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Familial hypercholesterolemia in pregnancy

Fahad Alnouri[a] *and Frederick J. Raal*[b]

Purpose of review
Individuals with familial hypercholesterolemia (FH), particularly those with homozygous FH (HoFH) who have markedly elevated LDL-cholesterol (LDL-C) levels from birth, present with unique complications during pregnancy. This review explores the complexities of FH care during pregnancy.

Recent findings
The worldwide burden of FH is much greater than previously thought. Still, underdiagnosis and undertreatment are substantial, necessitating increased awareness, genetic screening efforts, and better access to diagnostic tools. Although there is guidance for implementing best practices in the care of FH, including pregnancy, currently, there are no evidence-based guidelines that address HoFH at the time of pregnancy planning or during pregnancy and lactation.

Summary
FH management in pregnancy requires a reasonable balance between fetal safety and maternal LDL-C control. Discontinuing lipid-lowering medication during pregnancy and the postpartum period needs to be considered, and in severe cases, lipoprotein apheresis may be an appropriate substitute. Comprehensive patient care requires coordination by genetic counselors, cardiologists, lipidologists, and obstetricians. The management of HoFH in pregnancy requires further research efforts, enhancement of public knowledge, and worldwide cooperation. By focusing on these areas, we can make significant progress in diagnostics and develop efficient management plans for improving outcomes among pregnant women with HoFH.

Keywords
familial hypercholesterolemia, homozygous familial hypercholesterolemia, lactation, pregnancy

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic lipid disorder characterized by elevated LDL-cholesterol (LDL-C) levels from birth, increasing the risk of accelerated atherosclerotic cardiovascular disease (ASCVD) early in life [1]. Homozygous familial hypercholesterolemia (HoFH), which results from the inheritance of two pathogenic variants affecting the metabolism and clearance of LDL-C, is the most severe phenotype [2,3▪▪]. The most characteristic finding in HoFH is a marked, fourfold or greater elevation of LDL-C, often associated with clinical markers such as corneal arcus and tendon xanthomas, and particularly a premature predisposition to ASCVD. FH increases the risk of complications during pregnancy. HoFH and heterozygous (HeFH) have varying risks and severity levels, necessitating distinct management strategies during pregnancy. While both phenotypes require preconception counseling, full genetic counseling is particularly essential for HoFH. For the treatment of pregnancy-related hypercholesterolemia, HeFH might require medication adjustments, whereas HoFH necessitates more aggressive lipid-lowering therapies. Cardiovascular risk assessment and management of complications are key, especially for females diagnosed with HoFH, as the risk is considerably higher. However, during pregnancies in both HoFH and HeFH, the fetus needs to be carefully monitored, and both the mother's cardiovascular condition and fetal development must be considered in delivery planning. High-risk pregnancies often require specialized intervention. Additionally, personalized, multidisciplinary care is essential to achieve optimal results.

FH remains underdiagnosed and undertreated globally, leading to increased cardiovascular morbidity [1,2,3▪▪]. The low level of knowledge and awareness of FH supports the need for a high index of suspicion.

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KEY POINTS

- Homozygous familial hypercholesterolemia (HoFH) management in pregnancy requires a reasonable balance between fetal safety and maternal LDL-cholesterol control.
- Cardiovascular risk assessment and management of complications are key, especially for females diagnosed with HoFH, as the risk is considerably higher.
- Focused efforts must be made to raise awareness, develop genetic screening programs, and create accessible diagnostic resources for better diagnosis of FH, and in particular, HoFH.
- Although there is guidance for implementing best practices in the care of FH during pregnancy, there are currently no evidence-based guidelines that specifically focus on the treatment of HoFH during pregnancy.
- By prioritizing scientific research and awareness, we can create opportunities for improved clinical practices and the quality of life for women with familial hypercholesterolemia, particularly HoFH, during their pregnancy.

When FH is suspected, management must incorporate recent findings and trends. Because of the multifaceted factors, clinicians must have a deep understanding of FH during pregnancy to ensure optimal maternal well being and fetal growth are maintained.

This review offers a comprehensive overview of FH during pregnancy, including diagnostic procedures, incidence rates, epidemiology, and current treatment options. The review addresses findings from existing literature and incorporates recent epidemiological data to provide a useful tool for academics, physicians, and healthcare practitioners.

