**New perspectives on placental fatty acid transfer**

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Keywords: metabolism, omega 3, anatomy

**Abstract**

The human fetus depends on placental transfer for the fatty acids required for its growth and development. Long chain polyunsaturated fatty acids (LC-PUFAs) may specifically influence neurodevelopment. Therefore, it is important to understand the mechanisms of placental transfer of LC-PUFAs. The simple view of placental fatty acid transfer is that it occurs by diffusion down the maternal to fetal gradient, facilitated by membrane transporters. This view has been complicated by studies highlighting the role of placental metabolism in fatty acid transfer. Most fatty acids taken up by the placenta will be esterified and incorporated into lipid rather than diffusing directly across to the fetus. Furthermore, this esterification is likely to mean that placental intracellular “free” fatty acid concentrations are lower than in fetal plasma which would not be conducive to simple diffusion of fatty acids to the fetus. Placental structure poses additional questions, in particular how fatty acids cross the hydrophilic villous stroma separating the trophoblast from the endothelium and how they cross the endothelium itself. The understanding of placental fatty acid transfer needs to evolve to address these questions. The role of the placenta is not simply to mediate solute transfer; it is also a central endocrine organ of pregnancy. Placental-derived lipid mediators, such as prostaglandins, have well-established roles in parturition and, almost certainly, throughout gestation. Metabolic targeting of specific fatty acids to different lipid pools in the placenta may determine their availability as both nutrients and signalling molecules. Placental transfer will determine fatty acid availability within the fetus as well as influencing maternal levels. Fatty acids and their derivatives may also act as signals to the placenta indicating metabolic states in both mother and fetus. Placental uptake and metabolism of LC-PUFAs are important to meet both fetal and placental demands. This paper will review placental fatty acid transfer and metabolism and highlight issues which need to be addressed.

**Introduction**

Placental transfer of fatty acids underpins the growth and development of the fetus. Essential fatty acids, by their nature, cannot be synthesised in the body so the fetus must obtain them from the mother via the placenta. Long chain polyunsaturated fatty acid (LC-PUFA such as arachidonic acid and docosahexaenoic acid (DHA)) have specific roles in membrane composition which are particularly important for fetal neurodevelopment. In addition, fatty acids and their derivatives have important signalling roles, as eicosanoids, as ligands for receptors peroxisome proliferator activated receptors. Given the importance of fatty acids, particularly LC-PUFAs, to membrane synthesis and as substrates for generation of lipid mediators involved in key signalling processes, it is likely that any deficiency in maternal supply, or placental transfer, of these to the fetus will compromise its development.

How the baby grows in the womb has long-term consequences for its health [1]. Developmental compromises *in utero* are associated with increased rates of disease in infancy and across the life course [2]. In the case of fatty acids, there is a particular concern that impaired placental delivery of DHA may affect neurological development leading to lifelong impacts on cognition and behaviour [3]. This may be of particular importance in premature or growth-restricted infants where placental transfer of DHA may be impaired [3, 4]. Placental LC-PUFA uptake and transfer is also implicated as a determinant of gestation length [5] and childhood allergy [6]. Maternal metabolic state may also affect transfer of DHA to the fetus and placental DHA transfer is reported to be decreased in diabetic pregnancies [7].

Research into placental DHA transfer and postnatal outcomes is complicated as direct measures of placental DHA transfer are not available and surrogate measures, such as maternal or infant plasma levels, have been used instead. Developing a clear understanding of the mechanisms and determinates of placental fatty acid transfer is therefore highly important.

Placental fatty acid transport has been the subject of considerable research [8]. This work has focused on fatty acid transfer in the term placenta, when samples are most available, and the way in which trasnfer may change across gestation is unclear. In essence, it has been understood that fatty acids diffuse across the placenta down the maternal to fetal fatty acid gradient. While the fetus may synthesise some saturated and monounsaturated fatty acids from glucose, it is dependent on placental transfer to acquire essential fatty acids [9]. Fetal requirements for LC-PUFAs (i.e. arachidonic, eicosapentaenoic and docosahexaenoic acids) may be met by placental transfer of specific fatty acids or by transfer of the essential fatty acids alpha-linolenic acid and linoleic acid which may be subject to elongation and desaturation in the fetal liver [10]. LC-PUFA levels are enriched in neonatal plasma compared to the mother suggesting biomagnification of these fatty acids by the placenta [11-13]. Recently, there has been developing interest in the influence of placental lipid metabolism and the effect of maternal obesity on fatty acid transfer to the fetus [14-16]. Changes in placental metabolism could underlie changes in fatty acid transfer seen in diabetic pregnancies [7, 17].

