EFFECT OF PREGNANCY ON LIPID METABOLISM AND LIPOPROTEIN LEVELS

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ABSTRACT

Lipoprotein lipid physiology in pregnancy has important implications for the developing fetus and newborn as well as the mother. Cholesterol and essential fatty acids are essential for normal fetal development. In pregnancy, multiple physiological changes occur that contribute to the alterations in lipid profiles of healthy, gestating women. Initially, there is an anabolic phase with an increase in lipid synthesis and fat storage in preparation for the increases in fetal energy needs in late pregnancy. During the third trimester, lipid physiology transitions to a net catabolic phase with a breakdown of fat deposits. The catabolism increases substrates for the growing fetus. Overall, the changes in lipid physiology throughout the course of pregnancy allow for proper nutrients for the fetus and they reflect increasing insulin resistance in the mother. In a normal pregnancy, total cholesterol levels increase by approximately 50%, LDL-C by 30-40%, HDL-C by 25%, and triglycerides by 2- to 3-fold. Our understanding and appreciation of the full scope and implications of dyslipidemia in pregnancy on both maternal and fetal outcomes is not complete; however, it is well known that dyslipidemia in pregnancy is associated with adverse pregnancy outcomes affecting both maternal and fetal health. There are direct implications of dyslipidemia on perinatal outcomes as well as intricate relationships between dyslipidemia and other comorbid intrauterine conditions. There is also developing research indicating that the in-utero environment influences susceptibility to chronic diseases later in life, a concept known as “developmental programming.” Given all of these implications of dyslipidemia in pregnancy on maternal and fetal health, it is prudent to screen women for lipid disorders. The ideal time for this is before conception; if a woman has not been screening before pregnancy, the initial obstetrical visit is ideal. Abnormal lipids should be followed through pregnancy. The treatment of dyslipidemia in pregnancy is multifactorial, including diet, exercise, and weight management. Medical management is complicated by FDA classifications for medication risks to the fetus, however some evidence indicates there may be permissible pharmacological treatments for dyslipidemia in pregnancy. In certain instances, plasmapheresis or lipoprotein apheresis can be employed.

INTRODUCTION

Lipoprotein lipid physiology before and during pregnancy has important implications for the mother, the developing fetus, the newborn, and their future health. Cholesterol is important for normal fetal development. It is provided to the fetus via both endogenous and exogenous mechanisms. As our understanding of normal and abnormal lipid metabolism in pregnancy improves, it is clear that

abnormal lipid metabolism reflected as dyslipidemia is associated with adverse perinatal outcomes. Dyslipidemia has profound associations with other pathologies in pregnancy, most notably hypertensive disorders and gestational diabetes. There is accumulating evidence of the impact of hyperlipidemia in pregnancy on the epigenetic programming of a fetus and the subsequent risk for atherogenesis for the mother and her offspring.

CHOLESTEROL AND OTHER LIPIDS IN FETAL DEVELOPMENT

Cholesterol plays a key role in the formation of cell membranes. It is essential for the formation of cell membranes, maintaining membrane integrity, and preserving cholesterol-rich domains essential for most membrane-associated signaling cascades, including sonic hedgehog signaling (1). It is also the precursor for many important hormones, such as steroids, vitamin D, and bile acids.

There are multiple sources of fetal cholesterol. A significant portion is produced de novo by the fetus. Defects affecting cholesterol biosynthesis are associated with many, sometimes lethal, birth defects (2,3). Both endogenous and exogenous sources are important to fetal cholesterol homeostasis, as illustrated by a number of lines of evidence. Cholesterol in the maternal circulation, which similarly has endogenous and exogenous sources, contributes significantly to the fetal cholesterol pool in animals and in humans (4,5). Interestingly, Vuorio and colleagues noted that concentrations of plant stanols in the cord blood of healthy newborns were 40% to 50% lower than the maternal levels (6). Because the plant stanols evaluated can only be derived from the maternal diet, placental transfer is illustrated. Fetuses with null-null mutations of 7-dehydrocholesterol reductase (Smith-Lemli-Opitz syndrome), a disorder characterized by an inability to synthesize endogenous cholesterol at normal rates, have measurable amounts of cholesterol in their bodies. This also illustrates maternal derivation (7,8). The umbilical vein, which carries blood to the fetus, has higher levels of LDL-C than the umbilical artery (9).

For exogenous cholesterol to be available for fetal use, it must be transported across the tissues separating the mother and fetus. Early in pregnancy, the yolk sac is the site of the transport system between the two (10). Approaching 8 weeks of gestation, the placenta becomes fully functional and takes over as the nutrient transporter (10). The transfer of lipids across the placenta and yolk sac under normal and abnormal circumstances is complex and is still incompletely understood. Cholesterol is taken up on trophoblasts' apical or maternal side via receptor-mediated and receptor-independent transport processes. Apolipoprotein lipids are then transported across cellular barriers and delivered into the fetal circulation on the basolateral, or fetal, side of trophoblasts (4,10,11). Cultured trophoblast cells express low-density lipoprotein (LDL) receptors (LDLRs), and LDLR-cholesterol taken up by endothelial cells is well understood. How placental endothelial cells transport and deliver substantial amounts of cholesterol to the fetal microcirculation and regulate the efflux of cholesterol is undergoing intense study.

As opposed to adults, high-density lipoprotein (HDL) is the main cholesterol-carrying lipoprotein in fetal circulation. It differs from adult HDL by its higher proportion of apolipoprotein (Apo) E (12), but lower proportion of Apo A1 (13). The major HDL receptor, scavenger receptor class B type I (SR-BI), contributes to local cholesterol homeostasis. Arterial endothelial cells (ECA) from the human placenta are enriched with cholesterol compared to venous endothelial cells (ECV). Moreover, umbilical venous and arterial plasma cholesterol levels differ markedly. There is elevated SR-BI expression and protein abundance in endothelial cell arteries compared to veins in situ and

in vitro. Immunohistochemistry demonstrated that SR-BI is mainly expressed on the apical side of placental endothelial cells in situ, allowing interaction with mature HDL circulating in the fetal blood (14). This was functionally linked to a higher increase of selective cholesterol ester uptake from fetal HDL in endothelial arteries than in endothelial veins and resulted in increased cholesterol availability in ECA. SR-BI expression on endothelial veins tended to decrease with shear stress, which, together with heterogeneous immunostaining, suggests that SR-BI expression is locally regulated in the placental vasculature (15).

Changes in maternal vasculature enable an increased uterine blood flow, placental nutrient, and oxygen exchange, and subsequent fetal development. Potassium (K+) channels seem to be important modulators of vascular function, promoting vasodilation, inducing cell proliferation, and regulating cell signaling (16). Different types of K(+) channels, such as Ca(2+)-activated, ATP-sensitive, and voltage-gated, have been implicated in the adaptation of maternal vasculature during pregnancy. Conversely, K(+) channel dysfunction has been associated with vascular-related complications of pregnancy, including intrauterine growth restriction and pre-eclampsia. It is thought that vascular ischemia may lead to inflammation important in pregnancy complications. Abnormalities in these pregnancy-associated vascular dilation and remodeling processes are associated with the pregnancy complications of intrauterine growth restriction (IUGR) and pre-eclampsia, in which, the normal vasodilatory effects of acetylcholine (ACh), bradykinin, Nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and thromboxane-mediated responses are impaired (16).

