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## The Placenta in a Diabetic Pregnancy

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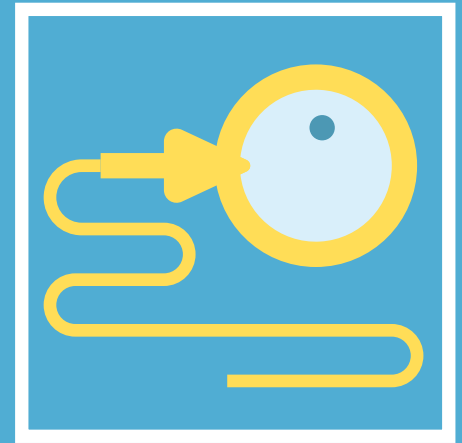
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## BACK TO THE FUTURE

# The Placenta in a Diabetic Pregnancy

U. Hiden, G. Desoye

Diabetes in pregnancy is associated with a derangement of hormones, cytokines, metabolites and growth factors in the maternal and foetal compartment. These may influence placental growth and development that are tightly regulated in time and space. The distinct effects of the diabetic environment depend on the time in gestation when diabetic insult occurs. Because of its establishment in the second half of gestation, gestational diabetes mellitus will influence placental processes in late gestation, whereas pre-gestational diabetes such as Type-I and Type-II diabetes may also affect processes in the first trimester.

Altered placental function in pre-gestational diabetes may include changes in invasion ultimately leading to an enhanced risk of early pregnancy loss, growth restriction and pre-eclampsia, as well as a long-term stimulatory effect on placental growth leading to placentomegaly, which is frequently associated with diabetic pregnancies. Diabetes later in gestation affects vascularisation, storage of maternal nutrients in particular glycogen and lipids and may also enhance oxygen transfer. It is still unresolved if the placental alterations in diabetes ultimately contribute to or prevent the foetal phenotype often seen in diabetes i.e., excessive fetal fat accretion.

**Key words:** placenta, vascularisation, invasion, insulin, lipids

**Die Plazenta bei Diabetes.** Mütterlicher Diabetes führt zu einer Deregulation einer Reihe von Hormonen, Zytokinen, Metaboliten und Wachstumsfaktoren in Mutter und Fetus. Diese Veränderungen können die Entwicklung der Plazenta beeinflussen. Die Auswirkung von Diabetes in der Schwangerschaft hängt vom Zeitpunkt des Auftretens der Krankheit und somit vom Typ des Diabetes ab. Schwangerschaftsdiabetes tritt erst im dritten Trimenon auf und kann deshalb Entwicklung und Funktion der Plazenta nur in diesem Schwangerschaftsabschnitt beeinflussen. Hingegen können bei Diabetes, der bereits vor der Schwangerschaft bestanden hat, schon frühe Prozesse in der Plazentaentwicklung gestört werden.

Mütterlicher Typ-1- und Typ-2-Diabetes ist beispielsweise mit einem erhöhten Risiko von Fehlgeburten, fetaler Wachstumsrestriktion und Präeklampsie verbunden, was eine gestörte Invasion der Plazenta in den Uterus vermuten lässt. Weiters führt ein gefördertes Plazentawachstum häufig zu Plazentomegalie. Bei Schwangerschaftsdiabetes wird vor allem eine veränderte Vaskularisierung der Plazenta beobachtet, um den Sauerstofftransport zu steigern. Darüber hinaus werden vermehrt Nährstoffe gespeichert, wie z. B. Glukose als Glykogen als auch Lipide. Ob die Veränderungen in einer diabetischen Schwangerschaft die häufig auftretende fetale Makrosomie fördern oder vermindern bleibt jedoch spekulativ. **J Reproduktionsmed Endokrinol 2010; 7 (1): 27–33.**

**Schlüsselwörter:** Plazenta, Vaskularisierung, Invasion, Insulin, Lipide

## ■ Introduction

The placenta is a foetal organ situated between mother and foetus. It is essential for foetal growth and development. In addition to serving as a conduit for maternal fuels destined to nourish the growing foetus it fulfils a wide spectrum of other functions including the synthesis of various hormones and growth factors, detoxification of maternal xenobiotics, immunologic barrier and dissipation of thermic energy resulting from foetal metabolism. Owing to its position the placenta is exposed to regulatory influences of mother and foetus albeit at different surfaces, i.e. the microvillous syncytiotrophoblast membrane as well as the basal syncytiotrophoblast membrane and the endothelial cells.

