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Demographic, clinical and hormonal characteristics of patients with premature ovarian insufficiency and those of early menopause: data from two tertiary premature ovarian insufficiency centers in Greece

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ABSTRACT

The aim of the study was to compare demographic, hormonal and clinical parameters in patients with premature ovarian insufficiency (POI) and women with early menopause in Greece. One hundred thirty-nine women of Greek origin, aged 14–45 years, referring for oligomenorrhea and having elevated FSH concentrations were divided into three groups regarding the age of menstrual disturbances onset [POI_1: </=30 years ($n = 42$); POI_2: 31–39 years ($n = 36$); early menopause: 40–45 years ($n = 61$)].

The mean age of menstrual disturbances onset and that of diagnosis in all POI and early menopause patients were 28.7 years (28.7 ± 7.7) versus 42.1 years (42.1 ± 1.5) and 33.8 years (33.8 ± 7.2) versus 43.3 years (43.3 ± 1.4), respectively. POI patients and women with early menopause were diagnosed, respectively, five years and approximately four to six months later than the age of menstrual disturbances onset. Moreover, FSH_2 (second confirmatory FSH measurement at 4-to-6-weeks interval) was greater in all POI patients than in early menopause women (55.4 ± 33.9 vs. 32.4 ± 19.4; $p < .05$) whereas mean age of menarche was greater in early menopause women than in POI patients (13 ± 1.3 vs. 12 ± 2.2; $p < .05$). Furthermore, FSH_2 was increased in all POI and decreased in early menopause patients.

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Premature ovarian insufficiency; premature ovarian failure; hypoestrogenism; subfertility; early menopause

Introduction

Premature ovarian insufficiency (POI), is a clinical syndrome defined by accelerated loss of ovarian activity, infertility and hypergonadotrophic hypogonadism before the age of 40 [1,2]. It is characterized by menstrual disturbance (oligo/amenorrhea) and elevated gonadotropins [3]. Women who present the above symptoms between ages of 40 and 45 are diagnosed with early menopause. POI is estimated to affect ~1% of women by the age of 40 years, 0.1% by 30 years and 0.01% by 20 years. Early menopause has been reported as affecting about 5% of women between age 40 and 45 [4,5]. Although POI pathogenesis remains unclear, it is believed that several causes via follicle depletion and dysfunction can lead to the disease [6].

POI patients may experience primary or secondary amenorrhea, menopausal symptoms (hot flushes, night sweats, vaginal dryness, low libido), subfertility and sex steroid deficiency. It can be detected in 10–28% of cases with primary amenorrhea and in 4–18% of those with secondary [7]. Moreover, it seems that patients have higher risk of long-term health problems such as cardiovascular disease (CVD), osteoporosis, neurological and psychological problems, reducing the quality and quantity of life [8].

Recent guidelines from the European Society of Human Reproduction and Embryology (ESHRE) recommend that women <40-year old with oligo/amenorrhea for at least 4 months and elevated FSH levels > 25 IU/L on two occasions >4 weeks apart can be diagnosed with POI [9].

So far, there has been no radical treatment. The main used treatment is hormone replacement therapy (HRT) which aims to relieve patients from menopausal symptoms and minimize the long-term health risks. Subsidiary treatments include androgens and fertility protocols [10–12].

In Greece, there is a lack of studies regarding data (age of diagnosis, hormonal and clinical characteristics) about patients with POI and women with early menopause. Although, there are similar symptoms in different ages (POI <40 years and women with early menopause with age 40–45 years) there is a lack of evidence whether these two groups differ in hormonal and demographic characteristics. For this reason, we aimed to assess and compare patients with POI and women with early menopause, regarding demographic, hormonal and clinical characteristics, in order to present information about the age of diagnosis, hormonal and clinical characteristics of those women and investigate if there are distinctive symptoms, regarding the above characteristics, which would address the patients who are at risk of presenting POI or early menopause. Furthermore, our aim is to stress the importance of early diagnosis and present a database created by our tertiary POI centers in an attempt to contribute to the international database and develop new protocols.

