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Associations Between BMI, Serum Hormone Levels, Time Since Ovarian Insufficiency Onset, Serologic Autoimmunity, and Prevalence of Common Parameters: A cross-sectional Retrospective Study of Premature Ovarian Insufficiency

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ABSTRACT

OBJECTIVE Premature ovarian insufficiency (POI) affects 1:100 women before the age of 40. The objectives include exploring correlations between body mass index, years since the onset of premature ovarian insufficiency, follicular stimulating hormone, and estradiol; and studying prevalence of five common serologic autoimmunologic parameters during POI diagnosis.

METHODS The records of idiopathic POI patients presenting with secondary amenorrhea who visited the Gynecologic Endocrinology Unit, Siriraj Hospital, between January 1, 2000 and December 31, 2016 were reviewed. Extracted data included body mass index, years since premature ovarian insufficiency onset, levels of follicular stimulating hormone and estradiol. Five common serologic autoimmunologic parameters were also retrieved where available.

RESULTS Among the 161 idiopathic POI patients analyzed, a significant reverse correlation was found between serum follicular stimulating hormone and estradiol ($r=-0.209$, $p=0.008$), while no correlations were identified between body mass index, years since the onset of premature ovarian insufficiency, and serum estradiol ($p=0.141$, $p=0.240$, respectively). After excluding cases with abnormal karyotypes which can potentially cause POI, the remaining 146 cases was comprised of 72 cases with a normal 46,XX karyotype (the first group) and 74 cases who declined karyotype investigation (the second group). At least one of the serologic autoimmunologic parameters was investigated in 43 cases in the first group and in 20 cases in the second group. Anti-nuclear antibody was the most prevalent in the first group (25.0%) while anti-thyroglobulin was the most prevalent in the second group (30.7%).

CONCLUSIONS Only serum follicular stimulating hormone and estradiol exhibited significant reverse correlation in POI cases with secondary amenorrhea. Baseline serologic autoimmunologic parameters were positive but didn't indicate autoimmune diseases during POI diagnosis.

KEYWORDS premature ovarian insufficiency, body mass index, years since premature ovarian insufficiency, follicular stimulating hormone, estradiol, serologic autoimmunologic parameters

INTRODUCTION

Premature ovarian insufficiency (POI) is defined as a premature cessation of ovarian function before the age of 40. It is an important etiology of deficiency in many sex steroids found in reproductive-aged women globally. When POI occurs after menarche, a patient usually presents with prior irregular menstrual cycles with or without menopausal symptoms or with secondary amenorrhea (SA). It is estimated that POI affects 1:100 women by the age of 40, 1:1,000 women by age 30, and 1:10,000 by the age of 20 (1-5). An increased level of follicular stimulating hormone (FSH) in a menopausal range and a low estradiol (E2) level, also defined as a hypergonadotropic hypogonadism state, are characteristics of this condition.

Androstenedione is the main steroid produced and secreted by postmenopausal ovaries and the level is about one-half of that before menopause (6). Estrone (E1) is produced mainly by the peripheral aromatization of androstenedione mostly in adipose tissue and then is continuously converted to E2 (7). The body mass index (BMI) has been hypothesized to finally affect E2 levels after menopause. One previous study of surgically menopausal women who were younger than naturally menopausal women assumed that extra-gonadal site estrogen production started approximately 12-18 months later in the surgically menopausal women compared with natural menopause (8). This is hypothesized to occur after POI since the POI patients are much younger than the naturally menopausal women. However, to date studies of correlations between BMI, years since premature ovarian insufficiency (YSP) and serum E2 of POI patients have been limited and in most cases the results reported were from mixed types of menopause.

Previously reported etiologies of POI are heterogeneous. Many advanced clinical investigations have attempted to identify additional etiologies of POI. Despite this effort, the cause of POI in the majority of cases remains unknown and idiopathic cases are reported in 74%-90% of POI patients (9,10). Known potential causes include identifiable underlying diseases, e.g., genetic diseases, chromosome abnormalities, autoimmune diseases, or iartrogenic causes such as previous chemotherapy or radiation therapy. Autoimmune diseases have been reported to be the cause of POI in 4-30% of cases, with the strongest association being with thyroid diseases (11-15). Nevertheless, many autoimmune antibodies have been reported to be prevalent at baseline in both POI cases with a normal 46,XX karyotype without clinical autoimmune diseases and in normal women controls (16).

