

# The Placental Exposome: Placental Determinants of Fetal Adiposity and Postnatal Body Composition

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## Key Words

Fetal adiposity · Maternal obesity · Nutrient · Obesity · Placenta · Postnatal environment

## Abstract

Offspring of obese and diabetic mothers are at increased risk of being born with excess adiposity as a consequence of their intrauterine environment. Excessive fetal fat accretion reflects additional placental nutrient transfer, suggesting an effect of the maternal environment on placental function. High plasma levels of particular nutrients in obese and diabetic mothers are likely to be the important drivers of nutrient transfer to the fetus, resulting in excess fat accretion. However, not all offspring of obese and diabetic mothers are born large for gestational age and the explanation may involve the regulation of placental nutrient transfer required for fetal growth. The placenta integrates maternal and fetal signals across gestation in order to determine nutrient transfer rate. Understanding the nature of these signals and pla-

cental responses to them is key to understanding the pathology of both fetal growth restriction and macrosomia. The overall effects of the maternal environment on the placenta are the product of its exposures throughout gestation, the 'placental exposome'. Understanding these environmental influences is important as exposures early in gestation, for instance causing changes in the function of genes involved in nutrient transfer, may determine how the placenta will respond to exposures later in gestation, such as to raised maternal plasma glucose or lipid concentrations. Longitudinal studies are required which allow investigation of the influences on the placenta across gestation. These studies need to make full use of developing technologies characterising placental function, fetal growth and body composition. Understanding these processes will assist in the development of preventive strategies and treatments to optimise prenatal growth in those pregnancies at risk of either excess or insufficient nutrient supply and could also reduce the risk of chronic disease in later life.

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## Introduction

Maternal obesity and diabetes alter the intrauterine environment and increase the risk of large for gestational age (LGA) offspring. A disproportionate increase in fat mass makes an important contribution to the increased birth weight in LGA babies [1, 2], but can also be found in offspring born with weight appropriate for their gestational age [3]. Excess fetal fat accumulation may predispose these individuals to develop obesity in later life and raises the possibility of an intergenerational cycle of obesity [4]. Maternal obesity is associated with a doubling in the rate of LGA births compared to women of normal weight [5]. While shared genetics and environment will contribute to this relationship it is likely that factors specific to the in utero environment are also important. The role of intrauterine environment is illustrated by the observation that babies born to women following bariatric surgery have half the risk of becoming obese relative to their siblings born prior to surgery [6].

While the association between in utero environment and fetal adiposity is clear, with maternal pre-gravid obesity and diabetes being the strongest maternal determinants [1, 7], the mechanisms through which maternal factors increase fetal adiposity are not fully understood. However, as the principal organ through which nutrients are transferred to the fetus, the placenta is likely to be an important mediator of this process. The placenta is not simply a passive conduit for nutrients but responds to both maternal and fetal signals, altering placental transport and metabolic function [8, 9]. At any point in gestation, placental function will reflect a progressive accumulation of external influences experienced during the course of its development. These can be conceptualised as the 'placental exposome'. The exposome of an individual encompasses the product of lifetime environmental exposures starting in utero and varying according to life stage [10]. The in utero environment experienced by the placenta is itself the product of the maternal exposome, for instance effects of maternal obesity on the placenta reflect a historical mismatch between food intake and energy expenditure.

Ideally, prevention of obesity and diabetes should occur prior to pregnancy. However, where this is not possible, the development of successful interventions will be facilitated by a more detailed understanding of those pregnancies in which maternal obesity and diabetes leads to increased placental nutrient transfer and greater fetal adiposity.

This review is based on discussions at the workshop 'The Placenta and Its Role for Fetal and Neonatal Development', which took place in Austria, October 2012, sup-

ported by the EU FP7 project EarlyNutrition. Themes emerging from this workshop included: the central role of placental function in determining fetal growth and body composition, how placental function is determined by its exposome, the potential for epigenetics to act as a mediator of environmental influence on placental function, and ways in which new technologies can be incorporated into longitudinal population studies to investigate the role of the placenta in mediating maternal exposures on fetal growth and postnatal health.

