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The Placenta and Gestational Diabetes Mellitus

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Abstract By its location between maternal and fetal bloodstreams the human placenta not only handles the materno-fetal transport of nutrients and gases, but may also be exposed to intrauterine conditions adversely affecting placental and fetal development. Such adverse conditions exist in pregnancies complicated by gestational diabetes mellitus (GDM), and have been associated with alterations in placental anatomy and physiology. These alterations are mainly based on changes on the micro-anatomical and/or even molecular level including aberrant villous vascularization, a disbalance of vasoactive molecules, and enhanced oxidative stress. The consequence thereof may be impaired fetal oxygenation and changes in transplacental nutrient supply. Although transplacental glucose flux is flow limited and independent of glucose transporter availability, transport of essential and nonessential amino acids and expression of genes involved in lipid transport and metabolism are significantly affected by GDM.

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Introduction

The placenta is a transiently established organ that operates exclusively for the time of pregnancy. Thereby, it acts as a natural barrier between the maternal and fetal blood circulations and fulfills a wide range of endocrine and transport functions. The location between the two bloodstreams makes the placenta not only a crucial regulator of fetal nutrition, gas exchange, and maternal immune tolerance, but makes this fetal organ also a target for maternal and/or fetal metabolic alterations associated with pregnancy pathologies. One of these pregnancy pathologies is gestational diabetes mellitus (GDM), which develops in 3% to 5% of pregnant women [1], but these figures are on the rise and may reach up to 20% in selected populations, mostly of obese women. Neonates of pregnancies complicated by GDM tend to have a higher proportion of fat mass, and a higher birth weight and ponderal index (an indicator of fetal growth) [2, 3]. Moreover, GDM is associated with increased perinatal morbidity and mortality [4]. The Developmental Origin of Health and Adult Disease (DOHAD) paradigm predicts long-term consequences for the offspring born to a GDM pregnancy resulting in endothelial/vascular dysfunction associated with obesity, hypertension, type 2 diabetes mellitus (T2D), and metabolic syndrome. Some of these pregnancy complications may arise from altered placental development, and thus aberrant morphology and transport capacities. The pathophysiology

of GDM is not fully understood, but classical characteristics of T2D and the metabolic syndrome, such as reduced maternal insulin sensitivity, hyperglycemia, and hyperlipidemia, have also been described for GDM. Thus, GDM may be considered as a prediabetic state and was discussed as transiently unmasking T2D and the metabolic syndrome [5, 6]. Depending on the onset of GDM, the diabetic environment may alter either placenta development and/or its function. In this review we focus on GDM-dependent effects on placental macro- and micro-anatomy and its associated changes in placental function.

Onset of Gestational Diabetes and Effects on Placenta Development

In the second half of gestation, when GDM has already developed or is about to become clinically manifest, placental villi undergo extensive angiogenesis and vascularization. In this period the placenta, and in particular the villous vasculature, may adapt to the diabetic environment. GDM has been associated with impaired placental development showing villous immaturity or alterations in villous branching [7–10]. Both villous maturation and branching are considered to complete during the second half of gestation, suggesting an earlier onset of GDM or its subclinical pathophysiologic condition. Among all pregnancies complicated by GDM, only around 30% to 40% of women had the disorder diagnosed during early pregnancy (ie, before gestational week 20) [11, 12]. The main problem in this context is to clearly differentiate between early-onset GDM and undiagnosed overt diabetes, which may not be detected in pregnant women until their first antenatal visit. However, it is obvious that early pathophysiologic derangements resulting in clinically manifest GDM later in pregnancy will have long-term effects by affecting placental morphology, whereas late onset of GDM may have short-term effects mainly on placental function.

