Maternal Heterozygous Familial Hypercholesterolemia and Its Consequences for Mother and Child

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During a normal pregnancy serum lipids (total, low-density lipoprotein [LDL]-cholesterol and high-density lipoprotein cholesterol, and triglycerides) rise steadily and take months to fall postpartum. LDL-cholesterol can increase by ~66% and triglycerides can rise 3-fold, and it has been suggested that elevated cholesterol during pregnancy may be associated with spontaneous preterm delivery. It is known that women with heterozygous familial hypercholesterolemia (FH) who become pregnant have very high levels of LDL-cholesterol early in pregnancy (260 mg/dL or 6.7 mmol/L) that rise to even higher levels near term (330 mg/dL or 8.6 mmol/L). These very high lipid levels raise the question of the potential risks of pregnancy to the mother and fetus. FH is caused by mutations in the low-density lipoprotein receptor. In this issue of Circulation, in a study linking the Medical Birth Registry of Norway (1967–2006) and the Medical Genetics Laboratory at Oslo University Hospital that has established the molecular diagnosis in 4400 patients, 2319 births of 1093 women were identified. The serum levels of cholesterol in the nonpregnant, nontreated FH women were 370 mg/dL (9.59 mmol/L). In this study, no maternal cardiovascular deaths were observed. In addition, the children of mothers with FH were no more likely than the general population to be born prematurely, have low birth weight, or have congenital malformations. Furthermore, even though the sample size was small, no congenital malformations were observed in the 19 pregnancies associated with the use of lipid-lowering drugs during pregnancy. Although this is a retrospective, registry-based study, the data likely reflect the birth outcomes of a representative cohort of childbearing FH women, as the authors claim. This is because the Medical Genetics Laboratory at Oslo University Hospital provides testing for FH at no cost to all the residents of Norway, and the data have been effectively linked to the Medical Birth Registry of Norway. The prevalence of heterozygous FH is ~1:500 in the general population. This autosomal dominant condition is characterized by elevated serum LDL levels (ie, an LDL-cholesterol above the 95th percentile for the general population, which is usually above 200 mg/dL [5.2 mmol/L] starting in childhood, tendon xanthomas, and a family history of premature coronary disease. The disease is highly genetically heterogeneous, with >1000 different mutations in the low-density lipoprotein receptor gene causing this disorder. Affected patients have a substantially increased risk of premature coronary heart disease morbidity and mortality. Approximately 50% of men have a myocardial infarction before 60 years of age if they are not treated with lipid-lowering agents. An important concept is that FH patients have continuous exposure of the vasculature to significantly elevated levels of plasma LDL-cholesterol from birth, and it is this cumulative effect that lowers the threshold for coronary heart disease by decades (Figure). This threshold is lowered further by other risk factors such as diabetes mellitus, smoking, and hypertension. Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in FH heterozygotes reduces the risk of cardiovascular events. In a Rotterdam study, statin treatment of FH heterozygotes was associated with an overall cardiovascular risk reduction of 76%, and resulted in rates of myocardial infarction similar to an age-matched sample from the general population. The importance of early identification of FH heterozygotes and the initiation of statin treatment was apparent in a prospective registry study of patients with heterozygous FH. In this study, primary prevention resulted in a 48% reduction in coronary heart disease mortality (an effect more pronounced in women) and a 25% reduction in patients with known coronary disease. Therefore, whereas the present study suggests that maternal risk during pregnancy is low and fetal outcomes are favorable among mothers with FH, high LDL-cholesterol levels during childbearing years may have long-term implications for women with FH. Nevertheless, statins should be avoided in pregnancy. The Food and Drug Administration classifies statins as category X in pregnancy, which means they have been linked to fetal abnormalities in animal and human studies, and the benefits of taking them do not outweigh potential risks. In a review of case reports of first-trimester statin exposure, defects of the central nervous system and unilateral limb deficiencies were observed in infants exposed to the lipophilic statins (cerivastatin, simvastatin, lovastatin, and atorvastatin). Pravastatin, which is hydrophilic, is similarly classified. The Food and Drug Administration classifies ezetimibe and niacin as category C in pregnancy, which means “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.” Because the data in humans are
Cumulative LDL Exposure & CHD

