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REVIEW

Dilemmas in treatment of women with familial hypercholesterolaemia during pregnancy

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ABSTRACT

Familial hypercholesterolaemia (FH) is a co-dominant monogenic disorder of lipoprotein metabolism, characterised by severely elevated levels of low-density lipoprotein cholesterol (LDL-C) from birth onwards. Treatment of FH patients with cholesterol-lowering medication is mandatory to prevent premature cardiovascular disease (CVD). As a result of a nationwide screening in the Netherlands, a large group of women with FH in the child-bearing age range has been identified. Physicians are faced with a treatment dilemma if these females present either with a wish for pregnancy or an established pregnancy, since all systemically absorbed lipid-lowering medication is contraindicated during pregnancy. Currently, no evidence-based guidelines exist on the optimal clinical approach in these patients. Animal studies have shown conflicting data on potential teratogenicity of statins. In humans, there is no strong adverse safety signal, but prospective studies are lacking. The consequences of maternal hypercholesterolaemia during pregnancy for both mother and child are not well determined, although it has been suggested that it may increase the risk of CVD in the offspring.

This review describes two representative cases from clinical practice, and discusses clinical considerations for treating pregnant FH patients supplemented with what is known from the literature.

KEYWORDS

Familial hypercholesterolaemia, pregnancy, statins, teratogenicity

INTRODUCTION

Heterozygous familial hypercholesterolaemia (FH) is a common inherited disorder of lipid metabolism with a prevalence of 1:500 individuals. The underlying molecular defect is a mutation in the low-density lipoprotein (LDL) receptor gene encoding for liver cell-surface receptors, and as a result, LDL cholesterol (LDL-C) uptake by the liver out of the circulation is dramatically reduced.[1,2] Hence, patients with FH are clinically characterised by severely elevated LDL-C levels from birth onwards which strongly predispose to premature atherosclerosis and subsequent cardiovascular disease (CVD). If left untreated, the age- and sex-standardised cardiovascular mortality is even four to five times higher than that in the general population. In general, FH patients are advised to adhere to a healthy lifestyle including strict diet, frequent physical activity and no smoking. Since these lifestyle modifications do not sufficiently reduce LDL-C levels, drug therapy is considered in almost all FH patients. Primarily, aggressive cholesterol lowering is achieved by statin therapy; the effectiveness of these compounds in reducing mortality and morbidity is well established today.

In the Netherlands, the total number of patients with FH is estimated at 40,000 individuals. Even though FH is a common disorder, many patients are not diagnosed or only after a premature cardiac event has already occurred. Therefore, in 1994 a nationwide screening programme started (since 2003 supported by the government) to identify these patients in order to make early cholesterol-lowering treatment possible.[3] At present, 20,000 FH patients have been identified, among whom approximately 2260 women in the age ranging from 20 to 40 years. For this growing number of female FH patients who are usually intensively treated with lipid-lowering medication, a pregnancy wish or an established pregnancy could lead to concerns for both mother and child. Physicians are also faced with a

genuine dilemma, as no evidence-based guidelines are available for the management of these patients. Current practice is to advise to discontinue all systemically absorbed lipid-lowering medications with an option to replace them by bile acid binding resins, in order to avoid potential teratogenic effects in the unborn child. The National Institute for Health and Clinical Excellence (NICE) has published guidelines for the identification and management of individuals with FH including recommendations on treatment in the childbearing age, which are summarised in *table 1*.[4] In short, these recommendations consist of cessation of lipid-lowering drugs and accept markedly increased cholesterol levels that are acknowledged to give rise to more atherogenicity for the mother (and possibly even the newborn). In this contribution, we will present two representative cases with all the clinical considerations.

Table 1. *Summary of NICE guidance on the management of fertility in women with familial hypercholesterolaemia*[4]

Period: prior to attempting to conceive
- When lipid-lowering medication is first considered for girls and women of childbearing age, risks to the pregnancy and the foetus while taking lipid-lowering medication should be discussed.
- Combined oral contraceptives are not generally contraindicated for women being treated with lipid-lowering therapy.

Period: attempting to conceive and during gestation
- There is no contraindication to pregnancy for the majority of women with FH.
- Women wishing to become pregnant should be advised to stop use of statins three months prior to attempting to conceive.
- Women with FH who are considering pregnancy or who are pregnant should be provided with shared care including expertise in both cardiology and obstetrics.
- In the unusual situation where a woman has symptoms of CHD or homozygous FH and is intending to become pregnant, she should discuss her intentions with her cardiologist.
- Women with FH who conceive while taking statins or other systemically absorbed lipid-lowering medications should be advised to stop treatment immediately and be referred to an obstetrician for foetal assessment.
- It is not useful to regularly measure cholesterol concentrations during pregnancy.

