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Familial Hypercholesterolemia and Pregnancy: Risk and Management

Roberta Mombelli[1] and Giuliana Mombelli[2]*

[1]*Clinic of Gynecology and Obstetrics in San Donato Hospital, Milan, Italy*

[2]*Dyslipidemia Center, Cardiotoracovascular Department, Niguarda Hospital, Milan, Italy*

***Corresponding author:** *Giuliana Mombelli, Dyslipidemia Center, Cardiotoracovascular Department, Niguarda Hospital, Milan, Italy, E-mail: giuliana.mombelli@ospedaleniguarda.it*

Abstract

Familial hypercholesterolemia (FH) is a dominantly inherited disorder present from birth with elevated levels of low-density lipoprotein (LDL) cholesterol and increased risk for premature coronary heart disease (CHD) with clinical manifestation between the first and the fourth decades of life. Although statins are the most effective therapy for individuals with FH the use of statins is contraindicated during pregnancy. For this reason, before of a pregnancy the lipid-lowering drugs are discontinued because of possible teratogenic effects with modifications in estrogen and progesterone levels that negatively influence the lipid metabolism. Pregnancy in women affected by FH is rare and might be a critical challenge for both mother and fetus. There are limited therapeutic options available to treat pregnant women with FH and the potential risks to mother and fetus related to elevated cholesterol levels are a certainty. Regarding how to treat these women during pregnancy remains a challenge.

Keywords: Familial hypercholesrolemia, Pregnancy risk, Treatment.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disease, present from birth that markedly elevates plasma low-density lipoprotein (LDL) cholesterol and causes premature coronary heart disease (CHD). Currently three genes are known that can result in the phenotype of FH when affected by a mutation: the LDL receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexintype9 (PCSK9). Historically, the clinical frequency of Homozygous FH (HoFH) has been estimated 1; 1,000,000. Heterozygous FH (HeFH) occurs in 1:500 individuals worldwide [1]. However, recent studies in unselected general populations suggest that the prevalence of HeFH based on the Dutch Lipid Clinic Network criteria may be as high as 1 in × 200 [2] or for molecularly defined HeFH, 1 in 244 [3]. Consequently, HoFH may affect as many as 1 in 160,000-300,000 people [2,3]. Heterozygous form is more frequent 1:85 in Christian Lebanese and in South African populations (1:67) [4]. Consequently in these countries HoFH are 1:28,800 in the first case and 1:18,000 in the second case [4]. Since birth, there are in both forms, very high levels of total cholesterol and LDL cholesterol (LDL-C) [5]. FH patients have a continuous exposition to cardiovascular disease (CVD) linked to elevated LDL-C levels. Subjects with FH have an increased risk to develop premature CVD approximately 20-fold increase respect to non-FH population if they not receive the lipid-lowering therapy [6-8]. Untreated women have a risk of 30% for a fatal or non-fatal coronary event by age 60 years. HoFH individuals have severe CVD before their 20 years. There is a very high incidence of mortality, coronary bypass surgery and severe aortic stenosis in young age. Diagnosis of FH can be made by clinical or genetic criteria [2]. There are elevated probabilities to find tendon xanthomas at any age (the most common in Achilles tendon and finger extensor tendons) or arcus corneae in patients under age 45.

