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Women with Homozygous Familial Hypercholesterolemia and Impact on Reproductive Life from Menarche to Menopause: Long-Term Case Series Observational Study

Claudia Stefanutti[a]*, Giuseppina Perrone[b], Giovanna Zeppa[a], Valentina Demarco[b], Paola Galoppi[b], Giuseppe Rizzo[b], Hofit Cohen[c], Handrean Soran[d] and the MIGHTY MEDIC – Multidisciplinary International Group for Hemapheresis Therapy and Metabolic Disorders Control

[a]Department of Molecular Medicine, Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Regional Centre for Rare Diseases, Immunohematology and Transfusion Medicine, Umberto I Hospital, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, 00161, Italy.
[b]Department of Maternal and Child Health and Urological Sciences, Umberto I Hospital, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, 00161, Italy.
[c]The Bert W. Strassburger Lipid Center, Sheba Medical Center, Tel-Hashomer, 5265601, Israel; Gray School of Medical Sciences, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Israel.
[d]NIHR/WELLCOME Trust Clinical Research Facility and Department of Endocrinology, Diabetes and Metabolism, Peter Mount Building, Manchester University Hospital NHS Foundation Trust, M13 9WL, Oxford Road, Manchester, United Kingdom.

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***Correspondence:**
Prof. Claudia Stefanutti, Department of Molecular Medicine, Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Regional Centre for Rare Diseases, Immunohematology and Transfusion Medicine, Umberto I Hospital, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, 00161, Italy.
Email: claudia.stefanutti@uniroma1.it

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Abstract

Homozygous familial hypercholesterolemia (HoFH) is a genetic disease in which LDL-C is high at birth, causing cardiovascular disease. Reproductive issues in women are also caused by lipid-lowering therapies (LLTs) that must be interrupted during pregnancy and breastfeeding. The only safe choice during pregnancy is lipoprotein apheresis (LA), although there are limited data regarding fertility, pregnancy, and menopause. This long-term case series observational study examined 23 genetically confirmed HoFH women in a tertiary health facility, obtaining clinical, cardiovascular, biochemical, and reproductive information through medical records and structured interviews. Cardiovascular disease and aortic valve disease were found in 48% and 52%, respectively; four women died prematurely. Menarche (12.1 years) and menopause (52.0 years) were in the normal range. The majority of these had regular menstrual cycles; there was one case of polycystic ovary syndrome. Twelve women became spontaneously pregnant. Obstetric complications included preterm delivery, gestational diabetes, hypertension, and fetal growth restriction. This study showed that continuous LA during pregnancy was associated with better lipid control and maternal-fetal outcomes, but cardiovascular impairment was observed in the case of interruption of LLT. LLT interruption affects the inherited lipid disorder, and a very short period of breastfeeding is recommended. HoFH in women under treatment has no impact on the menstrual cycle or on the timing of menopause. Pregnancy is a high-risk condition that needs the care of a multidisciplinary team. The need to ensure continuous LA, systematic reproductive counseling, early cardiovascular examination, and aligned lifelong care is critical in maximizing the outcome of HoFH women.

Introduction

Homozygous Familial Hypercholesterolemia (HoFH) is a rare genetic disorder characterized by biallelic mutations in genes that regulate low-density lipoprotein receptor (LDLR) activity, most commonly LDLR, APOB, or PCSK9 (1). The condition is characterized by markedly elevated LDL-C levels and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD) (2). Homozygous familial hypercholesterolemia (HoFH) occurs equally in women and men, although women are usually inadequately treated because of

pregnancy and breastfeeding, which increases their risk of acquiring ASCVD (3). The observational case series explores the gaps in diagnosing and treating women who have HoFH in the different stages of their lives, such as pregnancy, menopause, and hormonal use (4). The cardiovascular outcome of pregnancy in HoFH has been researched, but the reproductive life course has not been researched extensively. There is limited evidence on ovarian functioning, including menarche, menstrual cycles, fertility, and menopause, and this presents the necessity of end-to-end assessment (5). The prevalence of polycystic ovarian syndrome (PCOS) is associated with a significantly higher risk of various metabolic and cardiovascular disorders, type 2 diabetes (T2DM), gestational diabetes, and hypercholesterolemia (6). In fact, irregular cycles are associated with high cholesterol levels (7). Moreover, a recent study showed a positive correlation between fetuin-A and total cholesterol (TC) in women affected by PCOS (8). Further evidence links exceeding cholesterol levels and altered lipoprotein homeostasis with poor oocyte quality and female fertility (9). Thus, one can say that the reproductive life of healthy women is considerably different when compared to the reproductive life of women with HoFH. Although healthy women make autonomously and freely their reproductive decisions (fertility control, assisted reproductive technology, hormone therapy to manage menopause), the HoFH women are supposed to take into consideration the necessity of a life-saving lipid-lowering pharmacological therapy (Lipid Lowering Treatment - LLT) (10) that includes statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and most recently the ANGPTL3 inhibitor namely evinacumab. Such conditions tend to complicate or even render the management of pregnancy among HoFH women quite complex or even incompatible, particularly when it is occasional or not planned. Moreover, the physiological alterations of pregnancy include the aggravation of maternal hypercholesterolemia (Figure 1), which is already impaired by the disruption of LLT until the time of breastfeeding, and elevated ASCVD morbidity and mortality in the short and long-term (11).

