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2. Fat requirements in pregnancy and infancy

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Abstract

Fats are important during pregnancy and infancy not only as energy sources but also as structural components of cellular membranes and precursors of bioactive signalling compounds. Fats and particularly long-chain polyunsaturated fatty acids (LC-PUFA) are crucial for foetal and infant tissue development and organogenesis and may also play a role in the future health of the infant, i.e. in the child's neurodevelopment and his/her risk of developing a range of diseases such as allergic diseases. The mother-placenta-foetus interaction and the related adaptive and regulatory mechanisms ensure optimal foetal growth and development. These processes may be influenced by maternal dietary intakes and body composition during pregnancy and breast feeding, and again by the dietary intake of the infant. Reference values have been set for dietary intakes of fats for each of these periods, i.e. pregnancy, breastfeeding and infancy.

2.1 Introduction

Pregnancy is a critical phase in life when several metabolic adaptations take place to support foetal growth and development. When the metabolic balance is disturbed due to an inadequate dietary intake or an inappropriate maternal nutritional status, like obesity, the health of both mother and child may be disturbed. Obesity increases the risk for gestational diabetes (GDM), a condition affecting one in six live births worldwide, posing serious health risks for both mother and child [1].The risks during pregnancy and in the years to come include an increased risk for pre-eclampsia and type two diabetes in the mother and macrosomia and obesity in the child. Importantly foetal and early infancy events may permanently change the child's bodily structure, function and metabolism i.e. a kind of re-programming of the body's metabolic pathways, conferring a life-long risk of developing seríous diseases [2].

Fats play a key role in the growth and development of the foetus and infant. They also contribute to the health of both mother and child due to their many metabolic and structural roles in human body. Fat stores are needed as an energy source in the maternal and infant bodies during pregnancy but in addition, they have other functions acting as precursors for bioactive signalling compounds and immune regulation. The dietary quality of the fat is of major significance not only as a supply of long-chain polyunsaturated fatty acids (LC-PUFA), including the essential fatty acids linoleic acid (LA; 18:2 n-6) and alpha-linolenic acid (ALNA; 18:3 n-3) needed from dietary sources, but also their longer chain derivatives, arachidonic acid (AA; 20:4 n-6), eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 20:6 n-3). These fatty acids may be considered as being conditionally essential

during pregnancy, as the foetus obtains his/her supply from the mother [3]. Both AA and DHA are present at high concentrations in the structural lipids of the central nervous system; in the developing foetus, placental function is critically important for delivery of these fatty acids during the rapid phases of development, particularly during the last trimester of pregnancy. After birth, these fatty acids should be present in the newborn's diet [4]. These fatty acids are present in breast milk, and nowadays are included in most milk formulas, utilized for infant feeding when breast milk is not available in sufficient amounts due to some compelling reason (e.g. maternal illness).

While breast feeding is the natural mode of feeding an infant, it also supports the recovery of the mother from pregnany and aids in bonding between the mother and child. Breast feeding has also been linked with many health benefits for both mother and child [5] In the switch from breastfeeding to complementary feeding, the dietary intake of fat decreases as typically also does the supply of LC-PUFA. All these aspects of infant feeding may influence the growth and development and health initially of the foetus and later of the child. Energy and nutrient requirements during pregnancy, breastfeeding and infancy are driven by the elevated metabolic requirements due to the growth and development of foetus and infant as well as maternal tissue deposition (Figure 1). These needs are supplied by maternal and infant diet but also by maternal nutrient stores laid down before pregnancy and during the anabolic phases of the pregnancy.

All in all, pregnancy is an important phase in human life defining the health of both mother and foetus both in the short and in long-term with sequelae taking place

during breastfeeding and/or infant complementary feeding. In this book chapter, these issues are reviewed in more detail, emphasizing the importance of overall maternal-foetal-infant metabolic communication. Another focus is on the factors influencing the dietary intake and supply of LC-PUFAs.

2.2 Energy Requirements of Pregnancy and Foetal Adiposity

2.2.1. Energy Requirements of Pregnancy

Energy is required during pregnancy to meet the maternal demands of basal metabolism, placental and foetal tissue growth and function as well as physical activity [6]. The pregnant woman's energy requirements increase because of the need to accumulate maternal body mass and the demands of foetal growth as well as due to pregnancy-associated physiological changes including a higher cardiac output. Overall pregnancy is an anabolic state when energy is stored but on a closer look, while the first and second trimesters are anabolic, the third trimester is catabolic [7]. The energy needed during pregnancy is obtained from the diet but also from maternal stores, thus maternal dietary intake and nutritional status before as well as during pregnancy, are of crucial importance (Figure 2.1.). Energy requirements vary over the course of pregnancy, ranging from very little additional demands in early pregnancy to substantial needs in late pregnancy when the growth of the foetus is at its greatest. The estimated total cost of pregnancy is 375 kJ/day in the first trimester, 1200 kJ/day in the second and 1959 kJ/day in the third trimester [8]. The energy needed for physical activity is variable between women but commonly there are reductions in the amounts of physical activity toward the last phases of pregnancy.

The guidelines for weight gain during pregnancy are set based on the categories of the prepregnancy BMI. This is due to the fact that the risks for complications during pregnancy rise with an increase in BMI, and maintaining the weight gain within the limits set based on prepregnancy BMI secures foetal health and avoids either macrosomia or birth small-for-gestational age (SGA) [9]. Normal weight women (BMI 18.15-24.9 kg/m^2) should gain 11.5-16 kg over the course of pregnancy, women with overweight (25.0-29.9 kg/m^2) 7-11.5 kg, women with obesity (≥ 30.0 kg/m^2) 5-9 kg and underweight (<18.5 kg/m^2) women 12.5-18 kg.

2.2.2. Foetal Adiposity

Along with the maternal energy requirements, the foetal growth is fastest in the third trimester of pregnancy. There is only marginal accumulation of lipids for the first 25 weeks of pregnancy but it increases thereafter with the gestational age [3,10]. ranging from 1.6-3.4 g/day in the last weeks of gestation [11]. In the human foetus, precursors of fat lobules are found in the 14th week of gestation [12]. Both white and brown adipose cells are recognized by 28 weeks. The process of foetal adipogenesis and the prevailing regulatory factors have been explained in detail by Desoy and Herrera [12]. The fetal fat accretion is achieved by two mechanisms; 1) by fatty acids that cross the placenta and 2) by foetal lipogenesis [3]. In the latter case, the foetus has the capacity to use glycerol and fatty acids derived from glycolysis. Glucose is obtained from the maternal supply as the fetus does not synthesize glucose. Foetal lipogenesis for the deposition of triglycerides takes place in liver and adipocytes. An increase in the foetal lipogenesis is seen from 10 weeks of gestation onwards, the main precursors being glucose, lactate and ketone bodies [12].

It is estimated that at birth about 14% of the body weight is fat with baby girls having a slightly higher proportion of body fat than boys [13]. Due to differences in subcutaneous lipid mass, a large interindividual variation is observed in the newborn's body fat mass [14]. The largest constituent of white adipose tissue (WAT) fat at 40 weeks gestation is SFA (298 mg/g WAT) followed by MUFA (226 mg/g) and PUFA (23.2 mg/g) [14]. N-6 PUFA (21.3 g/g WAT) dominated over n-3 PUFA (1.8 g/g WAT) in this infant sample of stillborn infants from Curacao. These amounted to 262 g saturated fatty acids (SFA), 194 g monounsaturated fatty acids (MUFA) and 20.4 g PUFA (including 1.46 g DHA and 3.15 g AA) in a 3500 g term infant [14]. Foetal fat accretion is at its highest in the last five weeks of gestation when accretion rates of 342 mg/day for LA, 95 mg/d for AA and 42 mg/day for DHA were determined [15]. At term, about half of the total DHA is located in adipose tissue, 23% in brain and 21% in skeletal muscle. In fact, the newborn infant has accumulated a total of about 3 g DHA during gestation [15]. Foetal fat has many roles (reviewed in [12]); it provides insulation against the temperature changes after birth, acts as a energy store to sustain cerebral function (glycerol or ketone bodies) and further may contribute to molecular signaling and the infant's immune functions.

