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Clinical Research Article

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Primary Ovarian Insufficiency in Women With Addison's Disease

Elinor C. Vogt,[1,2,3] Lars Breivik,[1,2] Ellen C. Røyrvik,[1,2] Marianne Grytaas,[2,3] Eystein S. Husebye,[1,2,3,4] and Marianne Øksnes[1,2,3,5]

[1]Department of Clinical Science, University of Bergen, Bergen, Norway; [2]K.G. Jebsen Center for Autoimmune Disorders, University of Bergen, Bergen, Norway; [3]Department of Medicine, Haukeland University Hospital, Bergen, Norway; [4]Department of Medicine (Solna), Karolinska Institutet, Stockholm, Sweden; and [5]Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden

ORCiD number: 0000-0002-7886-2976 (E. S. Husebye).

Abbreviations: 17OH, 17-alpha hydroxylase; 21OH, 21 hydroxylase; AAD, autoimmune Addison's disease; ATC, Anatomical Therapeutic Chemical; FSH, follicle-stimulating hormone; GAD, glutamic acid decarboxylase; HRT, hormone replacement therapy; MAF, minor allele frequency; NALP-5, NACHT leucine-rich-repeat protein 5; NorPD, Norwegian Prescription Database; OER, observed to expected ratio; ROAS, National Registry of Organ-Specific Autoimmune Diseases; SCC, side chain cleavage enzyme; SNP, single nucleotide polymorphism; POI, primary ovarian insufficiency; TPO, thyroid peroxidase.

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Abstract

Context: Primary ovarian insufficiency (POI) is defined by menopause before 40 years of age. POI prevalence is higher among women with autoimmune Addison's disease (AAD) than in the general population, but their clinical characteristics are insufficiently studied.
Objective: To assess the prevalence of POI in a large cohort of women with AAD and describe clinical, immunological, and genetic characteristics.
Methods: An observational population-based cohort study of the Norwegian National Addison Registry. The Norwegian Prescription Database was used to assess prescription of menopausal hormone replacement therapy (HRT). A total of 461 women with AAD were studied. The primary outcome measure was prevalence of POI. Secondary outcomes were clinical characteristics, autoantibodies, and genome-wide single nucleotide polymorphism variation.
Results: The prevalence of POI was 10.2% (47/461) and one-third developed POI before 30 years of age. POI preceded or coincided with AAD diagnosis in more than half of the women. The prevalence of concomitant autoimmune diseases was 72%, and AAD women with POI had more autoantibodies than AAD women without (≥2 autoantibodies in 78% vs 25%). Autoantibodies against side-chain cleavage enzyme (SCC) had the

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highest accuracy with a negative predictive value for POI of 96%. HRT use was high compared to the age adjusted normal population (11.3 % vs 0.7%).

Conclusion: One in 10 women with AAD have POI. Autoantibodies against SCC are the most specific marker for autoimmune POI. We recommend testing women with AAD <40 years with menstrual disturbances or fertility concerns for autoantibodies against SCC.

Key Words: primary ovarian insufficiency, primary adrenal insufficiency, 21-hydroxylase, side-chain cleavage enzyme, hormone replacement therapy

Primary ovarian insufficiency (POI) is characterized by decreased follicle function and deficient steroid hormone production and is diagnosed by amenorrhea for >4 months and follicle-stimulating hormone (FSH) in the menopausal range before 40 years of age (1). It is a condition of multiple etiologies including genetic and immunological factors, although the majority of cases remain idiopathic (2). Autoimmunity is estimated to be responsible for approximately 5% to 30% of POI cases, reflecting heterogeneity of patient cohorts studied (3).

The prevalence of POI has been reported to be higher among women with autoimmune Addison's disease (AAD) (6-20%) than in the general population (1-2%) (1, 4-6). POI in these women is understood to be a consequence of an autoimmune oophoritis with immune infiltrate selectively involving the theca cells (7). The initial sparing of granulosa cells of primordial follicles is reflected by detectable levels of anti-Müllerian hormone and inhibin, as well as fluctuating ovarian function during the first years after debut (8, 9). Hormonal replacement treatment is recommended to prevent complications of estrogen deficiency (1).

