Atherosclerosis 335 (2021) 8–15

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia

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ARTICLE INFO

Keywords:
Familial hypercholesterolemia
Women's health
Pregnancy
Statin
Breastfeeding

ABSTRACT

Background and aims: Women with heterozygous familial hypercholesterolemia (FH) are recommended to initiate statin treatment at the same age as men (from 8 to 10 years of age). However, statins are contraindicated when pregnancy is planned, during pregnancy and breastfeeding. The aim of the study was to determine the duration of pregnancy-related off-statin periods and breastfeeding in FH women.

Methods: A cross-sectional study using an anonymous online self-administered questionnaire was conducted. Women with FH were recruited through Lipid Clinics in Norway and Netherlands and national FH patient organizations.

Results: 102 women with FH (n = 70 Norwegian and n = 32 Dutch) were included in the analysis. Total length of pregnancy-related off-statin periods was estimated for 80 women where data were available, and was median (min-max) 2.3 (0–14.2) years. Lost statin treatment time was estimated for 67 women where data were available, and was median (min-max) 18 (0–100)% at mean (SD) age of 31 (4.3) years at last pregnancy. More women breastfed in Norway (83%) and for longer time [8.5 [1-42] months] compared to the Netherlands [63%, $p = 0.03$; 3.6 (0–14) months, $p < 0.001$]. Eighty-six percent of the women reported need for more information on pregnancy and breastfeeding in relation to FH.

Conclusions: Young FH women lose years of treatment when discontinuing statins in relation to pregnancy and breastfeeding periods and should be closely followed up to minimize the duration of these off-statin periods. Whether these periods of interrupted treatment increase the cardiovascular risk in FH women needs to be further elucidated.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disease causing elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) from the first years of life [1]. The cholesterol burden accumulates through life and defines the risk of cardiovascular disease (CVD) [2], underlining the importance of early treatment start and lifelong treatment to reduce the risk of premature CVD in these patients [3,4]. Female heterozygous FH patients are recommended to be considered for statin treatment at the same age as men (8–10 years) [5,

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https://doi.org/10.1016/j.atherosclerosis.2021.09.003
Received 22 March 2021; Received in revised form 9 August 2021; Accepted 2 September 2021
Available online 3 September 2021

6]. However, lipid-lowering drugs including statins, ezetimibe and PCSK9-inhibitors are contraindicated during pregnancy due to concern on potential teratogenic effects [7]. Current ESC/EAS Guidelines recommend that lipid-lowering drugs are discontinued when pregnancy is planned, during pregnancy and during the breastfeeding period (pregnancy-related off-statin periods) [4,5]. Only bile acid sequestrants that are not absorbed, and/or LDL apheresis can be considered during pregnancy for severe FH [5,8].

Statins are the most common lipid lowering agent in treatment of FH and when discontinued in pregnancy and breastfeeding periods, cholesterol levels increase to pre-treatment levels. In addition, total cholesterol (TC) and LDL-C levels increase even further due to the physiological changes caused by pregnancy [9]. Pregnancy in FH women therefore represent a dual exposure to increased cholesterol levels. Amundsen et al. found that TC and LDL-C in FH women increased from baseline (gestational week 17–20) to week 36 by 29% and 39%, respectively, compared to 25% and 34% in healthy women. Triglyceride levels also increased by 116% in the FH women and 103% in the healthy women. Although the relative increase was similar, the FH women had higher absolute levels than the healthy women [10]. Little is known about how long FH women discontinue statin treatment in relation to pregnancy and breastfeeding periods. Only small studies and case reports have to our knowledge previously reported on pregnancy-related off-statin periods in FH women [11,12]. Elucidating these periods of interrupted treatment is therefore important for the management of FH in women of childbearing age.

In Norway and the Netherlands, FH women are recommended to breastfeed in line with the general population and there are no specific guidelines on breastfeeding for FH women. As statins are contraindicated also during breastfeeding [5], the breastfeeding period contributes to the duration of the total pregnancy-related off-statin period. However, few studies have examined the duration and extent of breastfeeding in FH women.

The primary aim of the present study was to examine and estimate the duration of pregnancy-related off-statin periods and breastfeeding in Norwegian and Dutch FH women, and whether the duration of breastfeeding was influenced by a wish to restart treatment. Secondary aim was to examine cardiovascular history and experienced concern in relation to pregnancy in Norwegian and Dutch FH women.

2. Patients and methods

A cross-sectional study using an anonymous online self-administered questionnaire was conducted among Norwegian and Dutch adult FH women who had given live birth to children. Norwegian women were recruited through the patient organization FH Norway and Lipid Clinics from all health regions. Invitations with link to the web address of the questionnaire were sent out via mailing list to the members of the patient organization FH Norway, advertised at the patient waiting room at all regional lipid clinics in Norway, through the Facebook page of the Norwegian National Advisory Unit on FH and in the member magazine of FH Norway. Dutch women were recruited through the Erasmus Medical Center, Rotterdam, flyers at lipid clinics of FH centres in the Netherlands, advertisement in the patient waiting room and via the Dutch national FH organization LEEFH as well as posts on Linked-in.