2.2.2.1. Factors Influencing Foetal Adiposity

When the fat mass at birth of 183 infants was modelled, the strongest predictors were found to be parity, gestational age, pregravid weight, maternal weight gain and neonatal sex [13]. Of interest here is that also maternal prepregnancy obesity has been demonstrated to associate with increased neonatal fat mass; infants of mothers with

overweight and obesity have a higher body fat proportion and more fat mass at birth compared to infants of normal weight mothers [16]. In addition, maternal GDM has been related to increased foetal adiposity [17]. A higher adiposity of the newborn baby *per se* has been linked with childhood obesity [18,19]. On the other hand, the higher adiposity of the human newborn may be important for supporting brain development [20]. The maternal diet during pregnancy may influence foetal adiposity as demonstrated in studies in which the newborn body composition has been measured with sophisticated equipment, air displacement plethysmography, within few days after birth [21–25]. A positive association has been found between maternal intakes of polyunsaturated fats and neonatal fat mass index (calculated with a body composition measurement using air displacement plethysmography) [23]. In another study, increases in the intakes of total fat, SFA, unsaturated fat and total carbohydrates were associated with elevated neonatal fat mass [21]. Investigations evaluating maternal diet patterns and indices have also revealed associations with the newborn fat mass. Starling and colleagues identified a diet pattern characterized by an intake of eggs, starchy vegetables, and non-whole grains, which was associated with greater newborn adiposity [25]. In a similar manner, lower healthy eating index (HEI-2010) scores were associated with a higher proportion of newborn fat mass [24] and the proinflammatory potential of the maternal diet, which was measured several times during pregnancy, was related to an increase in fat mass and the proportion of body fat mass in the newborn infants [22]. A study in obese women revealed an association between higher maternal carbohydrate intake (the highest quartile, median 238 g/d, compared to the lowest quartile, 188 g/d) in late pregnancy, but not in early pregnancy, with a higher proportion of body fat in the newborn as measured by dual-energy X-ray absorptiometry [26]

There have been very few intervention studies conducted; in one, the impact of a behavioural lifestyle intervention involving goals for both diet intake (glycaemic load and SFA intake) and physical activity in obese women during pregnancy on infant adiposity assessed by subscapular and triceps skinfold thicknesses was evaluated in the UK Pregnancies Better Eating and Activity Trial (UPBEAT) [27]. No benefit of the intervention was seen in the triceps skinfold thickness, but the subscapular skinfold thickness z-score was lowered on average by 0.26 sd in the intervention group indicating that maternal behavioural intervention during pregnancy could contribute to a reduction in infant adiposity. Bernard and colleagues suggested that the maternal plasma PUFA status during 26 to 28 weeks of gestation was related to newborn adiposity [28] They demonstrated that maternal LA levels were positively associated with neonatal abdominal adipose tissue volume, as measured by magnetic resonance imaging (MRI), but no association was detected with other measured fatty acids, AA, ALNA, EPA or DHA. In another study, plasma n-3 PUFA acid concentrations were measured at a median of 20.5 weeks of gestation and infants' body compositions somewhat later, at the age of 1.5 months by skin fold thicknesses [29]. With respect to the central-to-total subcutaneous fat ratio in the infants, maternal total n-3 PUFA, and EPA, docosapentaenoic acid (DPA) and DHA levels were associated with higher ratios whereas the n-6 to n-3 ratio was associated with a lower central-to-total subcutaneous fat ratio. The authors speculated that the maternal n-3 PUFA status may stimulate central subcutaneous fat mass development in early infancy, but as no assocations were found later at the age of two years, this is likely a transient effect which does not persist [29]. As a potential mechanism, they proposed that there could be an increased activation of

peroxisome proliferator-activated receptor (PPAR)-c with a subsequent increased deposition of subcutaneous fat mass.

2.3 Metabolic Adaptations in Pregnancy

Many metabolic adaptations take place during pregnancy. These adaptations are driven by the increased energy requirements of pregnancy to support foetal growth and development as well as preparing for the additional energy demands of lactation, i.e. deposition of maternal fat. The key metabolic adaptations take place in maternal glucose and lipid metabolism with an anabolic state present in early pregnancy and a subsequent catabolic state in late pregnancy. The main metabolic adaptations in pregnancy are summarised in Figure 2.2.

2.3.1. Lipid Metabolism in Pregnancy

During pregnancy, overall about 3.5 kg fat is deposited in maternal tissues, both subcutaneously and viscerally [30] . The fat is utilised as an energy source but also contributes to insulin resistance [31]. From the point of view of lipid metabolism, there is net lipogenesis in early pregnancy and net lipolysis in late pregnancy as reviewed in [7,10,32–34]. Briefly, lipid deposition is due to maternal hyperphagia but also due to the higher insulin concentrations and increased insulin sensitivity observed in early pregnancy. It is known that there is an enhanced *de novo* lipogenesis taking place in early pregnancy. The increase in lipoprotein lipase (LPL) activity results in an uptake of fatty acids from the circulation into adipose tissue. In the catabolic state of the last trimester of the pregnancy, the lipolytic activity of adipose tissue is enhanced due to

an increase in the activity of hormone sensitive lipase (HSL) and the lowered activity of LPL. The released glycerol is taken up for hepatic triglyceride synthesis and subsequently released into the circulation in very low density lipoprotein (VLDL) and an increase in the concentration of nonesterified fatty acids (NEFA). In the fasting state, glycerol may be also used for glucose synthesis thus securing the foetal requirements regardless of the mother's fasting state. As the metabolic requirements during late pregnancy are high, NEFA may be used for energy production with the synthesis of ketone bodies which are utilized as a glucose substitute by both mother and foetus during fasting states in the mother. Thus the transfer of ketone bodies across the placenta is considered to be of particular importance for securing embryonic development e.g. for brain lipid synthesis. Nonetheless, their presence may also be harmful as long periods of maternal hyperketonaemia may associate with fetal malformation, impaired neurophysiological development and stillbirth as reviewed in [34].

Overall, due to the prevailing catabolic state, late pregnancy is manifested by hyperlipidemia with an increased concentration not only of triglycerides (VLDL) but also of phospholipids, cholesterols and glycerol. Cholesterol is important for foetal development, it is an essential component of cell membranes, a precursor for bile acids and steroid hormones and has many other functional roles including cell communication. Thus, its supply to the foetus is secured by transplacental transfer from the maternal circulation and by foetal de novo synthesis as reviewed in Zeng et al. 2017 [34]. They also provided evidence that low maternal serum cholesterol levels during pregnancy would associate with reduced birth weights and an elevated incidence of microcephaly; in contrast hypercholesterolemia in term promoted

atherogenicity. Adipose tissue may also play a role in maternal gestational complications [35] and foetal growth with potential long-term health consequences [36,37], since it is a source of inflammatory mediators, i.e. adipocytokines. The cytokines are also expressed in placenta.

2.3.2. Regulation of the Metabolic Adaptations

Many hormones drive and regulate the metabolic adaptations in pregnancy [10,32,34,38]. The anabolic state in early pregnancy, including maternal lipogenesis and fat deposition, is driven by hyperinsulinemia and also the insulin sensitivity of the tissues is elevated. Insulin increases the activity of LPL in adipose tisse and consequently fatty acids are taken up from circulating triglycerides into adipose tissue. Towards the third trimester of pregnancy, insulin resistance develops in a progressive manner and consequently LPL activity is lowered. Furthermore, in pregnant women, adipose tissue derived cytokines and tumor necrosis factor (TNF)-alpha secreted by placenta mediate the state of insulin resistance. Insulin resistance, and an increase in the amounts of free fatty acids and glycerol, drives lipolysis in adipose tissue and hepatic gluconeogenesis and ketogenesis. The concentration of estrogen increases throughout the pregnancy and contributes to the catabolic state, and thus to the hyperlipidemia encountered in pregnant women. Hyperlipidemia is also induced by progesterone, cortisol, prolactin and leptin; these hormones are involved in decreasing the body's responsiveness to insulin. Two other hormones deserve a mention; human placental lactogen stimulates insulin secretion whereas human placental growth hormone evokes insulin resistance.

2.3.3. Impacts of Maternal Hypertriglyceridemia on Mother and Infant

Hyperlipidemia in pregnancy is a normal physiological situation that ensures the supply of nutrients to the foetus, but excessively elevated levels may be harmful. Two meta-analyses have explored this issue; in the first, based on an evaluation of case-control studies, higher serum levels of triglycerides were shown to associate with pre-eclampsia [39]. They also found evidence from cohort studies that hypertriglyceridemia preceded the onset of pre-eclampsia. In the second meta-analysis, also other lipid fractions were evaluated and pre-eclampsia was found to associate with higher levels of total cholesterol, non-high density lipoprotein (HDL) cholesterol and triglycerides in all trimesters and with lower levels of HDL cholesterol in the third trimester [40]. Based on yet another meta-analysis, also women with GDM were shown to display elevated triglyceride levels in all trimesters of pregnancy [41]. In the same analysis, the third trimester HDL cholesterol levels were found to be lower in women with GDM, whilst no differences in total cholesterol or low density lipoprotein (LDL) cholesterol levels were seen between women with or without GDM [41]. Hyperlipidemia may be harmful as it contributes to the risk of acute myocardial infarction of the mother in pregnancy, labor and delivery, and also postpartum [42] and to acute pancreatitis during pregnancy [43], although both conditions are rare, they are potentially lethal for both mother and child.