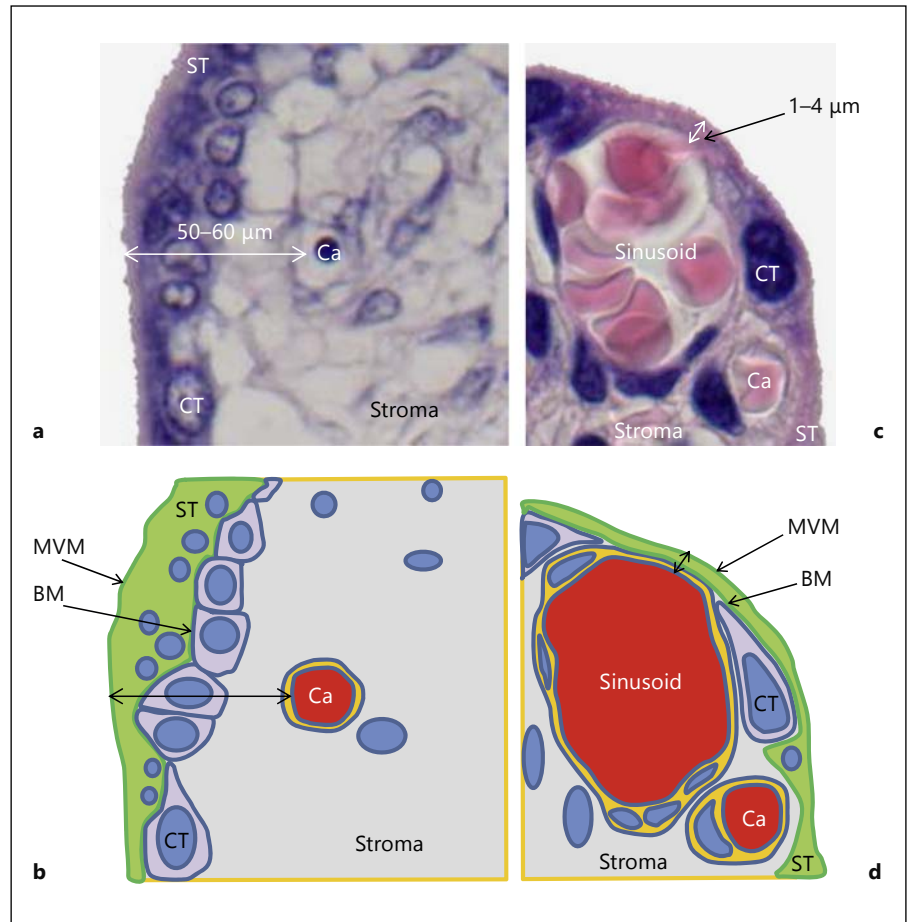
## Placental Structure, Function and Regulation

Placental nutrient transfer underpins fetal growth and development. The nutrient transfer capacity of a placenta will depend on its structure and fetal maternal blood flow, whereas actual transfer depends on how these factors and transporter density are regulated. This regulation can occur over long (e.g. structural or epigenetic changes in the placenta) and short (e.g. placental responses to maternal hormones or nutrients) time scales, and therefore it is important to understand all the determinants of placental function across gestation.

The growing fetus requires adequate and appropriate placental nutrient transfer but excessive nutrient transfer, or an inappropriate balance of nutrients, may cause the fetus to lay down excess fat and become LGA [1, 2]. In order to identify abnormal fetal growth, it is important to understand placental development, the mechanisms underlying placental function and their regulation.

