Fatty Acid Supply to the Human Fetus

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Abstract

Deposition of fat in the fetus increases exponentially with gestational age, reaching its maximal rate—around 7 g/day or 90% of energy deposition—at term. In late pregnancy, many women consuming contemporary Western diets may not be able to meet the fetal demand for n-3 long chain polyunsaturated fatty acids (LCPUFAs) from the diet alone. Numerous mechanisms have evolved to protect human offspring from extreme variation or deficiency in the maternal diet during pregnancy. Maternal adipose tissue is an important source of LCPUFA. Temporal changes in placental function are synchronized with maternal metabolic and physiological changes to ensure a continuous supply of n-3 and n-6 LCPUFA-enriched fat to the fetus. LCPUFA storage in fetal adipose tissue provides an important source of LCPUFA during the critical first months of postnatal life. An appreciation of these adaptations is important in any nutritional strategy designed to improve the availability of fatty acids to the fetus.

Contents

THE FATTY ACID REQUIREMENT FOR PREGNANCY

Fatty acids are required by the developing conceptus as a source of energy, to maintain the fluidity, permeability, and conformation of membranes and as precursors of important bioactive compounds such as the prostacyclins, prostaglandins, thromboxanes, and leukotrienes (**Figure 1**). All fatty acids can provide energy, but the structural and metabolic functions primarily require the polyunsaturated fatty acids. The human body cannot synthesize fatty acids with double bonds three (n-3) or six (n-6) carbons from the n terminus, and these structures must be obtained from the diet either as linoleic [18:2 n-6 (LA)] and α-linolenic [18:3 n-3 (αLN)], known as the essential fatty acids, or their long-chain polyunsaturated fatty acid (LCPUFA) derivatives. Of these, dihomogamma linolenic acid [18:3 n-6 (DGLA)], arachidonic acid [20:4 n-6 (AA)], eicosapentaenoic acid [20:5 n-3 (EPA)], and docosahexaenoic acid [22:6 n-3 (DHA)] are metabolically the most important. The LCPUFAs such as AA, EPA, and DHA are therefore not strictly essential in the diet, but an important practical issue in pregnancy is whether the conversion rate is sufficient to satisfy the fetal demand or whether these fatty acids can be considered as conditionally essential during pregnancy, and if so, at what level are they required.

Prenatal development can usefully be divided into the embryonic period, which covers the first eight weeks of life, and the fetal period, which lasts from the ninth week of gestation until term. At the earliest stages of development, the polyunsaturated fatty acids in particular are required by the embryo (62) and oocytes (103). These are required to support cell division—the transition from the 1- to the 4-cell embryo stage results in a 74% increase in membrane surface area (119)—and cell growth and differentiation (110, 112). Evidence from animal studies suggests that individual fatty acids may influence normal oocyte maturation, fertility, and embryo development (83, 84, 113, 139) but the net rate of utilization by the gametes and embryo is not sufficient to make a significant additional demand on the mother or her diet. Even during the fetal period, the net accumulation of lipid and specific polyunsaturated fatty acids, such as DHA, is relatively small up until around 25 weeks of gestation (**Figure 2**). Deposition of lipid in the fetus increases exponentially with gestational age (**Figure 2**), reaching its maximal rate of accretion—around 7 g/day—just before term (140). Fat deposition in the fetus accounts for over half the energy accretion from the twenty-seventh week of gestation and as much as 90% of the energy accretion at term, with a heavier baby being a fatter (higher% fat) baby at any given gestational age (126, 127). In terms of individual fatty acids, the average rate of DHA utilization in pregnancy may be met by the normal dietary intake in the majority of women, but the rate of deposition close to term is likely to exceed even

relatively high maternal dietary intakes of DHA (**Figure 3**). The DHA requirement in pregnancy rises from around 100 mg/day at 25 weeks to over 300 mg/day close to term. The average omnivore dietary intake of DHA has been estimated in the United Kingdom (220 mg/day) (89), Canada (160 mg/day) (75), and Norway (300 mg/day) (64) to be in the same range as the likely combined average rate of DHA utilization over the whole of pregnancy, but within populations there are much lower and higher intakes. The exclusion of meat or fish from the diet can result in very low intakes of DHA. Vegetarians make up a significant proportion (11%–12%) of women of childbearing age in the United Kingdom (66) and the majority of the population in some other countries, such as India. Intakes of DHA in vegetarians in Western countries are around 10–30 mg/day (89, 101). At the other end of the spectrum, women consuming diets dominated by marine products, or women regularly ingesting marine oil supplements, can achieve very high intakes of DHA (exceeding 1 g/day) (64), but this is unusual. A significant proportion of mothers do not ingest sufficient preformed DHA to meet the estimated rate of maternal and fetal DHA utilization in the latter stages of pregnancy. Chain elongation and desaturation may make up some of the shortfall, but other adaptive mechanisms, involving the complex synchronization of maternal, placental, and fetal fat metabolism, reduce the need to meet the entire fetal demand from only the maternal diet during pregnancy.

THE PLACENTA

From eight weeks of gestation until birth, the fetus is entirely dependent on the placenta for its supply of nutrients. Anatomically, the human placenta is a large structure weighing around half a kilogram. However, its physical bulk belies the flimsy nature of the separation between the maternal and fetal circulations, which consists of two cell layers: the syncytiotrophoblast and the capillary endothelium. The human placenta is a hemochorial, villous type, where the maternal blood enters the intervillous space via the spiral arteries and flows directly around the terminal villi without any intervening maternal vessel wall (82). The endothelium allows the passage of nutrients through pores within the interendothelial cleft and therefore is not a significant barrier to nutrient passage. Other cell types and structures within the placenta, such as maternal myometrium and decidua, connective tissue, Hofbauer cells, and persisting cytotrophoblast cells, contribute to the metabolic activity and nutrient requirements of the placenta, but again these are not significant barriers to transport. The effective barrier between the maternal and fetal circulation is provided by a thin trophoblastic cover in the form of a syncytium (a single cell or cytoplasmic mass containing several nuclei in which the cytoplasm of constituent cells is continuous), known as the syncytiotrophoblast. Any substance crossing between the maternal and fetal circulation has to pass through the syncytiotrophoblast, which consists of a microvillous membrane facing the maternal blood and a basal membrane facing the fetal blood (82). The surface area of the maternal-facing microvillous membrane is around 5–6 times that of the fetal-facing basal membrane. Between 10 weeks and term, the thickness of the villous trophoblast falls from around 10 um to 4 um and the overall materno-fetal diffusion distance from 40 um to 5 um (82). The total surface area available for exchange gradually increases throughout pregnancy until it reaches around 10–15 m^2 (approximately the surface area of a tennis court) in the last trimester (**Figure 4*b***). The nature of the exchangeable surface of the placenta also changes throughout gestation, with the mature intermediate villi appearing toward the end of the second trimester and the terminal villi, which represent the main site of feto-maternal exchange, appearing a few weeks later (82). The rate of fetal blood delivery to the placenta (umbilical flow) also changes markedly during pregnancy and is approximately linearly related to fetal weight (**Figure 4*b***).

