The Human Placenta in Diabetes and Obesity: Friend or Foe? The 2017 Norbert Freinkel Award Lecture

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The placenta plays a key role in sustaining fetal growth and development. Due to its position between mother and fetus, it is exposed to changes in the intrauterine environment in both circulations. The relative influence of changes in those circulations depends on the period of gestation. Early in pregnancy, maternal influences prevail and may affect the complex biological processes characteristic for this pregnancy period, such as placentation, early cell differentiation, and spiral artery remodeling. It is still unclear whether the placenta early in pregnancy is a friend or foe for the fetus. Later in pregnancy, when the fetal circulation is gradually establishing, fetal signals gain importance in regulating placental structure and function. Many of the placental alterations seen at term of pregnancy are the result of fetoplacental interactions often driven by fetal signals associated with maternal diabetes or obesity. These alterations, such as hypervascularization or enhanced cholesterol removal from placental endothelial cells, can be regarded as adaptations to maintain homeostasis at the fetoplacental interface and, thus, to protect the fetus. However, extreme conditions such as poorly controlled diabetes or pronounced obesity may exceed placental homeostatic capacity, with potentially adverse consequences for the fetus. Thus, in late pregnancy, the placenta acts mostly as a friend as long as the environmental perturbations do not exceed placental capacity for mounting adaptive responses.

Owing to its position between the maternal and fetal circulation, the placenta plays a central role in fetal nutrition to sustain fetal development and growth. Changes in either maternal or fetal circulation may alter placental structure and function with potential consequences for fetal growth and development. The question, which has puzzled me throughout my career, has been: does the placenta contribute to the fetal phenotype of diabetes, acting as a foe, or does it protect the fetus from adverse effects of the diabetic environment and is it, thus, a friend of the growing fetus?

In my quest to address this question, I have been considerably inspired by Norbert Freinkel. In particular, his concept of critical time periods in pregnancy during which different organs and structures of the fetus are susceptible to perturbations in the intrauterine environment, as seen with, for instance, maternal diabetes (and for sure also obesity), has influenced my thoughts (1,2). We have adapted this concept to the placenta. The placenta may be exposed to metabolic changes in the mother during critical periods of its development (Fig. 1), and, depending on the timing, different placental structures and processes could be affected. Therefore, we postulated that pregestational and gestational diabetes mellitus (GDM) affect the placenta differently,

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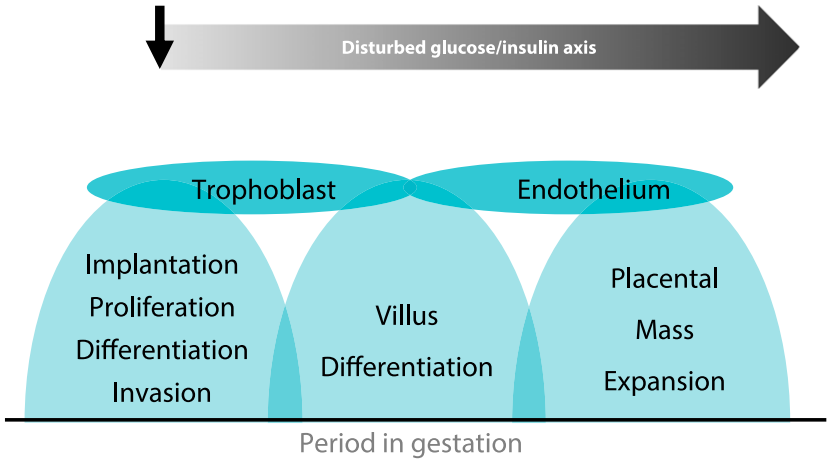

Figure 1—Diabetes effects on placenta depend on timing of metabolic derangements in pregnancy. Adapted from Freinkel (1), Metzger (2), and Desoye and Haugel-de Mouzon (3). Original artwork by biolution GmbH reproduced with permission.

since their associated metabolic changes are present in different developmental periods (3). Recent emerging evidence demonstrates that metabolic changes resulting in a diagnosis of GDM later in pregnancy are present early in gestation. However, in pregestational diabetes and maternal obesity, these changes are present as early as at conception. Hence, the placenta may be exposed to metabolic changes in the mother during different critical periods of its development (Fig. 1). Although at week 12 of pregnancy the placenta weighs only about 5% of its final weight at term of pregnancy, placental growth kinetics, i.e., placental weight change per week, is at its maximum between pregnancy weeks 10 and 14 (Fig. 2). Rapidly growing tissues are very susceptible to environmental perturbation (4), and metabolic or proinflammatory disturbances in early pregnancy may, therefore, have profound effects on placental growth. We have recently proposed that a compromised early placental development may track throughout pregnancy and contribute to the fetal phenotype through, among others, the glucose steal phenomenon (5,6). In the following sections, I have separated the discussion into two periods, early versus late pregnancy, mostly because there is no information available about the time in between. In the end, I shall try to synthesize the discussion into a comprehensive framework and provide the answer(s) to the main question of this review.

