Dyslipidemia in Pregnancy

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KEYWORDS

• Dyslipidemia • Hyperlipidemia • Pregnancy • Fetal metabolism
• Metabolic syndrome

KEY POINTS

- Exposure of the fetus to elevated levels of cholesterol and oxidative byproducts of cholesterol metabolism has been shown to result in programming of fetal arterial cells with a predisposition to atherosclerosis later in life.
- For many women, the reproductive years span 2 decades, representing an optimal time to reduce cardiovascular disease risk factors before conception.
- Recent discoveries highlight the importance of preventing or optimizing maternal dyslipidemia for the benefit of the mother and the child.
- Currently no reference standards are defined for lipid parameters during pregnancy, although it is well-known that pregnancy is a state of insulin resistance and that lipoprotein lipid profiles reflect this process.
- Overweight and obese women are significantly more likely to exceed the pregnancy-related weight gain recommendations.

INTRODUCTION

Historically dyslipidemia in pregnancy has been considered physiologic with little clinical relevance. Lipids and lipoproteins have not been routinely measured at any time point during pregnancy, irrespective of their role in cardiovascular disease (CVD) or pregnancy outcomes. Recent evidence describing fatty streaks in the aortas of 6-month-old fetuses of mothers who were hypercholesterolemic[1] and studies in animal models have challenged the assumption that maternal cholesterol does not cross the placental barrier. Poorly controlled cholesterol, triglycerides, and their metabolites associated with cardiometabolic dysfunction seem to have significant detrimental

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maternal and fetal vascular consequences. Maternal cardiometabolic dysfunction may not only contribute to long-term effects of the mother and child's vascular health but also potentially create CVD risk for generational offspring.

In providing an update on this rapidly expanding and multifaceted topic, this article first outlines the basic understanding of the importance of cholesterol in fetal development. New insight is then reviewed regarding why this new recognition of disordered maternal cholesterol and triglyceride metabolism is likely to have a long-term effect for future generations. Diagnosing and treating dyslipidemia before, during, and after pregnancy in an effort to provide the best opportunity to reduce the increasing atherosclerotic burden of the rapidly expanding population.

CHOLESTEROL AND FETAL DEVELOPMENT

Cholesterol is required for normal fetal development. It plays a key role in the formation of cell membranes, membrane integrity, and maintaining cholesterol-rich domains that are essential for most membrane-associated signaling cascades, including sonic hedgehog signaling.[2] Cholesterol is also a precursor of hormones, such as steroids, vitamin D, and bile acids. Sources of fetal cholesterol seem to include endogenous production, the maternal circulation, and synthesis within the yolk sac or placenta.

Because of its critical role in fetal development, it was previously thought that most cholesterol is synthesized de novo by the fetus. Emerging evidence, however, suggests that maternal cholesterol and the placenta may also play a meaningful role. For exogenous cholesterol to be available for fetal use, the yoke sac and placenta must take up maternal cholesterol via receptor-mediated or receptor-independent transport processes, transport lipids across cellular barriers, and/or secrete the maternally derived or newly synthesized cholesterol into the fetal circulation.[3,4] Cultured trophoblast cells have been shown to express low-density lipoprotein (LDL) receptors (LDLRs), LDLR-related proteins, scavenger receptors A, and high-density lipoprotein (HDL)–binding scavenger receptors B1 (SR-B1s) on their apical side. Cholesterol taken up by internalization of receptor-bound ApoB- or ApoE-carrying lipoproteins and oxidized LDL, and from SR-B1–bound HDL, is then released on the basolateral side.[4] Although the uptake of cholesterol by endothelial cells is well understood, knowledge about the mechanisms through which placental endothelial cells transport cholesterol to the fetal microcirculation, the regulation of efflux, and their ability to deliver substantial quantities of cholesterol is incomplete.