2.3.4. Foetal Perspective on Maternal Metabolic Adaptations

From the point of view of the foetus, metabolic adaptations in the pregnant woman are necessary to support foetal growth and development. Fatty acids are obtained

from the maternal circulation to supply energy, essential fatty acids and LC-PUFAs for growth and development including tissue development, primarily adipose tissue, [33,34]. The foetus also gains fat stores during pregnancy, as discussed in the previous paragraph. While the maternal hyperlipidemic state supports these metabolic needs of the foetus, it may contribute to an excessive growth of the foetus. In an Asian study population, highly elevated maternal fasting triglyceride levels (above 3.6 mmol/l) were associated with large-for gestational-age (LGA) status independently of prepregnancy BMI, GDM and insulin resistance [44]. Similar findings were found in another study; triglyceride levels in the mothers of LGA infants increased faster than those of the control group and the infants of mothers with the highest triglyceride levels (above 1.19 mmol/l) were larger than those with lower triglyceride levels [45]. The authors of a Chinese population based study (17,610 singleton pregnancies with lipid data from early and middle pregnancy) also reported that serum lipids are increased from early to middle pregnancy with the rise being related to adverse pregnancy outcomes including a risk of gestational diabetes and LGA [46]. Maternal hyperlipidemia may also influence uterine blood flow as measured by blood flow velocity waveforms in women with GDM, potentially indicating the presence of vascular damage [47]. Thus, excessive hypertriglyceridemia is clearly not desirable. Wang and co-workers calculated reference values for serum lipids that would lower the risk of adverse pregnancy outcomes, namely total cholesterol < 5.64 mmol/L, triglycerides < 1.95 mmol/L, HDL cholesterol > 1.23 mmol/L and LDL cholesterol < 3.27 mmol/L in early pregnancy and total cholesterol < 7.50 mmol/L, triglycerides < 3.56 mmol/L, HDL cholesterol > 1.41 mmol/L, and LDL cholesterol < 4.83 mmol/L in middle pregnancy.

The latest research has applied metabolomics to investigate lipid metabolism in maternal or cord blood. The cord blood lipidomics profile, and also the profiles of other metabolites like amino acids, have been linked with birth weight [48], and adiposity [49,50], as measured by skinfold thicknesses, and furthermore the lipidomics profile in pregnancy has been linked with birth weight [51], potentially these may represent new biomarkers for child health outcomes in the future. One example is a study in which the ratio of particular metabolites in maternal serum during pregnancy was shown to predict fetal growth restriction [52].

2.4 Placenta in the Maternal - Foetal Interface

Placenta has an important role in ensuring the success of the pregnancy; it influences the rate of foetal growth through the transport of nutrients from the mother to the foetus and the placenta also has a capacity to synthetize hormones [32]. Many placental hormones including growth hormone, prolactin, placental lactogens, and steroid hormones, mediate the maternal adaptations to pregnancy as reviewed in detail in [53]. In cases of placental insufficiency foetal development is endangered and manifested as conditions like intrauterine growth restriction. To secure the foetal demands, the structure and function of the placenta changes over the course of pregnancy. Placental structure allows a maximal surface area for the exchange of membrane-permeable molecules as well as those molecules that require transporters for crossing the cellular membranes [54]. Placenta has the capacity to affect nutrient availabity to the foetus by the transfer of nutrients from the mother and storage of nutrients for delivery to the fetus as needed. In addition, new substrates may be metabolized in the placenta for fetal needs. LC-PUFAs do not seem to be

synthetised in placenta, instead the foetus relies on the maternal supply and synthesis through chain elongation and desaturation processes [3]. Foetal growth is mainly attributable to glucose but in addition to carbohydrates, lipids and amino acids are needed for foetal growth. Considering lipid metabolism, foetus can synthetise some saturated and monounsaturated fatty acids from glucose but must obtain essential fatty acids from the mother through the placenta. LC-PUFAs are particularly important for foetal neurodevelopment and further fatty acids and their derivatives, e.g. eicosanoids, have important signalling roles including those necessary for the initiation and progression of labour.

2.4.1. Placental Fatty Acid Transfer

Placental fatty acid transfer has been recently reviewed in detail [54,55]. Briefly, placenta takes up fatty acids from the maternal circulation either as free fatty acids or from triglycerides by the action of lipases expressed in the placenta. The majority of the fatty acids are esterified in the placenta, and again oxidized or released by esterases. Placental fatty acid binding protein (FABS) and fatty acid transport protein facilitate the transport of fatty acids down a concentration gradient to the foetus. Fatty acids are also converted to acylcarnitines, which are particularly important for the selectivity of LC-PUFA transfer across the placenta.

It is noteworthy that not all the fatty acids are unidirectionally transferred to the foetus; fatty acids are also released into the maternal circulation. Some fatty acids may be selectively transferred to the foetus as demonstrated in ^{13}C-labelled fatty acid studies [56,57]. Pregnant women received ^{13}C-labelled palmitic acid, oleic acid, LA

or DHA 12 hours before caesarean section and cord blood and placenta were analysed. Higher concentrations of the labelled DHA were found in cord plasma than maternal plasma and furthermore, DHA was detected at higher concentrations than the other fatty acids in the placenta. This may be due to the need to sustain high foetal needs for brain and retinal development. In addition to placental function, also the maternal supply, i.e. the dietary intake but also fat stores are important for satisfying the fatty acids needs of the foetus, particularly for essential fatty acids and LC-PUFAs including DHA. DHA can also be formed by foetal endogenous synthesis. Interestingly, maternal metabolic conditions may influence the placental transfer of DHA to the foetus. A lower placental uptake and reduced transfer of DHA to the foetus were observed in women with GDM in comparison to controls [58]. Furthermore, an altered expression of genes involved in placental lipid metabolism has been demonstrated in women with obesity and GDM indicating that the transport and storage of lipids is modified under these conditions [59,60].

2.5 Foetal Fat Requirements and Maternal Reference Values of Dietary Intake

2.5.1. Foetal Fat Requirements

The foetus requires fatty acids for energy, to maintain the fluidity, structure and permeability of membranes and for precursors of a range of bioactive compounds including the eicosanoids. The LC-PUFAs are needed for structural and metabolic functions. Thus, although LC-PUFAs - AA, EPA and DHA - are not essential fatty acids, they may be viewed as conditionally essential during pregnancy as the foetus benefits from the supply from the mother [3]. Fatty acids are required already in very

early stages of development for cell division and cell growth and differentiation by the embryo and oocytes. Thereafter, the need for fats increases exponentially throughout the course of the pregnancy. The requirements of DHA are particularly high close to term, being aroung 300 mg/day whilst the requirement at 25 weeks of gestation is 100 mg/day [3]. The foetus efficiently stores DHA which is of particular importance after birth when the maternal supply through placenta has ceased. A rise in newborn plasma triglycerides and free fatty acids is seen within a few hours of birth, as reviewed by Haggarty [3]. Interestingly, a higher conversion of ALNA to its long-chain derivatives has been detected in women compared to men, one mechanism ensuring a sufficient supply of these important fatty acids for foetal growth and development [61].

2.5.2. Dietary Reference Values for Pregnancy

The European Food Safety Authority has set dietary reference values for the European Union [62]. https://efsa.gitlab.io/multimedia/drvs/index.htm Firstly, pregnant women should increase their energy intake by 0.29 MJ/day in the first trimester, by 1.1 MJ/day in the second trimester and by 2.1 MJ/day in the third trimester of pregnancy. The reference intake range for total fat is set at 20-35 % of energy intake and SFA intake and trans-fatty acid intakes should be as low as possible. Adequate intakes for LA and ALNA have been set to 4 and 0.5 percent of energy intake respectively and the DHA intake should be 100 to 200 mg higher than in non-pregnant women. The fatty acid requirements have been also evaluated in expert reports which have concluded that “dietary fat intake in pregnancy and lactation (energy%) should be as recommended for the general population; pregnant and

lactating women should aim to achieve an average dietary intake of at least 200 mg DHA/d" [63]. They also concluded that intakes of up to 1 g/day of DHA or 2.7 g/day n-3 LC-PUFA are safe, as no significant adverse effects have been noted in randomized clinical trials. A recommendation for fish intake was given; one to two portions of sea fish per week, including oily fish, for women of childbearing age. In another expert report, 300 mg/day of DHA was recommended for pregnant and lactating women [64].