The primary objectives of the present study were to study the correlations between body mass index (BMI), serum follicular stimulating hormone (FSH) level, years since premature ovarian insufficiency (YSP) and serum estradiol (E2) level in idiopathic POI patients presenting with secondary amenorrhea. The secondary objective was to study the prevalence of five common serologic autoimmunologic parameters (SAPs) at the time of POI diagnosis.

METHODS

This cross-sectional retrospective study was conducted at a single tertiary-care hospital in Bangkok, Thailand. The study was approved by the Siriraj Ethical Committee on Research Involving Human Subject (SiRB No. 609/2020). Informed consent was exempted as this was a retrospective study. However, permission to use the patients' electronic data in this study was approved by the Director of Siriraj Hospital. The records of patients who presented with SA, were idiopathic POI at diagnosis, and who were seen at the Gynecologic Endocrinology Unit, Faculty of Medicine Siriraj Hospital between 1 January 2000 and 31 December 2016 were reviewed. The inclusion criteria were: patients with available and complete electronic medical records, age < 40 years at the time of POI diagnosis, presented with SA ≥ 4 months without any hormonal treatment given during that time, and with serum FSH levels ≥ 40 mIU/mL on two occasions at least one month apart. The exclusion criteria were: patients with previous bilateral oophorectomy, a history of mumps oophoritis, previous chemotherapy affecting ovarian function, radiation therapy at the pelvic or the abdominal area, known autoimmune diseases, e.g., Hashimoto's thyroiditis, systemic lupus erythematosus, autoimmune polyglandular syndrome, at the time of POI diagnosis, or other known underlying diseases or conditions

which can cause POI, e.g., acquired immunodeficiency syndrome and heavy smoking. The flow chart for POI patient selection in this study is shown in Figure 1.

Patient data extracted included age at menarche, age at last menstrual period, age at registration at the hospital, duration of SA, YSP (calculated as full calendar years since the last menstrual period), serum FSH and E2 levels at the time of POI diagnosis, weight and height, body mass index (BMI) calculated as weight in kg divided by height in meter squared, and the results of five common SAPs where available.

Sample size calculation

As the correlation between the BMI and the serum E2 level of the POI patients was not available, the sample size was calculated based on a previous report of mixed menopausal cases who had been seen at the Gynecologic Endocrinology Unit, Faculty of Medicine, Siriraj Hospital. The correlation between the BMI and the serum E2 was found to be 0.27 (17). Based on an $r = 0.27$, $\propto = 0.05$ (two-sided test), and $\beta = 0.1$, it was determined that a total of 140 cases were needed. An additional 21 cases (15%) were added for a total of 161 consecutive cases identified without selection bias were finally enrolled. The last case included in the study was registered with the hospital in December 2016.

Serum FSH and serum E2 assays

Serum FSH and serum E2 assays were performed by the electrochemiluminescence immunoassay method (ECLIA) (Elecsys, Roche Diagnostics, Germany) at the Clinical Pathology Department, Faculty of Medicine, Siriraj Hospital. The sensitivity of the assay for FSH was 0.3 mIU/mL with inter- and intra-assay coefficients of variation of 5% and 5.2%, respectively. The sensitivity of the assay for E2 was 5 pg/mL, with both inter- and intra-assay coefficients of variation of 5%.

Autoimmune assays

The five common SAPs investigated in this study were as follows:

1. Rheumatoid factor (RF): RF was studied using the immunoturbidimetric assay. The results were reported as < 15.0 U/mL = negative, 15.0-25.0 U/mL = borderline and > 25.0 U/mL = positive. The test was performed to investigate for rheumatoid arthritis.

2. Anti-nuclear antibody (ANA): ANA was studied using the indirect immunofluorescence (IIF) method. The results were reported as Negative, Borderline or Positive based on the titer and pattern. The test was performed to investigate for systemic lupus erythematosus (SLE) and other connective tissue diseases.