Physiological modification and potential risk during pregnancy

Total cholesterol (TC) and triglycerides 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 [9] and an increase of cholesterol as a precursor for the production of steroid hormones in the placenta [10]. During pregnancy, physiological changes occur in lipids and lipoproteins, secondary to hormonal modifications: LDL-C increases to 42% at 36 weeks. In the second and third trimester, high-density-lipoprotein cholesterol (HDL-C) shows a 55% increase. Triglycerides increase from the third month until 36th week; they may raise even three-fold, achieving rapidly normal values after delivery, while cholesterol levels remain elevated for approximately 6 weeks after birth. It has been also observed an increase in Lipoprotein (a) [11-14] and PCSK9. Peticca et al. [15] have seen an elevated value of PCSK9 in pregnant women versus control cohorts (493,1 respect to 289,7 ng/ml, $p < 0,001$) whereas the newborn cohort was significantly lower than maternal level [15]. Napoli et al. [16] in FELIC study have reported that hyperlipidaemia may induce acute atherosclerosis in the utero-placental spiral arteries that, together with hypercoagulation, may result in local thrombosis and placental infarctions, leading to placental insufficiency and subsequent fetal compromise [16-17]. Some studies show that maternal hypercholesterolemia, independently of the FH status leads at formation atherosclerotic lesions in a larger extent in offspring compared to offspring of the mothers with normal cholesterol [5,16,18]. Furthermore, FH women develop aprothrombotic and proinflammatory phenotype, during pregnancy due to increased concentrations of several prothrombotic and inflammatory mediators compared to non-FHwomen [17,19]. In a previous study on over 2000 individuals it has been proved that FH patients born

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from a mother with FH have slightly but statistically significant higher LDL-C levels than those who inherited FH from their father [20], which suggests that patients who inherit FH through their mother may present, a more atherogenic lipidprofile. In ABCD study has been reported a positive association of adverse pregnancy outcomes with high TC and triglycerides levels in the last term of pregnancy. Toleikyte et al. [21] have observed that FH women do not appear to have a higher risk of preterm delivery or of having infants with low birth weight or congenital malformations respect to women in general [21]. The atherogenic lipid profile with higher levels of TC, LDL-C and triglycerides that develops during pregnancy in women with FH, determines an increase of their CV risk [22]. The Framingham Heart study, an extensive population cohort study investigating risk factors for CV 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) [23]. Versmissen et al. [24] have reported that the risk of CHD in untreated individuals with FH is more extreme when FH is transmitted maternally. Discontinuation of lipid-lowering medications for the relatively short duration of pregnancy is thought to have little impact on long-term therapy for primary hypercholesterolaemia [25] and is unlikely to affect outcomes of CHD. While, CV implications in HeFH women that for 5 years have not assumed statins for more pregnancies remain an unequivocal certainty.

Treatment and management of familial hypercholesterolemia in pregnancy

Considering the crucial role of cholesterol in fetal development as a background, therapeutic interventions should be meticulously titrated to achieve physiological cholesterol levels. Treatment consists in modifications of lifestyle (appropriate nutrition and physical activity are recommended for women with FH in pregnant), as well as aggressive cholesterol reduction with pharmacologic therapy [26,27]. Data in humans with respect to lipid-lowering interventions in pregnant women are scarce. 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 have shown teratogenic effects in animal studies [28]. The cases in which statins are continued during the first trimester of pregnancy are not rare being frequent the unplanned pregnancy [29]. The Food and Drug Administration (FDA) classifies the statins as category X in pregnancy. The exposition to lipophilic statins during first trimester determines defects of the central nervous system and unilateral limb deficiencies [30]. Colesevelam or cholestyramine (bile acid sequestrant) is located in *category B* during pregnancy, although there are no controlled studies that have assessed the safety of this agent in humans. 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, in spite of potential benefits may warrant use of the drug in pregnant women despite potential risks." Because the data in humans are limited it would seem prudent to avoid using these drugs during pregnancy or lactation. Women of childbearing age should be counseled to stop taking these medications at least 1 month before of the contraceptive therapy [26,30,31]. Recently, the FDA [32,33] approved two new drugs for treatment of FH, lomitapide (Juxtapid™) capsules and mipomersen sodium (Kynamro®) injection. Both of these medications are indicated as an adjunct for the management of HoFH, along with lipid-lowering medications and or LDL apheresis. Lomitapide is contraindicated during pregnancy (classified *category X*) as there is a risk of embryo-fetal toxicity, so women of child bearing age should be counseled on effective methods of contraception. If vomiting or diarrhea occurs, hormone absorption from oral contraceptives may be incomplete, necessitating the use of additional contraceptive methods. Before beginning treatment with lomitapide, a negative pregnancy test must be documented. Women who are taking mipomersen should be counseled to notify their health care provider if they become pregnant. It should not be used during pregnancy unless absolutely necessary. It is not known whether lomitapide or mipomersen is excreted in breast milk; therefore, women who are lactating should be counseled about decision-making to either discontinue the medication or to stop breastfeeding [34,35]. Because there are no controlled data on mipomersen in pregnant women (classified *category B*), it should only be used during pregnancy if extremely necessary. Studies on reproduction and embryo fetal development performed in mice and rabbits revealed no evidence an impaired fertility. Women who become pregnant while taking this medication should contact their health care provider [34]. Recently PCSK9 inhibitors have emerged as an alternative new class of cholesterol-lowering drugs. Until now, the best property of PCSK9 studied is to bind the hepatocyte-derived LDLR leading to its intracellular degradation. Disrupting this [PCSK9≡LDLR] protein–protein interaction prevents LDLR degradation, thereby raising LDLR levels, lowers LDL-C [36,37], keeping a protection for the development of atherosclerosis [38].This could be a very important therapeutic target in pregnant women.Evolocumab (Repatha™) representsthe first PCSK9 inhibitor approved in the world for treatment of high cholesterol. The safety or contraindication for evolocumab in pregnancy, have not yet been evaluated. Long-term studies will establish whether the beneficial effects of PCSK9 inhibition of LDL-C levels directly translate into safety and effectiveness in CVD risk reduction. Despite its apparent safety, there are concerns about the inhibition of PCSK9 because we still know little about its global physiological functions [39]. The European Atherosclerosis Society (EAS) has made HoFH-specific recommendations for target LDL-C levels of < 100 mg/dL (< 2.5 mmol/L) in adults or < 70 mg/dL (< 1.8 mmol/L) in adults with clinical CHD or diabetes [2,40].

