Childhood initiated statin therapy in familial hypercholesterolemia
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PREGNANCY IN WOMEN SUFFERING FROM FAMILIAL HYPERCHOLESTEROLEMIA: A HARMFUL PERIOD FOR BOTH MOTHER AND NEWBORN?


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ABSTRACT

Purpose of review: The present review aims to highlight the consequences for mother and child of profound hypercholesterolemia during pregnancy of women with familial hypercholesterolemia.

Recent findings: Familial hypercholesterolemia is increasingly diagnosed in younger patients due to the existence of screening programs and more widespread cholesterol testing. Increasing numbers of young female patients with familial hypercholesterolemia raise the issue of pregnancy and its consequences for the familial hypercholesterolemia patient herself but also for her offspring. When pregnancy is considered, lipid-lowering drugs are often discontinued because of the fear for teratogenic effects. The evidence for teratogenesis associated with statin use is scant and conflicting. On the other hand, several studies do suggest that pronounced hypercholesterolemia during pregnancy has adverse effects on both fetus and mother. In fact, human and animal studies reveal an enhanced tendency toward atherosclerosis in the offspring of women who suffer from hypercholesterolemia during pregnancy. In animal studies, some evidence exists that this can be reversed by treatment with lipid-lowering and antioxidative agents. Until today, however, no human studies exist that have evaluated efficacy or safety of lipid-lowering interventions in pregnant women with familial hypercholesterolemia.

Summary: Altogether, the suggested relationship between severe hypercholesterolemia and enhanced atherosclerosis in offspring and possibly the mother warrants further confirmation and, consequently, studies that focus on therapeutic strategies that can safely lower cholesterol levels during pregnancy in these women.
INTRODUCTION

During conception and pregnancy, lipid-lowering treatment is almost always discontinued because mothers and physicians alike fear the possible teratogenic effects of such therapy. However, an increasing number of studies suggest that pronounced maternal hypercholesterolemia during pregnancy has adverse consequences for both fetus and mother \textsuperscript{1 - 7}. This may have important consequences for lipid management in pregnant women with familial hypercholesterolemia, a prevalent inherited disorder occurring in one per 500 individuals in the general population. Familial hypercholesterolemia is characterized by elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular events \textsuperscript{8}.

The clinical question of how to treat pregnant women with familial hypercholesterolemia is increasingly becoming urgent, as nationwide screening programs for familial hypercholesterolemia are being developed in a number of countries. Such screening programs allow early identification and treatment of affected individuals often before or during childbearing age. Hitherto, no explicit guideline with respect to the treatment of pregnant women with familial hypercholesterolemia exists and literature about this issue is scarce or nonexistent. As an exception to this, the Adult Treatment Panel III of the American National Cholesterol Education Program states that bile acidbinding sequestrants could be considered for women with elevated cholesterol levels considering pregnancy \textsuperscript{9}. This review will summarize current evidence regarding the effect of pronounced hypercholesterolemia during pregnancy on the (unborn) child and future mother as well as the possible implications for the treatment of pregnant women with familial hypercholesterolemia.

Cholesterol levels during pregnancy

Maternal plasma TC as well as triglyceride levels increase during gestation. Proposed biological explanations for these changes include a metabolic shift from carbohydrates to lipids for maternal energy production in order to make glucose available for the fetus \textsuperscript{10} and an increased need for cholesterol as a precursor for the production of steroid hormones in the placenta \textsuperscript{11}. These increased lipid levels during pregnancy are the result of enhanced synthesis at the level of the liver, probably as a consequence of increasing estrogen levels \textsuperscript{10}. Increases of both TC and LDL-C of approximately 40\% are reported. Also, increments of apolipoprotein B, apolipoprotein A1 and very low-density lipoprotein cholesterol (VLDL-C) are present, as well as a shift toward a higher concentration of (more atherogenic) small dense LDL-C \textsuperscript{11 - 15}. LDL-C levels rise from the 12th week of pregnancy onward with a peak occurring in the second trimester. Along with LDL-C, atheroprotective high-density lipoprotein cholesterol (HDL-C) levels also rise from the first trimester onward and remain
high during the entire pregnancy. Triglycerides may rise even three-fold, but normalize rapidly after delivery, whereas cholesterol levels remain elevated for approximately 6 weeks after birth. Notably, hypercholesterolemia is most pronounced in women with preexisting hypercholesterolemia. A study comparing lipids in pregnancy between controls and females with familial hypercholesterolemia revealed a similar percentage rise in TC, LDL-C and triglycerides (25 vs. 29%; 29 vs. 30%; 103 vs. 116%, respectively) in the period between approximately the 18th and 36th week of gestation. As nonpregnant levels are severely elevated in women with familial hypercholesterolemia, the absolute magnitude of these changes is considerably higher in females with familial hypercholesterolemia.