EARLY PREGNANCY

Early pregnancy is characterized by a wide range of processes during which the blastocyst implants and differentiates to establish the two main component tissue types: inner cell mass, from which the fetus proper originates, and trophectoderm, which develops into trophoblast and placental tissue. In the first weeks of pregnancy, before remodeling of the spiral arteries in the decidua, the placenta develops in a low-oxygen environment. Subsequent spiral artery remodeling is accompanied by an increase of oxygen tension in the intervillous space (7), which results in a transient physiologic oxidative stress in the trophoblast (8), the placental cell type exposed to maternal blood. If this physiologic oxidative stress is superimposed by oxidative and/or proinflammatory stress, due to maternal diabetes or obesity, then a reduction in trophoblast growth results (9). The specific consequences of the changes in the first trimester in oxygen tension supplied to the placenta are unknown. The detailed mechanisms of placental responses also remain to be determined. This is a complex endeavor, because trophoblast invasion and, hence, spiral artery remodeling may be

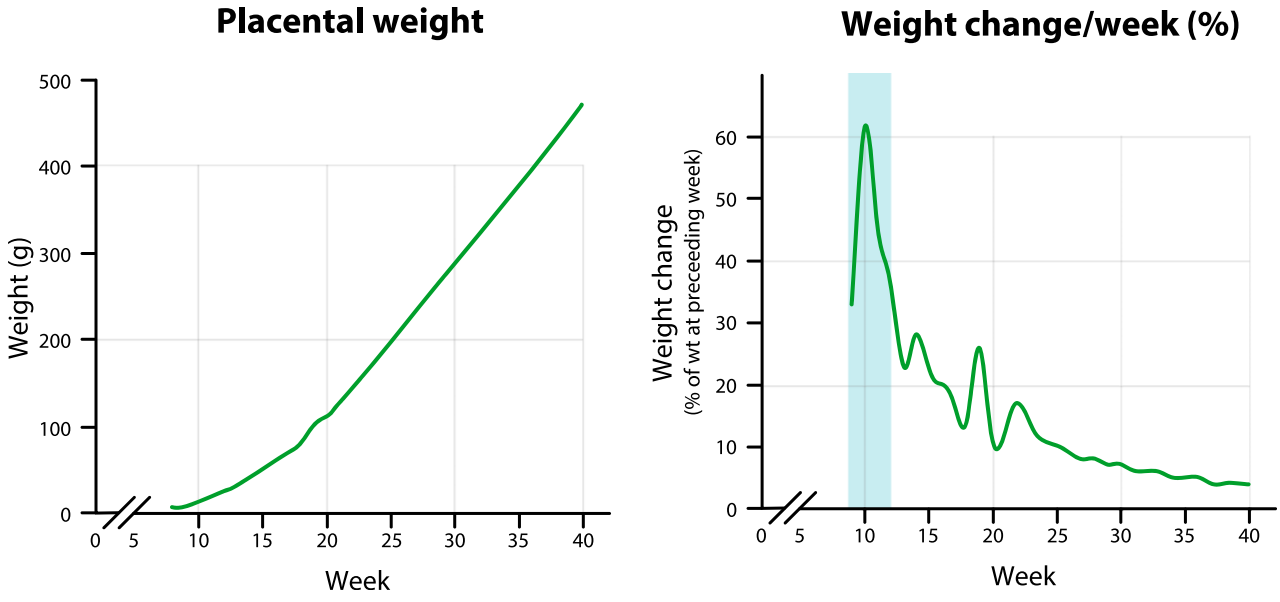

Figure 2—Placental growth throughout pregnancy. *Left*: Changes in absolute placental weight during pregnancy. *Right*: Placental growth dynamics shown as weight (wt) change per week. Data on placental weight per gestational week are taken from Benirschke et al. (65) and are based on information provided by Boyd and Hamilton (66) and O'Rahilly (67). Original artwork by biolution GmbH reproduced with permission.

modified by maternal obesity (10) and diabetes (11).

According to this concept, the increasing oxygen tension in early pregnancy, in combination with hyperglycemia and/or proinflammatory stress, may have an inhibitory effect on trophoblast and placental growth by inhibiting invasion and thereby delaying spiral artery remodeling, by directly inhibiting trophoblast proliferation, or by a combination of the two.

However, other components of the maternal environment may have opposing effects, i.e., stimulate placental growth. Insulin may be one candidate with a sustained effect that tracks throughout pregnancy. The recent demonstration of associations between the maternal insulin secretory response in early pregnancy (weeks 12–14) with placental volume at week 20 and placental weight at the end of gestation suggests such a sustained insulin effect (12).

Mechanistically, insulin cannot directly promote placental growth because of spatial reasons: the insulin receptor is located predominantly on the plasma membrane of the syncytiotrophoblast, whereas the cytotrophoblast is the proliferating trophoblast stem cell population (13) positioned subjacent to the syncytiotrophoblast. Placental growth at this stage of pregnancy requires an expansion of cytotrophoblast number and their fusion with the syncytiotrophoblast. This is a complex and tightly regulated process, in which a syncytiotrophoblast matrix metalloproteinase (MMP14) is directly involved (14). It can be upregulated by insulin and tumor necrosis factor-α and is present at higher levels in the first trimester placenta of women with type 1 diabetes (T1D) (15). In this situation, placental MMP14 levels directly associate with the total daily insulin dose these women received for managing their glycemia. These early placental responses to insulin might be modified by maternal obesity due to reduced insulin sensitivity (16).

