

Health & Research Journal

Vol 10, No 2 (2024)

Volume 10 Issue 2 April - June 2024



Volume 10 Issue 2 April - June 2024

EDITORIAL

INTENSIVE CARE UNIT: THE CONCEPT OF A SPECIAL CARE

RESEARCH ARTICLES

AN INVESTIGATION OF PARENTAL CONCERNS ABOUT THE EDUCATIONAL AND PSYCHOSOCIAL DEVELOPMENT OF THEIR CHILDREN AGED 2-6 YEARS DURING THE COVID-19 PANDEMIC

A NEGLECTED PROBLEM IN CAREGIVERS OF CANCER PATIENTS: SUPPORTIVE CARE

EXPERIENCES OF LOSS AND THEIR MANAGEMENT BY INFORMAL CAREGIVERS IN THE COMMUNITY. PERCEIVED QUALITY OF LIFE OF PEOPLE WITH CHRONIC DISEASES

THROMBOSIS IN SEVERELY ILL PATIENTS ADMITTED IN ICU DUE TO COVID-19 PNEUMONIA. DATA FROM A GREEK HOSPITAL

CASE REPORT

CUTANEOUS AMYLOIDOSIS IN A PATIENT WITH SYSTEMIC AMYLOIDOSIS DUE TO MULTIPLE MYELOMA

SPECIAL ARTICLE

HOW HAS PSYCHOLOGY IMPROVED UNDERSTANDING OF WHY PEOPLE LIE?

REVIEW

WOMEN AND FAMILIAL HYPERCHOLESTEROLEMIA

Published in cooperation with the Postgraduate Program "Intensive Care Units", the Hellenic Society of Nursing Research and Education and the Helerga

Women and familial hypercholesterolemia

Georgia Chasioti, Anastasia Kotanidou

doi: [10.12681/healthresj.37347](https://doi.org/10.12681/healthresj.37347)

To cite this article:

Chasioti, G., & Kotanidou, A. (2024). Women and familial hypercholesterolemia. *Health & Research Journal*, 10(2), 123–134. <https://doi.org/10.12681/healthresj.37347>

REVIEW

WOMEN AND FAMILIAL HYPERCHOLESTEROLEMIA

Georgia Chasioti¹, Anastasia Kotanidou²

1. Laboratory Department, General Hospital of Athens "Laiko"

2. Professor, Medical School of Athens, National and Kapodistrian University of Athens, Greece

Abstract

Cardiovascular diseases (CVD) are the leading cause of death worldwide. One of the risk factors of CVDs is dyslipidemia, defined as the imbalance of lipids in the blood. Early diagnosis and treatment of the disease is important. However, there appears to be a gender disparity, with women less likely to be diagnosed and start lipid-lowering therapy. In addition, it is difficult for them to continue treatment without interruptions, such as for reasons of childbearing, and as a result they do not achieve the target Low Density Lipoproteins (LDL) levels. Heterozygous Familial Hypercholesterolaemia (FH) is thought to occur in 1 in 500 people in most ethnicities in the world. However, in most cases, these figures are derived from limited numbers of data from selected populations or specific subgroups in the general population and therefore may lack the precision of more modern estimates. About 1 in 200 people have familial hypercholesterolemia, but the vast majority are undiagnosed. Women with untreated FH are at very high risk for early-onset atherosclerotic cardiovascular disease. In untreated women with FH, 30% will develop Atherosclerotic Cardiovascular Disease (ASCVD) by age 60. The onset of ASCVD occurs 20 years earlier in life for women with FH than for women without FH. Regarding women with FH during menopause, they had similar LDL values to premenopausal women and higher levels compared to men in the same age group. Postmenopausal women with FH may suffer the consequences of high LDL either from delayed diagnosis or because of interruptions in management they may have experienced during childbearing. The last 2 decades have seen the development of new therapies to lower LDL-cholesterol levels and delay premature atherosclerosis, especially in combination with lifestyle modifications. Management of patients with familial hypercholesterolemia requires a multiprofessional approach, including primary care providers, cardiologists, endocrinologists, dietitians, pharmacists, and nurses, to improve outcomes. Treatment strategies should be discussed extensively at diagnosis. Close follow-up to monitor treatment response and development of side effects from lipid-lowering agents is essential to optimize care. The representation of women in studies concerning the diagnosis and treatment of familial hypercholesterolemia must be improved, so that there is a more effective treatment of this disease.

Keywords: Familial hypercholesterolemia, incidence, dyslipidemia, cardiovascular disease, women, lifestyle modifications.