TRANSPLACENTAL POLYUNSATURATED FATTY ACID GRADIENT

Comparison of the maternal and fetal concentrations of two of the most important fatty acids for fetal development (AA and DHA) indicates a generally higher concentration of these LCPUFAs in all the major lipid classes in the fetal blood and tissues (**Figure 5**). This selective increase in the concentration of LCPUFAs, and of DHA and AA in particular, in the fetal circulation and tissues has been termed biomagnification (33). The time at which this gradient manifests also appears to be synchronized with the maximum fetal demand. Longitudinal data on maternal and umbilical blood phospholipid fatty acid composition from Al and colleagues (2, 3) indicates that, as with total fat deposition in the fetus, DHA percent in the fetal blood increases exponentially after around 20 weeks gestation (**Figure 4*d***). This appears to be a general phenomenon, with the DHA percent increasing in the phospholipid (PL) and cholesterol ester (CE) fraction and AA, LA, and αLN increasing in the CE and triglyceride (TG) fractions at this time (72).

Much has been made of the relatively high concentration of DHA in the fetal brain at term, but the concentration achieved is similar to that in the adult maternal brain and the absolute amount deposited in the fetal brain is relatively modest and not much greater than that present in the placenta (**Figure 5**). In terms of the potential additional dietary requirement for pregnancy, a more important issue is the fact that 16 times more DHA is stored in the fetal adipose tissue than is deposited in the fetal brain during in utero life and that the fetal adipose tissue has a much higher concentration of DHA and AA than does the maternal adipose tissue.

SUBSTRATE SUPPLY

In the course of pregnancy, the mother deposits approximately the same weight in fat (3500 g) as the entire weight of the average newborn (73), and the timing of that deposition is closely synchronized with the timing of fetal fat accretion (**Figure 2**). An appreciable amount of DHA is stored in the maternal adipose tissue, although it can vary over a wide range depending on the habitual dietary intake of n-3 fatty acids. Omnivores typically have DHA stores of around 19 g in the adipose tissue, although high levels of fish oil supplementation can result in DHA stores in excess of 100 g [calculated from the DHA content of human adipose tissue (92) and a body fat content of 15 kg (49) plus 3.5 kg stored in the course of pregnancy (73)]. On typical omnivore diets, the concentration of DHA in the adipose tissue is relatively low (0.1% of total fatty acids), and it would be necessary to mobilize all of the maternal adipose tissue in order to make the entire 19 g fully available to the developing fetus. Maternal body fat increases linearly until around 30 weeks of gestation, after which a modest net loss (73) occurs synchronous with the exponential increase in fetal fat accretion (**Figure 2**). Although the net loss of maternal fat is small at this time, the very high fasting lipid levels suggest that the maternal stores are turning over much faster than in the nonpregnant state. Also, the overall proportion of fat oxidized at this time appears to be reduced in the pregnant mother (14), implying that the purpose of this mobilization is to provide fatty acids for the fetus.

The maternal circulating concentrations of TG (37), PL (3), and NEFA (104) all increase throughout gestation (**Figure 4*a***), and this effect is particularly striking for maternal TG, which increases 250% (37). Perhaps more important is the constancy of this level throughout the day. Even in the fasted state, the pregnant woman has a TG concentration (37) that is almost twice the postprandial peak TG in a nonpregnant individual following the consumption of a high-fat meal (49).

The NEFA available at the microvillous membrane for transport to the fetus is derived from both the NEFA released into the maternal blood following mobilization from maternal adipose tissue and from circulating TG via the action of maternal or placental lipases (68, 69, 96). The human placental microvillous

membrane contains specific binding sites for the lipoproteins (very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein), which transport TGs and other esterified lipids (34, 111, 144). The presence of lipase activity in the placenta (7, 79, 121, 125) allows the production of NEFA from TG. The relative contribution of circulating NEFA and TG to total placental flux in human pregnancy is not known, although isotope studies in guinea pigs indicate that more of the fatty acid in the fetal circulation is obtained from maternal TG than from circulating NEFA (129). In vivo studies in humans have confirmed that fatty acids derived from maternal TG are taken up by the placenta and released into the fetal circulation (42), while in the perfused human placenta, there appears to be no detectable uptake from the maternal circulation of fatty acid from PL (87). The observation that TG increases much more than the other esterified fractions (**Figure 4*a***) with gestation also suggests that this is the major substrate for the placenta.

SYNTHESIS OF LONG-CHAIN POLYUNSATURATED FATTY ACIDS

Placental synthesis of AA and DHA has been proposed as one mechanism to explain the higher concentrations of these LCPUFAs in the fetal circulation (**Figure 5**), but Δ6 and Δ5 desaturase activity is undetectable in the placenta (23), and Δ5 desaturase mRNA in human placental tissue is low compared with other tissues (25). There is one report of incorporation of ^{14}C from labeled acetate into AA in slices of human placenta (147), although two subsequent studies in the perfused human placenta have been unable to detect chain elongation and desaturation of either LA or αLN (8, 61). Thus, there appears to be little evidence of significant augmentation of AA and DHA supply to the fetus by placental chain elongation and desaturation.

There is more convincing evidence for LCPUFA synthesis in fetal tissues. Stable isotope studies carried out in vivo have demonstrated that premature human infants are able to synthesize both AA and DHA at an age when they would still developmentally be dependent on the placenta (20, 123). It has also been deduced from these tracer studies that the capacity for AA synthesis is greater than for DHA synthesis. Additional circumstantial evidence that the human infant is better able to synthesize AA than DHA comes from the observation that the concentration of DHA in the neonatal brain is dependent on the intake of preformed DHA, whereas there is little effect of AA intake on the brain concentration (45, 77, 98). This difference in n-3 and n-6 conversion efficiency is consistent with the respective biochemical pathways; the final step in the synthesis of DHA is considerably more complex than that for AA (**Figure 1**) in that it requires the participation of enzymes in both peroxisomes and the endoplasmic reticulum as well as the controlled movement of fatty acids between these two cellular compartments (128). However, if (as seems likely) DHA synthesis from EPA were more efficient than from αLN, it may be appropriate to include some fraction of dietary EPA in a calculation of ingested "DHA equivalents." EPA is often present in similar amounts to DHA in omnivore diets; therefore, if its conversion to DHA were efficient, it would effectively double the intake of DHA equivalents from the diet. EPA is also present in vegetarian diets, but the ratio to DHA is lower than that in omnivore diets.

Synthesis of DHA in the maternal tissues could not explain the transplacental gradient in DHA concentration, but it could make an important contribution to the net fetal availability of DHA in women with habitually low dietary intakes of preformed DHA. There is evidence for conversion of αLN to DHA in the maternal tissues, and the rate of conversion is greater in women than men (11, 12, 13). This sex difference in the rate of conversion has been attributed to the response of Δ6 desaturase to sex hormones, raising the possibility that conversion could be synchronized with the stage of pregnancy and maximal fetal demand. However, the observation that the increase in

the percent DHA in fetal circulating PL is not matched by an increase in DHA in maternal circulating PL (**Figure 4*d***) would tend to argue against a physiologically significant change in the rate of maternal synthesis with stage of gestation. The gradual accumulation of synthesized DHA in maternal adipose tissue, the synchronization of its release with the period of maximal fetal demand, and the presence of placental mechanisms designed to concentrate the available DHA in the fetal circulation could help to overcome the dietary DHA deficit apparent in most women close to term and possibly in vegans and some vegetarians over much of pregnancy (**Figure 3**). However, it is not yet possible to factor the rate of LCPUFA synthesis into any balanced equation, as it has proved difficult, even in highly sophisticated tracer studies, to quantify absolute rates of conversion in vivo.