Placental lipid metabolism may influence pregnancy outcomes, fetal growth, development, and life-long health (17). The placenta converts circulating maternal lipids to free fatty acids (FFAs) for uptake and processing by trophoblast cells, for metabolic demands, to produce hormones for pregnancy maintenance, and to transfer them to the developing fetus. Robust lipid uptake and metabolism early in gestation are vital to meeting the high energetic demands needed to simultaneously grow the placenta and develop embryonic organ systems. Late in gestation the human fetus requires lipids for neurodevelopment and growth, so as pregnancy progresses, metabolic adaptations in the mother and placenta uniquely support increasing lipid transport and biomagnification of essential long-chain polyunsaturated fatty acids in the last trimester (18). These fatty acids serve as local mediators of metabolism, inflammation, immune function, platelet aggregation, signal transduction, neurotransmission, and neurogenesis for the developing fetal brain and retina (19). Because these fatty acids cannot be synthesized *de novo*, the fetus relies on increasing placental transport, especially during the last trimester when the peak *in utero* accretion can surpass maternal intake to support rapid fetal brain growth. Placental lipid uptake and metabolism is a critical, highly-regulated, and surprisingly dynamic process as gestation proceeds.

Lipids are crucial structural and bioactive components that sustain embryo, fetal, and placental development, and growth. Intrauterine development can be disturbed by several diseases that impair maternal lipid homeostasis and lead to abnormal lipid concentrations in fetal circulation. Deficiency in essential fatty acids can lead to congenital malformations and visual and cognitive problems in the newborn. Either deficient mother-to-fetus lipid transfer or abnormal maternal-fetal lipid metabolism can cause fetal growth restriction. On the other hand, excessive mother-to-fetus fatty acid transfer can induce fetal overgrowth and lipid overaccumulation in different fetal organs and tissues. The placenta plays a fundamental role in the transfer of lipid moieties to the fetal compartment and is affected by maternal

diseases associated with impaired lipid homeostasis. Studies investigating the relationship between gestational dyslipidemia and small for gestational age (SGA) have reported differing results. A recent meta-analysis found that gestations complicated with lower concentrations of TC, TG, and LDL-C, were at significantly higher risk of delivery of SGA (20). Postnatal consequences may be evident in the neonatal period or later in life. Indeed, both defects and excess of different lipid species can lead to the intrauterine programming of metabolic and cardiovascular diseases in the offspring (21)

NORMAL LIPID CHANGES IN A PREGNANT MOTHER

Figure 1 shows the average values of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) measured in normal women from pre-conception through several months postpartum. These values were from measurements in a cohort of women proceeding through normal pregnancy and delivery in the U.S. Circulating levels may differ depending upon the nutritional environment. It is reported that most lipoprotein concentrations increase throughout pregnancy in Gambian women for example yet are lower vs. U.S. women, the exception being medium-sized LDL and HDL particle concentrations which decrease during gestation and are similar in both cohorts (22). In a careful evaluation of normal pregnant women in Oklahoma traversing through pregnancy and delivering normal viable infants, we found that non-HDL particles, very small highly atherogenic LDL particles (small dense LDL), and total and active pcsk9 levels increase as pregnancies progress (23). BMI, an indicator of obesity, was associated with higher levels of atherogenic lipoproteins during each trimester. Most of the women in the Wiznitzer and Wild cohorts were of young reproductive age at the time of sampling and thus their values overlap values before pregnancy and are considered in the normal range for a nonpregnant woman. In the first trimester, there is a discernible decrease in levels during the first 6 weeks of pregnancy. As pregnancy progresses, there is a noticeable increase by the third month or at the end of the first trimester. There is a steady increase throughout pregnancy. By the third trimester or near the end of pregnancy (term), levels peak (24,25). Levels of lipoprotein particles and lipids, particularly in the later part of pregnancy, are in the atherogenic range when compared to non-pregnant levels in women of comparable ages without medical conditions. After delivery, lipid and lipoprotein levels rapidly return to normal. The changes in lipid metabolism throughout pregnancy allow for proper nutrients for the fetus and the normal, steady increase throughout pregnancy is associated with increased insulin resistance in the mother. Regardless of dietary differences in cholesterol, by late pregnancy, plasma cholesterol levels are approximately 50% higher than routinely seen pre-pregnancy while triglyceride levels are increased 2-3 times (see figure 1 and table 1) (25). These changes can be viewed as important for the enhanced availability of substrates for the fetus (26,27). However, derangements in lipids are associated with adverse pregnancy outcomes and likely are associated with residual vascular damage after some key obstetrical adverse events which may put the mother at risk for later cardiovascular disease.

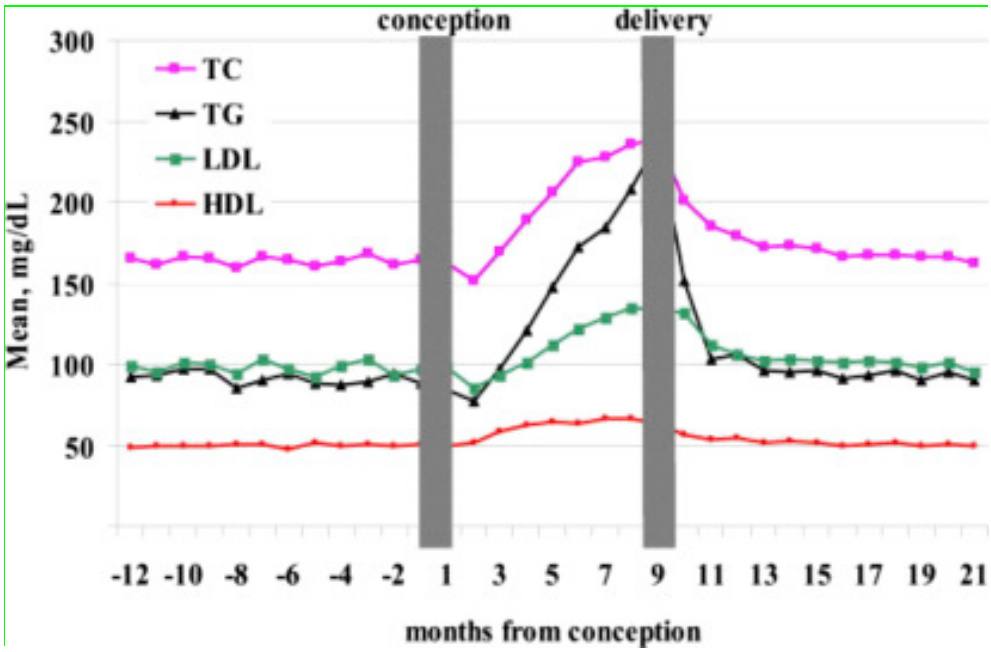

Figure 1. Lipid and Lipoprotein Levels During Pregnancy *(Adapted from* Wiznitzer A, Mayer A, Novack V, et al. Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study. Am J Obstet Gynecol 2009; 201(5):482.e1–8;)