LA is still representing the only available, effective, and safe treatment during pregnancy in women with HoFH (12). As compared to prior literature, as well as the recently published study by Mulder et al., this current investigation presents one of the most prolonged follow-ups of genetically identified women with HoFH, encompassing the entire reproductive life course from menarche to menopause over a period of 35 years (13). Apart from the analysis of pregnancy outcomes, this study investigates the menstrual functioning, fertility issues, breastfeeding, age at menopause, cardiovascular complications, and the quality of life in the same population of subjects. Moreover, the incorporation of genetic information in relation to reproductive and cardiovascular outcomes has significant clinical relevance that needs further exploration (14). This long-term case series observational study evaluated the course of menstrual history, outcome of pregnancy, breastfeeding,

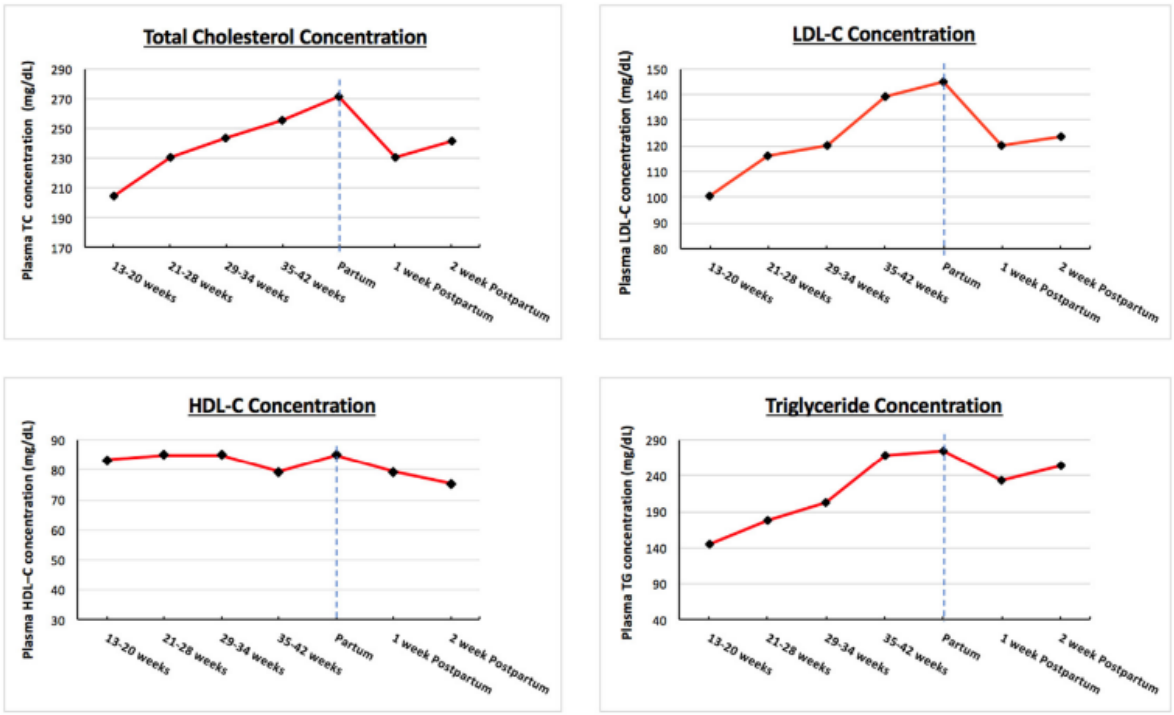

Figure 1. Lipoprotein and lipid levels before, during, and after normal pregnancy. Adapted from Journal of Clinical Lipidology (2024) 18, e664–e684.

menstrual periods after pregnancies, contraception, age at menopause, hormone therapy, CVD, and aortic valve disease (AVD) events, in HoFH women, genotyped and subjected to life-saving treatment with currently available therapies. Different from earlier investigations, which mainly focused on pregnancy management issues or contraceptive practices in FH, the current study presents an important life-course evaluation of genetically proven HoFH women in a 35-year follow-up study (15). Notably, the current study is unique in that it examines reproductive events from the onset of menstruation up until menopause in relation to cardiovascular risk, genotypic profile, and extended lipid-lowering therapy (16). In addition, the current patient group represents an early descriptive experience indicating the potential benefit of sustained LA therapy during pregnancy.

