RESEARCH

Premature menopause and autoimmune primary ovarian insufficiency in two international multi-center cohorts

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Abstract

Objective: To investigate markers of premature menopause (<40 years) and specifically the prevalence of autoimmune primary ovarian insufficiency (POI) in European women.
Design: Postmenopausal women were categorized according to age at menopause and self-reported reason for menopause in a cross-sectional analysis of 6870 women.
Methods: Variables associated with the timing of menopause and hormone measurements of 17β-estradiol and follicle-stimulating hormone were explored using multivariable logistic regression analysis. Specific immunoprecipitating assays of steroidogenic autoantibodies against 21-hydroxylase (21-OH), side-chain cleavage

Key Words

- premature ovarian insufficiency
- premature ovarian failure
- premature menopause
- primary ovarian insufficiency
- autoimmune

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enzyme (anti-SCC) and 17alpha-hydroxylase (17 OH), as well as NACHT leucine-rich-repeat protein 5 were used to identify women with likely autoimmune POI.
Results: Premature menopause was identified in 2.8% of women, and these women had higher frequencies of nulliparity (37.4% vs 19.7%), obesity (28.7% vs 21.4%), osteoporosis (17.1% vs 11.6%), hormone replacement therapy (59.1% vs 36.9%) and never smokers (60.1% vs 50.9%) ($P < 0.05$), compared to women with menopause ≥40 years. Iatrogenic causes were found in 91 (47%) and non-ovarian causes in 27 (14%) women, while 77 (39%) women were classified as POI of unknown cause, resulting in a 1.1% prevalence of idiopathic POI. After adjustments nulliparity was the only variable significantly associated with POI (odds ratio 2.46; 95% CI 1.63–3.42). Based on the presence of autoantibodies against 21 OH and SCC, 4.5% of POI cases were of likely autoimmune origin.
Conclusion: Idiopathic POI affects 1.1% of all women and almost half of the women with premature menopause. Autoimmunity explains 4.5% of these cases judged by positive steroidogenic autoantibodies.

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Introduction

Menopause is defined as the permanent cessation of menstrual periods and usually occurs around 50 years of age (1). Timing of menopause is influenced by genetics in addition to environmental and lifestyle factors including smoking habits, nutritional status and general health (2, 3, 4, 5, 6, 7, 8).

Menopause before age 40 years is considered premature and may be caused by a defect in any part of the hypothalamic–pituitary–ovarian axis, with subsequent hypoestrogenism. If the deficiency is located in the ovary, it is referred to as primary ovarian insufficiency (POI), characterized by low estradiol levels promoting high follicle-stimulating hormone (FSH) levels, due to lack of negative feedback (9). Early estrogen deficiency has negative long-term health consequences, including infertility, osteoporosis, declined neurocognitive function, increased risk of cardiovascular disease and total mortality (10, 11, 12, 13, 14, 15, 16). Hormone replacement therapy (HRT) is recommended for these women (17, 18).

The prevalence of POI in the general population is estimated to 1–3% (19, 20, 21, 22, 23). Important causes of POI include iatrogenic treatment (surgical, chemotherapy or radiation), genetic, infectious or autoimmune etiology (17, 18). However, in the majority of cases the cause remains unknown (9). According to European guidelines diagnostic autoimmune workup for POI should include measurements of ovarian associated autoantibodies (17). Autoantibodies against the steroidogenic cell enzymes have shown consistent association with autoimmune POI, including autoantibodies against 21-hydroxylase (21-OH), side-chain cleavage enzyme (anti-SCC) and 17alpha-hydroxylase (17 OH), as well as NACHT leucine-rich-repeat protein 5 (NALP5), which are highly expressed in the ovaries (24, 25, 26).

Previously reported prevalence of autoimmune POI varies greatly (0–30%), the broad estimate probably reflecting heterogenic study populations as well as use of variable autoantibody assays (27, 28, 29, 30). Clinically women with autoimmune POI have a more fluctuating ovarian function during the first years after onset and follicular activity seems to be intact initially as judged by higher anti-Müllerian hormone levels compared to other forms of POI. Thus, early diagnosis of autoimmune POI could improve fertility possibilities (31, 32). Identifying these women using specific immunoprecipitating assays of steroidogenic cell autoantibodies is possible but has not to our knowledge been done in large population-based cohorts. Here, we describe potential markers of premature menopause and estimate the prevalence of autoimmune POI in two large multi-center international cohorts providing menopausal age and information on health-, lifestyle factors and reproductive hormone levels.

