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Highlights

- Changes in the *in utero* environment, due to insufficient or excessive maternal nutrient intake have short and long-term implications
- Numerous rodent studies have examined the effects of maternal high-fat diet consumption on the susceptibility of metabolic diseases in the offspring
- Evidence from human studies regarding the effects of saturated or trans fat intake is limited

Maternal Fats and Pregnancy Complications: Implications for Long-term Health

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Abstract

Pregnancy imposes increased nutritional requirements for the well being of the mother and fetus. Maternal lipid metabolism is critical for fetal development and long-term health of the offspring as it plays a key role in energy storage, tissue growth and cell signaling. Maternal fat composition is considered as a modifiable risk for abnormal lipid metabolism and glucose tolerance during pregnancy. Data derived from observational studies demonstrate that higher intake of saturated fats during pregnancy is associated with pregnancy complications (preeclampsia, gestational diabetes mellitus and preterm delivery) and poor birth outcomes (intra uterine growth retardation and large for gestational age babies). On the other hand, prenatal long chain polyunsaturated fatty acids status is shown to improve birth outome. In this article, we discuss the role of maternal lipids during pregnancy on fetal growth and development and its consequences on the health of the offspring.

Key words: Developmental origins of health and disease, fatty acids, fetal development, gestational diabetes mellitus, lipids, nutrition, preeclampsia, preterm

Introduction

Pregnancy is a critical period during which the diet consumed by the mother can influence the health of both the mother and child. In recent years, there is a growing interest in examining factors which influence fetal growth as accumulating evidence suggests that adult non-communicable diseases (NCDs) have their origin in prenatal life and in early childhood [1,2]. Maternal obesity and pregnancy complications like gestational diabetes mellitus (GDM) and preeclampsia are early life risk factors associated with adverse birth outcomes such as impaired fetal growth and preterm birth [3,4]. The mothers diet and metabolism during pregnancy influences fetal development and are implicated in programming of adult diseases [5]. Maternal nutrition during pregnancy thus provides a "window of opportunity" to improve the health of the mother for the benefit of the offspring [6].

Over the past decades, research has focused on the role of fats due to their critical role in the fetal growth and development. It is suggested that both the quality and quantity of dietary fats during the prenatal period and in early childhood are the major determinants of fetal and infant growth and also influence the long-term health of the offspring. A recent review discusses a link between excessive or insufficient consumption of a specific nutrient and developmental programming of a variety of NCDs [7]. Among various nutrients, fat content of the diet plays a critical role in developmental programming since are involved in optimal growth and development of the fetus.

This article describes importance of fats during pregnancy and their role in fetal growth and development. Consequences of inadequate or excess fat intake on the long-term health outcomes of the offspring are also discussed.

1. Maternal Nutrition and Developmental Origins of Health and Disease

It is well known that the intrauterine environment can alter key developmental processes and have long lasting consequences on health and disease. A variety of terms have been used to describe this phenomenon such as fetal origins of disease (FOAD) and fetal beginnings of adult disease and mainly focuses on the intrauterine exposures leading to diseases later in life. In 2002, the term FOAD was expanded to "Developmental Origins of Health and Disease" (DOHaD). This concept is well associated with Late Prof. David Barker when he and his colleagues in 1993 first reported an association of low birth-weight as a result of adverse intrauterine environment with increased risk for diseases later in life, and this concept is also referred to as Barker's Hypothesis. The DOHaD concept hypothesizes the existence of mechanisms by which a 'memory' of the early life environment is retained into later life.

The DOHaD theory proposes that any environmental stimuli at critical periods of development increaes the risk of NCDs in adulthood due to changes in biological functions [8]. This hypothesis has been supported by a large number of epidemiological and animal studies. Today, the major focus of a number of studies has been in understanding the possible association between maternal nutrition, the primary environmental factor that influences fetal development and subsequent risk of postnatal disease.

