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 \( \approx 66\% \) 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 cholesteryl 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 \( \approx 1:500 \) 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...
restrictions do not appear to interfere with growth and gastrointestinal side effects are common and compliance is 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 and should be counseled to women of childbearing age to consider alternative treatments. None.

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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