PLACENTAL FATTY ACID TRANSPORT

Direct measurement of placental fatty acid transport in human pregnancy is practically and ethically extremely difficult. The available techniques all have drawbacks and involve a tradeoff between physiological relevance and the quality of the information derived. There are a very small number of studies in which stable isotope–labeled amino acids and fatty acids have been administered to the mother and their appearance measured in the cord blood. These studies have the potential to provide information on dynamic placental nutrient transfer rates in vivo, but their interpretation is severely constrained by the number of sequential cord blood samples that can be taken, and the conclusions have therefore been necessarily tentative. Placental function is often inferred from measurements of concentration differences in the maternal and fetal circulations. The most sophisticated of these involve measurements of arterio-venous differences across the umbilical cord at cesarean section before the cord is cut, but such studies are generally carried out in very late gestation. Cord blood levels may also be measured following delivery or, more informatively, at earlier stages of development using the invasive method of cordocentesis. However, an important disadvantage of any "snapshot" of cord blood nutrient concentrations is that these are the net result of both placental delivery and fetal utilization. Because of the problems with interpretation of results from vivo studies, a number of in vitro approaches have been developed. These include the dually perfused placenta, which retains the cellular structure and metabolic activity of the syncytiotrophoblast and the placental vascular structure but allows the nutrient composition of the maternal and fetal circulation to be controlled and transfer rates to be measured dynamically using isotopic tracers. The problems with this ex vivo technique are that the placenta tends to be very mature, the efficiency of perfusion cannot be assumed to exactly mimic the in vivo situation, and the composition of the maternal and fetal perfusates are not truly physiological. More detailed but less physiologically relevant to absolute rates of transfer are vesicles formed from the syncytiotrophoblast. These are particularly well suited to the study of nutrient transport mechanisms under highly controlled conditions. The most reductionist methodology involves the identification and characterization of individual transport proteins.

Placental Fatty Acid Transport Proteins

All fatty acids can cross lipid bilayers such as those in the syncytiotrophoblast by simple diffusion, and studies in pure phospholipid bilayers indicate that the process is rapid ($t_{1/2} \sim 20$ ms) (80). However, a number of fatty acid–binding proteins (FABPs) have been identified in the membrane and cytoplasm of mammalian cells, which are thought to facilitate the transfer across membranes and intracellular channeling of fatty acids (53, 54, 134, 135). The main membrane-associated FABPs are the plasma membrane fatty acid–binding protein (FABPpm) and the fatty acid transfer proteins (FAT/CD36 and FATP), but the

precise way in which membrane-associated FABPs facilitate trans-membrane passage of fatty acids is still a matter of speculation (40, 53, 54). FAT/CD36 and FATP are integral proteins with membrane-spanning regions, and it has been proposed that these could function as fatty acid transporters or translocases, but that FABPpm is more likely to act as an extracellular fatty acid acceptor because this is a peripheral membrane protein (53, 54), thereby facilitating fatty acid diffusion through the phospholipid bilayer by increasing the local extra- to intracellular fatty acid gradient and decreasing the diffusion distance in the unstirred bilayer (53, 54).

Much work on placental FABPs has been carried out by Duttaroy and colleagues (for a recent review, see 40). FAT/CD36 and FATP are found on both the microvillous and basal membranes, and a placenta-specific protein (p-FABPpm) is found exclusively on the microvillous membrane (15). This p-FABPpm is similar in size (~40 kDa) to the ubiquitous FABPpm found in most mammalian cells, but it differs from FABPpm in several aspects (e.g., pI, amino acid composition). The apparent order of fatty acid–binding preference by this protein is DHA>ARA_ALA>LA>OA (16–19). Thus, the p-FABPpm could be involved in preferential uptake of LCPUFAs. However, the presence of fatty acid–binding proteins on the microvillous membrane allows for bidirectional flux between the maternal circulation and the syncytiotrophoblast cytoplasm, and it is not clear how the binding affinities of the FABPs for individual fatty acids might translate into selectivity for unidirectional transport across membranes.

A number of researchers have emphasized the role of cytoplasmic FABPs in removing fatty acids from the inner membrane and channeling them to their respective metabolic fates as an important determinant of net uptake and transplacental flux (54, 55, 133). The syncytiotrophoblast also contains cytoplasmic-binding proteins, which were first identified in the heart (H-FABP) and liver (L-FABP) (40). The presence of FABPs on both the microvillous and basal membranes of the syncytiotrophoblast, the reversible nature of fatty acid binding to these proteins, and the presence of equivalent NEFA-binding sites in both circulations indicate a symmetry to the arrangement of fatty acid carriers linking the maternal to fetal blood (**Figure 6**). This symmetry extends the possibility of bidirectional binding protein–mediated transport to bidirectional transport between the maternal and fetal circulations. The largely symmetric and reversible nature of fatty acid transport across both membranes in the human placenta is supported by the studies of Lafond and colleagues who observed uptake of LA (88) and AA (40) by both the microvillous and basal membrane; Hendrickse and colleagues (67) measured net placental uptake of AA from the fetal circulation in vivo in human pregnancy at cesarean section. It has been reported that the uptake of AA by both the microvillous and basal membrane of the trophoblast is ATP dependent, while the basal membrane uptake is dependent on both ATP and Na^+ (67). However, there is little evidence from studies of FABPs in other systems of an ATP-dependent uptake of fatty acids, and it is thought that the FABPs mainly act to facilitate transport down a concentration gradient (54).

The Driver of Placental Fatty Acid Transport

The available evidence suggests that the net transfer of fatty acids to the fetal circulation is largely determined by the transplacental gradient of NEFA relative to available hydrophobic-binding sites (**Figure 7**). Cordocentesis data on fetal plasma from 18 to 36 weeks indicate an exponential fall in the concentration of circulating NEFA in the fetal circulation over this period (41), presumably because of the rapidly increasing fetal demand for fatty acids (**Figure 4*c***). The concentration of NEFA in the maternal plasma at term is around three times that in the fetal circulation, but the concentration of albumin, its primary carrier protein, is actually 10%–20% higher in the fetal than in the maternal circulation (4). This contrasts with the other lipoprotein

fractions that carry the esterified lipids, as these actually decrease in the fetal circulation with increasing gestation (5, 109). As a result of these changes, the ratio of plasma NEFA to albumin on the fetal side of the placenta is around a quarter of that on the maternal side at term (5). NEFAs in the fetal circulation are also carried on α-fetoprotein, which has a similar molar fatty acid–loading capacity to albumin (2–3 moles per mole protein), but this protein is only present in the fetal plasma at concentrations around one thousand times lower than albumin (5); therefore, its contribution to overall binding capacity in the fetal circulation is negligible. The higher concentration of NEFA relative to all available binding sites in the maternal compared to fetal blood is reflected in the concentration of unbound NEFA, which is greater in the maternal (12 nM) than fetal (9 nM) circulation (117).

Since the pull exerted by the fetal plasma on intracellular NEFA within the syncytiotrophoblast is affected by the availability of free binding sites in the fetal blood, it must also be influenced by the rate of delivery of those binding sites to the placenta and the effective exchange area of the syncytiotrophoblast. As noted above, changes in the exchangeable area of the placenta, the umbilical blood flow, and the nature of the exchangeable surface of the placenta are all synchronized with the exponential increase in demand for fetal fat deposition.