Maternal cholesterol has been shown to cross the placental and enter the fetal circulation, contributing substantially to the fetal cholesterol pool in animals and humans.[4,5] Vuorio and colleagues[6] found that plant stanol concentrations in cord blood of healthy newborns were 40% to 50% of maternal levels, demonstrating active maternal-fetal sterol transport. Compared with the umbilical arteries, the umbilical vein has been found to have a greater concentration of cholesterol.[7]

Maternal hypercholesterolemia, as seen in a woman with familial hypercholesterolemia (FH), may pose a significant risk to the fetus.[8] A substantial increase in maternal cholesterol has been shown to significantly increase cholesterol transfer from the mother to the fetus, without upregulation of liver X receptors.[9] Fetal cholesterol levels in mid-pregnancy are much higher than they are at term, and these levels correlate with maternal cholesterol before the sixth month of gestation.[9] This finding suggests maternal hypercholesterolemia does not, a priori, result in upregulation of cholesterol transport. However, exposure of the fetus to very high levels of cholesterol and oxidative products of cholesterol has been shown to result in programming of arterial cells with a predisposition to atherosclerosis later in life.[1] Similar findings have been

observed in pregnant women who are obese, have the metabolic syndrome, and/or have diabetes.[10] Napoli and colleagues[1] have shown a direct correlation between the concentration of maternal cholesterol and the presence of fatty streaks in the fetus; effects more strongly correlated earlier in gestation.

Studies have also shown adverse fetal effects as a consequence of decreased exogenous cholesterol. Women with lower plasma cholesterol levels, for example, were found to have smaller newborns; a correlation has been reported between low plasma cholesterol and microcephaly.[11] Ultimately, however, the mechanisms underlying fetal effects related to maternal hypercholesterolemia remain incompletely understood.[9]

PREVALENCE OF CARDIOVASCULAR DISEASE RISK FACTORS

According to the National Health and Nutrition Examination Survey 1999–2008 data, among women aged 18 to 44 years in the United States, 2.4% have diabetes, 7.7% are estimated to have hypertension, 25.4% use tobacco, 2.9% have chronic kidney disease, and 57.6% are either overweight or obese. Prepregnancy cardiometabolic and inflammatory risk factors predict the risk of hypertensive disorders of pregnancy. An increased risk of hypertension is seen in women who are obese. The odds of hypertension during pregnancy are 1.8 times greater for individuals who are normotensive yet obese before pregnancy. The odds of a hypertension-related complication during pregnancy are 3.5 times higher in women who are overweight and hypertensive before pregnancy.[12]

Approximately 50% of pregnancies are unplanned, limiting the ability to identify women with CVD risk factors before pregnancy. A Kaiser Family Foundation national survey recently noted that the rate of CVD screening for women aged 18 to 44 years was 58%, compared with 78% for women aged 45 to 64 years.[13] This proportion is even lower compared with blood pressure screening in 18- to 44-year olds. Another national survey found that among women aged 18 to 64 years, 15% were seen by general medicine physicians, 62% by gynecologists alone, and 23% by both. Those seen by gynecologists received more counseling and preventive services.[14] In an evaluation of 2 different health care plans servicing nearly 3.6 million members, hypertension was recognized in fewer than one-third of women during the course of their care. Furthermore, irrespective of which specialty provided the care, less than 70% of women received lipid screening, nutrition, or weight counseling. The survey also illustrated that limited knowledge about preeclampsia and future risk in reproductive age women was common among all specialties.

The most recent National Vital Statistics report illustrates that pregnancy rates for women aged 25 to 29 years have changed very little since 1990.[15] Rates for women in their 30s and 40s, however, have increased. Additionally, in the past 45 years, women aged 35 to 44 years in the United States have experienced the greatest increase in prevalence of obesity. With the known association between obesity and dyslipidemia, the implications of this trend are profound. Currently, 45% of women begin pregnancy either overweight or obese, a statistic that has almost doubled in the past 30 years. Furthermore, approximately 43% of pregnant women gain more weight than recommended during the course of their pregnancy. It is well understood that maternal obesity contributes to other high-risk conditions, such as gestational diabetes, hypertensive disorders, newborn macrosomia, and perinatal complications.[16] For many women, the reproductive years can span 2 decades, representing an optimal time to reduce CVD risk factors before conception, for the benefit of both the mother and her future offspring.

