In: "Functional foods, Cardiovascular Disease and Diabetes", A. Arnoldi, ed., Woodhead Publishing Limited and CRC Press, Cambridge, 2004, pgs. 283-306

14

Dietary fat, pregnancy and the prevention of heart disease

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14.1 Introduction: pregnancy and foetal growth

In his book, first printed in 1992,[1] Barker made a statement of 'foetal' or 'metabolic' programming. Based on studies using medical records in Britain and other countries,[2–5] the basic hypothesis is that impaired development *in utero*, leading to babies of low birthweight, is a strong predictor of heart disease, arterial disease, hypertension or type 2 diabetes mellitus in later life.[6–8] The statement could now be extended to include slow growth in the first year of life.[9,10] It is the intention of this chapter to consider whether changes in the content of fat, or the composition of that fat, in the maternal diet may, by improving the development of the foetus or by some other mechanism, help prevent such problems.

It is well known that the developing foetal brain has a definite requirement for the long-chain polyunsaturated fatty acid, docosahexaenoic acid (DHA), but other fatty acids are required for structural purposes (membrane synthesis), as a source of precursors (e.g. for eicosanoids, a group of compounds including prostaglandins and thromboxanes involved in cell-to-cell communication) or as the substrate for fat stores to be used after birth as a source of energy. Furthermore, the use of fats, as a source of energy for the mother, means that glucose is available for use by the foetus.

In this chapter, we first examine the mechanisms underlying the materno-foetal relationship in terms of lipid metabolism so that the roles of the maternal diet during stages of pregnancy and of maternal dietary history may be understood. We also examine the complex interactions between the dietary fatty acids, their synthesis *in vivo* and other complicating factors, such as susceptibility to oxidative stress. We finish by summarizing the complexity of the situation and by suggesting some avenues for future research.

14.1.1 Changes occurring in the mother during pregnancy that help to sustain foetal growth under normal conditions

Foetal development depends upon the continuous supply of metabolites, derived from the maternal circulation, across the placenta. Quantitatively, the most abundant nutrient crossing the placenta is glucose, followed by amino acids.[11–15] Placental transfer of lipid components is limited in comparison,[16,17] but the lipid components also play a major role in foetal development. Changes in the availability of lipid components, such as those produced by changes in dietary fat composition, are known to have implications for foetal and postnatal development.[18] In addition, the adaptations of maternal lipid metabolism during gestation also have major implications for foetal growth; for instance, it is known that deviations from normal maternal plasma lipid status, such as hypercholesterolaemia, even when temporary and limited to pregnancy, can trigger pathogenic events in the foetal aorta and may influence atherosclerosis later in life.[19–21]

From the metabolic point of view, there are two distinct stages of pregnancy. During the first two-thirds, foetal growth is small and the mother stores a large proportion of the nutrients she eats, which, in combination with her hyperphagic state, causes accumulation of fat stores.[22,23] This condition is facilitated by hyperinsulinaemia and normal, or even enhanced, insulin sensitivity.[24–26] During the last third of gestation foetal growth is very rapid, being sustained by an enhanced transfer of nutrients through the placenta. Hence the mother switches from the previous anabolic condition to a catabolic one. This change is seen most clearly in terms of an enhanced breakdown of lipid stores by lipolysis in adipose tissue,[27–29] and is facilitated by the development of an overt insulin-resistant condition.[30–32]

14.2 Carbohydrate, amino acid and maternal lipid metabolism in gestation

14.2.1 Carbohydrate and amino acid metabolism

During late pregnancy the mother tends to develop hypoglycaemia, which is especially evident during fasting.[33,34] Indirect studies in women[35] and direct experiments in rats[34,36] have shown that the rate of gluconeogenesis is enhanced during pregnancy under fasting conditions. Of the common gluconeogenic substrates, glycerol was converted into glucose even more rapidly than others such as pyruvate and alanine.[37] Thus, gestational hypoglycaemia must be a consequence of increased utilization of glucose: this is despite the decreased consumption of glucose by the insulin-resistant tissues and results from a rate of placental transfer much higher than for other metabolites, even amino acids.[11,38] The placental transfer of glucose is carried out by facilitated diffusion according to concentration-dependent kinetics[14,39] and is therefore dependent on the positive materno-foetal glucose gradient.[12] The gradient is maintained by the low concentration of glucose in the foetal circulation and, on occasion, by active maternal gluconeogenesis.