2.5.3. Dietary Intake of Pregnant Women

The dietary intake varies across countries and obviously between individuals. Overall total fat intakes are higher and intakes of PUFAs are commonly lower than recommended [65,66]. Forsyth and colleagues estimated the dietary intake of DHA and arachidonic acid in 175 countries around the world. The DHA was below 200 mg/day in 64% of the countries, with the lowest intakes in Sub-Saharan Africa and Central and Southern Asian populations [67]. The mean intake of DHA in the European Union was 198 mg/day; other values were as follows - Australia and New Zealand 184 mg/day, USA and Canada 221 mg/day, China 298 mg/day and Japan 473 mg/day, whilst the intake in the low-income countries was 96 mg/day. It was reported that only 27% of Canadian pregnant women met the recommended intake of DHA but women who consumed food supplements improved the likelihood that they would fulfil the recommendation [68].

A higher dietary intake of n-3 LC-PUFAs is reflected in the proportion of these fatty acids in maternal plasma during pregnancy, with the greatest changes being observed in the phospholipid fraction [69]. In a systematic review, in addition to higher

fish consumption and a higher PUFA intake, a higher maternal n-3 status was explained by a higher education level and older maternal age [70]. Similarly changes in cord blood fatty acids have been observed [71]. In supplement studies, a daily dose of 500 to 1000 mg of n-3 LC-PUFA, but not a smaller dose, effectively increased foetal n-3 fatty acid status as measured from cord blood [72].

2.5.3.1. Relation of Maternal Dietary n-3 LC-PUFAs with Child Health

Maternal higher dietary intake of n-3 LC-PUFAs, particularly EPA and DHA, as fish or fish oil supplements have been often claimed to improve health and development outcomes of the child. In a population based European study, fish consumption for at least once per week during pregnancy was related to a lower risk of preterm birth and to a higher birth weight compared to the situation in those women who ate fish less commonly [73]. A Cochrane systematic review of randomised controlled trials with n-3 LC-PUFA either as food or supplements during pregnancy concluded that there was a lower risk for preterm birth and increased the risk for prolonged gestation beyond 42 weeks in women who consumed n-3 LC-PUFA supplements [74] Furthermore, a reduced risk of low birthweight was seen. No benefits of the n-3 LC-PUFAs for child cognition, IQ, vision or other neurodevelopment and growth outcomes or language and behaviour were seen although the authors called for further follow-up of the completed trials to assess longer-term health outcomes of the supplementation [74]. A review of observational studies concluded that there were some benefits of fish intake during pregnancy for child neurodevelopment [75]. A study with a modern method for assessing neurodevelopment, pattern-reversal visual evoke potentials (pVEP), demonstrated that the maternal consumption of fish for at

least three times per week during the last trimester of pregnancy was associated with better neurodevelopment of the child's visual system when he/she was 2-years old [76]. The limited evidence from systematic reviews and meta-analyses indicates that n-3 LC-PUFA supplementation or fish consumption during pregnancy can lower the risk of allergy in the child [77,78]. In pooled estimates of data from nine clinical trials, a lowered risk of sensitization to egg and peanut allergy was demonstrated due to n-3 LCPUFA supplementation during pregnancy [78]. In addition to the reduction in the incidence of atopic eczema, any positive skin prick test, sensitization to egg and sentitization to any food in the first year of life were detected after the increased consumption of n-3 LC-PUFA or fish during pregnancy [77]. Instead, in another meta-analysis, no benefit was evident of fish intake during pregnancy for child allergy outcomes, but consumption of fish during the first year of life reduced the risk of eczema and allergic rhinitis [79]. It is of importance to acknowledge that dietary fat intake will influence the intakes of fat soluble vitamins, which are also of importance for brain development [80]. Evidently, the mother's overall diet quality is likely to be of significance with respect to her child's cognitive and behavioural outcomes [81].

2.6 Energy and Fat Requirements in Infancy

Infancy, the first year of life, is a period of rapid growth and development and thus the needs for energy and nutrients are high. The nutritional requirements vary but growth pattens are closely linked to nutrition [82]. The needs of the newborn for energy are high, 450 to 480 kJ/kg/day, being higher in boys due to their higher weight and thereby decline to about 400 kJ/kg/day by three months of life and to about 340 kJ/kg/day by six months of life [83]. EFSA, in its scientific opinion on dietary reference

values, estimated that the energy requirement of the infant at six months of age would be 2.3 MJ/day, increasing up to 2.8 MJ/day by 11 months of age [62]. The basal metabolic rate accounts for 60 to 70% of the energy requirements during the first year of life. The thermic effect of feeding amounts to 10% of the energy requirements. The energy needed for thermoregulation, i.e. for maintenance of normal body temperature and the energy needed for physical activity are variable; energy is needed more at lower than at higher temperatures and the energy expended on physical activity increases as the infant grows and develops [83]. The last element of total energy expenditure is the cost of growth, which is an indicator for the balance between energy supply and demand.

2.6.1. Fat Requirements in Infancy

Dietary fats are required for many purposes by the infants [84]. Fats are the main energy source in the infant diet, they slow gastric emptying and intestinal motility and thus affect satiety, they also facilitate the absorption of fat soluble vitamins and provide essential fatty acis. Lipids are structural components of tissues and membranes, they are particularly rich in brain, retina and other neural tissues, and act as precursors for eicosanoids as well as other autocrine and paracrine mediators that play a role in many physiological functions including immune responses. An essential fatty acid deficiency develops soon within 7 to 10 days in infants if adequate amounts are not supplied [82] In addition to the essential fatty acids, LA and ALNA, also AA and DHA may be considered as essential for the infants. The blood and tissue concentrations of AA and DHA decrease after birth if they are not supplied via the diet [85,86]. Thus, dietary sources of LC-PUFAs are needed, as the

endogenous synthesis from essential fatty acids is not sufficient to compensate for the lack of the long-chain fatty acid derivatives from the diet [87]. In addition, the DHA concentration in an infant's red blood cells is related to that in breast milk but a plateau is reached at breast milk DHA amounts above 0.8% of total fatty acids [88]. On the other hand, infants have the capacity to convert ALNA to DHA and a rapid phase of DHA accumulation is seen from the last trimester of pregnancy to 6 to 10 months of life [89]. Regarding many health effects, the focus has been on n-3 LC-PUFAs, but n-6 LC-PUFAs, particularly AA are also of importance for growth [90,91]. The European Food Safety Authority has set levels for an adequate intake of fats for infants aged 7 to 11 months: ALNA 0.5 % of energy intake, DHA 100 mg/day, LA 4 % of energy intake. Further, the total fat intake should be 40 % of energy intake and the intakes of SFA and trans-fatty acids should be as low as possible [62], although the reference values vary between different bodies [92].

2.6.2. Infant Feeding Modes

2.6.2.1. Health Effects of Breastfeeding

Breastfeeding is the natural mode of feeding an infant; it provides not only nutrients but also bioactive molecules that support the maturation of the infant's gastrointestinal tract. Breast milk has many important roles in growth and development, but it also acts as a determinant of current and later health. Breast-feeding has been shown confer protection from infections and to increase intelligence, and potentially lower the risk of overweight and diabetes, although the benefit with regard to asthma or blood pressure or cholesterol levels was not

demonstrated in a meta-analysis [5]. Infants, whether born term or preterm and also those at risk for allergic diseases do benefit of breastfeeding [93] However, another review of supplementation studies with n-3 LC-PUFAs in doses ranging from 200 mg to 1183 mg during pregnancy and/or lactation was not able to provide solid evidence for benefits with regard to obesity [94]. Yet another review on randomized controlled trials with n-3 LC-PUFA supplementation conducted over the past 10 years, did not detect any consistent benefits of supplementation during pregnancy and/or lactation on childhood cognitive and visual development [95]. Similarly it was concluded in a Cochrane systematic review that supplementation of LC-PUFA during breastfeeding (some studies also including during pregnancy) did not improve the neurodevelopment, visual acuity or growth of the child [96]. These investigators found a benefit from only one study with respect to child attention. In contrast, another systematic review and meta-analysis did conclude that n–3 PUFA supplementation for mothers or infants improved childhood psychomotor and visual development [97]. There are several reasons for the variable results e.g. why some trials have failed to detect positive effects, one being the follow-up time, as the benefits of consuming LC-PUFAs may not be evident in infancy, but may emerge later at 3 to 6 years of age [98]. It is nevertheless well known that the brain accumulates DHA during both the foetal and early postnatal periods up to two years of life and indeed an adequate supply of LC-PUFAs for the child is important for growth and development [99]. A recent study using multimodal MRI, indicated that infants consuming formula with added DHA displayed improvements in brain structure, signalling and function at the age of nine years [100]. A Cochrane systematic review of randomised controlled trials evaluated the effects on visual function, neurodevelopment and physical growth of

consuming LC-PUFA supplemented infant formulas, but found no benefits as compared to non-supplemented infant formula [101].