The temporal sequence of these events is unknown, but we envisage a scenario in pregestational diabetes or obesity in which early placental growth is initially reduced or delayed due to increased oxidative stress. This is paralleled by an early fetal growth delay as found in some T1D pregnancies (17–19). Subsequently, a placental growth spurt occurs in late first trimester (17–19). The larger placenta as a result of this growth spurt leads to enhanced glucose transfer, which relaxes the restraint on fetal growth. Thus, once the placenta has grown, fetal catch-up growth will follow. This scenario may explain biphasic fetal growth in T1D (20,21).

Why is early placental growth so important for fetal growth and development? It is unknown to date how glucose transfer at this early period is governed, but, as mentioned before, placental size may be one factor: more specifically, placental volume and, hence, surface area may define the total number of glucose transporters. Subtle increases in transporter number at this stage may contribute to an early onset of enhanced transplacental glucose flux. As a consequence, the maturation of the stimulus-secretion coupling mechanisms of the fetal pancreas may be accelerated. This leads to an earlier onset of fetal β-cell response to elevated glucose levels and results in elevated fetal insulin levels. These in turn stimulate fetal glucose uptake into peripheral tissues. As a consequence, fetal glucose levels will be transiently lowered, thereby steepening the maternal-to-fetal glucose concentration gradient. This steepened concentration gradient will drive maternal glucose flux to the fetus even under seemingly normal glucose control of the mother (glucose steal phenomenon) (6). The onset of this phenomenon is unknown, is likely multifactorial, and varies from pregnancy to pregnancy.

Collectively, it is currently unclear whether the placenta early in pregnancy acts as a friend or foe of the fetus.

END OF PREGNANCY

Almost all studies on the effects of maternal diabetes and obesity on the placenta have been carried out at the end of pregnancy. Based on the concept that effects of changes in maternal environment on placental growth and development differ per period of pregnancy (Fig. 1), one can predict that in the second and third trimester, placental functional differentiation and mass expansion are mostly affected. The results seen at the end of gestation are then the manifestation of these changes that have occurred earlier on.

Over the years we have identified many changes associated with maternal diabetes and/or obesity. In our view, these can be regarded as adaptive responses to protect the fetus rather than contributors to excessive growth and fat accretion. The two examples that follow support this notion.

Facilitating Oxygen Diffusion—Hypervascularization

It has been known for a long time that pregnancies of women with diabetes carry the risk for the fetus to be low in oxygen, a condition that can be transient or persist for a longer period of time. This is the result of augmented fetal oxygen demand because of enhanced fetal metabolism. Fetal metabolism is enhanced due to the elevated insulin levels paralleling hyperglycemia. At the same time, more maternal hemoglobin is glycosylated in diabetes. HbA_{1c} has a higher oxygen affinity than HbA_1. Hence, oxygen delivery to the intervillous space for fetal supply is reduced. This imbalance in maternal supply and fetal demand results in low fetal oxygen. The fetus responds by increasing its erythropoietin levels (22,23), thereby enhancing erythropoiesis, which eventually results in more nucleated red blood cells in the neonatal circulation (24). Although the placenta synthesizes erythropoietin in an oxygen-sensitive manner, its contribution to elevated fetal levels is unlikely because placental synthesis is restricted to the trophoblast populations facing the maternal circulation (25). Fetal insulin also stimulates growth of erythroid progenitors in cord blood and contributes to a higher number of erythroid cells (26).

The placenta also responds to the enhanced fetal demand for oxygen by expanding its surface area of exchange (27,28). This has been described mostly in T1D. Surface enlargement is achieved mostly by enhancing fetoplacental vascular growth through angiogenesis. The new, usually small-caliber vessels are homogeneously distributed across the core of the placental villi; in contrast, in pregnancies of women without diabetes, the small vessels are preferentially arranged in a subtrophoblastic location (29).

One of the key regulators for placental angiogenesis under these conditions is fetal insulin (30,31). We have delineated several of the mechanisms and pathways through which fetal insulin contributes to vascular growth in the placenta. These include *1*) degradation of extracellular matrix by a matrix metalloproteinase (MMP14), *2*) activation of endothelial nitric oxide synthesis and enhanced formation of nitric oxide, which stimulates endothelial tube formation, and *3*) stabilization of the F-actin cytoskeleton, which is necessary for lamellipodia formation

and cell migration. Insulin activates these individual processes through the protein kinase-3 pathway. Surprisingly, insulin does not activate the mitogen-activated protein kinase pathway to stimulate endothelial cell proliferation (31,32). The fetal signals for enlargement of surface area are likely generated before week 32 in pregnancy, as the placental surface area correlates with the day-to-day variation in maternal blood glucose levels only between week 12 and 32 of gestation and not thereafter (33).

The placental response to increased fetal oxygen demand is not limited to facilitating supply of maternal oxygen. As a further measure, it also facilitates the supply of iron needed for enhanced erythropoiesis. This is accomplished by upregulating the placental transferrin receptor, although more pronounced receptor glycosylation associated with hyperglycemia may reduce its affinity for transferrin binding (34–36). A direct effect of fetal oxygen on placental vascular function cannot be ruled out, but remains to be demonstrated.

Collectively, the fetoplacental unit adapts structurally and functionally to facilitate oxygen delivery to the fetus in normal pregnancy and beyond in situations of metabolically induced enhanced oxygen demand. These changes result in a shorter overall oxygen diffusive conductance (37,38).

