



# Women Living with Familial Hypercholesterolemia: Challenges and Considerations Surrounding Their Care

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## Abstract

**Purpose of Review** To highlight the gender-based differences in presentation and disparities in care for women with familial hypercholesterolemia (FH).

**Recent Findings** Women with FH experience specific barriers to care including underrepresentation in research, significant underappreciation of risk, and interrupted therapy during childbearing. National and international registry and clinical trial data show significant healthcare disparities for women with FH. Women with FH are less likely to be on guideline-recommended high-intensity statin medications and those placed on statins are more likely to discontinue them within their first year. Women with FH are also less likely to be on regimens including non-statin agents such as PCSK9 inhibitors. As a result, women with FH are less likely to achieve target low-density lipoprotein cholesterol (LDL-C) targets, even those with prior atherosclerotic cardiovascular disease (ASCVD).

**Summary** FH is common, under-diagnosed, and under-treated. Disparities of care are more pronounced in women than men. Additionally, FH weighs differently on women throughout the course of their lives starting from choosing contraceptives as young girls along with lipid-lowering therapy, timing pregnancy, choosing breastfeeding or resumption of therapy, and finally deciding goals of care during menopause. Early identification and appropriate treatment prior to interruptions of therapy for childbearing can lead to marked reduction in morbidity and mortality. Women access care differently than men and increasing awareness among all providers, especially cardio-obstetricians, may improve diagnostic rates. Understanding the unique challenges women with FH face is crucial to close the gaps in care they experience.

**Keywords** Familial hypercholesterolemia · Women · Girls · Statins · LDL

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## Introduction

When Katherine Wilemon experienced severe chest pain in her mid-thirties, as a young woman she did not expect to have heart disease, nor did the medical teams who initially evaluated her and dismissed her symptoms. Despite an LDL cholesterol above the ninety-fifth percentile, she was only taken seriously after a reluctant cardiologist performed a coronary angiogram which revealed significant coronary artery disease requiring percutaneous coronary intervention. Even after the diagnosis of early-onset atherosclerotic cardiovascular disease (ASCVD), it took her an additional 2 years to be formally diagnosed with familial hypercholesterolemia (FH). This story is all too common for individuals, especially women, with FH. Katherine Wilemon recovered and founded the FH Foundation ([www.thefhfoundation.org](http://www.thefhfoundation.org)). Her story, unfortunately, highlights how women with FH are managed and brings to the forefront the missed opportunities for preventive care.

FH is an autosomal dominant genetic disorder characterized by lifelong elevations in low-density lipoprotein cholesterol (LDL-C) levels. Approximately 1 in every 200 people has FH, but the vast majority are undiagnosed [1•]. Individuals with FH are often asymptomatic until a presentation with acute coronary syndrome (ACS) or stroke. Untreated women with FH are at very high risk for early-onset atherosclerotic cardiovascular disease (ASCVD) [2]. Early and aggressive lipid-lowering therapy can markedly attenuate this risk in both women and men. Women are not only less likely to be prescribed lipid-lowering therapy and initiate early statin therapy, but they are more likely to have interrupted management compared with men due to childbearing and are less likely to achieve goal LDL-C levels [3••]. Additionally, perception of lower ASCVD risk in women can be particularly deleterious for women with FH and lead to under-treatment. In this review, we highlight the gender disparities in the treatment of women with FH and provide perspectives for healthcare providers to consider while treating a young woman with FH throughout her life.

### Disparities in Care and Representation of Women in FH Research

In untreated women with FH, 30% will develop ASCVD by the age of 60 years. The onset of ASCVD occurs 20 years earlier in life for women with FH than in women without FH [4]. Even after an ASCVD event, women are 10% less likely to be diagnosed with FH upon hospital discharge compared with men [5•]. Furthermore, compared with men, women are less likely to receive appropriate guideline-based cholesterol management or have an adequate LDL-C reduction [3, 6•, 7–10]. The Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH) registry is a national registry that tracks treatment and outcomes of patients with FH in the USA [11]. In this dataset, women were 31% less likely than men to achieve LDL-C < 100 mg/dL, while women with FH and ASCVD were 25% less likely than their male counterparts to achieve LDL-C < 100 mg/dL (Fig. 1) [3••]. Women are more likely to experience statin-associated side effects than men (Fig. 1) [3••], but this is not the sole reason for this discrepancy. Implicit physician biases in treating women with ASCVD are established [12], and for women with FH, these become more dangerous, and provider and patient awareness is a key component in overcoming them.

Representation of women in registries and trials studying FH and lipid-lowering medication is a critical to improve their outcomes and reduce gender-based disparities. Some of the important FH registries and clinical trials are detailed in Table 1. Historically, many of these studies have had an underrepresentation of women [14••, 16, 18]. The CASCADE-FH registry has been more representative, with 60% of the