In conclusion, physiological changes in lipoprotein levels occur even in normal pregnancy; hence, the term ‘maternal hypercholesterolemia’ refers to cholesterol levels above those already observed in pregnancy of healthy individuals. Obviously, the questions to address are as follows: what is known about the (long-term) consequences for the developing child and the mother of maternal hypercholesterolemia in women with familial hypercholesterolemia and should we consider treatment?

**Gestational pathophysiology and consequences for (unborn) child**

Undoubtedly, cholesterol is crucial for fetal development. It is an essential constituent of cell membranes, a precursor of various hormones and it plays a significant role in metabolic processes such as the ‘Sonic Hedgehog signaling pathways’ that regulate morphogenesis and patterning of the central nervous system. Theoretically, cholesterol for fetal metabolism can be acquired through two routes: endogenous production by fetal tissues and transport of maternal cholesterol to the fetus.

**Endogenous fetal cholesterol production**

Fetal cholesterol synthesis rates have been shown to be considerably higher than in adults and the endogenous production of cholesterol has been proven an absolute requirement for fetal development. An inborn error of metabolism that highlights the necessity of fetal cholesterol synthesis is the Smith–Lemli–Opitz syndrome (SLOS), caused by a defect in the last step of the cholesterol synthesis pathway, in which 7-dehydrocholesterol is converted to cholesterol. Newborns suffering from this syndrome present with symptoms varying from learning disorders to lethal malformations.

**Transport of maternal cholesterol to fetus**

There are several indications that the fetus can acquire maternal cholesterol. First, fetuses unable to synthesize any cholesterol due to a severe form of SLOS do have some cholesterol in their blood and tissues, and the severity of SLOS inversely correlates
with maternal plasma cholesterol levels. Also, drug-induced SLOS in rodents could partly be reversed by increasing maternal cholesterol levels. Second, diet-induced modifications of maternal plasma cholesterol concentrations in rodents are correlated with fetal cholesterol concentrations. In humans, an association between maternal and fetal cholesterol levels could be demonstrated until 6 months of gestation, but no longer at term of delivery. Third, the LDL-C concentration in the umbilical cord vein, delivering blood from the placenta to the fetus, is higher than that in the umbilical artery that transports blood back to the placenta. It is postulated that up to 20% of the sterol used by the fetus in the first trimester is obtained from maternally derived cholesterol and that an even greater percentage could be derived from placentas with higher cholesterol concentrations.

In order to enter the fetal circulation, maternal cholesterol should pass the physiological barriers between maternal and fetal tissues. These consist of the yolk sac in early pregnancy, and from approximately the fourth gestational week the placental syncytiotrophoblasts and fetal endothelial cells. Several mechanisms have been proposed for cholesterol transport across these barriers.

**Cholesterol transport across yolk sac**

In animal studies, the yolk sac has been shown to secrete various lipoproteins, primarily apolipoprotein B-containing particles, including VLDL-C and LDL-C, into the fetal circulation. These particles were shown to contain newly synthesized cholesterol but the presence of maternally derived cholesterol in these nascent particles has yet to be proven. On the maternal side, the yolk sac expresses lipoprotein receptors such as those for apolipoprotein B and E and the HDL-C-binding scavenger receptor class B type I (SRB-I). In mice unable to synthesize apolipoprotein B because of genetic knockout, the yolk sac is devoid of maternally derived cholesterol and fetuses are resorbed early in pregnancy or have neurological disorders. However, in humans with hypobetalipoproteinemia, a condition characterized by very low apolipoprotein B levels, no adverse effects on fetal development have been observed. In-vitro studies suggest that the yolk sac is also able to transfer externally derived cholesterol by receptor-independent processes such as aqueous diffusion. These results, mostly acquired in animal studies, strongly suggest transport over the yolk sac membrane during pregnancy.