In contrast, the concentration of amino acids in foetal plasma is even higher than in the mother,[12,40,41] because placental transfer of amino acids is carried out by an energy-dependent process, using selective transporters.[12,14,42–44] This ensures the availability of these essential precursors in appropriate quantities to the foetus and can result in a tendency to maternal hypoaminoacidaemia.[11]

14.2.2 Maternal lipid metabolism

Two consistent manifestations of altered maternal lipid metabolism during normal gestation are the accumulation of lipids in early-pregnant maternal tissues[22,45] as a result of major changes in adipose tissue metabolism and the later development of maternal hyperlipidaemia.[46,47]

Adipose tissue metabolism: accumulation of body fat

Fat accumulation is a characteristic feature of pregnancy, occurring in both women[22,45,48] and experimental animals.[23,49,50] The accumulation of maternal fat in maternal depots takes place during the first two-thirds of gestation but stops or even declines during the last third,[45,49,51,53] as a consequence of enhanced adipose tissue lipolytic activity.

Body fat accumulation during early pregnancy seems to be the result of both hyperphagia and increased lipid synthesis. Hyperphagia during pregnancy occurs in women[54,55] and rats.[50,56] Both fatty acid synthesis and the conversion of glucose to form the 'glycerol backbone' of fat molecules have been found to increase progressively in rat adipose tissue until day 20 of gestation and then to decline sharply on day 21, just before parturition.[38,57]

Changes in adipose tissue lipoprotein lipase (LPL) activity could be a means by which fat accumulation is controlled during early pregnancy. This enzyme, present in the capillary endothelium of extra-hepatic tissues, hydrolyses triacylglycerols circulating in plasma in the form of triacylglycerol-rich lipoproteins,[58] and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue.[59] In this way, LPL activity is a prerequisite for the uptake of circulating fat by adipose tissue. Some reports suggest that there is an increase in the activity of LPL in rat adipose tissue by day 12 of gestation,[60,61] but the change is small and not always reproduced.[29] Furthermore, no significant change has been found in the postheparin LPL activity in pregnant women at mid-gestation.[46] During late pregnancy, however, LPL activity in rat adipose tissue has consistently been found to be decreased.[52,62–64] Postheparin LPL activity has also been found to decrease in pregnant women during the third trimester of gestation.[46]

Thus, it is proposed that fat uptake by adipose tissue decreases during late pregnancy and that this change, together with the enhanced lipolytic activity (see below), results in the net accelerated breakdown of fat depots during the last trimester of pregnancy, which coincides with the phase of maximal foetal growth.[52,65]

Adipose tissue metabolism: lipolytic activity

Increased lipolysis of adipose tissue fat stores occurs both in women and rats during the last third of gestation.[28,66–69] At the same time, increased activity of hormone-sensitive lipase (HSL, the key enzyme of adipose tissue lipolysis), and increased concentrations of the mRNA that codes for it, are observed in pregnant rats.[29]

The majority of the products of adipose tissue lipolysis, fatty acids (often called non-esterified fatty acids or NEFA) and glycerol, are released into the circulation. Since the placental transfer of these products is quantitatively low,[17] their main destination is the maternal liver[70] where, after conversion into active forms acyl-CoA and glycerol-3-phosphate respectively, they are re-esterified for the synthesis of triacylglycerols that are released into the circulation as part of very low-density lipoproteins (VLDLs). Since insulin inhibits both adipose tissue lipolytic activity[71,72] and hepatic VLDL secretion[73] but increases LPL activity,[74] the insulin-resistant condition of late pregnancy contributes to both the increased lipolysis of fat stores[75] and the increased VLDL production, although for the latter the enhanced oestrogen concentration at late pregnancy seems to be its major activator.[47]