Effect of GDM on Placental Anatomy

Depending on the degree of diabetic control during gestation, the placenta may be exposed to abnormal glucose metabolism and, thus, its development may be adversely affected. In general, the placenta of poorly controlled diabetic women is enlarged, thick, and plethoric. These circumstances may account for significantly higher placental weights and significantly lower fetal-to-placental weight ratios in GDM pregnancies [2, 7, 13–16]. Dietary modification during GDM pregnancies have been implicated to be partly responsible for the observed increase in placental size, since a significant inverse relationship between placental weight and protein intake was detected [17]. Besides increased placental weight, further in-depth macroscopic examination of GDM placentas revealed no significant anatomical difference when compared with normal placentas. Determination of the eccentricity index, which indicates the placental shape ranging from circular to elliptical, showed no significant difference between GDM placentas and controls [18]. Moreover, no significant differences were detected for the cord centrality index and the cord coiling index, which describe the umbilical cord insertion from the chorionic plate margin and the coiling direction and numbers of coils [18]. Thus, abnormalities may be detected on a microscopic level.

Calderon et al. [19] compared placentas from pregnancies complicated by mild hyperglycemia and GDM with healthy controls. Morphometric assessment included criteria such as area and number of terminal villi and respective villous vessels. No significant difference was observed regarding size, number of placental terminal villi, and villous total area between GDM and control groups. However, the glycemic gestational mean and the area of villous vessels in GDM placentas were directly correlated [19]. Moreover, histologic studies revealed apparent fibrinoid necrosis and vascular lesions such as chorangiosis more frequently in placentas from pregnancies complicated by GDM when compared with normal placentas [7–9]. Another histologic study compared placental tissue from patients with poorly controlled GDM with cases of overt diabetes and healthy controls [20]. Although the number of cases per group was low, the observed histologic changes under diabetic conditions were manifold. Poorly controlled GDM placentas showed villous edema, fibrin deposits in the syncytiotrophoblast, and marked hyperplasia of the cytotrophoblast [20]. These changes were less distinct in placentas from overt diabetic patients and not observed in normal cases. Together these observations suggest that the degree of glucose tolerance not only influences placental weight (ratio) but also its morphology at the micro-anatomical level.

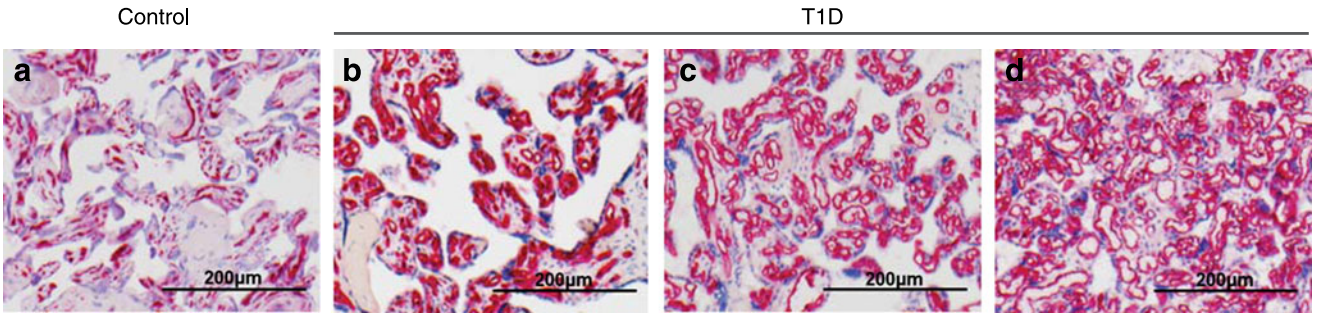
Angiogenesis and Villous Vasculature in the GDM Placenta

Placental angiogenesis is regulated by a widespread panel of angiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2, peroxisome proliferator-activated receptor (PPAR)-γ, or placental growth factor [21–23]. Most of these growth factors seem to act more potently on the microvascular compared with the macrovascular placental endothelium [24]. In general, the placental microvasculature seems more reactive compared with the microvasculature. This is substantiated by a

higher expression of homeobox genes such as *HLX1*, *TLX1*, and *TLX2* in placental microvascular than in macrovascular endothelial cells [25, 26]. Because any disbalance of angiogenic factors in the placental microenvironment may lead to aberrant villous vascularization, efforts have been undertaken to identify putative deregulated angiogenic factors in GDM placentas. Analysis of maternal and cord plasma levels of VEGF revealed no significant differences but tended to be lower in GDM cases. However, correlation analysis showed a highly significant negative correlation between VEGF levels and the villous immaturity [9]. FGF-2 mRNA expression was increased, whereas its receptor FGF-2R was downregulated in GDM placentas [27]. Upregulated FGF-2 mRNA expression was in line with protein data showing significantly increased FGF-2 levels in cord blood of GDM cases [28]. In addition to FGF-2, PPAR-γ also seems to be deregulated in GDM placentas, since less mRNA and protein were found compared with controls [29].