FETAL CONSIDERATIONS

Because gestational dyslipidemia has historically been considered physiologic, with little clinical significance, lipid and lipoproteins have not been measured routinely during pregnancy. However, the recent discoveries of fatty streaks in the aortas of 6-month-old fetuses of mothers with hypercholesterolemia, and the identification of aortic atherosclerosis at autopsy of deceased children with normal levels cholesterol born to mothers with hypercholesterolemia, highlight the importance of correcting maternal dyslipidemia.[1,17] In New Zealand white rabbits, diet-induced maternal dyslipidemia causes a dose-dependent fetal and postnatal atherogenesis, which was reduced by lowering maternal cholesterol with cholestyramine.[18] Similar data have been obtained in a murine model.[19]

A large body of literature suggests that an unhealthy uterine environment can lead to maladaptations in postuterine life, many of which are suspected to be the origin of chronic, noncommunicable diseases. Atherosclerosis is among the first of several conditions for which a role of developmental programming was described.[20] Several factors have been suggested that may play a role in developmental programming of the fetus.[21] Genetic factors, metabolic or environmental disturbances of the mother, and the father's lifestyle and genetics are important prepregnancy components that may contribute to fetal programming. During pregnancy, maternal malnutrition (either underfeeding or overfeeding), maternal stress, chemical exposure, preeclampsia, hypertension, gestational diabetes, maternal smoking, secondhand smoke exposure, metabolic syndrome, hyperlipidemia, obesity, intrauterine growth retardation, placental function, and hypoxia may be important influences. At the cellular level, adaptation occurs through DNA methylation, genetics, lifestyle choices during childhood, and altered immune responses, ultimately contributing to childhood atherosclerosis. Recent animal studies have revealed that changes in DNA methylation and chromatin modification may be responsible for the epigenetic programming and increased atherosclerotic susceptibility.[22] However, the exact mechanisms underlying the effects of maternal hypercholesterolemia in the offspring are still unclear.

Despite this lack of clarity, increasing evidence shows that epigenetic programming of metabolism during embryonic or fetal development might be involved.[23] Epigenetic phenomena occur at the interface between the genome and the environment. The environment can influence epigenetic information that is superimposed on the DNA, which may have long-term consequences for the transcription of specific regions of the genome. Results of animal studies show that permanent changes in either DNA methylation or chromatin modification, or both, may be responsible for the epigenetic programming of increased atherosclerotic susceptibility.[24] For instance, maternal hypercholesterolemia in ApoE-deficient mice leads to the activation of genes involved in cholesterol synthesis and LDLR activity in adult offspring.[17,24] Other animal studies have shown that the genes involved in immune pathways and fatty acid metabolism are upregulated in the offspring of hypercholesterolemic dams.[25] These findings indicate that an adverse maternal environment may alter basic cellular programming of the fetus.[24] Further research is needed to unravel the exact mechanisms through which maternal hypercholesterolemia influences this process.

Depending on what deleterious influences occur in utero and during childhood, the adult phenotype of insulin resistance and obesity that results in cardiometabolic disease is expressed at different genetic set points.[19]

In utero, the fetus handles lipid metabolism in a dynamic fashion. Pregnancy is associated with increased permeability of the vascular endothelium by small molecules, which can lead to vascular inflammation. This permeability is further increased

in the presences of diabetes. Additionally, it is now known that there is active transport of lipids to the fetus. This transport seems to vary at different stages of pregnancy. Early in gestation, the fetus seems to preferentially use lipids for the purposes of adequate membrane development and possibly for protection. Excess fat may, thereafter, be deposited in the liver, depending on gestational age and hepatic maturity. Additionally, fetal epicardial fat can be identified early in gestation. Presumably these mechanisms occur in an attempt to protect the fetal brain.[9]

The offspring of obese mothers have an increased risk of mortality in later life.[26] Minimal mortality is found in offspring of mothers with a normal body mass index (BMI).[26] Long-term studies have shown that offspring of mothers with a greater BMI and waist circumference have higher triglycerides and increased blood pressure and insulin resistance.[27]