This review seeks to explore our developing understating of placental fatty acid transfer and how the role of membrane transport needs to be placed in the context of placental metabolism and structure. It also seeks to address how placental metabolism may contribute to the role of lipids as mediators signalling between the mother, placenta and fetus. This review will focus specifically on human placental fatty acid transfer as placental structure and function differ significantly across species of animals [18, 19].

**Maternal supply of fatty acids**

While the placenta mediates fatty acid transfer to the fetus, it is maternal plasma which determines the availability of fatty acids to the placenta. The composition of maternal plasma will be determined by current diet, past diet (as reflected in maternal body stores) and maternal metabolic state. In pregnancy, placental hormones alter maternal metabolic state increasing plasma lipid levels and increasing their availability to the placenta. In maternal plasma, 97% of fatty acids are found in the esterified pools with non-esterified fatty acids (NEFAs) only contributing 3% to the total [20]. During pregnancy, maternal plasma concentrations of LC-PUFAs alter in a fatty acid and lipid class dependent manner, with significant increases in LC-PUFAs seen in maternal plasma phospholipids, and more modest or absent changes in NEFAs and or triglycerides [21].

While it is clear that the placenta takes up maternal NEFAs, it is not clear to what extent the fatty acids in esterified lipid pools are available to the placenta. Placental lipases, particularly endothelial lipase, are expressed on the surface of the placenta and are likely to release fatty acids but their effect on placental uptake is hard to estimate [17]. Endothelial lipase is able to release fatty acids from phospholipid and this may have implications for placental LC-PUFA transfer given the enrichment of LC-PUFAs in phospholipid during pregnancy. [21, 22]. Maternal partitioning of specific LC-PUFAs to different metabolic pools may, therefore, affect their availability for placental transfer. Increased maternal intake of omega-3 PUFAs results in higher omega-3 PUFA content in both maternal and fetal plasma although some studies report a more limited effect on maternal and fetal erythrocyte membranes [23, 24]; this may relate to the amount of omega-3 PUFAs provided in the diet. In plasma, enrichment of omega-3 PUFAs after dietary intervention occurs in all lipid pools but to different extents, with the greatest changes in omega-3 PUFA content among plasma phospholipids [25].

Cellular sensing of fatty acids, either in total or in specific lipid species, could allow the placenta to assess maternal nutrient reserves and adjust its transfer to balance the needs of the mother and child.

**Placental fatty acid transfer**

Placental fatty acid transfer has been studied in the perfused placenta and *in vivo* using stable isotopes [7, 26]. Observations made using the perfused placenta suggest that placental transfer of labelled fatty acids remains relatively constant even as maternal levels fall [26]. This questions the presumed role of the maternal to fetal gradient in driving placental fatty acid transfer and implies a more complex mechanism.

Fatty acid transfer should not be thought of as a unidirectional process as, at least in the perfused placenta, there is release of fatty acids into the maternal circulation [26]. Indeed more fatty acids are released into the maternal circulation than into the fetal circulation. Furthermore, the release of endogenous NEFAs from the placenta does not drop off precipitously as the placental NEFA acid pool is depleted, but continues at a steady rate. More non-esterified fatty acids are released from the placenta than could initially be measured in the tissue suggesting that fatty acids are released from esterified pools within the placenta into the maternal and fetal circulations.

There is evidence that there is selective transfer of LC-PUFAs across the placenta. Levels of LC-PUFAs are higher in cord blood than in maternal blood [12], suggesting that there is placental biomagnification of these fatty acids. Preferential uptake of LC-PUFAs has been observed in perfused placenta, and this was attributed to selectivity of the fatty acid transport proteins (FATPs) [11]. The importance of understanding placental transfer is illustrated by a supplementation trial showing that the total dose of DHA consumed by the mother in pregnancy only explained 21% of the variation in cord blood DHA levels [27]. This indicates that while maternal supply is important, other factors, such as placental metabolism and function or fetal endogenous synthesis, are key determinants of fetal DHA status.

