

Highlighting severe lipid disorders in pregnancy

Abstract

During pregnancy, significant physiological changes occur in lipid metabolism, which are fundamental for fetal development, but which may pose risks when associated with maternal dyslipidemias. Elevation of lipids such as LDL-cholesterol and triglycerides is common and physiological, but in women with genetic dyslipidemias, such as heterozygous or homozygous familial hypercholesterolemia, levels can reach pathological values. Despite this, most of these pregnant women do not present an increase in maternal-fetal risk, as long as they are adequately monitored. Severe dyslipidemias, such as hypertriglyceridemias (> 1,000 mg/dL), are associated with complications such as pancreatitis and preeclampsia. Lipoprotein (a), another risk factor, rises during pregnancy and may be linked to thrombotic events and preterm births. Lipid screening in pregnancy is recommended especially for women with a history of dyslipidemia. Preconception cardiovascular evaluation is ideal in cases of severe hypercholesterolemia. Treatment includes a balanced diet and, in specific cases, medications. Statins, although traditionally contraindicated, have been reevaluated: recent studies indicate relative safety, especially for women at high cardiovascular risk. Pravastatin has the best safety profile. Other therapeutic options include exchange resins (allowed), lipoprotein apheresis (indicated for severe cases), and omega-3 (effective in hypertriglyceridemias). Ezetimibe, PCSK9 inhibitors, ANGPTL3, bempedoic acid, lomitapide, and fibrates should be avoided or used with caution, depending on the severity and individualized risk-benefit. The therapeutic decision during pregnancy should be shared between physician and patient, balancing fetal risks and maternal benefits, always based on the most current evidence.

Keywords: pregnancy, hyperlipidemias, cardiovascular risk, cholesterol, triglycerides

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Abbreviations: FDA, food and drug administration; LDL-c, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/Kexin Type 9

Introduction

The physiological changes occurring during pregnancy are profound and include significant alterations in lipid metabolism. These shifts are not only adaptive mechanisms for supporting fetal development but may also pose risks when compounded by maternal dyslipidemia or poor dietary patterns. The interplay between maternal lipid profiles, dietary exposures, and offspring outcomes has been the focus of numerous recent studies, highlighting the multifactorial nature of metabolic programming.

The physiological increase in maternal lipids during gestation, driven by hormonal changes such as elevated estrogen and human placental lactogen, which modulate hepatic lipid metabolism and peripheral insulin sensitivity. While a certain degree of hyperlipidemia is considered physiological and necessary, particularly in the third trimester, exaggerated responses can lead to pathological conditions including preeclampsia, gestational diabetes mellitus, and intrauterine growth restriction.¹ It is noteworthy to mention that all pregnant women, whether or not presenting lipid disorders, must be accompanied by a multidisciplinary team; nutritionists, specialized nurses, psychologists and social workers.

Dyslipidemia of pregnancy in dyslipidemic women: maternal-fetal risk

The impact of lipid alterations in pregnant women with a predisposition to genetic dyslipidemias can modulate the cardiovascular risk of women. The most frequent primary or genetic dyslipidemias:

For didactic reasons each of the specific lipid disorders can be distinguished.

Heterozygous familial hypercholesterolemia: this is the most common genetic dyslipidemia in the population, characterized by high low-density lipoprotein cholesterol (LDL-c) and risk of early coronary artery disease.² In pregnancy, further increases in LDL-c are quite significant, since lipid-lowering therapy is interrupted during pregnancy and breastfeeding. Even with pronounced elevations of LDL-c, the maternal-fetal prognosis does not differ between pregnant women with and without heterozygous familial hypercholesterolemia.³ There is no evidence that years of discontinued treatment of pregnant women with heterozygous familial hypercholesterolemia increases cardiovascular risk.³

Homozygous familial hypercholesterolemia: this is much rarer and results from the inheritance of two pathogenic variants that cause marked elevations of LDL-c, with a predisposition to atherosclerosis and early aortic valve or supraaortic disease. During pregnancy, hormonal changes and the interruption of lipid-lowering therapy further raise LDL-c values, hindering lipid management and its impact on maternal-fetal risk. Maternal cardiac events during pregnancy are rare in these patients, and there are no prospective studies evaluating the risk of cardiovascular morbidity or mortality after discontinuation of lipid-lowering drugs during the short gestational period.^{4,5}