During late pregnancy, the lipolytic activity of maternal adipose tissue increases markedly under (experimental) fasting conditions.[27,28,69,76] In addition to the use of the lipolytic products in the resynthesis of triacylglycerols described above, glycerol may be used for glucose synthesis (required for brain function) and NEFA for β-oxidation to acetyl-CoA, leading to energy production and synthesis of ketone bodies; these pathways also increase markedly under fasting conditions in late pregnancy.[34,36,77,78]

The preferential use of glycerol for gluconeogenesis and the efficient placental transfer of the newly formed glucose may be of major importance to the foetus under such fasting conditions, where the availability of other essential substrates such as amino acids is reduced.[36,61] The enhanced maternal ketogenesis during fasting also benefits the foetus in two ways: ketone bodies are used by maternal tissues, thus sparing glucose for essential functions and delivery to the foetus; placental transfer of ketone bodies is very efficient,[79] attaining the same concentration in foetal plasma as is found in the maternal circulation.[80] Consequently, ketone bodies may be used by the foetus as oxidative fuels[81] as well as substrates for brain lipid synthesis.[82]

Maternal hyperlipidaemia

The catabolic condition of maternal adipose tissue during late gestation is associated with hyperlipidaemia, mainly corresponding to rises in triacylglycerols, with smaller rises in phospholipids and cholesterol in the circulation.[47] Although the greatest increase in plasma triacylglycerols corresponds to VLDL, there is also an enrichment of triacylglycerols in other lipoprotein fractions that normally do not transport them, such as low-density lipoproteins (LDL) and high-density lipoproteins (HDL).[46] This increase in plasma VLDL triacylglycerols during gestation results from enhanced production by the

liver[83,84] and decreased removal from the circulation as a consequence of reduced adipose tissue LPL activity.[29,46]

The abundance of VLDL triacylglycerols in the presence of an increase in cholesteryl ester transfer protein (CETP) activity taking place at mid-gestation[46,85] contributes to the accumulation of triacylglycerols in the lipoprotein fractions of higher density, LDL and HDL.[46,86] Another factor contributing to the same effect is the decrease in the hepatic lipase activity, which also occurs during late pregnancy.[46] The decrease in this enzyme's activity decreases the conversion of buoyant HDL_2 triacylglycerol-rich particles into smaller, denser, triacylglycerol-poor HDL_3 particles, allowing a proportional accumulation of the former.[46]

The hormonal factors responsible for the metabolic changes, which result in the development of maternal hypertriacylglycerolaemia, are the insulin-resistant condition and the increase in plasma oestrogen concentrations, both occurring during late pregnancy. The insulin-resistant condition contributes to the enhanced adipose tissue lipolytic activity, which, as described above, speeds the transport of glycerol and NEFA to the liver, to their subsequent conversion into circulating VLDL-triacylglycerols,[75] and to decreased LPL activity.[74] The increase in plasma oestrogen concentrations during gestation[87,88] also contributes to maternal hypertriacylglycerolaemia since it enhances hepatic production of VLDL[89,90] and decreases the expression and activity of hepatic lipase.[91,92]

14.3 Placental transfer of lipid metabolites

14.3.1 Availability of essential fatty acids to the foetus

Essential fatty acids (EFA) are fatty acids containing double bonds either six or three (or both) carbons from their methyl end, the so-called n-6 and n-3 positions (often referred to as ω-6 and ω-3) respectively. As animals are incapable of inserting such double bonds themselves, EFA can be obtained only from the diet and it follows that the foetus can obtain them only from the maternal circulation via the placenta. The simplest n-6 polyunsaturated fatty acid (PUFA) is linoleic acid with 18 carbons and two double bonds (18:2 in shorthand), which is a precursor of arachidonic acid (20:4 or AA). The simplest n-3 PUFA is α-linolenic acid (18:3), a precursor of docosahexaenoic acid (22:6 or DHA).