Evidence-based guidelines for FH from the National Lipid Association (NLA) recommend that treatment goals should focus on reducing LDL-C levels by 50% from pretreatment levels if target LDL-C levels cannot be achieved [41]. For high-risk patients (including HoFH patients), the NLA suggests that non-HDL-C and LDL-C levels must under < 130 mg/dL (3.4 mmol/L) and < 100 mg/dL (2.5 mmol/L), respectively. Many clinical trials exclude the women in pregnancy, determining a reduction of percentage of young women who participate in studies used to evaluate CV outcomes [41,42]. Moreover, this guideline has reported that the women with FH should receive pre-pregnancy counseling and instructions to stop lipid-lowering therapy at least four weeks before discontinuing contraception and should not use these drugs during pregnancy and lactation. Use of other lipid lowering medications (i.e. colesevelam or cholestyramine) may be considered. Furthermore, LDL-apheresis during pregnancy can be considered if there is CVD [42].

The International FH Foundation recommends that all women of child-bearing age should receive pre-pregnancy counseling with appropriate advice given by the clinician on contraception, before starting a statin and this should be reinforced at annual review. Statins and other lipid systemically absorbed lipid-regulating drugs should be discontinued 3 months before planned conception, as well as during pregnancy and breastfeeding. Furthermore, the adolescent girls should receive a pre-pregnancy counseling [43,44]. The implication is that pregnant women are unable to weight the potential benefits against the risks of treatment. Pregnant women traditionally have not participated in early stage clinical trials, creating significant safety concerns for treatment [45].

Summary

The management of FH becomes challenging in the women who have or wish to become pregnant because cholesterol levels increase during pregnancy and statins are contraindicated (Category X) during pregnancy and lactation. Actually, it is acceptable to use during pregnancy cholestyramine and colesevelam, because these medications do not pass into the systemic circulation, and have not been shown to have any adverse effects. Lomitapide is contraindicated in pregnancy, mipomersen can be used if it is absolutely necessary. LDL-apheresis procedure remains an important treatment that it must be considered in a clinical condition compromised (presence of CAD) in both forms. The use of PCSK9 inhibitor is unknown in pregnancy. In conclusion, in the future it will be very important to do studies that

focus on therapeutic strategies that can give safely lower cholesterol levels during pregnancy in these women. The testing and treatment of pregnant women is in another challenging problem, because of a reluctance to expose developing foetuses to investigational drugs.

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