The placenta has a complex anatomical structure which develops throughout gestation increasing its nutrient transfer capacity to match the requirements of the growing fetus [11]. The placental villi are the sites of nutrient exchange and, in broad terms, they form in the first trimester, branch in the second and assume their final structure during the third trimester. Once its final structure is established, the placenta remains a dynamic organ with continual turnover of villous trophoblasts as well as development and regression of placental vessels (fig. 1). This evolution throughout gestation means that disruptive factors can have persistent effects that will differ depending on their timing. The role of extravillous trophoblast cells, which associate with spiral arteries and uterine glands, is also important in mediating blood flow to the fetus [12]. Placental weight is a major determinant of fetal growth, reflecting a greater nutrient transport capacity. Maternal weight gain in early pregnancy has an influence on fetal weight, which is thought to be partly mediated

**Fig. 1.** Representation of the structures of a first-trimester immature intermediate villus (**a, b**) and a third-trimester terminal villus (**c, d**). **a, b** There is a double-layered epithelium with a thick syncytiotrophoblast (ST) and a complete layer of cytotrophoblasts (CT). The distance between a capillary (Ca) and the outer surface of the ST is depicted by an arrow and is in the range of 50–60  $\mu\text{m}$  at the beginning of pregnancy. **c, d** There is only a thin layer of ST with some CT underneath. Especially in terminal villi, Ca transform into larger sinusoids that are located subjacent to the ST. Hence, the distance between fetal and maternal blood – as depicted by the arrows – is very short (1.3–4  $\mu\text{m}$ ). The shortening of the diffusion distance between the maternal and fetal circulation during the course of pregnancy facilitates the transport of nutrients and oxygen paralleling the increasing needs of the growing fetus. The MVM and BM of the ST are indicated by arrows.



through its effects on placental growth [13]. Consequently, in some obese mothers, enhanced fetal growth could be mediated through raised placental mass [14]. Blood flow through the maternal side of the placenta starts at the end of the first trimester. Prior to the initiation of placental blood flow, the villi are nourished by secretions from uterine glands and plasma filtrate [15]. Maternal blood delivers nutrients and oxygen to the placenta and any disruption of this flow may affect fetal nutrient supply. One of the major causes of impaired maternal blood supply is the failure of spiral artery remodelling [16]. Reduced blood flow through the placenta as a result of failure to remodel the spiral arteries may decrease nutrient availability to the fetus and may affect fetal development in the second and third trimesters [17]. Failure to remodel the spiral arteries early in gestation may therefore limit placental nutrient transfer capacity throughout gestation.

Excess placental transfer of glucose and lipids are prime candidates for promoting fetal adiposity. Transfer of glucose, lipids and amino acids across the placenta requires

transport across a series of cell membranes by specific membrane transport proteins. Transport occurs across the maternal-facing microvillus membrane (MVM) and fetal-facing basal membrane (BM) of the placental syncytiotrophoblast (fig. 1). Glucose transfer is primarily through facilitated diffusion and is mediated by one family of transporters, the GLUTs, across both the MVM and the BM. There are multiple transporters for fatty acids and amino acids which are differentially localised to the MVM and BM [18]. Once across the BM, it is likely that glucose and amino acids can diffuse through endothelial junctions into the fetal circulation while fatty acids may also require mediated transport across the endothelium.

Metabolism of nutrients within the syncytiotrophoblast will affect fetal transfer and may be regulatory [19]. A proportion of the glucose taken up by the placenta is converted to lactate and in humans this lactate is primarily transported back to the mother [20]. Fatty acids and amino acids can be incorporated into lipid and protein pools, respectively, as well as being catabolised for energy.