2.1. Questionnaire

The online self-administered questionnaire was designed using a tool from the University Information Technology Center at the University of Oslo [13]. The questionnaire was anonymous and no person identifiable information was collected. The questionnaire was prepared based on the aims of the study. Initial questions were related to the FH diagnosis and lipid lowering treatment history, CVD history and risk factors. To collect data only on pregnancies where treatment most likely had been initiated, the women were asked whether they knew about their FH prior to each of the pregnancies. The same set of questions on pregnancy were asked the number of times corresponding to the number of children they had and were related to time of statin use prior to, during and after pregnancy; breastfeeding and statin use during breastfeeding; pregnancy complications and birth data. Statements on concern related to FH diagnosis and pregnancy were also asked. The questionnaire was designed based on branching of questions and answers in a dynamic view, where only relevant questions for each participant would show depending on answers to previous questions. For example, questions regarding discontinuation of statins during pregnancy were only shown to participants who answered to have used statins prior to the pregnancy. The questionnaire was designed in Norwegian and translated to Dutch and English (Supplementary material).

The online questionnaire was open for responding from September 2019 through December 2019 in Norway, and from October 2019 through July 2020 in the Netherlands. Before study start, the questionnaire was tested on two Norwegian and four Dutch FH women who gave feedback, and some changes in wording and additional questions were implemented to the questionnaire.

The project was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was submitted to the Norwegian Regional Committee for Medical Research Ethics for evaluation, and was evaluated to not require specific approval due to collection of only anonymous data. The Medical Ethical Review Committee of the Erasmus Medical Center, the Netherlands considered the protocol non-WMO (Wet Medisch Onderzoek) research, and therefore, it did not have to be reviewed and a waiver was obtained.

2.2. Estimating length of pregnancy-related off-statin periods

Of 206 respondents, 186 women with FH had children. One-hundred and two women knew about their FH diagnosis prior to the first pregnancy and were included in further analysis. Data for each of the women's pregnancies (range 1–6) were similar, therefore results from only the first pregnancy are presented. Total length of pregnancy-related off-statin periods was estimated in 80 FH women who had used statins before the first pregnancy. It was estimated by summarizing off-statin time before (planning pregnancy), during (gestational weeks with discontinuation of statins) and after (time after pregnancy until restart of statin treatment) all pregnancies. Proportion of lost statin treatment time was estimated in 67 women who had reported data on age at statin start and age at last birth, by dividing the following: *Proportion of lost statin treatment time = total length of pregnancy-related off-statin time/ length of potential statin treatment from statin start until restart of statins after last pregnancy.*

Potential statin treatment time corresponds to treatment time if the women had not been pregnant.

2.3. Statistics and data handling

Statistical analyses were performed using the statistical package for the social sciences (SPSS) version 26.0 (IBM corporation) and Microsoft Office Excel 2016. Result file and codebook from the online questionnaire were imported into SPSS. Due to the dynamic view of the questions not all questions were answered by all participants. Total number of respondents to each question are presented as n in tables and figures. Descriptive results are presented as median (min-max) unless noted as means (SD), and as frequencies [n (%)]. All values were checked for normality using the Kolmogorov-Smirnov test and histograms. Normally distributed variables were analysed using Independent Samples *t*-test, non-normally distributed variables by Mann-Whitney *U* test and categorical variables by chi-square test or Fisher's exact test. Alpha level of significance was set to 5%. All *p*-values were two-sided.

3. Results

One-hundred two women knew about their FH diagnosis prior to the first pregnancy and were included in the analysis (Fig. 1). Characteristics of the 102 FH women (n = 70 Norwegian and n = 32 Dutch) are shown in Table 1. Results are presented as median (min-max) or n (%) unless otherwise noted. Adult FH women who had given birth were invited to participate, and age at time of answering the questionnaire was 39 (23–74) years and they had 2 (1–6) children. FH had been genetically verified in 93 (91%) women at mean (SD) age 22 (12.5) years. Seventy-eight (76%) women were using statins. Eight (8%) women did not use statins due to pregnancy or planning of pregnancy or due to side effects in seven (7%) of them.

Eight (8%) women had experienced a CVD event, of whom seven (7%) had experienced ischaemic heart disease (IHD). Age at first CVD event in these women was 40 (28–52) years. For five of them, the IHD event occurred in relatively close proximity to pregnancy (from two years prior to first pregnancy to six years after last pregnancy) (Supplementary Table 1).

Gestational week at birth was 40 (33–42) and birthweight was mean (SD) 3376 (494) g. Cholesterol was measured during pregnancy in 37 (36%) women and total cholesterol level was 10.8 (4.5–17.0) mmol/L, measured at gestational week 20 (0–36). Three (3%) women had gestational diabetes, four (4%) had hypertension and three (3%) had preeclampsia during pregnancy (Table 1).