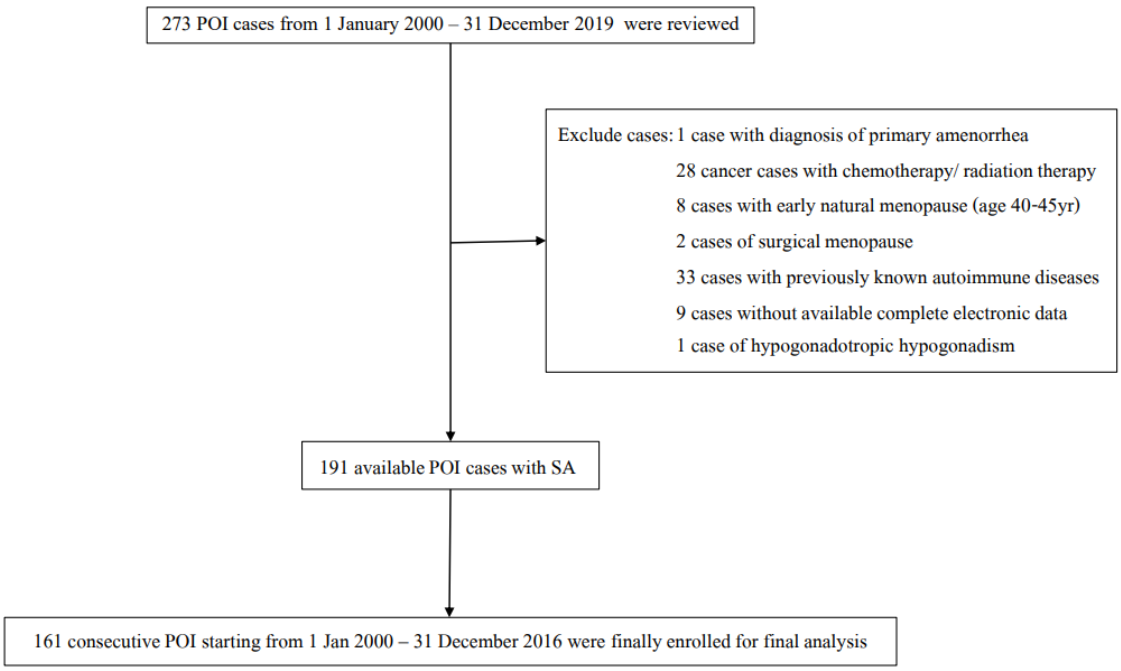

Figure 1. Flow diagram of patient selection in this study

3. Anti-doublestranded DNA (Anti-dsDNA): Anti-dsDNA was studied using the IIF method. The results were reported as negative, borderline or positive together with the titer. The test was performed to investigate for SLE.

4. Anti-thyroperoxidase antibody (Anti-TPO): Anti-TPO was studied using the electrochemiluminescent immunoassay (ECLIA) method. The results were reported as: ≤ 34 IU/mL = negative, > 34-65 IU/mL = borderline and > 65 IU/mL = positive. The test was performed to investigate for Hashimoto's thyroiditis and autoimmune thyroiditis.

5. Anti-thyroglobulin: Anti-thyroglobulin was studied using the chemiluminescent microparticle immunoassay (CMIA) method. The results were reported as: < 35 IU/mL = negative and ≤ 35 IU/mL = positive. The test was performed to investigate for Hashimoto's thyroiditis and autoimmune thyroiditis.

Statistical analysis

Descriptive quantitative data are presented as number, percentage, and mean ± SD, where appropriate. The t-test was used to compare the baseline clinical characteristics between the normal karyotype group and the group with no karyotype investigation. Pearson's correlation was used to determine the correlations between BMI, serum FSH, YSP and serum E2. The Statistics Package for the Social Science Program (SPSS 18.0 statistical package (IBM Corp. in Armonk, NY) was used for data analysis. *P*-values < 0.05 were considered statistically significant.