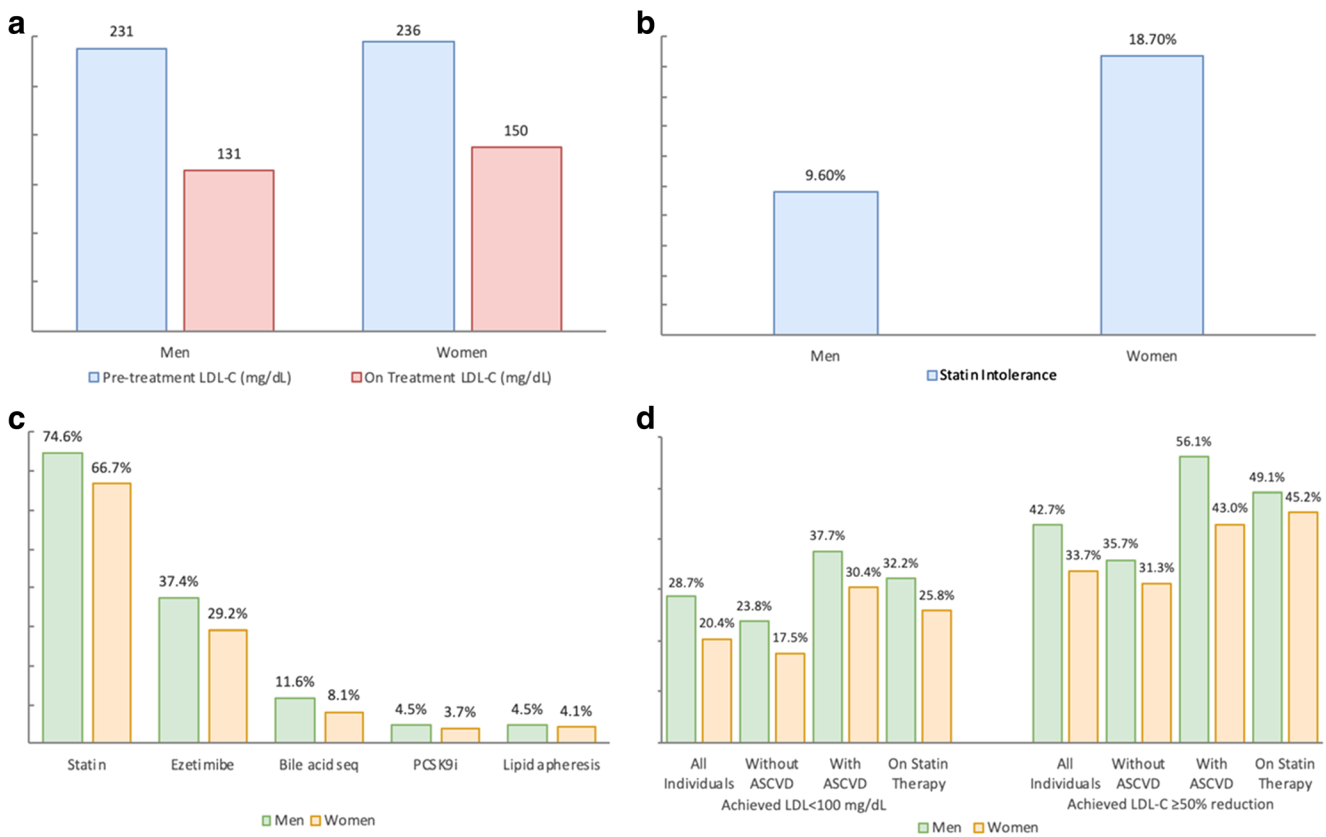
cohort being women. A caveat of this representation is that 79% of these women are white. Racial and ethnic disparities in the USA and in cardiovascular care are rampant today and it has even been shown that Asian and African American women are significantly less likely to achieve an LDL-C < 100 mg/dL [3••]. In the CASCADE-FH cohort, only 4.6% of the cohort identified as Black, 2.4% Hispanic, 2.3% Asian, and 3.4% other [23••]. Nevertheless, even with this small sample size, there is evidence that Blacks were less likely to be on guideline-based medical management and achieve target LDL-C levels. Therefore, while women's representation needs to improve, the granularity of this representation is an important consideration to truly ascertain the disparities experienced by women with FH.

### Diagnostics

Undiagnosed FH costs 16 years of life expectancy [24] and on average, women are diagnosed with FH 4 years later than men [3••]. Although FH is a dominant genetic disorder, caused by genetic mutations in one of three genes: *LDLR*, *APOB*, and *PCSK9*, diagnosis is based on a combination of lipid levels, personal and family history of heart disease, physical exam findings, and genetic testing results (if available) for mutations in one of the three genes. People often have just one disease-causing variant causing heterozygous FH (HeFH). Rarely, people may inherit two disease-causing variants (homozygous or HoFH). There is a free mobile phone-based application that provides a stepwise diagnostic tool that can be used by primary care providers and cardiologists alike to simplify the diagnostic process [25].

While recommendations for routine screening for hyperlipidemia start as early as 8–10 years, less than 3% of children are screened for lipids [26]. In part, this can be explained by data showing overall poor awareness of the guidelines: Only 26% of pediatricians were knowledgeable about the 2011 NHLBI Guidelines for lipid screening [27•]. There is also a general lack of knowledge about FH across medical fields: Only 15% of general practitioners are very familiar with FH, while 61% of cardiologists and 45% of other specialists were very familiar. As young girls and women receive care from pediatricians, general practitioners, and obstetricians/gynecologists, the key to early diagnosis lies in awareness among all practitioners.