Triacylglycerols circulating in plasma lipoproteins do not directly cross the placental barrier,[17] but EFA from maternal diet, which are transported as triacylglycerols in triacylglycerol-rich lipoproteins in maternal plasma,[93] must be made available to the foetus. The presence of both the VLDL/apo-E receptor and the LDL receptor-related proteins in placental trophoblast cells[94–99] allows these lipoproteins to be taken up by the placenta. In addition, the trophoblasts also express at least three different lipolytic activities including LPL,[100–102] phospholipase A_2[103,104] and an intracellular lipase.[105–107] Thus, maternal triacylglycerols in plasma lipoproteins are either taken up intact by the placenta

by receptors or, after hydrolysis, their constituent fatty acids are taken up by the placenta, where the fatty acids are re-esterified to synthesize glycerolipids to provide a reservoir of fatty acids.[108] Subsequent intracellular hydrolysis of the glycerolipids releases fatty acids to diffuse to foetal plasma, where they bind to the alpha-foeto protein.[109,110] In this way, they are transported to the foetal liver, where they are re-esterified and released back into the foetal circulation in the form of lipoprotein-triacylglycerols.

Thus, maternal hyperlipoproteinaemia seems to play a key role in the availability of EFA to the foetus, and reductions in maternal hypertriacylglycerolaemia, such as that caused by treatment with hypolipidaemic drugs, have detrimental effects on foetal development.[111,112]

Transport of non-esterified fatty acids

There are important differences among mammalian species in the net flux of fatty acids across the placenta. In species with placentas that comprise both maternal and foetal layers, such as sheep, pig and cat, the maternal foetal fatty acid transfer is small,[113–116] whereas species where the placenta is formed by layers of foetal origin, such as the rabbit,[117] guinea pig,[118] primates[119] and rat,[120,121] the amount of fatty acid crossing the placenta exceeds even that needed to provide an adipose store of lipids sufficient to support postnatal growth and development.[122] In humans, although small in proportion to lipoprotein triacylglycerols, maternal plasma NEFA are an important source of PUFA to the foetus.[123,124]

In human placenta there is a membrane fatty acid-binding protein ($FABP_{pm}$)[125,126] which is responsible for the preferential uptake of long-chain polyunsaturated fatty acids (LC-PUFA) and allows the preferential transfer of certain LC-PUFA: docosahexaenoic > α-linolenic > linoleic > oleic > arachidonic acid.[127] In the case of arachidonic acid, its uptake by syncytiotrophoblast membranes has been shown to occur by an ATP-dependent active process.[128] This selective transport of certain fatty acids may contribute to the efficacy of the overall placental transfer process and may contribute to a degree of selective metabolism such as the conversion of a proportion of 20-carbon fatty acids to prostaglandins and other eicosanoids,[124] the relative proportions of 2-series and 3-series prostaglandins being formed,[129,130] the incorporation of some fatty acids into membrane phospholipids,[131] placental fatty acid oxidation[132] and placental fatty acid synthesis.[133] Thus, the combination of all these processes determines the actual rate of placental fatty acid transfer and its selectivity, resulting in the proportional enrichment of certain LC-PUFA, such as arachidonic acid and docosahexaenoic acid in the foetal compartment compared to maternal compartment.[134]

An interesting point here is that that thromboxane A_3, a prostaglandin-like messenger derived from n-3 fatty acids, has been reported to be a less effective vasoconstrictor than thromboxane A_2, derived from n-6 fatty acids, and that this could provide a link between diet and hypertension.[135]

Cholesterol

The remaining major lipid, cholesterol, is an essential component of cell membranes, where it affects the fluidity and passive permeability.[136] It is the precursor of bile acids, used in the digestion of dietary lipids, of steroid hormones, required for cell proliferation[137,138] and development of the growing body (e.g. sexual differentiation),[139,140] cell differentiation and cell-to-cell communication,[141] and of oxysterols, which regulate certain metabolic processes.[142] Consequently, the demand for cholesterol in the embryo and the foetus is relatively high.