Although homozygous patients are at high cardiovascular risk, and not stopping statins during pregnancy can be considered, according to the latest more flexible recommendation of the Food and Drug Administration (FDA), there are no consistent data on the safety and efficacy of the continuous use of statins in pregnancy. The largest study is retrospective, which evaluated the use of statins in 20 homozygous pregnant women, in which more than half were diagnosed before the age of 10. Four patients had cardiac events (myocardial infarction,

stroke, disease requiring stenting, or coronary artery bypass grafting) before the first pregnancy.

Maternal risk: all patients had a favorable pregnancy. None required valve intervention (aortic valve replacement, aortic root surgery, or coronary artery bypass grafting) before the first pregnancy. There was no maternal death during pregnancy or in the postpartum period.

Therefore, from the maternal point of view, the overall pregnancy outcomes were favorable in both patients exposed and not exposed to statins.

Fetal risk: of the 39 pregnancies, 18 pregnancies were exposed to statins. Of these, 12 were exhibited in the last quarter. Eight of these pregnancies were exposed to statins during the first trimester (for approximately 4 to 8 weeks), and stopped using them as soon as the pregnancy was confirmed, resuming only in the second and third trimesters, when the risk of malformation was reduced.

Most of the babies had normal birth weight (2.5 kg and 4.0 kg). Two pregnancies were exposed to statin therapy during the first trimester and both infants were born preterm. A baby was born with congenital strabismus, which was surgically corrected. The pregnancy was not exposed to lipid-modifying treatment either during or before pregnancy. One infant exposed in the first trimester presented shortening of the lower limbs without the need for surgical correction. There is no data on what type of malformation was and whether it was related to the use of statins in the fetal formation phase.

Therefore, in homozygous patients, statins should be discontinued in the period of early brain development, since previous data show that statins in this period can cause severe structural changes. Statins can be used in the third trimester of pregnancy since the risk of teratogenicity of statins is almost nil at this stage.

Homozygous pregnant patients should discontinue lipid-lowering therapy in the first trimester of pregnancy, and resume in the third trimester, to minimize impacts on the fetus, especially in the early stages. The maternal risk of statin discontinuation during this short period of time has no impact on the short- and long-term outcomes of these pregnant women.

Hypertriglyceridemias: Severe gestational hypertriglyceridemia is defined by plasma triglyceride concentrations $> 1,000$ mg/dL, caused by monogenic or polygenic genetic alterations, or the presence of secondary factors (e.g., decompensated diabetes). Maternal risks include acute pancreatitis, hyperviscosity syndrome, and preeclampsia.⁶

There are very few data on the use of insulin therapy to reduce hypertriglyceridemia complicated with gestational diabetes in the third trimester of pregnancy.

In a retrospective study with 48 pregnant women with severe hypertriglyceridemia (triglycerides $\geq 1,000$ mg/dL) worsened or not by gestational diabetes, who received a low-fat diet and insulin treatment (insulin treatment group, $n=48$) and a group 7,056 with moderate hypertriglyceridemia and treatment with a low-fat diet. Intravenous insulin has been shown to reduce triglyceride in the group with severe hypertriglyceridemia by increasing lipoprotein lipase (LPL) activity and chylomicron degradation. Intensive insulin therapy during pregnancy was a safe, effective approach and reduced triglycerides efficiently, preventing hypertriglyceridemic pancreatitis. The protocol used was: insulin administration in pregnant patients,

in the third trimester of pregnancy, with or without diabetes, if triglycerides $\geq 1,000$ mg/dL, with an initial dose of 0.1 U-0.3 U/kg of body weight/hour and continuous intravenous pumping. Blood glucose was monitored once every one to four hours to adjust the insulin pumping dose. When blood glucose was 150 mg/dL to 200 mg/dL, intravenous glucose was added to insulin. When triglyceride values reached ≤ 500 mg/dL, the insulin infusion was suspended. If there was a risk of persistent hypoglycemia, insulin treatment was discontinued. Insulin therapy for severe hypertriglyceridemia in the third trimester of pregnancy reduced plasma triglyceride levels and the incidence of serious complications such as hypertriglyceridemic acute pancreatitis with good outcome during this period of pregnancy.

