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Brief Communication

Counseling couples at risk of having a child with homozygous familial hypercholesterolemia – Clinical experience and recommendations

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Abstract: Homozygous familial hypercholesterolemia (HoFH) is a rare, potentially life-limiting, inherited disorder of lipoprotein metabolism characterized by extremely high low-density lipoprotein cholesterol levels. When both parents have heterozygous FH, there is a 25% chance they will conceive a child with HoFH. Here we describe our clinical experience with two such prospective parent couples who were counseled regarding reproductive options and prenatal testing for HoFH. These cases showcase how, in consultation with a molecular geneticist and pediatric cardiologist, parents may be informed of the prognosis and treatment outlook of HoFH based on the FH-variants carried, to ultimately make personal decisions on reproductive options. One couple opted for prenatal testing and termination of pregnancy in case HoFH was found, while the other accepted the risk without testing. We review the available literature on preconception counseling for HoFH and provide practical guidance to clinicians counseling at-risk couples. Optimal counseling of prospective parents may help prevent future physical and psychological problems for both parent and child.

Introduction

Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant genetic disorder with a prevalence of approximately 1 in 300[1], characterized by elevated low-density lipoprotein cholesterol (LDL-C) causing accelerated atherosclerosis and increased risk of premature cardiovascular disease (CVD). Early detection and initiation of lipid-lowering therapy (LLT) are crucial to negate this elevated risk.[2,3] HeFH is caused by a pathogenic variant in

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Table 1 Characteristics of two couples referred for preconception counseling because both partners have heterozygous FH.

	Couple A		Couple B	
	Father	Mother	Father	Mother
Family history of CVD	None	Her mother underwent CABG at age 50	His father had two MIs at age of 42 and 51	Her father and paternal grandfather both had a MI at age 50
Age at genetic diagnosis of FH	37 years[a]	34 years	33 years	17 years
Variant in *LDLR* gene	c.2140+103G>T	c.(940+1_941-1)_(1186+1_1187-1)del	c.(1690A>C;2397-2405del) p.(Asn564His;Val800_Leu802del)[b]	c.314-1G>A
Type of variant	Synthesis defect (likely null variant)	Synthesis defect (null variant)	Partial transport defect (defective variant with residual LDLR function)	Synthesis defect (null variant)
Age at referral to clinical geneticist	38 years	36 years	34 years	32 years
Untreated LDL-C (mmol/L)	7.9	7.1	6.5	6.2
Lipid lowering medication	Atorvastatin 10mg, Ezetimibe 10mg	Diet only	Atorvastatin 40mg	Diet only
Most recent LDL-C (mmol/L)	2.7	6.4	2.5	4.3

CABG, coronary artery bypass grafting; CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MI, myocardial infarction.

[a]At age 12, lipid lowering therapy was already started following a clinical diagnosis of FH.

[b]The two variants are linked to the same allele. This variant, also known as FH-Hauwert, is the most frequently identified FH-variant in the Netherlands.

genes encoding proteins involved in cholesterol metabolism (*LDLR, APOB* or *PCSK9*).[3]

Patients who inherit two FH alleles have homozygous FH, the most severe form of FH, which may lead to CVD or death as early as in childhood if left untreated.[4] It is therefore critical that patients with HoFH receive intensive LLT from diagnosis, which frequently includes lipoprotein apheresis, a technique of recurrent extracorporeal removal of lipoproteins.

When both aspiring parents have HeFH, there is a one in four (25%) chance of having a child with HoFH. It is known that carrier status of genetic conditions influences couples' reproductive decision-making[5], but this has never been studied in in the context of FH and no formal guidelines exist for counseling HeFH couples in reproductive decision-making. Here we describe our experiences with two prospective parent couples with HeFH who were referred to the department of clinical genetics at the Amsterdam UMC between 2019 and 2021 for genetic counseling concerning having a child with HoFH. We provide a review of the literature and practical recommendations for pre-conception counseling and early testing for (Ho)FH.

Clinical experience

Couple A was referred to our clinical genetics department for counseling for prenatal testing twice, because both aspiring parents had HeFH (Table 1). Personal medical histories were unremarkable, but family history was positive for premature CVD because the mother's mother had undergone coronary artery bypass grafting at age 50 years. Before the father's HeFH diagnosis, the couple had already had a child who was later found to carry neither parental FH-variant.