3.1. Statin use before, during and after first pregnancy

Eighty-nine of the 102 women (87%) had given birth to their first child after 1990, when statins were initially available for treatment. Eighty (78%) women had used statins before the first pregnancy and 72 (90%) of these 80 women had discontinued statins before or during pregnancy (Table 2). Time of discontinuation of statins was 2 (0–34) months before pregnancy. Twenty-four (30%) had continued using statins for 6 (2–39) weeks into the pregnancy. Twenty-one (88%) of these women had used statins during the first trimester and three (13%) had used statins during the entire pregnancy. Sixty (75%) restarted statin treatment after pregnancy. A higher proportion of Dutch women restarted statin treatment after pregnancy [25 (89%)] compared to the Norwegian women [35 (67%)] ($p = 0.03$), and time of statin start after pregnancy was earlier in the Dutch women who started 3 (0–14) months after birth compared to 5 (0–13) months in the Norwegian women ($p = 0.02$).

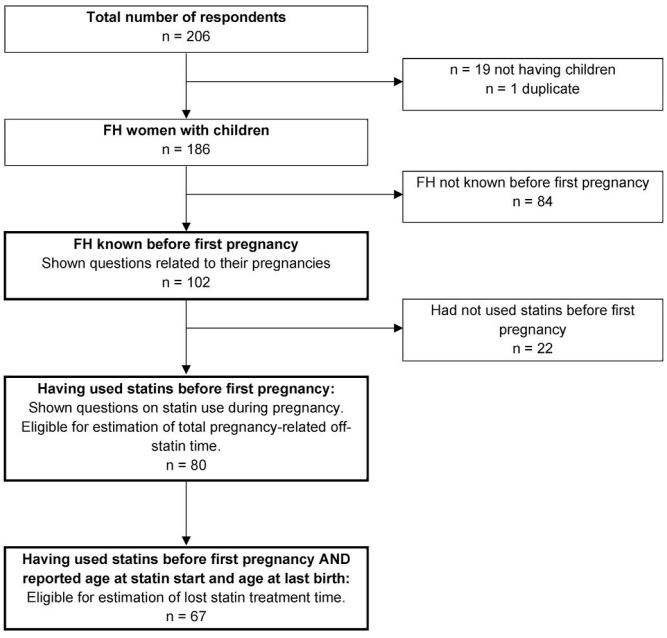


Fig. 1. Flowchart.
FH: familial hypercholesterolemia.

3.2. Breastfeeding

More Norwegian FH women breastfed the first child [58 (83%)] compared to the Dutch FH women [20 (63%)] ($p = 0.03$) and the Norwegian FH women breastfed for a longer duration [8.5 (1–42) months] than the Dutch FH women [3.6 (0–14) months] ($p < 0.001$) (Table 1). Eight (14%) of the Norwegian FH women who breastfed had used statins during part of or the entire breastfeeding period whereas no Dutch FH women had used statins during breastfeeding. Seventeen (22%) of the FH women who breastfed had stopped breastfeeding earlier than they wanted in order to restart statin treatment. Breastfeeding in the Norwegian and Dutch FH women and in the general population in both countries is shown in Fig. 2. The number of women who breastfed was significantly lower in the Norwegian FH study population compared to the Norwegian general population in each of the first six months of the child's life ($p < 0.001$). Time of return to work after birth was earlier in the Dutch FH women who returned to work after 13 (3–50) weeks, compared to 42 (8–80) weeks in the Norwegian FH women ($p < 0.001$) (Table 1).

3.3. Estimated total length of pregnancy-related off-statin periods

Total length of pregnancy-related off-statin periods before, during and after all pregnancies was estimated among the 80 FH women who had used statins before the first pregnancy and was median 2.3 years (Table 2), with large individual variation ranging from 0 to 14.2 years (Fig. 3). Total length of pregnancy-related off-statin periods per pregnancy was 1.3 (0–4.7) years. Proportion of lost statin treatment time was estimated in 67 women who had used statins before the first pregnancy and reported age at statin start and last birth. At mean age of 31 years at last pregnancy, these 67 FH women had lost 18 (0–100)% of their potential statin treatment time due to pregnancy-related off-statin periods. Total length of pregnancy-related off-statin periods was higher among the women who had several children (Fig. 3). In the 14 women who were post-menopausal at the time of responding to the questionnaire, and thereby at post childbearing age, total length of pregnancy-related off-statin periods was higher [3.0 (0.8–14.2) years].

3.4. Concern and follow-up of FH women

Fifty-one% of the FH women reported concerns related to use of cholesterol lowering medication and pregnancy (Supplementary Fig. 1) and 86% wanted more information on pregnancy and breastfeeding in relation to FH. Forty-seven% of the women had been concerned that statin use during pregnancy could affect the fetus and 42% had been concerned that statin use during breastfeeding could affect the health of the child. Only 29% of the Dutch women and 13% of the Norwegian women had an appointment with a physician specialized in FH during the first pregnancy ($p = 0.05$) (Table 1).

