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REVIEW ARTICLE

The Human Placenta in Dysglycaemic Pregnancy

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Introduction

The Human Placenta

The harbinger of life, a bridge between mother and child,
Sustaining the baby before it can blink,
Ushering in goodness, rejecting the harmful,
Sharing and growing with mother's bountiful
Proving to be both a generous cushion and a cradle
Without which the baby could never thrive!

The placenta is an important metabolic bridge between a mother and the growing foetus in her womb. It separates the maternal and foetal circulation, with which it is in contact through different surfaces, i.e., the syncytiotrophoblast exposes the placenta to the maternal circulation and the endothelium is in contact with foetal blood.

The placenta is a source and a target for cytokines at the same time. The type and the location of the cytokine receptors present on the placental cells will determine whether signals are generated by placentally (internal), maternally (presumably adipose-derived) or foetally derived cytokine The placenta expresses virtually all known cytokines including tumour necrosis factor (TNF-α), resistin, and leptin. Some of these adipokines modulate insulin function and their levels many times get dysregulated in gestational diabetes mellitus (GDM) or obesity.[1,2]

In order to ensure normal glucose homeostasis in pregnancy, maternal β-cells must compensate for the severe acquired insulin resistance of late gestation by significantly increasing their secretion of insulin. The mechanism of this compensation involves placental lactogens and prolactin acting through a series of downstream mediators [including the transcription factor Fox M1 (Forkhead box M1), the serotonin synthetic enzyme Tph1 (Tryptophan hydroxylase), and the cell cycle regulator Menin (a scaffold protein that controls gene expression and cell signalling)], facilitating the expansion of β-cell mass and enhanced insulin secretion (Fig 1).[3]

Maternal and foetal hyperleptinaemia, as well as increased placental leptin expression, are well established in diabetes and obesity. The continuous rise of maternal obesity is accompanied by increased gestational diabetes mellitus incidence. Inclusion of GDM into "the great obstetrical syndromes" highlights the role of the placenta in interactions of the maternal and foetal unit.

Placental Physiology and Pathological Aberrations

In a known diabetic mother the hyperglycaemic environment will predominantly alter placental

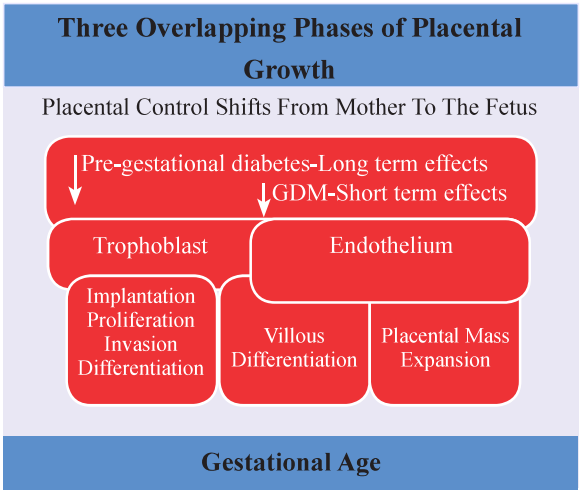

Figure 1: The three phases of placental growth and development.

development at the beginning of gestation. Changes in placenta function may include altered synthesis and/or secretion of growth factors, hormones, and cytokines that will act back on the mother. As gestation advances, the placenta gets impacted by the diabetic environment in the foetus. Foetal insulin can induce alterations in gene expression and instigate endogenous glycogen synthesis in the placenta (Fig 2).

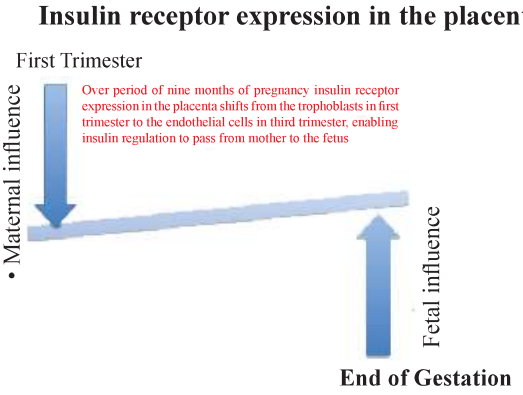

Figure 2: Insulin receptor expression in the placenta.

The feto-placental expression of insulin, IGF1, IGF2, and their receptors is developmentally regulated in a tissue-specific manner and is influenced by nutritional and endocrine conditions.[4] In the first trimester, maternal insulin influences the placenta by interaction with trophoblast insulin receptors. These may in turn affect the mother by secretion of cytokines, hormones, or metabolic waste products and along with the effects of foetal insulin on the placenta later in gestation may have repercussions on foetal development and metabolism. These alterations are mainly based on changes on the micro-anatomical and/or even molecular level including aberrant villous vascularisation, an imbalance of vasoactive molecules, and exaggerated oxidative stress. This may lead to impaired foetal oxygenation and changes in transplacental nutrient supply. While the limited transplacental glucose flux is independent of glucose transporter availability, transport of essential and non-essential amino acids and expression of genes involved in lipid transport and metabolism are significantly affected by GDM. (Fig 3)

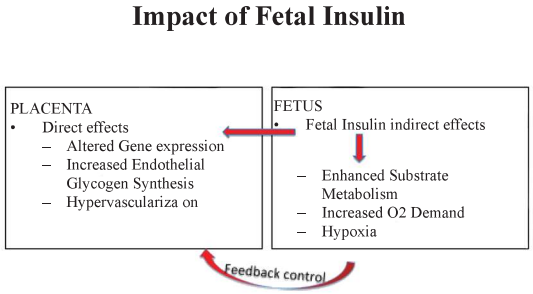

Figure 3: Impact of foetal insulin.