Some growth factors may be involved in mobilization and recruitment of endothelial progenitor cells. However, polychromatic flow cytometry of cord blood samples from GDM and normal cases showed no difference in the number of endothelial colony-forming cells (ie, a subset of progenitor cells with vessel-forming capacity) [30•]. Nevertheless, circulating hematopoietic progenitor cells, which were suggested to have strong angiogenesis-facilitating functions [31], were significantly reduced in cord blood of GDM pregnancies [30•]. Dysregulated angiogenic factors and a restricted capacity of progenitor cells may contribute to aberrant vascularization, including aberrations in branching and longitudinal growth of capillaries (Fig. 1). Three-dimensional visualization studies of the vascular topology showed no significant difference in the basic arrangement of villous capillaries in normal and GDM placentas [32]. The proportion of the most frequent and simplest forms (ie, U-shaped capillary loops) was not significantly different between GDM and normal. However, although the proportion of capillary loops consisting of three longitudinally arranged branches was significantly lower, the mean number of transversal interconnections between longitudinal branches was significantly higher in the capillary bed of GDM placentas [32]. The higher mean number of transversal interconnections per villus was suggested to evidence enhanced capillary sprouting in diabetic placentas during late pregnancy, contributing to higher total length, volume, and surface areas of villous capillaries found in diabetic placentas [32]. In contrast, another stereological study using perfusion-fixed placenta tissue failed to detect significant differences in the combined length of villous vessels in GDM placentas when compared with normal [33].

In addition to length and surface area of villous vessels, placental vascular permeability is another pivotal parameter in materno-fetal nutrient supply. In GDM placentas both adherence and tight junctional proteins were shown to be



Subjects, characteristics:

	T1D		
	b	c	d
Gestational week	40	40	38
Fetal weight (g)	2530	3020	3580
Placental weight (g)	580	630	990
Cord blood insulin (µU/mL)	16.6	23.7	112.0

Fig. 1 Hypervascularization in term placentas of diabetic pregnancies. Morphologic changes in the placenta that result from gestational diabetes mellitus are heterogeneous in their degree of severity and tissue areas that are affected, but they are similar in nature to the changes seen in type 1 diabetes (T1D) pregnancies. Here, tissue sections from term placentas after normal (control, **a**) and T1D pregnancy (**b–d**) were stained for the endothelial cell marker CD34 to highlight the vasculature. It can be clearly seen that the vasculature in placentas from T1D pregnancies is characterized by more vascular cross-sections per villus, likely the result from more vessel branching. This morphologic feature becomes more obvious from **b** to **d** and seems to correlate with cord blood insulin levels

significantly reduced, suggesting an impaired barrier function [33]. Whether this contributes to placental lesions associated with GDM, such as edema formation, remains to be studied.