Methods

Study population

In this retrospective cross-sectional study, the study population consisted of the second follow-up of the European Community Respiratory Health Survey carried out in 2010–2012 (ECRHS III) and The Respiratory Health in Northern Europe, Spain and Australia generation study carried out in 2013–2016 (www.ecrhs.org and www.rhinessa.net). The latter comprises the maternal

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or paternal offspring of the initial participants of the former and potential co-dependence was considered in the subsequent analyses. Both studies collected data in the same standardized way, using an interview-led questionnaire on anthropometrics, reproductive health- and lifestyle factors. In addition, both cohorts provided serum samples for analyses of reproductive hormones and autoantibodies.

Data weres obtained from 6870 women from 15 study centers in eight European countries (Spain, France, Germany, Sweden, Denmark, Iceland, Estonia and Norway). The women were born between 1945 and 1998 and the mean age (S.D.) at inclusion was 40 (13.7) years (median 39 (28–52) years). A flow chart describing the study population is presented in Fig. 1.

Ethical approval was obtained from the appropriate ethics committees of each study center, and all participants provided their informed written consent.

Variables

Women were defined as postmenopausal if they had not had a menstrual period within the last 12 months prior to answering the questionnaire. Women who reported using HRT were included even if they reported having menstrual periods within the last 12 months. Women whose date of last menstrual period was missing (n = 263), who were using hormonal contraception (n = 1637) or who were either pregnant or breastfeeding (n = 374), were excluded.

The main dependent variables, prevalence of premature menopause (<40 years) and POI, were based on self-reported age and reason for menopause. Four categories of postmenopausal women were created based on the response:

(1) Idiopathic POI is acknowledged as premature menopause of unknown reason.
(2) Iatrogenic-induced menopause (bilateral oophorectomy and/or hysterectomy, after cancer treatment).
(3) Menopause due to non-ovarian reasons (eating disorder/underweight, pituitary failure, disorder of uterus).
(4) Menopause ≥40 years.

Our independent variables consisted of potential predictors of menopausal timing such as age at menarche, parity, current and former smoking (for ≥1 year), ever use of oral contraceptives (OC's), in addition to information on other illnesses and potential consequences of premature menopause including eating disorders, cancer and osteoporosis and use of HRT. Variable details are presented in Supplementary Table 1 (see section on supplementary materials given at the end of this article).

Reported height and weight were used to calculate BMI (kg/m^2) and participants were classified as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) (33). Because of the low number of underweight women (n = 15), these were not analyzed separately.

Hormone samples

Hormone measurements were available for 1134 postmenopausal women, of whom 994 did not use HRT. FSH and luteinizing hormone (LH), were analyzed using

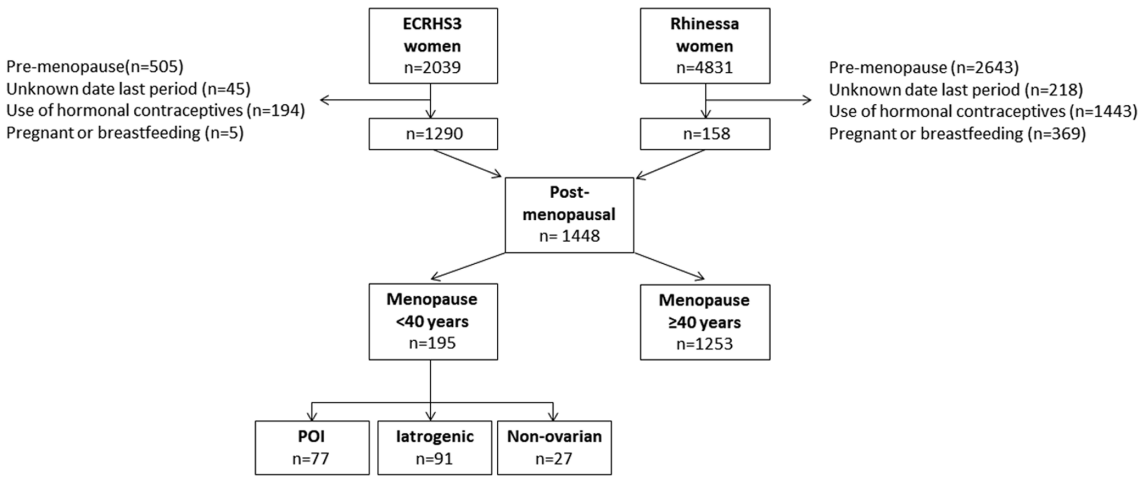

Figure 1
Study design. European Community Respiratory Health Survey (ECRHS3S). The Respiratory Health in Northern Europe, Spain and Australia (Rhinessa). Idiopathic premature ovarian insufficiency (POI).