Preventing Impairment of Fetoplacental Blood Flow—Avoiding Preatherosclerotic Lesions

Another example of placental responses aiming to protect fetal development can be found in the mechanisms preventing preatherosclerotic lesions in the fetoplacental circulation. On the maternal side, atheromas in spiral arteries have been found and are more frequent in T1D (39). Foam cells can form in the intervillous space in situations of maternal hypercholesterolemia (40), and in the fetal aorta, fatty streaks can be formed (41). However, no similar lesions have been identified yet in the fetoplacental circulation. This suggests that highly efficient mechanisms for cholesterol efflux from placental vessels must be in place. Indeed, we have identified cholesterol efflux transporters ABCA1 and ABCG1 on fetoplacental endothelial cells and have delineated a two-step mechanism for the endothelial cells to efflux cholesterol (42). The primary cholesterol acceptor on the fetal side is nascent HDL followed by HDL_3. The small, dense HDL_3 is modified by endothelial cell phospholipid transfer protein (PLTP) to cholesterol-rich HDL_2 and nascent HDL, which in turn will pick up cholesterol released from the endothelial cells. Fetal HDL_2 will then be taken up by the liver. This represents an efficient mechanism for fetoplacental endothelial cells to shuttle their cholesterol to the fetal liver, thus protecting against formation of preatherosclerotic lesions in the vasculature of the placenta proper. In GDM, placental endothelial cells synthesize more cholesterol because of upregulation of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. Yet total cholesterol content in the endothelium is unaffected by GDM, because cholesterol efflux mechanisms are upregulated by oxysterols in the fetal circulation, which form de novo from cholesterol through reactive oxygen species–induced oxidation (43). Enhanced cholesterol efflux in GDM leads to more HDL_3 in the fetal circulation, but, in parallel, PLTP is also upregulated. Fetal insulin is one of the regulators of PLTP activity (44).

Thus, in GDM, all mechanisms that ensure cholesterol homeostasis at the fetoplacental interface are upregulated to avoid vascular damage and compromised blood flow due to the formation of preatherosclerotic lesions. The mechanisms related to cholesterol homeostasis are further supported by a reduction of both forms of intercellular adhesion molecule 1 (ICAM-1)—the surface bound and the soluble form—on placental endothelial cells. Their levels are in an inverse relationship with maternal BMI. These proteins are markers of vascular inflammation (45). The low ICAM-1 protein levels in GDM can be regarded as an additional protective mechanism to avoid transmigration of fetal leukocytes into the subendothelial space of the fetoplacental circulation, thereby also contributing to reducing the risk of preatherosclerotic lesions.

In both examples above, the fetus provides the signals inducing the cellular and molecular mechanisms that facilitate placental adaptation (Fig. 3). This represents a change in paradigm: previously, maternal control of placental development and function was presumed; the findings discussed above establish the importance of fetoplacental signaling. On the basis of the developmental shift of the insulin receptor location from the surface facing the maternal circulation to that facing the fetal circulation, we have previously proposed that maternal factors govern placental development and function mostly early in pregnancy, whereas the fetus gradually takes over control of its own organ in later stages of pregnancy (46).

MODIFIERS OF PLACENTAL ADAPTATION

The processes described above are just examples of how the placenta protects the fetus at the end of pregnancy and, in doing so, acts as a friend for the fetus. However, these examples of placental changes to maintain a stable fetoplacental

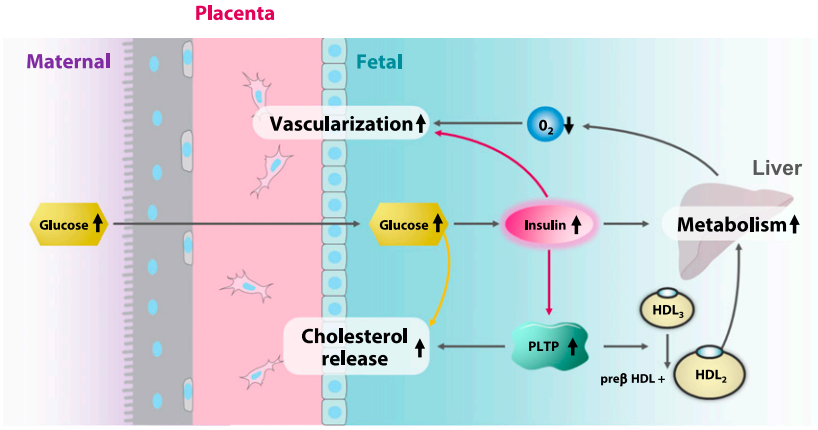

Figure 3—Placental adaptation for fetal protection. Fetal signals induce placental structural and functional adaptation as protective measures. Insulin is one of the drivers of the proangiogenic response to low oxygen levels, to which in turn fetal insulin contributes by stimulating metabolism. Insulin also upregulates PLTP, which facilitates removal of excessive cholesterol released from the placental endothelium. Glucose, through reactive oxygen species, leads to formation of oxysterols, which induce cholesterol efflux transporters. Cooperation of these mechanisms ensures that cholesterol content in the endothelium is unaltered in GDM despite enhanced cholesterol synthesis and that the cholesterol released into the fetal circulation is removed by the fetal liver. Original artwork by biolution GmbH reproduced with permission.

interaction through homeostatic mechanisms have been established under certain experimental conditions, and generalization is difficult at this point. There are some aspects that may modify the protective function or at least shift the level of tolerance toward metabolic and inflammatory disturbance. If maternal disturbances affect fetal growth and development, this depends not only on the placental homeostatic capacity, but also on the metabolic load to which the fetoplacental unit is exposed (Fig. 4). This model resembles the metabolic capacity/metabolic load model for fetal and neonatal programming (47).