The embryonic and fetal development at every stage is influenced by the nutrient supply from the mother. Any variation during these critical stages of development is associated with disease related outcomes in the offspring. These adaptations, known as 'programming' are associated with changes in fetal structure and/or function which may further increase the risk for non-communicable diseases [9]. Various studies have shown that exposure to suboptimal nutrition *in utero* (both under or over-nutrition) and during the first 2 years of life has a strong influence on an individual's predisposition to develop metabolic

diseases later in life [10, 11]. An imbalance or alterations in the fatty acid supply *in utero* is reported to change the fatty acid composition of membrane phospholipids, which can cause structural and functional alterations in cells [12]. Altered dietary fat composition during specific periods of pregnancy can affect maternal fatty acid profiles and their availability to the fetus [13]. It has also been reported that any disturbance in lipid metabolism both in the maternal and/or placental compartments may contribute to neonatal fat accretion and predispose the progeny to obesity and metabolic diseases [14].

2. Lipids

Lipids are important constituents of the diet and are required by the body for various biological functions such as storing energy, signaling, and acting as structural components of cell membranes. Lipids circulate in the blood stream as lipoproteins which are globular or spherical structures with nonpolar core lipid that mainly consists of cholesterol esters and triglycerides and is surrounded by an amphophilic layer that consists of phospholipids, apoproteins, and small amounts of unesterified cholesterol. The transport of lipid through plasma occurs by two pathways; an exogenous pathway which involves transport of cholesterol and triglycerides from dietary fat in the intestine, and an endogenous pathway for the transport of cholesterol and triglycerides from the liver and other nonintestinal tissues to the plasma.

2.1 Cholesterol

Cholesterol is an important structural component of all cell membranes and plays a crucial role in maintaining the integrity of cell membranes and faciltating membrane associated cell signaling. During pregnancy, cholesterol is involved in the signaling pathways that are essential for growth, proliferation and metabolism. Cholesterol is also required for

embryonic and fetal development as it activates the sonic hedgehog proteins and important nuclear receptors that are involved in brain development.

2.2 Triglycerides

During pregnancy, maternal plasma levels of triglyceride are known to increase as an adaptation to maternal and fetal requirements. Studies have shown that during pregnancy the triglyceride levels in women with hyperglycaemia are associated with increased birth weight [15,16]. Disturbances in maternal lipid metabolism are shown to be associated with various kinds of adverse pregnancy outcomes (eg. preeclampsia, gestational diabetes mellitus, and preterm delivery) [17,18].

Lower levels of maternal triglycerides and total cholesterol during pregnancy are linked with delayed prenatal growth and an increased risk of the infant to be born small for gestational age (SGA) [19,20]. A study by Liang et al reports the association of higher maternal triglyceride levels at first trimester with the increased risk of large for gestational age infant in non-obese pregnant women [21]. Higher levels of maternal cholesterol during pregnancy are associated with increased risks of preterm delivery, GDM and preeclampsia, as well as development of atherosclerosis in offspring in later life [22].

2.3 Phospholipids

Phospholipids are the fundamental components and most abundant lipids of all cell membranes. They are complex lipids having structural and functional properties that differentiate them from their counterparts, triacylglycerides. Phospholipids form bilayers with the hydrophobic tails towards the interior of the membrane and the polar head groups exposed on both sides thereby forming a stable barrier between two aqueous compartments and represent the basic structure of all biological membranes. The variation in the length and saturation of the fatty acid tails are important as they regulate the fluidity of the membrane.

The fatty acid composition of the diet directly determines fatty acid composition of phospholipids. The plasma phospholipid fatty acid content may be characterized as the "functional" lipid pool as it reflects the cell membrane phospholipids. Four major structural lipids that predominate in the plasma membrane are phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and sphingomyelin. The structural diversity in each type is due to the differences in the head group, differences in the chain length and degree of saturation of the fatty acid. Phospholipids play an important role in providing saturated and unsaturated fatty acids for carrying out various cellular functions.

2.4 Apolipoproteins

Apolipoproteins are amphipathic in nature, capable of interacting with both the lipids of the lipoprotein core and the aqueous environment of the plasma. They are the proteins associated with lipoprotein particles that play a key role in the transport of cholesterol, triglycerides, phospholipids, and fat-soluble vitamins between the intestine, liver, and peripheral tissues. Multiple apolipoproteins are present on the surface of the lipoprotein particle and synthesized in the liver and intestine. All tissues can degrade apolipoproteins, but the majority of them degraded in the liver. During pregnancy, it is known to contribute to hyperlipidemia by modulating lipid homeostasis in maternal plasma [23]. However, an increased hyperlipidemia and peripheral apolipoprotein levels are associated with inflammation and complications [24].