For understanding clinical management including healthy targets, maximum plasma cholesterol values usually do not exceed 250 mg/dL during normal pregnancy, even with the marked increases in triglyceride levels that occur normally as pregnancy progresses. If abnormal pregnancies are included in cross-sectional evaluations, cholesterol levels are commonly 300 mg/dL or higher. Higher levels are consistent with a variety of maternal adverse pregnancy conditions. In normal pregnant women, the atherogenic index, LDL/HDL, remains essentially unchanged during pregnancy. This suggests that while the total lipoprotein levels increase, the cholesterol-containing lipoprotein fractions are evenly distributed (28). Physiological hyperlipidemia/hypertriglyceridemia is distinguished from pathological dyslipidemias by a paralleled increase in HDL-C in normal women as they progress through pregnancy. During pregnancy LDL and HDL are enriched in triglycerides (29). There is an increase in large HDL late in gestation and a decrease in medium HDL (30).

Table 1. Increase in Lipid, Lipoprotein, and Apolipoprotein Levels (from (25))	
Triglycerides	2.7-fold increase
Total Cholesterol	43% increase
LDL Cholesterol	36% increase
HDL Cholesterol	25% increase
Lipoprotein (a)	190%*
Apolipoprotein B	56% increase
Apolipoprotein AI	32% increase

All increases are from 3rd trimester except the increase in HDL cholesterol
*from reference (31).

Small dense LDL levels increase during pregnancy, particularly in individuals who have a large increase in triglyceride levels (32,33). As one would expect given the increase in triglycerides, LDL-C, and HDL-C, apolipoprotein B, and A-I levels are also increased (table 1). In most cross-sectional studies Lp(a) levels are not elevated in pregnancy (33-35). However, in some studies that measured Lp(a) serially throughout pregnancy an increase in Lp(a) levels was observed near term (table 1) (31,36,37) (23). The failure of cross-sectional studies to find a difference in Lp(a) levels is likely due to the wide variation in Lp(a) levels between individuals. Values in individuals range from 1mg/dL to over 200mg/dL and are largely determined by genetic factors.

MECHANISMS ACCOUNTING FOR THE CHANGES IN LIPIDS DURING PREGNANCY

Multiple physiological changes occur during pregnancy (27,38). Hormonal and metabolic changes that occur in the mother contribute to changes in the lipid profile in healthy, gestating women. It is useful to think of two phases of lipid metabolism in normal pregnancy. During the first two trimesters, lipid metabolism is 'primarily anabolic. There is an increase in lipid synthesis and fat storage in preparation for the exponential increases in fetal energy needs in late pregnancy. This increase in lipid synthesis between 10 and 30 weeks of pregnancy is promoted by maternal hyperphagia in early pregnancy as well as an increase in insulin sensitivity. The increase in insulin sensitivity stimulates fatty acid synthesis in adipocytes and stimulates the expression of lipoprotein lipase, which results in increased uptake of fatty acids from circulating triglyceride-rich lipoproteins. Additionally, the increased production of progesterone, cortisol, leptin, and prolactin contributes to increased fat storage (24,26,27,38). There is also significant hypertrophy of the adipocytes to accommodate increased fat storage (26,27,38).

Lipid metabolism in the third trimester is in a 'net catabolic phase', associated with a decrease in insulin sensitivity (i.e., insulin resistance) (27,38). This decrease in insulin sensitivity is associated with enhanced lipolysis of stored triglycerides in adipocytes. The third-trimester elevation of human placental lactogen (HPL) also stimulates lipolysis in adipocytes. In addition, insulin resistance results in a decrease in lipoprotein lipase in adipocytes leading to a decrease in the uptake of fatty acids from plasma triglyceride-rich lipoproteins. These changes result in a reduction in fat stored in adipocytes.

The hypertriglyceridemia during pregnancy is due to both the increased production and the decreased clearance of triglyceride-rich lipoproteins (27). The increased production of triglyceride-rich lipoproteins by the liver is due to the increased lipolysis of

triglycerides that occurs in adipocytes, which increases free fatty acids transported to the liver. These free fatty acids are then packaged into VLDL and secreted by the liver. The high estrogen levels in the third trimester stimulate liver lipogenesis and VLDL production. Insulin resistance may also play a role in the increase in fatty acid synthesis in the liver as inhibition of glucose production can be resistant to insulin while lipogenesis is not. The increase in insulin levels that occur can stimulate hepatic fatty acid synthesis as shown in a mouse model (39). The decrease in clearance of triglyceride-rich lipoproteins is due to a decrease in lipoprotein lipase and hepatic lipase (29). The decrease in hepatic lipase is due to elevated estrogen levels (40). The decrease in lipoprotein lipase is believed to be due to a combination of factors including insulin resistance and elevated estrogen levels. The triglyceride enrichment of LDL and HDL is due to an increase in CETP activity (29) resulting in the transfer of triglyceride from VLDL to LDL and HDL and a decrease in hepatic lipase, which decreases the removal of triglycerides from these lipoprotein particles.

At term, LPL activity increases in the mammary glands, which will enhance the uptake of fatty acids to increase the formation of triglycerides for lactation (26). The increase in plasma cholesterol levels is likely due to increased hepatic cholesterol synthesis (41,42). The increase in PCSK9 during pregnancy suggests an additional mechanism. The PCSK9 could result in a decrease in hepatic LDL receptors leading to increased LDL-C levels (23).

Table 2. Role of Hormones in Inducing Hyperlipidemia in the Third Trimester	
Estrogen increase	Inhibits Hepatic Lipase
	Stimulates VLDL production
	Stimulates lipogenesis in the liver
Human Placental Lactogen increase	Induces insulin resistance
	Increases lipolysis
Insulin Resistance	Decreases LPL activity
	Increases lipolysis
	Increase CETP
	Stimulates lipogenesis in the liver

IMPLICATIONS FOR THE FETUS AND MOTHER

Our understanding and appreciations of the full scope and implications of dyslipidemia in pregnancy on both maternal and fetal outcomes are not complete. Maternal dyslipidemia, particularly, high triglyceride and low HDL-C levels, are associated with several adverse perinatal outcomes. To demonstrate that lipid abnormalities are causative, intervention studies to lower lipid levels demonstrating a reduction in adverse perinatal outcomes are needed. This is difficult because the study of pregnant women is protected, underfunded, and understudied, in part because of medical legal concerns and the first rule of do no harm.

Dyslipidemia, while asymptomatic, is an integral factor in the metabolic syndrome (MetS). Having the MetS has clear implications for maternal vascular health, and this portends a multitude of other health concerns for the mom and her fetus.