Lipoprotein (a): lipoprotein (a) is a risk factor for arterial and venous thrombosis. During pregnancy, it rises between the tenth and thirty-fifth weeks of pregnancy in 20-30% of pregnant women.⁷ Due to its structural similarity with plasminogen, at high concentrations, lipoprotein (a) is associated with the risk of maternal (preeclampsia) and neonatal (premature births) complications.⁸⁻¹⁰ Scientific societies in Poland recommend serum lipoprotein (a) determination for all pregnant women.¹¹

Screening: In patients with previous dyslipidemia, measurement of the lipid profile including lipoprotein (a) is recommended at the beginning and during pregnancy. In patients without previous dyslipidemia, the incorporation of the lipid profile into the prenatal examination is easy to perform and could help the diagnosis of dyslipidemias, for continuity of the evaluation after the gestational period. This conduct is individualized.^{12,13}

Cardiovascular assessment: Assessment of cardiovascular risk is limited during pregnancy, as cardiac symptoms resemble the physiological changes of pregnancy. The reduction of radiation exposure is another limiting factor to investigation procedures during the gestational period. Ideally, in pregnant women with severe hypercholesterolemias, cardiovascular evaluations should be performed before conception, considering the potential effects of pregnancy (lip-lowering interruption) on long-term health and thus guide therapeutic decisions in this population.⁵

Treatment

Diet: pregnant women with dyslipidemia of pregnancy or other forms of primary dyslipidemia should follow a diet with low fat content, high soluble fiber content, low glycemic index carbohydrates and ideal weight gain for pregnancy.¹³

Drug treatment

Statins: statins are the most widely used lipid-lowering agents in reducing cholesterol and cardiovascular risk. During pregnancy, its use is controversial and requires careful evaluation of its indication.

Safety: Previous animal studies have shown that statins cause fetal abnormalities, but have been criticized for using much higher doses than those administered to humans.¹⁴ In a series of case reports, a high incidence of structural malformations, including the nervous and skeletal system, has been described in infants exposed to lipophilic statins during the first trimester of gestation.¹⁵

FDA positioning: From these reports, the FDA assigned an X rating to statins, prohibiting their use. It was recommended that pregnant women (including those at increased risk of coronary artery disease) discontinue its use while trying to conceive, during pregnancy, and while breastfeeding.¹³

New evidence

Observational studies, systematic reviews, and meta-analyses have not demonstrated increases in rates of congenital malformations or other harms in women exposed to statins during pregnancy.^{16,17} The largest observational cohort study involved 886,996 pregnancies, with 1,152 pregnant women on statins, during the first trimester. In unadjusted analyses, the risk of congenital anomalies in the exposed group was 6.34%, compared to 3.55% in the unexposed group. After adjusting for confounders, particularly preexisting diabetes, the risk was not significant (1.07, 0.85–1.37).¹⁸ A recent cohort study compared 469 women who used statins during pregnancy, with 4,690 matched controls. No differences were observed between the groups in relation to the rate of congenital anomalies, however the group exposed to statins was associated with a higher risk of preterm birth and low birth weight.¹⁹ It is noteworthy that no study to date has evaluated the potential adverse effects of statin interruption in pregnancy in relation to long-term maternal health.²⁰

Systematic reviews and meta-analysis in women with hyperlipidemia or with comorbidities and risk of preeclampsia have not demonstrated an increase in the rates of congenital malformations or other harm in pregnant women exposed to statins.^{21,22}

In homozygous familial hypercholesterolemia, a retrospective study compared pregnant women who continued to use statins during pregnancy with pregnant women who stopped using them. No differences were observed in the general outcomes of pregnancy, cardiovascular complications or the presence of congenital malformations between the two groups.²³