**Cholesterol transport across placenta**

The actual placental barrier between the human fetal and maternal circulation from 10 – 12 weeks gestational age onward consists of a layer syncytiotrophoblasts, with maternal blood on their apical side and the fetal microvessels at their basolateral side.
Cholesterol uptake by these cells has been shown to be the result of receptor-mediated as well as receptor-independent processes. Various receptors are expressed by trophoblasts, including the LDL, VLDL and class A and class B scavenger receptors. Furthermore, an increase in maternal blood cholesterol was shown to induce a decrease in LDL receptor protein presence in trophoblasts, indicating a regulatory effect of maternal cholesterol on the expression of these receptors. After transport across the apical side of the syncytiotrophoblasts, maternal plasma-derived or newly synthesized cholesterol in the cell itself is available for transport across the basolateral membrane. This can be achieved by secretion of apolipoprotein B, apolipoprotein E, apolipoprotein A1 or by cholesterol efflux. Cholesterol efflux could take place through three routes: down a concentration gradient to phospholipid discs or HDL-C via a protein-independent process, by an SRB-I-mediated route to phospholipid discs or HDL-C or by efflux to lipid-poor apolipoproteins via ATP-binding cassette transporter A1 (ABCA1). Indeed, cholesterol added to the apical side of trophoblasts in vitro was shown to exit the basolateral side of the cells, and other in-vitro studies showed that maternally derived cholesterol can be effluxed from the basolateral membrane by aqueous diffusion or SRB-I. In conclusion, several mechanisms for cholesterol transport across the placenta have been identified that may well play a role in human pregnancy.

Consequences for (unborn) child

The fact that both maternal hypercholesterolemia and hypocholesterolemia have been associated with adverse outcome for the offspring suggests an optimal range of maternal cholesterol during pregnancy. Already a decade ago, an autopsy study that investigated preatherosclerotic lesions in aortas from spontaneously aborted fetuses and premature newborns showed that offspring from hypercholesterolemic mothers exhibited significantly more and larger lesions than those of normocholesterolemic mothers. Another autopsy study added that children born from hypercholesterolemic mothers exhibit faster progression of (pre)atherosclerotic lesions. In this study, hypercholesterolemia was defined as TC levels between 4.7 and 5.2 mmol/l (180 – 200 mg/dl), far below the levels found in pregnant women with familial hypercholesterolemia. The notion that maternal hypercholesterolemia enhances atherosclerosis in offspring has also been supported and further investigated in a number of animal studies. Diet-induced maternal hypercholesterolemia enhanced (pre)atherosclerotic lesion size in the aorta of rabbit newborns. Recently, more prominent atherosclerosis development was shown in normocholesterolemic offspring from apolipoprotein E-deficient hypercholesterolemic mothers vs. the offspring of an apolipoprotein E-deficient father. In a similar mouse model, a significant elevation of the transcriptional activity of genes involved in endogenous cholesterol synthesis and LDL-receptor activity in the liver was
found in mice born to hypercholesterolemic dams 28.

Two studies on humans investigated the effect of maternal hypercholesterolemia in familial hypercholesterolemia mothers on their offspring. One study compared intima–media thickness (IMT), a well validated surrogate marker for atherosclerosis in adults 29, in children with familial hypercholesterolemia born from a mother with familial hypercholesterolemia vs. those who inherited familial hypercholesterolemia from their father, but did not find a difference between the groups 30. However, in this study, potential confounders such as age, sex and BMI, which were not equally distributed in the small groups and were not corrected for in the analyses, may have masked a possible association. A second more recent study on over 2000 individuals showed that familial hypercholesterolemia patients born from a mother with familial hypercholesterolemia have slightly but statistically significant higher LDL-C levels than those who inherited familial hypercholesterolemia from their father 31, which suggests that patients who inherit familial hypercholesterolemia through their mother may have a more atherogenic lipid profile.

