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Review: Alterations in placental glycogen deposition in complicated pregnancies: Current preclinical and clinical evidence

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ABSTRACT

Normal placental function is essential for optimal fetal growth. Transport of glucose from mother to fetus is critical for fetal nutrient demands and can be stored in the placenta as glycogen. However, the function of this glycogen deposition remains a matter of debate: It could be a source of fuel for the placenta itself or a storage reservoir for later use by the fetus in times of need. While the significance of placental glycogen remains elusive, mounting evidence indicates that altered glycogen metabolism and/or deposition accompanies many pregnancy complications that adversely affect fetal development. This review will summarize histological, biochemical and molecular evidence that glycogen accumulates in a) placentas from a variety of experimental rodent models of perturbed pregnancy, including maternal alcohol exposure, glucocorticoid exposure, dietary deficiencies and hypoxia and b) placentas from human pregnancies with complications including preeclampsia, gestational diabetes mellitus and intrauterine growth restriction (IUGR). These pregnancies typically result in altered fetal growth, developmental abnormalities and/or disease outcomes in offspring. Collectively, this evidence suggests that changes in placental glycogen deposition is a common feature of pregnancy complications, particularly those associated with altered fetal growth.

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1. Introduction

Delivery of a healthy baby of optimal weight and size is largely dependent upon a well-functioning placenta. The placenta functions as the interface between the maternal blood supply and the developing fetus and is responsible for the oxygen and nutrient delivery required for normal fetal growth. Many perinatal complications including miscarriage, abnormal fetal growth and even some fetal defects can be attributed to poor placental function [1,2]. In addition, major obstetric complications such as early onset preeclampsia [3] also directly involve placental dysfunction. However, the impact of poor placental function does not cease upon delivery. There has been renewed interest in placental biology due to our understanding that many diseases of adulthood, including cardiovascular disease, diabetes and even mental disorders, have their origins *in utero* [4].

One aspect of placental morphology that appears to be indicative of alterations to normal fetal growth is excessive glycogen deposition. This review will begin by briefly summarizing the importance of the placenta for short and long-term health outcomes in offspring and the pregnancy complications that can interfere with this role. It will then present current knowledge on the normal process of glycogen storage and handling in the placenta during pregnancy, in both human and preclinical rodent models, and how this is thought to link to fetal nutrient demands and growth. Finally, preclinical and clinical evidence for altered glycogen deposition during various pregnancy complications will be summarized and discussed.

2. The impact of pregnancy complications on placental function, fetal growth and long-term offspring health

The placenta regulates the extent to which a healthy birth weight is achieved. Glucose and amino acids are the primary energy substrates required by the developing fetus and placenta and reductions in their availability result in reduced fetal growth and low birth weight [5]. The health and nutritional status of the mother can directly influence the availability of these substrates and thus impact on placental development [6]. This impairment often manifests as poor trophoblast invasion and spiral artery remodelling, or reduced vascularization and expansion of the villous tree. This can cause poor placental perfusion or a reduced surface area for substrate exchange respectively [7]. These disruptions can reduce the amount of glucose or amino acids transferred to the fetus and cause growth restriction.

In the human, many obstetric complications are directly related to placental abnormalities. The best characterized is preeclampsia (PE) which affects ~5–10% of pregnancies worldwide and is a major cause of preterm delivery and perinatal morbidity [8]. PE, particularly early-onset PE, significantly increases the risk for fetal growth restriction and this is thought to be due to complications in spiral artery remodelling leading to placental insufficiency [9]. Of great interest in current society is the effect of excess maternal glucose and nutrients which occur in maternal diabetes or obesity. With more than 40% of pregnant women being overweight or obese [10], there are increasing numbers of women with type 2 diabetes entering pregnancy or subsequently developing gestational diabetes. This often contributes to the delivery of large for gestational age (LGA) babies [11]. In diabetic pregnancies, the placenta undergoes structural and functional changes dependent on the modality and quality of glycemic control [12]. These include alterations to the insulin/IGF system [13] as well as cytokines similar to those found in adipose tissue that regulate insulin action [12]. Additionally, factors regulating glucose and lipid metabolism such as FGF21 and GLUT3 are dysregulated in diabetic placentas [14].

Rodent models also provide evidence that pregnancy complications can affect placental function and fetal growth. Maternal hypoxia, which in humans may be caused by smoking, asthma or sleep apnea, has been shown to alter placental development and expression of glucose transporters in mouse models [15,16]. This limits both oxygen and nutrients to the fetus, resulting in intrauterine growth restriction (IUGR).

Early studies associating fetal growth and adult health outcomes found the most severely affected individuals were those with a low birth weight to placental weight ratio. These individuals had a blood pressure ~25 mmHg higher than the groups with the healthiest birth and placental weights [1]. Other studies suggested a U-shaped relationship between the birth weight to placental weight ratio, as males born with placentas large or small for their body weight have an increased incidence of coronary heart disease as adults [17]. This dichotomy may be due to limited nutrient transfer in a small placenta versus diversion of maternal nutrients by a large placenta to meet its own needs. Collectively, these studies indicate the importance of a normally functioning placenta capable of balancing maternal-fetal nutrient exchange to fetal outcomes and long-term offspring health.

3. Glycogen deposition in the human placenta during pregnancy

Glycogen, a form of stored glucose, is readily deposited in tissues where glucose needs to be easily mobilised such as the liver and skeletal muscle. Whilst it is known the placenta can also store glycogen, there are relatively few studies examining glycogen in the human placenta.

In normal pregnancies, glycogen accumulation begins as early as the first trimester [18], but declines towards term [19]. A region in the human placenta known as the basal plate (bp) contains multilayered columns of cytotrophoblast cells, located at the ends of villi, and extravillous cytotrophoblast cells (EVT). EVT proximal to the villi contain low amounts of glycogen while the distal EVT are vacuolated and glycogen rich [20]. Strong staining for glycogen has also been reported in cytotrophoblast cells of chorionic villi in the placenta in early pregnancy, gradually decreasing in intensity as the pregnancy progresses [21]. In late first trimester placenta, some fibroblast cells also contain glycogen aggregates [22], but it is not clear if this continues throughout gestation or if it is affected by pregnancy complications.

Transport of glucose from mother to fetus is particularly critical to meet fetal nutrient demands and is controlled by a number of specific placental glucose transporters (see Ref. [23] for review). In the placenta, glucose can be converted into glycogen for storage either via the classical pathway (glycogen synthase) or through using glycogenin as a primer [18]. In healthy human placenta, it appears that glycogen synthesis via the classical pathway and degradation occurs in syncytiotrophoblasts, cytotrophoblasts and the decidua in the first trimester of pregnancy but is absent at term [24]. In term placenta, glycogen synthesis via the glycogenin pathway is stronger in endothelial cells, syncytiotrophoblasts, extravillous trophoblasts and basal decidual cells than in first trimester [18]. In the decidua, glycoprotein production helps to provide nutrients early in gestation and glycogen synthesis and breakdown may contribute by providing substrates to this process. The metabolically active Hofbauer cells express low levels of glycogen synthase but their expression of glycogen phosphorylase is more pronounced both early in gestation as well as at term [22]. However, glycogen aggregation does not occur in Hofbauer cells even though the expression of GLUT3 suggests that glucose is transported into these cells [22]. This suggests that Hofbauer cells, which are placental macrophages, are not a site for glycogen

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