Ovarian biopsy is not advised in routine diagnostic workup. Instead, autoantibodies are used as surrogate markers of ovarian autoimmunity (1). Earlier methods based on indirect immunofluorescence could detect reactivities towards tissue components, but not the specific autoantigen. These methods, which are tissue and investigator dependent and therefore difficult to standardize, have largely been replaced by more sensitive immunoassays testing the presence of specific autoantibodies (10, 11). Good correlations between histologically verified autoimmune oophoritis and autoantibodies against the steroidogenic enzymes 21 hydroxylase (21OH), side chain cleavage enzyme (SCC), and 17-alpha hydroxylase (17OH), as well as NACHT leucine-rich-repeat protein 5 (NALP-5), have been published (12-15). As steroidogenic enzymes are expressed in both the adrenal cortex and ovaries, the specificity of these autoantibodies in women with autoimmune adrenal cortex deficiency is uncertain.

Spontaneous POI has been linked to multiple genetic loci involved in oogenesis, folliculogenesis, DNA damage repair, homologous recombination, and meiosis (16, 17). To date, there are limited data on any potential genetic basis of autoimmune POI, but a recent genome-wide association study on AAD can perhaps provide hints to the pathogenesis (18).

To overcome previous limitation of smaller and potentially biased cohorts, we here provide data on epidemiology, clinical features, autoantibodies, and genetic background of autoimmune POI from a national registry on Addison's disease. We find that 1 in 10 women with AAD develop POI, a result that has widespread clinical implications.

Patients and Methods

Patients, Registries, and Data Collection

Individuals with POI were identified among AAD patients in the National Registry of Organ-Specific Autoimmune Diseases (ROAS), encompassing the Norwegian Addison Registry. The population is almost exclusively Caucasian/Scandinavian. Of the 540 women registered with Addison's disease, 57 were excluded because of nonautoimmune causes or incomplete data. We also excluded 22 women with known autoimmune polyendocrine syndrome type-1, leaving 461 women with AAD who all had autoantibodies against 21OH. The registry contains information on age at AAD diagnosis, age at menopause and other autoimmune manifestations autoantibody profiles, and genome-wide single nucleotide polymorphism (SNP) data (18, 19). POI was diagnosed based on standard clinical and biochemical criteria (1) oligo/amenorrhea, and (2) an elevated FSH level in menopausal reference range (1). The information was confirmed with self-reported biobank data and telephone interviews regarding time of menopause.

Autoantibody Assays

ROAS biobank serum samples are routinely analyzed for autoantibodies against 21OH, SCC, 17OH, glutamic acid decarboxylase (GAD), and NALP-5 using radiobinding ligand assays as described previously (20). Autoantibodies against thyroid peroxidase (TPO) were analyzed by electrochemiluminescence immunoassay (Roche Cobas).

Genetic Analyses

Recently generated whole-genome genotype data were retrieved for 432 women with AAD from ROAS, of whom 44 had POI (18). Due to the low number of patients with POI, we selected 104 candidate genes based on the Genomics England list of POI genes and risk loci for AAD (18, 21) (see supplementary table for details (22)). For each candidate gene, the longest gene transcript region (defined by the University of California Santa Cruz Gene Browser) was selected, and all SNPs within these regions were extracted from quality-controlled imputed genotype data (for details on input data and imputation, see (18)). The variant sets were pruned for triallelic markers and markers in linkage disequilibrium , and a set-based association test was performed in Plink (23). This allows the assessment of SNPs in a set (here, all SNPs in any given gene) in aggregate, increasing the power relative to testing them individually.

Medication Records From the Norwegian Prescription Database

The use of hormone replacement therapy (HRT) among women with AAD younger than 40 years was obtained using The Norwegian Prescription Database (NorPD), which contains information of quantity, dosage, expenditure, and reimbursement of all prescription drugs that have been dispensed from pharmacies to individual patients (24). NorPD does not contain information on diagnosis or indication for treatment and the data was anonymous linked to ROAS using personal identity numbers assigned to all individuals living in Norway. Age- and sex specific reference populations are provided. All drugs are classified according to the Anatomical Therapeutic Chemical system (ATC number). We used data on glucocorticoid therapy for systemic use (H02AB), mineralocorticoid replacement therapy (H02AA), hormonal contraceptives for systemic use (G03A), estrogens (CG03C), and progesterone and estrogens in combination (G03F), prescribed ≥1 time between 2004 and 2018. The expected number of users were found by calculating the proportion of women aged 20-39 years from the general population (n = 161 969) who had been prescribed drugs in the mentioned ATC groups, and multiplying by total number of women with AAD in the same age group (n = 194). Observed to expected ratio (OER) of users was found by dividing observed number of women with AAD prescribed a drug in the ATC groups with the expected number of users. Thus, an OER above 1 indicates an increased use, and an OER below 1 indicates a reduced use of the respective drugs in women with AAD.