New FDA position: with new data, the FDA has lifted the ban on statins in pregnancy, considering that statin treatment should be discontinued in the vast majority of pregnant women. However, in those with significantly elevated cholesterol and cardiovascular risk, the FDA argues that “the benefits of statins may include the prevention of serious or life-threatening cardiovascular events in a small group of very high-risk patients. Therefore, contraindicating these medications in all pregnant women is not appropriate”.²⁴

Recommendation: maintenance of statins during pregnancy should be indicated only for patients at very high risk and/or with familial hypercholesterolemia. This decision should be shared between physician and patient, considering the difficulty of assessing the maternal risks of discontinuing medication and the potential fetal risks of maintaining medication, emphasizing that safety data on statins in pregnancy have evolved, but are still extremely scarce.

If maintained, statins should be stopped in the first trimester of pregnancy and reintroduced in the third trimester. The statin with the greatest evidence of safety is pravastatin.

- I. **Bile salt sequestrers or sequestrators:** Exchange resins can be used in pregnancy and are not associated with a higher risk of congenital abnormalities. However, they tend to be poorly tolerated and still affect the absorption of fat-soluble vitamins.¹³ There have been reports of subdural hematomas in fetuses due to vitamin K deficiency in mothers on chronic cholestyramine use due to intrahepatic cholestasis.²⁵ Clinical data for colesevelam during pregnancy are scarce and no adverse effects have been shown in animals. Recommendation: they can be used during pregnancy.
- II. **Lipoprotein apheresis:** Extracorporeal removal of apolipoprotein B-containing lipoproteins by apheresis, if available, is the preferred treatment for severe familial hypercholesterolemia, particularly homozygous familial hypercholesterolemia, during

pregnancy, but it is invasive, costly, and time-consuming.²⁶ Recommendation: lipoprotein apheresis can be used during pregnancy.

- III. **Ezetimibe:** Animal studies in which ezetimibe was given alone or in combination with statins have shown a higher incidence of congenital malformations.¹³ Recommendation: they should not be used during pregnancy and breastfeeding.
- IV. **Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors:** Evolocumab and alirocumab are contraindicated in pregnancy and should be discontinued before conception. In genome-wide association studies, including approximately 1.3 million patients, instrumental variants of PCSK9 were used, lowering LDL-c values. LDL-c reduction correlated with a higher probability of congenital malformations.^{27,28} Studies in primates show that evolucumab crosses the placenta, and although there are no reported adverse effects in animals, there are no reports of its use in human pregnancy or lactation.¹³ Recommendation: they should not be used during pregnancy and breastfeeding.
- V. **PCSK9 inhibitors via RNA interference (Inclisiran):** Should not be prescribed in pregnancy because of the potential harm to the fetus of an agent that inhibits the PCSK9 protein.¹³ Recommendation: they should not be used during pregnancy and breastfeeding. Angiopoietin-like protein 3 (ANGPTL3) inhibitors (evinacumab), bempedoic acid, and lomitapide.¹³ Recommendation: they should not be used during pregnancy and breastfeeding.
- VI. **Fibrates:** There are insufficient data in humans to support the use of fibrates, and they are not consensually recommended in pregnancy.²⁹ Recommendation: according to the American Heart Association’s Scientific Statement for Cardiovascular Considerations in the Care of Pregnant Patients” consider fenofibrate or gemfibrozil in the second trimester of pregnancy if triglycerides > 500 mg/dL, despite lifestyle modifications.³⁰ The Presidential Council of the American Heart Association/American College of Obstetricians and Gynecologists states that pregnant patients with a history of pancreatitis may benefit from the use of fenofibrate if triglycerides > 1000 mg/dL.³¹ They should only be considered when the benefits clearly outweigh the risks.³¹
- VII. **Omega 3:** Recommendation: omega-3 fatty acids may be an effective option for patients with severe hypertriglyceridemia, especially those at risk for pancreatitis (triglycerides > 500 mg/dL).^{13,32}

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None.

Conflict of interest

None.

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