RESULTS

All the initial 161 patients had been newly diagnosed with POI and were sporadic cases. The baseline clinical characteristics of the cases in this study are shown in Table 1. POI diagnosis was made at or before age 30 years in 29.2% of the cases. The most delayed diagnosis was made 10 years after the onset of SA. The correlations between the FSH, BMI, YSP and serum E2 of the 161 cases are summarized in Table 2. There was a significant reverse correlation between the serum FSH and the serum E2 (r = -0.209, p = 0.008). The correlations between both the BMI and YSP with serum E2 were not statistically significant (p = 0.141 and p = 0.240, respectively). Figures 2A, 2B and 2C show scatterplots of the serum FSH, BMI, YSP and serum E2.

Table 1. Baseline characteristics and laboratory results of the 161 cases enrolled in this study

Baseline characteristics of patients	POI cases (n = 161)
Age at POI (mean±SD, yr)	32.48±6.15
Age at registration (mean±SD, yr)	35.08±6.84
Duration of SA (mean±SD, yr)	2.32±2.53
Age at menarche (mean±SD, yr)	14.32±2.27
Gravidity (mean±SD)	0.66±1.09
Parity (mean±SD)	0.58±0.95
Abortion (mean±SD)	0.07±0.32
Weight (mean±SD, kg)	53.78±8.71
Height (mean±SD, cm)	155.46±5.96
BMI (mean±SD, kg/m^2)	22.32±3.91
Serum FSH (mean±SD, mIU/mL)	92.10±37.09
Serum E2 (mean±SD, pg/mL)	16.36±16.61

Table 2. Correlations between the FSH, BMI, years since premature ovarian insufficiency (YSP) and E2 of all 161 cases in this study

Pearson correlation	E2
FSH Correlation Coefficient	-0.209
p-value	0.008*
BMI Correlation Coefficient	-0.116
p-value	0.141
YSP Correlation Coefficient	-0.093
p-value	0.240

*Statistically significant

A karyotype study was offered to all 161 patients, but was accepted by only 87 cases. After karyotype investigation, 15 of the 87 cases (17%) were found to have abnormal karyotypes, possibly causing POI (data not shown in the present study). Of the remaining 146 patients, 72 (49%) had a normal 46,XX karyotype and 74 (51%) did not undergo karyotype investigation. The baseline clinical characteristics of the 72 normal 46,XX karyotype cases and the 74 cases who did not undergo karyotype investigation are shown in Table 3. The mean age at POI, age at registration and duration of SA were all significantly lower in the group with a normal karyotype than in the group without a karyotype investigation (p = 0.001, 0.001 and 0.010, respectively).

Investigation of the five common SAPs was performed in 63 of the 146 patients. Of those, 43 cases with a normal karyotype (59.7%) and 20