2.6.2.2. Breast Milk Fat Composition

The majority of the fat in breast milk is present in milk fat globules that contain a triglyceride-rich core and a tri-layer membrane, the milk fat globule membrane [102]. There is recent evidence indicating that milk fat globules, including the membrane associated glycerophospholipids, sphingolipids, cholesterol, and proteins, have many biological properties that contribute to the maturation of the newborn's gut and subsequent infant growth as reviewed by Lee and co-workers [102]. The fat content of the breast milk varies pending on the feeding period, i.e. colostrum, transitional and mature milk, and on each feeding time as well [103]. The fat content of the colostrum (18 to 24 g/L) is lower than that of transitional or mature milk (31 to 44 g/L). The mother's diet also influences the fatty acid composition of her breast milk [104,105]. For example, its fat content as well as the n-3 and n-6 LC-PUFA concentrations are influenced by maternal dietary intakes of foods and supplements. Some evidence exists also that there is a higher concentration of SFA and an elevated n-6/n-3 fatty acid ratio in breast milk if the mother has a higher BMI value [105].

Palmitic acid (16:0), oleic acid (18:1 n-9) and LA are the most abundant fatty acids in breast milk [106]. The DHA concentration of breast milk, 0.32%, is less than that of AA, 0.47%, as indicated by data from 65 studies of 2474 women [107]. The concentration of AA appears to be at a relatively fixed level [91] but the concentration seems to vary across countries and regions, with diet being an important source for the differences

[108]. In the review of Hadley and co-workers, it was suggested that AA would be critical for infant growth, brain development, and health and that a balanced intake of AA and DHA is important, as DHA may suppress the benefits provided by AA [91]. Infant formulas and follow-on formulas (from 6 months onwards) aim to mimic breast milk; typically, they also have added AA and DHA to secure optimal foetal development and growth [109]. The supplemented infant formula, as compared to non-supplemented formulas, indeed yield higher concentrations of plasma DHA and AA, but the concentrations of LC-PUFAs are nevertheless higher in breast-fed infants as compared to formula-fed infants [110]. Similarly, fish consumption for at least three times per week by breastfeeding mothers increased their serum DHA and total n-3 LC-PUFA as compared to non-consumers measured at one month after delivery [111]. Furthermore, the maternal dietary intakes along with higher serum levels of n-3 LC-PUFAs were related to serum fatty acid levels in one-month-old infants.

2.6.2.3. Complementary Feeding of the Infants

Optimally the duration of exclusive breastfeeding lasts for at least four months and preferably the infant is fed predominantly breast milk for more than the first six months of her/his life, with breastfeeding continuing until 12 months of age. Complementary foods should be introduced after four months of age and at six months of age at the latest [112].

When the infant switches from breast feeding (or formula feeding) to complementary feeding, the proportion of fats in the diet becomes reduced [113]. Fat intake is still important as a supply of energy during the rapid growth in infancy. The consumption

of energy dense complementary foods resulting in a high fat intake may induce excessive weight gain in infancy and this has been associated with later obesity, although this proposal has not been universally accepted, as concluded in a position paper [112]. One recent longitudinal study indicated that a rapid increase of fat mass, as measured by air displacement plethysmograph, during the first six months of life was associated with higher adiposity at the age of two years [114].

The intakes of LC-PUFAs, including DHA and AA [91] decrease with the onset of complementary feeding and generally the intakes are lower than recommended [115]. The dietary supply can increase the circulating LC-PUFA levels as indicated in a trial in which the infants in the intervention consumed a good source of DHA (salmon) compared to a control group (LA rich corn oil), when the complementary feeding was started. The children in the intervention group exhibited increased erythrocyte and plasma EPA, DHA and total n-3 LC-PUFA levels [116]. The fat composition of the infant diet also influenced serum lipoprotein cholesterol concentrations, the higher PUFA and lower SFA intakes may reduce total cholesterol and LDL cholesterol levels, rather than the dietary cholesterol, which may be of importance considering the programming leading to the later cardiovascular disease risk [113,117].

2.7 Conclusions

An adequate supply of energy and all nutrients during pregnancy and lactation and by infants when transferring to the complementary feeding are important to secure the optimal growth and development of the foetus and not to increase the susceptibility from a lifestyle-related disease in both the mother and her child. In

particular, the intakes of LC-PUFAs, essential fatty acids LA and ALNA, but also those of AA and DHA during the vulnerable periods of life, are of importance, especially for foetal and infant brain development. Even though the clinical benefit of consuming the LC-PUFAs for many health oucomes is inconclusive, there is convincing evidence for the presence of mechanisms that would lead to beneficial health outcomes. Many dietary intake studies suggest that dietary intakes of LC-PUFAs, particularly n-3 fatty acids, are lower than optimal. The importance of an overall healthy maternal diet [118,119] must be emphasized for providing an optimal environment for foetal and infant growth and development, and for programming towards health [2]. Equally, it is important to ensure a sufficient supply of LC-PUFAs in the infant's diet when switching from breast milk to complementary feeding.

New research topics in the area include the role that the gut microbiota plays for infant health and nutrition, as the host-microbiota interaction is known to be of major significance for human physiology and health [120]. It has been claimed that the maternal microbiota already during pregnancy may influence the development of foetal microbiota with consequential effects on his/her health [121,122]. It should be remembered that breast milk contains a pool of microbes [123] and, there is an interaction between dietary fats and the gut microbiota [124], an interesting topic for further research.

REFERENCES

1. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Carlo G, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus : A Pragmatic Guide for Diagnosis , Management , and Care.
2. Barker DJP. The origins of the developmental origins theory. J Intern Med. 2007;261(5):412–7.
3. Haggarty P. Fatty acid supply to the human fetus. Annu Rev Nutr. 2010;30:237–55.
4. Innis SM. ESSENTIAL FATTY ACIDS IN GROWTH DEVELOPMENT Two independent families of fatty adds , the n-6 and n-3 , are known to be essential for normal mammalian cell function . The n-6 and n-3 fatty acids accepted as essential in the human diet are linoleic (18 : 2. Lipid Res. 1991;30(1):39–103.
5. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. Lancet [Internet]. 2016;387(10017):475–90. Available from: http://dx.doi.org/10.1016/S0140-6736(15)01024-7
6. Most J, Dervis S, Haman F, Adamo KB, Redman LM. Energy intake requirements in pregnancy. Nutrients. 2019;11(8).
7. Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50(4):938–48.
8. Butte NF, King JC. Energy requirements during pregnancy and lactation. Public Health Nutr. 2005;8(7A):1010–27.
9. Institute of Medicine of the National Academies. Healthy Weight Gain During

Pregnancy: Reexamining the Guidelines. National Academies Press; 2011. Available from: http://www.hc-sc.gc.ca/fn-an/nutri.

10. Herrera E, Desoye G. Maternal and fetal lipid metabolism under normal and gestational diabetic conditions. Horm Mol Biol Clin Investig. 2016;26(2):109–27.
11. Heim_1983_Energy_and_Lipid_Requirements_of_the_Fetus_and_the.4.pdf.
12. Desoye G, Herrera E. Adipose tissue development and lipid metabolism in the human fetus: The 2020 perspective focusing on maternal diabetes and obesity. Prog Lipid Res [Internet]. 2021;81:101082. Available from: https://doi.org/10.1016/j.plipres.2020.101082
13. Catalano PM, Kirwan JP. Maternal factors that determine neonatal size and body fat. Curr Diab Rep. 2001;1(1):71–7.
14. Kuipers RS, Luxwolda MF, Offringa PJ, Martini IA, Rudy Boersma E, Janneke Dijck-Brouwer DA, et al. Gestational age dependent content, composition and intrauterine accretion rates of fatty acids in fetal white adipose tissue. Prostaglandins Leukot Essent Fat Acids [Internet]. 2012;86(1–2):39–49. Available from: http://dx.doi.org/10.1016/j.plefa.2011.10.007
15. Kuipers RS, Luxwolda MF, Offringa PJ, Rudi Boersma E, Dijck-Brouwer DAJ, Muskiet FAJ. Fetal intrauterine whole body linoleic, arachidonic and docosahexaenoic acid contents and accretion rates. Prostaglandins Leukot Essent Fat Acids [Internet]. 2012;86(1–2):13–20. Available from: http://dx.doi.org/10.1016/j.plefa.2011.10.012
16. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol. 2006;195(4):1100–3.