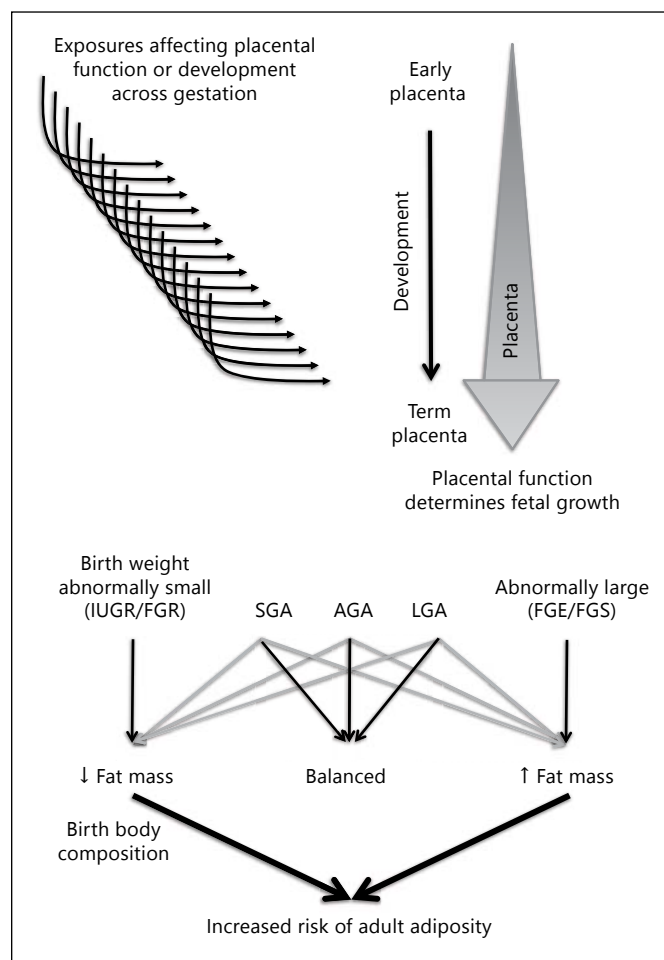
Membrane transporter abundance in the placenta is regulated in response to nutritional and endocrine signals from the mother [21]. Both maternal diet and body composition are associated with changes in placental transporter activity that reflect nutritional and endocrine signals [22, 23]. Decreased transporter activity is associated with fetal growth restriction that precedes the onset of intra-uterine growth retardation [24]. Changes in the pattern of expression and methylation of the different GLUT transporters in the placenta point to dynamic regulation across gestation [25].

For amino acid transport, and most likely for other nutrients as well, a change in the activity of one transporter cannot be assumed to correspond to an equivalent change in nutrient transport [26]. Computational modeling of these processes may provide an important tool to better understand these processes and to identify the rate-limiting steps, as these will be the best targets for therapeutic interventions [26, 27].

In some diabetic or obese woman, elevated nutrient levels may drive placental transfer down the concentration gradient thereby promoting fetal growth. However, in many obese and diabetic pregnancies, fetal growth is normal raising the question as to why fetal overgrowth occurs in some pregnancies but not in others. One explanation may be that maternal obesity and diabetes in themselves are not sufficient to induce fetal obesity, but that additional exposures are necessary, which in combination lead to excessive placental nutrient transfer and LGA offspring.

### The Placental Exposome and Placental Function

For a fetus to become LGA there must be an underlying placental capacity able to support this growth. In absolute terms, fetal growth is greatest in the last trimester and this is when placental nutrient transfer must be sufficient. As placental function develops progressively, it must acquire this capacity much earlier in gestation. For this reason, environmental exposure affecting the placenta in early gestation may interact with those acting in late gestation in order to determine the fetal growth outcome (fig. 2). For instance, an early exposure leading to a large placenta may, when coupled with a later nutrient-rich environment, increase the likelihood of an LGA baby (but may decrease the likelihood of fetal growth restriction in a nutrient-poor late-gestation environment). Alternatively, an early exposure which causes down-regulation of glucose transporters could reduce the likelihood of an LGA infant when exposed to a later glucose-rich environ-



**Fig. 2.** Placental development and function is determined by the product of its environmental exposures across gestation. This will determine how big the fetus grows and whether its body composition is balanced or imbalanced. Normally grown babies (AGA) as well as some small (SGA) or large (LGA) babies may have a balanced body composition, but most have either inappropriately low or high adiposity, respectively. Abnormally small (IUGR/FGR) infants may have a decreased fat mass, while abnormally large infants with fetal growth excess or fetal growth surplus (FGE/FGS) can have an increased fat mass. Both extremes of fetal growth may lead to adult adiposity.

ment (but might increase the likelihood of fetal growth restriction in a lower glucose environment).

