Perspectives in Diabetes article

Pregnancies in Diabetes and Obesity:

The Capacity-Load Model of Placental Adaptation

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New paper on how the fetus responds to the challenges of maternal diabetes and obesity. The fetus sends signals such as insulin to the placenta, which responds with protection. When this protection fails, adverse fetal outcomes may result.

Abstract

Excess nutritional supply to the growing foetus, resulting from maternal diabetes mellitus and obesity, is associated with increased risks of foetal maldevelopment and adverse metabolic conditions in post-natal life. The placenta, interposed between mother and foetus, serves as the gateway between the two circulations, and is usually considered to mediate maternal exposures to the foetus through a direct supply line. In this Perspective, however, we argue that the placenta is not an innocent bystander, and mounts responses to foetal 'signals of distress' to sustain its own adequate function and protect the foetus. We describe several types of protection that the placenta can offer the foetus against maternal metabolic perturbations, and offer a theoretical model of how the placenta responds to the intrauterine environment in maternal diabetes and obesity to stabilise the foetal environment. Our approach supports growing calls for early screening and control of pregnancy metabolism to minimise harmful foetal outcomes.

Introduction

The placenta is a foetal organ interposed between the maternal and foetal circulation, and thus exposed to influences from both sides. The placenta develops alongside, and initially in advance of, the foetus throughout pregnancy. Various factors can disrupt this development, and in this context, much attention has focused on maternal undernutrition and pre-eclampsia (1). However, the metabolic, endocrine and inflammatory effects of maternal diabetes mellitus or obesity are also associated with changes in placental structure and function (2). These changes are associated, potentially causally, with variability in foetal phenotype, and may have long-term health effects (3). In particular, compared with neonates of non-diabetic or lean mothers, those of diabetic or obese mothers typically demonstrate excessive fat accretion (4; 5).

However, at the individual level, neonates exposed to maternal metabolic dysfunction do not always show these changes. Why therefore are some diabetic or obese mothers prone to poorer neonatal outcomes? Beyond any heterogeneity in maternal metabolic phenotype, some reasons for variable foetal responses may relate to the placenta itself. However, this issue has received minimal attention.

The human foetus and neonate are unusual among mammals in demonstrating high fat accretion before birth (6), proposed to buffer the brain against potential malnutrition in early infancy (6). The human neonatal brain also consumes a much larger fraction of oxygen than any other species (6). These traits require adequate mechanisms of maternal oxygen supply across the placenta, not only under normal conditions, but also when foetal oxygen demand is high or maternal supply is impaired. The placenta

develops and operates in a low oxygen environment. At the end of pregnancy, placental glucose metabolism is mostly glycolytic, i.e. non-oxidative (7). This may prevent the excessive generation of reactive oxygen species (ROS) by the mitochondria, but also spares energy for the foetus through releasing a portion of placentally-derived lactate, which may aid foetal brain metabolism.

Several aspects of placental function indicate some kind of adaptive response to variability in maternal phenotype, which may benefit foetal outcomes. Until recently, the primary focus was on maternal undernutrition. Under the lens of 'genetic conflict theory', the placenta was considered to act in the interests of the foetus, for example releasing hormones into the maternal blood stream that elevate maternal blood pressure, to force more nutrients across the placental interface (8; 9). This would protect foetal fuel supply against low maternal circulating nutrient levels.

However, we suggest that such responses may also occur in the context of maternal diabetes or obesity. The placenta may respond to enhanced foetal oxygen demand by enlarging the surface area of exchange, thus facilitating maternal-to-foetal oxygen diffusion. Similarly, the placenta may remove cholesterol from its circulation, preventing formation of pro-atherosclerotic lesions that might impede foeto-placental blood flow. Manifold other placental changes have been described in diabetes and obesity at the end of gestation. However, little attempt has been made to interpret these changes within an adaptive framework.

Here, we describe in more detail how the placenta can protect the foetus against maternal metabolic perturbations, and offer a conceptual model of how this provides a stable environment for the foetus. We use these concepts to support the growing call for early screening (and control) of pregnancy metabolism, to minimise adverse foetal outcomes.