Fetal Placental Blood Flow and Oxygenation in GDM

An essential question that may arise in this context is to what extent the micro-anatomical aberrations observed in GDM placentas affect placental functions (ie, supply of oxygen and nutrition). Although fetal placental hemodynamics were almost normal in most cases of GDM [34, 35], fetal oxygenation was impaired. This was demonstrated by a Doppler velocimetry study, which showed that only 5% of pregnancies complicated by GDM had abnormal umbilical artery flow [36]. However, oxygen saturation and oxygen content were significantly decreased in the umbilical vein of GDM cases [7]. This is in line with significantly higher cord plasma erythropoietin (EPO) levels in GDM pregnancies [9]. EPO does not cross the placental barrier [37] and, thus, elevated cord plasma levels are indicative for fetal hypoxia. Increased EPO levels as a result of fetal hypoxia lead to enhanced erythropoiesis, which can be detected by increased nucleated red blood cells (NRBCs). Besides increased EPO cord plasma levels, also the number of NRBCs was significantly increased in GDM pregnancies [8, 9]. Fetal hypoxia may be explained by an imbalance in oxygen demand and supply. Maternal supply across the placenta may be impaired because of elevated maternal hemoglobin A_{1c}, which has a higher affinity for oxygen than nonglycosylated hemoglobin, by increased collagen synthesis in the placental stroma and moderate thickening of the basement membrane of the syncytiotrophoblast, which has been described for GDM placentas [20, 38]. Fetal oxygen demand may be elevated in the wake of fetal hyperinsulinemia and may result in more active aerobic metabolism. In this context, an increased placental size and surface area of exchange, which have been reported in GDM, may be seen as an attempt to counterbalance fetal hypoxia.

Uteroplacental Blood Flow in GDM Pregnancies

Fetal oxygenation not only depends on proper development of placental villi and in particular villous vessels, but is also determined by uteroplacental blood flow. Interestingly, abnormal uterine artery blood flow velocity was observed in only 16% of pregnancies complicated by GDM [36]. This observation is in contrast to data obtained from studies with animal models. Ultrasound biomicroscopy in a GDM mouse model, which is heterozygous for a leptin receptor mutation, showed impaired uteroplacental perfusion [39]. This fits well with immunohistochemistry studies of implantation sites in pregnant mice, showing shallower trophoblast invasion in the GDM mouse model when compared with control mice [40].

Oxidative Stress and Endothelial Dysfunction in the GDM Placenta

Fetal placental blood flow was suggested to be modulated by the local release of endothelium-derived vasoactive molecules, such as nitric oxide (NO) and eicosanoids [41, 42]. NO, a mediator of vasodilatation, arises from the conversion of L-arginine into L-citrulline—a reaction catalyzed in the normal placenta by endothelial nitric oxide synthase (eNOS). GDM conditions may affect placental eNOS, since its expression and activity was significantly increased in human umbilical vein endothelial cells (HUVECs) isolated from GDM placentas [43]. Moreover, inducible NO synthase, which is not expressed in normal placenta, was detected in GDM placentas [44]. These observations suggest that increased NOS expression and activity contribute to the increased NO synthesis observed in human placental veins and arteries, and in HUVECs from GDM pregnancies [45–48]. Increased NO synthesis seems to be in contrast to reduced endothelium-dependent vasodilatation observed in patients with diabetes mellitus [49, 50]. However, reduced vasodilatation was discussed to be a consequence of lower NO bioavailability due to its inactivation by reactive oxygen species (ROS) [51, 52•]. A disbalance in placental ROS production and antioxidant defenses may end up in GDM-associated oxidative stress [53••]. Measurement of oxidative stress markers, such as the release of 8-isoprostane and the activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, clearly indicated the presence of oxidative stress in the GDM placenta [54]. Enhanced ROS production and lipid peroxidation may affect the physiology of the placental vasculature. This assumption is substantiated by the observation that 8-isoprostane, which arises from a free-radical-catalyzed peroxidation of arachidonic acid, is able to induce vasoconstriction in the placenta [55]. The placenta may react on oxidative stress by upregulation of antioxidant enzymes, such as glutathione reductase and catalase, both of which were significantly upregulated in GDM placentas when compared with healthy controls [56]. Thus, the increased antioxidant gene expression in GDM placentas may be interpreted as an adaption to intrauterine oxidative stress. Inadequate adaptation to enhanced oxidative stress, however, may give rise to inflammatory conditions, since oxidative stress has been associated with inflammation [57].