PREVALENCE AND EPIDEMIOLOGY OF FAMILIAL HYPERCHOLESTEROLEMIA

HoFH is the most severe form of FH, significantly increasing the risk of premature ASCVD and associated death, often occurring in the second or third decade of life [3▪▪]. Understanding the inheritance patterns of FH is vital. Since FH is an autosomal codominant trait, a single copy of the faulty gene inherited from a parent can cause HeFH, while two copies can result in HoFH. As couples who frequently marry within their families are more prone to inheriting two copies of the gene, it is essential to consider consanguinity as one of the risk factors. Consanguineous marriages are fairly common in Middle Eastern culture and result in higher rates of hereditary diseases, including HoFH [4]. In Saudi Arabia, consanguineous marriages contribute to the majority of HoFH cases [5]. However, less consanguineous areas might be associated with fewer cases of HoFH within a family. For example, consanguinity is recognized as a risk in intermarriage in Oman, and hence, the detection rate of HoFH is reduced. For successful management techniques, cultural norms and inheritance trends must be considered [5].

It is estimated that about 14–34 million people worldwide have FH, including HoFH; however, only one percentage have been diagnosed (Fig. 1). FH prevalence has been reported in 17 countries (9% of 195 nations), with four countries reporting founder populations [1]. This means that the prevalence of FH is unknown in 178 countries (91%). FH prevalence studies were mainly conducted in Europe, North America, East Asia, and Australia. For example, based on hospitalization and patient registries, the estimated prevalence of FH in Denmark is 1 : 137 [6]. Significant data gaps exist in multiple regions, especially Africa, South America, and Asia, making the prevalence of FH in these areas largely unknown.

Although the prevalence of FH among the population in the Arabian Gulf was initially projected to be similar to that of Western countries, it is now estimated to be as high as 1 : 232. Unfortunately, the registry of FH in the Arabian Gulf region is not comprehensive enough to report on the prevalence of HoFH in the region. However, recent studies indicate that the prevalence of HoFH in Saudi Arabia is significantly underestimated, and there are indications that the Arabian Gulf region has one of the highest prevalences of HoFH in the world [5].

Underdiagnosis and undertreatment of HoFH have significant effects and can lead to dire consequences for the individuals affected. The underdiagnosis of HoFH can be attributed to several factors, including its rarity and the lack of national registries in most countries [2]. In the Middle East, as in many other countries, many cases of HoFH are not diagnosed due to a lack of systematic approaches or awareness of clinical signs pathognomonic of this condition [7]. This may lead to suboptimal treatment and higher cardiovascular disease risks.

Focused efforts must be made to raise awareness, develop genetic screening programs, and create diagnostic resources that are accessible for better diagnosis of FH, and in particular, HoFH [8▪▪]. The impact of ethnicity and consanguinity rates on prevalence underlines the need for targeted screening in regions where such practice is common. To reduce the burden associated with HoFH and improve FH outcomes for patients, an integrated approach to FH management that includes cultural, genetic, and geographic factors is required. The