Corresponding Author: Chasioti Georgia, E-mail: georgiachasioti18@gmail.com

Cite as: Chasioti, G., Kotanidou, A. (2024). Women and Familial Hypercholesterolemia. *Health and Research Journal*, 10(2), 123-134. <https://ejournals.epublishing.ekt.gr/index.php/HealthRes/>

INTRODUCTION

Cardiovascular disease

The term Cardiovascular Disease (CVD) includes a number of various diseases, namely Coronary Heart Disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism. CVDs are the primary reason for mortality globally, accounting for 32% of all deaths in the population, corresponding to 17.9 million people. The majority of deaths were due to cerebrovascular accidents. More than three-quarters of deaths from cardiovascular disease occur in low- and middle-income countries. It is noteworthy that in 2019, 38% of premature deaths, i.e. deaths in people under the age of 70, due to non-communicable diseases, were caused by cardiovascular diseases.¹

The risk factors of cardiovascular disease are primarily age and gender. The risk increases proportionally with age and is higher in men. However, after women's menopause, the risk equalizes between the sexes, perhaps due to protection from estrogen in younger women or the increase in obesity in men. Another factor is socioeconomic status, as studies have shown that the risk increases the lower the socioeconomic status. However, this factor is also related to other factors, more specifically smoking (which increases the risk of cardiovascular disease), physical activity (the better, the lower the risk) and diet. Regarding the latter, overweight and obese people have a higher risk of cardiovascular disease due to other risk factors, such as diabetes, cholesterol and blood pressure. One of the risk factors of cardiovascular diseases is dyslipidemia, defined as the imbalance of lipids in the blood. The most common form of dyslipidemia is cholesterolemia, in which the levels of Low Density Lipoproteins (LDL) cholesterol in the blood are elevated.²

Familial hypercholesterolemia is a genetic disorder of lipoprotein metabolism characterized by highly elevated plasma total cholesterol levels with deleterious cardiovascular consequences that begin in childhood.³ Early diagnosis and treatment of the disease is important. However, it appears to be a gender disparity, with women less likely to be diagnosed and start lipid-lowering therapy. In addition, it is difficult for them to continue

treatment without interruptions, such as for reasons of childbearing, and as a result they do not achieve the target LDL levels.

The present work aim at reporting extensively to cardiovascular disease and dyslipidemia, while more emphasis will be placed on familial hypercholesterolemia and its effect on women.

Dyslipidemia

Dyslipidemia is defined as the imbalance of lipids such as cholesterol, LDL cholesterol, triglycerides and High Density Lipoproteins (HDL) cholesterol. After intestinal absorption of lipids, lipids are transported throughout the rest of the body via lipoproteins to be used for energy production, steroids, or bile acid formation. If any of these factors is out of balance it can lead to dyslipidemia, which is an important risk factor for cardiovascular disease. Dyslipidemia is classified into:⁴ A) Primary, which is due to single gene mutations and is characterized by particularly high cholesterol values, usually LDL, triglycerides or more often a combination of both. B) Secondary, which is due to changes in the conditions of exogenous factors in lipid metabolism. Sometimes they may be related to a genetic predisposition. This category can also be distinguished into: 1) Hypercholesterolemia, 2) Hypertriglyceridemia, 3) Low HDL levels.

Hypercholesterolemia is the most common form of dyslipidemia and is associated with an increased risk of CVD, with elevated plasma LDL-cholesterol being the 15th leading risk factor for death in 1990, 11th in 2007, and 8th in 2019. The global burden of dyslipidemias has increased in the last 30 years.⁵

Review

Familial hypercholesterolemia

The inherited condition of lipoprotein metabolism known as Familial hypercholesterolemia (FH) is characterized by higher than normal levels of total cholesterol levels in plasma, leading to harmful effects on the heart starting from childhood.⁶ The main known genetic mutations associated with familial hypercholesterolemia involve alterations in the genes responsible for expressing the LDL cholesterol receptor (LDLR), apolipoprotein B (ApoB), or PCSK9 (proprotein convertase subtilisin/kexin type

9). The first mutation is also the most common. Each of these three mutations results in damage to LDL receptors, which cannot recruit and remove LDL cholesterol from the circulation, thus increasing its concentration in the blood.^{7,8} Patients may inherit one abnormal and one normal gene (heterozygous familial hypercholesterolemia) or two abnormal genes (homozygous familial hypercholesterolemia), where it makes the disease more severe. Children carrying both defective genes from two heterozygous parents have almost no LDL receptors to take up LDL, subsequently exhibiting exceedingly elevated levels of LDL cholesterol levels and early onset of cardiovascular condition. Approximately 10% of patients with familial hypercholesterolemia carry mutations on the expression gene of ApoB, with the vast majority of them having the Arg3500Gln gene mutation. The mutation in the PCSK9 gene is present in less than 5% of patients diagnosed with familial hypercholesterolemia. Moreover, it's important to note that only severe mutations in PCSK9 can result in familial hypercholesterolemia.⁹

LDL is responsible for transporting most of plasma cholesterol and binds to the cell membrane LDLR receptor via two LDL ligands, apoB-100 and apoE. After binding to the LDLR complex, the LDL enters the cell where it is released while the LDLR is recycled back to the membrane of the cell [9]. The PCSK9 proprotein affects LDLR activity through two pathways—the intracellular and the extracellular. In the intracellular pathway, the proprotein together with the receptor enters the lysosomes resulting in the degradation of the LDLR. In the extracellular pathway, the liver secretes PCSK9, which binds extracellularly to the LDLR and the formed complex enters hepatocytes, again resulting in degradation of the receptor.¹⁰ Therefore, PCSK9 increases LDLR degradation and LDL cholesterol.