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ELISAs (Demeditec Diagnostics, Kiel, Germany), and the steroid hormones (17β-estradiol, estrone, progesterone, testosterone and DHEA-S) were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the Core Facility for Metabolomics (University of Bergen, Norway, 2017) (34). Concentrations below the lower limit of quantification (LLQ) for 17β-estradiol (3.6 pmol/L), estrone (2.1 pmol/L), testosterone (106 pmol/L), DHEA-S (0.21 μmol/L), FSH (5.0 IU/L), LH (10.0 IU/L) and sex hormone-binding globulin (SHBG) (4.0 nmol/L) were included as LLQ/2 (32).

Autoantibodies

Serum samples from 66 women with POI and a control group of 64 age-matched women with iatrogenic premature menopause (bilateral ovariectomized) were analyzed for the following autoantibodies: 21 OH, SCC and 17 OH. NALP-5. All autoantibody assays were performed in the laboratory at the Faculty of Medicine (University of Bergen, Norway) using radio-binding ligand assays (35). Positive cut-offs were calculated using positive and negative controls with index thresholds of >57, >200, >102 and >65 for 21 OH, SCC, 17 OH and NALP-5, respectively. Positivity for ovarian associated autoantibodies was perceived as likely autoimmune POI.

Statistical analyses

To determine potential predictors and consequences of premature menopause and POI, clinical variables and hormonal data were compared to women with menopause ≥40 years. Continuous and normally distributed variables were presented as mean and S.D., and t-tests were used to evaluate between-group difference. Continuous variables with a skewed distribution were presented as median and interquartile range (IQR), and Mann–Whitney *U* test was used to evaluate between-group difference. Categorical variables were presented as frequencies (*n*) and/or percentages (%), and chi-square test (with Yates continuity correction) was used to evaluate between-group differences.

The variables associated with POI were first investigated with univariable logistic regression. Thereafter, relevant predictors were included in a multivariable logistic regression analysis. Statistical significance was set to a *P* value <0.05. Cohort co-dependency (family clusters) was examined by generalized estimate equations (GEE) and separate analyses of the ECRHS 3 cohort separately.

Differences in hormone levels were investigated using multivariable logistic and linear regression analyses controlling for the time since menopause and BMI. A two-way between-group ANOVA was used to explore the difference between groups. Due to skewed distributions, hormone values were log10-transformed for all comparative analysis, and then back-transformed for ease of interpretation.

Results

In this population of women aged 18–66 years, 21.1% (1448/6870) were postmenopausal. The mean age at menopause was 47 (7.7) years, median age 49 (IQR 44–52) years and normally distributed though slightly skewed toward a younger age (Fig. 2). There was no difference in the median age of menopause between European regions ($P = 0.168$).

Among women with menopause ≥40 years, 79% (988/1253) reported spontaneous reasons, 21% (260/1253) stated surgical reasons and <1% (5/1253)) non-ovarian reasons for menopause.

Premature menopause

The prevalence of premature menopause was 2.8% (195/6870. Among the women with premature menopause, 47% (91/195) had iatrogenic reasons, of whom 81 reported previous surgery and 10 cancer treatment. Non-ovarian reasons were identified in 14% (27/195), including 11 women with hypothalamic amenorrhea, 12 with eating disorders and 4 with pituitary failure. The etiology was unknown in 39% (77/195) of women with premature menopause. Taken together, the prevalence of idiopathic POI was 1.1% (77/6870).

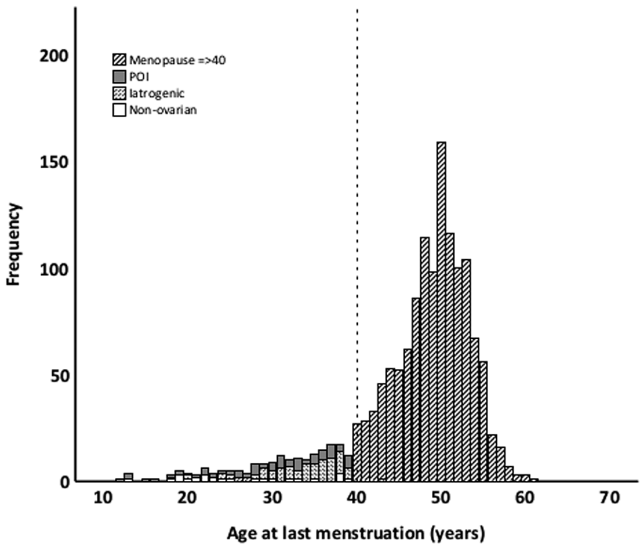

Figure 2
Timing and etiology of menopause.

