Brain food for babies

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How does a mother supply a key building block of the brain required for neurodevelopment to her fetus in pregnancy? The critical requirement of docosahexaenoic acid (DHA) for fetal brain development, and the poor efficiency of its synthesis in humans, is a tricky metabolic problem to be overcome in pregnant women. Supplying this unique fatty acid to the fetus requires exquisite specificity and timing, processes that can unravel in disease conditions such as pre-eclampsia.

Long chain polyunsaturated fatty acids (LC PUFA), particularly docosahexaenoic acid (DHA, 22:6 n-3), have been shown in population and intervention studies to be extremely important for neurodevelopment, learning and cognitive function. DHA comprises a high proportion of brain fatty acids, mainly found incorporated in brain membranes, and has particular structural properties that enhance membrane fluidity[1]. DHA has been shown to promote neurone survival and is required for neurone connectivity in the brain. In cases of DHA deficiency, another LC PUFA, omega-6 docosapentaenoic acid (n-6 DPA, 22:5n-6), appears to substitute for DHA in brain membranes. DHA is a LC PUFA of the n-3 series synthesized from an n-3 fatty acid precursor molecule obtained from the diet. The enzymes that synthesize the n-3 LC PUFA are shared with the n-6 series LC PUFA derived from an n-6 precursor in the diet. Given that human dietary n-6 precursor intake is up to eight-fold higher than dietary n-3 precursor intake[2,] this means that the n-6 pathway predominates and in humans the synthesis of n-3 LC PUFA is rather slow. The production of DHA is however higher in women than in men[3].

Metabolic adaptations in pregnancy

The first brain cells are formed by day 15 of gestation; at 22 days the primitive brain is developing and the first nerves with their extending fibres are observable. By 28 days of gestation, closure of the neural tube (the precursor to the central nervous system) occurs and the head of the embryo grows fastest over the earliest gestational weeks. Thus it is evident that a ready supply of DHA will be required by the embryo very early in gestation. Tracer experiments show transfer of DHA via the placenta resulting in fetal plasma that is enriched in DHA when compared with their mother[4]. These data show that the placenta is capable of selectively transferring DHA from maternal plasma to fetal plasma and a number of transport processes with selectivity for DHA have been described.

The physiological adaptation to pregnancy involves large increases in maternal plasma triglycerides: triglycerides are the storage form of fatty acids. We and others have shown that from the end of the first trimester until term there is a steady increase in maternal red blood cell and plasma DHA content of about 26%, which falls below trimester one concentrations after delivery[5]. This maternal mobilization may provide sufficient DHA for the rapid growth phase of the fetus. It has not yet been determined where this DHA comes from. Potential sources include maternal dietary intake, release from maternal adipose tissue and membrane stores or increased maternal liver synthesis, but there are no data that confirm whether one or more of these sources are important.

Studying the earliest changes in pregnancy

As mentioned above, some of the key events in neurodevelopment occur very early in the first trimester. The studies just described have only looked at time points that are conveniently sampled, i.e. end of the first trimester and beyond. Most women book for antenatal care between 9 and 13 weeks of gestation and it is very difficult to sample at earlier time points in a free-living population. Indeed, during the very earliest week of pregnancy many women are not aware that they are pregnant. We know from our longitudinal studies that red blood cell DHA content is already 19% higher at the end of the first trimester than it is after delivery, suggesting that DHA mobilization may be occurring prior to this time point[5]. In order to study these earliest changes we turned to a population of women undergoing assisted conception where accurately timed samples could be taken immediately before, and in the weeks after, conception. Women undergoing frozen embryo transfer, but who also retained their natural menstrual cycle were recruited so that we could avoid the potential metabolic interference of the high concentrations of reproductive hormones used for artificially reconstructing menstrual cycles in those women who have none.