Effects of Fetal Sex

The placenta is well known to show sex-specific differences in expression of genes and function, and the nature of these differences depends on placental cell type (48–50). Also, the response to environmental stimuli, such as maternal dietary factors, differs between sexes (51). This seems to favor flexibility and adaptive responses in placentas of female fetuses. Insulin resistance found in female neonates born to women with diabetes serves as a cellular antioxidant defense mechanism (52) and is a further protective strategy of the fetoplacental unit designed by evolution to favor reproductive outcome in females. The association of cord blood insulin with subcutaneous fat in the newborn is sex specific (53). This adds evidence to the notion of differential susceptibility of fetal tissues to diabetes- and/or obesity-associated neonatal hyperinsulinemia depending on fetal sex.

Therefore, it can be expected that some sex-specific differences exist in the placental capacity to mount adaptive responses to the maternal diabetic and/or obese environment. The presence of transcriptome sex differences in the late first trimester placenta suggests different susceptibility and stress response mechanisms early on (54).

The protective mechanisms described above were all established with endothelial cells from female fetoplacental units, and it remains to be seen whether they are also operative to a similar extent in male endothelial cells.

Heterogeneity of the Placenta

While it is obvious that distinct placental cell types respond differently to environmental cues, even within distinct placental cell types, regional differences in the protein repertoire may lead to different responses even within distinct cell types. A clear example of such regional differences is the presence and density of endothelial insulin receptors along the vascular tree (55), with high density in areas destined to drive vascular growth. Thus, the response to fetal hyperinsulinemia likely differs by region. Currently, it is unclear whether regions with low receptor density show similar responses as described previously. It can be hypothesized that regional differences are also present for all other cell-surface or intracellular molecules. Hence, functional responses of the placenta to changes in utero and the fetoplacental circulation may vary by region.

How Does the Placenta Respond to More Extreme Situations?

Most placenta studies in diabetes and/or obesity have been carried out in mild forms of the conditions, and only modest changes in the placenta were found. For example, proteomic analyses of placentas in well-controlled GDM at the end of pregnancy demonstrated only minor changes, although some proteins were hyperglycosylated (56,57).

Placental lipid metabolism is strikingly and nonlinearly affected by maternal conditions. The enzyme endothelial lipase (58) is the predominant lipase on the microvillous membrane of the syncytiotrophoblast. It is involved in hydrolyzing phospholipids and triglycerides, and the fatty acids released by lipolysis can be taken up by the syncytiotrophoblast for further metabolism. The enzyme expression is unaffected by maternal obesity or GDM, but it is profoundly upregulated by 100% when GDM is combined with obesity. This suggests the presence of a threshold of tolerance to inflammatory mediator levels such as leptin and tumor necrosis factor-α levels associated with maternal obesity and low-grade inflammation, which regulate endothelial lipase. The enzyme responds only when threshold levels are exceeded, again demonstrating a protective effect for the fetoplacental unit.

The free fatty acids taken up by the placenta enter metabolic pathways, one of which is their re-esterification and storage as triglycerides in syncytiotrophoblast lipid droplets (59,60). The removal of free fatty acids from the cytoplasm protects the syncytiotrophoblast from lipotoxicity (61) and, hence, can be regarded as a further protective mechanism. In mothers with modest obesity (obesity class I), the placental triglyceride content is higher than in lean women. However, more pronounced maternal obesity (obesity classes II and III) is not associated with a further increase in placental triglyceride content, which levels off, demonstrating the capacity limit of

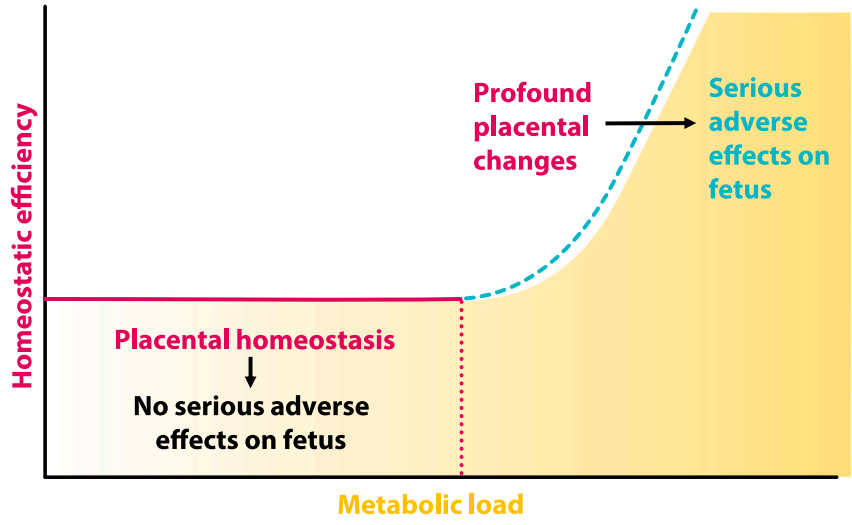

Figure 4—Homeostatic capacity vs. metabolic load concept. The placental homeostatic capacity allows adaptations to fetal needs. In this situation, the placenta serves as a friend to the fetus. However, with increasing metabolic load, i.e., maternal metabolic and inflammatory derangements exceeding placental capacity to mount these adaptive responses, major structural and functional changes can be predicted and may have adverse consequences for the fetus. The placenta would then be the foe of the fetus. Original artwork by biolution GmbH reproduced with permission.

protection. It is unknown whether the excess fatty acids in the syncytiotrophoblast not stored in triglycerides affect trophoblast function or spill over to the fetal circulation and contribute to fetal fat accretion.