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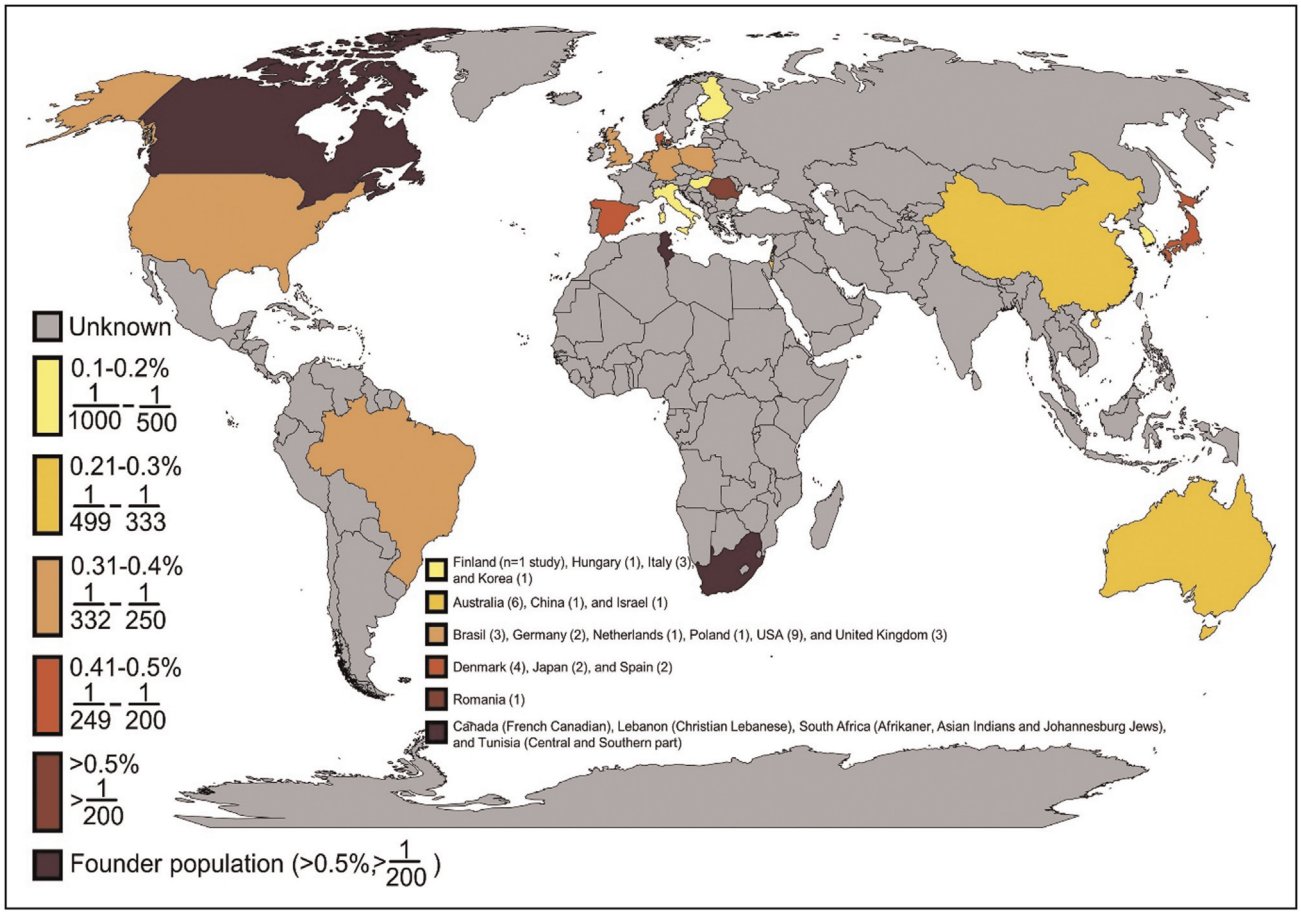


FIGURE 1. Worldwide prevalence of familial hypercholesterolemia.

global prevalence of HoFH is being better understood, and early diagnosis in combination with personalized treatments has become increasingly important.

THE GENETIC FOUNDATION OF FAMILIAL HYPERCHOLESTEROLEMIA AND DIAGNOSTIC METHODOLOGIES

Effective diagnosis and management of HoFH depend on understanding its genetic background. HoFH results from the inheritance of pathogenic variants in the genes linked to LDL-C metabolism; among them, the family of LDLR, PCSK9, APOB and LDL RAP1, with variants in the LDLR being by far the most common [3▪▪]. The inheritance of two pathogenic variants in the LDLR gene is also the cause of the majority of cases of HoFH, as loss-of-function variants disrupt the capacity for removal by LDL receptor action, resulting in markedly reduced clearance of LDL-C from the circulation [9]. Genetic testing developments have significantly increased the accuracy and efficiency of detecting pathogenic variants in HoFH. Next-generation sequencing (NGS) technologies, including whole exome sequencing (WES) or genetic panel approach, enable comprehensive analyses for multiple genes simultaneously; therefore, causative mutations can be more accurately detected.

Cascade screening is the best method for searching for mutations associated with FH in high-risk families. This method allows the identification of other family members, particularly first-degree relatives, after the diagnosis of FH has been confirmed by genetic testing. Cascade screening helps reduce the impact of FH-related cardiovascular risks by allowing for earlier initiation of effective therapeutic therapies and preventive measures (Fig. 2) [3▪▪,8▪▪]. However, before cascade screening, it is essential to first identify index cases, emphasizing the need to raise awareness and enhance diagnosis rates for FH.