Cascade screening (family-based testing of relatives of affected individuals) is a proven effective approach to improve FH diagnosis [28]. Cascade testing can be done with lipid and/or genetic testing. Early diagnosis of young FH children by screening children at immunization visits and reverse cascade screening of their parents can widen the reach of FH screening and increase diagnostic rates [29•]. In this paper, a majority of parents supported genetic testing. Importantly



**Fig. 1** Disparity outcomes in the CASCADE-FH registry [3]. **a** Differences in the reduction of LDL-C between men and women. Treated LDL-C levels are higher in women than men ( $<0.001$ ). **b** Statin intolerance between men and women. Women had a higher prevalence of statin intolerance ( $<0.001$ ). CASCADE-FH categorized individuals citing intolerance or allergy as a reason for not being on statins as statin intolerant. **c** Percentage of patients on lipid-lowering

therapy by drug and gender. Women were less likely to be on statin therapy than men ( $<0.001$ ). **d** Achievement of LDL-C levels less than 100 mg/dL or reduction by 50% LDL-C in men versus women. Women were less likely to achieve LDL-C  $<100$  mg/dL (odds ratio (OR) 0.68, 95% CI, 0.57–0.82) or reduction of 50% LDL-C (OR, 0.79, 95% CI, 0.65–0.96). Adapted from CASCADE-FH registry data [3]

cascade genetic screening has not been linked to psychological or social harm in adults or children [30]. Diagnosing children will dramatically reduce the age at which individuals are diagnosed and treated, especially benefitting women, who are likely to have interrupted management [31].

## Girls and Young Adult Women

Though ASCVD is thought to be a condition that only affects adults, in patients with HoFH, major coronary events and death can be seen in early childhood [32–34]. Pre-adolescence being a period of minimal dietary and hormonal influences is the optimal period to discriminate between FH and non-FH based on LDL-C concentration. Following dietary interventions, a child with an LDL-C level  $\geq 160$ –190 mg/dL has a high probability of genetically based FH [35]. Girls aged 5–19 years with FH have been shown to have higher total cholesterol, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol compared with

boys in the same age group [36] and therefore experience a higher risk burden from a younger age.

Early statin initiation is especially important for young girls as they are more likely to see interruptions in therapy. Current guidelines call for the initiation of statins in children around age 8 if the LDL-C is  $>190$  mg/dL especially if there is a family history of heart disease. However, this is often not done. While pediatricians believe statins are appropriate for children and adolescents, only a minority of pediatricians initiate statins [27•]. Statins are well-tolerated in the pediatric population and studies have shown no significant risk in growth and puberty delays, transaminitis, or myopathy. Additionally, a 10-year follow-up study on the initiation of statins in pediatric patients with FH showed normalization in the development of atherosclerosis when compared with their unaffected sibling [37•]. Earlier disease control minimizes the effects of interruptions during childbearing and allows women the possibility of safely starting their families at a younger age if they choose to.

Lipid-lowering therapy should not be withheld in young women of childbearing age, but appropriate contraception

**Table 1** Representation of women in familial hypercholesterolemia-related research

Registry/trial	Year	Number of participants	% women	Significant findings
CASCADE-FH Registry [3•, 11, 13]	2013-recruiting	3167	60.6%	<ol style="list-style-type: none"> <li>1. Registry population: multi-center US registry with dual enrollment, formally diagnosed by clinician or via self-enrollment.</li> <li>2. Majority (79%) of women were white.</li> <li>3. Women were older at time of entry compared with men.</li> <li>4. Women pretreatment had higher HDL, lower triglycerides, and comparable LDL with men.</li> <li>5. Women were significantly less likely to be on statin than men but experienced higher statin intolerance.</li> </ol>
YOUNG-MI Registry [14••]	2000–2016	1996	19.1%	<ol style="list-style-type: none"> <li>1. Registry population: patients who experienced an MI at or below 50 years. Probable or definite FH defined using Dutch Lipid criteria. Median age of 45 years.</li> <li>2. Clinically defined FH is present in nearly 1 in 10 patients with MI under the age of 50 years.</li> <li>3. Among probable/definite FH patients, 42.8% were not on any statin therapy prior to their MI, suggesting that they were unaware or not treated for their underlying condition.</li> <li>4. Among FH patients, only 63% were discharged on high-intensity statin therapy and the vast majority had elevated LDL at 1 year.</li> </ol>
Gulf FH Registry [15]	2020	3317	54%	<ol style="list-style-type: none"> <li>1. Registry population: adult (18–70 years), 9 hospitals/centers across 5 Arabian Gulf countries.</li> <li>2. Phase 1 recruited suspected FH patients based on lipid profile and clinical data. In phase 2, patients were stratified into definitive, probable, and possible FH according to Dutch Lipid criteria.</li> <li>3. Mean age: 47 ± 12 years.</li> <li>4. Patients with definitive FH are 203.</li> </ol>
French FH Registry [16]	2015–2018	781	28%	<ol style="list-style-type: none"> <li>1. Registry populations: clinical or genetic diagnosis of HeFH who had experienced a first CV event</li> <li>2. First cardiovascular event at the mean age of 47 years. Overall, 37% of patients had at least one recurrent cardiovascular event. A total of 55% of events occurred &gt; 3 years after the first event.</li> <li>3. A total of 48% of patients were on statin therapy.</li> <li>4. Mean LDL-C at the last clinic visit was 144 ± 75 mg/dL (132 ± 69 mg/dL for patients on high-potency statin therapy and 223 ± 85 mg/dL for untreated patients).</li> </ol>
HELLAS-FH Registry [17]		1093	49.1%	<ol style="list-style-type: none"> <li>1. Registry populations: Diagnosed FH patients were recruited by sites throughout Greece.</li> <li>2. Median age of FH diagnosis is 42.2 years.</li> <li>3. A total of 3% of the patients were receiving hypolipidemic drug treatment, mainly statins at inclusion in the registry.</li> <li>4. At diagnosis, LDL was 241 ± 76 mg/dL in adults and 229 ± 57 mg/dL in children. Mean LDL of patients receiving drug treatment was 154 ± 76 mg/dL in adults and 136 ± 47 mg/dL in children.</li> <li>5. Majority (88%) did not achieve LDL targets.</li> </ol>
ODYSSEY Trial [18, 19]	2012–2017	18,924	25%	<ol style="list-style-type: none"> <li>1. Trial population: 40 years or older and had been hospitalized with ACS 1–12 months before randomization, lipid levels on maximal tolerated statins of at least LDL ≥ 70, HDL ≥ 100, apo-B ≥ 80.</li> <li>2. Mean age of 58 ± 9 years with 80% of the cohort being white, 78 weeks of follow-up.</li> <li>3. Baseline mean LDL was 92 ± 31 mg/dL.</li> <li>4. In patients who had previous acute coronary syndrome and were receiving high-intensity statin, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab compared with placebo.</li> <li>5. When alirocumab was added to maximum tolerated statin dose, it reduced LDL-C by 62% compared with placebo, and this effect seen at 24 weeks remained consistent over a period of 78 weeks.</li> </ol>
RUTHERFORD-2 Trial [20]	2013	331	42%	<ol style="list-style-type: none"> <li>1. Trial population: 18–80 years, HeFH according to Simon-Broome criteria at screening on a stable dose of statin for at least 4 weeks before screening.</li> <li>2. Mean age of 51 years, 12 weeks duration of follow-up.</li> <li>3. Treatment of HeFH patients already on statins with evolocumab 140 mg every 2 weeks/ 420 mg every month resulted in significantly greater reduction in LDL (60%) levels at 12 weeks compared with placebo.</li> </ol>