CONCLUSIONS AND FUTURE PROSPECTS

In this article, I have attempted to bring together the available evidence and embed it in a conceptual framework encompassing early and late pregnancy periods.

In the past decades, during which I have attempted to understand the role of the placenta for the growing fetus especially in conditions characterized by maternal overnutrition, I have gradually come to the conclusion that the placenta at the end of pregnancy is regulated/controlled by the fetus and acts more as a friend of the fetus. Despite manifold studies, there is no evidence for a placental role late in pregnancy contributing to adverse outcomes. However, these studies including our own have the major limitation that *1*) only mild forms of maternal metabolic, endocrine, and inflammatory disturbance have been included and *2*) they have focused exclusively on the end of pregnancy. In other situations, placental response may be different.

Hence, the answer to my question raised at the outset of this article, of the placenta being a friend or foe for the fetus, is not straightforward but rather more complex. The major determinant for the answer to the friend/foe question certainly is the period in pregnancy in which the maternal metabolic and/or inflammatory disturbances begin to act on the placenta.

The scarce information about effects of the diabetic or obese environment on the placenta early in pregnancy does not yet allow a conceptual conclusion. This pregnancy period is an underresearched area because of ethical constraints. Animal studies do not help because animals follow different growth strategies than humans and their placentas are structurally and functionally different. In vitro studies need to take into account the changes in ambient oxygen tension during the first trimester as well as the week of pregnancy when the placental tissue was collected for research.

Clinical research can strongly contribute by measuring crown-rump length as well as placental volume from as early as possible in the first trimester and by correlating both measures with maternal metabolic and endocrine factors. This would allow determination of the effects of early metabolic changes on placental and fetal growth throughout pregnancy as well as on neonatal outcomes, including body composition.

Much more research is needed in more severe metabolic, endocrine, and inflammatory conditions of the mother at the end of gestation. The continuous improvement in maternal metabolic control has made it difficult to prospectively carry out these studies. Analyzing archival material with state-of-the-art methods developed especially for these types of samples may be an option. This will lead to a better understanding of which cellular and molecular processes are most susceptible to profound environmental perturbations. Establishing exposure-response relationships in the placenta will also allow assessment of whether and how these perturbations affect fetal growth and development and how this is manifested in the neonate. Explanations for the most severe adverse pregnancy outcome in maternal diabetes and obesity, i.e., stillbirth, may then be found. Placental failure to mount adaptive hypervascularization and to upregulate maternal-to-fetal iron transfer efficiency may turn out to be contributors.

Finally, in an ideal world, rather than associating placental changes with maternal or fetal/neonatal parameters, placental tissue collected from randomized controlled trials could be used to demonstrate cause-and-effect relationships. Statistical path analyses could then help to identify placental mediators of maternal changes early in pregnancy, leading to altered neonatal outcomes.

Emphasis on the early pregnancy period was suggested almost 35 years ago by Claude Michèle Poissonet, who raised the question, ". . .should diabetes in pregnant women be carefully managed in early gestation in the hope of preventing excessive body fat deposition in the conceptus?" (62). The time is now ripe to focus our research on this period, as has also been recommended by some international organizations (63,64).

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References

1. Freinkel N. Banting Lecture 1980: of pregnancy and progeny. Diabetes 1980;29:1023–1035
2. Metzger BE. Biphasic effects of maternal metabolism on fetal growth; quintessential expression of fuel-mediated teratogenesis. Diabetes 1991;40(Suppl. 2):99–105
3. Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus: the insulin and cytokine network. Diabetes Care 2007;30(Suppl. 2):S120–S126
4. Stockard CR. Developmental rate and structural expression: an experimental study of twins, 'double monsters' and single deformities, and the interaction among embryonic organs during their origin and development. Am J Anat 1921;28:115–277
5. Desoye G, van Poppel M. The feto-placental dialogue and diabesity. Best Pract Res Clin Obstet Gynaecol 2015;29:15–23
6. Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. Diabetologia 2016;59:1089–1094
7. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. Obstet Gynecol 1992;80:283–285
8. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress: a possible factor in human early pregnancy failure. Am J Pathol 2000;157:2111–2122
9. Fröhlich JD, Huppertz B, Abuja PM, König J, Desoye G. Oxygen modulates the response of first-trimester trophoblasts to hyperglycemia. Am J Pathol 2012;180:153–164
10. Perdu S, Castellana B, Kim Y, Chan K, DeLuca L, Beristain AG. Maternal obesity drives functional alterations in uterine NK cells. JCI Insight 2016;1:e85560
11. Björk O, Persson B, Stangenberg M, Václavínková V. Spiral artery lesions in relation to metabolic control in diabetes mellitus. Acta Obstet Gynecol Scand 1984;63:123–127
12. O'Tierney-Ginn P, Presley L, Myers S, Catalano P. Placental growth response to maternal insulin in early pregnancy. J Clin Endocrinol Metab 2015;100:159–165