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Table 1 Characteristics of reproductive and lifestyle factors by timing and reason for menopause. Continuous data are given as mean and s.d. and categorical data are given as percent (%).

	Menopause < 40 years (*n* =195)			**Menopause ≥40 years** (*n* =1253)	***P*-value Menopause <40 vs Menopause ≥40 years**
	POI (*n* =77)	Iatrogenic (*n* =91)	Non-ovarian (*n* =27)		
Age menopause, (years)	28.7 (7.3)	33.2 (4.9)	26.5 (7.7)	49.3 (4.1)	<0.001[a]
Age menarche (years)	12.9 (1.7)[c]	12.7 (1.6)	12.9 (1.9)	12.9 (1.5)	NS
Nulliparity	37.2	33.0	53.8	19.7	<0.001[b]
BMI, (kg/m^2)	26.75 (4.80)	27.69 (5.37)	24.80 (7.41)	26.36 (5.15)	NS
BMI categories:					
<18.5	0	0	27.3	1.2	NS
18.5–24.9	35.7	31.8	37.5	44.7	0.046[b]
25.0–29.9	35.7	38.6	10.2	32.8	NS
≥30.0	28.6	29.5	25.0	21.4	0.022[b]
Smoking status:					
Current	15.8	12.0	12.5	16.8	NS
Former	27.4	26.8	24.0	32.3	NS
Never	56.7	61.2	63.5	50.9	0.018[b]
Treated for cancer	7.6	9.9	7.7	8.4	NS
Osteoporosis	16.0	12.2	37.5	11.6	0.034[b]
Oral contraceptive use, ever	77.2	81.3	73.1	75.0	NS
HRT use, ever	60.8	58.2	57.7	36.9	<0.001[b]

[a]T-test; [b]Chi-square tests; [c]Six women reported primary amenorrhea.
NS, non-significant.

We found some differences in reproductive and lifestyle characteristics related to timing for menopause (Table 1). Women with premature menopause had a higher frequency of nulliparity (37.4% vs 19.7%, $P < 0.001$), obesity (28.7% vs 21.4%, $P = 0.002$), osteoporosis (17.1% vs 11.6%, $P = 0.034$), use of HRT (59.1% vs 36.9%, $P < 0.001$), never smokers (60.1% vs 50.9%, $P = 0.018$), and fewer women deviating from normal BMI (34.0% vs 44.7%, $P = 0.046$), compared to menopause ≥40 years of age.

We identified 20 family clusters (mother and daughter included in the study population), however, results of the applied GEE did not indicate altered results. Analysis restricted to ECRHS3 women showed very similar results as our main analysis, despite a higher frequency of cancer treatment among women with premature menopause (22.4 vs 8.6%, $P = 0.005$), and more former smokers (56.6 vs 54.2, $P = 0.935$) as well as lower HRT use (21.5 vs 17.7%, $P = 0.493$) in both groups.

Hormone levels did not differ between women with premature menopause and menopause ≥40 years adjusting for years since menopause and BMI (Table 2). The 17β-estradiol levels decreased with years since the last menstruation in all women (regression coefficient $\beta = -0.213$, $P < 0.001$), while no significant association was found for FSH. Women with higher BMI had higher levels of 17β-estradiol (regression coefficient $\beta = 0.127$, $P < 0.001$), and correspondingly decreased FSH levels (regression coefficient $\beta = -1.148$, $P < 0.001$) (Fig. 3).

Table 2 Hormone levels in premature menopause compared to menopause ≥ 40 years[b]. Hormone levels reported as median and interquartile range (IQR).

	Menopause <40 years (*n* =66)	**Menopause ≥40 years** (*n* =928)	***P*-value[a]**
FSH (IU/L)	102.5 (77.9–155.3)	125.9 (88.8–171.7)	0.222
LH (IU/L)	24.3 (13.5–31.2)	27.4 (19.7–36.6)	0.992
Estradiol (pmol/L)	13.3 (7.9–24.5)	11.6 (6.2–22.4)	0.395
Estrone (pmol/L)	64.9 (48.4–105.0)	69.1 (47.9–101.7)	0.982
Progesterone (nmol/L)	<0.21	<0.21	0.521
Testosterone (nmol/L)	0.57 (0.35–0.68)	0.53 (0.37–0.73)	0.338
DHEAS (umol/L)	1.86 (1.06–3.41)	1.16 (1.01–2.47)	0.790
SHBG (nmol/L)	65.4 (37.6–108.8)	65.4 (40.5–99.5)	0.911

[a]Mann–Whitney *U* test; [b]Women currently using OC or HRT and pregnant women were excluded.