CHARACTERISTICS AND PHENOTYPIC IDENTIFICATION

When genetic testing is not readily accessible or available, phenotypic diagnosis methods such as the FH Dutch Lipid Clinic Criteria and the Simon

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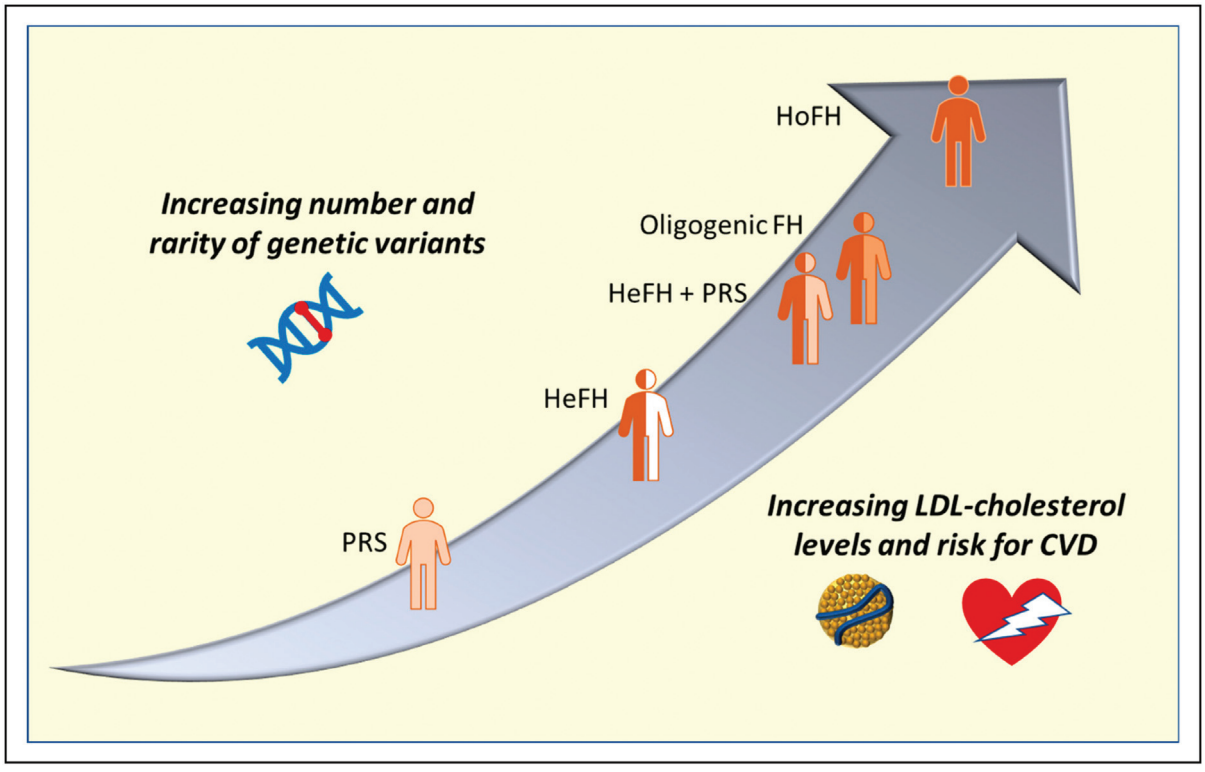


FIGURE 2. Variations in the genetic status of underlying hypercholesterolemia and the correlation with phenotype. The *x*-axis shows the rise in LDL cholesterol and the corresponding risk of CVD, while the *y*-axis shows the quantity of uncommon genetic variations.

Broom Method are used [10]. Important features of the Simon Broom Method include clinical and metabolic characteristics such as high LDL-C levels, corneal arcus, and tendon xanthomas. However, this method has some drawbacks since additional diagnostic techniques may be necessary, as there could be an overlap between specific LDL-C levels that suggest either HeFH or HoFH, as well as confusion with other causes of hypercholesterolemia, both genetic, such as sitosterolemia and acquired causes.

The second phenotypic diagnostic method, which provides a comprehensive basis for FH identification, including that of HoFH patients, is the Dutch Lipid Clinic Criteria for FH [10,11]. This approach incorporates clinical criteria such as lipid profile tests, physical examination findings, and family history. These factors are quantified, and FH is estimated as a cumulative point score based on these parameters. The scoring system is greatly influenced by tendon xanthomas found for HoFH, which supports the importance of clinical awareness in procession diagnostics.

While phenotypic diagnosis provides an initial assessment, genetic testing remains definitive in confirming homozygosity. Apart from assisting in identifying the mutations, it also simplifies the identification of affected relatives through cascade screening. Despite such effectiveness, many issues still need to be addressed, particularly in regions with minimal genetic testing resources, underscoring the global need.