13. Korgun ET, Celik-Ozenci C, Acar N, Cayli S, Desoye G, Demir R. Location of cell cycle regulators cyclin B1, cyclin A, PCNA, Ki67 and cell cycle inhibitors p21, p27 and p57 in human first trimester placenta and deciduas. Histochem Cell Biol 2006;125:615–624
14. Hiden U, Ghaffari-Tabrizi N, Gauster M, et al. Membrane-type matrix metalloproteinase 1 regulates trophoblast functions and is reduced in fetal growth restriction. Am J Pathol 2013;182:1563–1571
15. Hiden U, Glitzner E, Ivanisevic M, et al. MT1-MMP expression in first-trimester placental tissue is upregulated in type 1 diabetes as a result of elevated insulin and tumor necrosis factor-α levels. Diabetes 2008;57:150–157
16. Lassance L, Haghiac M, Leahy P, et al. Identification of early transcriptome signatures in placenta exposed to insulin and obesity. Am J Obstet Gynecol 2015;212:647.e1–e11
17. Pedersen JF, Mølsted-Pedersen L, Lebech PE. Is the early growth delay in the diabetic pregnancy accompanied by a delay in placental development? Acta Obstet Gynecol Scand 1986;65:675–677
18. Pedersen JF, Mølsted-Pedersen L, Mortensen HB. Fetal growth delay and maternal hemoglobin A1c in early diabetic pregnancy. Obstet Gynecol 1984;64:351–352
19. Brown ZA, Mills JL, Metzger BE, et al.; National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Early sonographic evaluation for fetal growth delay and congenital malformations in pregnancies complicated by insulin-requiring diabetes. Diabetes Care 1992;15:613–619
20. Siddiqi TA, Miodovnik M, Mimouni F, Clark EA, Khoury JC, Tsang RC. Biphasic intrauterine growth in insulin-dependent diabetic pregnancies. J Am Coll Nutr 1989;8:225–234
21. Lampl M, Jeanty P. Exposure to maternal diabetes is associated with altered fetal growth patterns: a hypothesis regarding metabolic allocation to growth under hyperglycemic-hypoxemic conditions. Am J Hum Biol 2004;16:237–263
22. Widness JA, Susa JB, Garcia JF, et al. Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic rhesus fetuses. J Clin Invest 1981;67:637–642
23. Salvesen DR, Brudenell JM, Snijders RJ, Ireland RM, Nicolaides KH. Fetal plasma erythropoietin in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1993;168:88–94
24. Yeruchimovich M, Mimouni FB, Green DW, Dollberg S. Nucleated red blood cells in healthy infants of women with gestational diabetes. Obstet Gynecol 2000;95:84–86
25. Conrad KP, Benyo DF, Westerhausen-Larsen A, Miles TM. Expression of erythropoietin by the human placenta. FASEB J 1996;10:760–768
26. Perrine SP, Greene MF, Lee PD, Cohen RA, Faller DV. Insulin stimulates cord blood erythroid progenitor growth: evidence for an aetiological role in neonatal polycythaemia. Br J Haematol 1986;64:503–511
27. Desoye G, Shafrir E. Placental metabolism and its regulation in health and diabetes. Mol Aspects Med 1994;15:505–682
28. Desoye G, Shafrir E. The human placenta in diabetic pregnancy. Diabetes Rev (Alex) 1996;4:70–89
29. Desoye G, Kaufman P. The human placenta in diabetes. In *Diabetology of Pregnancy*. Djelmiš J, Desoye G, Ivanišević M, Eds. Basel, Karger, 2005, p. 94–109
30. Nelson SM, Coan PM, Burton GJ, Lindsay RS. Placental structure in type 1 diabetes: relation to fetal insulin, leptin, and IGF-I. Diabetes 2009;58:2634–2641
31. Gauster M, Desoye G, Tötsch M, Hiden U. The placenta and gestational diabetes mellitus. Curr Diab Rep 2012;12:16–23
32. Lassance L, Miedl H, Absenger M, et al. Hyperinsulinemia stimulates angiogenesis of human fetoplacental endothelial cells: a possible role of insulin in placental hypervascularization in diabetes mellitus. J Clin Endocrinol Metab 2013;98:E1438–E1447
33. Björk O, Persson B. Villous structure in different parts of the cotyledon in placentas of insulin-dependent diabetic women: a morphometric study. Acta Obstet Gynecol Scand 1984;63:37–43
34. Petry CD, Wobken JD, McKay H, et al. Placental transferrin receptor in diabetic pregnancies with increased fetal iron demand. Am J Physiol 1994;267:E507–E514
35. Georgieff MK, Berry SA, Wobken JD, Leibold EA. Increased placental iron regulatory protein-1 expression in diabetic pregnancies complicated by fetal iron deficiency. Placenta 1999;20:87–93
36. Georgieff MK, Petry CD, Mills MM, McKay H, Wobken JD. Increased N-glycosylation and reduced transferrin-binding capacity of transferrin receptor isolated from placentae of diabetic women. Placenta 1997;18:563–568
37. Mayhew TM, Jackson MR, Boyd PA. Changes in oxygen diffusive conductances of human placentae during gestation (10-41 weeks) are commensurate with the gain in fetal weight. Placenta 1993;14:51–61
38. Mayhew TM, Sørensen FB, Klebe JG, Jackson MR. Oxygen diffusive conductance in placentae from control and diabetic women. Diabetologia 1993;36:955–960