The indirect effects mediated by foetal hypoxia on placental structure can be regarded as adaptive feedback responses to ensure adequate oxygen supply.

Role of placental versus maternal tissues in GESTATIONAL DIABETES MELLITUS

It is difficult to differentiate the relative contribution of placental *versus* maternal tissues for regulation through TNF-α, leptin or resistin. The influence of adiponectin is exclusively of maternal origin due to expression of adiponectin receptors in the placenta. Evidence suggests that placental leptin is poorly released into the foetal circulation and that leptin synthesised by foetal adipose tissue can be taken as a marker of foetal adiposity.[5] Some of the stimuli that disturb placental metabolism may be also conveyed through the vascular endothelium (such as oxidative stress, endothelial injury, etc.), induced by circulating foetal TNF-α, leptin, and IL-1 and IL-6.

Thus, the maternal–foetal control of the placenta is the culmination of cell interaction that may propagate a vicious cycle for enhancement of cytokine production. This ultimately may lead to obesity *in utero.*

Foetal Sex and Maternal Risk of Gestational Diabetes Mellitus

The incidence of GDM as a maternal disease is affected by foetal sex, and the mother's risk for developing GDM is higher with a male foetus.[6,7] The female foetus is more insulin resistant in-utero with higher leptin and C-peptide concentrations in cord blood despite weighing less at birth. The female foetus confers a decreased risk of insulin resistance to the mother from an early gestation.

Male foetus is associated with poorer β-cell function, higher postprandial glucose excursions, and an increased risk of GDM in the mother. A feature of the male foetus (possibly involving the Y chromosome) may impact the placental secretion of hormones or proteins involved in β-cell compensatory response.

What happens to the placenta in hyperglycaemic environment?

Owing to its unique position, the placenta is exposed to maternal and foetal derangements associated with glycaemic spikes which may lead to various structural and functional changes, including heavier weight, surface enlargement, and neovascularisation. Circulating maternal and foetal levels of insulin, IGF1, IGF2, and leptin are altered in diabetes and affect placental development. In turn, the placenta can produce molecules that will affect mother and foetus independently. Alteration of the placental development and subsequent vascular dysfunction are commonly present in most women who display varying degree of diabetic severity.

Placental Abnormalities Reported in Studies of Pre-gestational Diabetes

Increased villous immaturity[8–10] and increased volume and surface area of parenchyma tissue[11–13] happened to be the placental abnormalities most consistently reported in T2 DM cases. The prevalence of placental immaturity in the normoglycaemic obstetrical population has been reported to be 14% and the presence of pre-gestational diabetes nearly doubles the risk of delayed villous maturation.[9]

In an important study by Scott M. Nelson[14] and colleagues, intervillous space volume was increased in offspring of T1DM (OT1DM 250 ± 81 cm^3 vs. control 217 ± 65 cm^3; $P = 0.02$) with anisomorphic growth of villi ($P = 0.025$). The placentas showed a trend to increased weight (OT1DM 690 ± 19 g; control 641 ± 22 g; $P = 0.08$), but villous, non-parenchymal, trophoblast, and capillary volumes did not differ.

Circulating foetal IGF-I correlates well with many of the placental components. Cord IGF-I is strongly associated with birth weight and placental weight.[14,15]

Placental Abnormalities Reported in Studies of Gestational Diabetes Mellitus

Increased placental weight[16–18] was the placental abnormality most consistently studied and reported. Ashfaq et al. observed that placenta of women with GDM had 22% increase in weight, 33% increase in diameter, and 85% increase in central thickness compared to normal placentas.[18] Significant histopathological changes included a sizable increase in fibrinoid necrosis,[19] chorangiosis,[20] increased angiogenesis and ischaemia.

The type of dysfunction depends on how early in pregnancy glycaemia disorders occurred. Generally, if impaired glucose metabolism is diagnosed in the early pregnancy, mainly structural dysfunctions are observed. Diabetic placental changes are associated with inflammation and oxidative stress that can lead to chronic foetal hypoxia.

Summary

Maternal diabetes leads to alterations in placental structure and function. The specific nature and extent of these changes depend on the gestational period of occurrence of hyperglycaemia. Maternal and foetal concentrations of several growth factors, cytokines, and hormones are altered in diabetes

and may affect foetal and placental growth and development. Foetal sex is likely to modulate the effect of GDM on placental and fetal development and function. The diabetic environment of GDM alters DNA methylation profiles and, thus, may affect the offspring in the long term. Optimum control of diabetes can lead to improvement in villous morphology.

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