At the time of first referral the mother was 9 weeks pregnant. The couple already understood the autosomal dominant inheritance pattern of FH and consequent 25% chance of having a child carrying both FH-variants. After counseling by a clinical geneticist on HoFH and prenatal testing, the parents opted for chorionic villus sampling at 12 weeks gestation. DNA testing revealed that the fetus carried both FH-variants and the parents decided to terminate the pregnancy.

Preimplantation genetic testing was discussed as a reproductive option for future pregnancies, but the couple decided not to pursue this. Eight months later, the couple was again referred to us because of a new pregnancy. Chorionic villus sampling was performed at 14 weeks gestation. The fetus was found to be heterozygous for the maternal FH-variant only, and the pregnancy was carried to term. Parents were advised to visit a pediatric FH specialist from age 8 years on, to discuss initiation of LLT.

Couple B was also referred for preconception counseling because both aspiring parents were heterozygous carriers of an FH-variant (Table 1). The mother had been diagnosed with HeFH at age 17 through a nationwide screening program, and the father by his general practitioner through family cascade testing one year prior to referral. Personal medical histories were otherwise unremarkable. The aspiring

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mother did not take (lipid-lowering) medication because she wished to become pregnant in the near future. Family histories were strongly positive for CVD. Both the father and the paternal grandfather of the aspiring mother were FH-carriers and had suffered myocardial infarction at age 50. The aspiring father's father had two myocardial infarctions at age 42 and 51.

The couple was informed of the 25% chance of having a child with HoFH. Available options concerning pregnancy and prenatal testing were discussed (listed in the discussion). After deliberation, the couple was inclined to perform prenatal diagnosis after conception. However, in case the fetus was found to carry both FH alleles, potential termination of pregnancy would highly depend on the child's treatment options and prognosis. Therefore, a molecular geneticist and pediatric cardiologist specialized in FH were consulted. Because the aspiring father carried a relatively 'mild' FH-variant with residual *LDLR* function, pharmacotherapeutic interventions with oral and injectable medications (statin and PCSK9 inhibitors) that act via upregulation of the LDLR-pathway were expected to be effective. This would make the need for invasive treatment with regular lipoprotein apheresis to control LDL-C levels unlikely. Moreover, current rapid developments in LLT options may considerably improve future treatment and prognosis of patients with HoFH. Ultimately, the couple decided they would refrain from prenatal testing and accept the chance their child might inherit both FH-variants.

One year later, the couple became pregnant. In order to exclude or to diagnose and treat FH early, umbilical cord blood was obtained immediately after birth. Results showed that the child was heterozygous for the paternal FH-variant only.

Clinical recommendations

These recommendations are based on the scenario that pathogenic FH-variants have been identified and are not intended for use in the context of clinical FH without a genetic confirmation.

- Couples where both partners carry an FH-variant and who wish to become pregnant should be offered prenatal genetic counseling for HoFH on a case-by-case basis.
- Clinicians should inform at-risk couples of the autosomal dominant inheritance pattern of FH and consequent 25% chance of having a child with HoFH.
- Clinicians should discuss treatment and prognosis of HoFH, taking into account the FH-variants carried by the parents as well as availability of lipid-lowering therapies.
- Clinicians should explore and discuss reproductive options, including gamete donation, adoption, accepting the chance of having a child with HoFH or refraining from having (more) children.
- Preimplantation genetic testing ('embryo selection') and prenatal diagnosis through chorionic villus sampling or amniocentesis, potentially followed by termination of pregnancy, are prenatal diagnostic options that may be considered, depending on local medical and legal contexts.
- Umbilical cord blood can be used to diagnose or exclude (Ho)FH from birth to ensure timely initiation of lipid-lowering therapy.
- For individuals with FH who wish to become pregnant, we recommend screening their apparently healthy partners when there is an increased chance they also carry an FH-variant (e.g. in consanguineous marriage or populations with a known founder effect). In all other cases we recommend only to look for FH in partners upon patient request, or based on clinical suspicion triggered by a partner's (family) history of hypercholesterolemia or CVD.

