Fetal overgrowth in pregnancies complicated by diabetes is the result of an increased substrate availability which stimulates fetal insulin secretion and fetal growth. However, despite strict glycemic control in modern clinical management of the pregnant woman with diabetes, fetal overgrowth remains an important clinical problem. Recent studies in vivo provide evidence for increased delivery of amino acids to the fetus in gestational diabetes (GDM) even when metabolic control is strict. This could be due to that truly normal maternal substrate levels cannot be achieved in diabetic pregnancies and/or caused by altered placental nutrient transport and metabolism. Studies in vitro demonstrate an up-regulation of placental transport systems for certain amino acids in GDM associated with fetal overgrowth. GDM is also characterized by changes in placental gene expression, including up-regulation of inflammatory mediators and Leptin. In type-I diabetes with fetal overgrowth the in vitro activity of placental transporters for both glucose and certain amino acids as well as placental lipoprotein lipase is increased. Furthermore, both clinical observations in type-I diabetic pregnancies and preliminary animal experimental studies suggest that even brief periods of metabolic perturbation early in pregnancy may affect placental growth and transport function for the remainder of pregnancy, thereby contributing to fetal overgrowth. Ultrasound measurements of fetal fat deposits and abdominal circumference as well as 3D ultrasound assessment of placental volume represent non-invasive techniques for in utero diagnosis of fetal and placental overgrowth. It is proposed that these methods represent valuable additions to the clinical management of the diabetic pregnancy. In conclusion, altered placental function may be a mechanism contributing to fetal overgrowth in diabetic pregnancies with apparent optimal metabolic control. It is proposed that detailed information on placental metabolism and transport functions obtained in vitro and in vivo represent a placental phenotype that provides important information and may facilitate diagnosis and improve clinical management of fetal overgrowth.

Keywords: Diabetes in pregnancy; Large-for-gestational age; Placenta; Transport; Amino acids; Glucose; Metabolism

INTRODUCTION

In a brief introductory note, Jansson pointed out that fetal overgrowth, resulting in the delivery of a large-for-gestational age baby (LGA), represents a risk factor for operative delivery, traumatic birth injury and developing diabetes and obesity later in life. Fetal overgrowth is a common pregnancy complication and for example in the US, a birth weight > 4000 g was recorded in 7.9% of all deliveries in 2003, corresponding to approximately 300,000 babies [1]. Fetal overgrowth may occur in pregnancies complicated by maternal diabetes despite rigorous glycemic control in modern clinical management of these patients. This could be due to that truly normal maternal substrate levels cannot be achieved in diabetic pregnancies and/or caused by altered placental nutrient transport and metabolism. We will briefly review recent clinical and experimental studies, suggesting that alterations in the activity of placental nutrient and ion transporters and changes in placental metabolism may contribute to fetal overgrowth in diabetes. The possible clinical implications of these findings will be discussed and important directions for future research will be identified.

MACROSOMIA, LGA, EXCESS FETAL GROWTH AND FETAL OVERGROWTH

Many fetuses in pregnancies complicated by diabetes display accelerated intrauterine growth, so their birth weight exceeds
the normal range. Definitions of this condition at birth have been macrosomia, if birth weight exceeds 4000 g, or LGA, thus placing birth weight in relation to gestational age. As for the opposite condition of intrauterine growth restriction, Cetin argued that the change in growth trajectory can be diagnosed in utero by ultrasound based on multiple records showing an increasing abdominal circumference. However, intrauterine growth patterns based on serial ultrasound measurements have not been used in more strict definitions of fetuses growing larger than defined by their genetic potential, although many authors now refer to it as “excess fetal growth” or “fetal overgrowth”.

**INCREASED MATERNAL SUBSTRATE LEVELS – AN INSUFFICIENT EXPLANATION FOR FETAL OVERGROWTH?**

Fetal growth is regulated by the balance between the fetal nutrient demand, determined by its genetic growth potential, and the maternal—placental supply. As discussed by Cetin, factors that determine the maternal—placental supply of nutrients include maternal nutrition and metabolism, the transplacental concentration gradient, utero-placental blood flow, placental size and its transfer capabilities. According to the Pedersen's hypothesis [2], fetal overgrowth in pregnancies complicated by diabetes is the result of increased substrate availability together with a permissive endocrine environment that ultimately will lead to increased adiposity. In this model, increased maternal levels of glucose as well as amino acids and lipids are transferred to the fetus and stimulate fetal hyperinsulinemia [2]. Normal maternal glucose levels have usually been considered as the main target of any protocol for the management of pregnancies complicated by gestational diabetes. Nevertheless, the incidence of macrosomia is increased in GDM despite an optimal glycemic control. This may be due to an inability of the standard measurements of glucose control to identify periods of moderate hyperglycemia that are sufficient to increase fetal glucose availability. An additional possibility is that changes in placental nutrient transfer capacity and metabolism contribute to fetal overgrowth in diabetic pregnancies. Increased placental weights and placental ratios (placental weight to birth weight ratio) have been reported in pregnancies complicated by GDM [3], even in the presence of optimal maternal glycemic control throughout the third trimester [4]. The increased placental mass could then augment placental nutrient exchange by increasing the surface area available for substrate transfer.