**Table 1** (continued)

Registry/trial	Year	Number of participants	% women	Significant findings
CLEAR Harmony Trial [21••]	2016–2018	2230	27%	<ol style="list-style-type: none"> <li>4. Nearly two-thirds of patients were able to reduce LDL levels below 70 mg/dL.</li> <li>5. Most common adverse events in the evolocumab group were nasopharyngitis and muscle-related adverse events.</li> </ol>
REDUCE-IT USA [22•]	2011–2018	3146	32%	<ol style="list-style-type: none"> <li>1. Trial population: adults 18 years and older, with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia, on stable doses of maximally tolerated statin agent for at least 4 weeks, with a fasting LDL cholesterol level of at least 70 mg/dL.</li> <li>2. Mean age of 66, with 96% of cohort being white.</li> <li>3. A total of 1488 were assigned to receive bempedoic acid and 742 to receive placebo.</li> <li>4. Incidence of adverse events did not differ between treatment group and placebo group (78.5% versus 78.7%).</li> <li>5. Bempedoic acid reduced the mean LDL-B by 16.5% by week 12.</li> </ol>
				<ol style="list-style-type: none"> <li>1. Trial population: adults at least 45 years old with cardiovascular disease, or at least 50 years old with diabetes mellitus and 1 or more cardiovascular risk factors, with fasting triglycerides between 135 and 500 mg/dL, and LDL-C between 40 and 100 mg/dL on stable statin therapy for at least 4 weeks.</li> <li>2. Participants were followed for a median of 4.9 years.</li> <li>3. Icosapent ethyl provided a 30% relative risk reduction and a 2.6% absolute risk reduction in all-cause mortality (<math>P = .004</math>).</li> <li>4. Larger benefits were seen in the US subgroup compared with the original REDUCE-IT cohort</li> </ol>

must be advised to post-pubertal young girls on lipid-lowering therapy. Providing an overview of long-term care, discussing adherence strategies, time to achieve acceptable LDL levels, follow-up, and creating an environment for shared decision-making is imperative to effective treatment especially in those diagnosed young.

## Contraceptive Considerations

Contraception is advised for women on all lipid-lowering therapies used in FH except for bile acid-binding resins because of teratogenicity. In patients with FH and high risk of ASCVD, a preferred method of contraception is a non-hormonal intrauterine device, followed by progesterone-only containing contraceptives including levonorgestrel-releasing intrauterine device, subcutaneous implant, depot medroxyprogesterone acetate injection, or progestin-only pill [38]. Combined hormonal contraceptive pills, patches, and rings can also be used but are classified as “theoretical or proven risks usually outweigh the advantages” [38]. In the USA, after tubal ligation, oral contraceptive pills (OCPs) are the most commonly used contraceptives. Although combined oral contraceptives are not contraindicated in FH, they might increase the risk of ASCVD events and hormone-containing contraceptives have been associated with increased triglyceride and LDL-C levels in women. While it is the provider’s responsibility to bring these risks to a women’s attention, ultimately the decision on which

contraceptive method to use is a personal choice that should be made via shared decision-making between a woman and her care provider. Similarly, pre-pregnancy counseling is crucial in women with FH and these discussions should be started early in all adolescent girls with FH. These conversations should be patient-centric and include goals and expectations around pregnancy. It is important to discuss the side effects of lipid-lowering therapy should a woman become pregnant while on therapy and therefore stress the importance of adherence to her chosen contraceptive method.

## Fertility and Conception

Women with FH have fertility rates similar to women without FH, in spite of a higher incidence of polycystic ovarian syndrome than the general population [39]. Importantly, while statins and other lipid-lowering medications are teratogenic, they have no reported effect on fertility. If a woman with FH is dealing with infertility, her dyslipidemia is a major determinant in her infertility management [40]. She may not be an ideal candidate for hormonal therapy and evidence from in vitro fertilization (IVF) studies indicate that dyslipidemia is associated with poorer oocyte quality, thereby effecting fecundity [41]. Women with FH may need to consider alternate strategies to deal with infertility and there is a need for more research in the area of dyslipidemia, FH, fertility, and fecundity.