Placental transfer of maternal cholesterol has been shown to be effective in different species, such as the rat,[143] guinea pig[144] and rhesus monkey.[145] Cholesterol synthesis in foetal tissues, and especially in foetal brain, has also been shown to be highly active in some species,[146–150] and the expression of the genes for the enzymes involved in cholesterol synthesis, as measured by mRNA contents and by enzyme activities, is elevated in foetal tissues.[151–153]

Cholesterol can be transferred by the placenta and it can be synthesized from a simple two-carbon precursor by a complex biochemical pathway. In the rat, the foetus receives little or no cholesterol from its mother and satisfies its need for cholesterol through endogenous synthesis[149,150] as illustrated by the following experiment. Feeding late-pregnant rats with cholesterol, sufficient to increase the maternal plasma cholesterol concentration and to reduce maternal cholesterol synthesis, had no effect on these same parameters in the foetus[146,147,154,155] or on foetal development.[156] However, some circumstantial evidence exists for a role for maternal cholesterol during the early stages of gestation. Treatment of pregnant rats during early pregnancy with an inhibitor of the enzyme Δ^6-reductase, AY 9944, resulted in foetal teratogenesis, whereas simultaneous administration of oral cholesterol prevented this effect.[157–159]

In humans, comparison of concentrations of lipoprotein-cholesterol in maternal plasma with umbilical cord blood cholesterol gave positive correlations in some experiments[160,161] and no correlation in others.[162–165] Gestational age could influence these comparisons, since plasma foetal cholesterol levels are higher in 5-month than in 7-month-old foetuses, and in foetuses younger than 6 months, plasma cholesterol concentration is significantly correlated to the maternal concentration,[19] suggesting that, at these early stages of gestation, maternal cholesterol actively contributes to foetal cholesterol. At term, umbilical venous concentrations of HDL-, LDL- and total cholesterol were higher than in umbilical arterial plasma, indicating the delivery of cholesterol from placenta to the foetus; however, the contribution of such cholesterol to the foetal plasma cholesterol pool is very small.[162]

14.4 Foetal development: the role of dietary fatty acids

Essential fatty acids (EFA) and their LC-PUFA derivatives are required during normal foetal development to support the synthesis of structural lipids, notably

the phospholipids of brain and retinal tissue.[166–169] Although both term and preterm infants seem able to form arachidonic acid (20:4 n-6 or AA) and docosahexaenoic acid (22:6 n-3 or DHA) from their respective EFA precursors, linoleic acid (18:2 n-6) and α-linolenic acid (18:3 n-3) by a process of sequential desaturations and elongations,[170–175] the degree to which the foetus is capable of carrying out these processes is not clear. In fact, it has been shown in the newborn infant during the first week of life that the endogenous synthesis of AA seems to contribute very little to the plasma AA pool,[174] the limiting factor being a low Δ5-desaturation activity, although foetal baboons have been shown to synthesize both AA and DHA from their respective EFA precursors.[176, 177]

In humans, a reduced nutritional status with respect to EFA during gestation has been correlated with reduced neonatal growth[178] and, in untreated healthy women, maternal plasma concentrations of LC-PUFA have been consistently correlated with those in the foetus or newborn.[179–181] Furthermore, supplementation with fish oil during pregnancy increases DHA in both mothers and newborns.[182, 183] These results have led to the issue of advice that maternal diets should be routinely supplemented with fish oil during the last trimester of pregnancy.[182, 183] However, care must be exercised because the competitive inhibition of the Δ6- and Δ5-desaturases (two enzymes that control the conversion of EFA into LC-PUFA by the n-3 and n-6 pathways), by specific fatty acids present in excess, may inhibit the synthesis of other specific LC-PUFA that could be essential for foetal growth.[184] In fact, when fish oil is consumed, low plasma AA levels are found,[184, 185] the effect being caused by the abundance of both eicosapentaenoic acid (20:5 n-3 or EPA) and DHA (22:6 n-3) in this oil, which specifically inhibit the Δ6 desaturase activity – an obligatory step in the conversion of dietary linoleic acid into AA.[186, 187]

During the perinatal period, the inhibitory effects of an excess of certain dietary fatty acids on LC-PUFA synthetic pathways may acquire major relevance, since plasma AA concentrations have been correlated to body weight in preterm infants[188–190] and adverse effects of low AA concentrations on growth during infancy have been reported.[188, 191, 192]