17. Durnwald C, Huston-Presley L, Amini S, Catalano P. Evaluation of body composition of large-for-gestational-age infants of women with gestational diabetes mellitus compared with women with normal glucose tolerance levels. Am J Obstet Gynecol. 2004;191(3):804–8.
18. Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, De Mouzon SH, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr. 2009;90(5):1303–13.
19. Moore BF, Harrall KK, Sauder KA, Glueck DH, Dabelea D. Neonatal adiposity and childhood obesity. Pediatrics. 2020;146(3).
20. Cunnane SC, Crawford MA. Survival of the fattest: Fat babies were the key to evolution of the large human brain. Comp Biochem Physiol - A Mol Integr Physiol. 2003;136(1):17–26.
21. Crume TL, Brinton JT, Shapiro A, Kaar J, Glueck DH, Siega-Riz AM, et al. Maternal dietary intake during pregnancy and offspring body composition: The Healthy Start Study. Am J Obstet Gynecol. 2016;215(5):609.e1-609.e8.
22. Moore BF, Sauder KA, Starling AP, Hébert JR, Shivappa N, Ringham BM, et al. Proinflammatory Diets during Pregnancy and Neonatal Adiposity in the Healthy Start Study. J Pediatr. 2018;195:121-127.e2.
23. Kennedy RAK, Mullaney L, O'Higgins AC, Doolan A, McCartney DM, Turner MJ. The relationship between early pregnancy dietary intakes and subsequent birthweight and neonatal adiposity. J Public Heal (United Kingdom). 2018;40(4):745–55.
24. Shapiro ALB, Kaar JL, Crume TL, Starling AP, Siega-Riz AM, Ringham BM, et al. Maternal diet quality in pregnancy and neonatal adiposity: The Healthy Start Study. Int J Obes [Internet]. 2016;40(7):1056–62. Available from:

http://dx.doi.org/10.1038/ijo.2016.79

25. Starling AP, Sauder KA, Kaar JL, Shapiro ALB, Siega-Riz AM, Dabelea D. Maternal dietary patterns during pregnancy are associated with newborn body composition. J Nutr. 2017;147(7):1334–9.
26. Renault KM, Carlsen EM, Nørgaard K, Nilas L, Pryds O, Secher NJ, et al. Intake of carbohydrates during pregnancy in obese women is associated with fat mass in the newborn offspring. Am J Clin Nutr. 2015;102(6):1475–81.
27. Patel N, Godfrey KM, Pasupathy D, Levin J, Flynn AC, Hayes L, et al. Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy. Int J Obes. 2017;41(7):1018–26.
28. Bernard JY, Tint MT, Aris IM, Chen LW, Quah PL, Tan KH, et al. Maternal plasma phosphatidylcholine polyunsaturated fatty acids during pregnancy and offspring growth and adiposity. Prostaglandins Leukot Essent Fat Acids. 2017;121(January):21–9.
29. Vidakovic AJ, Gishti O, Voortman T, Felix JF, Williams MA, Hofman A, et al. Maternal plasma PUFA concentrations during pregnancy and childhood adiposity : the Generation R Study 1 – 3. 2016;(C):4–6.
30. Butte NF, Ellis KJ, Wong WW, Hopkinson JM, O'Brian Smith E. Composition of gestational weight gain impacts maternal fat retention and infant birth weight. Am J Obstet Gynecol. 2003;189(5):1423–32.
31. Catalano PM, Roman-Drago NM, Amini SB, Sims EAH. Longitudinal changes in body composition and energy balance in lean women with normal and abnormal glucose tolerance during pregnancy. Am J Obstet Gynecol. 1998;179(1):156–65.
32. Cetin I, Cardellicchio M. Physiology of pregnancy: Interaction between mother

and child: Overview of the nutritional interaction between the mother and fetus. Ann Nestle. 2010;68(1):7–15.

33. Ortega-Senovilla Henar, Alvino Giola, Taricco Emanuela, Cetin Irene HE. Gestational Diabetes Mellitus Upsets the Arterial but Not Venous Plasma. Diabetes Care. 2009;32(January):120–2.

34. Zeng Z, Liu F, Li S. Metabolic Adaptations in Pregnancy: A Review. Ann Nutr Metab. 2017;70(1):59–65.

35. Gutaj P, Sibiak R, Jankowski M, Awdi K, Bryl R, Mozdziak P, et al. The role of the adipokines in the most common gestational complications. Int J Mol Sci. 2020;21(24):1–32.

36. Briana DD, Malamitsi-Puchner A. The role of adipocytokines in fetal growth. Ann N Y Acad Sci. 2010;1205:82–7.

37. Parisi F, Milazzo R, Savasi VM, Cetin I. Maternal low-grade chronic inflammation and intrauterine programming of health and disease. Int J Mol Sci. 2021;22(4):1–16.

38. Herrera E, Ortega-Senovilla H. Maternal lipid metabolism during normal pregnancy and its implications to fetal development. Clin Lipidol. 2010;5(6):899–911.

39. Gallos ID, Sivakumar K, Kilby MD, Coomarasamy A, Thangaratinam S, Vatish M. Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: A meta-analysis. BJOG An Int J Obstet Gynaecol. 2013;120(11):1321–32.

40. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK. Maternal hyperlipidemia and the risk of preeclampsia: A meta-analysis. Am J Epidemiol. 2014;180(4):346–58.

41. Ryckman K, Spracklen C, Smith C, Robinson J, Saftlas A. Maternal lipid levels

during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG An Int J Obstet Gynaecol [Internet]. 2015;122(5):643–51. Available from: http://doi.wiley.com/10.1111/1471-0528.13261

42. Balgobin CA, Zhang X, Lima F V., Avila C, Parikh PB, Yang J, et al. Risk Factors and Timing of Acute Myocardial Infarction Associated With Pregnancy: Insights From the National Inpatient Sample. J Am Heart Assoc. 2020;9(21):e016623.
43. Cruciat G, Nemeti G, Goidescu I, Anitan S, Florian A. Hypertriglyceridemia triggered acute pancreatitis in pregnancy-diagnostic approach, management and follow-up care. Lipids Health Dis. 2020;19(1):4–9.
44. Samsuddin S, Arumugam PA, Md. Amin MS, Yahya A, Musa N, Lim LL, et al. Maternal lipids are associated with newborn adiposity, independent of GDM status, obesity and insulin resistance: a prospective observational cohort study. BJOG An Int J Obstet Gynaecol. 2020;127(4):490–9.
45. Liang N, Zhu H, Cai X, Le Z, Wang H, He D, et al. The high maternal TG level at early trimester was associated with the increased risk of LGA newborn in non-obesity pregnant women. Lipids Health Dis. 2018;17(1):1–7.
46. Wang C, Kong L, Yang Y, Wei Y, Zhu W, Su R, et al. Recommended reference values for serum lipids during early and middle pregnancy: A retrospective study from China 11 Medical and Health Sciences 1114 Paediatrics and Reproductive Medicine. Lipids Health Dis. 2018;17(1):1–16.
47. Bugatto F, Quintero-Prado R, Visiedo FM, Vilar-Sánchez JM, Figueroa-Quiñones A, López-Tinoco C, et al. The Influence of Lipid and Proinflammatory Status on Maternal Uterine Blood Flow in Women With Late Onset Gestational Diabetes. Reprod Sci. 2018;25(6):837–43.

48. Kadakia R, Talbot O, Kuang A, Bain JR, Muehlbauer MJ, Stevens RD, et al. Cord Blood Metabolomics: Association with Newborn Anthropometrics and C-Peptide across Ancestries. J Clin Endocrinol Metab. 2019;104(10):4459–72.

49. Kadakia R, Scholtens DM, Rouleau GW, Talbot O, Ilkayeva OR, George T, et al. Cord Blood Metabolites Associated with Newborn Adiposity and Hyperinsulinemia. J Pediatr. 2018;

50. Chia AR, de Seymour J V., Wong G, Sulek K, Han TL, McKenzie EJ, et al. Maternal plasma metabolic markers of neonatal adiposity and associated maternal characteristics: The GUSTO study. Sci Rep. 2020;10(1):1–11.

51. LaBarre JL, Puttabyatappa M, Song PXK, Goodrich JM, Zhou L, Rajendiran TM, et al. Maternal lipid levels across pregnancy impact the umbilical cord blood lipidome and infant birth weight. Sci Rep [Internet]. 2020;10(1):1–15. Available from: https://doi.org/10.1038/s41598-020-71081-z

52. Sovio U, Goulding N, McBride N, Cook E, Gaccioli F, Charnock-Jones DS, et al. A maternal serum metabolite ratio predicts fetal growth restriction at term. Nat Med [Internet]. 2020;26(3):348–53. Available from: http://dx.doi.org/10.1038/s41591-020-0804-9

53. Napso T, Yong HEJ, Lopez-Tello J, Sferruzzi-Perri AN. The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation. Front Physiol. 2018;9(AUG):1–39.