The above mentioned studies indicate adverse consequences of maternal hypercholesterolemia for the arterial health of the (unborn) child. The exact consequences, that is, with respect to – intermediate – cardiovascular endpoints, as well as the epigenetic or other (unknown) mechanisms underlying these effects are yet to be elucidated.

**Consequences for future mother**

It is attractive to speculate that the atherogenic lipid profile with higher levels of TC, LDL-C and triglycerides that develops during pregnancy 14, which is even more pronounced in pregnant women with familial hypercholesterolemia, adversely affects maternal cardiovascular disease (CVD) risk. Even more so, because treatment cessation often spans a period much longer than pregnancy itself. This is due to the fact that patients with familial hypercholesterolemia are advised to discontinue lipid-lowering drugs already when they consider pregnancy up to and including breast-feeding the newborn. The Framingham Heart study, an extensive population cohort study investigating risk factors for cardiovascular events, showed an elevated risk for CVD in women who had more than six pregnancies when compared with nulliparous women (relative risk 1.6; 95% confidence interval: 1.1 – 2.2) 7. However, another population-based study with IMT as a surrogate endpoint did not show a relationship between reproductive history and IMT after correction for age as a risk factor for increased IMT 32. Furthermore, unlike the lipid changes observed, endothelium-dependent vasodilatation
response improves with gestational age, whereas this measure is usually negatively associated with cholesterol levels. In all, with current data, it is impossible to estimate the consequence of pregnancy in women with familial hypercholesterolemia on their risk for CVD later in life. Large cohort studies should determine this risk in the future.

**Should we consider treatment for maternal hypercholesterolemia during pregnancy?**

With the crucial role of cholesterol in fetal development as a background, therapeutic interventions should be meticulously titrated to achieve physiological cholesterol levels. Data in humans with respect to lipid-lowering interventions in pregnant women are scarce. We are aware of one study that investigated the effect of a low-cholesterol, low-saturated fat diet on Doppler ultrasound indices in healthy pregnant women. This study indicated that diet modifies fetoplacental circulation in mid-pregnancy.