Materials and Methods

Study Design

This long-term case series observational study included 23 women with genetically confirmed HoFH managed by the Center for Rare Metabolism Disorders, Umberto I Hospital, Sapienza University of Rome, Italy. The study was conducted over nearly 35 years from 1990 to 2025, whereby clinical and laboratory parameters were measured along the long-term follow-up and investigated in a prospective manner. Medical records and structured interviews were used to gather clinical, biochemical, cardiovascular, and reproductive data. Both retrospective (historical, reproductive, and cardiovascular events) and prospective follow-up data were included in the study and were gathered during the regular, routine clinical treatment. Inclusion criteria were: female sex, genetically proven FH homozygosity, and the availability of a complete reproductive and cardiovascular history. Therefore, we included patients of any age at the time of collecting individual data. The exclusion criteria were the lack of genetic confirmation and any inadequate follow-up data.

The sample size was determined by the rarity of genetically confirmed HoFH and the availability of eligible patients. Since HoFH is an ultra-rare disease, the sample of 23 women is one of the largest long-term series that could be conducted.

Genetic Diagnosis

The criteria for the genetic diagnosis were the presence of two pathogenic mutant alleles for LDLR, ApoB, or PCSK9 loci; these were diagnosed as True HoFH (identical mutation in each allele of the same gene) and Composite Heterozygotes for Familial Hypercholesterolemia (FH) (non-identical mutations in each allele of the same gene), as shown in Table 1, which is implemented by Table 2.

Lipid-Lowering Treatment

All patients received a broad range of lipid-lowering therapies, including LA. Seven patients were given evinacumab 15 mg/Kg every 4 weeks, intravenously. All patients were informed in detail about the purpose of any treatment, and written informed consent was obtained. The application of LA in pregnant women included its continuation in those who had been treated with it before pregnancy to keep their LDL-C under control and minimize cardiovascular risks. In particular, various extracorporeal approaches depending on local clinical practice and availability were applied to these patients during a relatively long period of observation, namely dextran sulfate adsorption and other selective LDL-apheresis methods. However, full details on the procedures performed, including pre- and post-apheresis LDL-C concentrations and total numbers of sessions conducted during the entire pregnancy, were not always available since they relied partly on historical clinical data gathered throughout many years.

Biochemical Analyses

All routine biochemical analyses were performed to evaluate treatment efficacy and safety.

Reproductive and Cardiovascular Assessment

Reproductive Assessment

The reproductive variables measured in the study included age at menarche, menstrual regularity (flow occurs every 25 to 35 days and lasts three to seven days) and amenorrhea (absence of menstruation over three/six months), diagnosis of polycystic ovary syndrome (PCOS), conception modality, parity, pregnancy complications (gestational hypertension, pre-eclampsia, gestational diabetes, intrauterine growth restriction, preterm birth defined as < 37 gestational weeks), history of breastfeeding, occurrence and age of menopause, and the use of hormone therapy.

Cardiovascular Assessment

Cardiovascular outcomes involved having coronary artery disease (CAD), percutaneous coronary intervention

Table 1. Classification of HoFH women according to genetic diagnosis

Mutation Type	Number of Patients	Genes Involved	Notes / Examples
True HoFH	7	LDLR, LDLRAP1	Identical mutation in both alleles (e.g., P664L / P664L, ARH mutation)
Composite Heterozygotes	12	LDLR, ApoB, PCSK9	Two different mutations in the same gene or different FH genes (e.g., V502M / P664L, P685L / P664L)
Unclassified / Insufficient Info	4	NA	Second allele unknown or not reported (e.g., NA, G-D BARI)

Table 2. Age, phenotype, and genotype in women with HoFH

Patient #	Age	Phenotype	Genotype
1	53	HoFH	- G?A(Ex 10) V502M - G?A(Ex 14) P664L missense/missense
2	58	HoFH	c.2054 C>T, p.P685L, p.(P664L)
3	57	HoFH	c.2054 C>T, P664L
4	55	HoFH	c.2054 C>T, p. P685L, p.(P664L)
5	39	HoFH	1-2 c.1775 G>A, Gly571Glu
6	33	HoFH	c.2054 C>T; p.P685L
7	67	HoFH	D471N + C677W
8	22	HoFH	C358R + V502M
9	14	HoFH	C68R + G571E
10	35	HoFH	c.1478-1479delCT, S472CfsX42 + c.1230G>C, R389S
11	32	HoFH	IVS10 +1 G>A
12	10 (deceased)	HoFH	Del Ex13-15 + G528D
13	4	HoFH	DelEx 2-12
14	8	HoFH	LDLRAP1 gene Mutation ARH
15	8	HoFH	2446, A>T ex 17, cod 795, AAG(Lys)>TAG (Stop) (cod 816 including signal peptide)
16	35	HoFH	[c.682 G>A], p. E228K + [c.1486 C>T], p. R496W null/null
17	27 (deceased)	HoFH	P664L
18	27 (deceased)	HoFH	P664L
19	29	HoFH	NA
20	61	HoFH	NA
21	23 (deceased)	HoFH	Druze
22	38	HoFH	G-D BARI
23	32	HoFH	Druze

(PCI) history, having cardiac bypass surgery (CABG), having aortic valve disease (AVD), and major adverse cardiovascular events (MACE). Cardiovascular health data were collected by using a set of cardiology reports, imaging studies, and a set of surgical records to guarantee total reporting of patient outcomes.