2.5 Fatty Acids

Fatty acids are involved in the regulation of membrane structure and function, intracellular signalling, gene expression, and production of bioactive lipid mediators. During pregnancy, long chain polyunsaturated fatty acids (LCPUFA) such as arachidonic acid (AA) and docosahexaenoic acid (DHA), are critical to fetal and infant central nervous system

growth and development. The fatty acid levels in maternal blood lipids serve as indicators of maternal status as well as the immediate source of fatty acids for transport to the fetus [25]. Maternal, fetal and neonatal LCPUFA status are key determinants of health and disease in infancy and later in life.

3. Lipid Metabolism

The liver plays a key role in lipid metabolism. Lipid metabolism consists of catabolic processes that generate energy and primary metabolites of fatty acids and anabolic processes that create biologically important molecules from fatty acids and other dietary sources. Lipogenesis or fatty acid synthesis is the process by which fatty acids are synthesized from end products of glucose catabolism. It is a central event in lipid metabolism and these fatty acids in the cells can either be used for the synthesis of lipid moieties (triacylglycerol and cholesterol esters) or can undergo β-oxidation to produce energy.

3.1 Lipid Metabolism during Pregnancy

In pregnancy, lipids primarily provide energy to support the maternal energy needs as glucose supply is shunted to support fetal growth. There are two major changes that occur during pregnancy. During early pregnancy, fatty acids consumed through diet are accumulated and stored in the adipose tissue as a result of enhanced lipogenesis. This increases plasma triacylglycerol concentrations, with smaller increase in phospholipids, cholesterol and non-esterified fatty acids [26,27]. The major component involved in increase in plasma triglycerides corresponds to VLDL. Higher concentrations of VLDL-triglyceride is either due to their increased synthesis in the liver and/or due to decreased lipoprotein lipases activity. Accelerated transfer of triglycerides to lipoproteins of high density is due to increased activity of cholesteryl ester transfer protein. These changes contribute to accumulation of triglycerides during pregnancy.

Subsequently in the later stage of pregnancy, when the fetal growth rate is maximum, there is increased lipolytic activity in the maternal adipose tissue. During this transition from anabolic to catabolic state, maternal tissue lipids are used to fulfill maternal energy needs, whereas glucose and amino acids are utilized for the fetal growth [27]. Similar to esterified fatty acids, LCPUFA in maternal circulation are associated with plasma lipoproteins like phospolipids, triglycerides and esterified cholesterol. There is mobilization of LCPUFA from the maternal adipose tissue depots and selective delivery of maternal circulating LCPUFAs to the fetus through the placenta [26].

3.2 Maternal Lipids and Fetal Development

Maternal triglycerides and cholesterol are essential for the optimal development of the fetus. Increased levels of these two lipids during pregnancy indicate their significance in maintenance of pregnancy and fetal growth. These lipids are taken up by the placenta, metabolized and transported to the fetus in various forms.

Maternal cholesterol is used in the placenta for building cell membranes and also serve as precursor of bile acids and steroid hormones for the fetal development. It is required for cell proliferation, cell differentiation and cell to cell communication. Placental endothelial cells transport substantial amounts of cholesterol from the mother to fetus. Additionally, cholesterol can also be synthesized endogenously which serves as an important source of fetal cholesterol. Free fatty acids are oxidized in the maternal liver as ketone bodies, which are used as an alternative fuel for the fetus.

The fetus needs to obtain both essential fatty acids and their derivatives, LCPUFA from the mother. These fatty acids are mainly carried in the maternal plasma in their esterified form and are associated with the different lipoproteins. As maternal lipoproteins do not cross the placenta directly, activity of lipoprotein lipases, various lipoprotein receptors

and fatty acid binding proteins facilitate efficient transfer of maternal LCPUFA to the fetus. Studies report a significant correlations between maternal and fetal levels of omega-3 fatty acids [28].