Selective Placental Transfer of LCPUFA

Placental selectivity for the transfer of individual fatty acids to the fetus may be exerted at the level of placental lipase, uptake by the microvillous membrane, metabolism within the placenta, and the form in which placental fatty acids are exported to, and metabolized within, the fetal circulation. Measurements in the intervillous space of the placenta have demonstrated concentrations of AA and DHA in the NEFA fraction (partly produced by the action of placental lipase) three to four times greater than in the maternal peripheral blood (4). If this finding is not an artifact of the measurement, where the higher LCPUFA concentrations within the placenta are the result of re-release from the syncytiotrophoblast in the post-delivery placenta, it implies that there is significant selectivity by the placental lipase(s) for the release of LCPUFA from TG, and there are plausible mechanisms to account for this effect. Lipoprotein lipase is known to preferentially hydrolyze TG fatty acids in the sn-2 position of the glycerol moiety. Individual fatty acids are not distributed equally throughout the three positions of the glycerol backbone of plasma TG, and the sn-2 position is generally more unsaturated than are the sn-1 and sn-3 positions. Furthermore, TG molecules containing an unsaturated fatty acid at this position are better substrates for lipoprotein lipase (26, 108). Whatever the mechanism, the degree of enrichment of AA and DHA at the microvillous border reported by Benassayag and colleagues is sufficient to account for all of the biomagnification of these fatty acids within the fetal circulation without having to invoke any placental selectivity.

When the placenta is perfused with a mixture of fatty acids designed to mimic that of the circulating TG in the last trimester of pregnancy, the order of selectivity for uptake is AA>DHA>αLN>LA (61). There is a relatively high selectivity for AA uptake by the microvillous membrane, but the placenta also appears to preferentially retain AA in preference to the other fatty acids, resulting in a different order of selective transfer to the fetal circulation; DHA>αLN>LA>AA (61). Studies in BeWo cells indicate that selectivity in placental metabolism may also influence preferential placental transfer selectivity (130). When the concentration of AA in the maternal circulation of the perfused placenta is increased, there is a disproportionately greater increase in the selective transfer of AA relative to other fatty acids such that the order of selectivity changes from DHA>αLN>LA>AA to DHA>AA>αLN>LA (60). The relatively large effect on AA in particular may be related to the fact that the placenta is an important site of production of the prostacyclins, prostaglandins,

thromboxanes, and leukotrienes, and AA is the precursor of the eicosanoids: PGE_2, PGD_2, TXA_2, and 12-HETE. One possible explanation for the high sensitivity of AA transport to maternal supply may be that the placenta has a minimum requirement for AA to produce these metabolites and that it is only when this requirement is met that the remaining AA becomes available for transfer to the fetal circulation. Placental precedence for available AA and fetal precedence for DHA would be consistent with the observation that more AA is accumulated in placentas perfused with higher concentrations of AA (60, 61). Also, the fetus appears to be less dependent on a placental supply of AA than of DHA (45, 77, 98). The in vitro selectivity of the placenta for individual fatty acids agrees with that determined in vivo. Selectivity measurements based on maternal and cord blood arterio-venous difference at birth produce an order of selectivity within the NEFA fraction of DHA>AA>oleic>LA>αLN (122). This is similar to the selectivity observed when the maternal face of the human placenta is perfused with a mixture designed to mimic the maternal NEFA fraction: DHA>AA>αLN>LA (60). Tracer studies using ^{13}C-labeled fatty acids administered to the mother immediately before cesarean section have also demonstrated selective channeling of individual fatty acids to the fetal circulation (91).

A further control point at which selective concentration of LCPUFA in the fetal circulation may occur is the form in which fatty acids are exported by the placenta into the fetal circulation and the metabolism of fatty acids within the fetus itself. In studies where there has been specific fractionation of trophoblast membranes into microvillous and basal membranes, lipase activity and the presence of lipoprotein receptors have only been reported on the microvillous membrane. This suggests that fatty acids in esterified form in the fetal circulation may not be available to the placenta for reuptake. Kuhn & Crawford (87) reported that 93% of the LA exported into the fetal circulation was in the form of NEFA, whereas most of the AA (60%) was in the form of PL. Given the apparent absence of lipase activity on the basal membrane, such preferential incorporation of PUFA/LCPUFA into esterified lipids would effectively trap these fatty acids within the fetal circulation while allowing the NEFA, with a lower level of LCPUFA enrichment, to re-exchange to an unknown extent with the fatty acid pool within the syncytiotrophoblast. The same overall effect of trapping PUFA/LCPUFA in the fetal circulation would result from the conversion of NEFA into PL within the fetal liver (20), a process that naturally increases the concentration of LCPUFA in the product even in the nonpregnant state (90). The human placenta has multiple mechanisms available to generate the observed LCPUFA gradient between the maternal and fetal circulations.

GENETIC VARIATION

The outcomes most often considered in relation to fatty acids transport are heritable: birthweight—a proxy for body fatness (127)—is heritable (29, 95), as is cognitive ability (9, 39). The various adaptive mechanisms that prioritize n-3/n-6 delivery to the fetus are known to be influenced by genetic variants. The main ways in which genetic variation could influence fatty acid supply to the fetus are by altering overall substrate availability, the mix of fatty acids in the available substrate, and differential metabolism of different fatty acids.

A key adaptation in pregnancy is the extreme elevation in circulating triglyceride with increasing stage of gestation (**Figure 4*a***). The normal postprandial elevation in triglyceride has been shown to be modified by polymorphisms within the genes for apolipoprotein AI, apolipoprotein E, apolipoprotein B, apolipoprotein CI, apolipoprotein CIII, apolipoprotein AIV, apolipoprotein AV, lipoprotein lipase, hepatic lipase, the fatty acid transport proteins, microsomal triglyceride transfer protein, and scavenger receptor class B type I (94, 137). Variation in the gene coding for FATP1 has been associated with plasma triglyceride levels in women (105). Polymorphism in the

FABP-2 gene has been shown to affect the affinity of intestinal FABP for fatty acids, to alter whole-body lipid metabolism and the pattern of fat accumulation in adipose tissue, and to affect insulin resistance and its relationship to fetal growth (1, 81, 105, 106). Polymorphism within the FABP-1 gene has also been linked to fasting triglyceride levels in females (48). Polymorphisms resulting in functional changes have also been reported for CD36 (114, 145) and FATP (105). Variation in the *I-FABP* promoter has been linked to transcriptional activity, the affinity for fatty acids, insulin resistance, and altered body composition (35, 43). A missense mutation in the *L-FABP* gene has been associated with residual hypertriglyceridemia following a lipid-lowering therapy and an altered body mass index (10). In terms of reproductive outcomes, there is evidence that the apparently beneficial effect of human milk on intelligence may be modulated by genetic polymorphism in the pathway of DHA synthesis (21). Although considerable evidence suggests that variants in the genes controlling fat metabolism have functional effects on the phenotypes relevant to fatty acid handling in pregnancy, surprisingly little work has been done to assess their influence on human pregnancy.