Inflammation in GDM Placenta

Cytokines, mainly produced by cells of the immune system and adipose tissue, were also shown to be synthesized in human placenta [58]. Thus, placental cytokines were suggested to contribute to low-grade inflammatory conditions during the third trimester of gestation. Moreover, increased levels of circulating cytokines were discussed to enhance these inflammatory conditions in diabetic pregnancies. Gene expression profiling of GDM placentas and control subjects showed that genes involved in inflammatory responses and endothelial reorganization were the two main functional clusters changed under GDM conditions [2]. The two major inflammatory cytokines interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) were increased by 200% and 58%, respectively, in placental tissues obtained from pregnancies complicated by GDM [59]. The enhanced placental cytokine release may be associated with glucose concentration, since placental explants from GDM pregnancies released significantly higher levels of TNF-α in response to conditions of high glucose [60]. Signs of placental inflammation also include an increase in the number of CD14+/CD68+ macrophages in placental villi [61] as found in maternal obesity. It remains to be demonstrated whether this is also present in GDM, which shares several features with obesity.

Transport of Nutrients in the GDM Placenta

Lipids

Cytokines regulate the expression of key players of lipid metabolism. In vitro studies showed that high levels of IL-6 caused fatty acid accumulation in primary term trophoblasts [62]. Interestingly, well-described components in placental fatty acid transport and storage, such as adipophilin, fatty acid transport proteins, or the activity of lipoprotein lipase (LPL), were not changed by increased IL-6 levels [62]. This is in line with another study demonstrating no difference in LPL activity and protein expression in microvillus plasma membrane preparations from GDM placentas compared with control cases [63]. However, endothelial lipase (EL), a close relative of LPL, was recently shown to be significantly upregulated in placentas from obese women with GDM [64•], but was not upregulated in placentas from lean GDM cases. This suggests that metabolic inflammation together with diabetic conditions accounted for dysregulation of EL in pregnancies complicated by obesity and GDM. Cell culture experiments with placental endothelial cells, the prevalent source of placental EL expression [65], implicated TNF-α and leptin as putative key regulators. Both inflammatory cytokines are often elevated in GDM and may also contribute to upregulation of placental phospholipase A2 (PLA2) family members PLA2G2 and PLA2G5 [66]. Activation of these lipases may lead to the generation and accumulation of essential omega-3 fatty acids in placental tissue of GDM pregnancies [66]. In general, the diabetic environment may induce upregulation of placental genes involved in lipid pathways. This was shown by microarray analysis of placental tissue from pregnancies complicated by GDM and type 1 diabetes mellitus (T1DM), respectively. Hierarchical clustering revealed distinct categories of differentially expressed genes involved in lipid transport and activation, lipid metabolism, glycogen metabolism, and hexosamine pathways [67••]. Interestingly, there was a clear dichotomy in activated genes between GDM and T1DM. Although hexosamine pathways and glycosylation reactions were upregulated in T1DM placentas, pathways for triglyceride and cholesterol biosynthesis were selectively enhanced in GDM placentas [67••]. In this study GDM placentas were obtained from obese women, suggesting that maternal lipid fluxes contribute to the observed dysregulation of placental genes for lipid metabolism.

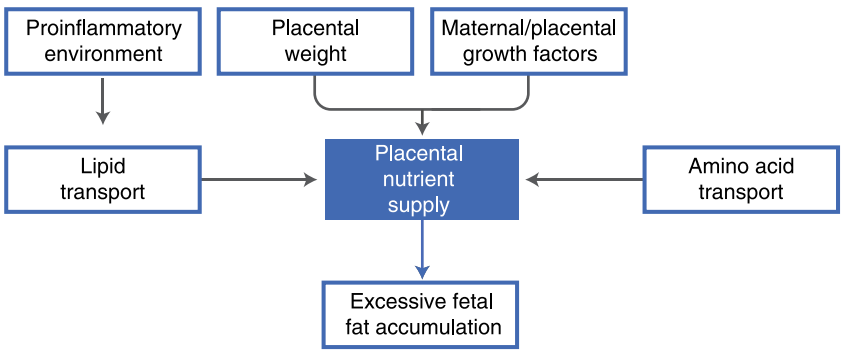


Fig. 2 Many factors contribute to the increased fetal nutrient supply: elevated expression of amino acid and lipid transport molecules in the placenta promotes materno-fetal nutrient transfer. Moreover, the total placental weight is elevated to which increased levels of maternal and placental growth factors may contribute. Higher placental weight will also enhance the total transport capacity of the placenta. The resulting augmented nutrient supply will contribute to excessive fetal fat accumulation in GDM. Maternal and placental low-grade inflammation, which are both exacerbated in obesity, may further contribute to placental and fetal changes