Period: lactation
- Women with FH should be encouraged to initiate breast-feeding. Only resins should be considered as lipid-lowering therapy during lactation.

FH = familial hypercholesterolaemia; CHD = coronary heart disease.

CASES

Patient A is a 35-year-old female diagnosed with FH five years previously. She was treated with atorvastatin 40 mg once daily (OD) and a cholesterol absorption inhibitor (10 mg OD). Her lipid profile was within target levels according to clinical guidelines with a LDL-C of 1.9 mmol/l. Because of a pregnancy wish, she discontinued lipid-lowering therapy and started folic acid substitution three months before stopping her oral contraceptives. She conceived three months later and the subsequent gestation period was uncomplicated. During pregnancy, LDL-C was elevated up to 7.7 mmol/l. After delivery of a healthy son (AD 40 0/7, birth weight 3420 gram), she continued breastfeeding for three months. As a consequence she did not receive lipid-lowering medication for 15 months. IMT measurement was done before and after pregnancy and showed a mean increase of 0.0625 mm. The expected IMT increase for a FH women is approximately 0.01 mm each year, so 0.0125 mm in 15 months.[5]

Patient B is a 36-year-old female. She was diagnosed with FH when she was 18 years old and treated with simvastatin 40 mg OD; since then she had adopted a healthy lifestyle. At the age of 29 years she discontinued statin therapy as she aimed to conceive. During her first pregnancy the LDL-C increased to 9.3 mmol/l. Colestyramine was prescribed; however she did not start with colestyramine in view of the expected side effects. She gave birth to a healthy daughter (AD 39 1/7, birth weight 3540 gram) and she restarted statin therapy three months after delivery. At the age of 32, she was considering pregnancy again. After cessation of statin therapy (before conception) she decided to start with colestyramine therapy, bearing in mind her high cholesterol levels during the first pregnancy. Unfortunately, similarly high lipid levels were measured. She gave birth to a healthy daughter (AD 36 4/7, birth weight 3200 gram). Again, after three months of lactation, she restarted statin therapy. Due to two pregnancies, the patient did not receive adequate lipid-lowering medication for a total of 30 months.

These two cases describe different dilemmas for both these female FH patients who are on statin therapy and have a wish for pregnancy, and for their treating physicians. Next to the direct teratogenic effect of statins, the estimated risk of developing or progression of atherosclerosis with a reduced life expectancy is still not well delineated. This fact poses FH females and their treating physicians with serious conflicts that we will discuss hereafter.

LIMITED EVIDENCE FOR CLINICALLY RELEVANT SIDE EFFECTS OF LIPID-LOWERING TREATMENT

There are no evidence-based guidelines with respect to the use of lipid-lowering compounds (e.g. statins) during pregnancy; observation and intervention studies are unfortunately lacking. Most information should therefore be considered as experience based instead of evidence based. Animal studies have shown conflicting evidence on potential teratogenicity of statins. Studies in both rat and rabbit models failed to show any teratogenic effect of simvastatin, however skeletal malformations have been noticed for lovastatin, cerivastatin and fluvastatin in the same animal models. Atorvastatin and mevinolin showed developmental toxicity and skeletal defects, respectively, but only at high supra-therapeutic doses that induced maternal toxicity, with a reduced maternal weight and reduced food

consumption. Due to results emerging from these animal studies, all statins are considered as contraindicated during pregnancy and therefore data on therapeutic statin doses during pregnancies in humans are scarce.