**Barriers to placental fatty acid transfer**

The placenta itself has not been perceived as a barrier to fatty acid transfer as fatty acids diffuse, or are transported, relatively easily across plasma membranes. However, plasma membranes are not the only barrier to placental fatty acid transfer. The placental barrier is not homogeneous but consists of multiple layers with different transfer properties (Figure 1). The syncytiotrophoblast has a high level of metabolism, the stroma is hydrophilic and the nature of the endothelial barrier will depend on whether fatty acids predominantly follow a transcellular or paracellular route (Figure 2). Despite these barriers, fatty acids do cross the placenta relatively rapidly and it is important to understand how this occurs [26].

***Membrane transport***

The plasma membrane is relatively permeable to fatty acids and, as in other tissues, is not thought to be rate limiting for fatty acid uptake [26, 28]. In the perfused placenta there is clear evidence of uptake and release of fatty acids suggesting bi-directional transfer [26]. Membrane proteins have been proposed to facilitate diffusion of fatty acids including the members of the SLC27 family (FATPs) [29, 30], CD36 and FABP-PM [8]. However, the mechanism by which these proteins mediate membrane transport is unclear and there are suggestions that FATPs and CD36 do not facilitate membrane transport as such, but facilitate intracellular esterification of fatty acids to acyl-CoA [31, 32]. The FATPs have long chain acyl-CoA synthetase activity, metabolically activating their substrates and trapping them within the cell [29]. In FATP1 knockout mice, the metabolic changes observed did not support the idea that this protein was mediating fatty acid efflux to the fetus [29].

The absence of evidence for efflux mediated by FATPs may reflect esterification of intracellular fatty acids meaning that there is no fatty acid gradient to drive net efflux. FATPs are reported to be expressed on the syncytiotrophoblast basal membrane where they are presumed to mediate efflux, but if this is not the case, they may be playing a different role [30]. As FATPs are long chain fatty acid transporters they may have a particular effect on LC-PUFA transfer.

The fact that there is release of fatty acids by the microvillous and basal membranes of the syncytiotrophoblast suggests that fatty acid efflux by either simple or facilitated diffusion does occur. FATPs are localised to the syncytiotrophoblast basal membrane and, while it is unclear if FATPs do mediate efflux, those on the basal membrane could potentially facilitate this [30]. However, if metabolism does keep intracellular non-esterified fatty acid concentrations low, it is not clear how this diffusion occurs against the gradient. It may be that metabolism and/or fatty acid binding proteins create localised fatty acid gradients allowing diffusion. Alternatively, other possibilities such as release of fatty acids from membrane phospholipids may need to be considered.

Fatty acids can also be transported across membranes by lysophospholipid transporters including the lysophosphatidylcholine transporter MFSD2A which is implicated in DHA transfer [33]. The activity or localisation of members of this family in the placenta are not well understood and this is a developing area.

***Metabolic barriers***

Esterification of fatty acids within placental cells, particularly the trophoblast and endothelium, poses a significant barrier to fatty acid diffusion. Only 6% of the labelled fatty acid taken up by the perfused placenta was transferred rapidly to the fetus [26]. Computational modelling suggests that placental fatty acid metabolism is rate limiting for fatty acid transfer [26]. Interestingly, metabolism may also play a role in regulating placental amino acid transfer [34]. Placental lipid metabolism has implications for the design and interpretation of tracer studies. Unless these experiments allow the tracer to reach equilibrium within placental lipid pools, the true extent of placental fatty acid transfer may be underestimated.

The release of endogenous (unlabelled) fatty acids from the perfused placenta suggests that fatty acids can be released from esterified pools and transported to both the maternal and fetal circulations. There is no *in vivo* evidence for placental release of fatty acids derived from esterified pools, so the extent to which this is a physiological phenomenon is not yet clear. However, turnover of lipid pools is necessary to maintain homeostasis and has been demonstrated in placental lipid droplets [14]. Fatty acids released from esterified pools will be available for reincorporation, oxidation or release into the maternal or fetal circulations. The placenta expresses acyl-CoA thioesterase so incorporation of fatty acids into acyl-CoA does not form an irreversible barrier to their release by the placenta [35].