MATERNAL CONSIDERATIONS

Lipid and lipoprotein levels have been tracked throughout pregnancy in groups of women with uncomplicated and complicated pregnancies. Nonetheless, no reference standards for lipid or lipoproteins during pregnancy currently exist.[9] Pregnancy is a state of insulin resistance reflected by the lipid and lipoprotein profiles of the mother. Within 6 weeks of gestation, lipid levels drop slightly, followed by an increase during each trimester of pregnancy. Triglyceride levels increase sharply during pregnancy, as do cholesterol levels. LDL increases in a similar pattern as that of total cholesterol. On average, cholesterol and triglyceride levels do not exceed 250 mg/dL. However, when abnormal pregnancies are included, levels can exceed 300 mg/dL.[28] Abnormally high triglyceride levels in the first trimester are significantly associated with gestational hypertension, preeclampsia, induced preterm birth, and fetuses considered large for gestational age.[29] Estrogens increase triglyceride levels through stimulating hepatic production of very-low-density lipoprotein (VLDL) and inhibiting hepatic and adipose lipoprotein lipase. Progesterone opposes these actions, whereas cytokines and inflammatory factors are important contributors of insulin resistance. However, this physiologic increase in lipids and lipoproteins is a mechanism aimed at accommodating fetal demands for normal growth and development.[23]

Preeclampsia is characterized by endothelial dysfunction prompted by an increase in triglyceride and free fatty acid levels. Triglyceride levels and ApoB and small LDL particles are all increased in preeclampsia, vascular cell adhesion molecule specifically is increased and serves as an indicator of endothelial dysfunction. Whether ApoB or small LDL particles cause this endothelial disruption is currently unclear.[30] Additionally, some indication exists that endothelial dysfunction may be caused partly by oxidative stress and decreased prostacyclin. Metabolic syndrome and gestational diabetes are conditions that predispose women to preeclampsia and overt diabetes.[29] Women with polycystic ovarian syndrome, for example, are more likely to have adverse pregnancy outcomes even if they are not obese.[31] This finding is particularly important because these women have insulin resistance and are prone to metabolic syndrome and diabetes.

Medical conditions that cause abnormal lipids and lipoproteins should be investigated and, if present, treated appropriately. Hypothyroidism, alcohol consumption, low-molecular-weight heparin, glucocorticoids, psychotropic medications, kidney disease, and lipodystrophy have all been associated with dyslipidemia; however, their effects during pregnancy are poorly characterized. The observed dyslipidemia is independent of diabetes, which is the most common reason for the disturbed lipid metabolism in general.[32] One of the more common reasons for high triglyceride levels

during pregnancy is the use of medications. Alcohol, estrogen, oral contraceptives, glucocorticoids, ß-blockers, valproate, sertraline, retinoic acids, cyclosporine, and tacrolimus are a few examples of potential causes. Cocaine use can also cause dyslipidemia. Offending agents should be identified and discontinued, ideally before conception.

Elevated VLDL and chylomicrons levels may occur and are thought to be secondary to a genetic predisposition. Triglyceride levels are typically very high, greater than 2000 mg/dL, increasing the risk of pancreatitis. Clinical features of severe hypertriglyceridemia include eruptive xanthoma, hepatosplenomegaly, abdominal pain, dyspnea, peripheral neuropathy, memory loss, and dementia. These neurologic symptoms need be addressed in pregnant women just as in nonpregnant persons. With severe hypertriglyceridemia, a reduction in fat calories to 15% to 20% daily is usually necessary. Insulin therapy may be used even in the absence of overt diabetes. Fish oil capsules are often used when triglyceride levels are greater than 500 mg/dL. Gemfibrozil or fenofibrate are widely used despite their classification as class C medications. The ultimate goal is to reduce triglyceride levels to less than 400 mg/dL in an effort to reduce the risk of pancreatitis. Other acute therapies reported in case studies include medium-chain triglycerides, niacin, sunflower oil, gene therapy, and plasmapherisis.[33]