A case series of FDA reports in humans that was published in 2004, reported 178 gestational statin exposures from 1987 to 2001. After exclusion of cases involving first-trimester elective or spontaneous abortions, pregnancy loss due to maternal illness, foetal genetic disorders, transient neonatal disorders, or loss to follow-up, 52 cases could be analysed. Reported maximum doses were 40 mg OD for lovastatin, 10 mg OD for atorvastatin, 20 mg OD for simvastatin, and 0.25 mg OD for cerivastatin. Twenty cases reported structural birth defects (such as severe defects of the central nervous system and limb deficiencies), more often present after exposure to lipophilic statins as compared with hydrophilic statins. Lipophilic statins have been shown to enter foetal tissues after passage of placental circulation in animal studies.[6] In a post-marketing study, results of 134 women were analysed who had used lovastatin or simvastatin during pregnancy (of which 89% only during the first trimester). Because the percentage of spontaneous abortions, congenital anomalies, foetal deaths and stillbirths was not higher than the expected incidence of the general population, the authors concluded that there was no evidence for a correlation between exposure to statins during pregnancy and pregnancy outcome.[7] More recent reports lend further support to these conclusions, e.g. the Slone Epidemiology Center Birth Defects Study and the National Birth Defects Prevention Study.[8,9] Limitations of these analyses are incomplete datasets and the relatively rare occurrence of statin use during pregnancy. In addition, the patient group is rather heterogeneous, for example due to the inclusion of patients with diabetes or obesity. In a similar study, three groups of pregnant women with a history of dyslipidaemia treated with a statin, a fibrate and/or nicotinic acid, or no treatment in the first trimester were compared all having a similar prevalence of congenital abnormalities. The question remains, however, whether significant differences in stillbirths exist between the various groups.[10] These retrospective observations imply that negative effects as a result of statin use during the first trimester may be less severe than earlier reports have claimed. A cohort study on teratogenic effects of statin therapy in 64 pregnant women taking statins in the first trimester, and 64 pregnant women without exposure to statins, has shown no differences in prevalence of congenital anomalies, but gestational age at birth (38.4 *vs* 39.3 weeks) and birth weight (3.14 kg *vs* 3.45 kg) were significantly lower in the statin group compared with the non-statin group.[11]

Limited data on teratogenicity concerning other lipid-lowering agents is currently available (*table 2*). Ezetimibe, nicotinic acid and fibrates have all been associated with teratogenic effects in animal studies. Ezetimibe is known to pass from the maternal circulation into breast milk in rats. According to FDA and EMEA advice, it is preferable not to prescribe these agents during pregnancy and lactation.[12] The use of the bile acid binding resin colestyramine during pregnancy in humans has not shown an increased risk for congenital anomalies thus far. Clinical data on the use of the newer bile acid binding resin colesevelam during pregnancy are still lacking, but animal studies showed no adverse effects.

Table 2. *Lipid-lowering drugs around pregnancy*

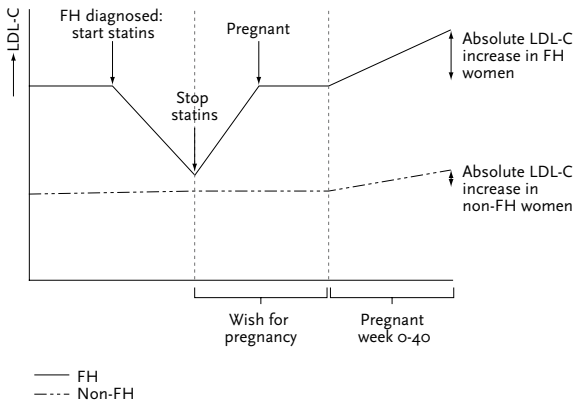
	Approved	**Contraindicated**
Preconceptional phase (<3 months before stopping contraceptives)	Colestyramine (12-16 g OD, max. 24 g daily) Vitamin supplementation MgO_2 in case of constipation Colesevelam?	Statins Fibrates Ezetimibe Nicotinic acid
During pregnancy	Idem	Idem
Lactation period	Idem	Idem

LIPID LEVELS DURING PREGNANCY

In the general population, maternal cholesterol levels (and subsequently LDL-C levels) increase by approximately 30 to 50% during pregnancy as a result of enhanced cholesterol synthesis in the liver, probably as a consequence of increased oestrogen levels. The increase in cholesterol levels starts from the first trimester onward and is the most pronounced in the third trimester. HDL-C also rise from the first trimester and will remain augmented during the rest of pregnancy. Triglyceride levels can rise even threefold compared with preconceptional levels.[13,14] The physiological explanation of this gestational hypercholesterolaemia and hypertriglyceridaemia may have a biological role in the need for increased sex steroids synthesis and maintenance of an adequate nutrient supply for both pregnant mother and foetus. Despite the increase in lipid levels, the lipid profile will not be considered as atherogenic in non-FH patients.

Currently, only one study on pregnant FH women has been published.[15] This Scandinavian study analysed lipid profiles between week 17 and 36 of gestation in 22 FH patients in comparison to 149 normocholesterolaemic individuals. In both groups, a significant increase in total cholesterol, LDL-C and triglycerides was found. Although the relative increase in lipid levels was equal between the two groups, the absolute increase (LDL-C: 1.9 mmol/l *vs* 0.8 mmol/l, respectively) was more pronounced in the FH group due to elevated levels at baseline. The average LDL-C increased from 6.7 mmol/l to 8.6 mmol/l between week 17 and 36, as for the normocholesterolaemic females these levels were 3.1 mmol/l and 3.9 mmol/l, respectively. These effects are schematically illustrated in *figure 1*. HDL-C remained unchanged in both groups. No differences in birth weight, birth length and gestational age at delivery were observed.