Placental homeostatic capacity

During intrauterine development the homeostatic capacity of the foetus itself is immature and will only begin to fulfil this function after delivery (as shown by the heterogeneity of neonatal glucose metabolism (10)). Variations in foetal metabolism can serve as signals to the placenta, in particular to the endothelium, which lines the foeto-placental vasculature. These signals can induce placental responses, which can be interpreted as adapting placental structure and function to protect foetal development. Broadly, this allows the placenta to play a key role in foetal metabolic homeostasis.

The classical example is the placental response to foetal hypoxia. It has long been known that maternal overnutrition leads to foetal hyperinsulinism, which stimulates glucose utilization through aerobic

metabolism. As a result, foetal oxygen demand rises. If this demand cannot be adequately satisfied, because of maternal undersupply, foetal hypoxia may ensue. To protect the foetus, the placenta enlarges its surface area of exchange to facilitate oxygen transfer (11). One of the foetal signals that stimulates this vascular growth (angiogenesis) through various cooperating mechanisms is insulin (12; 13). Thus, the same signal that causes the increased foetal demand for oxygen also stimulates the adaptive placental response.

At the same time, the foetus increases its number of red blood cells as acceptors for oxygen (14). In turn, this augmented erythropoiesis increases foetal iron demand, which is met by transplacental transfer of transferrin. This may be enhanced in diabetes, because placental transferrin receptor expression is increased in this condition (15). In sum, these adaptations link together metabolic responses in the foetus and placenta that allow higher oxygen uptake to be achieved.

A second example of placental adaptation relates to the protection of vessels from pre-atherosclerotic lesions, in order to maintain blood flow and nutrient/oxygen supply. While the maternal-decidual blood vessels, the intervillous space (which harbours maternal blood), and the foetal arteries all show signs of pre-atherosclerotic lesions in situations of maternal overnutrition/hyperlipidemia (16-18), such lesions have never been reported in the vessels of the placenta itself. Thus, efficient mechanisms must exist to protect these vessels from any pre-atherosclerotic lesions/foam cells/plaques, which may compromise blood flow.

Recently, we found that oxidative stress in the foetal circulation and placental endothelial cells associated with gestational diabetes mellitus (GDM) leads to higher cholesterol synthesis in the endothelial cells (19). At the same time, the endothelial cells enhance their cholesterol efflux capacity by upregulating two efflux transporters in response to signals emerging from the adverse consequences of the diabetic environment (ROS induced formation of oxysterols) as a stimulus for counter-regulatory measures (**Figure 1**). These serve to avoid intracellular toxic effects of cholesterol and, hence, maintain full function in the endothelial cells. Moreover, the formation of pre-atherosclerotic lesions is also avoided, because one enzyme on the surface of the endothelial cells, phospholipid transfer protein, is upregulated in GDM by insulin (20). Thus, this system efficiently removes free cholesterol from foetal endothelial cells and the foeto-placental circulation under conditions of GDM.

These examples highlight the capacity of the placenta, at least at the end of pregnancy, to mount adaptive responses to the adverse foetal environment generated by maternal over-nutrition, thereby protecting foetal development. Intriguingly, foetal insulin, which is elevated in GDM and metabolically abnormal obesity, seems to play a key role in inducing several of these adaptive changes at the end of pregnancy.

It is pertinent that early in pregnancy, the majority of insulin receptors are located on the syncytiotrophoblast, which represents the placental interface with the maternal circulation. Later in pregnancy, insulin receptor location undergoes a maternal-to foetal shift, such that the receptor majority is then on the surface of the endothelial cells that interact with the foetal circulation, and can receive foetal insulin signals (21). This shift makes the foeto-placental unit less susceptible to variations in maternal insulin levels. At the same time, it also establishes a mechanism for foetal protection, whereby 'signals of distress' from the foetus induce an adaptive placental response. The timing of onset of this mechanism has not been established yet, but will not be before pregnancy weeks 12-14, when insulin is secreted by the fetal pancreas into the circulation (22; 23).