Women are at higher risk of experiencing complications of FH during their reproductive years, as most cholesterol-reducing agents are contraindicated during pregnancy. Appropriately timing pregnancy in women with FH is a meaningful discussion that needs to be started early. Women with severe FH (especially those diagnosed late) may benefit from being aggressively managed in the years leading up to pregnancy to prevent pregnancy-related complications such as ACS. Improving cholesterol levels before conception not only benefits the mother but has important cardiovascular implications for her children. Elevated maternal cholesterol levels during pregnancy were associated with early fatty streak formations in fetal aortas, predisposing the fetus to atherosclerosis [42]. The FELIC Study (1999) showed that children born to mothers with hypercholesterolemia were more susceptible to atherogenic risk factors than children born to mothers with normal cholesterol levels [42]. Identifying women young allows greater flexibility in this timeline to ensure safe outcomes for both mother and child.

If a woman with FH is considering pregnancy, her partner should be tested for FH as well. Assuming her partner does not have FH, each child of a mother with HeFH will have a 50% chance of inheriting the condition. When both parents have FH, their child has a 25% chance of having HoFH and a 50% chance of having a child with HeFH. Prenatal counseling, risk discussions, and ensuring the couple is aware of these implications is an important second step. If a woman is planning to conceive after appropriate risk discussions, it is recommended to discontinue statins, ezetimibe, and niacin therapy 1–3 months before conception [43]. Apart from genetic counseling, prenatal or preimplantation genetic testing is only indicated if the parents have a homozygous child and are hoping to conceive again or if both parents have HeFH.

Women with FH commonly have healthy pregnancies, but unlike the general population, appropriate risk discussions and a thorough evaluation of their cardiovascular health may be necessary. Risk discussions for women with FH considering pregnancy vary based on the presence of cardiovascular symptoms and the progression of their atherosclerotic disease processes. Women with symptoms of cardiac disease need additional care and benefit from a multidisciplinary approach.

## Pregnancy and FH

During pregnancy, LDL-C levels increase by more than 40% in the general population [44]. Women with FH show relative changes in lipids that are similar to unaffected women. However, the absolute increase is amplified in women with FH [45]. The consequences of these changes are theoretical postulations that increased cholesterol levels are associated with reduced uteroplacental perfusion [39]. Studies addressing the pregnancy outcomes and newborns of women with FH are limited, and the results can be conflicting [39, 46•].

Generally speaking, pregnancy in women with FH is relatively safe for both mothers and babies. An analysis of a registry of 2319 births of 1093 women with heterozygous FH collected between 1967 and 2006 in Norway showed that there was no increased risk of preeclampsia, gestational diabetes, or pregnancy-induced hypertension. There was also no increase in preterm delivery, low birth weight, or congenital malformations [39, 47]. Despite reassuring data, it is important to consider each pregnancy on an individual basis, especially in women with FH. The presence of cardiovascular symptoms in these women before pregnancy must be taken into consideration, as they may become exacerbated during pregnancy. These include coronary artery disease, cerebrovascular disease, and aortic stenosis. Coordinating care in such instances with a cardio-obstetric expert may improve outcomes, and that being said, coronary artery disease is a known problem in pregnancy and is among the top causes of pregnancy-associated cardiac death [48].

Apart from the effects of the FH alone, the inability to remain on cholesterol reduction therapy during pregnancy and lactation makes managing FH in the peripartum period challenging (Table 2). Cohort studies examining birth outcomes in statin exposure during pregnancy have not shown increased risk. A multicenter, observational prospective controlled study analyzed 249 pregnancies in women exposed to statins during the first trimester. They found no difference in the rate of major congenital disabilities (4.1% versus 2.7% OR 1.5; 95% CI 0.5–4.5,  $P = 0.43$ ) [59], but data shows an increased risk of miscarriage in patients exposed to statins during pregnancy. The lack of prospective cohorts, however, leads to no conclusive evidence of statin safety in pregnancy. Although newer data suggest that statin therapy during pregnancy is not associated with fetal risk [60–62], avoiding use during pregnancy and breastfeeding is still standard practice [63, 64]. PCSK9 inhibitors have not been established to be safe and are also not recommended for use during pregnancy, though observational studies are ongoing [65].

The only FDA-approved lipid-lowering agents in pregnant women are Colesevelam and Mipomersen, and the latter of the two is no longer on the market [43, 66, 67]. Lipoprotein apheresis is rarely used but is an alternate option approved for controlling hypercholesterolemia in pregnant women who have homozygous or severe FH [68, 69]. Ideally, women with FH would have stopped all other lipid-lowering therapy 1–3 months before conception. If they are still on any medications, it is essential to stop them immediately, and they should not be resumed in women planning to breastfeed. Women who have been exposed can be considered for enrollment in registries that are investigating the effects of these exposures, and as randomized control trials in this population are unethical, these observational studies remain an essential source of information on managing women with FH during pregnancy and peripartum. In women whose FH has been managed earlier in life, interruption of therapy is often safe during pregnancy.