**CLINICAL STUDIES INDICATE AN INCREASED NUTRIENT DELIVERY TO THE FETUS IN DIABETES**

Cetin suggested that changes in placental nutrient transport, due to increased exchange surface area or increased transporter densities could further increase substrate levels and fetal growth in diabetic pregnancies. Recent observations in vivo demonstrate that the umbilical delivery of amino acids is significantly increased even in well controlled GDM pregnancies, with maternal substrate levels comparable to those observed in normal pregnancies [5]. These changes in fetal—maternal relationships are opposite to those which have been reported in pregnancies associated with intrauterine growth restriction [6]. Previous studies using in vitro perfused placenta have suggested unaltered glucose transfer in the maternal—fetal direction in GDM [7]. Recent preliminary data show that fetuses of GDM mothers have an increased glucose concentration in both umbilical vein and artery despite a good maternal glycemic control and normal maternal glucose levels [8]. Further in vivo studies involving stable isotope techniques will provide more conclusive evidence as to whether placental glucose transfer capacity is altered in well controlled GDM pregnancies.

Studies of body composition have shown that fetal fat deposition and neonatal fat mass are significantly increased in infants of women with GDM [9,10]. Therefore, ultrasound parameters indicative of the size of fetal fat deposits in utero have recently been proposed as markers of abnormal fetal growth that could be used in the clinical management of diabetes in pregnancy. Moreover, the possibility of evaluating placental volume by 3D ultrasound in utero in the first half of pregnancy should be considered in pregnancies with type-I diabetes and in women with increased risk of developing GDM. Fetal and placental growth criteria could then be used for determining clinical management of diabetes in pregnancy, avoiding unnecessary intervention in low risk pregnancies and intensifying therapy and controls in those showing alterations of fetal growth.

**UP-REGULATION OF PLACENTAL NUTRIENT TRANSPORTERS IN VITRO AND THE POSSIBLE ROLE OF INSULIN**

The reported alterations in placental transporter activity and expression, measured in vitro, in association to maternal diabetes and fetal overgrowth were reviewed by Powell. Glucose transport activity and glucose transporter isoform 1 (GLUT 1) expression have been shown to be increased in the syncytiotrophoblast basal plasma membrane (BM) isolated from pregnancies complicated by type-I diabetes [11]. Since glucose transport across BM represents the rate-limiting step in transplacental glucose transfer, these changes may result in an increased glucose flux to the fetus even when maternal glucose levels are maintained within the normal range. In contrast, GDM with LGA was not associated with changes in placental glucose transporting capacity [12]. Neutral amino acid transport capacity by System A is increased in both GDM and type-I diabetes with LGA, whereas the activity of placental transporters for the essential amino acid leucine is increased in GDM only [13]. In contrast, a previous study indicated that System A activity is reduced and the activity of system L is unaltered in microvillous plasma membrane vesicles isolated from type-I diabetic pregnancies with LGA.
The two main differences between these studies were that they were carried out in different populations and that placental weight was increased in parallel to fetal weight in one study [13] whereas placental weight was largely unaffected in the other [14]. Thus, the placental response to metabolic disease may differ between study populations although outcome with regard to fetal weight is the same. Other nutrient transport systems such as those associated with transplacental calcium (calcium pump in BM, [15]) and lipid (lipoprotein lipase in MVM, [16]) transport also show changes in placentas of type-I diabetic pregnancies in association with fetal overgrowth but not in cases of GDM. Recently, preliminary data have also been presented showing increased placental expression of SR-BI, a cholesterol transporter, in well controlled GDM pregnancies [17].

Differences in placental transport capacity in type-I diabetes/LGA vs GDM/LGA pregnancies suggest a potential role of insulin as a mediator of placental transport alterations. Studies demonstrating insulin regulation of placental transport function in villous explant culture include increased System A activity in term villous tissue [18] and increased glucose transport capacity in first trimester only [19]. Preliminary data suggest a possible role of insulin in regulating some aspects of ion (Na/H exchanger) and lipid (lipoprotein lipase) transport in cultured trophoblast cells. Taken together, the up-regulation of placental transporters for the primary nutrients in diabetes, possibly due to insulin regulation, provides an explanation for the occurrence of large babies in these pregnancies despite “normal” maternal blood-glucose levels. However, LGA fetuses also occur in GDM pregnancies without insulin administration and in the absence of a change in the placental transport functions observed in type-I diabetes. Clearly a variety of mechanisms lead to similar outcomes and additional information on the control of placental nutrient transport function and its role in regulating fetal growth are needed.