IMPLICATIONS

At the peak of fetal fat deposition in the last trimester of pregnancy, many women consuming contemporary Western diets are not able to meet the fetal demand for n-3 LCPUFA from the diet alone. However, this may not to be a significant problem as there is little evidence that maternal LCPUFA supplementation during pregnancy influences the major outcomes. In terms of birth outcome, a recent Cochrane review concluded that birthweight was slightly greater in infants born to women supplemented with marine oils but that there were no overall differences between the groups in the proportion of low-birthweight or small-for-gestational-age babies (97). These authors concluded that "there is not enough evidence to support the routine use of marine oil, or other prostaglandin precursor, supplements during pregnancy to reduce the risk of pre-eclampsia, preterm birth, low birthweight or small-for-gestational age" (97). A similar conclusion was reached in a separate meta-analysis (71). There is some evidence that supplementation during pregnancy may influence visual function and cognition in the offspring, but the studies carried out so far have been small, and significance has been detected for only a few of the many measured outcomes (63, 65, 99, 100). Data from premature infants, particularly boys, suggest that LCPUFA supplementation may have a beneficial effect on growth and neurodevelopment (46, 47). In prematurity, the supplementation occurs during the period when the conceptus would still be developmentally dependent on the placenta, but the extrapolation of these data to the situation in utero is complicated by the very poor adipose tissue stores of premature and growth-retarded infants. The results of observational studies are mixed (30, 36, 52) and may be confounded by factors such as the intake of heavy metals and other contaminants from fish (31, 78, 115). Overall, the evidence so far for a beneficial effect of LCPUFA supplementation in pregnancy on cognitive and visual function is patchy, but it is worth noting that LCPUFA supplementation, in addition to an already adequate omnivore intake, may not yield any measurable benefit but that very low LCPUFA intakes could result in loss of function.

LCPUFA supplementation during pregnancy even appears to have little effect on the LCPUFA composition of the maternal and fetal blood. Supplementation daily at 100 mg of DHA (107), 336 mg of fish oils (136), and 500 mg DHA with 150 mg EPA has no measurable effect on cord blood n-3 concentrations. To detect measurable changes, it is necessary to supplement the diet with much higher levels: 2600 mg/day (32) and 2700 mg/day of n-3 fatty acids (132). It has been suggested that additional intakes during pregnancy of up to 1 mg/day (three to five times the normal dietary intake) may be necessary to significantly increase cord blood n-3 concentrations (136). This is in

striking contrast to the observation that fairly modest differences between individuals in the n-3 content of their habitual prepregnancy diet can have significant effects on the cord blood composition (116). The most likely explanation for this contrast is the adaptive mechanisms that have evolved over millennia to protect the fetus against low intakes of important LCPUFAs during critical periods of fetal development and to ensure a constant supply of substrate to the fetus, free of large diurnal fluctuations in supply corresponding to the timing of maternal meals. The key component of this adaptation appears to be an emphasis on the maternal adipose tissue as the dependable source of fats during fetal development. The critical importance of adequate maternal adipose tissue stores to pregnancy is underlined by the fact that inadequate level of body fatness result in infertility and an inability to sustain a pregnancy (50, 138, 146).

Another measure of the importance of maternal adipose tissue is its effect on fetal fat stores. Heavier babies are fatter babies, and mothers who are obese are more likely to have babies with high birthweights (22, 85, 124). Even within the normal weight range, maternal prepregnancy weight and the weight gained during pregnancy are associated with the offspring's birthweight (86). This effect could be mediated through hormonal changes associated with maternal fatness, but it could also simply be due to a substrate effect, as obese women have higher levels of circulating NEFA and TG in pregnancy (85, 120).

Maternal adipose tissue provides a significant proportion of the raw material for the placenta in the form of relatively low-concentration LCPUFA, which can be enriched by selective transport mechanisms operating within the placenta. Temporal changes in placental function are synchronized with adaptive changes in substrate supply in a way that ensures a continuous supply of n-3/n-6 LCPUFA-enriched fat to the fetus. The placenta may also play a role in modulating its own substrate supply in response to the fetal demand. Placentally derived leptin is a potent stimulator of lipolysis (51, 56, 102), which the human placenta exports into both the maternal and fetal circulation (70, 93), and the rate of placental leptin export into the maternal circulation increases with increasing fetal-to-placental weight ratio (70).

The importance of the maternal adipose tissue in pregnancy is mirrored by the importance of the fetal adipose tissue as a source of LCPUFA for brain and retinal development during the critical first months of postnatal life. The fetal adipose tissue has a much higher concentration of DHA and AA than does the maternal adipose tissue, and one purpose of this seems to be to support postnatal brain and retinal development. Within a few hours of birth there is a dramatic rise in plasma TG and NEFA in the newborn, indicating mobilization of adipose tissue stores (131) such that the concentration of DHA in the adipose tissue is undetectable after two months of postnatal life on a diet devoid of preformed DHA (45). The fact that most of the LCPUFA that is accrued by the fetus is actually stored in fetal adipose tissue also implies that there is normally an excess available for development of the critical organs and tissues in utero. These mechanisms would protect the neonate against a poor dietary supply of LCPUFA during this critical period of brain and retinal development, and this may be important in low birthweight or premature babies, where the critical fat stores to support postnatal development are greatly diminished. This mechanism also complicates the concept of the dietary requirement during pregnancy, as the in utero "requirement" for DHA is likely to be affected by its interaction with postnatal nutritional status. If the baby has a good supply of DHA in the first months of life, then its adipose stores may not be critical; if it has a poor supply because it is given formula milk without added LCPUFA, or the mother's breast milk is poor in LCPUFA, or the baby does not feed well on any diet, then the availability in utero and the amount already laid down in the adipose tissue of the newborn may be critical.

Dietary fats and supplements of marine origin may contain significant concentrations of organochlorines, which include polychlorinated biphenols (PCBs) and dioxins (44, 76).

Because of their similar physiochemical properties, the fate of these undesirable components may mirror that of the n-3 LCPUFA by using the same physiological adaptations designed to optimize maternal delivery of n-3 LCPUFA to the fetus. There are reports of positive associations between maternal and cord concentrations of EPA, DHA, and PCBs (57). Although organochlorines may be relatively harmless when stored in the adipose tissue, fat mobilization increases the plasma concentrations of these toxins (24, 74), and the very high rate of mobilization of maternal fat stores in the last trimester of pregnancy and the possible remobilization of neonatal adipose tissue in early life are likely to lead to repeated washing out of these compounds into the circulation, organs, and tissues of the fetus and neonate during critical periods of development.

Maternal adipose tissue mass can influence the fetal fat mass, but the likelihood is that the fetus plays a significant role in controlling its own supply of fatty acids. The rate of placental fatty acid transport is directly influenced by the transplacental fatty-acid-to-binding-site concentration gradient, which is in turn largely determined by the rate of uptake of fatty acid by the fetal tissues and the fetal (umbilical) blood flow; the latter is approximately linearly related to the fetal weight, and hence the fetal nutrient requirement, throughout gestation.

The nutrient composition of the human diet varies enormously between and within populations, yet the healthy human newborn is essentially the same the world over as a result of adaptive mechanisms that have evolved to protect human offspring from extreme variation or deficiency in the maternal diet during pregnancy. Any nutritional strategy designed to improve the availability of fatty acids to the fetus would do well to accommodate these mechanisms.

FUTURE DIRECTIONS

The important practical issue of whether there is a dietary requirement for specific LCPUFAs in pregnancy requires further research in a number of areas. In vivo studies are needed to quantify the conversion of different n-3 precursors (αLN and EPA) to DHA in the pregnant state and prior to pregnancy. The key question is what proportion of the DHA utilized by the fetus is derived from the maternal diet and how much has been synthesized in the mother (before or during pregnancy) and the fetus. This will require more sophisticated stable isotope studies than have hitherto been carried out. It may even require the development of entirely novel approaches, for example, the exploitation of natural variations in the abundance of fatty acids from different sources to estimate DHA synthesis (59).