Maternal diabetes is associated with concentration changes of various hormones, cytokines and metabolites in the maternal as well as foetal circulation. Hence, these diabetes-associated changes are likely to affect the placenta, because

receptors, transporters and enzymes, the primary targets of circulating molecules, are expressed, often asymmetrically, on both placental surfaces. In addition to differential effects of the diabetic environment of mother and foetus, the distinct processes affected by maternal diabetes also critically depend on the time period in gestation when the diabetic insult occurs [1].

The present review will discuss some aspects of placenta alterations in maternal diabetes mellitus. Other aspects are comprehensively reviewed elsewhere [1–5]. For a detailed account of diabetes in pregnancy the reader is referred to recently published books [6, 7].

## ■ The Placenta in Early Diabetic Pregnancy

Pre-gestational i.e., Type-I and Type-II (T1DM, T2DM) diabetes is likely to alter the early processes of placentation with a potential to modify long-term placental development. Placental develop-

ment starts with the implantation of the blastocyst into the endometrial surface. Subsequently, the placental structure continuously develops by a series of differentiation and proliferation processes of trophoblast cells that eventually lead to placental villi of varying degree of maturation [8].

Most villi freely float in the intervillous space. At the tips of some villi cytotrophoblasts accumulate and invade into the decidua. These villi physically anchor the placenta and, hence, the foetus in the maternal endometrium, and are formed predominantly in the first trimester of pregnancy as a result of proliferation, differentiation and invasion of trophoblasts. A proportion of invasive extravillous cytotrophoblasts also invades the endometrial spiral arteries and remodels them into low resistance arteries. This increases the utero-placental blood flow into the intervillous space, thus ensuring adequate maternal nutrient supply to the foetus [9]. Since placental anchoring and establishment of maternal

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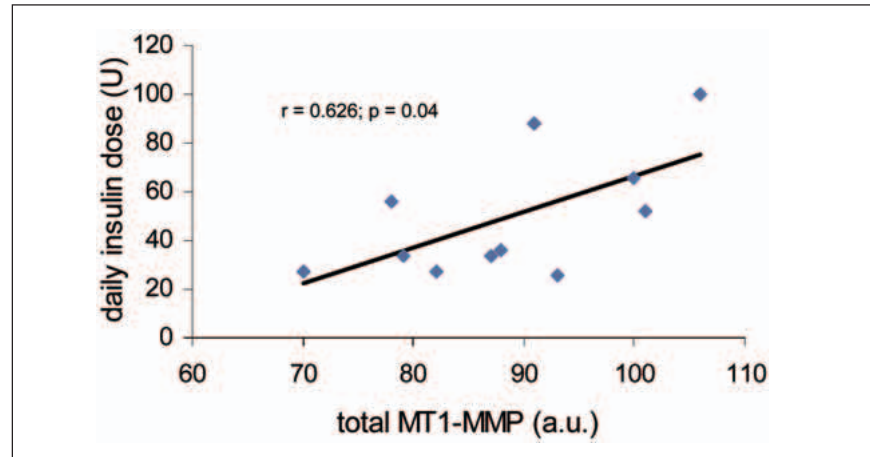
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blood supply are key processes in placental development, their dysregulation is associated with pregnancy diseases: Shallow invasion has been implicated in intra-uterine growth restriction (IUGR) [10] and pre-eclampsia [11]. In contrast, profuse invasion results in abnormally deep utero-placental adhesion such as seen in placenta accreta, increta and percreta.