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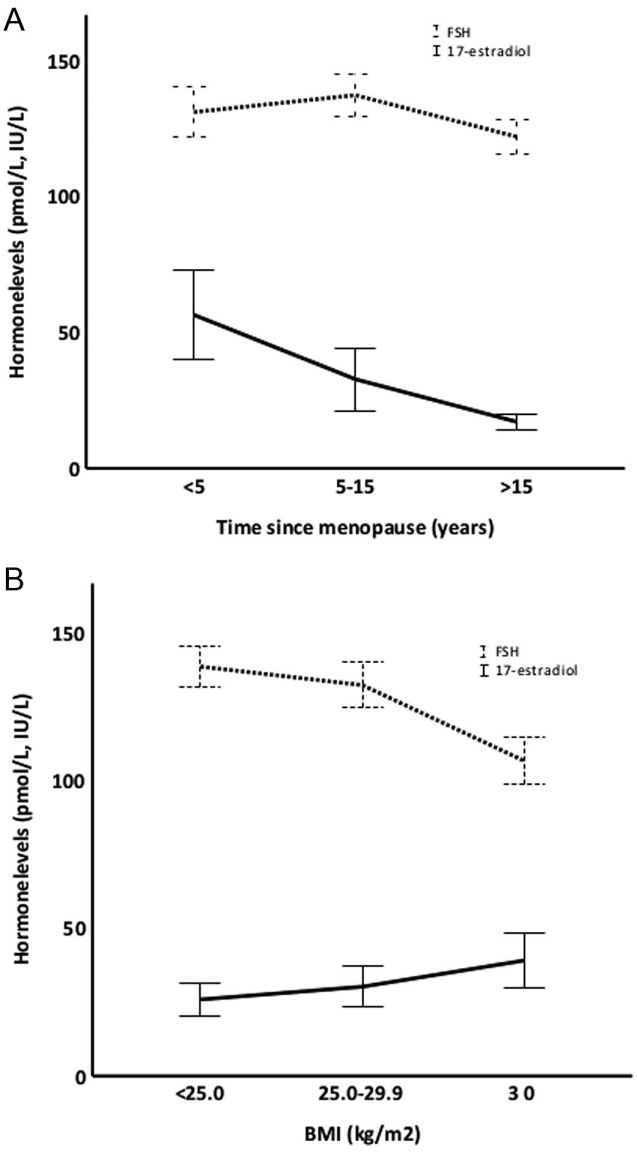

Figure 3
17β-estradiol and follicle-stimulating hormone (FSH) by (A) time since menopause and (B) BMI in all post-menopausal women (n = 1134). Hormone levels reported in mean and 95% CI.

Primary ovarian insufficiency

Nulliparity, obesity and smoking history were all independently associated with POI compared to women with menopause ≥40 years. However, after adjusting for BMI, smoking and age as well as study affiliation in a multivariable analysis, only nulliparity was statistically significantly associated with POI (adOR 2.46; 95% CI 1.63–3.42). Normal weight and never smoking showed a tendency toward being protective of POI (Fig. 4).

There were also some differences in reproductive and lifestyle characteristics related to the reason for premature

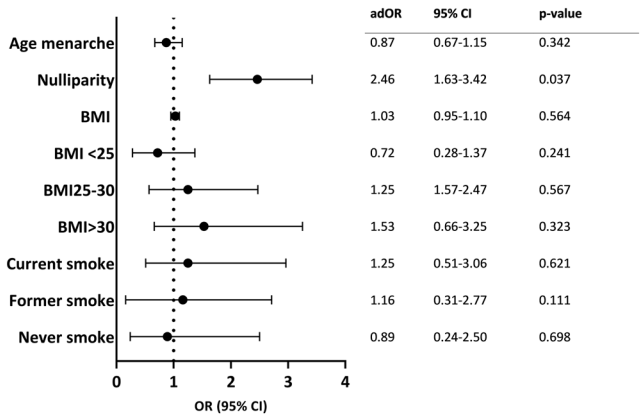

Figure 4
Multivariable logistic regression of reproductive and lifestyle factors associated with idiopathic primary ovarian insufficiency (POI) compared to menopause ≥40 years. Odds ratio adjusted for BMI, smoking, age and study affiliation (adOR) and 95% CI. Excluding women with surgically induced menopause ≥40 years (n = 261) or women with menopause at 40–44 years (n = 361) did not alter the results of the multivariable logistic regression analysis.

menopause (Table 1). We found that women with POI and women with iatrogenic reasons for premature menopause had similar characteristics, while women with non-ovarian reasons reported menopause at a slightly younger age, had a lower weight and a higher frequency of nulliparity and osteoporosis ($P < 0.05$).