The capacity-load model

Homeostasis is a key physiological principle, referring to a range of metabolic regulatory processes that maintain a relatively stable internal state in the face of environmental fluctuations. The brain plays a key role, but has also 'outsourced' many activities to other organs and tissues, whilst also protecting itself from metabolic perturbations through its resistant blood-brain barrier (24).

Whilst many challenges to homeostasis emerge directly from the external environmental (eg temperature, food supply, predators), other stresses relate more closely to 'internal' components of metabolism. We have previously proposed a 'capacity-load' model of metabolism, noting that many internal characteristics of the organism (eg lipogenic diet, abdominal adiposity, sedentary behaviour, psychosocial stress, infection and immune response), which we collectively term 'metabolic load', can pose major challenges to homeostasis. This load must be resolved by the functions of diverse organs, which we collectively term homeostatic 'metabolic capacity'. Failure to resolve these challenges allows the early accumulation of risk factors for a range of non-communicable diseases (24-26).

From a life-course perspective, the development of metabolic capacity occurs primarily in foetal life and early infancy, under the protective metabolic milieu of maternal phenotype (24). During this period, development is dominated by hyperplastic growth, which encompasses organogenesis (27). Other critical developmental processes include the emergence of epigenetic effects in DNA expression and the development of hormonal set-points (28; 29). Inter-individual variability in many of these traits tends to track on into later life, and has life-long impact on the capacity for homeostasis (24).

In contrast to metabolic capacity, metabolic load largely develops from birth onwards, though it may already be present in the later stages of foetal life, as demonstrated by the high fat content and hyperinsulinaemia of neonates born to obese or diabetic mothers (30; 31).

The capacity-load model assumes that cardiometabolic risk increases in association with both lower metabolic capacity, and higher metabolic load (24-26). Numerous studies support the hypothesis, for example birth weight (a proxy for metabolic capacity) shows an inverse association with the risk of type 2 diabetes or hypertension, whereas lipogenic diet, high BMI and sedentary behaviour in adulthood (markers of load) all increase the risk of these conditions (32). Whilst sharing much in common with the 'thrifty phenotype' hypothesis (33), a difference in the capacity-load model is that it assumes dose-response associations of foetal nutritional supply and early growth patterns with metabolic capacity. This helps explain why inverse associations of birth weight with the risk of non-communicable diseases are observed across the majority of the range of birth weight, rather than being evident only in those of low birth weight (32; 34).

For most of the life-course, both metabolic capacity and load can be considered properties of individual organisms. However, we suggest that this model should be adapted to address pregnancy, where metabolic load is broadly generated by the mother rather than the foetus, and the foetus has very limited direct capacity for homeostasis.

The examples of placental adaptability reviewed above may therefore be reconceptualised as components of placental metabolic capacity unique to the developmental stage of foetal life. When a mother develops a high metabolic load, the placenta is uniquely positioned to protect the foetus. We would then expect maternal metabolic aberrations, or their correlated responses in the foetus, to become vital signals for the placenta, eliciting protective responses. However, such placental protection is expected to have limits, above which it is overwhelmed by maternal and foetal metabolic perturbations with adverse consequences for the foetus (**Figure 2**).

Variation of placental tolerance

This model offers the advantage of incorporating several factors, relating to both mother and offspring that may collectively modify the threshold of metabolic load that the placenta is capable of tolerating. These are briefly reviewed below.

<u>Foetal sex</u>

In terms of the model illustrated in **Figure 2**, substantial evidence indicates that females have a higher tolerance threshold than males, resulting in males being more susceptible to metabolic perturbations. These differences may ultimately be due to the two sexes being subject to contrasting selective pressures to maximise inclusive fitness, resulting in different growth strategies in foetal life (35). Male foetuses typically accrete more lean mass than females (36), who accrete slightly more fat and demonstrate a more central fat distribution (37).

Pregnancy outcomes have long been established to be worse in males than in females (38). Sex-dichotomy in placentas may contribute to these different outcomes, because male and female placentas differ molecularly and functionally. The effect of foetal sex on gene expression differs even within the placenta, in ways that are cell-specific and related to different functional pathways. In male placentas these encompass signalling pathways for graft-versus-host disease as well as immune function and inflammation, both of which parallel poorer pregnancy outcomes among male foetuses (39).