It is noteworthy that these pregnancy pathologies related to placental dysfunction i.e., IUGR, pre-eclampsia as well as spontaneous abortions, occur more frequently when mothers are diabetic [12, 13]. This strongly argues for an influence of the maternal diabetic environment on trophoblast invasion. Leptin [14] and the oxidative stress-associated isoprostanes [15] are candidate causative factors that may lead to such diabetes-associated invasion defects. On the other hand insulin may stimulate invasion [16] by transcriptional upregulation and activation of the matrix-metalloproteinase MT1-MMP (MMP14) [17]. Invasion regulation is a complex process involving a range of invasion inhibiting and invasion promoting factors. Collectively, the diabetic environment appears to shift the balance between control switches towards invasion inhibition.

Proliferation of the cytotrophoblast is another key process for placental development. Indirect evidence suggests compromised placental development early in diabetic pregnancy because maternal serum levels of human placental lactogen are lower in the first trimester, whereas those of placental protein 14, an endometrial hormone, are not [18]. Since placental lactogen is a trophoblast-specific hormone, and because its synthesis is mainly determined by trophoblast mass, by inference, trophoblast proliferation is impaired in the first trimester. If this were true then it could explain the retarded growth of some foetuses early in these pregnancies (early foetal growth delay) [19]. The distinct factors in the diabetic environment that have the detrimental effect on placental i.e., trophoblast, growth early in gestation are unclear, but hyperglycaemia may be one of these [20].

Since placentomegaly at the end of gestation is a distinct feature of many diabetic pregnancies one has to postulate a



**Figure 1:** Total placental MT1-MMP protein expression (given as arbitrary units, a.u.) correlates with daily insulin dose (units) in first trimester T1DM. According to data from [17].

period of accelerated placental growth in these pregnancies, similar to placental growth in diabetic rats [21]. This may also lead to or parallel the biphasic growth pattern of the foetus in T1DM pregnancies [22].

In the first trimester of pregnancy not only trophoblast differentiation and invasion, which ultimately optimize materno-placental nutrient transport and uptake, as well as trophoblast proliferation occur as key processes, but also the fetoplacental surface – the placental vessels – becomes established [23, 24]. Placental vasculogenesis and angiogenesis are regulated by various growth factors and cytokines. Among the angiogenic factors vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2), angiopoietins, placental growth factor (PlGF), tumor necrosis factor (TNFA), interleukin 8 (IL-8) and insulin-like growth factors 1 and 2 (IGF1, IGF2) have been identified, of which TNFA can as well act in an angiostatic manner [24]. Most of them are altered in maternal diabetes mellitus [25–31]. The effect of these factors on the early processes in angiogenesis is unclear and awaits investigation.

Because of the limited studies little is known about the placental changes in the first trimester of gestation. Even a full analysis of the maternal diabetic environment early in gestation is pending. Besides hyperglycaemia and hyperinsulinemia the diabetic environment in the mother in the first trimester is characterized by reduced IGF1 [32, 33] levels. No published data about serum TNFA levels of T1DM women in the

first trimester are available, but like insulin [34]. TNFA is elevated in non-pregnant T1DM patients [35]. However, likely a variety of other growth factors and cytokines may be altered that are yet to be determined.