Amino Acids

Besides changes in placental lipid handling, amino acid transport was also shown to be altered in GDM. Analysis of amino acid concentrations in cord blood revealed a significant increase in a number of essential and nonessential amino acids in umbilical venous and arterial plasma of well-controlled GDM pregnancies [13]. Importantly, the concentrations of the respective amino acids were not altered in the maternal circulation [13], substantiating that placental amino acid exchange or metabolism is changed under conditions of GDM. The transport capacity for neutral amino acids by system A was increased in pregnancies complicated by GDM or type 1 diabetes [68]. Another study also analyzed system A amino acid transporter activities in placental microvillus membrane vesicles from diabetic women with macrosomic or appropriately grown babies and compared them with preparations from normal cases [69]. These data indicated that system A transporter activity was lower in placentas from diabetic pregnancies with macrosomic babies. Kinetic data indicated that the reduced transporter activity is due to a reduced number of transporters. However, these data should be interpreted with some caution, since amino acid transporters in the syncytiotrophoblast have overlapping substrate specificity, and one transporter may compensate for another.

Glucose

Fetal glucose production is minimal [70]. Thus, the fetus almost completely depends on maternal glucose supply. The transplacental glucose flux follows a maternal-to-fetal concentration gradient and is handled by three transporter isoforms of the classic glucose carrier (GLUTs) family. Although GLUT1, the major player among the placental GLUTs, is regulated by ambient glucose concentrations [71], transplacental glucose flux was suggested to be flow-limited, but not regulated by transporter availability (ie, transporter localization or expression level). This assumption is based on 1) the high capacity of the placental glucose transport system, 2) flow regulation of transplacental glucose transport [72], and 3) observations in placenta perfusion studies, showing no difference in glucose flux between placentas from GDM and normal pregnancies [73, 74] at a fixed maternal-to-fetal glucose gradient. Collectively, all available evidence supports the notion that the placenta is not involved in enhanced maternal-to-fetal glucose transfer in GDM and that the maternal-to-fetal concentration gradient is the key driver. Uterine-placental and umbilical-placental blood flow changes may contribute.

Higher placental weight as well as increased placental nutrient transport will contribute to the enhanced fetal fat accumulation in GDM. Both GDM and obesity are characterized by a proinflammatory environment associated with higher levels of inflammatory cytokines. These may alter expression of genes involved in lipid pathways and, thus, contribute to augmented placental lipid transport function (Fig. 2).

Conclusions and Directions for Future Research

Although past efforts have strongly focused on placental glucose handling, which has been thought to underlay fetal glucose oversupply in GDM, more research is needed to identify potential changes in amino acid and lipid transport across GDM placentas. Given the multitude of transporter molecules, investigations will have to measure transplacental transport of individual amino acids and more complex lipids across the GDM and normal placenta. The technique of choice would be the placental perfusion model, which integrates transport, metabolism, and structural alterations, and thus comes close to the complex in vivo situation.

It is not difficult to predict an increase in GDM incidence given the continuous rise in maternal obesity prevalence. The low-grade inflammation associated with obesity and resulting elevation of circulating and locally produced proinflammatory cytokines will further contribute to placental changes, which may not become manifest with GDM in lean mothers [75•].

An exciting new avenue of research will be to identify the consequences of maternal inflammation, associated with obesity or GDM or both, not only for the placenta, but also for the fetus and offspring. There is mounting evidence that the intrauterine processes have a long-lasting effect on the offspring not only in laboratory animals but also in humans. These may differ in male and female offspring and translate to differential disease susceptibility later in life. Gender differences in placental gene expression and function may contribute to these effects. The intrauterine programming will likely involve changes in the placental and, presumably, also fetal epigenome, which will become a hot topic in GDM research.

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- • Of importance
- •• Of major importance

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