These molecular sex differences may underlie sex-dependent placental responses to environmental challenges. Supplementing mothers with n-3 fatty acids modifies the placental transcriptome in a sexually dimorphic manner with female placentas being more responsive to treatment (40) potentially reflecting better plasticity to mount adaptive responses.

As detailed above, foetal insulin is a driver of placental adaptation (12; 41; 42). However, these findings were obtained using endothelial cells from female placentas, and males may respond differently. For example, placental vascularization in maternal diabetes shows a significant interaction with foetal sex (43). Similarly, the higher rate of stillbirths in males than females (44) can be interpreted as metabolic load exceeding placental homeostatic capacity and, thus, placental failure to adapt to foetal oxygen demand by hypervascularization.

Foetal responses also differ by sex. Female neonates born to GDM pregnancies are less insulin-sensitive than males (45). Since insulin is a key determinant of foetal phenotype in maternal overnutrition, this may represent a protective mechanism that is especially pronounced in females. In particular, the deposition of triglycerides in foetal/neonatal adipocytes may be reduced in females. Consistent with that hypothesis, a sex-dependent association between insulin and neonatal fat was found for some depots, indicating that fat deposition seems to be less affected by insulin in female neonates compared to males (46).

Such sex differences are also apparent during maternal undernutrition, as shown in the Dutch famine, where exposure early in gestation was associated with a greater reduction in placental area in boys than girls (47). In a situation of maternal overnutrition such as GDM, estrogen receptor-alpha in the decidual vessels, in particular the extravillous trophoblast subpopulation, is down-regulated in pregnancies with male, but not female foetuses (48). The functional consequences are unclear.

Heterogeneity of the placenta

The placenta is a heterogeneous organ composed of diverse different cell types. Their activity and spatial arrangement depends on the specific function of the anatomical key structures (villi) in which they are located. The surface repertoire of molecules such as receptors and transporters may therefore vary, depending on the cells' location within the placental tissue. Even among endothelial cells, phenotypic

heterogeneity suggests differential functional responses along the vascular tree (49). Such heterogeneity may influence the placental capacity for protecting the foetus. For example, insulin receptors are heterogeneously distributed along the vascular tree (42), hence, insulin-mediated adaptive responses may vary by location.

Time period in gestation

The capacity of the placenta for adaptive responses will undoubtedly increase with gestational age. At the very beginning of pregnancy, i.e. the blastocyst stage, even minor environmental perturbations such as culture media used in *in vitro* fertilization influence placental growth (50), suggesting a high degree of sensitivity and vulnerability at this stage.

Although at week 12 of pregnancy the placenta weighs only 5% of its total final weight, it is in this period that it grows most rapidly (51). It is known that rapidly growing tissues/proliferating cells are most sensitive to environmental perturbations (52). Indeed, there is circumstantial evidence suggesting that placental growth is reduced in the first trimester of T1DM pregnancies (53).

The consequence of impaired placental growth as a response to the diabetic environment is a reduction in foetal growth rate. Given that placental size limits foetal growth early in pregnancy, shorter foetuses at this pregnancy stage may be the consequence of smaller placentas. However, later in pregnancy, the foetus can undergo catch-up growth, and at the end of pregnancy its weight may exceed that of the neonate born to normal pregnancies (54). Parallel to its growth, the adaptive capacity of the placenta may increase, increasing its threshold for tolerating metabolic disturbances.

Genetic factors

Aside from any maternal genes associated with maternal obesity and gestational diabetes (55),the placental response to metabolic load may also be determined by its genetic makeup. As a foetal tissue, the placenta is under the genetic influence of both parents, with the paternal genome promoting nutrient supply to the foetus, while the maternal genome acts in the opposing direction (56; 57). As discussed above, these asymmetric roles are assumed to have evolved in the evolutionary context of energy scarcity, though whether genomic imprinting evolved through overt conflict between the two parents regarding the magnitude of maternal nutritional investment (58; 59), or whether it evolved more as a co-adaptive process (60; 61), remains unresolved. Importantly, genomic imprinting may have different effects depending on the trimester of pregnancy, for example impacting placental structure at earlier gestational age and placental function at later gestational age (62; 63).