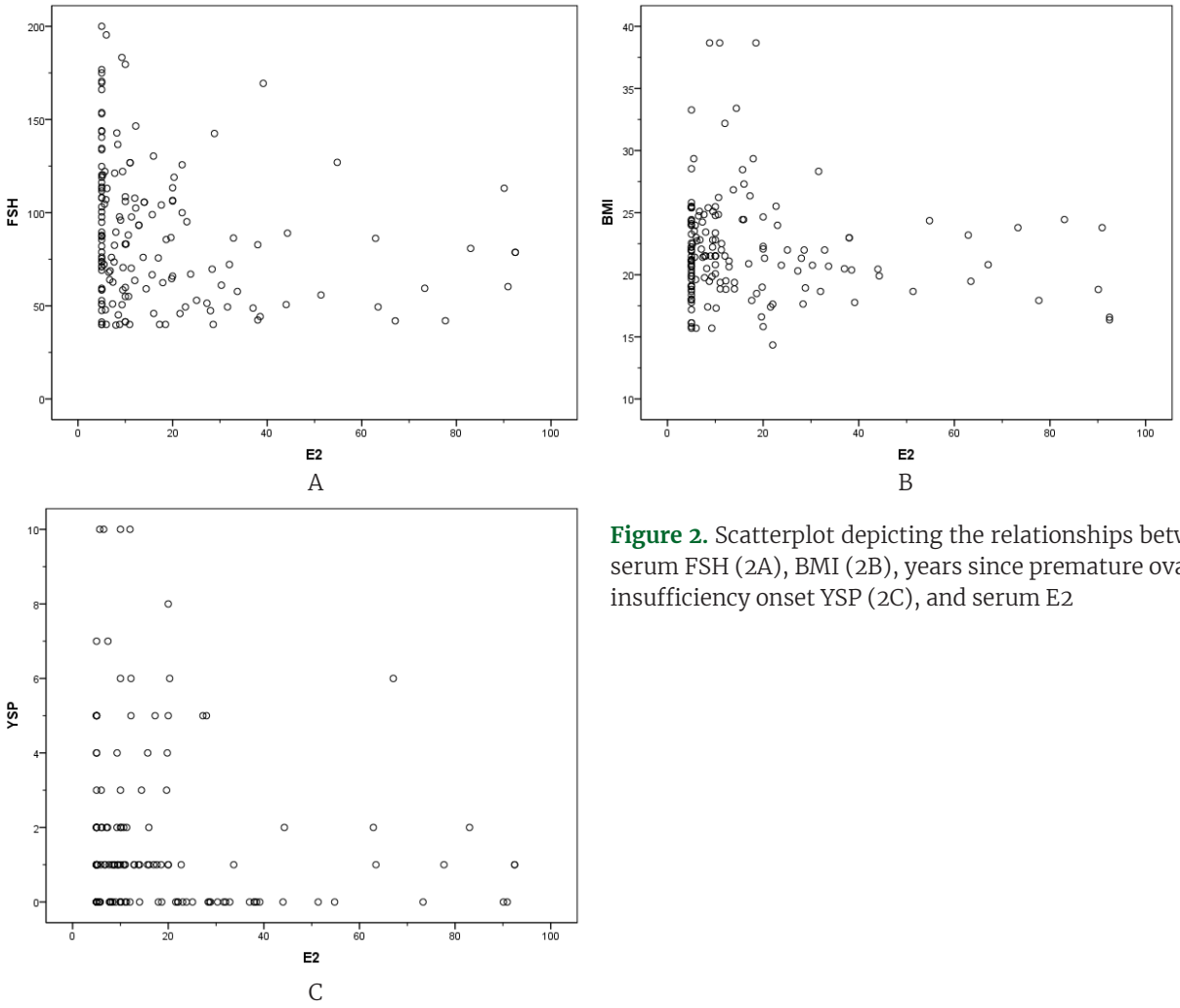

Figure 2. Scatterplot depicting the relationships between serum FSH (2A), BMI (2B), years since premature ovarian insufficiency onset YSP (2C), and serum E2

Table 3. Baseline characteristics of the 72 cases with a normal karyotype and 74 cases without a karyotype investigation in this study

Baseline characteristics of patients	POI with a normal karyotype (n=72 cases)	POI without a karyotype study (n=74 cases)	*p*-value
Age at POI (mean±SD, yr)	30.72±6.23	35.45±3.94	0.001*
Age at registration (mean±SD, yr)	32.72±7.06	38.43±4.53	0.001*
Duration of SA (mean±SD, yr)	1.74±2.07	2.64±2.56	0.010*
Age at menarche (mean±SD, yr)	14.05±2.23	13.75±2.72	0.428
Gravidity (mean±SD)	0.56±1.00	0.85±1.22	0.099
Parity (mean±SD)	0.46±0.85	0.77±1.08	0.060
Abortion (mean±SD)	0.08±0.36	0.08±0.32	0.785
Weight (mean±SD, kg)	52.29±7.77	54.09±8.67	0.201
Height (mean±SD, cm)	156.00±6.34	154.55±4.81	0.175
BMI (mean±SD, kg/m^2)	21.51±3.11	22.71±4.01	0.124
Serum FSH (mean±SD, mIU/mL)	97.11±39.42	88.48±32.33	0.264
Serum E2 (mean±SD, pg/mL)	16.28±19.48	16.92±14.60	0.324

*Statistically significant

cases in the without a karyotype study (27.0%) had at least one of the five common SAPs investigated. As shown in Table 4, anti-dsDNA was negative in all the cases investigated in the normal karyotype group whereas RF and anti-dsDNA were negative in all the cases without a karyotype study. The most prevalent positive antibody in the first group was for ANA (40/43