Statistical Analyses

Categorical statistics were presented as absolute numbers and percentages while continuous data were presented as medians and range (minimum–maximum), or mean ± SD or 95% CI, as appropriate. For between-group comparisons, we used the independent sample t-test or the Mann–Whitney independent sample U test as appropriate depending on data distribution. A chi-squared test for independence (with Yates continuity correction) was used for assessing the association between categorical variables. Correlations were investigated using Pearson product moment correlation or the Spearman rank correlation.

Ethics

All study participants gave informed and written consent. The study was approved by The Regional Committee for Medical and Health Research Ethics (permit no. 2018/1573/REK Vest). The study was conducted in agreement with the local and international guidelines and regulations, including the Declaration of Helsinki (2013 version) and the principles of good clinical practice (CPMP/ICH/135/95).

Role of Funding Source

Regional health authorities of Western Norway and the University of Bergen covered the salaries and cost connected to the registry. Stiftelsen Kristian Gerhard Jebsen and the Norwegian Research Council covered immunological and genetic analyses.

Results

Prevalence and Clinical Characteristics

Altogether 47 of 461 women (10.2%) with AAD in The Norwegian Addison registry had POI (Fig. 1) with a mean age at menopause of 33.2 years (95% CI 31.5-35.0 years). The corresponding age for women with AAD without POI was 48.9 years (95% CI 48.1-49.8) compared with the general reference population 52.7 years (95% CI 52.6-52.8 years) (25). Women with POI were nonsignificantly younger at AAD diagnosis (34.5 vs 37.0 years, P = .129), but had a longer AAD disease duration than those without POI (26.8 vs 20.1 years, P = .003). There was a strong positive correlation between age at diagnosis of AAD and age at menopause (P < .001), with lower age at AAD diagnosis associated with lower age at menopause. We found that POI was diagnosed before or at the same time as AAD in 27 women (57%), and after AAD in 15 women (32%) (Fig. 2). In 5 women the chronological timing of events was uncertain.

The prevalence of associated autoimmune diseases was high among all women with AAD, with 72% exhibiting at least 1 autoimmune comorbidity. Hypothyroidism was most frequent affecting more than half of the women in both groups. The frequency of associated autoimmune disease did not differ between women with and without POI (Table 1).

Autoantibodies

There were significantly higher frequencies of autoantibodies against both SCC and 17OH in AAD women with POI than in AAD women without (P = 0.01 and $P \leq$ 0.001, respectively) (Table 2). Except for 21OH autoantibodies, those against SCC were the most common in AAD women with POI (specificity 84% [341/406]; sensitivity 72% [33/46]), giving a negative predictive value of 96% and a positive predictive value of 34%. Longitudinal data on SCC autoantibodies were limited with multiple measurements available only for 17 AAD women with POI. We did however find stable SCC autoantibody titers in 15 of these women, indicating a long-lasting presence of the autoantibodies similar to what has been reported for 21OH autoantibodies in Addison's disease (26). Autoantibodies against 17OH were the third most common autoantibodies among AAD women with POI, but the specificity (71%, 179/251) and sensitivity (49%, 22/45) was lower. Likewise, the negative (92%) and positive (16%) predictive values were lower than autoantibodies against SCC. Combining the results from SCC and 17OH autoantibody testing did not increase the accuracy compared with testing autoantibodies against SCC alone. None of the women with AAD tested positive for NALP-5 autoantibodies. The AAD women with POI where positive for more autoantibodies towards the 3 steroidogenic enzymes than AAD women without POI, exhibiting ≥2 positive autoantibodies in 78% vs 25% of cases and ≥3 positive autoantibodies in 37% vs 5% (P < .01).