While growth-promoting paternal genes may appear to play a disproportionate role in generating the *need* for placental protection, by increasing foetal exposure to maternal metabolic excess, maternal genes may still play an important role. Paternally-expressed genes appear to promote growth of functional tissues in the foetus such as skeletal muscle, bone and organ mass, whereas maternal-expressed genes favour foetal fat accretion, which is augmented in maternal obesity and diabetes (57). Moreover, it is not clear which of paternal and maternal genes might then drive the adaptive responses we have outlined above. One the one hand, paternal genes might themselves promote this protection, to 'insure' against the costs of increasing nutrient demand. On the other hand, maternal genes might promote placental homeostasis, to protect the foetus from such aggressive paternal tactics. It is also possible that the genes of both parents might contribute to the capacity for placental homeostasis.

Limits to homeostatic capacity

Any of these adaptive responses may, however, have a limited capacity. When the metabolic load exceeds this capacity, then the placental changes described above will not be enough to protect the foetus, and foetal compromise may ensue. There are several examples for limited placental capacity and tolerance towards environmental changes/stresses:

1) First, endothelial lipase (EL) is an enzyme on the surface of the syncytiotrophoblast and on placental endothelial cells. It mediates the uptake of fatty acids from high-density lipoproteins. Its expression is unchanged in GDM or obesity. Only when both conditions are combined (ie GDM and obesity) is EL upregulated, indicating that placental homeostatic capacity has been exceeded (**Figure 3**, left panel). We have identified pro-inflammatory cytokines as key signals inducing this upregulation (64).

2) Second, the placenta can store fatty acids as triglycerides in lipid droplets, potentially serving as a protective mechanism to avoid lipotoxic effects in the placenta/syncytiotrophoblast (65). The storage capacity has a limit: With increasing BMI of the mother, ie with increasing metabolic load as reflected by increasing fatty acid and insulin concentrations, more triglycerides can be stored (BMI < 25 versus BMI 30-35). However, with further increasing BMI the placenta does not store any more triglycerides (**Figure 3**, right panel) (66), indicating that metabolic load has exceeded placental capacity.

3) Third, studies show that transmission of the stress generated by maternal obesity to the foetus may depend not only on the placenta, but also on the mother's own metabolic capacity. In a study of Swedish mothers, for example, the association of maternal obesity with childhood obesity in the offspring was exacerbated if the mother was also born with low birth weight (67). This suggests that the capacity to maintain homeostasis and regulate substrate supply to the foetus during pregnancy is reduced among

mothers with lower metabolic capacity. Likewise, we propose that placental protection will be more quickly exhausted among obese/diabetic mothers who developed lower levels of metabolic capacity in early life.

Conclusion and Implications

During evolution the human placenta developed mechanisms that support its role not only in sustaining foetal development, but also to protect the growing foetus from an affluent metabolic environment and potential adverse consequences. Although it is difficult to reconstruct maternal pregnancy metabolism in ancestral populations, apes such as orang-utans are capable of storing fat to fund lactation (68), while high levels of female body fat in pre-agricultural human populations are indicated by figurines that clearly depict very high BMI (69). Therefore, it is plausible that natural selection could have favoured the evolution of such protective mechanisms. Moreover, the prevalence of GDM worldwide is inversely associated with the historical duration over which high-glycaemic diets have been consumed, indicating recent selection for blunted metabolic responses to such diets (70).

Key components of these protective mechanisms are foetal signals, which interact with placental endothelial cells to induce adaptive responses that maintain homeostasis at the foeto-placental interface. The homeostatic capacity of the placenta depends on various factors including gestational age and foetal sex and may regionally vary along the vascular tree. These protective effects, however, can be overwhelmed by an excessive metabolic load of maternal overnutrition associated with diabetes, obesity or both. This model offers an opportunity to integrate future results on foeto-placental interactions into a framework aligned with concepts on human evolution.