In this population we observed that maternal plasma DHA concentrations started to rise at day 18 of pregnancy with the greatest rate of increase between day 18 and day 29, exactly the time of the earliest neurodevelopmental events including neural tube closure[6]. Furthermore, we observed that DHA concentrations were higher in twin compared with singleton pregnancies. As we had measured a full fatty acid profile in the samples we could also see that omega-6 DPA (the 'back-up' brain fatty acid) was also much higher in the women with twin pregnancies. It is impossible to directly measure tissue activities of the enzymes involved in LC PUFA synthesis in pregnant women; however, product precursor ratios are often used to infer particular enzyme activities in the pathway. Using this substitute measure for Δ6-desaturase (a key enzyme in the DHA synthetic pathway), a strong correlation between Δ6-desaturase activity and the rate of change of DHA concentration at day 29 of pregnancy was observed, suggesting that maternal DHA synthesis may indeed be switched on in early gestation. It was also seen that plasma levels of the precursor of the n-6 pathway decreased markedly over the first 45 days of pregnancy, which would reduce the competition between the parallel n-6 and n-3 series pathways and allow the n-3 pathway to proceed at a greater rate.

Pre-eclampsia – when pregnancy lipid metabolism goes awry

Pre-eclampsia is a disease of pregnancy that only occurs naturally in humans and higher apes, although animal models for the disorder have been created. While the number of maternal deaths resulting from pre-eclampsia are in decline, at least in the developed world, the disease still results in many prematurely delivered infants. The primary defect in pre-eclampsia is located at the placenta with inadequate or compromised formation of the blood supply to the placenta. The defective placental function is associated with a maternal response of widespread endothelial dysfunction which results in the clinical features of water retention, protein in the urine and hypertension. The only real cure for the disease is to deliver the placenta and child, hence the high rates of prematurity. Pre-eclampsia is a rather mysterious disease and the disease pathways are not well understood (see feature by Eric George on p22). The ability to understand pre-eclampsia is not helped by the variety of presentations of the disease (early or late presentation, mild or severe disease) and the variety of risk factors (first pregnancy, maternal obesity, etc.). The maternal metabolic adaptation to pregnancy also goes awry in pre-eclampsia

and, amongst other changes, there are exaggerated increases in plasma triglycerides[7].