Observational studies in humans have demonstrated a significant relationship between maternal lipid concentrations with placental weight, neonatal size and neonatal body composition [29,30]. Maternal lipid concentrations are shown to be related to newborn size in normoglycemic, undernourished Indian women [31]. In pregnancies complicated by intrauterine growth restriction, impaired placental transfer of LCPUFA and lipophilic vitamins is associated with decreased birth weight and metabolic dysfunction. In GDM pregnancies, maternal triglyceride and NEFA levels are correlated with anthropometric measures of neonates [32]. Evidence suggests that dietary lipid intake during early pregnancy modulates lipid metabolism in the fetus [33]. Maternal fasting triglyceride levels are significant predictors of the fatty acid composition in the muscle membrane of the child [34]. Rodent studies indicate that maternal calorie restriction or consumption of high-fat foods is associated with perturbed glucose and lipid metabolism in the offspring [35,36]. It is suggested that metabolic set points of lipid metabolism are determined prenatally and have long term consequences in the offspring in later life [37].

4 Maternal Fat Intake/ Status and Pregnancy Complications

4.1 Trans Fat / high-fat diet Intake:

Trans fatty acids (formed by partial hydrogenation of vegetable oils) are associated with higher serum concentrations of cholesterol, triglyceride and lipoproteins [38]. Women in the highest tertile of trans fatty acids (elaidic acid) are reported to have a 7.4 fold greater risk of preeclampsia compared to women in the lowest tertile [39]. A study from Zimbabwe reports a strong positive association of erythrocyte trans fatty acids, particularly diunsaturated

trans fatty acids, with the risk of preeclampsia [40]. In contrast, two prospective cohort studies from Denmark and USA report no relationship between trans fat intake during pregnancy and risk of developing preeclampsia [41,42]. It has been reported that a high fat diet consumption induces preeclampsia like syndromes in pregnant rats by altering lipid metabolism [43].

Saturated fats have an independent role in the development of gestational hyperglycaemia [44]. Various cross sectional and prospective studies suggest that high maternal intakes of total fat [45], diets rich in red and processed meat and diets with high glycaemic load [46] lead to glucose abnormalities which in turn increases the risk of developing glucose intolerance and GDM. Maternal intake of high fat diet during pregnancy is known to affect metabolic parameters in mothers in rats [47].

A case control study from China suggests that women delivering preterm have a lower level of fats and vitamin E and lower energy than women delivering at term [48]. Similarly, a lower saturated fatty acid intake was reported in women giving preterm birth [49]. These studies indicate that an optimal intake of dietary fat is important in preventing preterm births.

4.2 Polyunsaturated fat Intake

A higher maternal intake of the omega-3 fatty acids particularly DHA and eicosapentaenoic acid (EPA) is associated with a lower risk of preeclampsia [42]. A recent study in Danish women reported that higher intake of DHA is inversely related to preeclampsia while alpha-linolenic acid (ALA) was found to increase the risk of severe preeclampsia [50]. Increased polyunsaturated fat intake is associated with a reduced incidence of glucose intolerance during pregnancy [51].

There are conflicting data regarding the impact of omega-3 fatty acids on the length of gestation. A number of randomized controlled trials (RCTs) have demonstrated that the maternal seafood or DHA intake during pregnancy can prolong high risk pregnancies, reduce early preterm delivery and improve birth outcome [52,53]. Fish oil supplementation from 19 weeks of gestation till delivery was shown to be associated with an increased rate of postterm births [54]. On the other hand, some studies report that omega-3 fatty acid supplementation is not associated with risk of preeclampsia, GDM, preterm birth and intrauterine growth restriction [55-57].

5 Maternal fat intake/ status and pregnancy outcome

The quantity and quality of dietary fat during pregnancy plays a key role in the growth and development of the fetus. It has been suggested that maternal fatty acid intake during pregnancy and lactation is associated with fetal and postnatal development.

5.1 Human studies

A study in South Indian population reports that higher intake of saturated fatty acids (milk and milk products) in early stages of pregnancy improves birth weight, and reduces the incidence of SGA babies [58]. Intake of monounsaturated fatty acids during pregnancy is reported to have beneficial effects on birth outcome. A study by Ogundipe et al. have shown that higher maternal monounsaturated fatty acids are associated with preterm birth and low birth weight [59].