4. Discussion

4.1. FH women lose several years of statin treatment

In the current study, we demonstrate that young FH women lose years of statin treatment due to pregnancy-related off-statin periods (before, during and after pregnancy), accounting for approximately 20% lost statin treatment time at mean age of 31 years. The length of pregnancy-related off-statin periods was median 2.3 years, however with large individual variation ranging from 0 to 14 years. Thus, in some FH women pregnancy-related off-statin periods constitutes a

Table 1
Subject characteristics of FH women and first pregnancy.

	All	n[a]	Norway	n[a]	Netherlands	n[a]	p[b]
Age (years)	39 (23–74)	101	39 (24–74)	69	39 (23–59)	32	0.62
BMI (kg/m^2)	26.1 (4.6)	101	26.0 (4.5)	70	26.4 (4.7)	31	0.63
No. of children (n)	2 (1–6)	102	2 (1–5)	70	2 (1–6)	32	0.12
FH diagnosis and lipid-lowering treatment							
Age FH known (years)	14.1 (8.1)	80	14.4 (8.2)	54	13.3 (8.0)	26	0.58
Genetically verified, n (%)	93 (91.2)	100	64 (92.8)	69	29 (93.5)	31	>0.99
Age genetic test (years)	22.1 (12.5)	91	23.6 (12.8)	63	18.8 (11.2)	28	0.09
Age start lipid-lowering treatment (years)	18 (6–43)	99	18 (6–43)	68	15 (6–33)	31	0.02
Age start statin treatment (years)	19 (6–53)	92	20 (9–53)	62	18 (6–33)	30	0.02
Current lipid-lowering treatment							
Statins, n (%)	78 (75.5)	102	50 (71.4)	70	28 (87.5)	32	0.08
Ezetimibe, n (%)	57 (55.9)	102	38 (54.3)	70	19 (59.4)	32	0.63
Resins, n (%)	6 (5.9)	102	5 (7.1)	70	1 (3.1)	32	0.66
PCSK9-inhibitors, n (%)	13 (12.7)	102	10 (14.3)	70	3 (9.4)	32	0.75
History of CVD events							
No. of women with CVD events, n (%)	8 (7.8)	102	5 (7.1)	70	3 (9.4)	32	0.70
Current age among women with CVD events (years)	55.5 (31–74)	8	64 (31–74)	5	54 (43–57)	3	0.79
Age first CVD event (years)	40 (28–52)	7	40 (28–52)	5	38 (30–46)	2	0.86
No. of CVD events per person (n)	2 (1–5)	8	2 (1–5)	5	2 (1,2)	3	>0.99
No. of women with IHD events, n (%)	7 (6.9)	102	5 (7.1)	70	2 (6.3)	32	>0.99
No. of women with stroke, n (%)	0 (0)	102	0 (0)	70	0 (0)	32	–
No. of women with other events[c], (%)	3 (2.9)	102	1 (1.4)	70	2 (6.3)	32	0.23
Birth and pregnancy							
Age mother at birth (years)	28.5 (3.9)	97	28.1 (4.1)	66	29.3 (3.4)	31	0.17
Gestational week	40 (33–42)	93	40 (33–42)	62	40 (35–42)	31	0.45
Premature birth[d], n (%)	5 (5.0)	100	4 (5.7)	70	1 (3.1)	32	>0.99
Birthweight (g)	3376 (493.5)	101	3400 (488.8)	69	3323 (507.3)	32	0.47
Appointment with physician specialized in FH during pregnancy, n (%)	18 (17.8)	101	9 (12.9)	70	9 (29.0)	31	0.05
Number of women who measured cholesterol during pregnancy, n (%)	37 (36.3)	102	23 (32.9)	70	14 (43.8)	32	0.29
Total cholesterol during pregnancy (mmol/L)	10.8 (4.5–17.0)	33	11.0 (4.5–17.0)	20	9.7 (4.5–14.0)	13	0.21
Time of cholesterol measure (gestational week)	20 (0–36)	28	20 (6–30)	16	20 (0–36)	12	0.72
Pregnancy complications							
No. of women with one or more complications, n (%)	8 (7.8)	102	4 (5.7)	70	4 (12.5)	32	0.26
Gestational diabetes, n (%)	3 (2.9)	102	3 (4.3)	70	0 (0)	32	0.55
Hypertension, n (%)	4 (3.9)	102	1 (1.4)	70	3 (9.4)	32	0.09
Preeclampsia, n (%)	3 (2.9)	102	2 (2.9)	70	1 (3.1)	32	>0.99
Other complications[e], n (%)	17 (16.7)	102	14 (20.0)	70	3 (9.4)	32	0.18
Breastfeeding (BF)							
No. of women who breastfed, n (%)	78 (76.5)	102	58 (82.9)	70	20 (62.5)	32	0.03
Length of BF (months)	7.1 (0–42)	74	8.5 (1–42)	54	3.6 (0–14)	20	<0.001
Statin use during part of or entire BF period, n (%)	8 (10.3)	78	8 (13.8)	58	0 (0)	20	0.11
Length of statin use during BF among statin-users (months)	6 (3–20)	7	6 (3–20)	7	0 (0)	0	–
Length of BF among statin-users (months)	9 (6–24)	8	9 (6–24)	8	0 (0)	0	–
Stopped BF earlier to restart statins, n (%)	17 (21.8)	78	12 (20.7)	58	5 (25.0)	20	0.76
Length of BF among those stopped earlier (months)	6 (1–12)	17	6 (1–12]	12	3 (2–12)	5	0.36