Figure 1. *LDL-C levels during pregnancy in women with and without FH*



LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolaemia.

CONSEQUENCES FOR THE MOTHER

Currently, it is unknown whether increased cholesterol levels during pregnancy will lead to enhanced atherosclerosis for the FH mother. Given the average birth rate of 1.8 children for a Dutch female and a lactation period of three months, the total 'unprotected' period consists of at least 27 months, plus the time it takes to conceive from the moment of discontinuing contraceptives. Considering the achieved cholesterol levels that exceed approximately threefold the physiological range, this growth of atheroma is not unlikely, even more so if treatment cessation spans a period much longer than the pregnancy itself. Subsequent pregnancies, long-term breastfeeding, or an unfulfilled pregnancy wish can prolong this period substantially. In normocholesterolaemic mothers, it has been shown that elevated lipid levels during pregnancy do not have adverse effects on endothelial function.[16] Results of the Framingham Heart Study (an extensive population cohort study) showed an elevated risk for CVD in (non-FH) women who had more than six pregnancies when compared with nulliparous women (relative risk 1.6; 95% confidence interval: 1.1 to 2.2).[17] However, another population-based study did not show a relationship between reproductive history and intima-media thickness, a surrogate marker for atherosclerotic disease, after correction for age.[18] The case of our first patient suggests that there is a considerable IMT increase during the period around pregnancy when therapy is discontinued, but currently no studies have investigated this hypothesis in FH women.

Finally, women with FH could have an increased risk for hypertensive disease during pregnancy since preeclampsia is associated with hypercholesterolaemia.[19] The same holds true for recurrent miscarriage. Theoretically and from animal experiments statins might reduce the risk for these pregnancy complications.[20] However, further research is needed to investigate this hypothesis.

FOETAL DEVELOPMENT

Besides maternal complications, it is also unknown whether high cholesterol levels in utero has a negative impact on foetal development. There are several recent indications that the foetus can acquire maternal cholesterol and use it for its own metabolic needs, such as cellular growth.[12] Currently there are no reports indicating lipotoxicity of high maternal cholesterol levels for the foetus, but it is has been suggested that maternal hypercholesterolaemia during pregnancy could induce increased cardiovascular risk for offspring. An autopsy study in spontaneously aborted foetuses showed that offspring from (non-FH) hypercholesterolaemic mothers exhibit significantly more and larger preatherosclerotic aorta lesions than offspring from normocholesterolaemic mothers.[21] Another autopsy study showed that children from hypercholesterolaemic mothers show faster progression of preatherosclerotic lesions, compared with children from normocholesterolaemic mothers.[22] These results have been supported in animal studies.[23-25] Experiments in murine models showed that differences in arterial gene expression between offspring of normo- and hypercholesterolaemic mothers persist long after birth, supporting the assumption that foetal lesion formation is associated with genetic programming, which may in turn affect postnatal atherogenesis.[26,27] Maternal treatment of hypercholesterolaemia during pregnancy may reduce atherosclerosis in offspring.[28] However, this observation has not been repeated in human studies.

CONCLUSION AND CLINICAL IMPLICATIONS

Thus far, prospective studies on statin use in FH patients around pregnancy are lacking[12] and this fact will raise some concern for FH patients with a pregnancy wish. Results from animal studies indicate that statins are associated with adverse foetal outcomes predominantly at supra-therapeutic levels. From available reports in humans, there is no clearly adverse safety signal, but the 'primum non nocere' principle does argue against the use of statins during pregnancy and lactation presenting absence of 'proven' safety. Women who experience an unplanned pregnancy can be reassured that the chance of an adverse pregnancy outcome is minor. When FH patients are using contraceptives, they should stop taking statins approximately three months

before discontinuation of contraceptives. Concerning lipid-lowering therapy, treatment with bile acid binding resins is the only option. However, since this drug reduces lipid levels by only 15% at the expense of significant side effects, the majority of women will not reach target levels for LDL-C even if they continue to use the drug throughout pregnancy. Using these drugs, supplementation of fat soluble vitamins needs to be considered. However, tolerance to colestyramine is poor, mainly because of constipation. An alternative may be the recently introduced compound colesevelam, a bile acid binding resin with significantly less side effects.[29] Currently, colesevelam is registered for patients with primary hypercholesterolaemia with LDL-C above target levels despite optimal therapy, and for patients who do not tolerate statin therapy.

In conclusion, teratogenicity of statins and other lipid-lowering medications should be further investigated. In addition, large follow-up studies are needed to determine the effect of hypercholesterolaemia during pregnancy on CVD risk for FH women, as well as for their offspring.

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