In addition to those associated with FATPs, there is a family of acyl-CoA synthetases which will convert fatty acids to acyl-CoA within the cell [36]. These proteins have different cellular localisations and can differentially affect a wide range of lipid-associated pathways. There is indirect evidence that long chain acyl-CoA synthetases may determine whether a fatty acid enters degradative or synthetic pathways [36]. The activity of these proteins in the placenta could therefore potentially provide selectivity in LC-PUFA transfer across the placenta.

Fatty acids may also be released from the placenta in an esterified form. This is best described on the maternal side of the placenta where large numbers of placental microvesicles formed from phospholipid are released into the maternal circulation [37]. These placental microvesicles are thought to be involved in signalling from the placenta to maternal tissues.

Transfer of esterified fatty acids from the placenta to the fetus has also been proposed based on the incorporation of fatty acids into lipid pools within the cytotrophoblast [38]. Umbilical venous arterial differences have not been reported for triglyceride or phospholipid, although one paper has reported increased cholesteryl ester levels in the umbilical vein [39]. Further work is required to investigate the transfer of esterified fatty acids from the placenta to the mother or fetus, in particular how the fluxes through these pathways compare to NEFA transfer.

Synthesis of fatty acids or elongation and desaturation of fatty acids within the placenta could also affect fatty acid availability to the fetus. Cultured placental trophoblasts appear to have a limited capacity to synthesise fatty acids, so placental synthesis is unlikely to be an important source of fatty acids for the fetus [40]. Elongation or desaturation of PUFAs as they cross the placenta may be more relevant in terms of providing the fetus with biologically important fatty acids but no evidence for this has been observed in perfusion studies [11].

***Villous stroma***

Modelling of placental fatty acid transfer in the perfused placenta demonstrates that transfer of fatty acids between the mother and placenta, in both directions, occurs at a much higher rate than between the placenta and the fetus [26]. This observation suggests that there is a greater diffusive barrier on the fetal side of the placenta. The diffusive barrier on the fetal side may be the need to cross the basal membrane, stroma and the endothelium but may be more complex than this. The villous stoma is a hydrophilic environment and it is possible that this constitutes a particular barrier to transfer. Consistent with this hypothesis, a recent study using another hydrophobic compound, cortisol, also found placental to fetal transfer was considerably less than placental to maternal transfer [41]. It has been hypothesized that fatty acid transfer may primarily occur in regions of vasculosyncytial membrane where the syncytiotrophoblast and capillary endothelium are in close association and the diffusion distance across the stroma is least [20].

***The endothelial barrier***

Fatty acids are known to cross the fetal capillary endothelium but little is known about how this occurs. If fatty acids take a paracellular route they would need to traverse a relatively tight endothelial junction while, presumably, bound to a carrier protein in the lipophobic interstitial fluid. If fatty acids cross the endothelium via the transcellular route they would be subject to metabolism and all the issues discussed above would apply.

As fatty acids are poorly soluble, they must bind albumin in plasma. Albumin levels have been shown to be an important determinant of placental fatty acid transfer [42].

***Blood flow***

Placental blood flow and the efficiency of mixing within the intervillous space could also influence fatty acid transfer. This would certainly be the case if transplacental gradients were driving transfer. However, work using perfusion suggests that maternal concentrations of 13C-fatty acids are poorly correlated with their placental transfer suggesting flow is not likely to be a strong determinant of fatty acid transfer within the physiological range [26]. Modelling of maternal blood flow within the placenta suggests there will be regional differences in substrate concentrations and substrate depletion in regions of poorly mixed blood could potentially impair transfer [43].

**Signalling**

Placental secretion of steroid hormones such as progesterone and oestrogen and of peptide hormones such as human chorionic gonadotropin, human placental lactogen, placental growth hormone and leptin has important roles in adapting maternal physiology to support the pregnancy including the metabolic changes leading to increased maternal plasma concentrations of lipids and glucose [44]. In addition to these endocrine hormones, synthesis and secretion of eicosanoids from fatty acid precursors by the placenta play a vital role in parturition and almost certainly play important roles across gestation [45]. However, lipid mediators secreted by the placenta are not limited to eicosanoids but may also include fatty acids themselves and their metabolic products including phospholipids [46, 47].