THE MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA DURING PREGNANCY

Managing FH in pregnancy involves many complex challenges. Pregnancy in FH, particularly HoFH, represents a dual exposure to elevated LDL-C levels due to the discontinuation of lipid-lowering therapy as well as physiological changes associated with pregnancy itself. Total cholesterol and LDL-C increase by 30–50% during the second and third trimesters. The absolute increase is even higher in individuals with HoFH [12,13]. Therefore, it requires an all-encompassing strategy attentive to the mother's health and fetal development. Patients with HoFH or with HeFH and established ASCVD are at increased risk of cardiac events during pregnancy from both coronary artery disease as well as aortic stenosis, which may be fatal and ongoing or even more aggressive lipid-lowering therapy, although relatively contra-indicated, should be considered

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[14]. A comprehensive and personalized solution is thus required to find a balance between regulating LDL-cholesterol levels in the mother, which could prove unsafe for her fetus. Of special importance to the management of FH is to consider the discontinuation of statin and other lipid-lowering therapy before conception and during pregnancy [8▪▪]. Early concerns regarding the safety of statins, which resulted in the assignment of a category X safety rating in pregnancy, arose from reports of an association between statin use and anomalies of the CNS, limbs, and/or VACTERL anomalies [15]. Since then, however, several systematic reviews and a meta-analysis in women with hyperlipidemia as well as women with or at risk of preeclampsia have shown no increased rates of congenital malformations or other adverse effects from statins [16–19] One should, therefore, consider ongoing statin therapy during pregnancy in high-risk women with HoFH or HeFH and established ASCVD. Statin therapy is temporarily stopped during the first trimester while the fetus is forming and when there is a theoretical risk for congenital malformation. However, reintroduction during the second trimester, when the risk is negligible, is another option, which appears to be safe with no apparent adverse effects and good pregnancy outcomes [20]. The uncertainty regarding possible long-term effects on the offspring from exposure to statins during pregnancy needs to be weighed up against the possible long-term benefits for the offspring in terms of the development of atherosclerosis and the benefits for the mother from a vascular viewpoint. Importantly, the FDA has recently acknowledged the benefits of ongoing statin use in women with HoFH and those at very high risk for ASCVD [21,22]. Bile sequestering resins have been used in pregnancy and are not associated with an increased risk of congenital abnormalities [23]. However, they tend to be poorly tolerated and may affect the absorption of fat-soluble vitamins. The cholesterol absorption inhibitor ezetimibe is much better tolerated, but there is also a lack of safety evidence during pregnancy.

PCSK9 inhibitors should be discontinued before conception. Primate studies show that evolocumab crosses the placenta, and although there are no reported adverse effects in animals, there are few reports of its use in human pregnancy or lactation. There is also no available data on the safety of novel lipid-lowering agents such as bempedoic acid, lomitapide, inclisiran, or the ANGPTL3-inhibitor, evinacumab, so these agents should all be avoided during pregnancy [24]. Nevertheless, an abrupt stop leads to a worsening of cardiovascular problems for the mother and means that substitute treatments should be sought.

A successful alternative is lipoprotein apheresis, particularly if more traditional medications are either unavailable or contraindicated. This extracorporeal method provides an acceptable solution that removes the LDL-cholesterol directly from the circulation, making it safe for both the mother and the fetus [25▪]. However, despite the highly resource-intensive nature of lipoprotein apheresis and its efficacy, access remains an ongoing issue.

Currently, statins and PCSK9 inhibitors are also not recommended while breastfeeding due to insufficient safety data. The decision regarding whether to breastfeed, the duration thereof, and the use of cholesterol-lowering medications while breastfeeding should be discussed on an individual basis [26▪]. Lipoprotein apheresis is an effective modality of treatment during breastfeeding for high-risk lactating mothers, particularly those with HoFH, if available.

The management of HoFH during pregnancy requires complex and integrated strategies. Therefore, for full management of this multidimensional genetic disorder and to ensure the best possible outcomes for the mother and child, teamwork among health professionals is becoming increasingly important as our knowledge of HoFH progresses. Effective approaches are critical for the management of HoFH during pregnancy. As explained in the preceding text, it is essential to comprehend the genetic background to diagnose and treat HoFH accurately [27].