54. Bowman CE, Arany Z, Wolfgang MJ. Regulation of maternal–fetal metabolic communication [Internet]. Vol. 78, Cellular and Molecular Life Sciences. Springer International Publishing; 2021. 1455–1486 p. Available from: https://doi.org/10.1007/s00018-020-03674-w

55. Lewis RM, Childs CE, Calder PC. New perspectives on placental fatty acid

transfer. Prostaglandins Leukot Essent Fat Acids [Internet]. 2018;138(March):24–9. Available from: https://doi.org/10.1016/j.plefa.2018.10.001

56. Larqué E, Demmelmair H, Berger B, Hasbargen U, Koletzko B. In vivo investigation of the placental transfer of 13C-labeled fatty acids in humans. J Lipid Res. 2003;44(1):49–55.

57. Gil-Sánchez A, Demmelmair H, Parrilla JJ, Koletzko B, Larqué E. Mechanisms involved in the selective transfer of long chain polyunsaturated fatty acids to the fetus. Front Genet. 2011;2(SEP):1–8.

58. Pagán A, Prieto-Sánchez MT, Blanco-Carnero JE, Gil-Sánchez A, Parrilla JJ, Demmelmair H, et al. Materno-fetal transfer of docosahexaenoic acid is impaired by gestational diabetes mellitus. Am J Physiol Endocrinol Metab [Internet]. 2013;305(7):E826-33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23921142

59. Hirschmugl B, Desoye G, Catalano P, Klymiuk I, Scharnagl H, Payr S, et al. Maternal obesity modulates intracellular lipid turnover in the human term placenta. Int J Obes. 2017;41(2):317–23.

60. Segura MT, Demmelmair H, Krauss-Etschmann S, Nathan P, Dehmel S, Padilla MC, et al. Maternal BMI and gestational diabetes alter placental lipid transporters and fatty acid composition. Placenta [Internet]. 2017;57:144–51. Available from: http://dx.doi.org/10.1016/j.placenta.2017.07.001

61. Burdge GC, Wootton SA. Conversion of α-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr. 2002;88(4):411–20.

62. European Food Safety Authority. Dietary Reference Values for the EU

[Internet]. Available from: https://efsa.gitlab.io/multimedia/drvs/index.htm

63. Koletzko B, Cetin I, Brenna JT. Dietary fat intakes for pregnant and lactating women. Br J Nutr. 2007;98(5):873–7.

64. Simopoulos AP, Leaf A, Salem N. Workshop statement on the essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. Prostaglandins Leukot Essent Fat Acids. 2000;63(3):119–21.

65. Blumfield ML, Hure AJ, MacDonald-Wicks L, Smith R, Collins CE. Systematic review and meta-analysis of energy and macronutrient intakes during pregnancy in developed countries. Nutr Rev. 2012;70(6):322–36.

66. Caut C, Leach M, Steel A. Dietary guideline adherence during preconception and pregnancy: A systematic review. Matern Child Nutr. 2020;16(2):1–20.

67. Forsyth S, Gautier S, Salem N. Global estimates of dietary intake of docosahexaenoic acid and arachidonic acid in developing and developed countries. Ann Nutr Metab. 2016;68(4):258–67.

68. Jia X, Pakseresht M, Wattar N, Wildgrube J, Sontag S, Andrews M, et al. Women who take n-3 long-chain polyunsaturated fatty acid supplements during pregnancy and lactation meet the recommended intake. Appl Physiol Nutr Metab 2015;401-8. 2015;8(August 2014):1–8.

69. Hautero U, Laakso P, Linderborg K, Niinivirta K, Poussa T, Isolauri E, et al. Proportions and concentrations of serum n-3 fatty acids can be increased by dietary counseling during pregnancy. Eur J Clin Nutr [Internet]. 2013;67(11):1163–8. Available from: http://dx.doi.org/10.1038/ejcn.2013.169

70. Wilson NA, Mantzioris E, Middleton PF, Muhlhausler BS. Influence of sociodemographic, lifestyle and genetic characteristics on maternal DHA and other polyunsaturated fatty acid status in pregnancy: A systematic review.

Prostaglandins Leukot Essent Fat Acids. 2020;152(August 2019).

71. Niinivirta K, Isolauri E, Laakso P, Linderborg K, Laitinen K. Dietary counseling to improve fat quality during pregnancy alters maternal fat intake and infant essential fatty acid status. J Nutr. 2011;141(7):1281–5.

72. Velzing-Aarts F V., Van Der Klis FRM, Van Der Dijs FPL, Van Beusekom CM, Landman H, Capello JJ, et al. Effect of three low-dose fish oil supplements, administered during pregnancy, on neonatal long-chain polyunsaturated fatty acid status at birth. Prostaglandins Leukot Essent Fat Acids. 2001;65(1):51–7.

73. Leventakou V, Roumeliotaki T, Martinez D, Barros H, Brantsaeter AL, Casas M, et al. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. Am J Clin Nutr. 2014;99(3):506–16.

74. Middleton P, Jc G, Jf G, Shepherd E, Sf O, Makrides M. Omega-3 fatty acid addition during pregnancy (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. 2018;(11).

75. Starling P, Charlton K, McMahon AT, Lucas C. Fish intake during pregnancy and foetal neurodevelopment-A systematic review of the evidence. Nutrients. 2015;7(3):2001–14.

76. Normia J, Niinivirta-Joutsa K, Isolauri E, Jääskeläinen SK, Laitinen K. Perinatal nutrition impacts on the functional development of the visual tract in infants. Pediatr Res [Internet]. 2019;85(1):72–8. Available from: https://doi.org/10.1038/s41390-018-0161-2

77. Best, Gold, Kennedy, Martin M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. Am J Clin Nutr. 2016;128–43.

78. Vahdaninia M, Mackenzie H, Dean T, Helps S. ω-3 LCPUFA supplementation during pregnancy and risk of allergic outcomes or sensitization in offspring: A systematic review and meta-analysis. Ann Allergy, Asthma Immunol. 2019;122(3):302-313.e2.
79. Zhang GQ, Liu B, Li J, Luo CQ, Zhang Q, Chen JL, et al. Fish intake during pregnancy or infancy and allergic outcomes in children: A systematic review and meta-analysis. Pediatr Allergy Immunol. 2017;28(2):152–61.
80. Sánchez-Hernández D, Anderson GH, Poon AN, Pannia E, Cho CE, Huot PSP, et al. Maternal fat-soluble vitamins, brain development, and regulation of feeding behavior: an overview of research. Nutr Res. 2016;36(10):1045–54.
81. Borge TC, Aase H, Brantsæter AL, Biele G. The importance of maternal diet quality during pregnancy on cognitive and behavioural outcomes in children: A systematic review and meta-analysis. BMJ Open. 2017;7(9):1–14.
82. Patel JK RA. Infant Nutrition Requirements and Options. In: StatPearls [Internet]. Updated 20. Treasure Island (FL): StatPearls Publishing LLC; 2021.
83. Butte NF. Energy requirements of infants. Publich Heal Nutr. 2005;8(7a):953–67.
84. Uauy R, Dangour AD. Fat and fatty acid requirements and recommendations for infants of 0-2 years and children of 2-18 years. Ann Nutr Metab. 2009;55(1–3):76–96.
85. Makrides, M; Neumann, MA, Byard, RW, Simmer, K, Gibson R. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr. 1994;60(2):189–94.
86. Birch EE, Castan YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR, et al. Visual maturation of term infants fed long-chain polyunsaturated fatty acid –

supplemented or control formula for 12 mo 1 – 3. 2005;(1).

87. Sauerwald UC, Fink MM, Demmelmair H, Schoenaich P V., Rauh-Pfeiffer AAM, Koletzko B. Effect of different levels of docosahexaenoic acid supply on fatty acid status and linoleic and α-linolenic acid conversion in preterm infants. J Pediatr Gastroenterol Nutr. 2012;54(3):353–63.

88. Gibson RA, Neumann MA, Makrides M. Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. Eur J Clin Nutr. 1997;51(9):578–84.

89. Barceló-Coblijn G, Murphy EJ. Alpha-linolenic acid and its conversion to longer chain n-3 fatty acids: Benefits for human health and a role in maintaining tissue n-3 fatty acid levels. Prog Lipid Res [Internet]. 2009;48(6):355–74. Available from: http://dx.doi.org/10.1016/j.plipres.2009.07.002

90. Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. Proc Natl Acad Sci U S A. 1993;90(3):1073–7.

91. Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N. The essentiality of arachidonic acid in infant development. Nutrients. 2016;8(4).

92. Hermoso M, Tabacchi G, Iglesia-Altaba I, Bel-Serrat S, Moreno-Aznar LA, García-Santos Y, et al. The nutritional requirements of infants. Towards EU alignment of reference values: The EURRECA network. Matern Child Nutr. 2010;6(SUPPL. 2):55–83.

93. Haschke F, Haiden N, Detzel P, Yarnoff B, Allaire B, Haschke-Becher E. Feeding patterns during the first 2 years and health outcome. Ann Nutr Metab. 2013;62(SUPPL. 3):16–25.

94. de Waard M, Brands B, Kouwenhoven SMP, Lerma JC, Crespo-Escobar P, Koletzko B, et al. Optimal nutrition in lactating women and its effect on later health of offspring: A systematic review of current evidence and recommendations (EarlyNutrition project). Crit Rev Food Sci Nutr [Internet]. 2017;57(18):4003–16. Available from: https://doi.org/10.1080/10408398.2016.1158149

95. Chmielewska A, Dziechciarz P, Gieruszczak-Białek D, Horvath A, Pieścik-Lech M, Ruszczyński M, et al. Effects of prenatal and/or postnatal supplementation with iron, PUFA or folic acid on neurodevelopment: Update. Br J Nutr. 2019;122(s1):S10–5.

96. Mf D, Ja C, X BC, Ep K, Delgado-noguera MF, Calvache JA, et al. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development (Review) Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for impro. 2015;(7).

97. Shulkin M, Pimpin L, Bellinger D, Kranz S, Fawzi W, Duggan C, et al. n–3 Fatty Acid Supplementation in Mothers, Preterm Infants, and Term Infants and Childhood Psychomotor and Visual Development: A Systematic Review and Meta-Analysis. J Nutr [Internet]. 2018;148(3):409–18. Available from: https://academic.oup.com/jn/article/148/3/409/4930799

98. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr. 2013;98(2):403–12.

99. Guesnet P, Alessandri JM. Docosahexaenoic acid (DHA) and the developing central nervous system (CNS) - Implications for dietary recommendations.

Biochimie [Internet]. 2011;93(1):7–12. Available from: http://dx.doi.org/10.1016/j.biochi.2010.05.005

100. Lepping RJ, Honea RA, Martin LE, Liao K, Choi IY, Lee P, et al. Long-chain polyunsaturated fatty acid supplementation in the first year of life affects brain function, structure, and metabolism at age nine years. Dev Psychobiol. 2019;61(1):5–16.
101. Jasani B, Simmer K, Patole SK, Rao SC. Long chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev. 2017;2017(3).
102. Lee H, Padhi E, Hasegawa Y, Larke J, Parenti M, Wang A, et al. Compositional dynamics of the milk fat globule and its role in infant development. Front Pediatr. 2018;6(October).
103. Leghi GE, Middleton PF, Netting MJ, Wlodek ME, Geddes DT, Muhlhausler BS. A Systematic Review of Collection and Analysis of Human Milk for Macronutrient Composition. 2020;1–19.
104. Bravi F, Wiens F, Decarli A, Dal Pont A, Agostoni C, Ferraroni M. Impact of maternal nutrition on breast-milk composition: A systematic review. Am J Clin Nutr. 2016;104(3):646–62.
105. Samuel TM, Zhou Q, Giuffrida F, Munblit D, Verhasselt V, Thakkar SK. Nutritional and Non-nutritional Composition of Human Milk Is Modulated by Maternal, Infant, and Methodological Factors. Front Nutr. 2020;7(September).
106. Rudolph MC, Young BE, Jackson KH, Krebs NF, Harris WS, MacLean PS. Human Milk Fatty Acid Composition: Comparison of Novel Dried Milk Spot Versus Standard Liquid Extraction Methods. J Mammary Gland Biol Neoplasia [Internet]. 2016;21(3–4):131–8. Available from:

http://dx.doi.org/10.1007/s10911-016-9365-4

107. Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr. 2007;85(6):1457–64.
108. Salem N, Van Dael P. Arachidonic acid in human milk. Nutrients. 2020;12(3).
109. Ganesan B, Brothersen C, McMahon DJ. Fortification of Foods with Omega-3 Polyunsaturated Fatty Acids. Crit Rev Food Sci Nutr. 2014;54(1):98–114.
110. Fleddermann M, Demmelmair H, Grote V, Nikolic T, Trisic B, Koletzko B. Infant formula composition affects energetic efficiency for growth: The BeMIM study, a randomized controlled trial. Clin Nutr [Internet]. 2014;33(4):588–95. Available from: http://dx.doi.org/10.1016/j.clnu.2013.12.007
111. Hautero U, Poussa T, Laitinen K. Simple dietary criteria to improve serum n-3 fatty acid levels of mothers and their infants. Public Health Nutr [Internet]. 2016;1–8. Available from: http://www.journals.cambridge.org/abstract_S136898001600238X
112. Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al. Complementary Feeding. J Pediatr Gastroenterol Nutr [Internet]. 2017;64(1):119–32. Available from: http://insights.ovid.com/crossref?an=00005176-201701000-00021
113. Mize CE, Uauy R, Kramer R, Benser M, Allen S, Grundy SM. Lipoprotein-cholesterol responses in healthy infants fed defined diets from ages 1 to 12 months: Comparison of diets predominant in oleic acid versus linoleic acid, with parallel observations in infants fed a human milk- based diet. J Lipid Res. 1995;36(6):1178–87.
114. De Fluiter KS, Van Beijsterveldt IALP, Breij LM, Acton D, Hokken-Koelega

ACS. Association between Fat Mass in Early Life and Later Fat Mass Trajectories. JAMA Pediatr. 2020;174(12):1141–8.

115. Schwartz J, Dube K, Alexy U, Kalhoff H, Kersting M. PUFA and LC-PUFA intake during the first year of life: Can dietary practice achieve a guideline diet. Eur J Clin Nutr. 2010;64(2):124–30.
116. Libuda L, Mesch CM, Stimming M, Demmelmair H, Koletzko B, Warschburger P, et al. Fatty acid supply with complementary foods and LC-PUFA status in healthy infants: results of a randomised controlled trial. Eur J Nutr. 2016;55(4):1633–44.
117. Öhlund I, Hörnell A, Lind T, Hernell O. Dietary fat in infancy should be more focused on quality than on quantity. Eur J Clin Nutr. 2008;62(9):1058–64.
118. Krzeczkowski JE, Boylan K, Arbuckle TE, Muckle G, Poliakova N, Séguin JR, et al. Associated with Autonomic Nervous System Function in 6-Month-Old Offspring. 2019;(11).
119. Tahir MJ, Haapala JL, Foster LP, Duncan KM, Teague AM, Kharbanda EO, et al. Higher maternal diet quality during pregnancy and lactation is associated with lower infant weight-for-length, body fat percent, and fat mass in early postnatal life. Nutrients. 2019;11(3):1–14.
120. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:36–44.
121. Codagnone MG, Spichak S, O'Mahony SM, O'Leary OF, Clarke G, Stanton C, et al. Programming Bugs: Microbiota and the Developmental Origins of Brain Health and Disease. Biol Psychiatry. 2019;85(2):150–63.
122. Mesa MD, Loureiro B, Iglesia I, Gonzalez SF, Olivé EL, Algar OG, et al. The evolving microbiome from pregnancy to early infancy: A comprehensive

review. Nutrients. 2020;12(1):1–21.

123. Fitzstevens JL, Smith KC, Hagadorn JI, Caimano MJ, Matson AP, Brownell EA. Systematic Review of the Human Milk Microbiota. Nutr Clin Pract [Internet]. 2017;32(3):354–64. Available from: http://journals.sagepub.com/doi/10.1177/0884533616670150

124. Mokkala K, Houttu N, Cansev T, Laitinen K. Interactions of dietary fat with the gut microbiota: Evaluation of mechanisms and metabolic consequences. Clin Nutr. 2019;39:994–1018.

FIGURE CAPTIONS

Figure 2.1. Energy and nutrient requirements during pregnancy, breastfeeding and infancy are driven by metabolic needs due to the growth and development of the foetus and infant as well as the process of maternal tissue deposition. These needs are supplied by the maternal and infant diet but also by maternal nutrient stores laid down before pregnancy and during the anabolic phases of the pregnancy.

Figure 2.2. The main maternal metabolic adaptations occurring in pregnancy (see text for details). LPL = lipoprotein lipase, TAG = triglycerides, VLDL = very low density lipoprotein, NEFA = nonesterified fatty acids.