Quality of Life Assessment

The EQ-5D-3L questionnaire was used to measure health-related quality of life (HRQoL), and it is a standardized instrument that is used to assess the overall well-being of patients in five important dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) (17). The questionnaire was given to each participant at a time and on a routine clinical visit, which gave a rather in-depth perspective on the impact of their condition on their daily functioning and their psychological well-being. This approach enabled systematic assessment to systematically and patient-reportedly measure physical and mental quality of life. The assessment of QoL by questionnaire was possible only for the cohort of HoFH women attending the specialist centre in Rome (Italy).

Potential threats to bias were recall bias during patient interviews and selection bias because the tertiary referral centers were recruited. To reduce them, there was cross-checking of reproductive and cardiovascular data with medical records and cardiology reports. However, the residual bias could not be ruled out due to the observational design.

Statistical Analysis

Data were descriptively analyzed using Excel software. Data are given either as mean ± SD or median and range for continuous variables and as frequencies and percentages for categorical variables. Descriptive comparisons were made between women who underwent lipoprotein apheresis (LA) during pregnancy and those who did not; however, no formal statistical test, such as Fisher's exact test or Mann-Whitney U-test, was performed owing to the highly insufficient data sample, considerable clinical differences between patients, and the high degree of heterogeneity, inadequate follow-up data of some patients, and also due to the descriptive nature of this study. This was largely due to the very low number of women undergoing LA treatment during pregnancy. Consequently, the results are descriptively discussed hereafter. Missing data were marked as "NA" in tables. The reason for missingness was incomplete medical history documentation, lack of follow-up due to patient death or lost to follow-up, lack of reproductive documentation, or early death during the observation period. Since HoFH is a rare condition and descriptive analysis was conducted in this study, no imputation technique could be used, and the analysis was conducted using the information that was actually available. Continuous variables were described using the means ±

standard deviations or medians with ranges/interquartiles depending on their distribution characteristics. Categorical variables were presented using frequencies and percentages. Due to the very low prevalence of genetically confirmed HoFH cases and the low number of participants in the study (n=23), there were no statistical comparisons between groups using inferential statistics (for example, Mann-Whitney U test, Fisher's exact test). No p-values or confidence intervals are provided for any results in this study, since all results, including the difference between women undergoing LA during pregnancy and non-exposed women, are descriptive in nature.

Ethical Considerations

This study was an observational cohort study with data collected via clinical follow-up visits of women diagnosed with genetic homozygous familial hypercholesterolemia (HoFH). All subjects gave informed consent to participate in the anonymous collection of their medical and reproductive data for research purposes. The study was performed in accordance with the Declaration of Helsinki guidelines. Because the study involved no intervention or manipulation and used exclusively de-identified clinical data that had been gathered as part of routine treatment, formal review by an institutional ethics committee was not required under local institutional policies. In particular, in line with the Ethics Committee of Sapienza University of Rome / Umberto I Hospital policy, studies that are both retrospective and not interventional and observational, carried out only based on anonymous data derived from the normal routine of clinical practice, do not need formal approval by an ethics committee, under the condition that no further procedures or treatments or any other data collection besides those deriving from clinical practice are added to the patient's burden and that proper informed consent is achieved. Quality-of-life questionnaires were completed only among those patients undergoing treatment in the Extracorporeal Therapeutic Techniques Unit of the Center for Rare Metabolism Disorders, Umberto I Hospital, Sapienza University of Rome, Italy.

Results

Among 23 genetically confirmed HoFH women, all were involved in the analysis. Four of them passed away early in the follow-up, and three of them failed to fill in the quality-of-life questionnaire. Missing values were common for the cardiovascular follow-up variables, reproductive history data, and newborn results due to missing archival documents, missed follow-ups, and early mortality. Missing data varied across Tables 2-4, from single unavailable data fields to missing follow-up data on some subjects. The inclusion and follow-up are described in a schematic flow diagram provided in Figure S1 (Supplementary material).

Cardiovascular Burden and Mortality

Previous literature has shown that HoFH patients are often affected by CVD early in life, including coronary artery disease (CAD) due to progressive coronary atherosclerosis and AVD. Similarly, this study's findings suggest that the earlier HoFH patients are submitted to LLT and LA, the milder the impact of CVD and AVD; sometimes, it is nearly absent. HoFH women who refused treatment inevitably died at a young age. CVD had been reported in 11 out of 23 patients (48%) and aortic valve disease in 12 (52%), as represented in Figure 2 and Table 3. Four patients (22%) passed away due to premature deaths because they refused the extracorporeal (LA) treatment. Moreover, elevated Lp(a) levels were detected in 26% of cases. Women who had early LLT and frequent LA showed less severe or no cardiovascular events as opposed to those who refused LA. Severe manifestations of the disease were the coronary artery disease of the multivessel type that requires the intervention of either PCI or CABG, acute calcific aortic stenosis with valve replacement, and coronary and valvular diseases. However, in contrast, younger patients who received early intensive LLT often demonstrated hemodynamically insignificant stenosis at follow-up. These results confirm the protective effect of the lifelong lipid-lowering measures in HoFH women.