Women with POI and iatrogenic reasons for premature menopause had comparable hormonal patterns with low levels of 17β-estradiol (median 15.6 (9.2–28.0) and 14.7 (9.0–27.2)) and corresponding high levels of FSH (median 111.6 (90.0–122.0) and 102.0 (87.3–119.1)), while women with

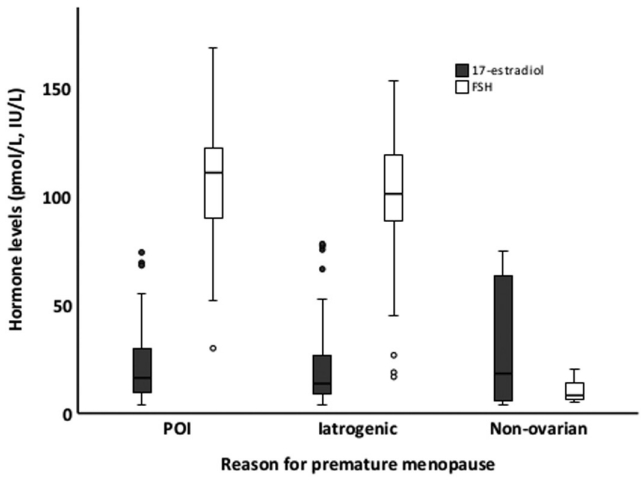

Figure 5
Hormonal patterns of 17β-estradiol and follicle-stimulating hormone (FSH) in three groups of women with different reasons for premature menopause. Idiopathic primary ovarian insufficiency (POI), iatrogenic and non-ovarian premature menopause.

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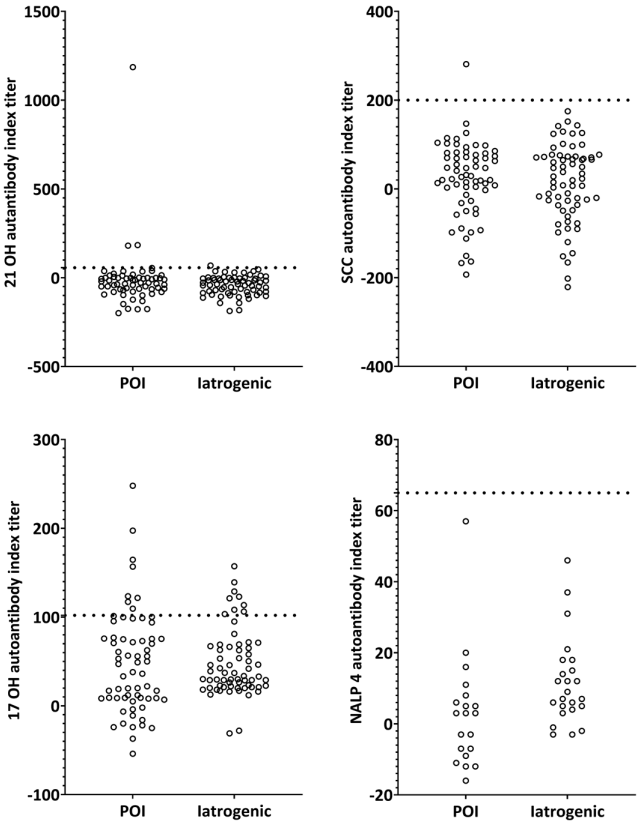

Figure 6
Autoantibody index levels in 66 women with idiopathic primary ovarian insufficiency (POI) and a control group of 64 age-matched women with iatrogenic premature menopause (bilateral ovariectomized). Dotted line shows the cut-off threshold for positive test in this radio-binding ligand assay.

non-ovarian reason for premature menopause had similar 17β-estradiol levels (median 18.3 (6.2–63.2)) but significantly lower FSH levels (median 11.1 (9.7–16.9)) ($P = 0.016$) (Fig. 5).