Studies to evaluate the effect of n-3 LCPUFA supply on physiological function have generally been carried out in omnivores, where the intake may already be adequate, and once pregnancy has been established. More supplementation studies are needed in mothers with habitually low intakes of n-3 LCPUFA (vegetarians and vegans). Although difficult to achieve, ideally the supplementation period should begin before pregnancy is established and should continue for long enough to alter the fatty acid composition of the maternal adipose tissue. For observational studies, it would be useful to assess the prepregnancy adipose tissue mass and fatty acid composition in relation to functional outcomes. More work is needed to understand the role of the fetal adipose tissue LCPUFA stores in postnatal development and how the availability of LCPUFA in utero influences the dietary requirement for LCPUFA in the neonate.

More work is needed on how the dynamic changes in maternal fat during pregnancy influence the fetal exposure to environmental contaminants such as PCBs and dioxins.

Remarkably little is know about how variation in the genes involved in the control of fat metabolism influence fatty acid accretion by the fetus, pregnancy outcome, and visual and cognitive function in the offspring. It may also be possible in genetic studies to use the technique of Mendelian randomization (38) to infer nutritional effects on the outcomes of interest from genetic associations.

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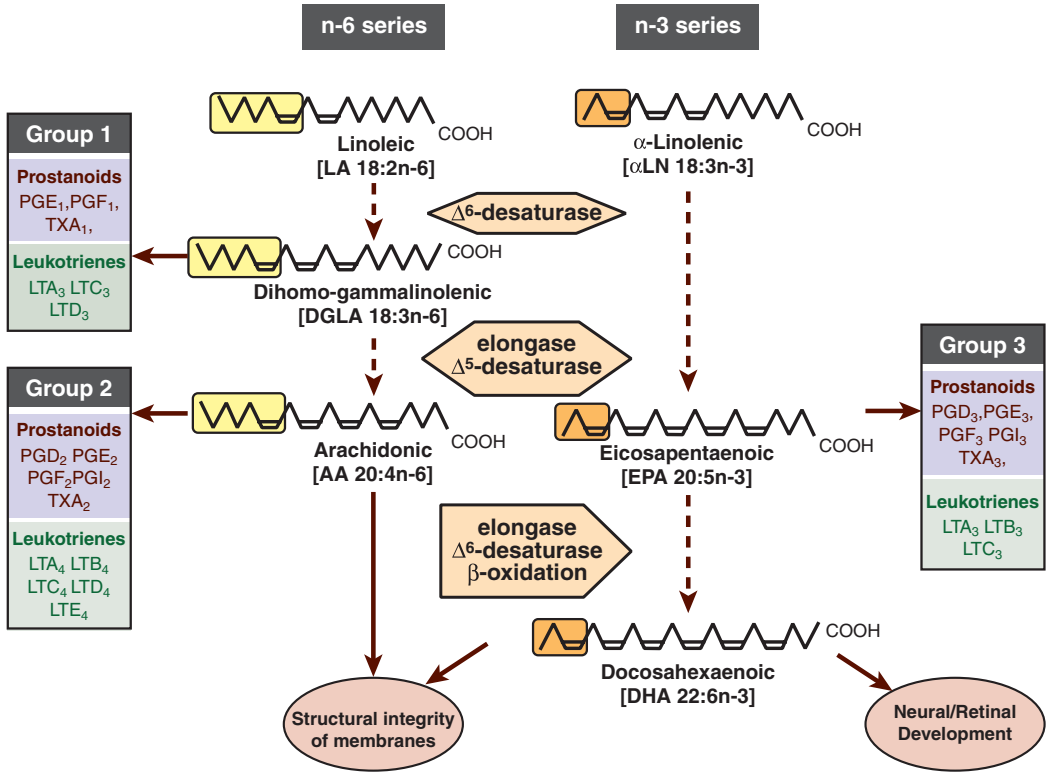


Figure 1

Pathways of chain elongation and desaturation of the essential fatty acids, linoleic [18:2 n-6 (LA)] and α-linolenic [18:3 n-3 (αLN)], to produce their long-chain polyunsaturated fatty acid (LCPUFA) derivatives, of which dihomogamma linolenic acid [18:3 n-6 (DGLA)], arachidonic acid [20:4 n-6 (AA)], eicosapentaenoic acid [20:5 n-3 (EPA)] and docosahexaenoic acid [22:6 n-3 (DHA)] are metabolically the most important. These LCPUFAs are the precursors for the group 1, 2, and 3 prostanoids and leukotrienes, they are important in the structural integrity of membranes, and DHA in particular is thought to be required for normal brain and retinal development in the fetus and neonate.

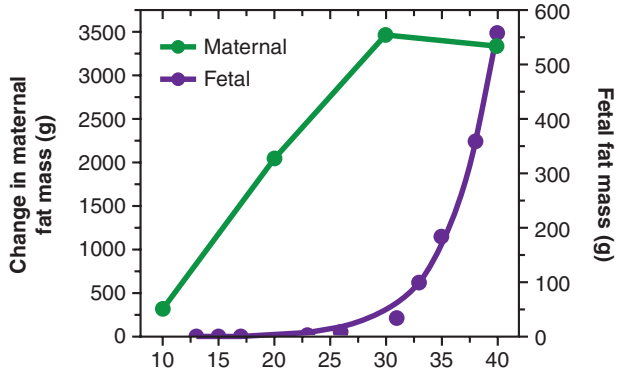


Figure 2

Change in body fat in the mother (73) and fetus (141) with stage of gestation.