Adopting a cross-cutting strategy involving genetic counselors, lipidologists, cardiologists, and obstetricians is crucial. This collaborative approach will assure continuous monitoring, informed decision-making, and a complete patient risk assessment and evaluation. Critical components are periodic cardiovascular health assessments, fetal development, and LDL-C levels. In addition, family planning options and cascade screening of family members should be coordinated, ideally by genetic counselors. At the same time, obstetricians manage pregnancies and potential associated complications, and lipidologists advise on optimal lipid management (Fig. 3).

CONCLUSION

In conclusion, the management of HoFH in pregnancy is considered a challenge that requires multidisciplinary efforts between different medical specialists and appropriate planning regarding treatment strategies. It is essential to weigh the risks and benefits of ongoing lipid-lowering therapies and to consider other treatment options, such as lipoprotein apheresis, which requires close collaboration between obstetricians, cardiologists, and lipidologists/endocrinologists. Although there is

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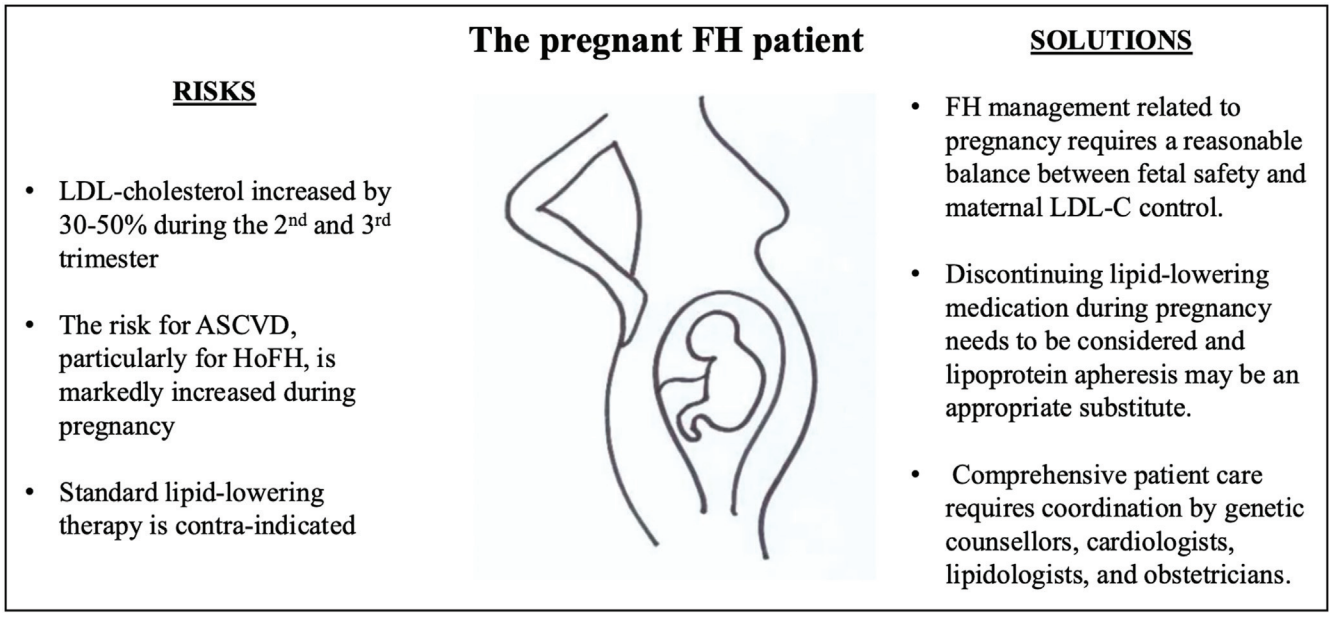


FIGURE 3. Risks and solutions to the management of pregnant FH patient. FH, familial hypercholesterolemia.

guidance on best practices in the care of FH, including pregnancy in FH, currently, there are no evidence-based guidelines on the treatment of FH, particularly HoFH at the time of pregnancy planning or during pregnancy and lactation [8▪▪]. This highlights the need for further studies and greater recognition, noting that FH during pregnancy requires sustained efforts to understand this condition better and emphasizes the need for innovative solutions, accessible diagnostics as well as international cooperation on behalf of medical specialists. As we learn more, continuous projects of ongoing research and continued public awareness endeavors are fundamental to ensure that management practices improve and, ultimately, outcomes for mothers with FH with their children will be enhanced. By prioritizing scientific research and awareness, we can create opportunities for improved clinical practices and the quality of life for women with FH, particularly HoFH, during their pregnancy.

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Conflicts of interest

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