Data are presented as mean (SD) or median (min-max) for continuous variables and as frequencies (%) for categorical variables.
FH: familial hypercholesterolemia. BMI: body mass index. LDL-C: low-density lipoprotein cholesterol. HDL-C: high-density lipoprotein cholesterol. PCSK9: proprotein convertase subtilisin/kexin type 9. CVD: cardiovascular disease. IHD: ischemic heart disease. BF: breastfeeding.

[a] Total number of respondents to the question.

[b] Norway *versus* Netherlands. Independent samples *t*-test or Mann-Whitney *U* test for continuous variables, chi square test or Fishers exact test for categorical variables.

[c] Cardiac arrest, atrial fibrillation, heart failure, heart valve disease.

[d] Birth before gestational week 37.

[e] Self-reported, e.g. bleedings, hyperemesis gravidarum, one stillbirth, headache, pyelonephritis, edema, one vanishing twin syndrome.

considerable lost statin treatment time. We also found that FH women seem to breastfeed to a lesser extent than the general population, possibly due to a wish of restarting statin treatment after pregnancy.

4.2. Women with FH wish for more information on pregnancy and statins

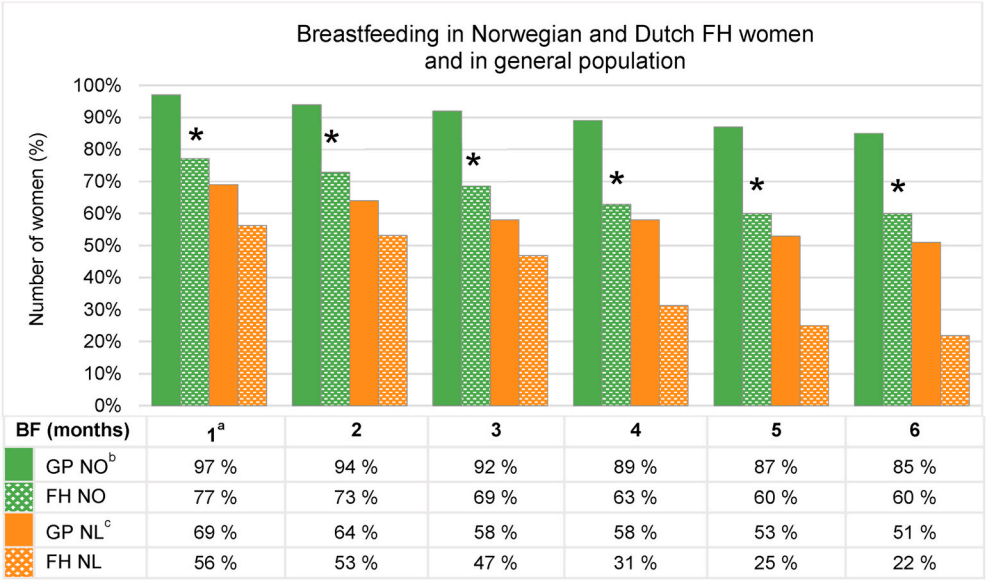
Thirty% of the FH women had used statins during pregnancy, however, most of them had discontinued statins within the first trimester, most likely when the pregnancy was discovered. Considering that approximately half of all pregnancies may be unplanned [14], statin exposure during the first trimester when pregnancy is not discovered is therefore not uncommon. Studies on the safety of statin use during pregnancy are inconclusive [15–17]. Botha et al. reported that statin exposure during pregnancy in homozygous FH women appeared to be safe and suggests that statin could be an alternative during pregnancy in high-risk FH patients [18]. No clear evidence for teratogenic effects on the fetus of maternal statin use during pregnancy has been found in other studies and reviews [15,19–21]. Although reassuring reports, the difficulties of assessing teratogenic risk has been pointed out and statins should be discontinued during pregnancy [22].

Despite clear guidelines on discontinuation of statins, three FH women in the present study had used statins during the entire pregnancy. In Norway, no specific clinic for following up pregnant FH women exists such as in diabetes care. Several of the FH women wished

Table 2
Statin use in relation to first pregnancy and total pregnancy-related off-statin periods in FH women.