Studies linking maternal body composition to placental function and gene expression suggest a role for longer-term, pre-pregnancy influences of maternal diet on the placenta although it is not clear at which point in gestation these act [22, 23, 28]. Environmental exposures during gametogenesis could influence placental development and thus should be considered as part of the placental exposome [29].

From an evolutionary perspective, co-adaptation suggests that genes will be selected that promote signalling between the mother and offspring to optimise nutrient partitioning in a given environment [30]. In our evolutionary past, under- rather than over-nutrition will have been the predominant selective pressure on the placenta. In this case, signalling between the mother and the fetus via the placenta may be poorly adapted to protect the fetus where there is an overabundance of maternal nutrients such as in maternal obesity or diabetes [31].

### **A Role for Epigenetics in Pregnancy Adaptation and Placental Function?**

Epigenetic mechanisms encompass a range of covalent and other modifications to DNA and associated proteins that together regulate gene activity. The epigenetic profile (epigenome) is dynamic in early life and sensitive to environmental influences, yet the role of epigenetic variation in regulating placental function and pregnancy outcome in humans remains unclear. Epigenetic change in response to an in utero environmental exposure may manifest as an alteration in placental development potentially as an 'adaptation' of the developing pregnancy to a 'perceived' postnatal environment related to the in utero exposure.

Epigenetic changes are therefore likely to be an important mechanism by which early exposure affects placental function in gestation. There is evidence for increased inter-individual variation in the DNA methylation profile in the third-trimester placenta relative to first and second trimesters, supporting an accumulation of environmentally induced changes in DNA methylation patterns [32]. The mechanisms underlying this variation remain unclear, as does the potential link between altered methylation and adverse pregnancy outcomes. However, parallel changes in methylation and expression in glucose transporters across gestation support a functional role for epigenetic regulation in the placenta [25].

### **Maternal Determinants of Placental Function**

It is currently unclear which aspects of maternal obesity or diabetes predispose to LGA offspring and whether there are common or distinct pathways. Obvious candidates include differences in plasma nutrient and metabolic hormone levels, but other factors such as the systemic inflammatory status could also be important.

The altered energy homeostasis of an obese woman, specifically her higher systemic insulin concentrations and insulin resistance, may also impact on placental function. Even though the placenta is not a typical insulin-sensitive tissue with regard to the stimulation of glucose transport, it is equipped with functional insulin receptors and downstream signalling molecules [33]. Leptin is another potentially relevant endocrine signal since plasma leptin is elevated in obese and diabetic women and is synthesized in excess by the placenta [34].

Some diabetic and obese pregnant women have chronic low-grade systemic inflammation, which extends to the placental tissue [35]. The source and nature of the inflammatory stimuli are currently unknown. However, factors originating from the maternal environment are strong candidates to enhance inflammation. Increased systemic lipopolysaccharides in obese pregnant women support a role of innate immune regulation by maternal stimuli in increasing inflammation at the maternal-fetal interface [36]. Lipids, particularly saturated fatty acids, can also trigger immune responses in the placenta increasing in situ inflammation in a manner similar to lipopolysaccharides. The response of the placenta to inflammatory stimuli is demonstrated by enhanced production of cytokines and inflammatory factors released locally and systematically in diabetes and obesity [37].

In addition to dietary factors and hormones, chemicals, such as endocrine disruptors, in the maternal environment can also change the phenotype of offspring by stably altering the epigenome, as has been demonstrated in rodents [38, 39].

### **Postnatal Outcomes**

The long-term consequences of being born with excess fat or LGA are potentially very significant and further research is required to better understand these relationships. Being born large is associated with an increased risk of obesity in childhood although the extent to which this persists into adulthood has not yet been fully defined [40]. If being born LGA is established to be causally associated with adult obesity it might also be expected to predict the risk of metabolic disease and in certain populations LGA may directly be associated with type-2 diabetes. In most populations, the risk of type-2 diabetes decreases with increasing birth weight [41], but in those with a high prevalence of gestational diabetes, the risk of later diabetes is greatest at the highest birth weights [42]. Further research is required to establish whether fetal adiposity contrib-

utes to the risk of adult adiposity and the associated health consequences. This research needs to make use of more detailed analysis of body composition at birth to distinguish those born with a high proportion of body fat from those who are genetically large.