All three major gene mutations result in the dysfunction of binding of LDL to its receptors.

Subsequently, LDL cholesterol's uptake and destruction is reduced in the liver, which results in increased level of LDL in the serum.⁸

Epidemiological data of heterozygous hypercholesterolemia

Heterozygous familial hypercholesterolemia is thought to occur in 1 in 500 people in most ethnicities worldwide.¹¹ However, typically, these statistics are based on restricted data from particular populations or specific subgroups within the general population, which may lead to less precise estimates compared to more contemporary methods.⁷

In fact, overall contemporary data suggest that heterozygous familial hypercholesterolemia is much more common, affecting 1 in 200–300 individuals worldwide.¹² This could mean that more than 30 million people worldwide could be affected by heterozygous familial hypercholesterolemia. In contrast, homozygous hypercholesterolemia occurs more frequently—1 in 1,160,000–300,000 people.¹¹

Moreover, the occurrence of heterozygous hypercholesterolemia appears to vary depending on ethnicity and geography, with increased prevalence observed in subgroups sharing ancestry or in populations with higher rates of consanguinity (eg, Africans in South Africa, Lebanese Christians, Tunisians, some French Canadians).^{7,13,14}

Diagnostic criteria

Screening for the diagnosis of the disease occurs in individuals who are older than 2 years old and have a family history of familial hypercholesterolemia or early coronary disease. Specifically, for children aged 9–11 years it is recommended to measure non-HDL concentration without fasting and if it is 145 mg/dL or higher then evaluation with a lipid profile after fasting is recommended.¹⁵

Familial hypercholesterolemia is suspected in the following cases:^{9,15,16,17} a) In individuals aged 20 years or younger, where the fasting LDL concentration is higher than 160 mg/dL or the non-HDL concentration is greater than 190 mg/dL. b) In people over 20 years of age, where the concentration of LDL after fasting is greater than 190 mg/dL or the concentration of non-HDL is higher than 220 mg/DI. c) When there is a history of familial hypercholesterolemia in the family or the total cholesterol concentration is higher than 240 mg/DI in one of the parents. d) If tendon xanthomas are present in people of any age, "arcus senilis" in people under 45 years of age and yellow-orange nodular xanthelasma or xanthomas in people aged 20–25

years.

The Dutch Lipid Clinical Diagnostic Criteria and the Simon Broome criteria are used widely for the evaluation and diagnosis of heterozygous familial hypercholesterolemia.

The diagnostic criteria for both methods include measurement of LDL levels, presence of xanthomas, genetic mutation or family history of FH, early cardiovascular incidents, tendon xanthomas or arcus senilis, and high LDL levels at early ages.⁹ The Dutch criteria separates the patients into 4 categories namely, definite, very likely, probable or unlikely FH. On the other hand, Simon Broome characterizes patients as definite or probable FH, (Tables 1 and 2).

Although, genetic testing is not mandatory for diagnosis of FH, it is useful in cases with unclear diagnosis. However, a large number of patients (~20%) with FH are diagnosed by clinical criteria and are negative for all the known mutations by genetic testing.¹⁵ In the case of homozygous familial hypercholesterolemia, the diagnosis is based on untreated or untreated plasma LDL levels. Untreated LDL concentration is greater than 500 mg/dL and with treatment LDL concentration is equal to or greater than 300 mg/dL. Also, tendon xanthomas or skin manifestations are present in children younger than 10 years old or both parents meet criteria for heterozygous familial hypercholesterolemia based on untreated elevated LDL levels.¹⁷

Another way to screen for familial hypercholesterolemia is screening family members of the FH patient.¹⁸

In this screening, patient's all first-degree family members undergo a lipid profile test. The chances of detecting FH in first-, second- and third-degree family members are 50%, 25% and 12.5%, respectively. When genetic mutations are found in an individual, all of his/her family members should take a genetic test.¹⁵

Finally, a skin lesion biopsy may be performed when there is lesion on the skin or in uncertain heterozygous FH diagnosis. Cholesterol accumulations are found in FH xanthelasma as well as in FH xanthomas.⁹