Our approach highlights placental function as a new target to be considered in future intervention strategies, and the window of early pregnancy may be especially important as the placenta develops ahead of the foetus. Although the experimental results used to develop this concept relate to the end of pregnancy, these mechanisms must be in place at earlier time periods. This perspective supports the growing call to control maternal metabolism as early as possible (71). Early disturbance of maternal metabolism especially in high risk women such as those with obesity, history of GDM and/or a family history of diabetes is associated with poorer pregnancy outcome of the newborn manifested e.g. in excessive fat accretion *in utero*. We propose this is in part the result of underdeveloped placental homeostatic capacity.

Authors contributions:

Both authors have jointly developed the theoretical concept and written the manuscript.

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Figure legends

Figure 1: Foetal signals related to excess nutritional supply facilitate placental adaptation to prevent atherosclerotic plaques being formed

Foeto-placental endothelial cells synthesize more cholesterol in GDM than in normal pregnancies (19). At the same time, two cholesterol efflux transporters (ABCA1, ABCG1) are upregulated through activation of the LXR transcription factor in response to higher concentrations of circulating and intra-endothelial oxysterols formed by ROS-induced cholesterol oxidation. Cholesterol efflux from these endothelial cells is also enhanced by insulin-induced upregulation of phospholipid transfer protein (PLTP) on the surface of the endothelial cells in GDM (20; 72). This enzyme transfers cholesterol from HDL_3 to HDL_2, while pre-beta HDL remains. Pre-beta HDL can pick up cholesterol from the endothelial cells, as it is a cholesterol acceptor (73). The majority of HDL_2 will be taken up by the foetal liver and the cholesterol converted into bile acids. Thus, there is a very efficient system for removing free cholesterol from foeto-placental endothelial cells and the foeto-placental circulation to avoid foetal hypercholesterolemia under conditions of GDM. A second system to prevent formation of atherosclerotic plaques involves the downregulation of intercellular adhesion molecule-1 (ICAM-1) expressed on the surface of foeto-placental endothelial cells in GDM (74). ICAM-1 mediates the adhesion of leukocytes to endothelial cells, which then transmigrate into the subendothelial space. Outside pregnancy, this mechanism plays a pivotal role in the inflammatory component of atherosclerosis (75). Loss of endothelial cell surface and soluble ICAM-1 in GDM may be induced, among other factors, by foetal insulin (76). Foetal insulin also increases endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) synthesis (12) providing atheroprotection (77). These three systems, and probably more, act in concert to ultimately protect the foeto-placental circulation.

Footnote: This is a schematic depicting the coordinated action of the players and not their precise location. PLTP is located on the endothelial surface.

Figure 2: **Placental homeostatic capacity/efficiency model**.

During pregnancy, the placenta has a homeostatic capacity that will maintain foeto-placental homeostasis and determine the efficiency, with which the placenta protects the foetus from adverse consequences of a disturbed intrauterine environment. Up to a certain level of maternal metabolic load, the placenta can respond to signals such as insulin and orchestrate adaptive homeostatic responses that preserve an optimal metabolic milieu for foetal development. We hypothesise that this capacity is negligible during the early weeks in pregnancy and fully developed at the end. However, above the limiting threshold, such

placenta capacity is exhausted and adverse foetal effects ensure. This threshold may differ according to both maternal and foetal traits (53).

Figure 3: Placental homeostatic capacity has its limits resulting in potentially adverse changes when the metabolic load exceeds this limit.

Left panel: Expression of endothelial lipase, a gene that is involved in lipid metabolism and perhaps fatty acid supply to the foetus, is stable in maternal obesity and gestational diabetes mellitus (GDM), and only responds when metabolic load is high, i.e. in GDM and obesity (64). Importantly, the association of maternal obesity with adverse outcomes such as high neonatal fat mass is independent of maternal (gestational) diabetes (5).

Right panel: Placental accumulation of triglycerides as a means to protect against lipotoxicity (63) increases with increasing maternal metabolic load i.e., between lean and class I obese women. This capacity is exhausted with a further increase in load i.e., in class II and III obese women and no further additional triglycerides are stored (64).