While the focus of this review has been on LGA babies it should not be forgotten that babies who do not reach their growth potential in utero are also prone to develop obesity and other conditions related to the metabolic syndrome in later life which are associated with excess adiposity [43].

If fetal adiposity leads to adult adiposity how might this be mediated? One mechanism may be through effects on the hyperplasia of white, beige or brown adipose tissue [44]. Adipocyte number appears to be a major determinant of adult adiposity and suggests a tight regulation of adipocyte cell number during adult life [45]. Brown fat remains active into adult life [46] and if its abundance was determined in utero this would have implications for energy expenditure and the propensity to develop obesity. While the relationship between early environment and brown fat mass has not been determined it is interesting to note that morbidly obese adults have less brown fat, suggesting a role in the development of obesity [47]. Other mechanisms may involve reprogramming of neural appetite control and there is evidence for reprogramming of the hypothalamus-pituitary-adrenal axis [48]. The relationship between fetal adiposity and early growth should also be investigated as there are strong correlates between early growth and later obesity [49] (fig. 2).

### **Population Studies and the Power of New Technologies**

Population studies are needed to identify the effects of maternal obesity on placental function, fetal growth and postnatal consequences. Developing technologies mean that the level of insight that can be gained from these studies is now substantial. For instance, birth weight is an imprecise marker of fetal growth and while some LGA babies will have a disproportionate increase in adipose tissues others may be proportionately large. If fetal adiposity is key to future health then it is those infants with disproportionately high adiposity rather than those who are proportionately large that need to be identified. The use of neonatal dual-energy X-ray absorptiometry and densitometry to measure body composition allows us to make this distinction and has great potential to enhance the power of these studies.

Furthermore, in order to demonstrate the role of the placenta in mediating maternal environment, it is important that we are able to make better estimates of placental function. It is now possible to make in utero measurements of fetal and placental blood flow and growth [50, 51]. The use of stable isotopes provides an important means to study placental transfer in vivo avoiding the drawbacks of ex vivo systems [52] when coupled with increasingly powerful biochemical and molecular approaches to study plasma and tissues samples [25, 53]. An example of the use of these techniques in a longitudinal study comes from the Southampton Women's Survey, where fetal growth measures have been determined by ultrasound and related to placental gene expression and post-natal bone density [54]. Other studies have related maternal body composition and placental weight to fetal blood flow distribution in the fetus [50, 55]. Increased fetal liver blood flow is associated with fetal macrosomia in the third trimester [51] and greater offspring fat mass measured by dual-energy X-ray absorptiometry, both in the infant at birth and at age 4 years [50]. In the Generation R study, analysis of placental haemodynamics demonstrated associations between maternal lifestyle characteristics and placental resistance indices [56].

This review has focused on the consequences of maternal obesity in humans, however, it should not be forgotten that there is a large body of related work in animal models, which has been reviewed elsewhere [57, 58]. These animal models provide supporting evidence that maternal obesity has long-term effects on the offspring. They also allow study of the underlying processes in ways that are not always possible in humans [59, 60]. As such, animal models provide an important research tool which compliment human studies.

### **Conclusion**

Maternal obesity and diabetes increase the risk of excessive fat accretion in the offspring and are strong risk factors for being born LGA. However, not all such pregnancies lead to fetal overgrowth, and understanding why some fetuses are protected will assist the characterisation of future intervention strategies. Increased nutrient transfer is required to produce an LGA infant, and the factors which determine whether or not placental function mediates this nutrient transfer will determine how the fetus grows. We suggest that to understand this problem will require an appreciation of how exposures across development may affect placental function and that this should be a focus of new and ongoing longitudinal studies.



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