Disease Management-Treatment

The disease can be managed in the following ways: targeting lipid levels, lifestyle changes, medication. Regarding the reduc-

tion of lipid concentrations, there are different recommendations regarding the target LDL concentration. The National Lipid Association aims for an LDL concentration of less than 130 mg/dL or a 50% reduction from baseline values. In patients with an aggravated profile, such as diabetes, obesity or a history of cardiovascular disease, more stringent targets are recommended. In contrary, the Belgian multi-societal guidelines recommend targets depending on the patient's age. In patients aged 10-14 years, the LDL level should reach a value of less than 160 mg/dl or decrease by 30% from the initial levels. In children aged 14-18, it should drop to something under 130 mg/dL. In patients over 18 years of age, it should be reduced below 100 mg/dL.⁶ Notably, in a cross-sectional study in the Netherlands was found that only 21% of patients with heterozygous familial hypercholesterolemia had understood the goals of treatment and were receiving the maximum dose of approved drugs, thus suggesting that there are deficiencies in adequate monitoring and implementation of treatment.¹⁹

The therapeutic lifestyle adjustments play a significant role in the management of FH. Lifestyle changes include changes in diet, physical activity, alcohol consumption and smoking. A proper diet for FH patients is advised to be low in calories with total fat intake less than 3% of total dietary intake including less than 8% saturated fat and less than 75 mg/1,000 kcal of cholesterol.²⁰ However, dietary limitations are observed to have a slight impact on reducing lipid levels with uncertain long-term clinical advantages. As a result, simultaneous drug therapy is recommended for patients with severe hypercholesterolemia.⁶

Next approach is pharmaceutical. As per guidelines from the National Heart, Lung, and Blood Institute (NHLBI), the initial treatment approach involves prescribing bile acid sequestrants, which can be initiated as early as 10 years of age. This recommendation is based on the favorable long-term safety record of these medications, attributed to their limited absorption into the bloodstream. These agents work by binding to bile acids in the intestines, thereby preventing their systemic absorption. Consequently, this leads to increased conversion of cholesterol into bile acids and stimulates the liver to produce more LDL receptors. Cholestyramine and colestipol are among the most

commonly utilized drugs in this category. However, their effectiveness was moderate (10-20% LDL reduction) and they also caused gastrointestinal intolerance. Recently, a novel drug in this group of medications, colesvelam hydrochloride, has been tested in individuals with heterozygous FH. A brief, randomized study demonstrated favorable tolerance and effectiveness of colesvelam, both when used independently and when combined with statins. This outcome has sparked a revived interest in this drug category.²¹ In one of their recent announcements the American Heart Association advised statins as the primary medication and lowered the age for initiating treatment to 8 years. This guideline was later endorsed by the American Academy of Pediatrics.²² Statins, also known as 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, are presently the primary medications for treating FH in children and adolescents. They impede the pivotal step in cholesterol synthesis, thus boosting the expression of LDL receptors and swiftly reducing LDL levels in the bloodstream. However, their efficacy is limited in patients with homozygous FH displaying a null phenotype, as they necessitate receptor production for their function. The Food and Drug Administration (FDA) has authorized pravastatin among the various generic statins available for children aged over 8 years and lovastatin, atorvastatin, and simvastatin for children aged over 10 years.

The commencement of statin therapy during preadolescence continues to be a topic of debate due to its potential to disrupt the body's steroid hormone production. Additionally, concerns persist regarding their impact on muscles and liver function. However, a recent examination of placebo-controlled trials involving statins in children and adolescents with FH revealed no notable adverse effects concerning growth, sexual development, or muscle and liver toxicity. At the same time, it demonstrated outstanding effectiveness in lowering lipids, achieving a mean relative reduction of 26.5% in LDL-cholesterol levels. Concerns regarding statins affecting growth during adolescence were somewhat alleviated by the unexpected discovery of increased growth in children receiving the medication. However, it's important to note that only short-term outcomes were evaluated in these trials, leaving the long-term safety of statins in this age group uncertain. The most

extensive follow-up data on the impact of statin therapy in children comes from a retrospective study spanning 7 years, involving 185 children with FH treated with pravastatin. This study revealed minor side effects in 13% of patients, with four cases of myopathy. Despite these long-term safety concerns, current patterns in drug usage among children indicate a growing use of statins in the pediatric population.²³

However, patients can undergo monitoring upon initiating statin therapy. Initially, assessing creatine phosphokinase (CK) for muscle toxicity and measuring aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for liver toxicity is imperative before commencing statin treatment. Follow-up assessments should occur 1-3 months after initiating the medication and then annually thereafter. Discontinuation of medication is recommended if CK levels reach five times and AST and ALT levels rise three times above the upper normal limit. After a drug-free interval of 3 months, the same medication at a lower dose or a different statin can be considered. If statins are still not tolerated despite these measures, alternative medications can be explored.⁶