Gestational Diabetes

Pregnancy is an insulin resistance state and gestational diabetes (GDM) is thought to be unmasked due to the stress test of insulin resistance of pregnancy. Risks to the fetus from GDM include brachial plexus injuries, hypoglycemia, respiratory distress, hyperbilirubinemia, and cardiomyopathy. Women with GDM are at increased risk of pre-eclampsia and after pregnancy, a very high risk of developing overt diabetes.

A meta-analysis of thirteen cohorts and three nested case-control studies found that high triglycerides early in pregnancy were associated with an increased risk of the development of GDM (43). Similarly, increasing triglycerides **during** pregnancy was also associated with an increased risk of developing GDM (43). An HDL-C of <51mg/dL was associated with higher odds of GDM (43). Another meta-analysis similarly found a link between GDM and high triglyceride levels and low HDL-C levels (44). Total cholesterol levels and LDL-C levels during pregnancy were not associated with an increased risk of GDM (44).

In women with a history of GDM, triglyceride, total cholesterol, and LDL-C levels are increased and HDL-C levels are decreased signaling the need to closely follow lipid levels in women with a history of GDM (45). Additionally, women with GDM have an increased risk of developing cardiovascular events later in life even in the absence of developing diabetes (46)

Several high-risk groups may have derangements in lipid levels that put them at risk before pregnancy. In the PPCOS II study, conducted by the Reproductive Medicine Network, having the metabolic syndrome before ovulation induction for fertility enhancement was associated with a lower rate of live birth success, independent of obesity, and it was also a risk factor for pregnancy complications, in particular gestational diabetes and macrosomia (47). Efforts to reduce weight before fertility treatments have been challenging. In an obese population with unexplained infertility, although weight loss was not associated with an improvement in healthy live birth success, it was associated with a reduction in the risk of preeclampsia (48)

High Birth Weight

A review of 46 publications with 31,402 pregnancies reported that maternal high triglycerides and low HDL-C levels during pregnancy were associated with increased birthweight, a higher risk of large-for-gestational-age, macrosomia, and a lower risk of small-for-gestational-age (49). Another meta-analysis also found a link between high triglycerides and low HDL-C levels and large birthweight (50). Elevations in triglyceride levels in the first trimester are associated with increased birth weight (51). The concentration of triglycerides in the third trimester is a stronger predictor of birth weight than glucose parameters (52-54). Additionally, in women with a normal glucose tolerance test during pregnancy triglyceride levels are still predictive of birthweight (55). Elevated levels of maternal triglycerides predict macrosomia independently of other maternal factors, such as BMI and glucose levels (52-54). In contrast, total cholesterol and LDL-C levels were not predictive of large birthweight (50). Some studies suggest that high levels of maternal HDL-C are significantly associated with a decreased risk for macrosomia, perhaps indicating that HDL might have protective qualities (56,57).

Pre-Eclampsia

Pre-eclampsia is a rapidly progressive condition that affects 5-8% of pregnancies and is characterized by hypertension and proteinuria. Risks to the fetus with preeclampsia include poor fetal growth and sometimes devastating consequences of preterm birth, whether spontaneous or induced. These can

manifest as cerebral palsy, epilepsy, small size, and even death.

In a meta-analysis of 74 studies, pre-eclampsia was associated with elevated total cholesterol, non-HDL-C, and triglyceride levels, regardless of gestational age at the time of blood sampling, and with lower levels of HDL-C in the third trimester (58). Other meta-analyses have confirmed the linkage of elevated triglyceride levels with pre-eclampsia (59,60). LDL-C levels were not associated with pre-eclampsia in one meta-analysis (58) but in another meta-analysis, it was (60). Enquobahrie et. al followed a cohort of women from early pregnancy onward and found that women who developed pre-eclampsia had significantly higher concentrations of LDL-C and triglyceride levels as early as 13 weeks of gestation compared to women who remained normotensive (61). They also found that HDL-C was 7.0% lower in pre-eclamptic women than in the control group. They noted a 3.6-fold increase in risk for pre-eclampsia in women with total cholesterol >205 mg/dL, compared to women whose total cholesterol levels were <172 mg/dL, even after adjusting for confounders. Not all recent studies have found an increase in LDL-cholesterol concentration with preeclampsia during pregnancy however (62). In a secondary analysis of the FIT-PLESE randomized controlled trial, we found that elevated highly atherogenic very small LDL particles were elevated in those persons who developed pre-eclampsia after ovulation induction (63).

In a meta-analysis comparing women with a past history of eclampsia/pre-eclampsia vs. without, there was an increase in total cholesterol (Mean Difference = 4.6 mg/dL, CI 1.5 to 7.7), LDL-C (MD = 4.6 mg/dL; 95%CI 0.2 to 8.9), and triglycerides (MD = 7.7 mg/dL, 95%CI 3.6 to 11.7) and a decrease in HDL-C (MD = -2.15 mg/dL, 95%CI -3.46 to -0.85) (64). It is now well recognized that women who have a history of having had eclampsia/pre-eclampsia have approximately twice the risk of cardiovascular disease later in life (65,66).

Preterm Birth

In a meta-analysis of three nested case-control studies and eight cohort studies of 13,025 pregnant women, women with elevated lipid levels were at increased risk of preterm birth (OR 1.68; 95% CI 1.25-2.26) (67). The increased risk was seen for elevated levels of total cholesterol (OR 1.71), triglycerides (OR 1.55), LDL-C (OR 1.19 not significant), and lower levels of HDL (OR 1.33). A study by Vrijkotte et al that was not included in the meta-analysis also found that elevated triglycerides but not elevated total cholesterol were associated with an increased risk of preterm birth (51).

Developmental Programming

Preclinical models demonstrate that interventions that reduce maternal cholesterol during pregnancy, that decrease oxidative stress associated with gestational dyslipidemia, or that enhance active immune defenses against oxidative stress in offspring protect against developmental programming (68-70). This is thought to be because of excess maternal cholesterol during pregnancy, all factors collectively provide evidence for causality. Early atherogenic processes in the human aorta begin during fetal development and are accelerated by dyslipidemia during pregnancy. Maternal hypercholesterolemia is associated with greatly accelerated atherogenesis in normocholesterolemic children, as shown by the FELIC study (71). In experimental models lacking the genetic and dietary variability of humans, postnatal atherosclerosis increases in proportion to the maternal cholesterol levels well into adult ages (69,72). A molecular mechanism explaining the transfer of maternal cholesterol to the fetus has been elucidated (73) and involvement of increased oxidative stress has been established (68-70).

The absence of routine cholesterol determinations during gestation in most countries has limited investigations of the impact of elevated maternal cholesterol during pregnancy on the clinical manifestations of dyslipidemia in adult offspring. In the Framingham Heart Study gestational dyslipidemia in mothers was predictive of dyslipidemia in their offspring (74). Adults who had been exposed to elevated maternal LDL-C levels had 3.8 times higher odds of having elevated LDL-C levels. They found that this explained 13% of the variation in adult offspring LDL-C levels beyond common genetic variants and classic risk factors for elevated LDL-C levels. A positive association has also been reported between maternal cholesterol and newborn HDL cholesterol and subclasses (75).