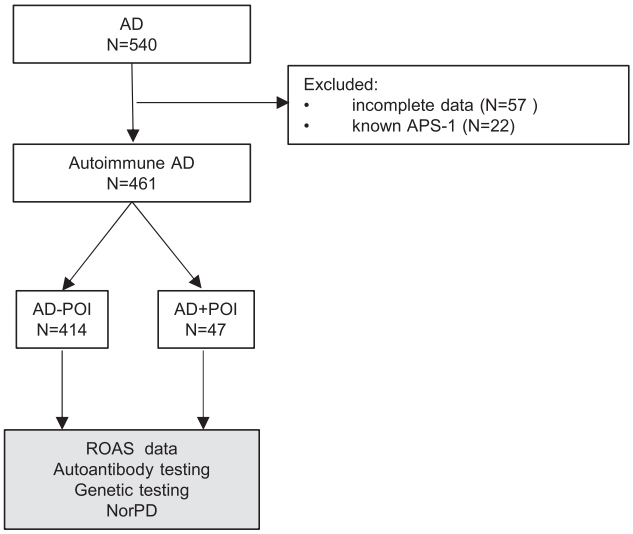

Figure 1. Study design. AAD, Addison's disease; POI, primary ovarian insufficiency; ROAS, National Registry of Organ-Specific Autoimmune Diseases.

Genetic Associations

We tested associations to 104 POI- or AAD-associated genes. When applying the Bonferroni-adjusted significance level of 0.00048, no between-group differences were detected for any of the 104 genes tested for. Eight of the 104 loci reached nominal significance, including 3 (FOXL2, PNO1, and DDX4) with a minor allele frequency >5% (Table 3 and (22)). Since genotyping and imputation of rare alleles (defined as <5%) are prone to inaccuracy for technical reasons, the genotypes reported for the remaining

Figure 2. Age at menopause. (A) Age at menopause in women with AAD. (B) Age at menopause compared to age at AAD diagnosis. (X) POI after/same time as AAD, (□) POI before AAD, (·) menopause after 40 years. (C) Timing of POI diagnosis in relation to AAD diagnosis. POI, primary ovarian insufficiency; AAD, Addison's disease.

Table 1. Associated autoimmune conditions in women with Addison's disease (AAD) with and without Primary Ovarian Insufficiency (POI)

	AAD with POI	AAD without POI
	n = 47	n = 414
	Frequency (%)	Frequency (%)
Hypothyroidism	24 (51.1)	217 (52.8)
Hyperthyroidism	5 (10.6)	35 (8.5)
Diabetes type 1	5 (10.6)	50 (12.2)
Hypoparathyroidism	0 (0.0)	1 (0.2)
Alopecia	0 (0.0)	19 (4.6)
Vitiligo	7 (14.9)	46 (11.2)
Vitamin B12 deficiency	6 (12.8)	36 (8.8)
Celiac disease	2 (4.3)	27 (6.6)

Table 2. Autoantibodies in Addison's disease (AAD) women with and without primary ovarian insufficiency (POI)

	AAD with POI	AAD without POI
	n = 47	n = 414
	Positive/Tested (%)	Positive/Tested (%)
21 OH	47/47 (100)	414/414 (100)
SCC	33/46 (71.7)[a]	65/406 (16.0)[a]
17 OH	22/45 (48.9)[b]	72/251 (28.7)[b]
NALP-5	0/34 (0.0)	0/28 (0.0)
TPO	14/33 (42.4)	99/214 (46.3)
GAD	11/35 (31.4)	67/247 (27.1)

[a]$P < .001$, [b]$P = .01$ (chi-squared test).
Abbreviations: 17OH, 17-alpha hydroxylase; 21OH, 21 hydroxylase; GAD, glutamic acid decarboxylase; NALP-5, NACHT leucine-rich-repeat protein 5; SCC, side chain cleavage enzyme; TPO, thyroid peroxidase.

5 rare alleles were not reliable in our POI cohort and were therefore not reported.

Use of Hormone Replacement Therapy

All women with AAD had been prescribed glucocorticoid therapy for systemic use (H02AB) and 459 (95.0 %) mineralocorticoid replacement therapy (H02AA). The use of menopausal HRT (G03C or G03F) was higher in women with AAD <40 years (n = 22) than in the age-adjusted normal population (11.3 % vs 0.7%, $P < .00001$; OER 16.0). The use of hormonal contraceptives for systemic use (G03A) was also higher among women with AAD <40 years of age (n = 112) than in the general population of women 20-39 years (57.7% vs 35.2%, $P < .00001$; OER 1.6). Among the women with POI, two-thirds were treated with HRT.