Ezetimibe belongs to a novel class of cholesterol absorption inhibitors that target the epithelium of the small intestine. Due to their mechanism of action not relying on the expression of LDL receptors, they offer particular advantages in managing homozygous FH. Clinical studies have demonstrated their efficacy in reducing LDL levels, either as standalone therapy or when used alongside statins. However, a large trial found that the addition of ezetimibe to high-dose simvastatin did not decrease carotid intima thickness, despite significantly lowering LDL levels. Furthermore, the discovery of a slight yet significant rise in cancer incidence among patients treated with ezetimibe raises concerns, especially considering the lifelong treatment required for FH patients.²⁴ Hence, there is a necessity for further data concerning clinically significant outcomes and safety indicators before ezetimibe becomes widely adopted in pediatric healthcare. While the US FDA has sanctioned ezetimibe treatment for children aged over 10 years, existing guidelines advise commencing the medication before 18 years of age solely for statin-intolerant individuals or patients unable to reach lipid targets with statin monotherapy.²⁵

For patients who have not attained their lipid targets despite maximal medical treatment, there are alternative options in the form of newer medications. Mipomirsen, an antisense oligonucleotide designed to target apoB-100 mRNA in the liver, is currently undergoing investigation for the management of FH. Recent phase 3 trials have shown that this drug significantly reduces LDL and lipoprotein(a) levels in adults with both heterozygous and homozygous hypercholesterolemia. However, while the mean reduction in LDL was notable with a weekly subcutaneous dose of 200 mg mipomirsen in patients with homozygous FH, concerns persist regarding its potential hepatotoxicity, despite the most common side effects being injection site reactions and flu-like symptoms. Additionally, since mipomirsen has not been subject to prospective clinical trials in children, its safety profile in this patient group remains undetermined.

Furthermore, various molecular techniques aimed at inhibiting the action of PCSK9 to decrease LDL levels are being investigated. These include the development of monoclonal antibodies targeting PCSK9, antisense nucleotide therapy, and siRNAs. In a randomized controlled trial involving monoclonal antibodies conducted on adults with different types of hypercholesterolemia, combining this drug with 10 and 80 mg of atorvastatin proved more effective in reducing LDL levels than using 80 mg of atorvastatin alone. However, since this antibody needs some residual function of the LDL receptor to be effective, it is only beneficial for patients with heterozygous FH and a non-null phenotype of homozygous FH.

Lomitapide represents a novel lipid-lowering agent with a unique mechanism of action: it inhibits microsomal triglyceride transfer protein (MTP). MTP's role in LDL production involves aiding in the transfer of triglycerides to apolipoprotein B.⁶

In addition to the previously mentioned medications, various other drug classes such as thyroid mimetics (e.g., eprotirome and sobetirome), HDL-bound cholesterol ester transfer protein inhibitors (e.g., torcetrapib, anacetrapib), and rHDL are currently under investigation for the treatment of elevated LDL levels, with differences in efficacy and safety profiles. However, all ongoing trials investigating drug treatments for dyslipidemia are focused on adult patients and exclude the pediatric popu-

lation. Since the majority of these novel therapies have yet to demonstrate clinical efficacy and safety endpoints, their current role is predominantly restricted to treating patients with homozygous FH who have not reached their lipid goals. Further studies involving children are imperative before considering their clinical application in the treatment of heterozygous patients.

Another treatment option involves LDL removal. Patients with homozygous and compound heterozygous FH often experience elevated lipid levels despite receiving optimal medical therapy. These individuals are considered good candidates for LDL removal, which has demonstrated significant efficacy in lowering LDL levels. Several studies have validated its ability to reduce LDL cholesterol levels by 55-75%. However, the reduction of LDL levels achieved through apheresis is temporary and is accompanied by a rebound effect in lipid levels post-procedure. This rebound is rapid in patients without FH, slower in those with heterozygous FH, and delayed in patients with homozygous FH. For patients with homozygous FH, weekly to fortnightly sessions are recommended, as these have been shown to mitigate the degree of rebound and decelerate the progression of atherosclerosis. The combination of LDL apheresis with medication in patients with homozygous FH has resulted in a significant increase in life expectancy, exceeding 50 years compared to the previously estimated 20-30 years. Despite its established efficacy, lipid apheresis has not been widely integrated into clinical practice due to various factors including limited accessibility for the majority of patients, high cost, invasiveness of the procedure, and patient reluctance.²⁷

Incidence of the disease in women

Roughly 1 in 200 individuals are affected by FH, yet the majority remain undiagnosed.²⁸ Individuals with FH often do not exhibit symptoms until they experience an acute coronary syndrome (ACS) or stroke. Untreated FH significantly heightens the risk of early-onset atherosclerotic cardiovascular disease (ASCVD) in women.²⁹ Early and aggressive lipid-lowering therapy can substantially mitigate this risk in both women and men. Unfortunately, women are less likely to be prescribed lipid-lowering therapy or initiate early statin therapy. Moreover,

they are more prone to discontinuing therapy due to childbearing, consequently failing to attain target LDL levels.³⁰ Furthermore, there exists a common perception that women face a lower risk of ASCVD, leading to inadequate treatment of women with FH.