The placental amount of the matrix metalloproteinase MT1-MMP, a major protease involved in tissue remodelling processes associated with invasion, angiogenesis and proliferation, is elevated in the first trimester of T1DM [17]. Besides its expression also the conversion of the inactive zymogen into the active MT1-MMP is altered. In normal placentae, active MT1-MMP decreases in the late first trimester, whereas in T1DM the levels remain high. In isolated first trimester trophoblasts insulin and TNFA up-regulate MT1-MMP expression. In addition to its transcriptional regulation also MT1-MMP enzyme activation is increased. The insulin effect is not only found *in vitro* but, indirectly, also *in vivo*. The average daily insulin dose with which T1DM mothers were treated correlates with MT1-MMP expression in these placentae (Fig. 1). As pro-MT1-MMP is cleaved and activated by furin, which is under transcriptional control of the hypoxia-sensitive transcription factor HIF-1, hypoxic conditions in the villous placental structure in diabetes may be hypothesized. Up-regulation of metalloproteinase expression by TNFA is not only restricted to MT1-MMP and has further be shown for MMP15 [36]. Higher expression and activation of trophoblast proteases indicates dysregulation of invasion control systems and demonstrates the sensitivity of placental development towards differential ex-



**Table 1:** Maternal, foetal and placental levels of insulin, IGF1 and IGF2 in maternal T1DM or GDM. The arrows indicate an up (↑) or down (↓) regulation, NC indicates no change.

	Insulin		IGF1		IGF2	
	T1DM	GDM	T1DM	GDM	T1DM	GDM
Maternal circulation	↑ [44]	↑ [44] insulin treated NC [44] diet ↑ [46]	↓ [48, 49]	↑ [53]	NC [49]	NC [49, 53]
Placental expression				↓ (mRNA) <sup>94</sup>	↑ [31]	↑ [31]
Foetal circulation	↑ [44, 45]	↑ [44, 47]	↑ [48–52]		↑ [30, 31, 51]	↑ [31]

pression of growth factors and cytokines.

It has been known for long that the maternal diabetic environment may impair embryonic development already before the placenta has developed and the maternal-fetal nutrient transport systems have been established. Experiments in rodents clearly demonstrated that teratogenesis in maternal pre-gestational diabetes is a multifactorial event that affects the preimplantation [37, 38], peri-implantation [39, 40] and the postimplantation phase [41] of the embryonic development. This is reflected by the different occurrence of fetal congenital abnormalities in women with preconceptional vs. postconceptional care, results which underscore the importance of good glycaemic control already prior to pregnancy [42]. A detailed discussion of diabetes-associated teratogenesis is outside the scope of this review and has been comprehensively reviewed elsewhere [42, 43].

### ■ The Placenta in the Third Trimester of a Diabetic Pregnancy

Like in the first trimester the circulating maternal and foetal concentrations of cytokines, hormones and growth factors are changed in diabetes also in the last period of gestation. They all may have an impact on the placenta via the microvillous syncytiotrophoblast membrane (maternal factors) or via the endothelium or the basal syncytiotrophoblast membrane or both (foetal factors). The effect on the placental endothelium may be-

come more prominent, because of the higher degree of vascularization at this stage. The diabetic environment may in turn change placental production of cytokines, hormones and growth factors. These may act locally in an autocrine or paracrine manner or, along with metabolites, may be secreted into both the maternal and foetal circulation and thus affect mother and foetus alike (Tab. 1).

Various studies describe structural and functional alterations of the placenta in maternal diabetes at term of gestation. Although these changes do not occur in every diabetic placenta, they appear independent of the type of diabetes: Placentae from gestational diabetes mellitus (GDM) show alterations similar in character to those found in placentae with pre-gestational diabetes, albeit less marked [55]. Notably, these changes are still observed despite improvement in glycaemic control of the mothers in the last decades [56, 57].

Growth and ultimate size of the placenta is usually proportional to the size of the foetus. Hence, placentae from diabetic pregnancies tend to be heavier. Recent data show that the phenotype of fetuses born to diabetic mothers is characterized by an excessive accumulation of fat even when the fetuses are of normal weight [58, 59]. Neither placental weight nor any other changes in composition or function of the placenta in these well-characterized cases have been studied so far.

The reasons for the relationship between elevated foetal and placental weight are

not clear. It has remained the most challenging and still unresolved question in research in this area if the placental overweight is the cause or the consequence of excessive foetal growth or fat accumulation, respectively.