We were interested to find out how disturbed triglyceride metabolism in pre-eclampsia might affect DHA metabolism and found that, in pre-eclampsia, the third trimester maternal DHA levels were 40% lower than normal pregnancy levels and fetal plasma levels only a little better at 35% lower than normal[8]. In maternal adipose tissue in women delivered by Caesarean section, we found that expression of enzymes involved in the synthesis of LC PUFA in pre-eclampsia was less than half of that in control tissues, suggesting that maternal LC PUFA synthesis may be inhibited in pre-eclampsia. LC PUFA synthesis is also inhibited in non-alcoholic fatty liver disease where high amounts of fat are deposited in the liver. We wondered whether the same thing might be happening in pregnant women
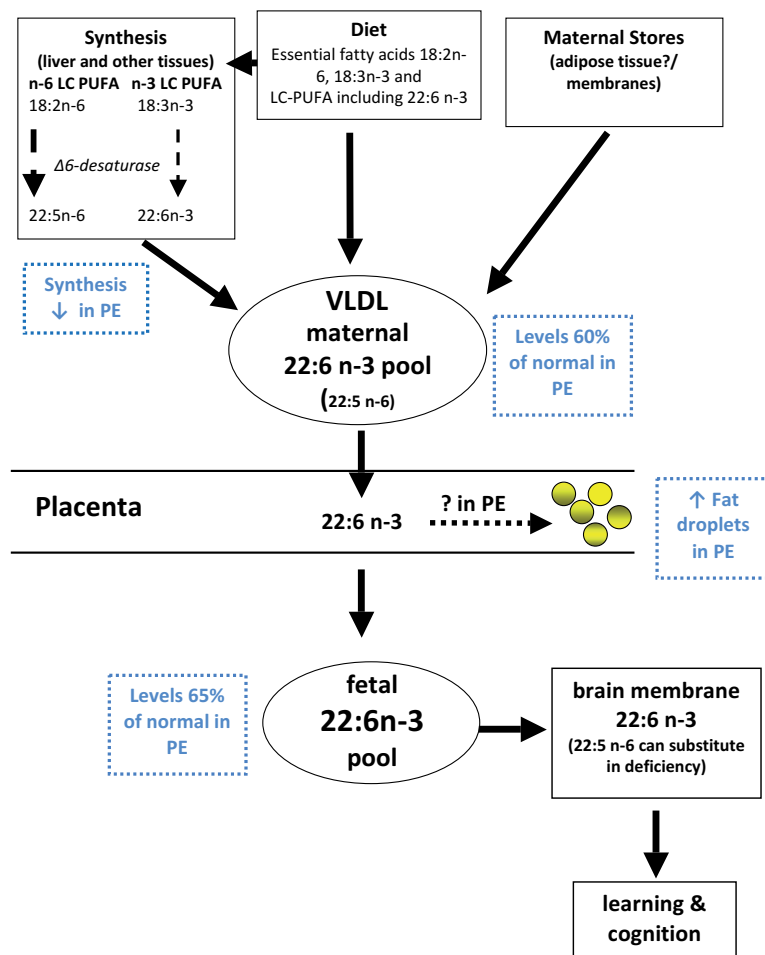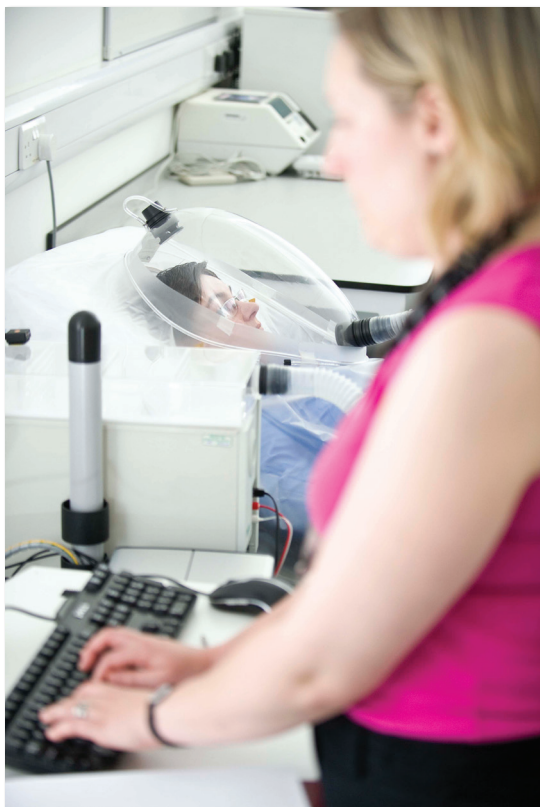