Around 30% of untreated women with FH will develop ASCVD by the age of 60. ASCVD tends to manifest approximately 20 years earlier in life for women with FH compared to those without the condition. Even following an ASCVD event, women are 10% less likely to be diagnosed with FH upon hospital discharge in comparison to men.³¹ Moreover, women are less likely than men to receive appropriate guideline-based cholesterol management or achieve adequate LDL reduction.³⁰ The CASCADE-FH (Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia) is a national registry in the USA that monitors the treatment and outcomes of FH patients.³² Within this dataset, women were found to be 31% less likely than men to attain LDL concentrations below 100 mg/dL. Similarly, women with FH and ASCVD were 25% less likely than their male counterparts to reach LDL-C concentrations below 100 mg/dL. Women also tend to experience statin-related adverse events more frequently than men. However, biases among physicians in treating women with ASCVD can pose significant risks for women with FH who are not adequately treated.³⁰

Undiagnosed FH results in a significant loss of life expectancy, with patients losing approximately 16 years of life.³³ Additionally, on average, women are diagnosed with FH four years later than men.³⁰ There is a notable lack of awareness regarding guidelines for FH diagnosis across various medical fields. Only a small percentage of pediatricians (26%) are aware of lipid screening guidelines,³⁴ and a minority of general practitioners (15%) are very familiar with FH. However, a higher proportion of cardiologists (61%) and other specialists (45%) exhibit a good level of familiarity with FH. Given that young girls and women seek care from pediatricians, general practitioners, and obstetricians/gynecologists, it is crucial for all practitioners to be aware of FH for early diagnosis. Improving female representation in trials studying FH and lipid-lowering drugs is essential for enhancing outcomes and reducing racial disparities. Many

studies have had low female representation, except for the CASCADEFH registry, where 60% of participants were female.³⁵

In childhood, girls aged 5–19 years with FH exhibit higher levels of total cholesterol, LDL, and non-HDL compared to boys in the same age group, putting them at a heightened risk from a younger age. Early initiation of statins is especially crucial for young girls, as they are more prone to discontinuing treatment during childbirth. Consequently, early screening for the disease enables women to safely consider starting a family at an earlier age if they desire.³⁵

Furthermore, lipid-lowering therapy should not be withheld in young women of reproductive age. However, it is essential to recommend appropriate contraception for young post-adolescent girls receiving lipid-lowering therapy. An exception to this is treatment with bile acid sequestrants due to their teratogenic effects. Simultaneously, it is crucial to have discussions about the potential side effects of lipid-lowering therapy in the event of pregnancy during treatment. Thus, emphasizing the importance of adherence to the chosen contraceptive method is essential in these discussions.³⁵

Women with FH demonstrate similar fertility rates to those without FH, despite a higher prevalence of polycystic ovary syndrome (PCOS) than the general population.³⁶ However, if a woman with FH experiences infertility, her dyslipidemia becomes a crucial factor in managing infertility, since she may not be an ideal candidate for hormone therapy, and evidence from in vitro fertilization (IVF) studies suggests that dyslipidemia can negatively impact oocyte quality, thus affecting fertility. Therefore, women with FH may need to explore alternative strategies to address infertility, highlighting the necessity for further research into dyslipidemia, FH, and fertility.³⁷ The majority of cholesterol-lowering medications are not recommended during pregnancy due to the heightened risk of miscarriage associated with their use. Enhancing cholesterol levels before conception not only offers advantages for the mother but also carries substantial cardiovascular implications for her children. Elevated maternal cholesterol levels during pregnancy have been associated with an augmented predisposition to the development of atherosclerosis in the fetus.³⁵

In postmenopausal women with FH, LDL values are comparable

to those of premenopausal women and tend to be higher than those of men in the same age group. Postmenopausal women with FH may experience the repercussions of elevated LDL concentrations, either due to delayed diagnosis or as a result of interruptions in management that may have occurred during childbearing.³⁵

CONCLUSIONS

FH is a severe condition with potentially devastating consequences later in life for affected individuals. While the necessity for implementing a screening test to detect this disease early is widely acknowledged, there remains a lack of consensus on the optimal timing and responsibility for conducting such tests. Early initiation of lipid-lowering therapy and adoption of lifestyle measures may contribute to improved clinical outcomes for individuals with FH.

Over the past twenty years, there has been significant progress in the development of new therapies aimed at reducing LDL-cholesterol levels and postponing premature atherosclerosis, particularly when combined with lifestyle modifications. However, the majority of children fail to reach their targeted lipid goals due to shortcomings in diagnosis, monitoring, and treatment.

