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