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Material and methods

Subjects

Archived information of 139 women of Greek origin (age range: 14- to 45-year old) followed in the departments of menopause of Aretaieion and Attikon Hospital between 2015 and 2019 were retrospectively retrieved by the same observer (MSB). These women consulted for menstrual disturbances (oligo/amenorrhea), subfertility or a positive family POI history. Oligomenorrhea was defined as presence of eight or less menstrual cycles during a year. Amenorrhea was defined as primary (absence of menstrual cycles till the age of 16 years) or secondary (absence of menstrual cycles for six months or longer in a previously normally cycling woman) [13]. Subfertility was defined as any form of reduced fertility with prolonged time of unwanted non-conception [14]. Diagnosis of POI was based on ESHRE definition (women <40-year old; oligo/amenorrhea for at least 4 months and elevated FSH levels > 25 IU/L on two occasions >4 weeks apart) [9]. Early menopause was diagnosed in women, who presented the aforementioned symptoms at the age between 40 and 45. In our study, we excluded patients with iatrogenic POI (after chemotherapy, radiotherapy, gynecological surgery). All patients were informed about the study and gave their consent.

Protocol

Collected information about the patients in the first visit included: demographic data (age, nationality), personal history (chronic diseases, medication, surgical history, obstetrical and gynecological history), family history (maternal age of menopause, POI history and chronic diseases) and smoking. All patients had a complete physical, gynecological and anthropometric examination. Furthermore, transvaginal or transabdominal ultrasound of pelvis, blood tests and dual-energy X-ray absorptiometry (DEXA) scan of lumbar spine were performed. Anthropometry (weight and height) of each patient was used to calculate the body mass index (BMI) according to following formula: weight (kg) divided by the square of height (m^2). Blood samples from patients were collected in the early follicular phase (second–fifth cycle day) at 8 am after a 12-h fast for measurement of basal concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), antimüllerian hormone (AMH), estradiol (E2), thyroid stimulating hormone (TSH) and prolactin (PRL). For patients with FSH levels at first visit (FSH_1) >25 IU/L, a second sample (FSH_2) was collected at least 4 weeks later the first sample. Transvaginal or transabdominal ultrasound was used to assess the ovarian volume and the antral follicle count (AFC) for both ovaries. Ovarian volume was calculated using the prolate ellipsoid formula: length × height × width × 0.523. A DEXA scan of lumbar spine (*Z*-score) was performed to measure the bone loss of each patient. A *Z*-score above −2.0 was considered normal. Patients with higher values (> −2.0) and osteoporotic fractures may be diagnosed with low bone density (osteopenia) or osteoporosis. All POI patients were compared to early menopause women regarding hormonal and clinical characteristics. Furthermore, patients with POI and early menopause were divided in three groups regarding the age of menstrual disturbances onset: I.POI_1: ≤30 years ($n = 42$), II.POI_2: 31–39 years ($n = 36$) and III. early menopause group: 40–45 years ($n = 61$) to have a better knowledge of POI pathophysiology.

Hormone measurements

FSH, LH, E_2, PRL and TSH concentrations were measured using architect FSH, LH, estradiol, prolactin and TSH second Gen kits (Abbott Ireland, Diagnostics Division, Lisnamuck, Longford Co. Longford, Ireland), respectively. For AMH concentrations Elecsys AMH Plus kits (Roche Diagnostics GmbH, Mannheim, Germany) were used.

Statistics

For the statistical analysis SPSS program (edition 21) was used. Descriptive data were expressed as mean ± standard deviation, count and percentages. An unpaired *t*-test and χ^2 test were used to compare continuous and categorical variables, respectively between patients with POI and early menopause. $p < .05$ was considered statistically significant.

