**Placental Fatty Acid Transfer**

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**Abstract**

***Purpose of review***: This review outlines recent advances in placental lipid transport in relation to maternal metabolic status and pregnancy outcome. A particular focus of the review will the way these findings may influence our understanding of placental transfer of the essential fatty acid DHA which is crucial for fetal neurodevelopment and of lipid transfer as a predisposing factor for childhood obesity.

***Recent findings***: Placental metabolism may determine the quantity and composition of fatty acids delivered to the fetus. Maternal factors, such as obesity, appear to regulate placental lipid metabolism and may influence fatty acids delivery to the fetus. While the role of placental metabolism is now recognised, new evidence also suggests important roles for non-traditional fatty acid transporters such as Mfsd2a which facilitate transfer of DHA.

***Summary***: Placental lipid metabolism is likely to be a determinant of placental transfer of fatty acids to the fetus. Maternal conditions, such as obesity, have now been shown to regulate placental lipid metabolism and so may influence fatty acid transfer and fetal development. However, it is not yet clear how regulation of placental lipid metabolism affects fatty acid delivery to the fetus and its long-term health.

**Key points:**

* Both membrane transport and placental metabolism influence placental transfer of fatty acids to the fetus
* Maternal obesity may regulate placental lipid metabolism and so may influence fatty acid transfer
* There may be significant roles for non-traditional fatty acid transporters such as Mfsd2a which facilitates transfer of DHA

***Keywords*:** transport, metabolism, obesity, omega-3, neurodevelopment, human placenta

**Introduction**

This review address recent work on the mechanisms and regulation of transplacental lipid transport [1]. Lipids are a complex class of molecules encompassing fatty acids, 1-3% of which circulate in non-esterified form (NEFAs) in the maternal plasma. The vast majority of fatty acid is esterified in triglycerides, phospholipids and cholesteryl esters which in plasma are transported within lipoproteins.

Fatty acids provide the fetus with energy, the building blocks for plasma membranes, the precursors for eicosanoids and peroxisome proliferator-activated receptor (PPAR) ligands. The mechanisms and regulation of placental fatty acid transfer have implications for fetal development and its health across the life course [2]. In particular, maternal-fetal transfer of arachidonic acid (AA) and docosahexaenoic acid (DHA) is key for the fetus, because both are essential fatty acids and serve as precursors for vasoactive substances. Moreover, DHA is also the precursor for resolvins and protectins, and its fetal levels are positively correlated with insulin sensitivity. Overall, this has led to two questions of particular interest: 1) how do fatty acids in the fetus and, hence placental fatty acids transport, contribute to the offspring's risk of developing obesity and 2) how does the delivery of the essential fatty acid DHA affect fetal and neonatal metabolism and neurodevelopment.

This review will specifically address placental fatty acid transfer in humans, which is different from most other mammals as human neonates have a high proportion of body fat. The mechanisms of placental fatty acid transport will also be discussed in the context of maternal diet, body composition and metabolic status which are now known to influence placental function. In particular, how the modern epidemic of overnutrition can affect placental lipid transfer and the consequences this may have for the offspring [2].

***Transfer of fatty acids across placental barriers***

To cross the placenta nutrients must be taken up from the maternal plasma, cross the syncytiotrophoblast, diffuse through the placental villous stroma and pass across the fetal capillary endothelium. Fatty acids, which circulate as NEFA bound to albumin, can disassociate from the albumin and pass across the plasma membrane of the syncytiotrophoblast. However, in both plasma and tissue the bulk of fatty acids is esterified in triglycerides and phospholipids. Prior to uptake into the syncytiotrophoblast, the esterified fatty acids from different stores will have to be hydrolyzed by lipases.

Whether fatty acids diffuse across membranes or are transported by membrane transporters has been a source of much debate. Fatty acids transporters including FATPs, FABPpm and FAT(CD36) are present in the syncytiotrophoblast plasma membrane [1]. However, modelling placental fatty acid transfer suggests that this process occurs very quickly and that, at least for uptake from the maternal circulation, membrane transport may not be a rate limiting step [3]. Within the syncytiotrophoblast fatty acids are rapidly converted to acyl-CoA, the primary substrate entering all intracellular metabolic pathways, e.g. oxidation, re-esterification. The formation of acyl-CoA prevents efflux via transporters or diffusion. Fatty acid release from the syncytiotrophoblast could occur following dissociation of free fatty acids bound to cytoplasmic binding proteins or following the activity of thioesterases and hydrolases. However, the specific mechanisms underlying fatty acid release from the placenta remain an area of interest.

While research into membrane transport of fatty acids has primarily focused on FATPs, FAT and FABPpm new data suggest that other classes of transporters are important, especially for essential fatty acids. The sodium‐dependent lysophosphatidylcholine symporter Mfsd2a has been shown to mediate DHA delivery across the blood brain barrier, and there is now evidence for its presence in the placenta. In diabetic pregnancies, lower Mfsd2a levels are associated with lower DHA in the cord blood [4]. Consistent with studies in the general population, DHA in the cord blood of these diabetic pregnancies correlated with psychomotor skills at 6 months of age [4]. This work highlights how specific transport mechanisms exist for biologically important fatty acids such as DHA.