Due to its role in prostaglandin synthesis, the regulation of arachidonic acid metabolism in the placenta and fetal membranes is thought to be central to the maintenance of pregnancy as well as the initiation and progression of labour [45]. The enzymes mediating these processes are upregulated towards the end of gestation and will consume arachidonic acid that has been laid down within placental lipid pools during gestation. The relative availability of omega-6 and omega-3 fatty acids may, therefore, affect the placenta’s ability to synthesize eicosanoids, with potential changes to both the quantity and quality of eicosanoids synthesised.

Randomised controlled trials have indicated that dietary supplementation with LC omega-3 PUFAs can increase gestation length [48] and omega-3 fatty acid supplementation is being trialled as a treatment for preterm delivery [5]. It is noteworthy that the doses of LC omega-3 PUFAs used in these studies (500-800 mg/day) are greater than intakes currently recommended for pregnant women (300 mg/day; [49]) and far in excess of typical dietary intakes, with worldwide median intakes estimated at 134 mg/day [50].

Placental transport and metabolism will affect fatty acid levels in the placenta itself, the mother and the fetus; sensing of fatty acids in all these compartments could lead to metabolic adjustments. These metabolic adjustments may lead to a homeostatic cross talk which balances nutrient partitioning by the placenta based on maternal capacity and fetal demand. While this hypothesis remains to be tested, there is evidence that maternal obesity and diabetes are associated with changes in placental lipid metabolism and transport [7, 14, 33, 51].

In addition to their role in eicosanoid synthesis, LC omega-3 PUFAs are precursors for signalling molecules with key roles in neurological protection, the resolvins and neuroprotectins [52]. An adequate supply of LC omega-3 PUFAs to the fetus may therefore also influence the capacity of the infant to generate an anti-inflammatory response to neurological insults such as birth hypoxia.

Omega-3 fatty acids are known to directly interact with transcription factors. Some of these receptors have key roles in inflammation, such as nuclear factor kappa B and peroxisome proliferator activated receptor-γ [52] and there is evidence that omega-3 fatty acids can affect placental inflammatory status [53]. The exact mechanisms involved are unclear and they might involve altered lipid mediator profiles or effects mediated via altered transcription factor activation or both of these. Anti-inflammatory activity of omega-3 LC-PUFAs could protect the placenta and help maintain placental function*.*

GPR120 has been reported to be a receptor for fatty acids with a strong affinity for DHA [54]. GPR120 has been shown to play a role in the anti-inflammatory effects of DHA in macrophages and in the insulin-sensitising effects of DHA in adipocytes [54]. GPR120 has been implicated in metabolic diseases and in the placenta of small for gestational age babies the gene encoding GPR120 is hypomethylated resulting in decreased expression [54, 55]. Changes in LC-PUFA levels in the placenta may also have indirect effects upon cell signalling by altering the fluidity of the membrane and thereby the function of transmembrane or membrane bound proteins.

Lysophospholipid is another class of lipid that may have signalling roles between the mother and placenta. Lysophospholipid species are thought to play important signalling roles in pregnancy acting via G protein coupled receptors in target cells [47]. Lysophospholipids can be secreted from placental tissue and are also produced in the circulation via the action of autaxin, a secreted enzyme that produces lysophosphatidic acid, and which is altered in preeclampsia [56].

Gut microbiota produce short-chain fatty acids, such as butyrate, which have epigenetic effects on tissues via inhibition of histone deacetylates [57]. In pregnancy maternal uptake of gut-derived short-chain fatty acids could affect the placenta. Placental alkaline phosphatase has been shown to be regulated by butyrate and in rodents the intestinal form of the enzyme is implicated in lipid uptake and metabolism, lipid transport and the development of obesity [58, 59]. This may be a way in which changing maternal diet could affect the placenta.

**Conclusion**

Placental fatty acid transfer is important for fetal development and may have long-term health consequences. Fatty acids may be important not just as substrates but as signals between the mother, placenta and fetus matching fetal demand with maternal capacity and mediating key events such as parturition. In understanding placental fatty acid transfer, and how it may become suboptimal, we need to look beyond membrane transport and consider the placenta is a heterogeneous physical and metabolic barrier.