All lipid-lowering medications, aside from bile sequestrate and omega-3-fatty acids, should be stopped before conception or immediately when pregnancy occurs unexpected. Lifestyle changes and glycemic control should be instituted where needed. During pregnancy, elevated cholesterol levels can be treated safely with a bile acid sequestrant. Severe hypertriglyceridemia associated with pancreatitis can be treated with omega-3 fatty acids, parenteral nutrition, plasmapheresis, and other lipid-lowering agents in the last trimester of pregnancy, notably gemfibrozil. Monitoring is recommended, at a minimum, every trimester or within 6 weeks of initiating treatment. Close follow-up of the mother with FH or with dysmetabolic issues of pregnancy is strongly recommended.

Women with gestational diabetes and/or preeclampsia are also at increased risk for elevated triglyceride levels, development of chronic hypertension, recurrent gestation diabetes and/or overt diabetes, recurrent preeclampsia, and development of albuminuria later in life. Two registered clinical trials are currently evaluating the effects of lipophilic statins to prevent preeclampsia in pregnancy. The true risk of congenital anomalies caused by statins in pregnancy is not well substantiated in humans. However, because statins are category X, statin use in pregnancy should be conducted only in a research setting until more information is available.[33]

A lipid profile should be obtained before conception and every trimester in women with FH who become pregnant. In these women, *N*-terminal pro-brain natriuretic peptide has been suggested as a useful marker for possible cardiac ischemia. FH can be treated with lifestyle and bile acid sequestrates, preferably colesevelam. Lastly, mipomersen (class B) and LDL apheresis may be necessary in pregnancy. Evaluation and treatment in a specialized center where facilities are available is recommended.

A thorough understanding of pregnancy and lactation-safe medications is imperative to ensure maternal and fetal safety. Class A and B medications are widely used as needed. Class C medications are often used when the benefit outweighs the risk. The chance for fetal harm is greatest during the first trimester. Category D medications have shown definitive evidence of human fetal risk, although potential benefits may warrant use. For category X medications, however, which have investigational or marketing data showing fetal abnormalities, the risks clearly outweigh the benefit. Class N medications have not been classified. Statins are currently classified as

category X, whereas fibrates, ezetimibe, niacin, cholestyramine, and omega-3 are category C. Colesevelam and mipomersen are class B.

POSTPARTUM CONSIDERATIONS

Postpartum follow-up of women with dyslipidemia during pregnancy includes close observation, specifically for those who experienced preeclampsia and/or diabetes. Compared with women who underwent an uncomplicated pregnancy, women who had preeclampsia were found to have worse cardiometabolic profiles at 1-year postpartum. Given the variety of providers who may participate in a women's antepartum, intrapartum, postpartum, and postpuerperal care, there is often loss of continuity and appropriate follow-up of pregnancy-related conditions. Women often do not lose the weight gained during pregnancy, which frequently goes unrecognized or may not be properly addressed. Overweight and obese women are 6 times more likely to exceed the pregnancy-related weight gain recommendations. These women are predisposed to higher postpartum weight gain and retention after pregnancy, with 13% to 20% of women being 5 kg or more above their preconception weight by 1-year postpartum.[16] The Health, Aging, and Body Composition Study found that the odds ratio for developing CVD was 3.31 for women and infants that were both <2500 gm and preterm compared with women having normal weight infants at term.[34] Weight gain and overweight status during midlife were strong independent predictors of the development of metabolic syndrome, type II diabetes mellitus, and early mortality.[35,36] Additionally, a positive obstetric history for preeclampsia doubles the long-term risk of CVD in the mother.[35] An obstetric history that includes gestational diabetes increases the 10-year risk for developing overt type II diabetes to approximately 40%. The prevalence of a significant and treatable dyslipidemia is approximately one-third in these populations.[36]

Although understanding of maternal dyslipidemia and its impact on the future health and well-being of the mother and her offspring is incomplete, increasing evidence suggests that providers must be more vigilant in assessing and treating CVD risk factors during pregnancy.[36,37] Additional assessments and studies addressing individual and public health consequences of the obesity epidemic are also urgently needed.

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