An excess of LC-PUFA may also increase the susceptibility to lipid peroxidation. The susceptibility of LDLs to oxidative modification *in vitro* was reported to increase when the LDL were isolated from animals given diets rich in n-6 PUFA.[193–195] Also, an increase in plasma thiobarbituric acid-reacting substances (TBARS – a measure of lipid peroxidation) was found after periods of dietary enrichment with n-6 PUFA.[196] Whether or not a diet high in n-3 PUFA also increases lipid peroxidation is controversial.[197, 198] Whereas several studies in humans have shown that dietary supplementation with fish oil rich in n-3 PUFA does not increase lipid peroxidation *in vivo*,[199–202] studies in rats and in cell culture have shown that this same treatment reduces the antioxidant capacity[185, 203] and increases susceptibility to oxidative damage.[204–206]

That increased lipid peroxidation is a 'bad thing' is not in doubt. Experimental studies in diabetic pregnancy have shown that increased reactive oxygen species and lipid peroxidation result in foetal damage, the effect being

prevented by treatment with the anti-oxidant vitamin E.[207–213] The detrimental effect on offspring of high dietary fish oil intake during pregnancy could be mediated either by the reported consequent decrease in AA[214–216] or by an increased usage of α-tocopherol (a form of vitamin E) to protect the high LC-PUFA content of fish oil. Experiments, in which pregnant and lactating rats were fed diets supplemented with 10 per cent fish oil or olive oil, concluded that low AA, rather than low α-tocopherol, was responsible for the delayed postnatal development seen in the offspring of the rats fed the fish oil diet.[185]

14.4.1 Possible effects of dietary fat on 'foetal programming'

The role of foetal and childhood nutrition in the development of long-term effects on its health has been firmly documented during the past years.[217–227] Although most problems in foetal nutrition may be rapidly corrected after birth, as recently reviewed,[228] there are conditions such as maternal hypercholesterolaemia during the early stages of pregnancy that may promote lesion formation in the foetus, increasing the susceptibility to atherosclerosis later in life. Hypercholesterolaemia is known to be accompanied by increased lipid peroxidation,[229–231] and evidence for a role for oxidative stress in the effects of maternal hypercholesterolaemia has been obtained in a rabbit model,[20] where plasma concentrations of cholesterol in offspring were unchanged but lipid peroxidation end products increased. Thus, it may be hypothesized that conditions enhancing the susceptibility of oxidative stress, such as the exaggerated proportional increase in certain dietary LC-PUFA referred to above, could also increase the susceptibility to atherosclerosis later in life.

Several studies have addressed the question of whether early fat-feeding practices are relevant in the development of atherosclerosis (for a recent review see Viikare *et al.*).[225] Breast milk has a high cholesterol content, and prolonged breastfeeding in infancy was related to impaired arterial distensibility 20 years later.[232] However, other studies have proposed a protective effect of exclusive and prolonged periods of breastfeeding against type 2 diabetes, dyslipidaemia and overweight in adults[233] or in adolescents.[234]

14.5 Dietary recommendations for the avoidance of heart disease later in life

In order to avoid future heart disease it is possible to take two approaches. On the one hand, simply addressing the Barker Hypothesis[1] and aiming to improve (increase) birth weight by better foetal nutrition is predicted to improve the cardiac outcomes. On the other hand, identifying a mechanism by which a specific fat may predispose to, or protect from, cardiac disease could lead to much more precise advice.

Given the complexity of the physiology of fat transfer to the foetus from the maternal circulation, it is difficult to make precise recommendations for dietary

modifications for the pregnant mother. The question may be broken down into three components: 'how much dietary fat?', 'what type of fat?' and 'at what stage of pregnancy should it be taken?'