Hence, achieving optimal control and accurate diagnosis of FH is crucial for preventing premature cardiovascular events. Managing patients with FH necessitates a collaborative approach involving various healthcare professionals, including primary care providers, cardiologists, endocrinologists, dietitians, pharmacists, and nurses, to enhance outcomes. It is imperative to thoroughly discuss treatment strategies upon diagnosis. Close and regular monitoring is essential to assess treatment response and identify any potential side effects from lipid-lowering medications, thereby optimizing patient care.

Improving the representation of women in studies related to the diagnosis and treatment of FH is crucial for enhancing the effectiveness of managing this condition. The sensitivity of this representation plays a significant role in recognizing the inequalities experienced by women with FH. By ensuring adequate inclusion of women in research studies, we can better understand and address the unique challenges and needs faced by

female patients with FH, ultimately leading to more equitable and improved treatment outcomes.

REFERENCES

1. WHO. (2021). Cardiovascular diseases (CVDs). Accessed: September 15, 2023 [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
2. Badimon L, Chagas P, Chiva-Blanch G.: Diet and Cardiovascular Disease: Effects of Foods and Nutrients in Classical and Emerging Cardiovascular Risk Factors. *Curr Med Chem.* 2019;26:3639-3651. 10.2174/0929867324666170428103206.
3. Pavlatou N, Rovina N, Toyli G, Kadda O, Marvaki C, Kapadochos T, Kolovou G, Koutsoukou A. Prevalence of familial hypercholesterolemia in Attica region, Greece. *Health and Research Journal* 2021;7(1):26-38.
4. Mosca S, Araújo G, Costa V, et al. Dyslipidemia Diagnosis and Treatment: Risk Stratification in Children and Adolescents. *J Nutr Metab.* 2022;2022:4782344. doi:10.1155/2022/4782344
5. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL: Global epidemiology of dyslipidaemias. *Nat Rev Cardiol* 2021;18:689-700. 10.1038/s41569-021-00541-4
6. Varghese MJ: Familial hypercholesterolemia: A review. *Ann Pediatr Cardiol* 2014;7:107-117. 10.4103/0974-2069.132478
7. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J* 2015;36:560-565. 10.1093/eurheartj/ehu058
8. Khera AV, Won HH, Peloso GM, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol* 2016;67:2578-2589. 10.1016/j.jacc.2016.03.5209.
9. Vaezi Z, Amini A. Familial Hypercholesterolemia. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; September 26, 2022. Bookshelf ID: NBK556009

10. Seidah NG, Prat A: The Multifaceted Biology of PCSK9. *Endocr Rev* 2022;43:558-582. 10.1210/edrev/bnab035
11. Singh S, Bittner V: Familial hypercholesterolemia--epidemiology, diagnosis, and screening. *Curr Atheroscler Rep* 2015;17:482. 10.1007/s11883-014-0482-5
12. Watts GF, Lewis B, Sullivan DR: Familial hypercholesterolemia: a missed opportunity in preventive medicine. *Nat Clin Pract Cardiovasc Med* 2007;4:404-405. 10.1038/ncpcardio0941
13. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011;5:133-140. 10.1016/j.jacl.2011.03.001
14. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation* 2014 ;129(25 Suppl 2):S46-8] [published correction appears in *Circulation*. 2015 Dec 22;132(25):e396]. *Circulation*. 2014;129:S1-S45. 10.1161/01.cir.0000437738.63853.7a
15. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ: National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011;5:S9-S17. 10.1016/j.jacl.2011.03.452
16. Nordestgaard BG, Chapman MJ, Humphries SE, et al.: Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society [published correction appears in *Eur Heart J* 2020;41(47):4517]. *Eur Heart J*. 2013;34:3478-90a. 10.1093/eurheartj/eh273
17. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;35:2146-2157. 10.1093/eurheartj/ehu274
18. Vaseghi G, Arabi S, Haghjooy-Javanmard S, et al. CASCADE screening and registry of familial hypercholesterolemia in Iran: Rationale and design. *ARYA Atheroscler* 2019;15:53-58. 10.22122/arya.v15i2.1899
19. Pijlman AH, Huijgen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. *Atherosclerosis*. 2010;209:189-194. 10.1016/j.atherosclerosis.2009.09.014
20. Descamps OS, Tenoutasse S, Stephenne X, et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. *Atherosclerosis* 2011;218:272-280. 10.1016/j.atherosclerosis.2011.06.016
21. Stein EA, Marais AD, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. *J Pediatr* 2010;156:231-6.e63. 10.1016/j.jpeds.2009.08.037
22. Daniels SR, Greer FR: Committee on Nutrition: Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198-208. 10.1542/peds.2008-1349
23. Carreau V, Girardet JP, Bruckert E: Long-term follow-up of statin treatment in a cohort of children with familial hypercholesterolemia: efficacy and tolerability. *Paediatr Drugs* 2011;13:267-275. 10.2165/11591650-000000000-00000
24. Phan BA, Dayspring TD, Toth PP: Ezetimibe therapy: mechanism of action and clinical update. *Vasc Health Risk Manag* 2012;8:415-427. 10.2147/VHRM.S33664
25. Kavey RW, Manlhiot C, Runeckles K, et al.: Effectiveness and Safety of Statin Therapy in Children: A Real-World