**GDM IS ASSOCIATED WITH MARKED ALTERATIONS IN PLACENTAL GENE EXPRESSION**

Fetal overgrowth in GDM has been associated with an increased risk to develop obesity and type-2 diabetes in later life [23]. Maternal anthropometric factors together with the maternal carbohydrate metabolism have been highly correlated with fetal growth and body composition [24]. However, these factors can explain only part of the fetal fat mass variance, suggesting that other mechanisms may be involved [24] such as altered placental function. The effect of GDM on placental gene expression has not been widely studied. Radaelli reported studies in which the gene expression profile of term placenta from women with normal glucose tolerance and with GDM was investigated using oligonucleotide microarray analysis [25]. Twenty percent of the significantly modified genes identified in GDM placentas were related to inflammatory response and extracellular matrix, including TNF-α, Leptin, IL-1, Endothelin-1 and Angiotensin-2 genes which were significantly up-regulated. Other significantly regulated genes in the GDM placenta were related to lipid metabolism primarily encoding rate-limiting enzymes for fatty acid transport, triglycerides and cholesterol synthesis. Based on these data, it is suggested that there is a link between insulin resistance during pregnancy and the inflammatory response originating at the level of placental gene transcription while the increase in placental lipid biosynthetic pathways has functional significance for fetal fat accretion as a step towards enhanced placental transfer of FFA [25].

**THE ROLE OF BRIEF PERIODS OF METABOLIC PERTURBATIONS IN EARLY PREGNANCY FOR FETAL OVERGROWTH**

Even in the strictly controlled pregnant woman with type-I diabetes, glucose control may be sub-optimal early in pregnancy. Indeed, maternal first trimester HbA1c correlates strongly to birth weight [26]. However, the mechanisms underlying this association are unknown. Ericsson discussed a series of experiments in the pregnant rat designed to test the hypothesis that brief periods of hyperglycemia early in pregnancy may affect placental transport functions for the remainder of gestation, resulting in fetal overgrowth [27]. Transient moderate hyperglycemia in early pregnancy increased placental and fetal weights at term. The in vivo placental System A activity was significantly decreased whereas placental glucose transport was unaltered at term. In concert with this data, placental protein expression of the System A isoform SNAT 2 was decreased and placental GLUT 1 and 3 expression unchanged. These studies demonstrate that brief periods of metabolic perturbations early in pregnancy can alter placental transport functions and placental and fetal growth for the duration of pregnancy. The underlying mechanisms remain to be established but may be related to the increased placental size or
an enhanced transport of key nutrients (such as lipids or essential amino acids) not assessed in the study.

**STUDY POPULATIONS NEED TO BE BETTER CHARACTERIZED IN FUTURE STUDIES**

The placenta undergoes a variety of structural [28] and functional [22] changes in maternal diabetes. As pointed out by Desoye, it is unclear whether these changes are the primary response of the placenta to the adverse diabetic environment in the mother, or secondary to alterations in the fetus in the wake of maternal diabetes. These changes may protect the fetus from maldevelopment, or may contribute to, or even promote, the diabetes-associated increased incidence of fetal morbidity or mortality. A clear answer to these questions is yet pending, because studies do not report on the many variables that may have an impact on the placenta studied at term in diabetic pregnancy. These variables include the quality of metabolic (glycemic) control of mother and fetus, the type of diabetes (type-I/-II vs gestational diabetes), the modality of treatment (oral hypoglycaemic agents, insulin, diet), pre-existing vascular complications in the mother, maternal obesity and fetal outcome in terms of oxygenation. The influence of some of these factors may vary with time e.g., the onset of insulin therapy in gestational diabetics may influence the placental changes as may the quality of maternal metabolic control not only in the third trimester, but also in earlier periods of gestation.

**REFERENCES**


**CONCLUSIONS, CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS FOR RESEARCH**

In a concluding remark Sibley emphasized that understanding the role of the placenta in fetal overgrowth, either in the context of diabetes or otherwise, has received less attention than in relation to IUGR. However, this workshop highlighted the fact that, on the one hand, diabetic macrosomia cannot be explained entirely by poor maternal glycemic control and, on the other, that changes in placental nutrient supply capacity might contribute to fetal overgrowth.

The hypothesis has been advanced recently that improved diagnosis and, eventually, treatment of IUGR might arise from understanding, and being able to measure in vivo, the placental phenotypes associated with the condition [29]. The same hypothesis might equally apply to fetal overgrowth. The placental phenotypes that should be considered include utero-placental and umbilical blood flows, placental exchange barrier dimensions (particularly surface area and barrier thickness) and the expression and activity of placental transporters. As discussed, these phenotypes should be assessed in relation to strict definitions of diabetes, or of macrosomia in the absence of diabetes, with as many as possible being measured on individual placentas. Such work needs to continue alongside the development of new techniques for assessing key aspects of placental nutrient supply capacity in vivo [29].