**Table 2** Drug safety profile of medications used in familial hypercholesterolemia

Drug name/class	Mechanism of action	FDA status	Important studies/trials	Hormonal contraceptives/therapy	Pregnancy	Breastfeeding
Statins	Inhibits HMG-CoA reductase	FDA-approved for treatment of FH		Limited data on interactions. One study: induced hormone levels nor efficacy of statin effected	Class X, limited studies: lipophilic statins known to cause holoprosencephaly and the VACTERL. No known malformations with exposure to hydrophilic statin.	Rosuvastatin was detected in the milk of a lactating woman who was started on rosuvastatin 40 mg/day. Breast milk concentrations ranged from 21.9 to 22.8 ng/mL compared with maternal serum concentration of 18 ng/mL [49]. Atorvastatin levels in the plasma and the liver of nursing rats were 50% and 40%, respectively, of that in the maternal rat's milk [50]. Pravastatin was excreted in the milk of lactating rats at levels 0.2 to 6.5 times those of maternal rat plasma concentration [51]. Fluvastatin ratio concentration between breast milk and plasma ratio in humans was 2:1 [52].
PCSK-9 inhibitors Evolocumab Alirocumab	PCSK-9 enzyme inhibition	FDA-approved for treatment of FH	FOURIER ODYSSEY RUTHERFORD RUTHERFORD-2 SPIRE Evolocumab Pregnancy Exposure Registry	No documented interactions	No available data on use in pregnant women. Unlikely to cross placenta during the first trimester. Likely to cross placenta in increasing amounts	No data on clinical use during breastfeeding. Benefit should outweigh risk
Colesevelam	Bile acid sequestrants/-resins	FDA-approved for treatment of FH		Use of an oral contraceptive containing ethinyl estradiol/norethindrone in patients on colesevelam was associated with decreased bioavailability of the oral contraceptive [53]. Oral contraceptives containing ethinyl estradiol/norethindrone should be taken at least 4 h prior to colesevelam.	Class B, only approved treatment of hyperlipidemia during pregnancy. Not systemically absorbed.	Safe for breastfeeding.
Ezetimibe	Cholesterol absorption inhibitor	FDA-approved for treatment of FH	IMPROVE-IT ENHANCE	No documented interactions	Class C Crosses the placenta in animal studies	Maternal breast milk concentration was up to half the level of measured serum concentration [54].

**Table 2** (continued)

Drug name/class	Mechanism of action	FDA status	Important studies/trials	Hormonal contraceptives/therapy	Pregnancy	Breastfeeding
Inclisiran	Small-interfering RNA (siRNA) therapy that blocks the production of the PCSK9 in the liver. Used for statin intolerant patients	Not yet approved for use by the FDA	CLEAR Wisdom Randomized Clinical Trial ORION	No documented interactions		Limited data
Lomitapide	Inhibits the function of microsomal triglyceride transfer protein (MTP)	FDA-approved for treatment of FH		Use of lomitapide, a CYP3A4 substrate, with oral contraceptives, weak CYP3A4 inhibitors, increasing risk of lomitapide toxicity [55]. When initiating an oral contraceptive in a patient already taking lomitapide, a decrease the lomitapide dose by 50% is recommended [56].	Animal studies done Contraindicated in pregnancy	Contraindicated, as tumorigenicity observed in animal studies [56].
Bempedoic acid	Inhibits adenosine triphosphate citrate lyase, an enzyme upstream of HMG-CoA reductase	FDA-approved for treatment of FH	Clear Harmony Trial	No documented interactions	Animal studies done. Based on mechanism of action, may cause fetal harm.	No information regarding presence of drug in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Potential for serious adverse effects based on mechanism, therefore breastfeeding not recommended during treatment [57].
Icosapent ethyl	Mechanism of action not completely understood	FDA-approved as an adjunct in adults with elevated triglyceride levels	REDUCE-IT	No documented interactions	Category C	Studies with omega-3 acid ethyl esters demonstrated excretion in human milk. Effect of this excretion on the infant is unknown and caution should be exercised when drug is administered to nursing mothers [58].

## Breastfeeding

There are no definitive guidelines on the management of FH in women that are breastfeeding. Research examining the concentration of lipid-lowering agents excreted in breast milk and its effect on a breastfed infant is limited (Table 2). Lipid-lowering regimens have the same limitations as they do in pregnancy. Bile acid resins are the only lipid-lowering therapy

not systemically absorbed and can be continued during lactation. Two significant choices need to be considered; maintain lactation for breastfeeding and delay resuming FH treatment, or forego breastfeeding, and resume aggressive therapy. Risks versus benefits for the woman and breastfed infant should be discussed. Ultimately, the decision should be made by the mother, with the clinician supporting and providing guidance. For women who have completed their family planning, long-



term contraception strategies and long-acting injectables such as PCSK9 inhibitors can be considered once breastfeeding is stopped.

## Menopausal Women with FH

In a study of a UK cohort of HeFH patients, mean LDL-C in men versus women 20–39 years old was 292 mg/dL and 276 mg/dL, while in men and women aged 60–74 years old, LDL-C was 228 mg/dL versus 272 mg/dL [70]. Per this study, menopausal women with FH had similar LDL values to premenopausal women and higher levels compared with men in the same age group. Menopausal women with FH may suffer the consequences of high LDL-C from delayed diagnosis or due to interruptions in management they may have faced during childbearing. These women now have an opportunity for an aggressive and uninterrupted approach to management. Some women attain menopause as early as forty and with appropriate care can significantly improve their life expectancy and quality of life. There are no specific guidelines for LDL-C management in postmenopausal patients. The necessity of medication escalation, reduction, or cessation should be made via shared decision-making between patient and provider based on their specific goals.