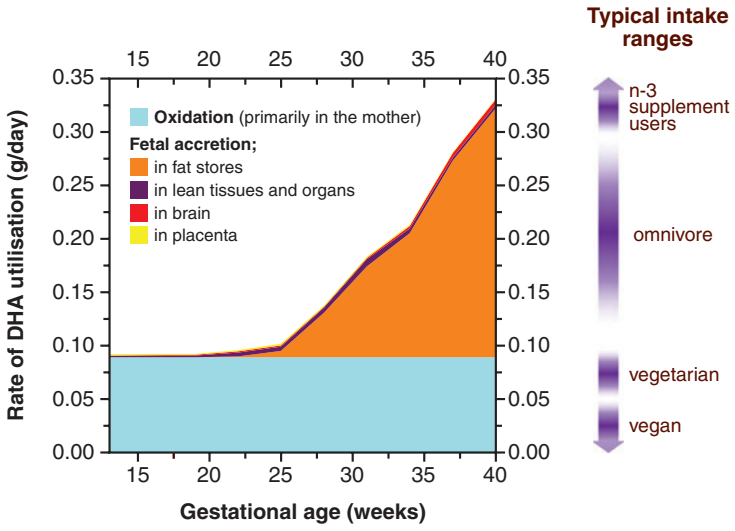
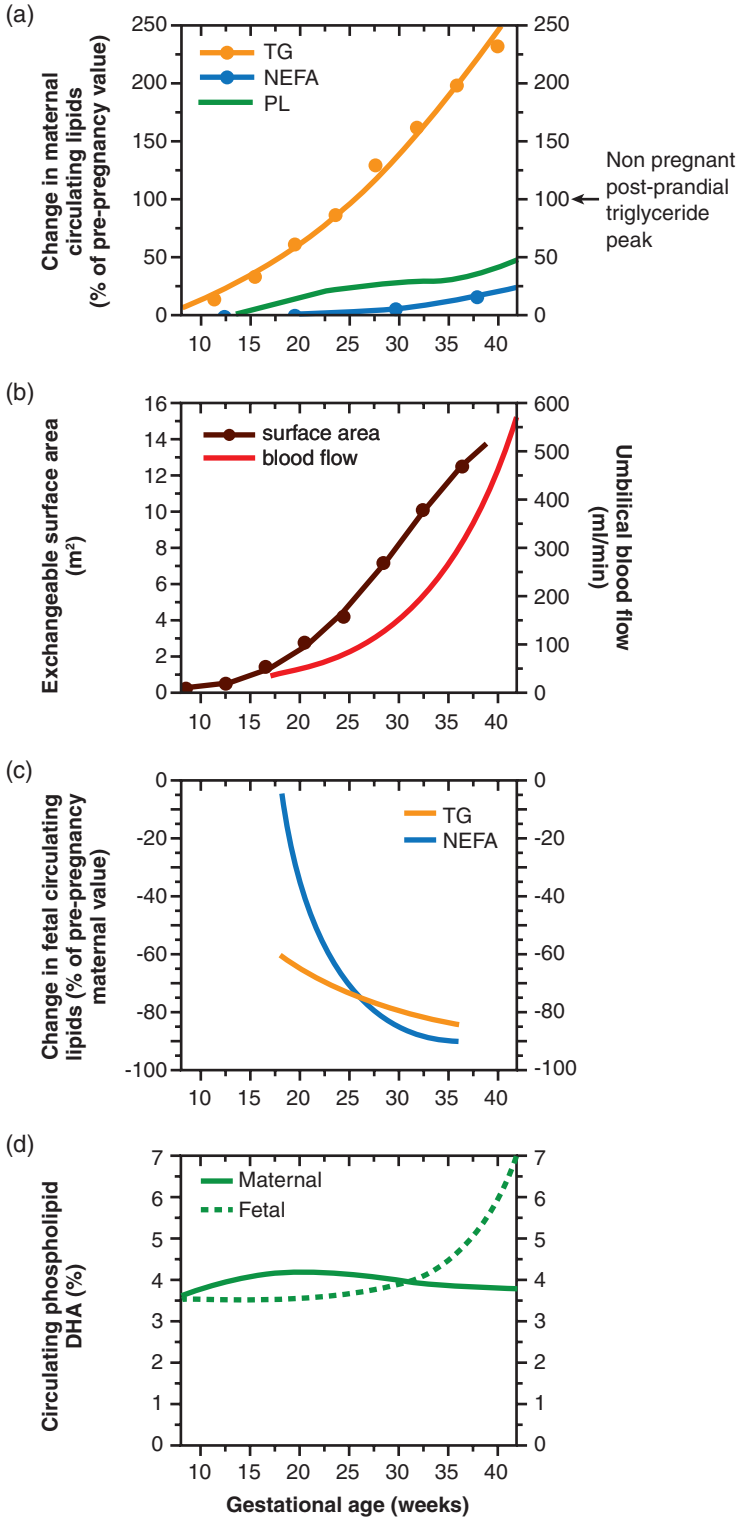


Figure 3

Change in the rate of docosahexaenoic acid (DHA) utilization with stage of gestation and its relationship to dietary intake. The theoretical rate of oxidation was calculated from the rate of maternal energy expenditure (9453 MJ/day), the proportion of that energy derived from fat (30%), the energy content of fat (39 kJ/g) (14), and the proportion of DHA in the oxidized fat (0.1% DHA). The DHA content of fetal tissues was calculated from the lean mass [calculated as body weight minus the weight of fat, skeleton, and skin (142)]; the fat mass (142) and the weight of the placenta (73) and brain (28); and the fat and DHA concentration of the brain (28, 77), placenta (89, 143), and adipose tissue (27). For the purposes of the calculation, the DHA content of the fetal lean tissue, blood vessels, etc., was assumed to be the same as that of the placenta. Typical ranges for the daily dietary intake of DHA in different groups are shown on the right.

Figure 4

Change in maternal and fetal circulating lipids and placental function with stage of gestation: (*a*) Percentage change in the concentration of maternal circulating plasma triglyceride (TG) (37), phospholipid (PL) (3), and nonesterified fatty acid (NEFA) (104) relative to prepregnancy value. A typical maximum value for plasma triglyceride in a nonpregnant individual following a high-fat meal (49) is also shown. (*b*) Placental blood flow and exchangeable surface area (82). (*c*) Percentage change in the concentration of fetal circulating plasma TG and NEFA in the fetal circulation (4, 5, 41). (*d*) Maternal and umbilical blood phospholipid fatty acid composition (2, 3).