On leaving the syncytiotrophoblast, it is unclear how hydrophobic fatty acids diffuse through the villus stroma. It has been hypothesised that transfer may primarily occur in regions of vasculosyncytial membrane, where the syncytiotrophoblast and endothelium are separated only by the basement membrane and no villus stroma has to be passed [5]. However, these structures, in which the distance between the maternal and fetal circulation is smallest, are only fully developed at the end of pregnancy, while in earlier pregnancy periods fatty acids will have to pass across the aqueous medium of the stroma.

Transfer of fatty acids across the endothelium is also poorly understood and whether trans-endothelial lipid transfer occurs by paracellular or transcellular routes remains unclear.

Placental Lipid Metabolism

Fatty acids taken up by the placenta must meet both placental and fetal demands. Recent studies suggest that in addition to diverting fatty acids to fulfil its own needs, placental metabolism contributes to fatty acid transfer to the fetus. Intracellular free fatty acid concentrations are low and while free fatty acids can exist bound to binding proteins most are rapidly esterified to acyl-CoA by cytosolic and FATP-associated ligase activity after their uptake. This acyl-CoA can be incorporated into esterified lipid pools or directed to beta-oxidation pathways [6]. Modelling of fatty acid transport across the perfused placenta suggests a role for placental metabolism in determining transport with metabolic rate being a major driver of fatty acid uptake highlighting the importance of metabolism [3].

As placental lipid pools are turned over, fatty acids will be released and may become available for transport to the fetus or could be directed down catabolic pathways [6]. Regulation of metabolic processes could affect the amount and type of fatty acids delivered to the fetus. Fatty acids that are less efficiently esterified, or which are preferentially released from placental lipid pools, may be more available to the fetus [7].

Maternal and fetal NEFA levels do not correlate at term or in perfused term placentas, which is consistent with a significant role for placental metabolism [3,8]. If, as perfusion data suggest, the placenta esterifies maternal fatty acids as they are taken up, this would serve as a reserve that could buffer fatty acid supply to the fetus in the face of diurnal variations in maternal plasma fatty acid levels. However, the release of NEFA from esterified pools within the placenta has yet to be demonstrated *in vivo*.

***Compartmentalisation of lipid transport and metabolism***

Placental fatty acid uptake is assumed to occurr across the whole syncytiotrophoblast surface of the placental villi. However, it may be that there is compartmentalisation of transport and metabolism within the villi and that this may be an important determinant of fatty acid transport. Compartmentalisation can be both physical (e.g. different regions or cell types [9]), metabolic (e.g. into different lipid pools [7]) or both (e.g. into a phospholipid that is preferentially localised to the basal membrane).

The absence of a clear mechanism for fatty acid transport across the hydrophilic villous stroma has led to suggestions that fatty acid transfer may primarily occur in regions of vasculosyncytial membrane [5]. If this were the case, the area available for fatty acid transfer would be much reduced amounting to about 9% of the total placental surface at the end of pregnancy. Answering these question are important if we are to understand why fatty acid transfer may become impaired and so that we can intervene to optimise placental fatty acid transfer.

There is evidence for cellular compartmentalisation of lipid metabolism within the placental villi from a study using fluorescently labelled fatty acids. This study observed that these fatty acids were esterified and incorporated into lipid pools within the cytotrophoblast rather than the syncytiotrophoblast [9]. Cytotrophoblast cells have not previously been implicated in placental lipid transport or metabolism, but rather they have been seen as playing a supporting role for the syncytiotrophoblast. This study speculated that fatty acids might be released from these cytotrophoblast cells in an esterified form, providing a novel route for transfer of esterified fatty acids to the fetal circulation. However, the balance of evidence is that the primary mechanism for fatty acid transfer to the fetus is as NEFA.

Evidence for metabolic compartmentalisation of fatty acids comes from cytotrophoblast culture where, despite a general decrease in lipid content as they syncytialise, omega-3 and 6 LCPUFA levels are maintained within the phospholipid pool [7]. Transporters such as MFSd2a may provide a mechanism to deliver these fatty acids within phospholipid pools to the fetus [4].

***Maternal influences on placental lipid transfer***

Maternal diet and metabolic status have been shown to alter placental lipid handling and biology. The effects of maternal diet and metabolic status on the placenta could be mediated directly via alterations in maternal plasma lipid composition or, indirectly, via altered maternal endocrine status resulting from the dietary changes or effects on body composition.

While the mechanisms by which maternal factors affect placental function are unclear, the placenta may be responding to both hormonal and nutritional signals. Circulating factors in plasma from women with gestational diabetes have been shown to alter adipocyte lipid metabolism, and these may affect the placenta in a similar way [10]. Evidence in gestational diabetic women that maternal insulin treatment is associated with alterations of placental mediators of fatty acids transport provides further support for the role of maternal metabolic status in affecting the placenta [11].