39. Kitzmiller JL, Watt N, Driscoll SG. Decidual arteriopathy in hypertension and diabetes in pregnancy: immunofluorescent studies. Am J Obstet Gynecol 1981;141:773–779
40. Nielsen FH, Jacobsen BB, Rolschau J. Pregnancy complicated by extreme hyperlipaemia and foam-cell accumulation in placenta. Acta Obstet Gynecol Scand 1973;52:83–89
41. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest 1997;100:2680–2690
42. Stefulj J, Panzenboeck U, Becker T, et al. Human endothelial cells of the placental barrier efficiently deliver cholesterol to the fetal circulation via ABCA1 and ABCG1. Circ Res 2009;104:600–608
43. Sun Y, Kopp S, Strutz J, et al. Gestational diabetes mellitus modulates cholesterol homeostasis in human fetoplacental endothelium. Biochim Biophys Acta. 17 May 2018 [Epub ahead of print]. DOI: 10.1016/j.bbalip.2018.05.005
44. Scholler M, Wadsack C, Lang I, et al. Phospholipid transfer protein in the placental endothelium is affected by gestational diabetes mellitus. J Clin Endocrinol Metab 2012;97:437–445
45. Díaz-Pérez FI, Hiden U, Gauster M, et al. Post-transcriptional down regulation of ICAM-1 in feto-placental endothelium in GDM. Cell Adhes Migr 2016;10:18–27
46. Hiden U, Maier A, Bilban M, et al. Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy. Diabetologia 2006;49:123–131
47. Wells JC. The thrifty phenotype: an adaptation in growth or metabolism? Am J Hum Biol 2011;23:65–75
48. Cvitic S, Longtine MS, Hackl H, et al. The human placental sexome differs between trophoblast epithelium and villous vessel endothelium. PLoS One 2013;8:e79233
49. Jiang S, Teague AM, Tryggestad JB, Aston CE, Lyons T, Chernausek SD. Effects of maternal diabetes and fetal sex on human placenta mitochondrial biogenesis. Placenta 2017;57:26–32
50. Evans L, Myatt L. Sexual dimorphism in the effect of maternal obesity on antioxidant defense mechanisms in the human placenta. Placenta 2017;51:64–69
51. Sedlmeier EM, Brunner S, Much D, et al. Human placental transcriptome shows sexually dimorphic gene expression and responsiveness to maternal dietary n-3 long-chain polyunsaturated fatty acid intervention during pregnancy. BMC Genomics 2014;15:941
52. Hoehn KL, Salmon AB, Hohnen-Behrens C, et al. Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci U S A 2009;106:17787–17792
53. Eder M, Csapo B, Wadsack C, et al. Sex differences in the association of cord blood insulin with subcutaneous adipose tissue in neonates. Int J Obes 2016;40:538–542
54. Gonzalez TL, Sun T, Koeppel AF, et al. Sex differences in the late first trimester human placenta transcriptome. Biol Sex Differ 2018;9:4
55. Hiden U, Glitzner E, Hartmann M, Desoye G. Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. J Anat 2009;215:60–68
56. Lapolla A, Porcu S, Roverso M, et al. A preliminary investigation on placenta protein profile reveals only modest changes in well controlled gestational diabetes mellitus. Eur J Mass Spectrom (Chichester) 2013;19:211–223
57. Roverso M, Lapolla A, Cosma C, et al. Some preliminary matrix-assisted laser desorption/ionization imaging experiments on maternal and fetal sides of human placenta. Eur J Mass Spectrom (Chichester) 2014;20:261–269
58. Gauster M, Hiden U, van Poppel M, et al. Dysregulation of placental endothelial lipase in obese women with gestational diabetes mellitus. Diabetes 2011;60:2457–2464
59. Perazzolo S, Hirschmugl B, Wadsack C, Desoye G, Lewis RM, Sengers BG. The influence of placental metabolism on fatty acid transfer to the fetus. J Lipid Res 2017;58:443–454
60. Hirschmugl B, Desoye G, Catalano P, et al. Maternal obesity modulates intracellular lipid turnover in the human term placenta. Int J Obes 2017;41:317–323
61. Saben J, Lindsey F, Zhong Y, et al. Maternal obesity is associated with a lipotoxic placental environment. Placenta 2014;35:171–177

62. Poissonnet CM, Burdi AR, Garn SM. The chronology of adipose tissue appearance and distribution in the human fetus. Early Hum Dev 1984;10:1–11
63. Schaefer-Graf U, Napoli A, Nolan CJ, Diabetic Pregnancy Study Group. Diabetes in pregnancy: a new decade of challenges ahead. Diabetologia 2018;61:1012–1021
64. McIntyre D, Desoye G, Dunne F, et al. FIGO analysis of research priorities in hyperglycemia in pregnancy. Diabetes Res Clin Pract. 27 March 2018 [Epub ahead of print]. DOI: 10.1016/j.diabres.2018.03.026
65. Benirschke K, Kaufmann P, Baergen RN. *Pathology of the Human Placenta*. New York, Springer, 2006
66. Boyd JD, Hamilton WJ. *The Human Placenta*. Cambridge, Heffer, 1970
67. O'Rahilly R. Developmental Stages in Human Embryos. Part A: Embryos of the first three weeks (stages 1 to 9). Washington, DC, Carnegie Institution of Washington, 1973 (Publication 631)