- Clinical Practice Experience. *CJC Open* 2020;2:473-482. 10.1016/j.cjco.2020.06.002
26. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA: Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med* 2012;367:1891-1900. 10.1056/NEJMoa1201832
27. Thompson GR: The scientific basis and future of lipoprotein apheresis. *Ther Apher Dial* 2022;26:32-36. 10.1111/1744-9987.13716
28. Onorato A, Sturm AC: Heterozygous Familial Hypercholesterolemia. *Circulation* 2016;133:e587-e589. 10.1161/CIRCULATIONAHA.115.020701
29. Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association [published correction appears in *Circulation* 2015;132(25):e397]. *Circulation*. 2015;132:2167-2192. 10.1161/CIR.0000000000000297
30. Amrock SM, Duell PB, Knickelbine T, et al. Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. *Atherosclerosis* 2017;267:19-26. 10.1016/j.atherosclerosis.2017.10.006
31. Mundal L, Veierød MB, Halvorsen T, et al. Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994-2009, a registry study. *Eur J Prev Cardiol* 2016;23:1962-1969. 10.1177/2047487316666371
32. O'Brien EC, Roe MT, Fraulo ES, et al. Rationale and design of the familial hypercholesterolemia foundation CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia registry. *Am Heart J* 2014;167:342-349.e17. 10.1016/j.ahj.2013.12.008
33. Wong B, Kruse G, Kutikova L, Ray KK, Mata P, Bruckert E. Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature. *Clin Ther*. 2016;38:1696-1709. 10.1016/j.clinthera.2016.05.006
34. de Ferranti SD, Rodday AM, Parsons SK, et al. Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians. *J Pediatr* 2017;185:99-105.e2. 10.1016/j.jpeds.2016.12.078
35. Balla S, Ekpo EP, Wilemon KA, Knowles JW, Rodriguez F.: Women Living with Familial Hypercholesterolemia: Challenges and Considerations Surrounding Their Care. *Curr Atheroscler Rep* 2020;22:60. 10.1007/s11883-020-00881-5
36. Toleikyte I, Retterstøl K, Leren TP, Iversen PO.: Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. *Circulation* 2011;124:1606-1614. 10.1161/CIRCULATIONAHA.110.990929
37. Wang S, Wang J, Jiang Y, Jiang W.: Association between blood lipid level and embryo quality during in vitro fertilization. *Medicine (Baltimore)*. 2020;99:e19665. 10.1097/MD.00000000000019665

ANNEX

TABLE 1. Dutch lipid clinical diagnostic criteria for familial hypercholesterolaemia. Only one score per team (the highest) is selected.
Definitive diagnosis >8 points, Very probable 6-8 points, Probable: 3-5 points.

Criteria	Grading
1) Family history	
First-degree relative with known premature coronary artery disease or with known LDL* values above the 95th percentile	1
First degree relative with xanthomas and/or arcus senilis or children under 18 with LDL above the 95th percentile	2
2) Clinical history	
Patient with premature coronary artery disease	2
Patient with advanced cerebral or peripheral vascular disease	1
3) Physical examination	
Typical xanthomas	6
Arcus senilis before the age of 45	4
4) LDL levels	
>325 mg/dL	8
251-325 mg/dL	5
191-250 mg/dL	3
155-190 mg/dL	1
5) DNA** analysis	
Functional mutation in LDLR, apoB or PCSK9 gene	8

LDL:** Low Density Lipoproteins, *DNA:** Deoxyribonucleic Acid

TABLE 2. Simon Broome diagnostic criteria for familial hypercholesterolaemia. Definitive diagnosis: criteria a and b or only c. Possible diagnosis: criteria a and d or a and e.

Criteria	Description
a	Total cholesterol in adults > 290 mg/dL or in children > 259 mg/dL LDL* concentration in adults > 189 mg/dL or in children > 155 mg/dL.
b	Typical xanthomas in the same or first degree relative
c	Mutation in the LDLR**, apoB or PCSK9*** gene
d	Family history of myocardial infarction at the age of less than 50 years in a second-degree relative or at the age of less than 60 years in a first-degree relative
e	Family history of elevated total cholesterol concentration > 290 mg/dL in a first or second degree relative

LDL**: Low Density Lipoproteins, *LDLR**: Low Density Lipoprotein Receptor; *****PCSK9**: Proprotein Convertase

Subtilisin/Kexin type 9