There is evidence that maternal diet alters placental lipid composition and metabolism. Dietary composition may directly alter the pool of fatty acids available for uptake by the placenta, as illustrated by the relationship between maternal consumption of trans-fats and their placental accumulation [12]. Alternatively dietary composition may be sensed, for instance via the G protein-coupled receptor 120 (GPR 120), a DHA receptor/sensor present in the placenta whose expression correlated with neonatal fat [13].

Maternal diet may also alter placental lipid transfer indirectly. In a randomised trial, maternal omega-3 supplementation was shown to inhibit the placenta's ability to esterify and store lipids without affecting rates of beta oxidation [14]. In this trial, the omega-3 to omega-6 ratio was correlated with PPAR-gamma protein levels suggesting that the effect may be mediated through changes in this fatty acid sensitive transcription factor. Maternal supplementation with omega-3 fatty acids is believed to affect placental inflammatory status, and this may be another mechanism by which diet affects placental metabolism and perhaps transfer [15].

As with maternal diet, maternal obesity will affect both plasma biochemistry and endocrine status both of which may affect the placenta. There is now clear evidence that maternal obesity is associated with altered placental lipid metabolism. Studies on the metabolism of neutral lipids within lipid droplets and fatty acid catabolism in placentas from obese pregnancies show differences as compared to lean pregnancies [6,16]. Understanding the mechanism underlying these observations may allow us to develop targeted interventions to modulate lipid transfer to the fetus.

Maternal disease status may also influence placental lipid transfer. Maternal diabetes mellitus has previously been reported to alter placental fatty acid transfer, and recent data had demonstrated effects of maternal obesity and preeclampsia. Lipidomic profiles altered in pre-eclamptic pregnancies, which may reflect altered fatty acid metabolism or an altered cellular composition of these placentas [17]. Gestational diabetes mellitus is associated with changes in the methylation of placental genes, which could be part of the mechanism underlying longer term effects of maternal disease on the offspring [18].

It is important to note that in these studies on placentas from obese, diabetic or pre-eclamptic pregnancies it is not always possible to determine whether placental changes corresponded to changes in fatty acid delivery to the fetus or the long-term health of the offspring.

***Sex differences***

Sex differences in placental function and whether these lead to different fetal growth strategies in male and female fetuses are of considerable current interest. A recent study has suggested that male and female placentas may transfer DHA differently [19]. This study needs confirmation but is important because fetal (and therefore placental) sex may be an unappreciated confounder in studies of placental lipid transport.

***Fetal and postnatal consequences of placental lipid transfer***

Fatty acids are key nutrients, and impaired placental delivery may have long-term consequences. There are two main areas of interest, whether placental lipid handling may predispose to obesity in the offspring and the effects of DHA transfer on fetal neurodevelopment.

Placental lipid transfer may affect fetal development and predispose to the development of obesity in childhood and later life. We do not argue that placental fatty acid transfer per se causes obesity in later life but that it leads to an altered regulatory environment, perhaps by altering the development of the fetal pancreas or hypothalamus. Maternal obesity is associated with increased rates of childhood obesity. While shared lifestyle and environmental factors are involved, there is evidence that the associations between maternal obesity and offspring obesity are in part determined by *in utero* environment, for instance, the effect of placental glucose transfer on fetal insulin levels [2] and in turn the effect of fetal insulin levels on transplacental glucose flux [20].

Babies born to diabetic mothers have a higher proportion of fat mass, which may be due to increased fetal fatty acids synthesis from glucose as well as delivery of maternal fatty acids. However, to promote increased adiposity in the long term, it is likely that there is an underlying metabolic programming in the fetus. This programming could persist due to epigenetic changes in the fetus. DNA methylation in the placenta, a fetal tissue, has been shown to be altered in response to gestational diabetes and related to childhood body composition [18]. Alternatively, more rapid postnatal growth, which could be driven by fetal nutrient deposition, has also been associated with later body composition [21].

The essential fatty acid DHA is enriched in fetal plasma compared to the mother, and this enrichment could be mediated via selective placental transport or metabolism of long chain poly unsaturated fatty acids such as DHA [1]. This ability to bio-magnify DHA is important as impaired placental DHA transfer is associated with impaired fetal neuro development and subsequently postnatal intelligence, behaviour and psychiatric illness. Evidence for this relationship comes from studies in both animals and humans. In animal studies, maternal DHA restriction causes specific defects in neural function and behaviour. Studies in humans show associations between cord plasma omega-3 levels with later outcomes, although in these studies it is harder to adjust for confounders than in animal models [22]. Together these studies provide a body of evidence implicating placental DHA transfer with fetal neurodevelopment. Future studies need to address whether impaired delivery to the fetus reflects placental dysfunction or low maternal availability.

**Conclusion**

Our understanding of how placental lipids cross the placenta and the maternal factors that influence this process are rapidly evolving. The role of placental lipid metabolism both in terms of the mechanism of transport and its alteration by maternal factors such as obesity is of particular interest. Progress in the area of placental lipid transfer now needs to be matched by an enhanced understanding of what fetal lipid requirements are under various metabolic conditions and in both sexes, and how altered delivery affects fetal development.

1. **Acknowledgements.** None

2. **Financial support and sponsorship.** *The authors received funding from the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement n°28934.*

3. **Conflicts of interest.** None.

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