Three animal studies have focused on the effect of lipid-lowering interventions in pregnant hypercholesterolemic animals. In the first study, five groups of pregnant rabbits were fed either standard chow, cholesterol-enriched chow, or cholesterol-enriched chow with vitamin E or colestyramine or both vitamin E and colestyramine. Colestyramine reduced maternal cholesterol levels, whereas vitamin E had no effect on plasma cholesterol. The offspring from the rabbits was fed a mildly hypercholesterolemic diet and all had similar cholesterol levels, but atherosclerotic lesion progression in offspring of hypercholesterolemic rabbits was greater than that in all other groups. Maternal lipid-lowering treatment reduced lesions at birth by 1 – 53%, compared with offspring of untreated animals, with the most profound effect observed in the vitamin E group. At 12 months, lesion progression in offspring of vitamin E and colestyramine-treated mothers was similar to those of normocholesterolemic mothers, which suggests that maternal treatment of hypercholesterolemia with colestyramine or vitamin E reduces atherosclerosis in the offspring. A subsequent study compared atherosclerotic lesion progression during the first year of life between offspring of rabbits fed a hypercholesterolemic diet only and those fed a hypercholesterolemic diet with addition of vitamin E, colestyramine or both. Maternal vitamin E treatment alone or in combination with colestyramine reduced lesion size to, or even below that of offspring of normocholesterolemic mothers. A more recent study investigated the effect of treatment of hypercholesterolemia with pravastatin in a murine model. This study demonstrated that treating pregnant animals that are hypercholesterolemic and hypertensive with pravastatin induces a reduction of cholesterol in their offspring, even if they consume a similar high-fat diet.
The above mentioned studies are a first suggestion of benefit of treating pronounced hypercholesterolemia during pregnancy and warrant a search for well tolerated and effective drugs. Currently, statins are the mainstay of the treatment of hypercholesterolemia, and it is therefore tempting to consider these drugs for treatment of hypercholesterolemia during pregnancy. However, statins in doses that are toxic for the mother have been shown teratogenic in animal studies and, are therefore, considered contraindicated during pregnancy. As a consequence, data on therapeutic doses during pregnancy in humans are scarce. Due to the frequent occurrence of unplanned pregnancy, cases in which statins are continued coincidentally during the first trimester of pregnancy are not rare (Table 1). Edison and Muenke published a case series of Food and Drug Administration (FDA) reports, literature and manufacturer data on statin exposure during pregnancy. In 178 exposures, of which only 52 cases could be analyzed, there were 20 cases of newborns with structural birth defects. Adverse outcomes were more commonly reported following exposure to lovastatin and simvastatin than to other statins. These relatively lipophilic agents have been shown to enter fetal tissues in animal studies. No malformations were reported among 14 newborns exposed to the hydrophilic pravastatin. This study is, however, hard to interpret due to the small sample size. In another study on humans, three exposure groups were compared: in the first group, statins were discontinued at least 1 month before conception; in the second group, statins were continued during the first trimester of pregnancy; and in a third group, nonstatin lipid-lowering drugs were taken before the end of the first trimester. One hundred and fifty-three women used a statin in the first trimester of pregnancy, 29 were treated with a fibrate or nicotinic acid and 106 used a statin from 1 year to 1 month before conception. The percentages of cases with a congenital anomaly were 4.7, 21 and 10% in the three groups, respectively with overlapping confidence intervals, compared with an incidence of 6.8% of congenital anomalies in a general registry. All abnormalities were found in patients on lipophilic statins and none in patients treated with the hydrophilic agent pravastatin. Although not significant, the highest number of congenital abnormalities was reported in the group treated with nonstatin lipid-lowering drugs. A recent prospective cohort study examined fetal toxicity of statins in 64 women exposed to statin therapy (atorvastatin, simvastatin, pravastatin and rosuvastatin) during the first trimester of pregnancy with a control group of 64 women without exposure to known teratogens. No differences between these groups were found with respect to rate of major malformations, spontaneous abortions and stillbirths. Gestational age at birth and birth weight were slightly lower in the statin group.

The outcomes of these studies do not suggest extreme teratogenicity of statins, especially not for hydrophilic compounds, although large-scale studies are needed to further
characterize the teratogenic potential of statins. In addition to statins, other frequently
prescribed cholesterol-lowering drugs have also been investigated with respect to
teratogenicity. The cholesterol absorption inhibitor ezetimibe as well as niacin and
fenofibrate have shown teratogenic effects in reproductive animal studies. According
to the FDA advice, these agents should only be prescribed if potential benefits justify
the potential risks for the fetus \(^{49}\). Bile acid binding sequestrants such as colesevelam,
that inhibit intestinal cholesterol (re)absorption, are not systemically absorbed and
therefore considered safe during pregnancy. However, they are of limited efficacy and
are associated with gastrointestinal side effects in non-pregnant women that may well
be even more pronounced in pregnancy. At this moment, bile acid-binding sequestrants
are considered the only safe agents to treat hypercholesterolemia during pregnancy.
Studies are still inconclusive with regard to the safety of statins and it could well be that
(specific) statins are safe in pregnancy. Better studies are warranted, however, before
such therapy can be advised.