Autoimmune POI

In total, 4.5% (3/66) of POI cases were considered to have autoimmune POI based on presence of autoantibodies (Fig. 6). Positive 21 OH autoantibodies were found in three women with POI. One of these women also had positive SCC autoantibodies. Autoantibodies against 17 OH were abundant in both groups. None had positive NALP 5 autoantibodies. Case 1 had POI from age 28, positive autoantibodies against 21 OH (titer 181.0 IU/mL) and 17 OH (titer 157.25 IU/mL), known hypothyroidism and coeliac disease. Case 2 had POI from age 36, positive autoantibodies against 21 OH autoantibodies (titer 1186.0 IU/mL) and SCC (281 IU/mL), known hypothyroidism, hypertension, and scoliosis. Case 3 had POI from age 35 and positive 21 OH autoantibodies (titer 184.0 IU/mL). There was no information about intercurrent disease in general or adrenal insufficiency in particular regarding case 3. Hormonally these women did not differ from other women with POI.

Discussion

We found immunological markers suggesting an autoimmune etiology in 4.5% of women with POI, using specific autoantibody assays. We identified several reproductive and lifestyle-related factors associated with the timing of menopause, but no determinant that could distinguish autoimmune POI from other causes of premature menopause.

Finding the true prevalence of premature menopause and POI is challenging because of heterogenic etiology, terminology and diagnostic criteria as well as variation in study designs and statistical methods (19). Use of OC's can also disguise symptoms and delay diagnosis. We found a prevalence of premature menopause and POI that was in coherence with previous studies (19, 20, 21, 22, 23, 36). One in four of all postmenopausal women in our study reported surgically induced menopause and was even more common among women with premature menopause (47%). Although the frequency of surgically induced menopause varies across populations, in accordance with Dratva *et al.*, the determinants of age at surgically induced menopause, did not differ from other causes of menopause in our study (5).

The association between nulliparity and premature menopause is not unexpected (3, 37, 38). It was also the only variable directly associated with POI in our study. Infertility is an inevitable result of menopause but reproductive decline in the years preceding menopause is well known (39). Since the majority of women with premature menopause in this study had their final menstrual period between age 27 and 37 years, there was potentially time to conceive prior to the diagnosis indicating that infertility can be both a predictor and a consequence of early menopause. However, other reasons for lower fertility rates in women with premature menopause and POI, such as concomitant disease or a secular trend of lower birth rates, cannot be excluded.

We found that women with normal weight were less likely to report premature menopause than women who were overweight or obese. A U-shaped relationship between BMI and the risk of earlier menopause has been shown in previous studies (7, 8, 40). Underweight associated with malnutrition, over-exercising and chronic illness can cause

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premature menopause due to hypothalamic-pituitary deficiency (8, 41, 42, 43). Because of a relatively low number of underweight women in this study we did not have enough power to address this issue. Weight increases with age in a majority of women, but evidence regarding the association between BMI and timing of menopause has been inconsistent and remains controversial (2, 7, 8, 21, 43). Longitudinal studies have reported that weight gain during midlife is associated with a sedentary lifestyle and aging itself, not menopausal status (44). An increase in BMI with age is however accompanied by an adverse change of body composition that manifests during the first years of menopause with estrogen depletion resulting in a decline of lean body mass and increase in adipose abdominal fat (45).

Smoking is the predictive factor most consistently associated with younger age at menopause (2, 3, 6, 7). We could not confirm a direct association with current or former smoking. This could be due to fewer smokers among the younger birth cohorts in this population (5).

Use of HRT was more common among women with premature menopause (59.1%), but in total less than half of the women in this study had ever used HRT. According to European guidelines, HRT is indicated both for the treatment of symptoms related to hypoestrogenism and to prevent complications, that is osteoporosis (17). Variations in national recommendations and culture are factors that may influence use. With regards to the timing of the data collection in this study, the lower usage of HRT in the ECRHS3 cohort could be attributed to the debate following publications at the beginning of this millennium initially reporting an increased risk of breast cancer and venous thromboembolism in HRT users, resulting in a marked decrease in prescription the following years (46, 47).

We found no evidence that age at menarche is a predictor of the timing of menopause. It seems intriguing that these two events in a woman's reproductive life could be related. However, no consistent association between ages at menarche and menopause has been observed in epidemiological studies (2, 48, 49, 50, 51). This is further supported by newer genetic data revealing limited overlap in genomic regions associated with the timing of the two events (52, 53).

Major alterations in reproductive hormones take place through the menopausal transition and years following menopause (54, 55). Our results are consistent with others in finding that postmenopausal women with high BMI and shortest time since menopause had the highest levels of 17β-estradiol (45, 56). This was most pronounced in women with premature menopause. Our results suggest that BMI as well as years since the last menstrual period and age should be considered when interpreting hormone levels of postmenopausal women, although it is essential to be aware of the limitations of group differences when applied to individual patients.