	All	n[a]	Norway	n[a]	Netherlands	n[a]	p[b]
Statin used before first pregnancy	80 (78.4)	102	52 (74.3)	70	28 (87.5)	32	0.13
Statin discontinued before or during first pregnancy, n (%)	72 (90.0)	80	45 (86.5)	52	27 (96.4)	28	0.25
Time of discontinuation (months before pregnancy)	2 (0–34)	67	2 (0–34)	42	3 (0–18)	25	0.40
Advised to discontinue, n (%)	66 (82.5)	80	40 (76.9)	52	26 (92.9)	28	0.12
When pregnant, n (%)	21 (26.3)	80	12 (23.1)	52	9 (32.1)	28	0.38
When planning/trying to conceive, n (%)	37 (46.3)	80	21 (40.4)	52	16 (57.1)	28	0.15
Unsure, n (%)	8 (10.0)	80	7 (13.5)	52	1 (3.6)	28	0.25
Statin use during first pregnancy, n (%)	24 (30.0)	80	17 (32.7)	52	7 (25.0)	28	0.47
Length of statin use during pregnancy (weeks)	6 (2–39)	24	7 (2–39)	17	5 (3–10)	7	0.09
Statin use 0–12 weeks of pregnancy, n (%)	21 (87.5)	24	14 (82.4)	17	7 (100)	7	0.85
Statin use during entire pregnancy, n (%)	3 (12.5)	24	3 (17.6)	17	0 (0)	7	0.55
Statin start after first pregnancy, n (%)	60 (75.0)	80	35 (67.3)	52	25 (89.3)	28	0.03
Time of statin start (months after birth)	3.6 (0–14)	54	5 (0–13)	30	2.8 (0–14)	24	0.02
Total pregnancy-related off-statin periods							
Total length of pregnancy-related off-statin periods by one pregnancy (years)	1.3 (0–4.7)	80	1.3 (0–4.7)	52	1.3 (0.7–3.0)	28	0.99
Total length of pregnancy-related off-statin periods by all pregnancies (years)	2.3 (0–14.2)	80	2.0 (0–14.2)	52	2.6 (0.7–7.6)	28	0.13
Age at last birth	31.4 (4.3)	67	30.7 (4.0)	42	32.5 (4.7)	25	0.10
Length of statin treatment time up until last birth (years)	14.0 (5.2)	67	12.9 (5.6)	42	15.9 (4.0)	25	0.02
Lost statin treatment time due to pregnancy-related off-statin periods (%)	18.4 (0–100)	67	19.1 (0–100)	42	14.4 (4.5–50.0)	25	0.90

Data are presented as mean (SD) or median (min-max) for continuous variables and as frequencies (%) for categorical variables.
FH: familial hypercholesterolemia.
[a] Total number of respondents to the question.
[b] Norway *versus* Netherlands. Independent samples *t*-test or Mann-Whitney *U* test for continuous variables, chi square test or Fishers exact test for categorical variables.



BF (months)	1[a]	2	3	4	5	6
GP NO[b]	97 %	94 %	92 %	89 %	87 %	85 %
FH NO	77 %	73 %	69 %	63 %	60 %	60 %
GP NL[c]	69 %	64 %	58 %	58 %	53 %	51 %
FH NL	56 %	53 %	47 %	31 %	25 %	22 %

Fig. 2. Breastfeeding in Norwegian and Dutch FH women and in the general population.
[a] 58 (83%) Norwegian and 20 (63%) Dutch FH women reported to have breastfed the child, of whom 54 (77%) Norwegian and 18 (56%) Dutch women reported length of breastfeeding for one month or more. [b] Data from the Infant Cholesterol study 2019 (n = 627). [c] Data from Peiling melkvoeding van zuigelingen 2015. *$p < 0.001$ for GP NO *versus* FH NO (Chi Square test or Fishers Exact test).
FH: familial hypercholesterolemia. BF: breastfeeding. GP: general population. NO: Norway. NL: Netherlands.

for more information and advice on pregnancy and breastfeeding when having FH, and especially more knowledge among general practitioners. Primary health care and general practitioners are important arenas in addition to specialized lipid clinics for these women to receive information and advice regarding FH and statin use in relation to pregnancy and breastfeeding.

4.3. FH women seem to breastfeed to a lesser extent

More Norwegian FH women breastfed than Dutch FH women and they breastfed for a longer period. The Dutch FH women started statins earlier after birth and returned to work earlier than the Norwegian FH women, which may explain the shorter duration of breastfeeding among the Dutch women. Difference in length of maternity leave between the two countries most likely explains the difference in breastfeeding and statin restart. We also found that Norwegian FH women breastfed to a significantly lesser extent than the women in general in Norway. Moreover, 22% of the FH women who breastfed reported that they had stopped breastfeeding earlier than they wanted in order to restart statin treatment. The duration of breastfeeding in FH women may therefore be shorter due to a wish to restart lipid lowering treatment after delivery. The effect of breastfeeding in FH women explicitly is less known. A recent study suggests that being breastfed in infancy may protect against atherosclerosis development later in life [23]. Moreover, breastfeeding has been found to improve the lipid profile; the "reset hypothesis" and it is conceivable that this will apply to FH women similarly to healthy women [24]. Breastfeeding therefore has several benefits for both mother and child [25,26], however, balancing risks and benefits regarding restart of statin treatment after delivery highlights the need for more research on this topic.