From studies of 78 fetal aortas, maternal cholesterol explained 61% of the variance of early lesion sizes by multivariate analysis, independent of HDL-C, triglycerides, glucose, and body mass index (BMI). Maternal total cholesterol and LDLC levels were positively associated with methylation of SREBP2 in fetal aortas, suggesting a role of maternal cholesterol levels during pregnancy on epigenetic signature in offspring as reported by Napoli et al (71). SREBP2 methylation has been mapped (71). The long-term effects of maternal dyslipidemia on the progression of atherosclerosis and, its clinical manifestations are understudied. In several cohort studies, whole blood DNA methylation signatures of diet were associated with cardiovascular disease (76). Dyslipidemia can persist well into adult age and affect clinically relevant outcomes (72). In studies where elevated maternal cholesterol during pregnancy is associated with atherogenesis in childhood, maternal lipid levels during pregnancy have been associated with adult BMI, atherosclerosis-related risk, and the severity of anterior myocardial infarctions as reported by Cacciatore et al (72).

Pre-eclampsia (77) and gestational diabetes (46) are linked to having a greater risk for early maternal cardiovascular events.

LIPID SCREENING

The National Lipid Association (NLA) supports checking lipids routinely if there is no normal current pre-pregnancy lipid profile (78). Screening for reproductive-aged women, in general, remains deficient in part due to disparities in health services (79). Identifying pregnant women with prior atherosclerotic cardiovascular disease (ASCVD), familial hypercholesterolemia, or hypertriglyceridemia is important to allow for multi-disciplinary collaborative care. Increased knowledge and awareness are needed at both the patient and provider levels. In a survey study of 200 pregnant women within the University of Pennsylvania Health System, 59% self-reported previous lipid screening; non- Hispanic Black women were less likely to report screening (43% vs. 67%) and they had lower awareness of high cholesterol as a risk factor for ASCVD (66% vs 92%) (80). The perinatal period, when a woman sees a physician most regularly, is an opportunity to screen for lipid disorders and facilitate prevention by bringing lipid values to normal age specific target ranges. Hypertensive disorders of pregnancy are among the leading causes of maternal morbidity and mortality in the US. Pre-eclampsia, which includes hypertension and proteinuria during pregnancy, is thought to result from placental ischemia. Risk factors for pre-eclampsia parallel those for cardiovascular disease and recent studies point to hyperlipidemia, specifically hypertriglyceridemia. Current practice does not routinely include lipid testing pre-conception or during pregnancy. Professional and societal recommendations should advocate for hyperlipidemia screening, followed by appropriate management, pre-conception, and during pregnancy as an important evaluation for risk of preeclampsia during pregnancy (48).

A recent review recommended measuring lipids at the first visit and if normal at the beginning of third trimester (81). High risk patients should have lipids measured at first visit, beginning of second trimester, and monthly during the 3rd trimester. If triglyceride levels are greater than 250mg/dl at any time the lipid panel should be measured monthly. When and if more specialized lipid testing such as NMR or ion mobility to measure small dense LDL levels, apo B and apo A1 levels, and Lp(a) levels is needed is not defined and further studies are required. Measuring Lp(a) levels at the first visit is reasonable in patients who have not had their Lp(a) levels determined previously. If lipid abnormalities are noted during pregnancy follow-up lipid panels post-pregnancy should be obtained.

TREATMENT OF DYSLIPIDEMIA DURING PREGNANCY

Lifestyle Modifications

Addressing lifestyle modifications is vital in the management of any lipid disorder regardless of pregnancy status. Counseling patients regarding a heart-healthy dietary pattern that includes vegetables, fruits, whole grains, legumes, healthy protein sources, and limiting intake of sweets, sweetened beverages, and red meats along with an emphasis on weight management and exercise is essential (82). To counsel patients with elevated lipids to lower their intake of saturated fats and increase dietary fiber is important. Approaches to Stop Hypertension (DASH) diet or Mediterranean diet are well described diets that are beneficial in reducing cardiovascular risk (83). Given that women report increased motivation to enact dietary changes during pregnancy, this is an ideal time to intervene with lifestyle modifications. Diet is a critical pillar of management for hypertriglyceridemia. A very low-fat diet is recommended to mitigate the risk of pancreatitis particularly when triglyceride levels are >500 mg/dL. Severe gestational hypertriglyceridemia can lead to acute pancreatitis and the maternal mortality rate is approximately 20%.

Dietary interventions have benefits beyond LDL lowering due to their effects on the placenta. A low-cholesterol low-saturated fat diet in a trial of 290 pregnant patients led to a decrease in the umbilical artery pulsatility index, a method for fetal surveillance in high-risk pregnancies (less vascular resistance) (84). Increased vascular resistance is associated with adverse pregnancy outcomes such as preeclampsia, preterm delivery, and small for gestational age infants.

Drug Therapy

STATINS

While statins are the first-line treatment of hypercholesterolemia in the general population, their use is not recommended during pregnancy in several guidelines. The 2018 AHA/ACC/multi-society cholesterol guidelines give a class 1 recommendation that women of childbearing age with hypercholesterolemia who plan to become pregnant should stop statins 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as possible (85). Similarly, the European Society of Cardiology (ESC) 2019 guidelines have a class III recommendation that statin therapy is not recommended in premenopausal patients with diabetes who are considering pregnancy or are not using adequate contraception (86). Historically, statins became contraindicated in pregnancy as a result of a case series in 2004 that demonstrated an association between first-trimester statin exposure and fetal malformations. Other cohort studies of statin exposure in pregnancy have not shown an increase in teratogenic risk (87). Of all the statins, hydrophilic statins, such as pravastatin, have not been associated with anomalies (88). Meta-analyses of studies of pregnant women exposed to statins showed no

increased risk of birth defects (RR 1.15) but did reveal an increased risk of miscarriage (RR 1.35) (87,89). This increased risk of miscarriage may be due to confounders such as older age and ASCVD risk factors.

In a retrospective review of 39 pregnancies including 20 patients with FH and 18 patients on statins, miscarriage rates were not higher in statin-exposed patients as compared to the healthy population; there was also no difference in birth weights between statin-exposed and not-exposed (90). Given the lack of clear evidence on the teratogenicity of statins, in July 2021 the FDA requested the removal of the strongest recommendation against using statins during pregnancy. They continue to advise against the use of statins in pregnancy given the limited data and quality of information of studies. The decision of whether to continue a statin during pregnancy requires shared decision-making between the patient and clinician, and healthcare professionals need to discuss the risks versus the benefits in high-risk women, such as those with homozygous FH or prior ASCVD events, that may benefit from statin therapy (91).