Hormonal therapy is not indicated for primary or secondary prevention of coronary artery disease and is especially not advisable for women with FH. When treatment is necessary for the relief of postmenopausal symptoms, preparations associated with lower thrombotic risk, such as patches and creams, are preferable [71]. As postmenopausal women with FH fall under a high-risk category, non-hormonal therapies, such as gabapentin or duloxetine, should be actively considered. These drugs are an alternative for treating vasomotor symptoms that do not increase coronary artery disease risk.

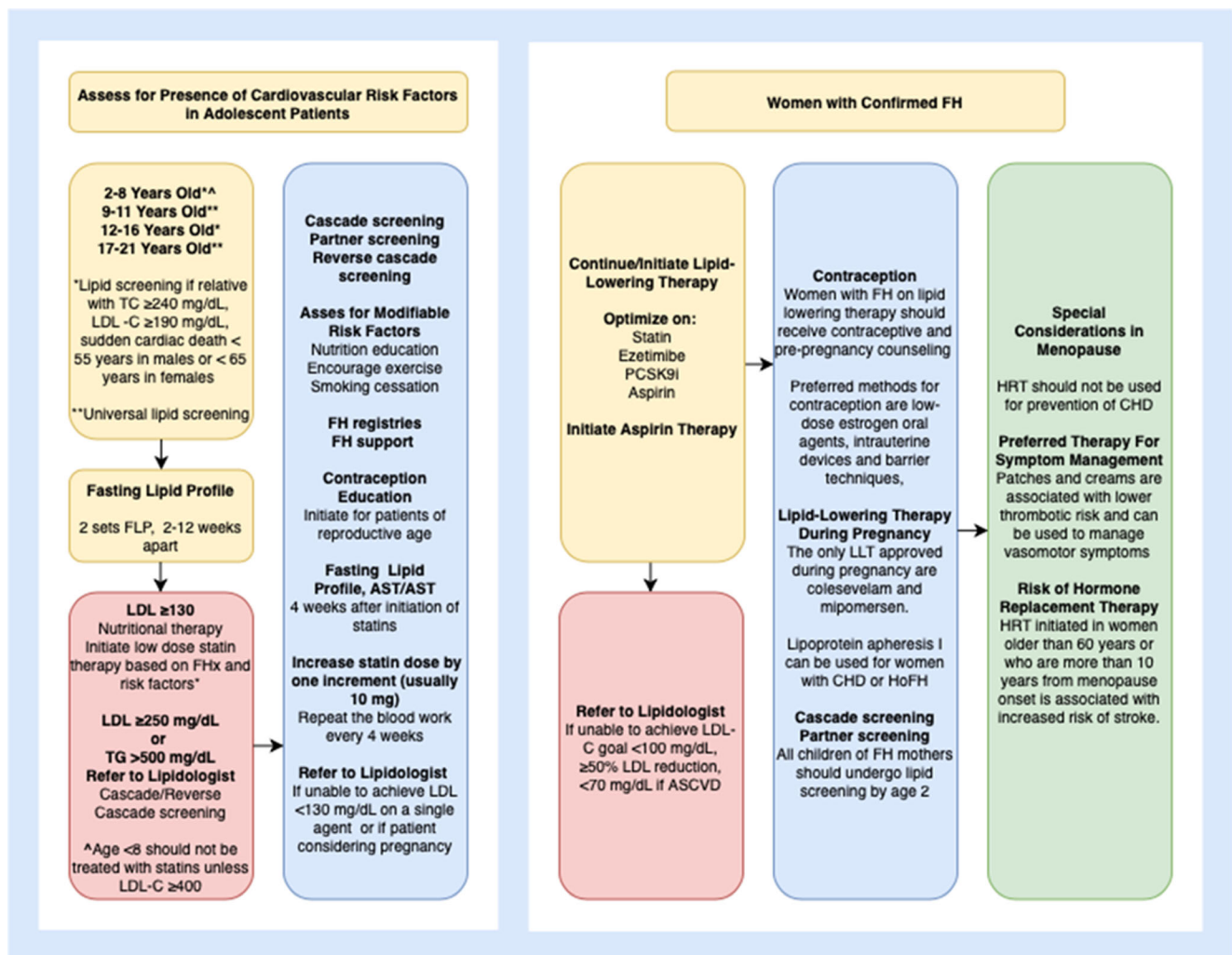
## Caring for Women with FH Throughout Their Life

FH affects a woman in every stage of her life, from adolescence to menopause. Each stage represents a new set of unique challenges that must be addressed, from the selection of birth control to family planning (Fig. 2). Intensive management in the years before puberty if diagnosed as a child could be potentially lifesaving and has been shown to improve outcomes [37•]. If the diagnosis is made after the onset of puberty, initiation of lipid-lowering therapy and birth control as soon as possible is imperative. Regular assessments of adherence to lipid-lowering therapy and contraception are encouraged, while also discussing family planning as most medications should be interrupted months before conception. Goals of care discussions and shared decision-making are

paramount as patients may have to make difficult decisions that might lead to personal dilemmas, such as breastfeeding, or the desire for hormonal therapy.