Discussion

In this first comprehensive national survey of POI in AAD we found that 1 in 10 women with AAD developed menopause before 40 years of age, one-third of these before the 30 years of age. This has important implications for the women involved and should be communicated clearly so that females with AAD can take informed decisions with regard to family planning and HRT. Autoantibodies against SCC are useful biomarkers to identify POI in women with AAD, with a high negative predictive value.

Although the prevalence of POI in our cohort of women with AAD is higher than in the general population, it is in the lower range of what has been reported in previous studies on women with AAD (4-6). These differences can be explained by methodological factors, inclusion criteria or diagnostic precision. Here, we believe to have minimized the potential selection bias by recruiting women with AAD from a national registry, to our knowledge the largest cohort of women with AAD studied so far. We have validated the registered diagnosis to overcome reporting bias by verification of self-reported menopausal age, demonstrating good coherence on timing of menopause.

In clinical practice, endocrinologists need to be aware that women with AAD have a higher risk of POI and earlier menopause than the reference population which has a reported menopausal age of 52.7 years (95% CI 52.6-52.8 years) (25). Contrary to previous studies that showed POI to precede AAD, we here demonstrate that POI can emerge many years or even decades after AAD diagnosis, emphasizing the need for conscientious clinical follow-up (4). Importantly, we also confirm that POI precedes or coincides with AAD in most of the patients, highlighting the importance of screening for AAD with 21OH autoantibodies in women with newly diagnosed POI of unknown cause.

We confirmed a high frequency of concomitant autoimmunity against multiple endocrine organs among women with AAD (5, 19). Similar underlying autoimmune mechanisms have been proposed in both autoimmune adrenalitis and oophoritis (27). As there is a shared embryonic primordium of both organs, and similarities in steroidogenesis, the immunological mechanisms involved in destruction may be analogous (28). The fact that AAD women with POI in this study had a higher frequency of autoantibodies towards steroidogenic enzymes points towards a more aggressive immunological attack.

Autoantibodies towards the steroidogenic enzyme 21OH have repeatedly proven to have the highest sensitivity in diagnosing autoimmune POI in women without AAD, even though this enzyme is exclusively expressed in the adrenal cortex (4, 9, 12, 13). However, most women

Table 3. Nominal significant SNPs associated with primary ovarian insufficiency

Gene	Variants in signal	Function	Minor allele	Cases (MAF)	Controls (MAF)	European (MAF)	*P* value
FOXL2	**rs11924939**	**5′ UTR**	**T**	**0.341**	**0.178**	**0.211**	**.003069**
NR5A1	rs72761481	Intron	T	0.057	0.009	0.030	.00748
CYP17A1	rs45609333	Intron	A	0.045	0.006	0.030	.007841
PNO1	**rs10153623**	**Intron**	**T**	**0.136**	**0.314**	**0.229**	**.01311**
LHX8	rs115689198	Intron	T	0.045	0.006	0.000	.01557
LPP (mir28)	rs76686113	Introns	G	0.079	0.012	0.032	.02136
	rs115389480		A	0.079	0.014	0.046	
	rs62289608		T	0.079	0.016	0.048	
	rs143350743		A	0.045	0.006	0.012	
CTLA4	rs73993040	Intron	T	0.045	0.009	0.000	.04447
DDX4	rs111944699	Introns	A	0.136	0.041	0.046	.04612
	rs4865982		**C**	**0.205**	**0.124**	**0.098**	

Variants with population MAFs greater than 5% in bold. European MAF from European gnomAD, based on nearly 19 000 samples.
Abbreviations: MAF, minor allele frequency; SNP, single nucleotide polymorphism;UTR, untranslated region.
Genes in bold have a reported minor allele frequency > 5% (0.005).

with AAD will already have disease-associated 21OH autoantibodies and they can therefore not be used to diagnose POI. Our study confirms SCC as the most sensitive autoantibody for autoimmune POI in AAD (4, 13, 27). Although the negative predictive value of SCC is high, the positive predictive value is low. Thus, a negative test result predicts that POI is unlikely to develop, while a positive score predicts that it might happen, although many will not develop POI, limiting the use of SCC as a sole screening test. We therefore recommend testing young women with AAD with symptoms of menstrual disturbances or concerns about fertility for autoantibodies against SCC.