Discontinuation of statins in patients with FH allows cholesterol levels to increase even beyond pre-treatment levels due to higher physiologic levels during pregnancy. This period is a vulnerable time as interruptions of treatment can increase the lifelong risk of ASCVD. In women with familial hypercholesterolemia (FH), the percent increase in LDL-C levels during pregnancy is similar to that observed in women with a normal lipid profile before pregnancy even though the baseline LDL-C levels are much higher in women with familial hypercholesterolemia (92). Despite the markedly higher LDL-C levels in women with FH, the incidence of prematurity, low birth weight, and congenital malformations did not differ, however, maternal hypertension incidence was higher than for women without dyslipidemia before pregnancy who became pregnant (92,93).

In a retrospective review of women with homozygous familial hypercholesterolemia of which 18/39 were exposed to statins with or without ezetimibe,1 was treated with a statin, ezetimibe, and a PCSK9 inhibitor, and 5 patients were exposed to cholestyramine, and only 14 patients were not exposed to lipid-lowering therapy, complications associated with pregnancy included 3 premature infants, one preeclampsia related, the other two because of chorioamnionitis and maternal cardiac disease (90). One Intrauterine death was because of intrauterine infection.

More studies examining outcomes in pregnant women with FH are needed to assess short-term and long-term outcomes on the mother and the offspring. The FDA has taken a wait and see approach. Certain statins, such as pravastatin, are being investigated for use in the prevention of preeclampsia. Given the impact of statins on endothelial dysfunction and their potential ability to mediate pathways of inflammation and oxidative stress, statins are promising agents for preeclampsia treatment in persons at high risk for a severe disease which centers on vascular dysfunction. Pravastatin is the most hydrophilic statin with a short half-life and is also a substrate for multiple efflux transporters, which leads to lower transplacental transfer. The safety of pravastatin 10 mg (low-intensity) was evaluated in a very small 20-patient randomized controlled trial for the prevention of preeclampsia in high-risk pregnant women, in which the primary outcome was maternal-fetal safety. There were no differences between groups in rates of drug side effects, congenital anomalies, or other adverse events. In a larger trial, 1120 women at high risk of pre-eclampsia were randomized to either pravastatin 20 mg (low-intensity) or placebo. There was no significant reduction in the incidence of preeclampsia or differences in other biomarkers such as soluble fms-like tyrosine-kinase-1 in either treatment arm (94). Hirsch et all reviewed cohort studies assessing the effects of pravastatin on placental insufficiency disorders and found that pravastatin treatment

prolonged pregnancy duration and improved associated obstetrical outcomes in pregnancies complicated with uteroplacental insufficiency disorders in cohort studies (95). Additional studies will help ascertain the efficacy of statins, such as pravastatin, during pregnancy for preeclampsia prevention.

BILE ACID SEQUESTRANTS

Bile acid sequestrants such as cholestyramine and colestipol can be used for LDL-C lowering during pregnancy (96). Since bile acid sequestrants are not absorbed they do not pass into the systemic circulation and are safer than other lipid-lowering agents. However, they do decrease the absorption of fat-soluble vitamins. Patients should be monitored for vitamin D and K deficiency (96). According to the 2011 NLA recommendations, Colesevelam was classified as a Class B pregnancy category medication, as there are no adequate studies in pregnant women and animal studies have failed to demonstrate a risk to the fetus (97). Thus, bile acid sequestrants are considered safe for use in treating LDL-C elevations during pregnancy and breastfeeding. However, there is a lack of controlled trial data during pregnancy. Additionally, bile acid sequestrants are well known to increase triglyceride levels. They can be associated with constipation in pregnancy.

EZETIMIBE

Ezetimibe was classified as Class C pregnancy category; Class C meant that there is a lack of adequate studies in pregnant women, but animal studies have demonstrated a risk to the fetus (78). Animal studies have found that ezetimibe crosses the placenta. At levels higher than those achieved with human doses, there appears to be a slightly increased risk of skeletal abnormalities in rats and rabbits. Therefore, this agent is not recommended for use during pregnancy. If used prior to pregnancy, ezetimibe should be discontinued prior to attempting to become pregnant (98). The 2011 NLA Familial Hypercholesterolemia guidelines state that ezetimibe should be stopped at least 4 weeks before discontinuing contraception for women with familial hypercholesterolemia who are planning on conceiving and should not be used during pregnancy and lactation (97).

PCSK9 INHIBITORS (EVOLOCUMAB, ALIROCUMAB, AND INCLISIRAN)

Evolocumab and alirocumab, have not been tested for safety during pregnancy so their role in dyslipidemia treatment in pregnancy is unclear. While older medications were labeled with pregnancy categories, such as A, B, C, D, and X, the FDA has removed these labels for all prescription medications approved after 2015 so there is no pregnancy classification for PCSK-9 inhibitors. The FDA drug package insert for evolocumab and alirocumab describe that monoclonal antibodies are unlikely to cross the placenta in the first trimester, but may cross
the placenta near term, in the second and third trimester.

Inclisiran, a small interfering RNA that targets hepatic PCSK9 synthesis, has been shown to significantly lower LDL-C levels. Given its infrequent dosing regimen, it could hypothetically be used before conception and immediately afterward though further trials and outcome data are needed (99). The product labeling states that there is no available data on its use in pregnant patients, although animal reproduction studies have shown no adverse developmental effects.

PCSK9 inhibitors are not approved for use in pregnancy nor currently recommended.

BEMPEDOIC ACID

Bempedoic acid, an inhibitor of ATP citrate lyase (an enzyme in the cholesterol synthesis pathway), is a lipid-lowering therapy shown to reduce the levels of LDL-C. Per the product labeling by the FDA, there is no available data on its use in pregnant women though animal reproduction studies did not show teratogenicity in rat and rabbit models (package insert). It is not recommended that bempedoic acid be taken during breastfeeding. They suggest discontinuing bempedoic acid when pregnancy is recognized, unless the benefits of therapy outweigh the potential risks to the fetus. Based on the mechanism of action of bempedoic acid may cause fetal harm.

EVINACUMAB

No data are available on use during pregnancy (96). Based on animal studies, exposure during pregnancy may lead to fetal harm. Evinacumab is a monoclonal antibody and human immune globulin are known to cross the placental barrier (96). Therefore, evinacumab could be transmitted from the mother to the developing fetus.

LOMITAPIDE

This drug is contraindicated during pregnancy due to the risk of fetal toxicity (formerly Class X pregnancy category) (100).

FIBRATES

While fibrates were classified as the Class C pregnancy category, they can be considered later on in pregnancy depending on the risk vs. benefit discussion. The AHA Scientific Statement for Cardiovascular Considerations in Caring for Pregnant Patients proposes the consideration of fenofibrate or gemfibrozil in the second trimester if triglycerides are >500 mg/dL despite lifestyle modifications (101). The AHA/ American College of Obstetricians and Gynecologists (ACOG) Presidential Advisory states that pregnant patients with a history of pancreatitis may benefit from the use of fenofibrate when triglyceride levels are >1000 mg/dL (66). The use of fibrates during the second trimester is after embryogenesis occurs reducing the risk. Studies in animals have found no increased risk of congenital malformations (98).

