

## Dyslipidemia and pregnancy

### History:

A 16-year-old adolescent girl was seen for a routine clinic follow up visit. She was initially referred at age 10 for elevated cholesterol noted in a maintenance health screening examination.

Prior to screening, she was in good health. She actively participated in sports, followed an age-appropriate diet, had no chronic illnesses and was taking no medications. The child's mother, age 42, was taking a statin for elevated cholesterol (total cholesterol > 300 mg/dL). The maternal grandfather had a myocardial infarct at 44 years of age and subsequently required a stent. The parents are divorced; the paternal family history is unknown.

### Laboratory studies:

At the time of initial referral, the child's fasting laboratory findings were as follows:

#### Lipid profile:

- **Total cholesterol:** 364 mg/dL
  - Triglycerides: 65 mg/dL
  - HDL cholesterol: 55 mg/dL
  - LDL cholesterol: 300 mg/dL
- **Glucose:** 88 mg/dL
- **ALT/AST:** Normal
- **TSH:** Normal

The child was diagnosed with heterogeneous familial hypercholesterolemia and placed on 20 mg of pravastatin daily. Compliance has been excellent, and follow up laboratory studies confirm a good response, with no adverse events.

At the time of her most recent clinic follow up, the patient noted missing her last menstrual period. Subsequent laboratory studies confirmed that she is 8 weeks pregnant. Other than pravastatin 20 mg per day, she was taking no medications.

Her most recent fasting laboratory studies are as follows:

#### Lipid panel:

- **Total cholesterol:** 146 mg/dL
  - Triglycerides: 70 mg/dL
  - HDL cholesterol: 54 mg/dL
  - LDL cholesterol: 90 mg/dL
- **Glucose:** 90 mg/dL
- **ALT/AST:** Normal
- **TSH:** Normal
- **HCG:** Positive

## Questions:

1. Which of the following statements best describes maternal lipid levels during normal pregnancy?

- a. Total and LDL-C levels are unchanged while HDL-C levels are reduced.
- b. Total and LDL-C levels are unchanged while HDL-C levels are increased.
- c. Total and LDL-C levels are increased while HDL-C levels are increased.
- d. Total and LDL-C levels are decreased while HDL-C levels are increased.

**Answer: c.** Total and LDL-C levels are increased while HDL-C levels are increased.

**Discussion:** Total cholesterol, LDL-C and triglycerides are normally increased during pregnancy to 1) provide a source of energy for both mother and fetus and 2) increase precursors for placental hormone production. Compared with levels before pregnancy, total cholesterol and LDL cholesterol are typically increased by 30 to 50 percent. Maternal lipid levels may be altered by a variety of factors including the mother's health before and during pregnancy, use of medications, BMI and weight gain during pregnancy, smoking and genetics. The expected rise in total cholesterol and LDL-C during pregnancy is more pronounced in women with pre-existing hypercholesterolemia (e.g., those who are heterogenous for familial hypercholesterolemia).

In addition to elevation of cholesterol and triglycerides, there are increases in apolipoprotein-B, apolipoprotein-AI and VLDL cholesterol, and a shift toward higher concentrations of small, dense LDL-C. HDL-C rises during the first trimester and remains high throughout pregnancy. Cholesterol levels may remain elevated for approximately 6 weeks after birth.

**2. Given the teenager's clinical history, which of the following would you recommend?**

- a. Decrease her pravastatin to 10 mg daily and add ezetimibe 10 mg daily.
- b. Change pravastatin to a cholesterol-binding agent.
- c. Discontinue all lipid-lowering medications during pregnancy.
- d. Change the pravastatin to niacin.

**Answer: b.** Change pravastatin to a cholesterol-binding agent.

**Discussion:** The National Lipid Association recently advocated universal screening for familial hypercholesterolemia. As a result of an increasing number of screening programs and increased public and professional awareness, younger patients are being identified and treated with lipid-lowering medications, especially statins. The issue of pregnancy in young heFH female patients raises several interesting issues, both for the health of the mother as well as that of the fetus. Currently, no evidence-based guidelines exist on the optimum clinical approach to treatment of hypercholesterolemia in pregnant women with familial hypercholesterolemia. Statins and other lipid-lowering medications are classified by the USFDA as Class X drugs. Both water soluble (pravastatin) and fat soluble (cerivastatin) statins can impede placental growth. Cholesterol is essential for fetal development. Disruption of maternal or fetal cholesterol production and utilization may result in teratogenic effects. The evidence, however, for teratogenicity associated with statin use is scant and somewhat contradictory.