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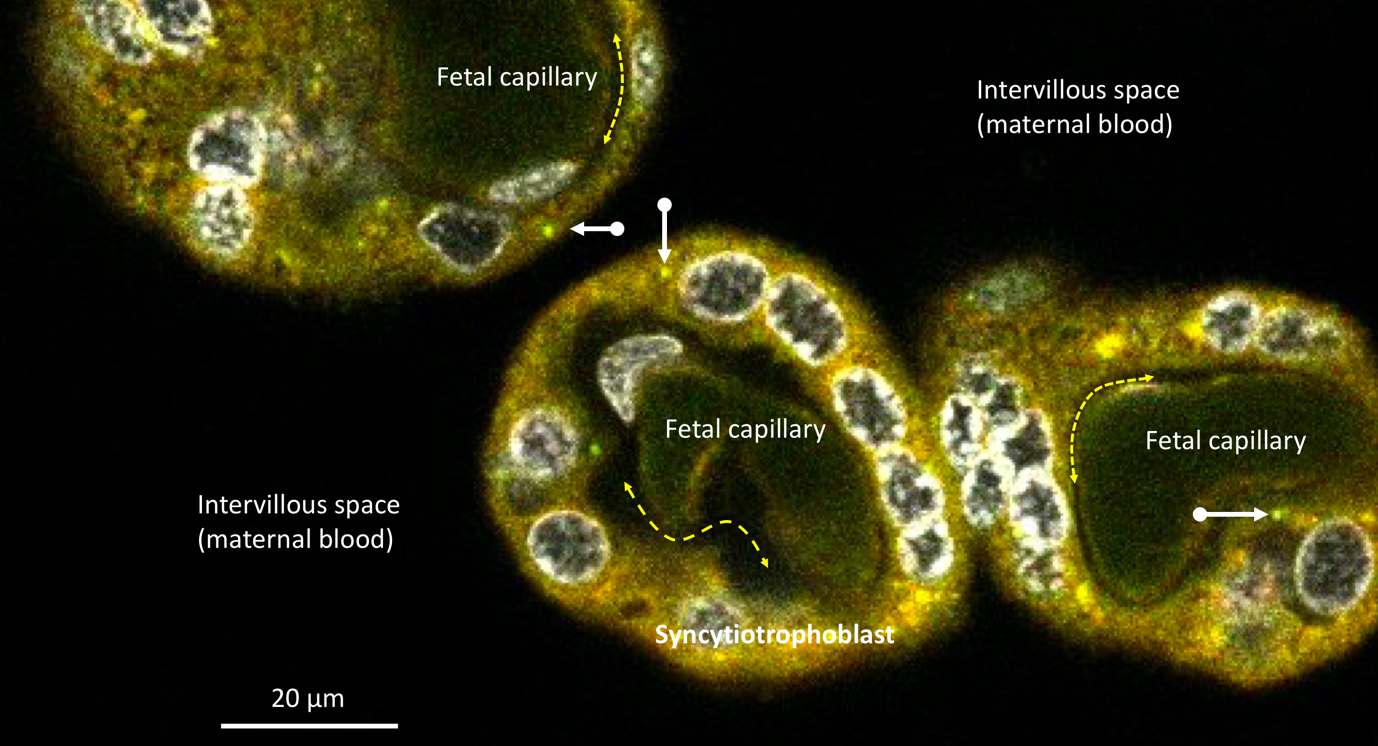
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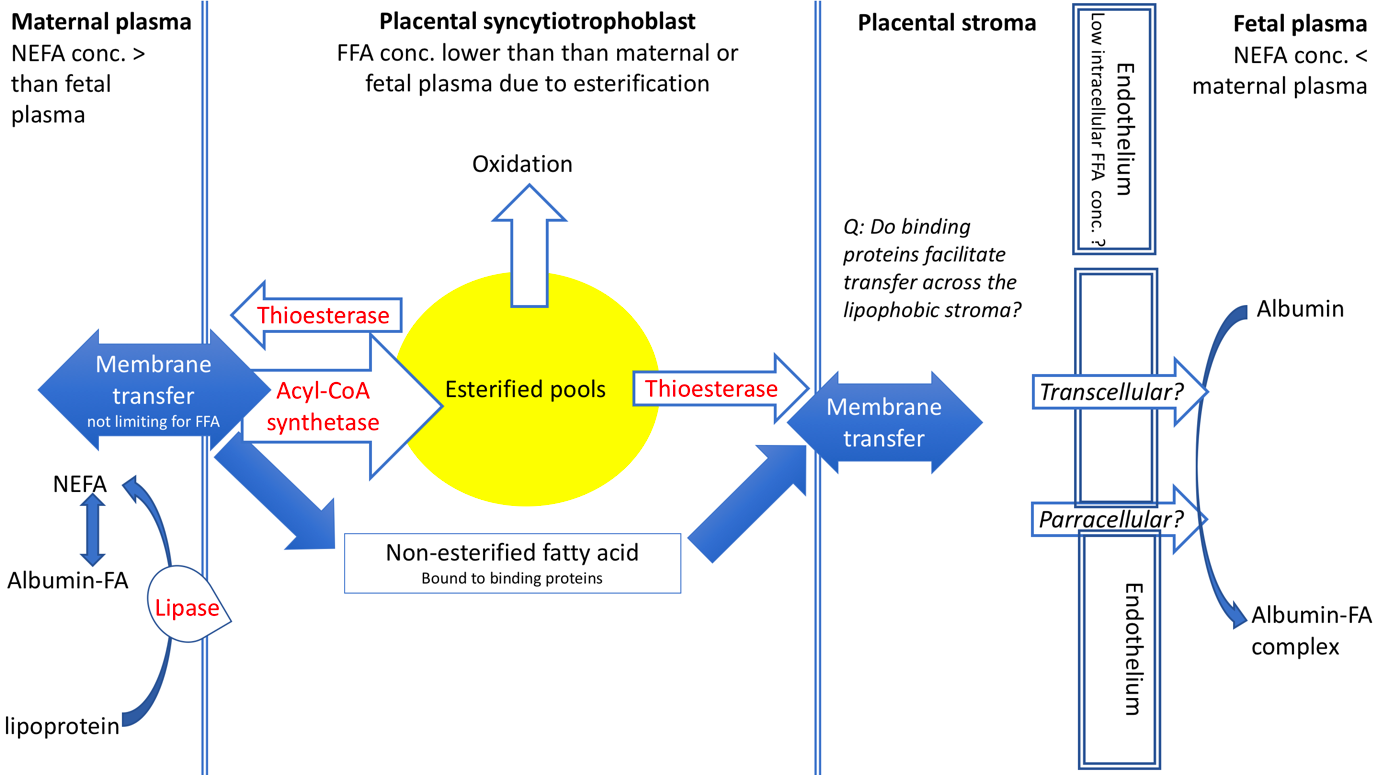
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**Figure 1**. Localisation of Bodipy fatty acids in cross sections of placental villi. A confocal image showing localisation of Bodipy fatty acids (Thermo Fisher, D3835 and D3821, yellow) and DAPI to highlight the nuclei (white) in a cross-section of term human placental villi after 30 minutes incubation in C12 and C16 Bodipy fatty acids. This image highlights the different placental compartments that fatty acids must cross to reach the fetal circulation. Fatty acids and lipoproteins pass through the intervillous space and NEFAs will be taken up by the syncytiotrophoblast. Within the syncytiotrophoblast, they will be incorporated into esterified lipid pools including phospholipid and triglyceride stored in lipid droplets (arrows). Once they cross the syncytiotrophoblast, they enter the villous stroma (yellow dashed lines) and finally the fetal capillary endothelium. In fetal plasma, NEFAs bind to albumin.



**Figure 2**. Fatty acid transfer pathways across the placenta. Placental uptake of fatty acids derived from plasma fatty acids or lipoproteins is not rate limiting. Within the placenta a large proportion of the fatty acids taken up will be esterified; these may be oxidised or, via the activity of esterases, released to the maternal circulation or fetal stroma. A smaller proportion of fatty acids may avoid esterification and cross the cytoplasm bound to fatty acid binding proteins for transfer to the stroma. It is assumed that fatty acids diffuse across the stroma but given the lipophobic nature of this environment, there may be some form of fatty acid binding protein to facilitate this. Fatty acids must then cross the endothelium which could occur by either transcellular or paracellular routes but which predominates remains unclear. In addition to the syncytiotrophoblast, fatty acid transfer across the stoma and endothelium should also be considered as a potentially rate-limiting step in the placental transfer of fatty acids. Within fetal plasma, fatty acids will bind albumin. Fatty acid transporters are not shown for simplicity, but it should be noted that many of these have intrinsic Acyl-CoA synthetase activity. FFA = Free fatty acid.