Review of the literature and clinical recommendations

We described two couples at risk of having a child with HoFH, and show how each followed a different approach to reproductive decision-making. The first couple opted for prenatal diagnosis, while the second accepted the possibility of HoFH.

Reproductive decision-making and prenatal testing for couples at risk of having a child with HoFH has been described in several reports. In 1976, Wienker et al. were the first to perform prenatal testing for HoFH using extensive functional studies on cultured amniotic cells retrieved via amniocentesis.[6] These tests showed that the fetus was unaffected, a finding that was later confirmed by measuring the plasma LDL-C level when the child was 11 months old. In 1978, Brown et al. diagnosed a fetus with HoFH using similar methods, and termination of pregnancy was done at 20 weeks gestation.[7] In 1985, de Gennes et al.[8] similarly cultured cells obtained from amniocentesis. However, a fungal contamination rendered these in vitro studies inconclusive, so a fetal blood sample was obtained directly *in utero* at 24 weeks gestation. This showed LDL-C levels consistent with HoFH and termination of pregnancy ensued.[8] Later case reports used DNA testing to investigate the FH status from material obtained from chorionic villus sampling or amniocentesis,[9–12] similar to the approach that we used in couple A. All reports described above concerned parents who already had a child with HoFH and, to the best of our knowledge, we are the first to describe genetic counseling and prenatal testing in couples without.

FH is a common condition that is increasingly being recognized and diagnosed, so preconception counseling of HeFH couples will likely be requested more often in the future. It is important that a genetic confirmation of FH is sought whenever possible, as the FH phenotype is not always due to a pathogenic FH-variant with an autosomal dominant inheritance pattern that will put couples at risk of having a child with HoFH. In this context and based on our experience, we provide recommendations for counseling HeFH couples at risk of having children with HoFH.

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Discuss the available reproductive options

Couples at risk of transmitting a genetic condition to their children may consider various reproductive options including gamete donation, adoption, accepting the chance of having a child with the condition or refraining from having (more) children.[13] Preimplantation genetic testing (PGT) and prenatal diagnosis are invasive options for selective reproduction that are only available if there is significant risk of transmitting a serious disorder. PGT requires *in vitro* fertilization and testing the embryo for the genetic condition, after which an unaffected embryo is transferred to the uterus. Whether or not PGT is accepted for a specific genetic condition is mostly decided by national committees (either centrally or on a case-by-case basis), or sometimes by individual centres.[14] HoFH is a serious condition and treatment is invasive when lipoprotein apheresis is necessary. PGT for HoFH has been allowed in the United Kingdom[15], but this may differ in other countries. PGT can be a time-consuming and burdensome process with potential health risks for the woman, and is not without ethical dispute. The overall success rate for pregnancy with PGT is approximately 25% per oocyte retrieval and 30% per embryo transfer procedure.[16]

Prenatal diagnosis using chorionic villus sampling, as described in couple A, can first be performed between 11 and 14 weeks gestation, and amniocentesis from 16 weeks onwards. Turnaround-time of these tests is usually within two weeks, which allows termination of pregnancy within statutory time limits. However, this option may be considered ethically sensitive and is not available in all countries. Chorionic villus sampling is associated with a procedure-related miscarriage risk of about 0.5%, which has to be discussed and weighed before pursuing this approach.

Discuss predicted treatability of HoFH based on genotype of the parents

Disease severity and response to treatment varies considerably between HoFH patients, due at least in part to the degree of residual LDL-receptor activity.[4,17] Patients carrying two *LDLR*-variants that produce (nearly) no functional protein ('LDLR-null') are the most severely affected because therapeutic options that act via upregulation of the LDL-receptor (i.e. statins and PCSK9 inhibitors) are largely ineffective. These patients nearly always require recurrent lipoprotein apheresis; an invasive therapy associated with reduced quality of life.[18] The extent to which a genetic disorder can be treated has a clear impact on the decision-making process. This is exemplified by couple B, who, after consultation of a geneticist and pediatric cardiologist, decided against prenatal testing. This decision was largely based on the fact that current LLT options were anticipated to sufficiently lower LDL-C in case a HoFH child was born, without the need for lipoprotein apheresis.