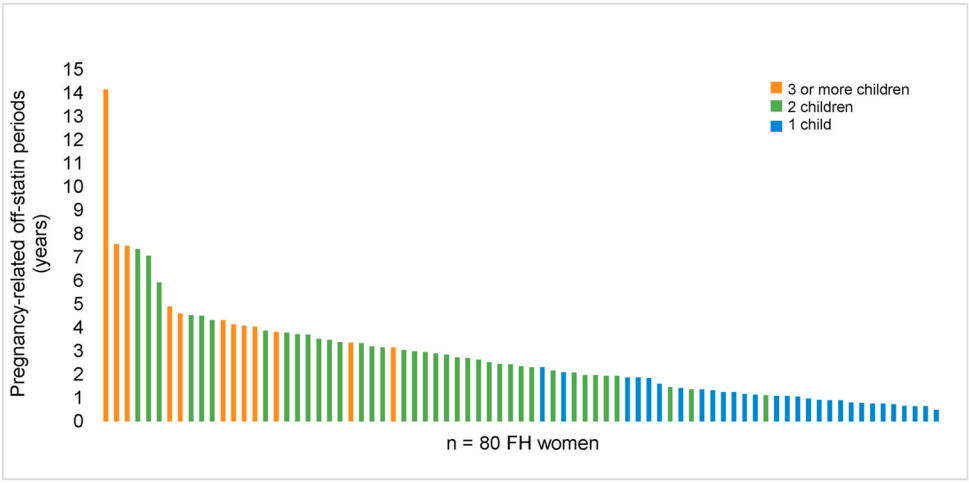


Fig. 3. Pregnancy-related off-statin periods in 80 FH women. Each bar represent one individual, colored by number of children per woman in orange (3 or more children), green (2 children) and blue (1 child).
FH: familial hypercholesterolemia. CVD: cardiovascular disease.

4.4. Statin use during breastfeeding is understudied

Eight (14%) Norwegian women and no Dutch women who breastfed their first child had used statins during breastfeeding. This difference may reflect that the Dutch women were mainly recruited through a specialized lipid clinic, while the Norwegian women were recruited through the national patient organization and therefore may have been followed up by general practitioners as well. More than 40% of all the FH women had been concerned that statin use during breastfeeding could affect the health of the child. There are few studies on breastfeeding and statins in humans. Two studies showed that rosuvastatin is transferred into breast milk, but that statin exposure for the infant seems to be low [27,28]. Others have suggested that the health benefits of breastfeeding while using rosuvastatin may outweigh the low risk of statin exposure for the child [29]. More and larger studies are needed to examine the risks *versus* benefits of statin use during breastfeeding.

4.5. Length of pregnancy-related off-statin period varies widely

The estimated total length of pregnancy-related off-statin periods in the FH women who had a median of two children was a little more than two years. This finding is in line with Kusters et al. who described two cases of FH women, where length of pregnancy-related off-statin periods was 15 and 30 months in two women who had given birth to one and two children, respectively [12], but shorter than the four years per child birth in 22 Norwegian FH patients reported by Arnesen et al. [11]. As most Norwegian women breastfeed for less than one year, the four years off-treatment per child reported by Arnesen et al. may have been due to longer off-treatment periods in planning pregnancy and after breastfeeding, or planning next pregnancy as most of the women had one child. The length of pregnancy-related off-statin periods by one pregnancy in our study ranged from 0 years to 4.7 years. These large inter-individual differences show that for some FH women, the period of lost statin treatment time is considerably even by one pregnancy and multiple pregnancies will increase this extensively as illustrated in Fig. 3. This is also reflected by longer duration of pregnancy-related off-statin periods in the post-menopausal women at median 3 years (*versus* 2.3 years in all women).

4.6. Childbearing represents a considerably lost statin treatment in FH

At mean age of 31 years at last pregnancy, the FH women had lost approximately 20% of their statin treatment time due to pregnancy and breastfeeding periods. The reproductive period poses a challenge for FH women regarding cholesterol management as these periods of interrupted treatment may increase the lifelong cholesterol burden, and further the cardiovascular risk. We have previously shown that there is no gender difference in age at first CVD event and death among Norwegian FH women and FH men [3], in contrast to the 10-year gender gap observed in the general population with later CVD onset in women than in men [30]. Moreover, among FH patients, the excess risk of coronary heart disease is higher in the youngest age groups (25–39 years) and young FH women seem to have an even higher excess risk than young FH men [31]. This was recently supported by data from the UK Simon Broome register, which also demonstrated that excess CVD morbidity was markedly higher in FH women than in FH men in the age group 30–50 years [32].

Eight women reported previous CVD, with the first event occurring at median age of 40 years. For five of these women, the first event was IHD and occurred in close proximity to pregnancy. To our knowledge, parity and CVD risk have not been examined in FH women. Two studies in the general population found highest risk of CVD in women who had five or more children [33,34], while other studies have not shown this association [35,36].