Results

Demographic, clinical and hormonal and characteristics of POI patients

The mean age at the first visit of POI patients was approximately 33.7 years old (33.7 ± 7.2). Among those women, 3/78 (4%) were under 19 years, 18/78 (23%) between 20 and 29 years, 40/78 (51%) between 30 and 39 years and 17/78 (22%) over 40 years. The mean age of menstrual disturbances onset was 28.7-years old (28.7 ± 7.7). However, diagnosis came five years later at the age of 33.8-years old (33.8 ± 7.2). At diagnosis time, 26% of POI patients were under 30 years, the majority (56%) between 31 and 40 years and 18% were below the age of 40. Studying the etiology of POI, we found out that the majority of POI patients (77%) was diagnosed with idiopathic POI (there was an unknown cause), 6% of patients had a positive family history, 17% had autoimmune POI (16% of those had hypothyroidism) and 6% had a genetic background (one patient with Turner syndrome and four patients with a FMR premutation).

Presenting symptoms and clinical characteristics of POI patients at first visit are shown in Table 1. The most common symptom was oligo/amenorrhea (97%), followed by hot flushes (41%) and vaginal dryness (35%). The mean age of menarche for POI patients was approximately 12 years old. The most common referred autoimmune disease was hypothyroidism (15%; Table 1).

At the time of diagnosis, the mean FSH levels were 55.4 IU/L. At this time, 29/78 patients had performed a DEXA scan. Among those women, 16 had a normal bone density, 10 were diagnosed with osteopenia and 3 with osteoporosis.

Seven POI patients (9%) had delivered a baby (cesarean or normal childbirth) in the past, 7 (9%) had a spontaneous miscarriage and 4 (5%) an abortion.

At the first visit, 27% of patients were smokers, 67% were nonsmokers whereas smoking history was not recorded in 5% of them.

Lastly, at first visit 29/78 (37%) POI patients referred that due to menstrual disturbances they had received either oral (75%) or transdermal (25%) estrogen/progestogen combination. When the diagnosis of POI in each patient was complete, hormone replacement therapy was given in the form of transdermal estrogen/progesterone in all POI patients. The recommendation was treatment once or twice per week depending on patient's symptoms until the age of natural menopause (~51 years).

Table 1. Symptoms, clinical, hormonal (>4 weeks apart) and ultrasonographic characteristics between all POI patients and women with early menopause.

	POI patients ($n = 78$)	Early menopause patients ($n = 61$)	p^c
Primary amenorrhea[a]	2 (3%)	0 (0%)	NS
Secondary amenorrhea[a]	75 (97%)	61 (100%)	NS
Hot flushes[a]	32 (41%)	31 (50%)	NS
Vaginal dryness[a]	28 (35%)	26 (42%)	NS
Night sweats[a]	10 (13%)	16 (26%)	NS
Low libido[a]	10 (13%)	16 (26%)	NS
Mood changes[a]	9 (12%)	13 (21%)	NS
Mean age of menarche for women with secondary amenorrhea (years)[b]	12 (±2.2)	13 (±1.3)	$p < .05$*
Present/previous sexual activity[a]	74 (95%)	61 (100%)	NS
Pre-existing autoimmune disease[a]	13 (17%)	6 (10%)	NS
Pre- existing medical illness[a]	13 (17%)	12 (20%)	NS
Gynecological surgeries[a]	12 (15%)	8 (13%)	NS
Surgical history[a]	14 (18%)	8 (13%)	NS
Family POI history[a]	5 (6%)	3 (5%)	NS
Smoking[a]	21 (27%)	11 (18%)	NS
BMI (kg/m^2)[b]	22.6 (±3.8)	22.9 (±1.7)	NS
FSH_1 (IU/L)[b]	50.3 (±32.3)	50.4 (±23.8)	NS
FSH_2 (IU/L)[b]	55.4 (±33.9)	32.4 (±19.4)	$p < .05$*
LH_1 (IU/L)[b]	30.2 (±22.1)	29.5 (±18.3)	NS
LH_2 (IU/L)[b]	31.8 (±18.1)	27.3 (±15.7)	NS
E_2 (pg/mL)[b]	47.8 (±77.6)	27.1 (±19.7)	NS
PRL (ng/mL)[b]	15.7 (±10.8)	18.2 (±17.8)	NS
AMH (ng/mL)[b]	0.3 (±0.6)	0.05 (±0.07)	NS
TSH (μIU/L)[b]	2.3 (±1.5)	1.8 (±0.8)	NS
AFC (follicles)[b]	2.4 (±1.9)	3.8 (±1.2)	NS
Ovarian volume (cm^3)[b]	5.9 (±4.1)	7.2 (±4.6)	NS
Ovarian atrophy[a]	36 (46%)	26 (43%)	NS

NS: no statistically significant ($p > .05$); POI: premature ovarian insufficiency; BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; AMH: antimüllerian hormone; TSH: thyroid stimulating hormone; AFC: atrial follicle count.
[a]Data are expressed as count, percentage.
[b]Data are expressed as mean ± standard deviation.
[c]Statistically significant when $p < .05$ (*).