Where possible, a clinician specialized in the treatment of pediatric HoFH may be contacted to inform prospective parents of the potential therapeutic outlook. Novel therapies that act independently of the LDL-receptor, such as lomitapide and evinacumab, might reduce the need for lipoprotein apheresis in future.[3] Replacement of *LDLR* using gene therapy is currently being investigated (NCT02651675) and may transform treatment in the future. With advancements in therapeutic options, the concepts of 'treatability' and thus 'severity' of HoFH may shift.

Diagnose and treat FH early

If prenatal testing is not applicable, we advise to test for (Ho)FH using umbilical cord blood obtained directly after birth. When HoFH is diagnosed, start of LLT should not be delayed. Currently, not all add-on LLTs are registered or available for young chilldren[3], so in severe cases (bi)weekly lipoprotein apheresis may need to be initiated once technically possible. In case of HeFH, LLT should start from approximately 8 to 10 years old[2].

Lipid lowering therapy during pregnancy

Conventionally and in the cases we describe, statins and other LLT are discontinued before conception and during pregnancy to avoid any potential fetal toxicity. For female FH patients, it has been reported that the interruption of statin treatment with each pregnancy amounted to a median of 2.3 years[19]. However, in 2021 the FDA removed the strongest warning against statins in pregnancy recognizing that unintended exposure is unlikely to harm the fetus[20]. Thus, rather than stopping statins before conception, patients may discuss with their healthcare professional to only stop statin therapy once they find out they are pregnant.

Should the partner of a HeFH patient also undergo genetic FH-testing?

The question is whether partners of genetically confirmed FH-patients should also be tested for presence of an FH-variant. Carrier screening is generally accepted for several autosomal recessive conditions, although carrier frequencies in these disorders are usually higher than the prevalence of approximately 1 in 300 for FH.[1] An example is carrier screening for cystic fibrosis with a carrier frequency of about 1 in 30 in white Europeans.[21] In certain populations the prevalence of HeFH is higher due to a founder effect, and in consanguineous marriages the chance that a partner will also have HeFH could be even higher. In these high-risk situations, we recommend screening the partner for FH using existing scoring systems to diagnose FH clinically, followed by genetic confirmation if needed. In all other cases the expected risk of having a child with HoFH is smaller than 0.1% (1:300 chance the partner also has HeFH and 1:4 chance both variants are passed on). We recommend discussing and screening the partner for FH only upon patient request or based on clinical suspicion triggered by a partner's (family) history of hypercholesterolemia or CVD. Interestingly, all patients we described carried different FH-variants, and three presented

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with a family history of premature CVD. This shows that serendipitous union of FH-variant carriers is a reality, and that family history may alert clinicians to potentially undiagnosed HeFH.

In conclusion, we describe how genetic counseling and informed shared-decision-making resulted in different decisions in two couples at risk of having a child with HoFH. Based on our experiences we provide recommendations for clinicians counseling these couples concerning reproductive options, predicted treatability of HoFH based on FH-variants of the parents, early diagnosis and treatment of FH, lipid lowering therapy during pregnancy and whether the partner of a patient with HeFH should be also tested for FH.

Author contributions

TRT and MDR collected the data and wrote the first version of the manuscript. AW, GKH, JCD, MCvM and IBM provided critical revisions. All authors gave approval for submission of the final version of the manuscript.

Declaration of Competing Interest

AW has received consulting fees from Novartis, is chair of the Steering Committee for the ORION-13 and ORION-16 trial, received payment or honoraria from Amgen, Regeneron and Novartis, and participated on a Data Safety Monitoring Board or Advisory Board of Amgen.

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TRT, MDR, JCD, MCvM and IMA declare no conflicts of interest.