Maternal omega-6 fatty acid intake is shown to be inversely associated with birth weight and fetal growth [60-62]. It has been reported mothers with a low intake of alpha linolenic acid acid deliver SGA babies [58]. Pregnant women who consume a Western diet containing high omega-6 fatty acids are reported to give birth to SGA babies [63]. Our earlier study reports higher levels of total omega-6 fatty acids and AA in maternal

erythrocytes in mothers delivering LBW babies (< 2.5 kg) than those whose newborns weighed more than 2.5 kg [64].

A population based cohort study of multiparous pregnant women reported that low plasma phospholipid concentrations of EPA, DHA and dihomo-γ-linolenic acid (DGLA) while high concentrations of AA during early pregnancy are associated with reduced birth weight and an increased risk of SGA infants [61]. Maternal DHA content in early pregnancy is shown to be positively associated with birth weight and head circumference while AA and DGLA were negatively associated with birth weight and length [65]. Low intakes of ALA as well as omega-3 fatty acids while high intakes of LA are shown to be associated with increased risk of SGA infants [58].

Intrauterine growth restriction (IUGR) is reported to be associated with impaired placental development, structure and morphology, which in turn alter placental function and capacity of delivering nutrients to the fetus. It is suggested that the size, morphology, and nutrient transfer capacity of the placenta determine the prenatal growth trajectory of the fetus to influence birth weight [66]. Reports suggest alterations in the lipid profile in maternal and cord blood in IUGR pregnancies [67,68]. Lower proportions of AA and DHA in fetal blood in comparison with maternal blood have been reported in pregnancies complicated by IUGR which could be possibly due to inadequate trans-placental supply [69]. Reduced placental lipoprotein lipase activity and placental fatty acid binding protein expression in IUGR pregnancies indicates disrupted lipid metabolism in these pregnancies [70]. A recent study reported that fatty acid transport protein (FATP6) and CD36 protein expression is increased in the IUGR placenta, compared to appropriate for gestational age placenta suggesting that there exists a regulatory response to maintain fatty acid delivery to the fetus [71]. Our earlier cross sectional human studies have extensively demonstrated lower maternal and placental

levels of DHA in women delivering low birth weight babies and altered placental expression of transcription factors involved in the fatty acid metabolism [64, 72].

5.2 Animal studies

Several animal studies have demonstrated that maternal consumption of high fat diet leads to higher pregnancy weight gain, lower litter size and higher litter weights and fetal resorptions [73-75]. In contrast, no effect on pregnancy outcome is reported as a consequence of feeding a high fat diet during pregnancy [76-78].

Supplementation of maternal diet with olive oil (rich in MUFA) in the first half of gestation is reported to reduce the incidence of LBW in piglets [79]. In contrast, Priego et al. found that maternal supplementation with olive oil from day 14 of pregnancy to day 20 of lactation decreased body weight gain of the dams [80]. Fish-oil supplementation in the third trimester is reported to prolong length of getstation without adverse effects on the fetal growth or on the course of labour [81]. In contrast, no association between maternal omegs-3 fatty acids at gestational week 24 with fetal weight gain is reported [82].

6. Intervention/ Supplementation with Omega-3 Fatty Acids during Pregnancy and Birth Outcome

LCPUFA requirement of the fetus is fulfilled by preferential placental transfer of preformed LCPUFA from mother. During the third trimester of pregnancy, DHA accumulation increases as it is required for the developing brain and retina. It is suggested that additional maternal supply of omega- 3 fatty acids, especially DHA, during pregnancy may improve maternal and infant outcomes.

Some RCTs report that 600 mg DHA/d [83], 800 mg DHA/d [54] and 135 mg DHA/egg/d [84] significantly increase length of gestation. A daily dose of 600 mg of DHA has been shown to increase the percent of DHA in red cell phosphatidylethanolamine during

delivery in women with type 2 diabetes mellitus and in their neonates [85]. On the other hand, 400 mg DHA/d supplementation showed no effect on the gestation duration [86].

Findings of randomised controlled trials indicate that maternal omega-3 fatty acid supplementation of 2.7 g/d can increase birth weight by 50 g [87] while DHA supplementation of 600 mg/d can increase birthweight by 172 g [83]. A recent meta-analysis on the effects of omega-3 fatty acid supplementation during pregnancy and lactation period revealed that it can improve birth weight but not length. It also reports improvement in postnatal waist circumference, but no influence on postnatal BMI, skinfolds, fat mass and body fat percentage of the children during postnatal period [88].