By its very nature, pregnancy is a time of growth and therefore a time of greater energy requirement. In the first two-thirds of gestation this is seen mostly as fat storage in the mother and in the last third by mobilization of those stores to satisfy the requirements of the now rapidly growing foetus. Greater energy requirements are met most easily by consumption of the most energy-dense nutrient, fat, and it seems sensible that the total proportion of fat in the diet should rise, above that normally recommended for an adult, to meet these requirements. If fat can be used to meet normal energy requirements, maternal hypoglycaemia and ketosis can be avoided and the materno-foetal glucose concentration gradient, enabling glucose transport to the foetus, can be maintained. The more glucose that can be 'spared', the more that can be used directly to fulfil foetal needs.

In terms of foetal growth and development, specific fatty acids – DHA and AA – are required, especially at times of brain and retinal development. As neither of these fatty acids are available by synthesis *de novo*, the maternal diet must be sufficient to ensure adequate supply to the placenta. As a dietary supplement, the n-3 acid, DHA is most readily available as part of the triacylglycerols constituting the oils of oily fish. Oils rich in its precursor, α-linolenic acid, are less common. There is no obvious dietary source of AA; so shorter n-6 acids such as linoleic acid, found in most vegetable oils, or γ-linolenic acid of the fashionable oil of evening primrose or blackcurrant oil can provide precursors for subsequent desaturation and elongation. The fact that, as stated above, other acids of fish oils can interfere with these enzymic processes illustrates just how complex the situation is.

The timing of dietary manipulations, if required, is complicated by the role of adipose tissue in the process. Maternal mobilization of adipose stores in late pregnancy means that the fatty acids available to the placenta, which itself selectively transports those most required, depends not only upon her current diet but also on her diet during the anabolic phase of pregnancy and even on her dietary history as reflected in the fatty acid composition of her stores. This argues for intervention on a woman-by-woman basis rather than the issuing of blanket advice for a whole population. Hence, a woman with low reserves of DHA and AA (or their precursors) may well be advised to supplement their diets appropriately and a woman with low total fat reserves could be advised to increase her fat intake from the time of becoming pregnant.

Although the studies reported above in Section 14.4.1 together indicate that early fat-feeding can have a significant influence on future vascular health, the mechanisms are not yet understood and more studies are required to establish the safety window for an appropriate quantity and quality of fat components before dietary supplements with high intakes of LC-PUFA, with or without supplements of antioxidant vitamins, can be recommended with confidence.

14.6 Future trends

After reviewing the literature above, the questions asked at the outset might be revised. Instead of looking for a 'functional food' which may, at a stroke, improve foetal growth and development, or elicit some protective mechanism, thereby reducing the likelihood of future arterial disease, we perhaps should be looking for particular sets of circumstances for which individual dietary treatments are more or less appropriate.

If future advances in technology make it possible to monitor in detail the fatty acid status of a potential mother prior to and during her pregnancy (without resorting to numerous and painful biopsies) and given a knowledge of how dietary fats affect adipose stores, in early pregnancy, and plasma lipids in later pregnancy and of how placental transfer responds to changes in the available substrates, it may become possible to design regimes that maximize the benefits for the growing foetus and to avoid the distinct syndromes, such as hypercholesterolaemia, which predispose to later problems.

In the more immediate future, research work is likely to concentrate on the unknowns identified above. What are the complex interactions between n-3 and n-6 acids in the diet and how can a diet containing an optimum mix of the two be devised? When and by how much should diets be supplemented with antioxidant vitamins? Experiments with animal models have been useful in examining the effects of a single lipid source on the animals' subsequent physiology but we need to develop those models to give answers about more complex and variable mixtures as consumed by humans.

14.7 Sources of further information and advice

The references cited throughout this chapter provide details that we have sometimes only been able to summarize. Some of the references are to review articles which provide substantial information on the subject. Some of the questions herein analysed, as well as being addressed by several research groups throughout the world, are the subject of a project funded by the European Union called PERILIP, a collaboration of groups in six European countries in which both authors are active partners. In the website of this project, at http://www.perilip.org, besides a detailed account of the background to the project and news of recent developments, there is an extensive list of references in the bibliography section. Under 'Useful links' there is a list of other websites that we judge to be useful and carefully prepared. These sites cover such topics as intrauterine development, placental research, lipid research, nutrition in pregnancy and lactation, and neonatal care. The site is revised and updated at regular intervals.

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