### Transplacental Transport

This raises the question about a potential contribution of augmented transplacental transport in diabetes. Despite several reports about possible changes at the molecular level of glucose transporters, perfusion experiments demonstrated an unaltered, if not even reduced, transplacental glucose transport in GDM [60, 61]. These data argue for the maternal-to-foetal glucose concentration gradient as the major if not only reason for increased glucose fluxes across the placenta in diabetes. This conclusion is also supported by unchanged concentration differences for glucose between umbilical arteries and vein in GDM [62].

Controversial results were published on amino acid transporters. Syncytiotrophoblast amino acid transport system A, which transports alanine, serine, proline and glutamine was either increased [63] or unchanged [64, 65] in GDM. Amino acid transport systems are complex and several transporter systems exist with overlapping specificity. Hence, any conclusion from one transport system on general amino acid transport is impossible. Moreover, molecular changes of transporters do not allow such conclusions, because transport is determined by several other factors. Measurements by placental perfusion have not been carried out to date. This is surprising given that some of the amino acids i.e., leucine, isoleucine or arginine act as potent insulin secretagogues and may, thus, contribute to foetal hyperinsulinemia in GDM [66], which in turn will promote foetal and placental growth resulting in a greater demand for nutrients. It is unclear if this will stimulate foetal growth or just serve to cover the increased foetal nutrient requirements when its overgrowth is driven by other factors.

### Structural Changes Facilitating Oxygen Delivery

In all types of diabetes, gross placental structure may be altered, particularly the surface and exchange areas are enlarged: the maternal i.e., villous surface is enlarged by about 30–50 % [67] and the

total length of villous capillaries is greater by 30 % as well as the capillary surface area by 40 % as a result of hyper-vascularisation [68].

The greater placental capillary surfaces may result from foetal counter regulatory mechanisms to a potential reduction of placental oxygen transport. Maternal hyperglycaemia induces synthesis of increased amounts of collagen, predominantly of collagen type IV. This results in thickening of the trophoblast basement membrane and in a longer diffusion distance for maternal-foetal exchange [69, 70] although thinner placental basement membranes in diabetes at term have been described as well [71]. Thickening of the basement membrane, however, will impair oxygen diffusion. Moreover, maternal hyperglycaemia results in decreased arterial oxygen saturation and increased proportion of HbA1c, which has a higher affinity for oxygen than non-glycosylated haemoglobin [72, 73]. Reduction of utero-placental blood flow in diabetic pregnancies [74], especially when maternal hyperglycaemia is more pronounced, also reduces oxygen transport to the placenta and, hence, further impairs oxygen delivery. In the foetus plasma and amniotic fluid erythropoietin levels are frequently elevated in diabetes suggesting chronic foetal hypoxia. This notion is also supported by the polycythaemia and increased nucleated red cells often observed in the foetuses and newborn infants of diabetic women [75, 76].

In addition to impaired oxygen supply, foetal hyperglycaemia and the ensuing hyperinsulinemia stimulate aerobic metabolism that even further enhances foetal oxygen demand, which in the situation of reduced supply will result in foetal hypoxia. This is further augmented by the reduced placental iron transport resulting from more pronounced placental transferrin receptor glycosylation [77]. The resulting low foetal oxygen levels ultimately stimulate placental vascularisation by up-regulating the transcriptional synthesis of pro-angiogenic factors in the fetoplacental compartment. Established examples include FGF-2, VEGF and leptin, which all contain binding sites for the hypoxia-inducible factor HIF1- $\alpha$  in their promoter regions [78–80]. Their higher levels promote endothelial cell proliferation, a key

process contributing to angiogenesis, which may thus compensate the compromised oxygen supply to the foetus. Hence, foetal hypoxia will induce an increase in placental vascular exchange area. This appears paradox in a situation of maternal nutritional oversupply and underlines the supreme significance of adequate oxygen delivery to the foetus.