Table 4. Prevalence of five serologic autoimmunologic parameters of 63 POI patients

SAPs	Cases with a normal karyotype and at least 1 SAP studied (Total number = 43 cases)			Cases without karyotype investigation and with at least 1 SAP studied (Total number = 20 cases)		
	No. of cases studied (%)	Results	% Prevalence	No. of cases studied (%)	Results	% Prevalence
1. RF	30 (68.1)	N = 25/30	83.3	10 (50.0)	N = 10/10	100.0
		B = 3/30	10.0		B = 0	0
		P = 2/30	6.6		P = 0	0
2. ANA	40 (90.9)	N = 27/40	67.5	12 (60.0)	N = 9/12	75.0
		B = 3/40	7.5		B = 2/12	16.6
		P = 10/40	25.0		P = 1/12	8.3
3. Anti-dsDNA	31 (70.4)	N = 31/31	100.0	13 (65.0)	N = 13/13	100.0
		B = 0	0		B = 0	0
		P = 0	0		P = 0	0
4. Anti-TPO	24 (54.5)	N = 21/24	87.5	10 (50.0)	N = 8/10	80.0
		B = 0	0		B = 0	0
5. Anti-thyroglobulin		P = 3/24	12.5		P = 2/10	20.0
	31 (70.4)	N = 26/31	83.8	13 (65.0)	N = 9/13	69.2
		P = 5/31	16.1		P = 4/13	30.7

RF, rheumatoid factor; ANA, antinuclear antibody; Anti-dsDNA, anti-double stranded deoxyribonucleic acid; Anti-TPO, anti-thyroperoxidase; N, normal; B, borderline; P, positive

cases = 25.0%) and the most prevalent positive antibody in the second group was for anti-thyroglobulin (4/13 studied cases = 30.7%), respectively. Nevertheless, at a three-year follow-up, only one case in the normal karyotype group had developed autoimmune thyroiditis. This patient did not initially undergo RF investigation and was negative for all the other four antibodies. At the three-year follow-up, anti-thyroglobulin in that patient was positive with a level of 112.3 IU/mL. None of the cases in the second group had clinical autoimmune disease at the end of the third year.

DISCUSSION

The results of the present study show a reverse correlation between the serum FSH and serum E2, but no significant correlations between the BMI, YSP and serum E2 were observed. However, no previous study of POI patients only from Thailand was available for comparison. As previously mentioned, an increase in serum FSH and a decrease in serum E2 are characteristics of menopause. These findings have been reported to be influenced by ethnic differences (18). A later study reported that obese postmenopausal women had significantly lower serum FSH compared to overweight and normal weight women (19). The number of subjects in the present study was too small to compare the results with that report. The same results might be expected in both POI patients and women with natural menopause since both groups have intact ovaries, although the age of the POI group is undoubtedly younger.

After natural menopause, which occurs at approximately age 50 in Thai women (20), the ovaries cease producing many sex steroids, in particular, E2. The mean E2 level starts to decline two years before the final menstrual period, decreases rapidly after menopause and then plateaus (21). Also, the relationship between the BMI and the percentage of body fat by body composition analysis have been reported to be different across ethnic groups and to vary between Asian and White populations. It has also been reported that urban Thais, young Japanese, Hong Kong Chinese, Singaporean and Indonesian women have lower BMIs when compared with Europeans with a similar percentage of body fat (22). In one previous study of natural menopausal women, statistically significant positive correlations between the ideal body weight as well as serum E1 and serum E2 were reported (6). A later study also showed a significant positive correlation between the BMI and the serum E2 level (21). Another study reported that obese postmenopausal women

had significantly higher E2 levels compared to overweight or normal-weight women, and concluded that obesity is an important factor affecting hormone dynamics, but without a clear mechanism (19). Conversely, in another study of natural menopause at a six-year follow-up no correlation between the BMI and the log E2 was observed (23). Due to the relatively small number of patients in the present study, subgroups of our patients by weight were not compared. The results of this research also support the hypothesis that POI ovaries have the same pathophysiology for sex steroid production after cessation of ovarian function in the same fashion as cases of natural menopause. In the present study, YSP did not show a significant correlation with serum E2. This might be explained by the observation that the serum E2, after a rapid decline in levels since POI, plateaus in the same way as in natural menopause.