There were marked instances of missing data that were denoted as NA in tables. These are incomplete follow-up or unavailable genetic/cardiovascular histories. There was no imputation done, and the descriptive analysis was limited to available data.

Menstrual Cycle

Menses functioning was mostly normal in 12 HoFH women. The menarche and menopause ages stood at 12.1 (9-14) and 52.0 (49-56) years. Most of the cycles were regular, 1 case of PCOS, 25% irregular cycles, and 16 cases

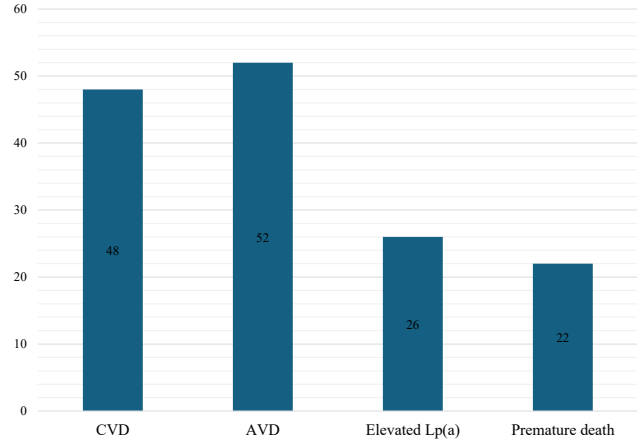

Figure 2. Distribution (%) of CVD, AVD, elevated Lp(a), and incidence of premature death in HoFH women.

Table 3. Cardiovascular disease (CVD), Aortic valve disease (AVD), and Lp(a) level in HoFH women

Patient #	Cardiovascular disease (CVD)	Aortic Valve disease (AVD)	Current CVD	Lp(a) Elevation
1	-Right coronary: ostial occlusion surgically treated with aorto-coronary bypass. -Left coronary: calcifications; no evidence of hemodynamically meaningful stenosis (30-35%)	Ascendant aortic stenosis and massive calcifications treated with decalcification and intravascular tubular prosthesis	2017 -Right and left coronary stenosis, respectively, of 30-35% and 35-40%: not flux metrically meaningful. -No evidence of aortic hemodynamically meaningful stenosis	YES
2	-Right coronary: no proximal stenosis (40%); -Left coronary: fibrocalcific plaque at the carotid bifurcation, no evidence of hemodynamically meaningful stenosis (around 40%). PCI on IVA	Aortic ostial common trunk stenosis (34 %), diffuse calcification: function preserved	2024 -Cardiac function globally preserved, moderate mitral prolapse -Aortic supravalvular calcification; function preserved	NO
3	-Common trunk coronary disease (unstable angina): triple aortocoronary bypass; - Graft occlusion and critical stenosis (70-90%): quadruple coronary common trunk stent (PCI)	Slight valve thickening: function preserved	2021-2022 -no evidence of hemodynamically meaningful stenosis; -Valve sclero-calcification: function preserved. Slight mitral and tricuspid prolapse	YES
4	NA	No evidence of AVD	2022 No evidence of CVD	NO
5	No evidence of CVD	No evidence of AVD	2022 No evidence of CVD	YES
6	Atherosclerotic Aortic Disease	No evidence of AVD	2024 No evidence of CVD	NO
7	Ischemic coronary cardiopathy (double bypass)	Severe aortic valve stenosis with calcific and degenerative alterations	NA (deceased)	NO
8	No evidence of CVD	Aortic insufficiency and calcifications	NA	NO
9	No evidence of CVD	Hypoplastic left coronary flap	NA	NO
10	No evidence of CVD	Moderate aortic insufficiency, calcifications	NA	NO
11	Ischemic coronary cardiopathy; Congenital mitral stenosis (mechanical prosthesis)	Congenital aortic stenosis (mechanical prosthesis)	2023 No evidence of CVD	NO
12	Ischemic coronary cardiopathy (triple bypass)	Mild aortic insufficiency	NA (deceased)	NO
13	No evidence of CVD	2024: Moderate aortic valve stenosis solved with a biological valvular prosthesis; Partially prosthetic ascending aorta	No evidence of CVD	NO
14	No evidence of CVD	No evidence of AVD	NA	NO
15	No evidence of CVD	No evidence of AVD	NA	NO
16	Ischemic coronary cardiopathy (quadruple bypass)	No evidence of AVD	NA	YES
17	Ischemic coronary cardiopathy: right coronary complete occlusion solved with collateral heterocoronary circle	Aortic valve severe stenosis	NA (deceased). The patient refused LA to treat hypercholesterolemia to plan a pregnancy, despite being warned of the risks. She died after autonomously choosing to be submitted to aortic valve surgery (balloon pre-dilation of the stenosed aortic valve, because of complications)	NO
18	Ischemic coronary cardiopathy: right coronary 80% stenosis, 70% common trunk stenosis	Aortic valve insufficiency and calcifications	NA (deceased). The patient refused LA to treat hypercholesterolemia during pregnancy; this led to severe CVD and AVD onset. She underwent valve replacement surgery and reconstruction of pulmonary efflux with a non-cryopreserved pulmonary homograft of caliber 26 mm (Ross intervention). The patient then died because of Acute Coronary Syndrome (ACS)	NO

