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Placental control of metabolic adaptations in the mother for an optimal pregnancy outcome. What goes wrong in gestational diabetes?

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ABSTRACT

As pregnancy progresses the placental syncytiotrophoblast increasingly assumes control of maternal glucose homeostasis through the release and counter-balancing effects of placental lactogen (PL) and placental variant growth hormone (GH-V). While local actions of these hormones on placental growth and function are likely to exist, each also exerts indirect actions to ensure fetal nutritional availability through modulation of the maternal insulin/insulin-like growth factor axis. Peripheral insulin resistance results from the increasing levels of GH-V in the maternal circulation and is counter-balanced by an increase in insulin availability through an expansion of maternal pancreatic β-cell mass. GH-V also increases maternal IGF-1 synthesis leading to enhanced placental growth and nutrient transporter activity. Maternal obesity and the presence of diabetes in pregnancy is associated with a disrupted balance in the placental expression of PL and GH-V. Several parallel mechanisms are likely to contribute to the increasing maternal β-cell mass as gestation progresses, including a reactivation of β-cell proliferation, an expansion of subsequent differentiation of resident β-cell progenitors, and α-to β-cell transdifferentiation. Each of these pathways could potentially be modulated during pregnancy to increase β-cell mass and prevent the onset of gestational diabetes.

1. Introduction

Glucose homeostasis during the increased metabolic demands of pregnancy is maintained through the coordinated actions of two hormones expressed by the placental syncytiotrophoblast and secreted into the maternal circulation, these being placental lactogen (PL) and placental, or variant growth hormone (GH-V). Together, PL and GH-V ensure that nutrient availability and transfer to the fetus is optimal. However, the fine balance of glycemic control can be disrupted in pregnancies complicated by gestational diabetes mellitus (GDM), for which pre-gestational maternal obesity and/or excessive gestational weight gain are major risk factors. Gestational diabetes occurs in up to 35% of pregnancies in obese women, carries immediate health risks to the mother, and is a risk factor for obesity and type 2 diabetes in the offspring [1,2]. The major risk to fetal and child health derives from maternal hyperglycemia, as shown from the HAPO clinical cohort with the demonstration that newborn weight and cord blood insulin values were positively correlated with maternal glycemic control, even without a diagnosis of maternal diabetes [3]. The potential for prevention of GDM with drugs, such as metformin, is complicated by the risks associated with trans-placental passage and possible deleterious effects on fetal development and/or future child health. Attention has therefore focused on lifestyle interventions during pregnancy using dietary modification and increased exercise to reduce hyperglycemia through a reduction in peripheral insulin resistance. However, recent clinical trials have shown limited success in reducing the risk of GDM in at-risk populations through lifestyle change alone. An alternative strategy to improve glycemic control in pregnancy might be to modulate glucose-stimulated insulin secretion from the pancreas. In this review we assess the relative advantages and limitations of each of these approaches from a physiological perspective, and review the available evidence and remaining knowledge gaps.

2. Insulin resistance during pregnancy

Most GH-V synthesized within the syncytiotrophoblast is released predominantly into the maternal circulation, and from

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mid-gestation GH-V becomes the major source of growth hormone in the mother with an associated suppression of pituitary growth hormone release. The GH-V becomes the major driver of maternal insulin-like growth factor-1 (IGF-1) release in the second half of gestation [4]. GH-V has been shown to promote trophoblast invasion into the uterus [5] and a correlation exists between decreasing uterine and peripheral arterial resistance and increasing GH-V levels in normal pregnancies [6]. In pregnancies where uterine blood flow was impaired, lowered levels of GH-V and IGF-1 were reported in maternal serum [7] and this is associated with intrauterine growth retardation [8]. The presence of GH-V is therefore likely to promote fetal growth through both direct and indirect actions in the placental bed. However, GH-V is also responsible for creating a relatively insulin resistant state during pregnancy within maternal insulin-sensitive tissues, resulting in a diabetogenic stimulus that increases the dynamic flow of glucose and other nutrients across the placenta [9]. This may be exaggerated in pregnancies complicated by diabetes. GH-V can interfere with insulin actions through an increase in the levels of p85α leading to the competitive inhibition of insulin receptor substrate-1 and phosphoinositol-3 kinase signaling in insulin-sensitive tissues such as skeletal muscle, and less GLUT-4 plasma membrane translocation and glucose uptake [10]. The emergence of insulin resistance is also aided by the normal gestational decline in circulating adiponectin [11]. During normal pregnancy the ratio of PL to GH-V gene expression within the placenta changes through gestation; the term placenta having a seventy-fold higher relative expression of PL relative to GH-V compared to that in first trimester [12]. Term placentae from diabetic pregnancies express a relatively lower amount of PL but higher GH-V, and resemble a mid-gestational profile. It is unclear if this represents a more general failure of terminal placental differentiation, but the net effect will be to amplify the diabetogenic actions of GH-V in third trimester.