NIACIN

Niacin was classified in the Class C pregnancy category. Niacin should not be used during pregnancy and lactation.

OMEGA-3-FATTY ACIDS

Omega-3 fatty acids are widely used albeit without controlled clinical trials during pregnancy.
Studies are limited on the use of omega-3 fatty acids for dyslipidemia management during pregnancy. In one study of 341 pregnant women, omega-3 fatty acids in the form of 10 mL cod liver oil given daily until 3 months after delivery increased docosahexaenoic acid (DHA) levels in both maternal and infant plasma while also reducing maternal plasma lipid levels. Most other medications used to treat hypertriglyceridemia are not considered safe during pregnancy, but omega-3 fatty acids are considered safe as most prenatal vitamins and baby formula
contain DHA. Omega-3 fatty acids can potentially be utilized for their triglyceride-lowering effect, but evidence is only based on a small number of case reports (102). Prescription omega-3-fatty acids are not approved for use during pregnancy.

VOLANESORSEN

No data are available on use of volanesorsen during pregnancy. If used prior to pregnancy, volanesoren

should be discontinued one month before attempting conception (103). This drug is approved in Europe but not in the U.S.

SUMMARY

Several recent reviews have provided information on the use of lipid lowering drugs during pregnancy and breast feeding (96,104,105). The class of evidence and levels of evidence for lipid lowering drugs are not strong for any of the options given a lack of definitive studies regarding efficacy and safety.

Plasmapheresis and Lipoprotein Apheresis

In patients with severe elevations in triglyceride levels with pancreatitis or who are at high risk for pancreatitis plasmapheresis has been employed to rapidly and safely decrease triglyceride levels (81,106). Plasmapheresis should be considered early in asymptomatic pregnant women with fasting triglyceride levels >1000 mg/dL or in pregnant women with clinical signs and symptoms of pancreatitis and triglyceride levels >500 mg/dL despite maximal lifestyle changes and pharmacologic therapy.

Lipoprotein apheresis can be safely used during pregnancy and may be beneficial for some women with severely elevated LDL-C levels (85,106,107). An expert American College of Cardiology expert committee suggests consideration of lipoprotein apheresis in pregnant patients with homozygous familial hypercholesterolemia and patients with severe heterozygous familial hypercholesterolemia and an LDL-C ≥ 300 mg/dL despite lifestyle therapy (96). In patients with familial hypercholesterolemia, ASCVD, and pregnancy, lipoprotein apheresis may be considered when the LDL-C ≥190 mg/dL.

MANAGEMENT OF PREGNANT WOMEN WITH PRE-EXISTING LIPID ABNORMALITIES

Patients with the following disorders are best managed using a team approach that includes a lipid and maternal-fetal specialist. Persons with these disorders should be provided with genetic counseling in addition to multi-specialty team management and pregnancy offers an important opportunity to address the impact in families and how to recognize, prevent, and treat these disorders.

Elevated LDL-C Levels Including Homozygous and Heterozygous Familial Hypercholesterolemia

In women with familial hypercholesterolemia the percent increase in LDL-C levels during pregnancy is similar to that observed in women with a normal lipid profile prior to pregnancy even though the baseline LDL-C levels are much higher in women with familial hypercholesterolemia (92). Despite the markedly higher LDL-C levels in women with familial hypercholesterolemia the prevalence of hypertension, duration of gestation, and fetal body weight were similar between patients with familial hypercholesterolemia and women without dyslipidemia before pregnancy (92).

Decisions to use lipid-lowering medications involve a risk-benefit decision. In patients at very high risk of a heart attack or stroke, such as individuals with homozygous familial hypercholesterolemia and those who have clinical ASCVD the benefits of therapy may outweigh the risks of therapy. If the patient and physician elect to continue or add LDL-C lowering medications it is recommended that these be used after the first trimester of pregnancy if possible. Additionally, the hydrophilic statin, pravastatin, would be a good choice if one elects to use a statin (108). If the patient is on lipoprotein apheresis this can be continued during pregnancy or initiated if available.

Familial Chylomicronemia Syndrome (TG> 500mg/dL)

This is managed primarily with a very low-fat diet (<20 g total fat/d or <15% total calories) that requires consultation with an expert in nutritional advice to ensure adequate caloric intake during pregnancy and sufficient vitamins. Medium-chain triglycerides can help provide calories and make the very low-fat diet tolerable. In the third trimester as triglyceride levels increase hospitalization with parenteral feeding has been employed. In patients with familial chylomicronemia syndrome drug therapy often is not beneficial but one can consider omega-3 fatty acids in high doses. In patients with episodes of pancreatitis or with very high triglyceride levels at high risk for pancreatitis plasmapheresis can be beneficial.

Multifactorial Chylomicronemia Syndrome (TG> 500mg/dL)

This disorder is typically due to a genetic predisposition to high triglyceride levels combined with secondary factors that increase triglyceride levels into the range that causes pancreatitis. Therefore, one should try to control secondary disorders (Table 3) and if possible, stop drugs that increase triglyceride levels (Table 4). Additionally, a low-fat diet, avoidance of simple sugars and alcohol, and exercise can be helpful.

Table 3. Disorders Associated with an Increase in Triglyceride Levels
Obesity
Alcohol intake
High simple carbohydrate diet
Diabetes
Metabolic syndrome
Polycystic ovary syndrome
Hypothyroidism
Chronic renal failure
Nephrotic syndrome
Inflammatory diseases (Rheumatoid arthritis, Lupus, psoriasis, etc.)
Infections
Acute stress (myocardial infarctions, burns, etc.)
HIV
Cushing's syndrome
Growth hormone deficiency
Lipodystrophy
Glycogen Storage disease
Acute hepatitis
Monoclonal gammopathy

Table 4. Drugs That Increase Triglyceride Levels
Alcohol
Oral Estrogens
Tamoxifen/Raloxifene
Glucocorticoids
Retinoids
Beta-blockers
Thiazide diuretics
Loop diuretics
Protease Inhibitors
Cyclosporine, sirolimus, and tacrolimus
Atypical antipsychotics
Bile acid sequestrants
L-asparaginase
Androgen deprivation therapy
Cyclophosphamide
Alpha-interferon
Propofol

If these are not successful in keeping triglyceride levels in a safe range treatment with omega-3- acids and the addition of fenofibrate later in pregnancy is indicated. If despite therapy there is an episode of pancreatitis due to poorly controlled triglyceride levels or very high triglyceride levels at high risk for pancreatitis plasmapheresis can be employed.

Patients with Moderate Hypertriglyceridemia (TG 200-500mg/dL)

These patients should be treated the same as patients with the multifactorial chylomicronemia syndrome described above. Diet therapy, treatment of secondary disorders, and stopping, if possible, drugs that increase triglyceride levels can frequently prevent an increase in triglycerides into the range that causes pancreatitis. If this approach is not successful treatment with omega-3- acids and the addition of fenofibrate later in pregnancy is indicated if the triglyceride levels are greater than 500mg/dL.