Patient #	Cardiovascular disease (CVD)	Aortic Valve disease (AVD)	Current CVD	Lp(a) Elevation
19	No evidence of CVD	No evidence of AVD	2024 No evidence of CVD	YES
20	Multiple but not significant coronary stenosis	Aortic stenosis (solved with a mixed mechanical and biological valvular prosthesis)	2025 No evidence of CVD	YES
21	2013 Carotid IMT is within the normal range	Mitral valve replacement at age 23	NA (deceased)	NA
22*	NA	NA	NA	NA
23	No evidence of CVD	No evidence of AVD	No evidence of CVD or AVD	NA

NA: Not Available. Missed the follow-up. CVD data not available.

of amenorrhea. The use of contraceptives was also minimal (IUD: 3, pill: 1), and only one of the women was given hormone therapy to manage menopause, which means that HoFH does not have a significant effect on ovarian cycles and menopause.

Pregnancy Outcomes and Obstetric Complications

Obstetric statistics on 12 HoFH patients (10 deliveries) indicated 6 natural births and 4 cesarean births (1 breech birth, 3 maternal cardiovascular risk). The complications were preterm delivery (5), severe hypercholesterolemia (6), gestational diabetes (3), cholestasis (1), threatened miscarriage (2), fetal growth restriction (2), abruptio placentae (1), and maternal hypertension (2) (Table 4). LA was administered to three women during pregnancy, with the use of which they obtained controlled LDL-C and positive maternal-fetal results, and one woman without LA died after the valve operation. In such patients, LA was done regularly during the entire period of pregnancy by selective LDL-apheresis. The timing was personalized in terms of either once per week or twice per week, targeting optimal levels of LDL-C to ensure no worsening of cardiovascular conditions. Clinical data showed that patients who underwent LA during pregnancy had better results in lipid control and maternal and fetal health than those who discontinued or declined treatment.

Genotype-Stratified Observations

Patients with genuine HoFH had an earlier onset of cardiovascular problems, whereas patients who were compound heterozygotes exhibited later manifestations. The lack of sufficient sample sizes prevented a comparison of these findings between these patient groups. Pregnancy problems such as premature birth, high cholesterol levels, and cardiac complications occurred more often among those with more severe types of the disorder and lower levels of functional LDL receptors. Those individuals under intensive lipid-lowering treatments and lipoprotein apheresis seemed to achieve better results in both their cardiovascular and reproductive health. However, due to the rarity of the condition, interpretation of these findings is difficult.

Breastfeeding and Postpartum Management

Three females breastfed for 3 months. The interruption of lipid-lowering therapy during pregnancy and lactation usually resulted in the short-term exacerbation of hypercholesterolemia and reduced exposure of a newborn to breastfeeding in the puerperium (Table 4). The general results were positive regarding both HoFH mothers and children, except for a nurse who declined extracorporeal treatment throughout pregnancy and died of a sudden cardiovascular event after aortic valve and coronary surgery after childbirth.

Quality of Life (QoL)

Individual HoFH patients' responses to five descriptive questions of the EQ-5D-3L (mobility, personal care, activities of daily living, pain/discomfort, and anxiety/depression) have been investigated in the Italian cohort (Table S1). Interestingly, health utility and visual analogue scale (VAS) were similar to the estimates for the general Italian population (0.980 ± 0.048 and 78.2 ± 18.4, respectively) (17).

Discussion

The reproductive health statistics of women affected with HoFH in the world are very few and are frequently misdiagnosed. Pregnancy is a dangerous disorder that demands the help of multiple disciplines. The latest EAS guidelines recommend family planning and cardiovascular evaluation before pregnancy. According to Mulder et al. (2025), 72.4% of women were contraceptive users, with 50.8, 49.2, and 46.0 being the predominant IUDs, oral contraceptives, and barrier methods (18). HCPs advise that women who want to conceive should abandon the use of LLT, unless LA and colesevelam are used. Recommendations on similar LLT were also issued in the case of pregnancy, whose management entails a coordinated effort by genetic counselors, cardiologists, clinical lipidologists, and gynecologists/obstetricians. There are a few selective LA techniques, such as immunoadsorption, dextran sulfate adsorption, HELP, and polyacrylate hemadsorption. Acute pancreatitis in pregnant women with severe hypertriglyceridemia has also been treated using plasma