All women with hypercholesterolemia who wish to become pregnant, especially those receiving treatment, should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe and niacin at least 4 weeks before discontinuing contraception. These treatments should not be used during pregnancy. In the case of an unintended pregnancy, a woman with FH should discontinue statins, ezetimibe and niacin immediately and consult her healthcare provider about treatment options. The use of other lipid-lowering medications (e.g., colesvelam) may be considered. In women who are breastfeeding, lipid-lowering medications should also be withheld. In women with severe hypercholesterolemia (i.e., homozygous FH), options may include LDL apheresis.

**3. Which of the following is true regarding the exaggerated elevation of cholesterol levels in pregnant women with heFH?**

- a. Both total and LDL-C levels are normally increased during pregnancy; therefore, the exaggerated elevation of cholesterol levels in pregnant women with heFH should be of no consequences.
- b. The exaggerated elevation of cholesterol levels in pregnant women with heFH often results in spontaneous abortion of the fetus.
- c. The exaggerated elevation of cholesterol levels may result in an enhanced tendency toward atherosclerosis in the child.
- d. The exaggerated elevation of cholesterol levels in pregnant women with heFH justified the use of statins during pregnancy and a consideration of supplemental LDL apheresis.

**Answer: c.** The exaggerated elevation of cholesterol levels may result in an enhanced tendency toward atherosclerosis in the child.

**Discussion:** Although dyslipidemia during pregnancy is unlikely to have adverse short-term effects, studies suggest that hypercholesterolemia in utero may predispose the fetus to increased risk of premature atherosclerosis. Both human and animal studies reveal an enhanced tendency toward atherosclerosis in the offspring of mothers who have hypercholesterolemia during pregnancy. Animal studies suggest that this tendency can be reversed by treatment with lipid lowering and anti-oxidative agents. However, it appears that no human studies have evaluated the efficacy and safety of lipid-lowering interventions in pregnant woman, especially those with familial hypercholesterolemia.

## Key points:

1. Although pregnancy is normally characterized by physiologic dyslipidemia, exaggerated elevation of lipid levels may have adverse consequences for the mother and her child.
2. Currently, no evidence-based guidelines exist on the optimum clinical approach to treatment of hypercholesterolemia in pregnant women with familial hypercholesterolemia. Studies suggest an enhanced tendency toward atherosclerosis in the offspring of women with hypercholesterolemia during pregnancy.
3. Women who wish to become pregnant should discontinue use of statins, ezetimibe and niacin at least 4 weeks before discontinuing contraception. These treatments should be stopped immediately in the case of unintended pregnancy, and they should not be used during lactation.
4. Evidence for statin-related teratogenesis is conflicting and limited. Studies that evaluate the safety and efficacy of lipid-lowering therapies in pregnant women with hypercholesterolemia are lacking.
5. Although limited data exist, ezetimibe, nicotinic acid and fibrates have been associated with teratogenicity in animal studies.
6. Bile acid sequestrants are currently considered the only safe lipid-lowering agent to treat hypercholesterolemia during pregnancy. The need for supplemental fat-soluble vitamins should be considered when using bile acid sequestrants.

## References/suggested reading:

1. Ito MK, McGowan MP, Moriarty PM. Management of familial hypercholesterolemia in adult patients: recommendations from the National Lipid Association expert panel on familial hypercholesterolemia. *J Clin Lipidol*. 5(3SUPPL):S38-45, 2011 June.
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3. Peterson EE, Mitchell AA, Carey JC, Werler MM, Louik C, Rasmussen, SA. Maternal exposure to statins and risks for birth defects: a case series approach. *Am J Med Genet A*. 146A(20):27015.
4. Kazmin A, Garcia-Bournissen F, Koren G. Risks of statin use during pregnancy: a systemic review. *J Obstet Gynaecol Can*. 29(11):906-8, November 2007.
5. Avis HJ, Hutten BA, Twickler, MTB, Kastelein JP, van der Post JA, Stalenhoef, AF, and Vissers MN. Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn? *Curr Opin Lipidol* 2009, 20(6):484-90.