CONCLUSION

An increasing number of both animal and human studies suggest that maternal
hypercholesterolemia during pregnancy has deleterious effects on offspring with respect
to the risk of CVD later in life. Cholesterol levels have been shown to be severely elevated
in pregnant women with familial hypercholesterolemia when compared with those
without familial hypercholesterolemia. Studies on non-familial hypercholesterolemic
animals showed beneficial effects of treatment of maternal hypercholesterolemia. As
bile acid sequestrants are nonsystemically absorbed and are therefore very unlikely
to affect fetal metabolism, these agents are permitted for treatment of maternal
hypercholesterolemia in humans. Acquiring efficacy outcomes on the risk for CVD in
offspring of hypercholesterolemic mothers with familial hypercholesterolemia will be
exceedingly difficult. However, in our opinion, this should not withhold researchers from
initiating such studies. Furthermore, teratogenicity of specific statins should be further
investigated. Large cohort studies could determine the effect of hypercholesterolemia
during pregnancy on CVD risk for women with familial hypercholesterolemia themselves.
The outcomes of the studies discussed in this review justify the initiation of trials
evaluating safety, tolerability and efficacy of bile acid sequestrants in both pregnant
women with familial hypercholesterolemia and their offspring.
### Table 1. Published articles on statin exposures in human pregnancy.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Type of statin</th>
<th>Exposures with follow-up (n)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taguchi et al.</td>
<td>2008</td>
<td>Prospective case-series with matched control group.</td>
<td>various</td>
<td>64 (64 controls)</td>
<td>All exposures during first trimester. No difference in the rate of major malformations, spontaneous abortions or stillbirth. Gestational age and birth weight somewhat lower in statin group.</td>
</tr>
<tr>
<td>Ofori et al.</td>
<td>2007</td>
<td>Retrospective case-series of statin exposure compared to non-statin antihyperlipidemic drugs and statin use before pregnancy.</td>
<td>various</td>
<td>64 (14 en 67 controls)</td>
<td>All exposures during first trimester. No evidence of an increased risk of fetal anomalies. No discernable pattern of congenital anomalies among live births, no outcomes on non-livebirths.</td>
</tr>
<tr>
<td>Pollack et al.</td>
<td>2005</td>
<td>Prospective and retrospective cases-series.</td>
<td>simvastatin/lovastatin</td>
<td>225 prospective, 91 retrospective</td>
<td>97% of exposures in first trimester. Rate of congenital anomalies in prospective cases similar to background population rate. No specific pattern of anomalies in either prospective and retrospective reports.</td>
</tr>
<tr>
<td>Kenis et al.</td>
<td>2005</td>
<td>In vitro study of effect of simvastatin on first trimester human placental explants.</td>
<td>simvastatin</td>
<td>not reported</td>
<td>Simvastatin inhibits migration of extravillous trophoblast cells from villi to a matrigel. Simvastatin inhibits half of proliferative events in villi and increased apoptosis of cytotrophoblast cells. Simvastatin decreased secretion of progesterone from placental explants.</td>
</tr>
<tr>
<td>Yaris et al.</td>
<td>2004</td>
<td>Case report</td>
<td>atorvastatin</td>
<td>1</td>
<td>Exposure until 7 weeks of pregnancy. No congenital anomalies observed.</td>
</tr>
<tr>
<td>Edison et al.</td>
<td>2004</td>
<td>Retrospective case-series</td>
<td>various</td>
<td>52</td>
<td>All exposures during first trimester. 20 reports of anomalies. No specific pattern in anomalies observed.</td>
</tr>
<tr>
<td>Teelucksingh et al.</td>
<td>2004</td>
<td>Case report</td>
<td>pravastatin</td>
<td>1</td>
<td>Exposure until 24 weeks of pregnancy. No anomalies observed. Low birth weight (2.4 kg at 38+1 weeks gestational age). Normal progression of development up to 6 months of age.</td>
</tr>
<tr>
<td>Seguin et al.</td>
<td>1999</td>
<td>Case report</td>
<td>fluvastatin</td>
<td>1</td>
<td>Exposure until 9 weeks of pregnancy. No anomalies observed. Normal development up to 20 months of age.</td>
</tr>
<tr>
<td>Manson et al.</td>
<td>1996</td>
<td>Prospective and retrospective case-series</td>
<td>lovastatin/simvastatin</td>
<td>134</td>
<td>98% of exposures in first trimester. Proportion of anomalies, spontaneous abortions, foetal death, and stillbirths similar to what would be expected in general population. No consistent pattern in reported anomalies.</td>
</tr>
<tr>
<td>Freyssinges et al.</td>
<td>1996</td>
<td>Prospective and retrospective case-series</td>
<td>simvastatin</td>
<td>125</td>
<td>Except for induced abortions, pregnancy outcome was comparable to that of a general population.</td>
</tr>
</tbody>
</table>
REFERENCES