In contrast to the vascular enlargement that results from changes in the foetal compartment, the villous surface increase is likely driven by maternal growth factors and cytokines. The detailed underlying mechanisms are not clear, but hyperinsulinemia potentially stimulates proliferation in cell models of the first trimester trophoblast [16] and, thus, could already early in gestation promote the increase of syncytial surface found at term of gestation. Moreover, higher levels of other maternal growth factors may also contribute.

### Other Placental Changes

Further placental changes observed in maternal diabetes include non-enzymatic glycation of molecules following the exposure to hyperglycaemia. This has been described for extracellular matrix components that consequently contain a higher proportion of carbohydrates [70, 81] as well as for cell surface proteins such as the IGF1 receptor [82]. Foremost examples of molecules with altered placental expression in response to the diabetic environment include Na(+)/K(+)-ATPase [83]; GLUT1 [84]; iNOS [85], leptin [29], FGF-2 [86], perlecan [87], VE-cadherin,  $\beta$ -catenin, zonula occludens-1 [88] and liver-type fatty acid binding protein (FABP) [89]. The insulin and IGF1 receptor not only have higher expression levels [44, 90, 91] but also an increased tyrosine kinase activity [92, 93] in GDM, overt diabetes or both.

### Lipids and Fatty Acids

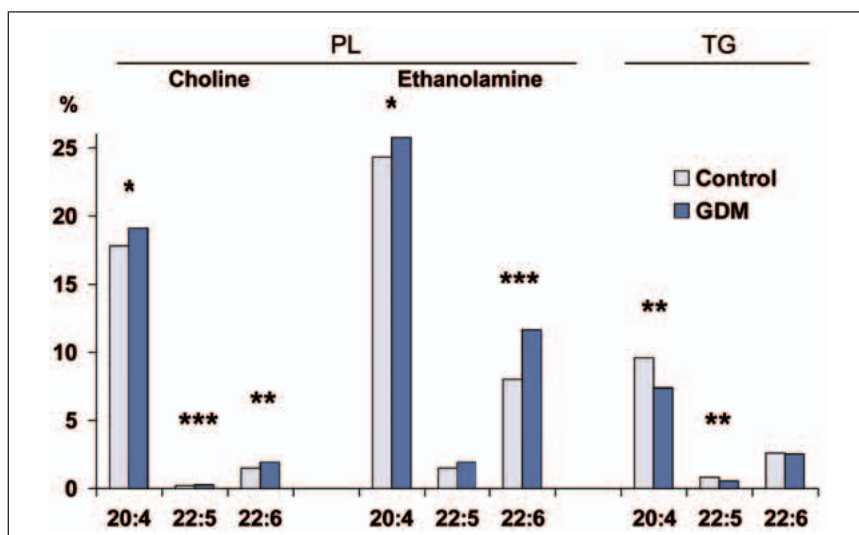
At birth about 12–15 % of the foetal body mass is fat. Excessive foetal fat accretion has been recognized as the characteristic feature of the offspring from diabetic mothers. About half of foetal fat is derived from maternal sources passing across the placenta over the whole period of gestation. The remainder may be due to the lipogenic activity of the foetal liver and other tissues. For most fatty acids a downhill

concentration gradient from mother to foetus exists. This would make possible a direct transplacental transfer of free fatty acids by simple diffusion. However, the major proportion will bind to fatty acid transfer proteins on the microvillous membrane that will facilitate their passage across this membrane. Once having reached the cytoplasm the free fatty acids will bind to FABPs. These will serve as ‘transporters’ for the fatty acids enabling them to traverse the cytoplasm either to the basal syncytiotrophoblast membrane for immediate release into the foetal circulation or to intracellular organelles for various other purposes. Re-esterification of free fatty acids to triglycerides and subsequent storage as lipid droplets,  $\beta$ -oxidation, fatty acid incorporation in phospholipids as well as conversion into eicosanoids within the placenta are the main pathways.