Patients with Very High Lp(a) Levels

High Lp(a) may promote atherosclerosis as well as thrombosis by affecting fibrinolysis, inflammation, endothelial function, macrophage lipid uptake, and oxidative stress. Lipoprotein(a) level correlates with the severity of preeclampsia and Lp(a) may be involved in the pathogenesis of preeclampsia (109). Further studies are required to determine if Lp(a) has a detrimental role during pregnancy and whether therapies that lower Lp(a) levels are beneficial. To prevent pre-eclampsia aspirin therapy is recommended and can be considered for persons with high Lp(a).

Patients with Monogenic Disorders Causing Hypobetalipoproteinemia (i.e., Low LDL-C Levels)

There are a number of causes of low LDL-C including secondary factors such as a strict vegan diet, malnutrition, malabsorption, hyperthyroidism, malignancy, and chronic liver disease, polygenic

disorders due to small effect variants in a number of genes, and several monogenic disorders (110). Amongst the monogenic disorders only the most severe are associated with pregnancy issues including bi-allelic FHBL-SD1 due to mutations in microsomal triglyceride transfer protein (abetalipoproteinemia), bi-allelic FHBL-SD2 due to mutations in Apo B, and bi-allelic FHBL-SD3 due to mutations in SAR1B (chylomicron retention disorder) (111). These disorders are characterized by very low LDL-C levels and malabsorption (111). The dietary treatment of these individuals is summarized in table 5 (111). Other monogenic disorders causing low LDL-C levels, such as mono-allelic FHBL-SD2 due to mutations in Apo B (familial hypobetalipoproteinemia), bi-allelic FHBL-EC1 due to mutations in ANGPTL3 (combined hypolipidemia), and bi-allelic FHBL-EC2 due to mutations in PCSK9 do not cause major issues during pregnancy because they do not lead to malabsorption.

Table 5. Treatment of Patients with Severe Monogenic Hypobetalipoproteinemia (Low LDL-C)
Low-fat diet- Less than 10-15% (<15 g/day) of total daily calories. Can be adjusted depending upon the tolerance
Essential fatty acids- 2-4% daily caloric intake (alpha-linolenic acid/linoleic acid)
DHA and EPA- Supplementation may be considered depending on the diet
Vitamin E- 100-300 IU/kg/day
Vitamin A- 100-400 IU/kg/day
Vitamin D- 800-1200 IU/day
Vitamin K- 5-35 mg/week

Dosing of vitamins A, D, and K can be tailored to plasma vitamin A/β-carotene levels, 25-hydroxy vitamin D levels, and INR reference intervals.

Preconception and pregnancy medical counseling, including genetic counseling, should be provided. Because patients with these disorders are very uncommon ideally these patients should be cared for in specialty clinics. During pregnancy, one must balance the need to limit fat intake and the need to increase caloric intake. Consultation with a dietician is important. Supplementation with medium-chain triglycerides can be used to increase caloric intake if needed (111). Because maternal serum DHA concentrations have been linked to neurocognitive and anti-inflammatory benefits supplementation with DHA (1-3 g/day) can be utilized to increase plasma concentrations (111). Additionally, to prevent neural tube defects in pregnancy, a daily supplement of 400-800 µg folic acid is also recommended. The dosing of vitamins A, D, and K should be adjusted as indicated by plasma vitamin A/β-carotene levels, 25-hydroxy vitamin D levels, and INR reference intervals (111). In normal individuals, excess vitamin A can cause toxicity during pregnancy and therefore it is recommended to set the vitamin A goal at the lower limit of normal levels, which may decrease the dose by 50% during pregnancy (111). Vitamin E supplements should be continued during pregnancy as vitamin E deficiency has been shown to increase miscarriages (111)

Progesterone production during pregnancy may be reduced during pregnancy and it is recommended to monitor progesterone levels throughout pregnancy and consider the use of exogenous progesterone if levels are low (111).

CONSIDERATIONS FOR BREASTFEEDING

The postpartum period is a critical time requiring proactive counseling and shared decision-making regarding plans for lactation. Enabling women to breastfeed is a public health priority because, on a population level, interruption of lactation is associated with adverse health outcomes for the woman and her child, including higher maternal risks of breast cancer, ovarian cancer, diabetes, hypertension, and heart disease, and greater infant risks of infectious disease, sudden infant death syndrome, and metabolic disease. Contraindications to breastfeeding are few. Most medications and vaccinations are safe for use during breastfeeding, with few exceptions. Breastfeeding confers medical, economic, societal, and environmental advantages; however, each woman is uniquely qualified to make an informed decision surrounding infant feeding.

Risks vs. benefits need to be considered to determine the optimal management of lipid disorders, as all lipid-lowering medications are contraindicated during pregnancy and remain contraindicated during breastfeeding. Breastfeeding has enormous benefits and is encouraged. Medications taken by the mother can transfer into breast milk through passive diffusion or active transport by membrane proteins and therefore expose the baby to the medication. Therefore, continuing breastfeeding given its benefits in metabolic health needs to be balanced with stopping breastfeeding to resume lipid-lowering therapies and the progression of atherosclerosis (112). Shared decision-making and discussions of risks and benefits of both time without statin treatment and breastfeeding vs. treatment during pregnancy and lactation are best initiated before delivery and every visit in the fourth-trimester period (after delivery) (113,114). The LactMed database (National Institute of Child Health and Development) contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency. The consensus opinion is that women taking a statin should not breastfeed because of a concern with disruption of infant lipid metabolism. However, others have argued that children homozygous for familial hypercholesterolemia are treated with statins beginning at 1 year of age, that statins have low oral bioavailability, and that risks to the breastfed infant are low, especially with pravastatin and rosuvastatin.

In a recent systematic review of 33 articles from 15 randomized controlled trials limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. There was insufficient evidence to evaluate the effects of omega-3 fatty acid supplementation during pregnancy and/or lactation on other developmental outcomes (115).

CONCLUSION

There is an increase in lipid levels in normal gestation. Dyslipidemia in pregnancy beyond physiologic levels is associated with adverse pregnancy outcomes. Adverse pregnancy events enhance the risk of clinical ASCVD events in later life. Screening for and adequately addressing atherogenic dyslipidemia before and during pregnancy is a priority. Major barriers to the management of hyperlipidemia during pregnancy and the postpartum period include limited studies in pregnant patients. Many therapeutic agents are categorized as contraindicated without adequate evidence. Future research is needed to allow for evidence-based decisions to guide therapeutic options. Pregnancy is a unique opportunity for multidisciplinary and collaborative care across various

specialties to improve rates of screening and optimize the long-term cardiovascular health of women. Many women are overwhelmed post-partum. They need to be encouraged to prioritize ASCVD risk reduction as integral to their care. Improving access to quality preventive care is still in need of improvement.

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