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Figure 1

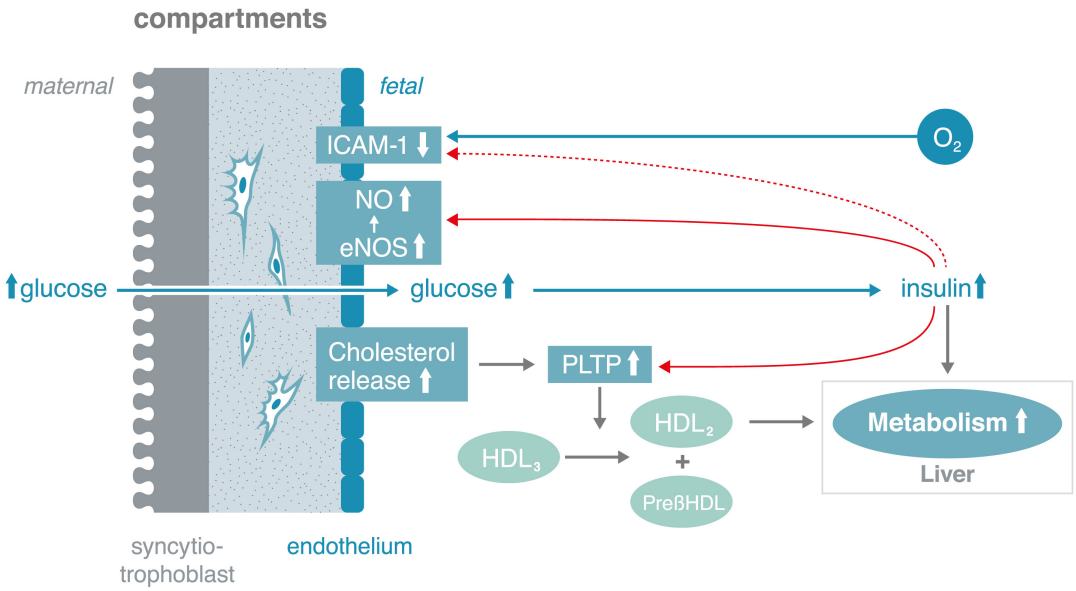
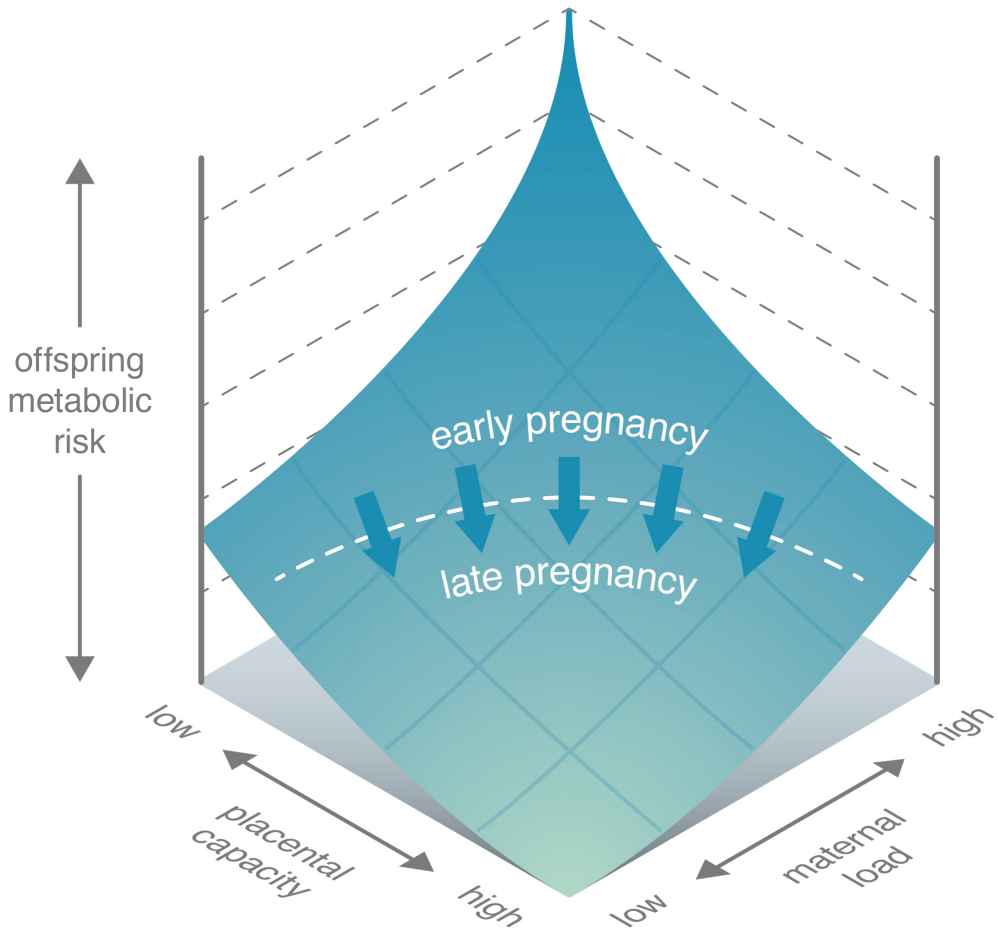