NALP-5 autoantibodies have previously been shown to be present in 7% of women with AAD and 12% of women with autoimmune POI (15). We could not replicate these findings in our study. Although prevalent in the cohort compared to the normal population, autoantibodies against TPO and GAD did not differ between AAD women with and without POI and are therefore not useful as markers of ovary-specific autoimmunity.

Elucidating the complex interplay between immunological and genetic mechanisms of autoimmune POI is essential, not only for understanding the connection between AAD and POI, but also in providing genetic counseling and fertility guidance. The lack of any statistically positive genetic associations in the current study may be due to several factors: (1) There may be no relevant genetic differences between AAD women with and without POI; (2) this element of the study is underpowered to detect any but the strongest of effects and any existing effects may be more subtle; or (3) the selected candidate gene set may not include variants that more strongly predispose patients to develop autoimmune POI. Nevertheless, the 3 variants of nominal significance in FOXL2, PNO1, and DDX4 may be of relevance. First, variants in the *FOXL2* gene are known to cause blepharophimosis–ptosis–epicanthus inversus syndrome, but are also associated with spontaneous POI in 1% to 2.9% cases, possibly by impairment of transcriptional repression activity on target genes involved in granulosa cell steroidogenesis and proliferation (17). Second, PNO1 (Partner of NOB1 Homolog) is involved in rRNA processing and has recently been linked with POI in women with autoimmune polyendocrine syndrome type-1 (29). DDX4 is involved in embryogenesis and germ cell development through alteration of RNA secondary structure (30). Thus, these candidate genes are of particular interest when investigating genetic susceptibility for POI in women with AAD and should be included in future larger studies.

In addition to menopausal symptoms of estrogen deficiency and infertility, POI increases the risk of osteoporosis, neurodegenerative disease, cardiovascular disease, and premature death (1). HRT with estrogen and progesterone alleviates these consequences to some extent, and their use is recommended until regular menopausal age (1). Merging data from ROAS with a high-quality prescription register has given us insight into the unique prescription pattern among women with AAD <40 years, demonstrating a significant higher prescription rate for HRT than the same age group in the general population. This indirectly confirms a higher prevalence of POI in women with AAD.

Women with AAD from this cohort have not reported reduced sexual activity or satisfaction compared with the general population, but their fertility is lower (6). In contrast to previous findings in a Swedish study, we found a higher prescription rate of hormonal contraceptives among women with AAD than in the general population, possibly

because of the younger age in our cohort study (31). It is important to be aware that the use of hormonal contraceptives potentially can camouflage menstrual disturbances resulting in delayed diagnosis of POI. The global trend of increasing maternal age at first time pregnancy emphasizes the importance of evaluation the risk of POI and infertility in young women with AAD (32).

Some limitations apply to our study, including the use of candidate markers of autoantibodies and genetic variants. This approach allows us only to identify already known variants of interest, limiting the possibility to discover new and potentially more specific immunological and genetic markers of POI in women with AAD. Another potential weakness is the lack of chronological autoantibody index levels. POI is a continuum of ovarian dysfunction and may proceed through several biochemical stages. Autoantibodies are also known to predate clinical symptoms in some cases and may not be detectable after some years (19). Also, the anonymous structure of the data from NorPD did not allow us to identify who did receive HRT or oral hormonal contraceptives.

To conclude, our national study of women with AAD has demonstrated a high prevalence of POI. Although POI diagnosis preceded AAD in more than half of the women, later POI debut was also common. Diagnosing autoimmune POI remains challenging and relies on clinical, biochemical and immunological testing. Autoantibodies against SCC seem to be the most specific marker for autoimmune POI in women with AAD and we recommend testing all women with AAD <40 years with menstrual disturbances or fertility concerns for autoantibodies against SCC. We also identified 3 possible gene variants of interest in AAD women with POI.

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Additional Information

Correspondence: Eystein Husebye, Department of Clinical Science, University of Bergen, N-5021 Bergen. Email: eyhu@helse-bergen.no.

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Data availability: All data generated or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request. Supplementary data are available in the data repositories listed in References.

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