The recommended goal for LDL-C is less than 100 mg/dL for patients with FH, with a minimal acceptable standard of a reduction of at least 50% from pretreatment. Follow-up should include LDL-C monitoring at regular intervals. While statins are the mainstay of disease prevention in FH, women were 40% less likely than men to be on a statin and if on a statin were 40% less likely than men to be on a high-intensity statin (Fig. 1) [3••]. Additionally, 40–75% of patients discontinue their statin therapy within 1 year of initiation, with higher rates for women than men [75]. Women were also more likely to have rejected or unfilled PCSK9i prescriptions [76••]. The discrepancies in prescription could be the lack of perceived risk for premature disease or due to misconceptions regarding fertility, pregnancy considerations, or higher reported statin adverse effect rates among women. When a woman with FH is not on appropriate statin or lipid-lowering therapy, her provider must initiate a discussion to investigate the cause. Additionally, stepwise escalation of lipid-lowering agents should be implemented, especially in patients who are on sub-optimal first-line statin therapy due to adverse effects. Women are more likely to experience statin-associated side effects than men [3••] and it is appropriate to re-challenge these women following appropriate discussions. This is accomplished by restarting current statin with every other day dosing, restarting on the lowest dose possible or a lower intensity statin, and slowly titrating until the highest tolerable dose is established. Newer agents have been shown to reduce the level of LDL-C in women significantly. In the CLEAR Harmony clinical trial, bempedoic acid, an ATP citrate lyase inhibitor, reduced LDL-C by 19.2 mg/dL or 18.1% (95% CI, –20.0 to –16.1%;  $P < .001$ ) when used in combination with a maximally tolerated moderate- or high-intensity statin, with the most significant reduction in LDL-C observed in women [21••]. The use of bempedoic acid was also associated with lower incidences of muscle-associated statin sensitivity [21••, 77, 78].

Standard risk calculators are not appropriate for FH patients, and titration of medication is based on risk factors, coronary heart disease, and LDL-C goals. Women with FH are less likely than men to achieve goal LDL-C (Fig. 1) [3••]. For women that are still not at their goal LDL-C on the highest tolerated regimen of statin, add a second lipid-lowering agent, such as ezetimibe. It is also appropriate to add a PCSK9 inhibitor at this point. When added to the maximum tolerated statin dose, alirocumab reduced LDL-C by 62% ( $P < 0.001$ ) and reduced major cardiac events [18]. Ensuring adherence through education and risk discussions is a necessary step to reach target LDL-C levels. For patients who remain above goal, referral to a lipidologist for consideration of PCSK9i should not be delayed. The FH Foundation website has a “Find an FH Specialist” link, which allows patients to connect to specialists in their area [79]. Considering lower rates of



**Fig. 2** Overview of screening and management of FH in (a) women and young adult (b) children and adolescents. Adapted from Lloyd-Jones DM et al. [72]; Expert Panel on Integrated Guidelines for Cardiovascular

Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute, Pediatrics [73]; de Ferranti et al. [74]

statin use and higher LDL-C values, this is especially important in women with FH. Women and families with FH are best treated by a multidisciplinary team of cardiologists, obstetricians/gynecologists, and genetic counselors.

## The Future of FH in Women

FH is a common but vastly under-diagnosed condition. Strategies to improve diagnosis, especially for women, are essential to improve their outcomes. Women can be instrumental in overseeing the wellness visits and medical care their children receive. Screening in childhood is vital as each child in an FH family has a 50% chance of inheriting the genetic defect. Despite long-established medical guidelines, established heart disease, and the hard-won diagnosis of FH, Katherine Wilemon found her pediatrician unwilling to screen her first born. Another practice performed the screening and found her daughter had FH.

Cascade screening has shown great promise in countries around the world, increasing the rate of early FH diagnosis and dramatically reducing the risk of premature morbidity and mortality. Centering care around women and providing them with adequate tools and knowledge to care for themselves and their families with FH can dramatically reduce the burden of premature heart disease for future generations.

Considerations surrounding lipid-lowering therapy for women are different than men. Cardio-obstetrics allows for comprehensive care of women with unique cardiovascular conditions and may be an effective approach for managing women with FH longitudinally. Women experience interrupted management during childbearing due to teratogenicity of these medications, leading to difficulties in treating women with FH perinatally. CURE ATHERO trial proposes lowering LDL-C at a younger age via an intensive period of LDL-C/non-HDL-C/apo B reduction, with subsequent periodic retreatment every decade or so [80]. Adaptations of this approach may be viable for young girls

and women. Optimizing LDL levels in the years before women with FH consider motherhood is ideal and innovative strategies to achieve this may be necessary. While this is an intermediary step, there is a need for further investigation into therapies that do not need to be discontinued with pregnancy or have incrementally beneficial effects in women in particular.

FH registries provide a unique opportunity to study women in the population to identify shortcomings. Observational studies, like the CASCADE-FH registry, highlight the disparities in both representation of non-white women and management of high LDL-C in women compared with men. Women with FH face delayed diagnosis and interrupted management, making them more likely to require escalation of therapy. Though the price of statins is relatively affordable, and ezetimibe is generic, escalation to a PCSK9i remains costly. Unfortunately, women, minorities, and individuals of low socioeconomic status are often disproportionately affected with studies showing these populations to be more likely to have rejected or unfilled prescriptions [76••]. Given the heterogeneity of the USA, it is important that granular healthcare disparity data including outcomes in non-white women and women of low socioeconomic status is available. To understand these disparities and improve minority outcomes, representation in research is of utmost importance, while education and raising awareness will lead us to address them.

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## Compliance with Ethical Standards

**Conflict of Interest** Fatima Rodriguez reports personal fees from HealthPals, personal fees from Janssen, The Medicines Company and personal fees from NovoNordisk outside the submitted work. Sujana Balla, Eson P. Ekpo, Katherine Wilemon, and Joshua W. Knowles declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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