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References

1. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol*. 2020;75(20):2553–2566. doi:10.1016/j.jacc.2020.03.057.
2. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolæmia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36(36):2425–2437. doi:10.1093/eurheartj/ehv157.
3. Reijman MD, Kusters DM, Wiegman A. Advances in familial hypercholesterolaemia in children. *Lancet Child Adolesc Heal*. 2021;5(9):652–661. doi:10.1016/S2352-4642(21)00095-X.
4. 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(32):2146–2157. doi:10.1093/eurheartj/ehu274.
5. Gee M, Piercy H, Machaczek K. Family planning decisions for parents of children with a rare genetic condition: a scoping review. *Sex Reprod Healthc*. 2017;14:1–6. doi:10.1016/j.srhc.2017.08.001.
6. Wienker TF, Utermann G, Ropers H-H. Prenatal diagnosis of homozygous familial hypercholesterolemia: Investigation of a case at risk. *Clin Genet*. 2008;9(6):545–552. doi:10.1111/j.1399-0004.1976.tb01611.x.
7. Brown MS, Kovanen PT, Goldstein JL, et al. Prenatal diagnosis of homozygous familial hypercholesterolaemia. Expression of a genetic receptor disease in utero. *Lancet (London, England)*. 1978;1(8063):526–529. doi:10.1016/s0140-6736(78)90552-4.
8. de Gennes JL, Daffos F, Dairou F, et al. Direct fetal blood examination for prenatal diagnosis of homozygous familial hypercholesterolemia. *Arteriosclerosis*. 1985;5(5):440–442. doi:10.1161/01.atv.5.5.440.
9. Reshef A, Meiner V, Dann EJ, Granat M, Leitersdorf E. Prenatal diagnosis of familial hypercholesterolemia caused by the "Lebanese" mutation at the low density lipoprotein receptor locus. *Hum Genet*. 1992;89(2):237–239. doi:10.1007/BF00217130.
10. Coviello DA, Bertolini S, Masturzo P, et al. Chorionic DNA analysis for the prenatal diagnosis of familial hypercholesterolaemia. *Hum Genet*. 1993;92(4):424–426. doi:10.1007/BF01247350.
11. Stefanutti C, Vivenzio A. [First prenatal diagnosis of familial hypercholesterolemia by a molecular biology technic]. *Clin Ter*. 1993;143(2):99–103. http://www.ncbi.nlm.nih.gov/pubmed/7900953.
12. Vergotine J, Thiart R, Langenhoven E, Hillermann R, De Jong G, Kotze MJ. Prenatal diagnosis of familial hypercholesterolemia: importance of DNA analysis in the high-risk South African population. *Genet Couns*. 2001;12(2):121–127. http://www.ncbi.nlm.nih.gov/pubmed/11491306.
13. Severijns Y, de Die-Smulders CEM, Gültzow T, de Vries H, van Osch LADM. Hereditary diseases and child wish: exploring motives, considerations, and the (joint) decision-making process of genetically at-risk couples. *J Community Genet*. 2021;12(3):325–335. doi:10.1007/s12687-021-00510-x.
14. Dondorp W, De Wert G. Refining the ethics of preimplantation genetic diagnosis: a plea for contextualized proportionality. *Bioethics*. 2019;33(2):294–301. doi:10.1111/bioe.12534.
15. Boddington P, Parker M. Preimplantation genetic diagnosis for familial hypercholesterolaemia: a commentary on the recent HFEA decision. *Clin Ethics*. 2008;3(3):145–148. doi:10.1258/ce.2008.008021.
16. Coonen E, van Montfoort A, Carvalho F, et al. ESHRE PGT Consortium data collection XVI–XVIII: cycles from 2013 to 2015†. *Hum Reprod Open*. 2020;2020(4):1–11. doi:10.1093/hropen/hoaa043.
17. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet*. 2022;399(10326):719–728. doi:10.1016/S0140-6736(21)02001-8.
18. Kayikcioglu M, Kuman-Tunçel O, Pirildar S, et al. Clinical management, psychosocial characteristics, and quality of life in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis

in Turkey: results of a nationwide survey (A-HIT1 registry). *J Clin Lipidol*. 2019;13(3):455–467. doi:10.1016/j.jacl.2019.02.001.

19. Klevmoen M, Bogsrud MP, Retterstøl K, et al. Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia. *Atherosclerosis*. 2021;335(March):8–15. doi:10.1016/j.atherosclerosis.2021.09.003.
20. Administration UF and D. FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy; still advises most pregnant patients should stop taking statins. 07-20-2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-strongest-warning-against-using-cholesterol-lowering-statins-during-pregnancy. Published 2021. Accessed August 20, 2022.
21. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(10):1793–1806. doi:10.1038/s41436-021-01203-z.

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