Lipid droplets, the intracellular storage compartment for lipids, are surrounded by droplet-associated proteins such as adipophilin and perilipin. These proteins are a prerequisite for recruitment of intracellular lipases. Subsequent lipolysis is required before the fatty acids can then be released into the foetal circulation.

Additional sources of foetal lipids are lipoprotein-borne triglycerides, phospholipids and cholesterol. The lipoproteins have to bind to their receptors, which can all be found on the syncytiotrophoblast surface. The binding of very low density (VLDL) and high density (HDL) lipoproteins to their receptors i.e., the VLDL receptor [94] and the major HDL receptor SR-BI [95] is mediated by lipases. In the cytoplasm cholesterol esters may also be stored in the lipid droplets. A proportion of the cholesterol esters will be metabolised to serve as precursor for placental biosynthesis of steroid hormones. The mechanisms of further transfer from within the syncytiotrophoblast cytoplasm into the foetal circulation remain elusive.

Diabetes is associated with alterations of maternal lipid composition and rise of maternal lipid levels. The elevated lipid concentration may increase placental transfer of free fatty acids and triglycerides resulting from the steeper maternal-foetal concentration gradient. This may be further augmented by other diabetes-



**Figure 2:** Proportion (%) of long-chain polyunsaturated fatty acids arachidonic acid (20:4), eicosapentaenoic acid (22:5), docosahexaenoic acid (22:6) in placental phospholipid (PL) fractions and in triglycerides (TG) in control and GDM pregnancies. According to data from [98].

related alterations facilitating placental fat accumulation.

Among the placental FABP the liver-type FABP is increased in diabetes whereas the heart-isoform is unchanged [89]. The liver-type predominantly binds n-3 fatty acids such as  $\alpha$ -linolenic acid, eicosapentaenoic acid and docosahexaenoic acid, whereas the heart-type preferentially binds n-6 fatty acids such as linolenic acid and arachidonic acid. In T1DM placental transfer and distribution among lipid classes of arachidonic acid are altered, and arachidonic increments are stored in the placenta [96]. Also the linoleate content is higher in placental tissues [97] which may be converted into arachidonic acid and further contribute to the increase. Long-chain polyunsaturated fatty acids are important for foetal development in general and for the brain in particular. In GDM their proportion in the placental phospholipid fraction is enhanced, but reduced in the triglyceride fraction (Fig. 2) demonstrating a preferential storage in phospholipids from where they can be released by phospholipases.

These phospholipases such as PLA2 are involved in the release of lipid mediators of inflammation such as arachidonic acid, DHA and other 20 carbon polyunsaturated fatty acids from cellular phospholipids. In placentae of GDM women having macrosomic babies, the expression of secretory PLA2G2 and G5 is up-regulated [99]. The concentration of pla-

cental products of PLA2 hydrolysis such as DHA is positively correlated with placental weight. Furthermore, the increase of PLA2G2 and G5 may enhance the release of arachidonic acid and may, thus, represent a mechanism through which 3–6 times more arachidonate is converted to eicosanoids in a diabetic pregnancy. In addition, the transfer of eicosanoids into the opposing circulation was doubled in placentae from T1DM compared to normal placentae. The predominant direction of eicosanoid transfer is directed from the foetus into the maternal circulation. Besides the total amount of eicosanoids, the relative amount produced was also altered in placentae from T1DM pregnancies. The preferential conversion of the arachidonic acid increment taken up into thromboxane over prostacyclin  $I_2$  leads to a lower ratio of prostacyclin  $I_2$  to thromboxane  $A_2$  in T1DM vs. non-diabetic pregnancies. This imbalance in eicosanoid production may be a strong contributing factor to placental vasoconstriction in these pregnancies [100].

Collectively, these data indicate qualitative and quantitative modifications of placental lipids associated with alterations of foetal growth in diabetic pregnancies.

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