FH weighs differently on women through life than on men as the treatment in women is interrupted during pregnancy and breastfeeding periods [37]. As even a few years without statin treatment and increased cholesterol levels could impact the lifelong cholesterol burden, more knowledge on pregnancy in the FH population is needed. It should be considered whether female FH patients in childbearing age should receive more intensive lipid-lowering treatment from earlier age to compensate for an increased early accumulated cholesterol burden.

4.7. Future implications

Future guidelines on the management of FH women should take into account the exposure of increased cholesterol during pregnancy-related off-statin periods, and include recommendation on close follow-up of the FH women in these periods, preferably by a lipid specialist or FH specialist in order to reduce the duration of pregnancy-related off-statin periods to a minimum. As the periods before and after pregnancy are most susceptible to be extended in time, these periods should especially be discussed. Until further research on the safety of statins is available, only bile acid sequestrants and LDL apheresis can be considered during pregnancy [5]. The off-statin periods during pregnancy and breastfeeding may also be an opportunity for FH women to benefit even

further from a healthy diet and perhaps counterbalance some of the cholesterol increase in these periods [38,39].

Two recent placebo-controlled trials on pravastatin given to women with pre-eclampsia in the second and third trimesters have shown promising results, with no adverse effects of pravastatin use in the last part of pregnancy [40,41]. Further studies on the safety of statin use during pregnancy are needed to explore the possibility of statin use for some time during pregnancy. If shown to be safe, early statin restart could reduce the length of pregnancy-related off-statin periods considerably.

4.8. Strengths and limitations of the study

Limitations of the study are that using self-reported data on previous pregnancies may be subject to over- and underreporting and recall bias. Maternal recall of prescription medication use during pregnancy in a self-administered questionnaire has been found to be moderate to poor [42]. Underreporting could therefore have occurred in the present study. Moreover, as most of the FH women were recruited through patient organizations and specialized lipid clinics, these women may have higher awareness of FH and effects of high cholesterol levels than the general FH population, potentially affecting the results on reported off-statin time and concerns. Another limitation is lack of validation of the questionnaire. The questionnaire was prepared based on the aims of the study, as a similar survey among FH women has not previously been conducted. The small sample size is also a limitation, as it is not large enough to make definite conclusions on the topic. We also emphasize the cross-sectional study design as a limitation, as it cannot conclude on the implications of off-statin periods in relation to cardiovascular disease.

Another limitation is lack of questions regarding other lipid lowering treatments than statins during pregnancy and breastfeeding, such as ezetimibe, resins and PCSK9-inhibitors. These treatment options were only questioned on current use and use prior to each of the pregnancies to limit the amount of questions to answer. Statin was the main focus of the study as this is the most commonly used lipid lowering agent in the treatment of FH. Duration of pregnancy-related off-statin time was estimated by summarizing separately reported length of statin discontinuation before, during and after pregnancy. Other factors contributing to off-statin time were therefore not accounted for, such as prolonged periods of trying to conceive or miscarriages. Strength of the study is that we used an anonymous questionnaire, which may have increased the response rate and true reporting.

In conclusion, FH women of childbearing age lose considerably statin treatment time in relation to pregnancy, planning of pregnancy and breastfeeding. Whether these periods of interrupted treatment increase the cardiovascular risk in FH women and may contribute to explain the lack of gender difference in age at first CVD event in the FH population remains to be explored.

Financial support

This work was supported by the University of Oslo, Oslo; the Norwegian National Advisory Unit on FH, Oslo University Hospital, Oslo, Norway; the Throne-Holst Foundation for Nutrition Research, Oslo, Norway.

Author contributions

Conceived and designed the study: MK, MPB, KR, JRvL, KBH. Collected the data: MK, AH, EV, CB, TS, JRvL, KBH. Performed the analyses: MK, MPB, KR, JRvL, KBH. Drafted the paper: MK, MPB, KBH. All authors contributed to the interpretation of the data and critically reviewed the paper. MK, MPB, KR, JRvL and KBH hold primary responsibility for the content.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Bogsrud has received research grants and/or personal fees from Amgen and Sanofi, none of which are related to the content of this manuscript. Dr. Retterstøl has received research grants and/or personal fees from Akcea, Amgen, Mills, Sanofi and Sunnovion, none of which are related to the content of this manuscript. MD. Berge has received research grants and/or personal fees from Amgen, Sanofi, MSD and Boehringer Ingelheim, none of which are related to the content of this manuscript. Dr. Holven has received research grants and/or personal fees from TINE, Mills, Amgen, Sanofi and Olympic Seafood, none of which are related to the content of this manuscript. Msc. Klevmoen, Dr. Svilaas, MD. Vesterbekkmo, Dr. Hovland and Dr. Roeters van Lennep have nothing to disclose.

Acknowledgements

We thank all the FH women in Norway and the Netherlands who participated in the study; FH Norway by Margaretha Hamrin for distribution of invitations; and Linn Øyri for sharing data from the Infant cholesterol study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.09.003.

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