Table 4. HoFH women's data on pregnancy, delivery, and breastfeeding

Patient	Age at delivery (years)	Obstetric complications	Neonatal weight at birth	Type of birth	Breastfeeding
1	28	Preterm delivery; Severe Hypercholesterolemia (900 mg/dL); Cholestasis	3300 g	Natural birth	NO
2	20	Preterm delivery; Threatened miscarriage.	2750 g (Down syndrome)	Cesarean section (foetus in breech position)	NO
3	28	Preterm delivery; Fetal growth restriction; Abruptio placentae #2; Threatened miscarriage.	2750 g	Natural birth	NO
4	31	Preterm delivery. Gestational diabetes; Fetal growth restriction.	2650 g	Cesarean section (preventive)	NO
6	31	Preterm delivery; Gestational diabetes; -Lipoprotein apheresis (LA) during pregnancy to treat hypercholesterolemia.	2840 g	Cesarean section (preventive)	NO
8	NA	-Hypertension; - LA during pregnancy to treat hypercholesterolemia.	NA	NA	NO
9	30	NONE; LA during pregnancy to treat hypercholesterolemia.	3190 g	Natural birth	NO
18	25 (Deceased at 27)	NONE (The patient refused LA during pregnancy to treat hypercholesterolemia)	3000 g	Cesarean section (preventive)	YES
20	37	-Severe Hypercholesterolemia (800-900 mg/dL); -Hypertension; -Gestational diabetes.	3840 g	Natural birth	YES
21	22	NA; NO LA during pregnancy	NA	NA	NA
22	25	NA; NO LA during pregnancy	NA	NA	NA
23	20 yrs 1st pregnancy; 23 yrs 2nd pregnancy	NA; NO LA during pregnancy	NA	Natural births	NA

exchange (PEX) and LA. The initiation of apheresis is an important factor that leads to the reduction of morbidity and mortality (19). Liposorber D, in which dextran sulfate is used to eliminate the positively charged molecules (LDL, VLDL, Lp(a)) by the action of negatively charged polyanions, has been described in pregnant HoFH. The sessions of weekly LA (24 sessions in total) are safe, effective, and well-tolerated during pregnancy (20). Lipid apheresis (LA) is indicated in the community of females with HoFH during pregnancy in addition to conventional care. Therapeutic interventions, such as LA, are safe, effective, and can lead to better maternal and fetal outcomes. In addition to the beneficial impact of reducing LDL-C levels, other physiological effects of continuous LA during pregnancy may be responsible for the positive maternal and fetal outcomes seen in patients with HoFH. High maternal cholesterol levels are known to result in endothelial dysfunction, oxidative stress, inflammation in blood vessels, and poor placental circulation. This leads to a risk of pre-term delivery, intrauterine growth retardation, and hypertensive pregnancy diseases. Through acute reduction of LDL-C and lipoprotein(a) levels, LA can positively affect endothelial function and reduce inflammation during pregnancy. Although specific biomarkers were not studied in our observational study, these results suggest that continuous lipid depletion therapy is capable of producing beneficial effects on placenta and vessel function during pregnancy. This emphasizes the need to take care of the reproductive issues, including fertility testing, infertility treatment, pregnancy follow-up, menstrual control, and menopausal care. According to Beigel et al. (1998), repeated plasma exchange in five HoFH pregnancies was effective in dealing with excessive cholesterol (21). The burden of cardiovascular diseases in this cohort was substantial: 48% among participants had heart disease, and 52% among the participants had aortic involvement. Only those who delay and/or interrupt and/or refuse intensive lipid-lowering therapy were found to die prematurely (22%), which highlighted the aggressive nature of HoFH. These results are consistent, indicating the presence of a high cardiovascular risk even in the face of modern treatment (22). It is vital to have lifelong lipid-lowering, particularly at the reproductive age, when treatment lapses are frequent.

Reproductive functioning was mostly normal (menarche 12.1y, menopause 52y), and there was a single case of PCOS. Pregnancy exerted cardiometabolic stress based on high cholesterol. The number of obstetric events noted in this group, especially preterm delivery (5/12 pregnancies) and gestational diabetes (3/12 pregnancies), seems to be higher compared with what is normally seen in the background obstetric population, where preterm delivery prevalence ranges from 8-10%, while gestational diabetes ranges from 5-10%, based on maternal age and geographical location. While no comparative statistics could be performed due to the limited patient numbers in our study, the findings seem to indicate an increase in the cardiometabolic burden associated with pregnancy in women with HoFH. Other reports on women with heterozygous familial

hypercholesterolemia (HeFH) have shown maternal cardiovascular and metabolic risks during pregnancy, but at much lower levels compared to what we see in HoFH because of less exposure to LDL-C. The protective effect of LA had been demonstrated by women who were better in control of lipids and maternal neonatal outcomes, and those who declined LA deteriorated and died of cardiovascular causes (23). The connection between continuous LA during pregnancy and better maternal and fetal health results can be biologically feasible. Low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) are greatly lowered by LA therapy. These two factors play a role in endothelial dysfunction, vascular inflammation, oxidative stress, and placental blood flow impairment. Hence, through lowering maternal vascular inflammation and atherosclerotic plaque buildup, LA could have a beneficial effect on uteroplacental blood flow and prevent complications such as intrauterine growth retardation, hypertension, and early cardiovascular damage. Furthermore, LA could minimize inflammatory and thrombotic mediators, which lead to placental insufficiency.