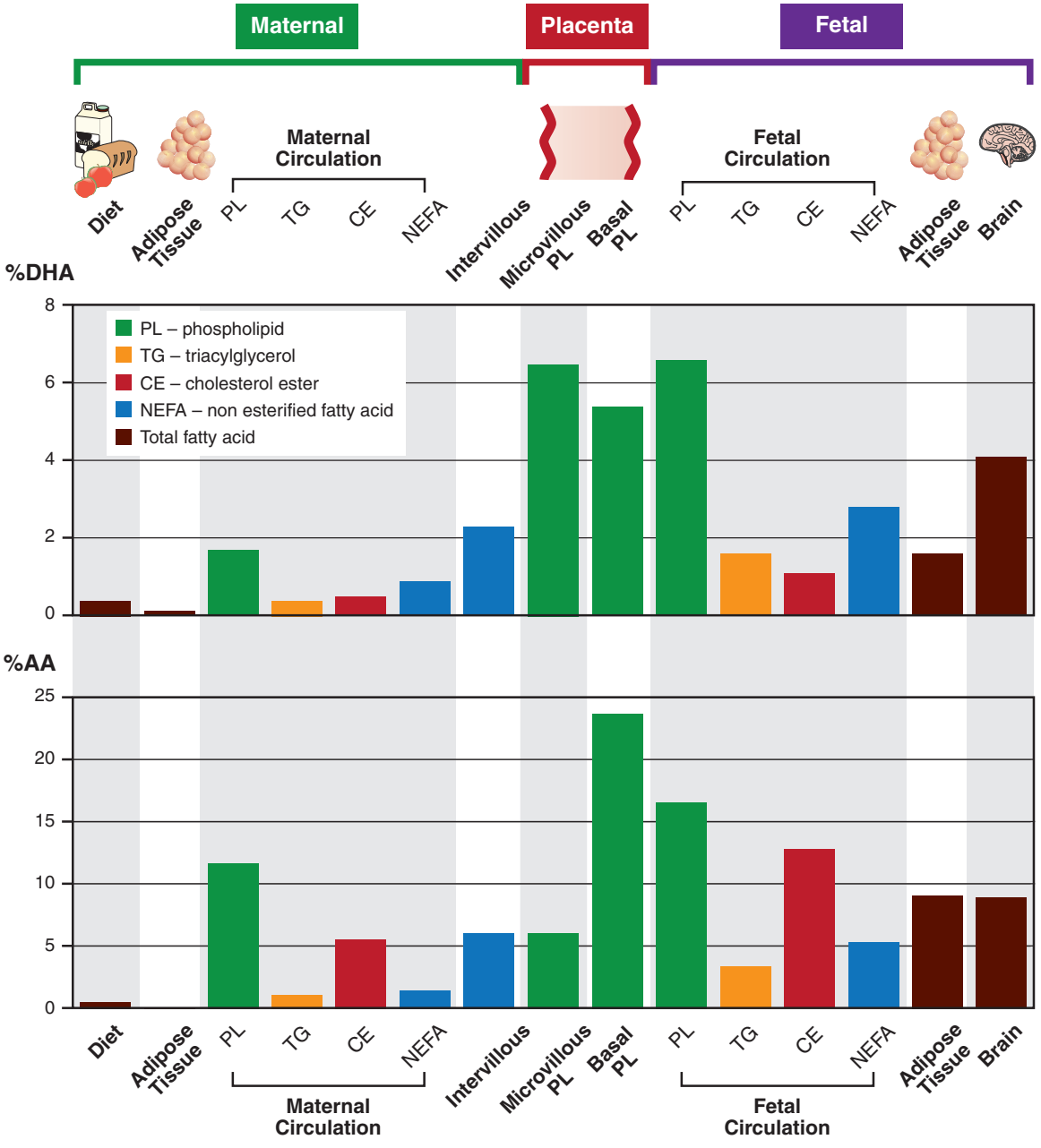


Figure 5

Arachidonic acid (AA) and docosahexaenoic acid (DHA) as a proportion of total fatty acids in the diet of pregnant mothers (89), the adipose tissue (92), maternal and cord blood plasma phospholipids (PL) (116), triglyceride (TG) (6), cholesterol ester (CE) (72), and nonesterified fatty acid (NEFA) (5), the placental microvillous and basal membranes (118), and adipose tissue and brain at birth (27).

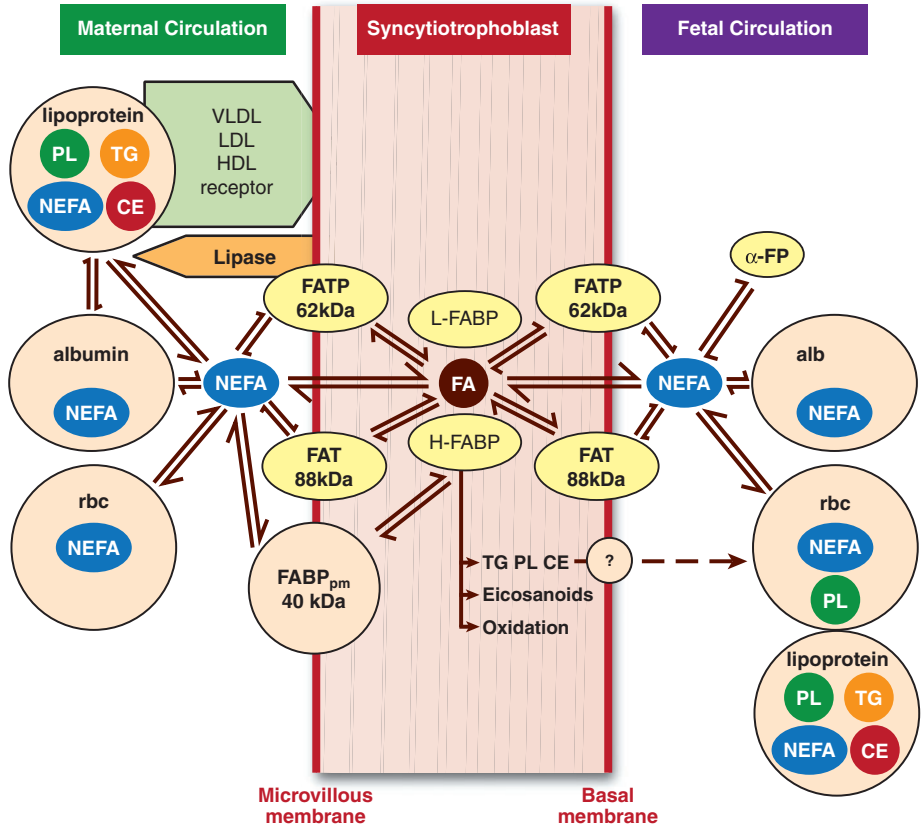


Figure 6

Schematic of fatty acid transport across the placental barrier. Only nonesterified fatty acids (NEFAs) are taken up by the plasma membrane. These may be derived from NEFA in the maternal circulation or from triglyceride (TG) following the action of placental lipases on the microvillous membrane (96) in concert with specific binding sites for the lipoproteins [very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] (34, 111, 144). The NEFAs are mainly bound to albumin (alb) in the maternal and fetal circulation, though some may be associated with α-fetoprotein in the fetal circulation or may be associated with red blood cell (rbc) membranes. The center panel shows the distribution of fatty acid–binding proteins [plasma membrane placental fatty acid–binding protein (FABPpm, FAT/CD36), fatty acid–transfer protein (FATP)] on the microvillous and basal membranes and within the cytoplasm [liver and heart fatty acid–binding protein (L- and H-FABP)] of the syncytiotrophoblast (40). There is one report of placental export of phospholipid (PL), cholesterol ester (CE), and TG into the fetal circulation (87).

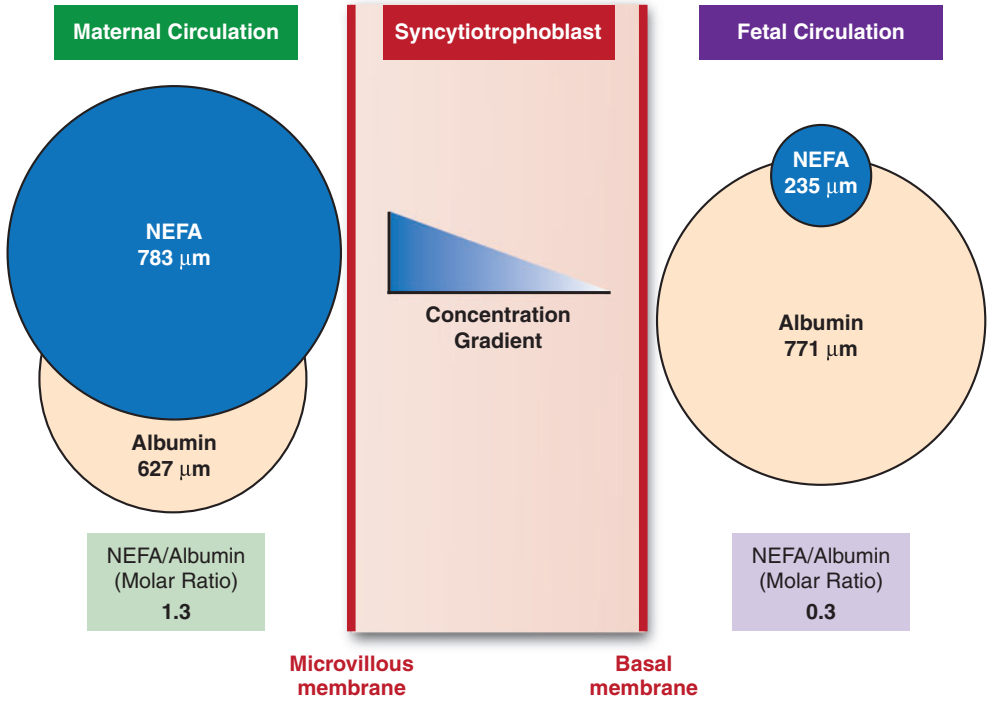


Figure 7

The driving force for net maternal-to-fetal transfer of fatty acids. The concentrations of nonesterified fatty acid (NEFA) (58, 117), albumin (4, 5), and the ratio of NEFA to albumin in the maternal and fetal plasma at term are illustrated. The areas of the circles are proportional to the concentrations.

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Contents

Indexes

Errata

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