compartments
maternal
fetal
ICAM-1
O2
NO
eNOS
glucose
glucose
insulin
Cholesterol release
PLTP
HDL2
HDL3
+
PreßHDL
Metabolism
Liver
syncytio-trophoblast
endothelium

Figure 2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metabolic
risk
early pregnancy
late pregnancy
low
placental
capacity
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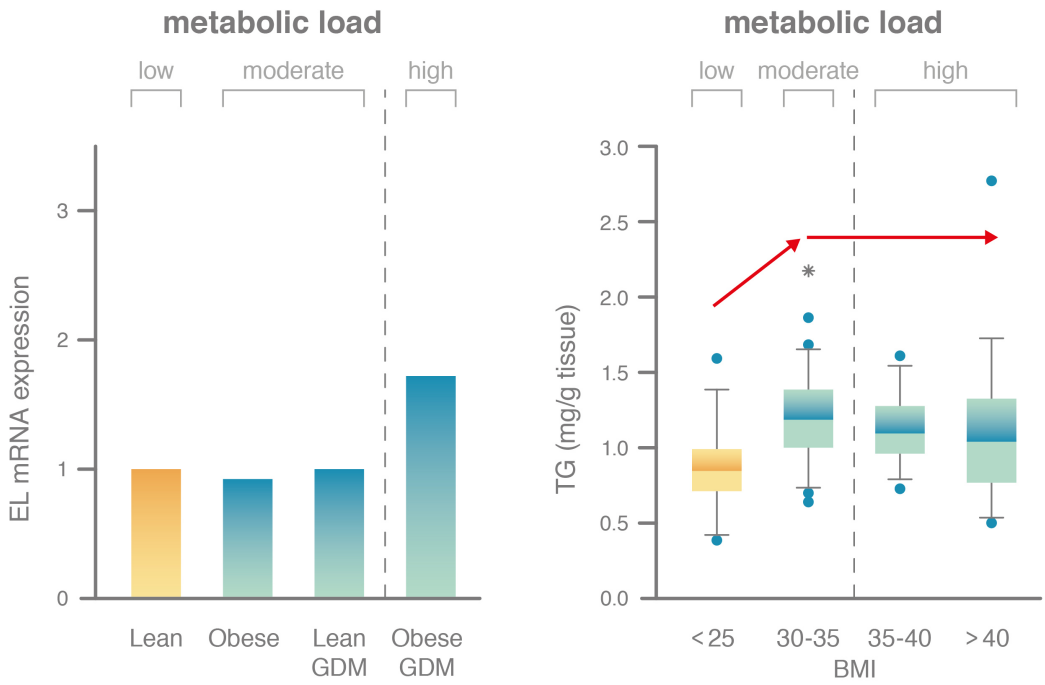
load
high

Figure 3


metabolic load
low
moderate
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EL mRNA expression
3
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Lean
Obese
Lean GDM
Obese GDM
metabolic load
low
moderate
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TG (mg/g tissue)
3.0
2.5
2.0
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*
<25
30-35
35-40
>40
BMI