Diagram highlighting the main sources of DHA and the transport pathway of DHA from mother to fetus. PE = pre-eclampsia; VLDL = very low density lipoprotein.
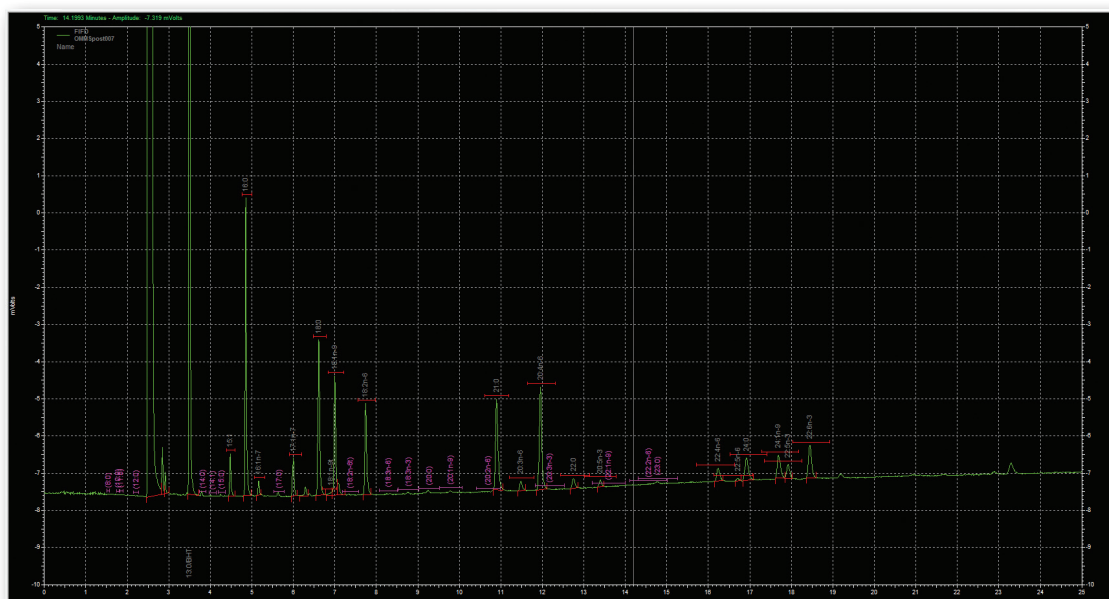
A study picture of one of our pregnant study participants undergoing indirect calorimetry

with pre-eclampsia. In the absence of being able to sample maternal liver, we looked at the key organ involved in the transfer of DHA to the fetus, the placenta itself. A detailed comparison of all the fats in healthy and pre-eclampsia placenta demonstrated that placenta from women with pre-eclampsia did indeed have significantly higher levels of stored fat[9].

Parallels with type 2 diabetes

The characteristics of poor fat handling we observed in pre-eclampsia, or at least that subset of pre-eclampsia with maternal obesity as a risk factor, made us think of the parallels with type 2 diabetes. Our current understanding of the disease process in type 2 diabetes involves the failure of subcutaneous adipose tissue cells to expand and hence safely store excessive fatty acids as lipid droplets resulting in fat accumulation in tissues such as the liver. Therefore we looked more closely at adipose tissue in pre-eclampsia and found that there was a higher proportion of smaller adipose cells in women with pre-eclampsia compared with healthy women suggesting a reduced ability of these cells to expand and store fat[10]. Functional studies of adipose tissue cells in the laboratory also confirmed that pre-eclampsia adipose tissue released more fatty acids than that from healthy pregnant women. Thus it is possible that a similar disease process to that observed in type 2 diabetes is occurring in obese women who develop pre-eclampsia in pregnancy.

Gas Chromatogram of extracted erythrocyte fatty acids showing the main peaks. Docosahexaenoic acid (DHA) is the last peak (at 18.5 minutes) of the chromatogram.

Where next?

We are only a part way down the road of understanding how DHA is mobilized in pregnancy by the mother, transferred to her baby and how this might be disrupted in pre-eclampsia. Further interrogation of our database on the detailed fat composition of placenta will tell us about LC PUFA levels and composition in healthy and pre-eclampsia placenta. We are currently undertaking studies to look specifically at particles secreted by the liver that carry fats in maternal plasma (very low density lipoprotein) both in very early and later gestation in order to get a window into the fat composition of the maternal liver. Very little is understood about how DHA is preferentially transported across the placenta and in what form. What we do know is that DHA is an extremely important nutrient for the fetus and that transport processes in pregnancy appear to be exquisitely geared towards the early maternal mobilization of DHA. As the fetus can only acquire this important building block for the synthesis and development of brain tissue from the mother and our data demonstrate that the mother mobilizes DHA just prior to neural tube closure, this suggests that DHA supplementation (commonly taken as fish oil capsules) around the time of conception and in early pregnancy has the potential to be as important as folate supplementation over the same time period. ∎

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