The relationship between nutrition, obesity and the control of GH-V secretion is likely to be complex. The pregnancy-associated changes in insulin, progesterone and prolactin promote maternal fat storage, resulting in a greater dependence on lipids as a source of maternal energy and releasing glucose availability as substrate to enable placental and fetal growth. GH-V stimulates maternal hepatic lipolysis and hepatic gluconeogenesis [13,14]. Glucose has been shown to inhibit GH-V secretion from term human placental explants or isolated trophoblasts *in vitro* [15], and circulating GH-V in women with GDM is decreased following a glucose tolerance test [16]. It has been suggested that elevated glucose levels may alter GH-V expression through epigenetic changes in gene methylation [17]. These effects should not be viewed, however, outside of the context of parallel changes in lipid levels. Placental dysregulation of PL and GH-V expression have been reported in the placentae of obese pregnant women and in the pregnant, obese mouse fed a high fat diet [18]. These changes have been linked to a decreased expression of the transcription factor CCAAT-enhancer binding protein (C/EPB) which is co-expressed with PL and GH-V in syncytiotrophoblasts, and is required for normal placental development in mouse [19], as well as being linked to changes in adipogenesis during obesity outside of pregnancy [20]. C/EBP binds at a downstream enhancer site of the PL gene, but which also distally flanks GH-V such that the expression of both genes is altered [21]. Knockdown of endogenous C/EBP expression in human placental tumour cells using a siRNA decreased the expression of both PL and GH-V [18]. A resulting change in the relative amounts of available PL and GH-V due to the actions of C/EBP in obese pregnancies may be a precipitating factor in the development of GDM.

Pregnancy is associated with the appearance of low grade inflammation, and this is enhanced during obese pregnancies, with a greater expression of pro-inflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor-α in the placenta [22]. The extent to which such cytokines present systemically in the mother can contribute to enhanced insulin resistance is unclear, or how such cytokines might alter the expression of PH-V or PL.

An inherent problem with prevention strategies for GDM is that hormonally-driven insulin resistance is an important metabolic adaptation of pregnancy and is difficult to modify, perhaps especially so in obese mothers. Recent clinical trials aimed at preventing the risk of GDM through lifestyle change during pregnancy have shown largely disappointing results [23,24] with only one demonstrating a reduction in the incidence of disease [25]. As part of the Vitamin D And Lifestyle Intervention for GDM prevention (DALI) trials consortium, we implemented dietary change, increased moderate exercise, or both interventions in a pan-European group of obese pregnant women at risk of GDM prior to 20 weeks' gestation [26]. The combined intervention resulted in a greater than 2 kg reduction in gestational weight gain compared to a control group at term, but did not alter glucose tolerance or insulin resistance. The percentage of subjects who developed GDM was not reduced. A post-hoc analysis of the most successful study sites showed that even reducing mean pregnancy weight gain by over 3 kg impacted maternal insulin resistance by only 5%. It would seem that the hormonally-mediated placental control on maternal glycemic regulation is so strong that it is unlikely that lifestyle changes alone during pregnancy can alter this significantly, and change the trajectory of GDM. Therefore, an alternative approach should be explored, such as enhancing insulin release.

3. Changes in β-cell mass during pregnancy

The increased insulin resistance of pregnancy is normally compensated by an adaptive increase in maternal pancreatic β-cell mass, allowing for enhanced glucose-stimulated insulin release. The increase in β-cell mass involves cell hyperplasia, hypertrophy, and likely neogenesis leading to enhanced insulin secretion [27]. Van Assche et al. [28] found a two-fold increase in the fractional area of β-cells in women deceased in third trimester or at delivery compared to non-pregnant subjects of comparable age. Butler et al. [29] also measured the fractional area of β-cells in pancreata during pregnancy and reported a 1.4-fold increase during pregnancy. However, this included women who died in first trimester possibly explaining the differences from Van Assche et al. A failure of β-cells to undergo an adaptive increase after first trimester has been associated with a risk for GDM [30]. Therefore, sustaining the increase in β-cell mass and functionality that should occur in pregnancy could help prevent GDM in at-risk women. However, this requires a detailed understanding of mechanisms underlying changes to β-cells during pregnancy.

4. Modeling adaptive changes to β-cell mass

The compensatory expansion of β-cell mass and function during pregnancy is transitory, and is followed by a regression of β-cell mass following delivery, largely through apoptosis. Adult β-cells normally have a low proliferative turnover, but in the pregnant mouse an increase in β-cell mitogenesis contributes to a 2–3-fold increase in mass, peaking at around gestational days (GD) 15 (term 19.5 days) [31]. The increase in β-cell proliferation correlates with the appearance and rise of circulating PL [32]. Targeted overexpression of PL in β-cells resulted in increased β-cell proliferation [33], mediated by the prolactin receptor. Targeted deletion of the prolactin receptor, as would be expected, caused a failure of β-cell compensatory growth in pregnancy, impaired insulin release and glucose intolerance [34,35]. Conversely, prolactin receptor over-

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