Figure. This research was originally published in the Journal of Lipid Research. The relationship between cumulative LDL-cholesterol and age is demonstrated. Cumulative plasma levels of LDL-cholesterol were estimated from mean plasma levels of LDL-cholesterol for FH homozygotes (LDLR $^{-/-}$), FH heterozygotes (LDLR $^{+/}$), age-adjusted LDL-cholesterol levels in normals, and PCSK9 heterozygotes (PCSK9 $^{-/-}$). The horizontal line represents a theoretical threshold of the cumulative LDL exposure required for the development of coronary heart disease. LDL-C indicates low-density lipoprotein cholesterol; FH, familial hypercholesterolemia; CHD, coronary heart disease; LDLR, low-density lipoprotein receptor.

Limited, it would seem prudent to avoid using these drugs during pregnancy or lactation, and women of childbearing age should be counseled to stop taking these medications at least 1 month before discontinuing contraception. Colesevelam, a bile acid sequestrant, has been assigned category B during pregnancy by the Food and Drug Administration, although there are no controlled studies that have assessed the safety of this agent in humans.

The diagnosis of maternal FH also offers an opportunity to enhance preventive care of the child. First-degree relatives of mothers with heterozygous FH have a 50% chance of inheriting the disease. Early detection to identify the children is important so that effective treatment can be initiated in a timely fashion. Dietary recommendations for these children includes restricting the intake of saturated fat to 7% of total calories and dietary cholesterol to 200 mg/d, and these restrictions do not appear to interfere with growth and development or sexual maturation. The Food and Drug Administration approves the use of lovastatin, simvastatin, pravastatin, and atorvastatin in boys after 10 years of age and in girls after the onset of menses. Children should preferably be at Tanner stage II maturation level or higher before treatment is initiated. A study in the Netherlands showed that early initiation of statin treatment in children with FH between 8 and 18 years of age is safe. In this study, early treatment was associated with delayed progression of carotid intimal wall thickness. Children appear to tolerate the tablet form of bile acid-binding resins better than the powder, but gastrointestinal side effects are common and compliance is poor. Niacin is not recommended for use in pediatric practice because of problems with flushing and liver function abnormalities.

A more recent American Academy of Pediatrics Clinical Report recommended that pharmacological intervention should be considered for children 8 years and older who have one of the following:

- An LDL-cholesterol concentration of $\geq 190$ mg/dL (4.92 mmol/L) despite diet therapy.
- An LDL-cholesterol concentration $\geq 160$ mg/dL (4.14 mmol/L) and a family history of heart disease or at least 2 additional risk factors present.
- An LDL-cholesterol $\geq 130$ mg/dL (3.37 mmol/L) and diabetes.

Although these recommendations remain controversial among pediatricians, I believe that the referral of young children with FH to physicians with specialized knowledge of lipid disorders should be encouraged so that the issue of the advisability of lipid-lowering treatment is addressed with the child’s parents. Given the efficacy and safety of statin therapy, and the cumulative cardiovascular burden of sustained high levels of untreated LDL-cholesterol, a more aggressive approach to treatment of FH in children may be warranted.

Acknowledgments

I thank my colleagues James A. de Lemos, MD, and Helen H. Hobbs, MD, for their appraisal and suggestions for the manuscript.

Disclosures

None.

References


**Key Words:** Editorials | familial hypercholesterolemia | low-density lipoprotein-cholesterol | pregnancy
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Circulation. 2011;124:1599-1601
doi: 10.1161/CIRCULATIONAHA.111.059311
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/15/1599

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