The research points to the necessity of pregnancy safety information about new lipid-lowering agents and an organized postmenopausal cardiovascular surveillance. There exist strengths such as long-term follow-up and combined cardiovascular-reproductive insights, but they are limited by small sample size and not because of causal statistical analysis. Overall, it provides one of the most in-depth life-course studies of reproductive health in women with HoFH.

Evinacumab, a monoclonal antibody against angiopoietin-like 3 (ANGPTL3), is one of the newest approved lipid-lowering drugs for homozygous familial hypercholesterolemia. Nevertheless, no reproductive safety information about its use during pregnancy and lactation is available. Due to its large size (IgG4 monoclonal antibody), the transplacental passage is likely to be higher, especially in the second and third trimesters, and fetal exposure cannot be ruled out. Reproductive guidelines currently recommend that evinacumab be avoided during pregnancy because of a lack of adequate safety information, and its use should be restricted to selected cases with a clear indication where the benefit to the mother surpasses the risk for the fetus. In this study, patients received evinacumab before pregnancy or discontinued during pregnancy according to clinical judgment on an individual basis. No adverse outcomes have been reported in this cohort of pregnancies exposed to evinacumab; however, further research is needed to establish its safety in reproduction. A total of seven female patients among our group were administered evinacumab for the management of HoFH. The advent of evinacumab, as well as PCSK9 inhibitors, is undoubtedly considered a breakthrough when it comes to the reduction of LDL-C levels for severe HoFH cases. Nevertheless, there is virtually no data available concerning the safety profile of the said drugs with respect to reproduction. Though the reduction of LDL-C before pregnancy might be considered advantageous for ensuring stable cardiovascular health, the influence of these biological drugs on the course of gestation and breastfeeding is still unknown.

There are several limitations in this research. The sample is very small because of the scarcity of genetically confirmed HoFH, which diminishes external validity. Moreover, incomplete data on some subjects had an impact on various long-term factors related to cardiovascular disease, reproduction, and newborn babies, owing to incomplete historical data, non-compliance with follow-ups, and early mortality. This could have brought about information bias. The observational design does not allow making any causal concluding statements, and the results can be evaluated rather cautiously. Several issues need to be noted with regard to interpreting the results of this study. The first limitation of the research is the smallness of the cohort sample that stems from the fact that genetically proven HoFH is a highly rare condition. Although descriptive comparisons were used to generate hypotheses about differences between groups, no formal inferential statistical analysis was performed, and the study lacked the power and external validity necessary for drawing conclusions and controlling confounders. Another potential problem is the possible presence of a recall bias in the reproductive history of some patients, as this information was obtained retrospectively, even though corroborated by medical records when available. Missing cardiovascular and genotypic follow-up information for certain individuals prevented more thorough stratification. Finally, individual variations in the degree of genotype pathogenicity, LDL receptor activity, and lipid-lowering treatment might have affected reproductive and cardiovascular outcomes in this cohort.

Conclusions

Finally, there is a lack of evidence regarding the reproductive mechanisms of women with HoFH. The existing data indicate that, when cardiovascular examination and multidisciplinary care are appropriately performed, pregnancy has a rather positive maternal and fetal outcome. Lipoprotein apheresis (LA) is one of the foundations of the treatment of severe lipid disorders, which is safe and effective during pregnancy. The findings in the study highlight the significance of the planned preconception counseling, cardiovascular assessment, and combined care with lipidologists, cardiologists, genetic counselors, and obstetricians. There are noticeable gaps in menstrual health, fertility, hormone therapy, and long-term menopausal treatment, which makes it desirable to have evidence-based reproductive practices based

on prospective multicenter and longitudinal studies. Moreover, the extremely small number of pregnancies controlled by LA made it difficult to perform inferential statistical analysis on LA and non-LA patients.

Declarations and Statements

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Conceptualization: Claudia Stefanutti; Giuseppina Perrone; Hofit Cohen; Handrean Soran

Data Curation: Claudia Stefanutti; Giuseppina Perrone; Hofit Cohen; Giovanna Zeppa

Formal Analysis: Valentina Demarco; Giovanna Zeppa; Paola Galoppi; Handrean Soran

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Investigation: Claudia Stefanutti; Giuseppina Perrone; Hofit Cohen; Giovanna Zeppa

Methodology: Claudia Stefanutti; Giuseppina Perrone; Handrean Soran; Hofit Cohen

Project Administration: Claudia Stefanutti

Resources: Claudia Stefanutti; Hofit Cohen

Software: Giovanna Zeppa; Valentina Demarco

Supervision: Claudia Stefanutti; Giuseppina Perrone; Hofit Cohen; Handrean Soran

Validation: Valentina Demarco; Paola Galoppi; Giuseppe Rizzo; Handrean Soran

Visualization: Paola Galoppi; Valentina Demarco; Giuseppe Rizzo

Writing – Original Draft: Claudia Stefanutti; Giuseppina Perrone; Giovanna Zeppa; Hofit Cohen

Writing – Review & Editing: Claudia Stefanutti; Giuseppina Perrone; Hofit Cohen; Handrean Soran; Giuseppe Rizzo

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