7. Consequences of Maternal Lipid Inadequacy/ Excess on Cardio-metabolic Outcomes of the Offspring

The quality and quantity of dietary fat supply during the prenatal period and in early childhood is a major determinant of fetal growth and long-term health of the offspring. Two prospective studies examining the effect of maternal high fat intake during pregnancy on offspring body composition report that infant adiposity is independently associated with increased maternal intake of high fat diet [89,90]. A prospective study with 20 years of follow-up examined the effects of maternal fat intake on the metabolic health of offspring and stated that maternal high fat intake increases adiposity in boys at adult age but has no effect on anthropometry of girl children [91].

Animal studies demonstrate that maternal feeding of high fat diet during pregnancy and lactation leads to higher body weight, adiposity [92,93], increased fat mass, hyperleptinemia, and dyslipidemia [94], hypercholesterolemia [95], obesity, adrenal and thyroid dysfunction [96], and hepatic triglyceride accumulation and oxidative stress [97]. It also reported to cause mitochondrial abnormalities and impaired glucose homeostasis [98],

insulin resistance and fatty liver [99], increased blood pressure [100] and cardiac hypertrophy [101] in the adult offspring.

Fat and carbohydrate intake over three generations is shown to alter growth and metabolism and induce cardiovascular dysfunction in female mice [102]. These rodent models consistently show that offspring born to dams fed a high fat diet exhibit metabolic abnormalities that closely resembles human metabolic syndrome.

RCTs on omega-3 fatty acid supplementation in pregnancy and/or during lactation have shown diverging results on cardiometabolic risk factors. Prenatal DHA supplementation is reported to have no effect on height, weight, or BMI in children at 5 yrs of age [103]. Fish oil supplementation from the second trimester of pregnancy is reported to increase BMI in the offspring from 0 to 6 yrs of age but did not increase obesity at 6 yrs of age [104]. Higher PUFA intake (EPA, DHA and AA) during mid-pregnancy was shown to be associated with lower BMI and z score of height in offspring during peripuberty [105]. A study showed that maternal intake ratio of omega-6:omega-3 fatty acids has a U-shaped association with obesity wherein AA: DHA+EPA ratio is positively associated with obesity in boys but not in girl children [106]. In contrast, no association between maternal intake of omega-3 fatty acids during mid-pregnancy with cardiometabolic risk factors in the children at 20 yrs is reported [107]. The findings of the above studies indicate that although most of the studies highlight beneficial effects of maternal omega-3 fatty acid intervention or prenatal DHA status in reducing incidences or severity of pregnancy complications, other factors such as socio-economic background and life-style should also be considered as they can influence these outcomes.

Animal studies have shown that maternal and post-weaning diet containing fish oil or omega-3 fatty acids lower total cholesterol and triglyceride levels [108,109], decrease liver steatosis [110] and improve insulin sensitivity in the offspring [111,112] when compared to

offspring born to dams fed diets rich in saturated fats, omega-6 fatty acids or diets low in omega-3 fatty acids.

Concluding Remarks

Maternal fat intake during pregnancy in relation to birth outcome and cardiometabolic health of the progeny is well studied in animal models. However, human studies examining the effect of fat intake and risk for pregnancy complications are limited. These studies have mainly focused on 'Western diets", which are high in fat content. The effect of saturated fat intake in a population consuming a relatively low total fat diet is not well elucidated. Dietary patterns are population specific and are also influenced by socio-cultural and lifestyle factors. Hence, there is a need for longitudinal studies in low and middle income countries to better understand the role of fats in pregnancy and their consequence on the offspring health. Such studies will have implications for reducing the risk of pregnancy complications and subsequent burden for non communicable diseases.

Conflict of interest statement

The authors report no conflict of interest.

Author contribution

Amrita Khaire, Nisha Wadhwani, Shweta Madiwale and Sadhana Joshi contributed to writing the manuscript.

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Figure legends

Fig. 1: Maternal supply of lipids: short and long term outcome

NEFA: non-esterified fatty acids, **LPL**:lipoprptein lipases, **TG**:triglycerides, **VLDL**: very low density lipoprotein