We also demonstrated how hormone tests can be useful in confirming POI as compared to non-ovarian reasons for premature menopause in non-clinical settings. Women with idiopathic POI and iatrogenic premature menopause had high levels of FSH and low levels of 17β-estradiol, while women with non-ovarian reasons had low levels of both FSH and 17β-estradiol, pointing toward a pituitary–hypothalamic deficiency. In previous studies, FSH and 17β-estradiol concentrations have shown good confirmation with the classification of causes of menopause based on questionnaires (44).

We found ovarian-associated steroidogenic cell autoantibodies in 4.5% of women with idiopathic POI, pointing to a prevalence of autoimmune POI in the lower range of what has previously been reported (27, 28, 29, 30). This could be due to the unselected study population, supporting the diagnosis of POI on self-reported data, not clinical evaluation. However, it could also be due to use of specific immunoprecipitating assays in the present study, whereas most previous studies have applied sensitive but less specific indirect immunofluorescence methods for autoantibody detection (17, 18, 27, 30, 57, 58).

Multiple ovarian autoantigens have been proposed as possible targets for autoimmune POI. However, autoantibodies toward the steroidogenic cell enzymes have specific diagnostic value for autoimmune disease in the ovary as well as the adrenal gland. Primary adrenal insufficiency affects approximately 2–3% of women with spontaneous POI, a 300-fold increase compared with the general population (26, 28, 30). We found that positive 21 OH autoantibodies were significantly more common in POI women, compared to the general population, confirming its role as a potential marker for autoimmune POI. In our study, the women with positive 21 OH autoantibodies did not have clinical or biochemical markers of AD. This does however not exclude the diagnosis as POI can develop both before and after the onset of AD. Women with positive steroidogenic cell autoantibodies should therefore be assessed with adrenal function tests (17, 59). In contrast to autoantibodies against 21 OH and SCC, we showed that autoantibodies against 17 OH and NALP-5 did not differ between the groups and thus seem to be more unspecific markers in this setting and unsuitable for screening.

Autoimmune POI represents a continuum from impaired ovarian function to complete ovarian failure

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and the disease is often diagnosed at an end stage (30). Autoantibody detection could be hampered by the timing of testing in relation to the disease stage. At the final stages of an autoimmune disease, lower titers of autoantibodies are expected due to antigen elimination, however, autoantibodies against 21 OH have proven remarkably stable over time (60).

A major strength of this study was access to data from populations across different European regions, suggesting that our results are not biased by varying cultures and environmental factors. Another major strength of our analysis is the high sensitivity of the LC-MS/MS assay used for hormone measurements. However, some limitations need to be acknowledged. As our study population consisted predominantly of Caucasian women, our findings might not be generalizable to all women. Previous studies have shown that there are ethnic differences in the timing of menopause as well as levels of reproductive hormones (36, 61).

The cross-sectional design allows assessment of association but not demonstration of causality. Our study population is heterogenic with regards to postmenopausal chronology complicating interpretation of the influence of lifestyle factors and several exposures may mask the connection, including interactions between genetic and environmental influences. However, there was no indication that present family clusters altered our results. In addition, universally standardized autoantibody assays are missing. Retrospectively reported age at menopause can potentially suffer from recall bias. Misclassification is however less likely to occur among women with premature menopause as studies suggest that unusual events (such as menopause before normal age) are easier to remember (62). Several studies have also demonstrated high accuracy and reliability of self-reported age of menopause (63, 64).

In conclusion, POI affects 1.1% of all women and almost half of the women with premature menopause. Autoimmunity explains 4.5% of these cases as judged by the presence of autoantibodies. Nulliparity is the variable most strongly associated with POI. Evaluation of hypothalamic–pituitary–gonadal axis hormonal levels are useful in distinguishing different causes of premature menopause in cross-sectional studies. Future studies on the subject should include longitudinal data on hormone and autoantibody levels.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0024.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Elinor Chelsom Vogt did statistical analysis and manuscript drafting. Kai Triebner and Marianne Øksnes participated equally in the methodology, statistical analysis and reviewal of the manuscript. Francisco Gómez Real took the initiative for the use of this dataset and has actively discussed and reviewed the study design and manuscript. The remainder authors participated in the study design, recruitment of participants and data collection as well as constructive contributions in reviewal of the manuscript. K Triebner and M Øksnes contributed equally to this study.

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