In the present study, the mean age at POI, mean age at registration with the hospital and duration of SA were all significantly lower in the group with a normal karyotype. This could be explained by the fact that these cases were younger patients, mostly before their third decade of life. They had been adequately informed of the risk of possessing the Y chromosome or Y-chromosome sequences for which early prophylactic gonadectomy is strongly recommended to prevent a possible germ cell tumor later in life. This type of tumor can be found in one or both gonads in 30% of cases, usually before the age of 30 (24). Therefore, more of the younger POI patients had decided to undergo karyotype investigation as they knew the importance of this investigation.

In idiopathic POI, evidence suggesting an autoimmune involvement is weak (25). The antibodies investigated in the present study were comprised, both organ-specific and non-organ-specific types. POI resulting from autoimmunity, although most strongly associated with thyroid disorders, is at increased risk of occurring in cases of adrenal insufficiency, myasthenia gravis, rheumatoid arthritis, SLE, etc (26). The five common SAPs studied were chosen for the detection of common autoimmune diseases. Positive results for the antibodies investigated in this study among the normal karyotype patients were also described in a report of Chinese POI patients. In that report, the prevalence in POI patients was significantly higher than in the normal controls, although both groups had no clinical autoimmune diseases (16). The prevalence of the antibodies investigated in the present study are shown in Table 4. Some of the SAPs in this study (RF, ANA, anti-dsDNA) were the same as in the Chinese report, although a lower number of SAPs were investigated in the present study. Interestingly, ANA, a non-organ specific autoantibody, was reported to be positive in 42%-77% of cases among POI patients with a normal karyotype in one study although without clinical significance (27). Anti-TPO, which was investigated for thyroid autoimmunity, has been previously reported to be positive in 14.6% of healthy women in the United States National Health and Nutrition Examination Survey (NHANES III) (28). Anti-TPO was also later reported to be positive in 24.1% of the POI women, significantly higher than the 9% of the healthy controls (29). Nevertheless, the European Society of Human Reproduction and Embryology guideline in 2016 recommended anti-TPO screening for all POI women (30).

From the results of this study, screening for common SAPs is not routinely recommended due to the high false positive rates. Only one case in the normal karyotype group of the present study whose RF was not studied at baseline and for whom the results of the other four SAPs were initially negative, developed autoimmune thyroiditis by the the third-year follow-up. This finding suggests the importance of the correlation between positive SAPs and the subsequent occurrence of autoimmune diseases, an area that needs further exploration. This study also found some positive SAPs results at baseline among patients without a karyotype study, but without clinical significance. A longer follow-up time of all cases might show the clinical significance of autoimmunity.

Strengths and limitations

The strengths of this study include that all the initial 161 cases were idiopathic at the time of POI diagnosis and were without clinical autoimmune diseases. Also, the patients were

consecutively enrolled without a clinical bias. All the patients were Thai and so were expected to possess similar adipose tissue aromatase activity without ethnic variation. The hormonal assays and the SAPs investigated were performed at the same laboratory. All the cases were accessed and followed-up via electronic data. False-positive common SAPs have not been previously reported among Thai POI patients presenting with SA who possess a normal karyotype.

As this was a retrospective study, there were inevitably some limitations. For instance, the number of patients was relatively small. All the five common SAPs were not performed with every patient. Also, other SAPs related to other autoimmune diseases, e.g., anti-ovarian antibodies, were not investigated, so the true prevalence of relevant SAPs was not determined. More complete investigations, including additional SAPs, should be performed and a larger number of patients need to be studied.

CONCLUSIONS

In the present study, among idiopathic POI patients presenting with SA the serum FSH was significantly inversely correlated with serum E2, whereas BMI and YSP were not correlated with serum E2. Baseline positive SAPs were not correlated with autoimmune diseases at the time of POI diagnosis. However, these positive SAPs might play a role in causing autoimmune diseases later in life. Karyotyping should be the first investigation for POI etiology in Thai patients presenting with SA. If normal, then extensive investigation of SAPs might be conducted.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest related to this research.

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None.

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