and therapeutic benefits. There are ongoing efforts to develop a panel of biomarkers to identify mothers at high risk of GDM before glucose intolerance develops. Most currently suggested biomarkers are steroid hormones and metabolites [52*], but peptide hormones may be a useful addition. Adiponectin and leptin would appear the most promising candidates to screen for and identify GDM risk, whilst kisspeptin represents a novel candidate that may also be promising with further research.

In terms of therapeutic potential far more work is required. The PL, HGF and the adipokines have off-target effects and may consequently not be useful as therapies. Perhaps the most promising therapeutic candidates are novel placental GPCR ligands. One-third of all prescription drugs in use target GPCRs, including GLP-1 receptor agonists for T2DM, placental GPCR ligands could include as yet unidentified therapeutics. Indeed kisspeptin has recently been shown to safely stimulate glucose-induced insulin secretion in humans [66^{••}] and is currently the subject of clinical trials (NIH Clinical Trials: <https://clinicaltrials.gov/ct2/show/study/NCT02953834>) which may be of future use in pregnancy.

In summary, key placental peptides have been identified to play roles in regulating the islet adaptation to pregnancy in rodent models. Some signals may be of diagnostic use in biomarker screening for GDM risk. However, our understanding of β -cell adaptation to pregnancy in humans is still at a relatively early stage and further studies are required to identify potentially safe and effective therapeutics.

Conflict of interest

Nothing declared.

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