Demographic, clinical and hormonal characteristics of women with early menopause

The mean age at first visit of women with early menopause was 43.3 years old (43.3 ± 1.3) whereas the mean age of menstrual disturbances onset was 42.1 years old (42.1 ± 1.5). Women with early menopause were diagnosed four to six months after the first visit at the age of 43.3-years old (43.3 ± 1.4).

Table 1 illustrates the symptoms and clinical characteristics of women with early menopause at the presentation. As in POI patients, the most common symptom in women with early menopause was secondary amenorrhea (100%). The mean age of menarche was approximately 13 years. At the time of diagnosis, the mean FSH levels were 32.4 IU/L. Moreover, 31 women performed a DEXA scan. Seventeen of those had normal bone density, 11 were diagnosed with osteopenia and 3 with osteoporosis. None of the women with early menopause had a pregnancy or a miscarriage/abortion history. At the presentation, 11 women were smokers, 42 nonsmokers and 8 unrecorded. Regarding treatment, 14/61 patients were on treatment and of those (14) reported use of oral (71%) and transdermal (29%) estrogen/progestogen combination. The treatment management after the final diagnosis was initially transdermal estrogen/progesterone combination for each woman.

Comparison of demographic, clinical, hormonal and ultrasonographic characteristics between all POI patients and women with early menopause

The mean age of diagnosis for both groups was 33.8 and 43.3, respectively. Patients with POI and women with early menopause were diagnosed, respectively, five years and four to six months later than the age of menstrual disturbances onset. The comparison of presenting symptoms and clinical characteristics showed a statistically significant difference regarding the age of menarche ($p < .05$; Table 1).

POI patients had greater FSH_2 (FSH levels 4–6 weeks later of FSH at first visit) levels than women with early menopause ($p < .05$). For all POI patients, FSH_2 and LH_2 were greater than FSH_1 and LH_1 levels, whereas for women with early menopause FSH_2 and LH_2 were lower than FSH_1 and LH_1 (Table 1).

There was no significant difference in the ultrasound parameters (AFC, ovarian volume and atrophy) between both groups (Table 1).

Comparison of clinical, hormonal and ultrasonographic characteristics among POI patients under 30 years, between 31 and 39 years and women with early menopause

Subsequently, POI patients were divided in two age groups regarding the age of menstrual disturbances onset (POI_1: ≤30 years and POI_2: 31–39 years). Both groups were compared with the early menopause group, regarding hormonal, menstrual and ultrasonographic characteristics.

By comparing the personal and family menstrual history (age of menarche, maternal age of menopause and presence of POI in the family) we found out that early menopause women were statistically significant older than POI_1 and POI_2 patients when menarche appeared ($p < .05$; Table 2).

By comparing the hormonal and ultrasonographic characteristics of all groups, we found out that FSH_2 for both POI groups was greater than early menopause group ($p < .05$). Ultrasonographic characteristics had no difference (Table 2).

Table 2. Clinical, hormonal and ultrasonographic characteristics among subgroups of patients with POI (under 30 years, between 31 and 39 years) compared to women with early menopause.

	POI_1 (≤30 years) ($n = 42$)	POI_2 (31–39 years) ($n = 36$)	Early menopause patients ($n = 61$)	p^c POI_1 vs. POI_2	p^c POI_1 vs. early menopause patients	p^c POI_2 vs. early menopause patients
Age of menarche (years)[a]	11.8 (±2.6)	12.1 (±1.41)	13 (±1.3)	NS	$p < .05$*	$p < .05$*
Maternal age of menopause (years)[a]	50.1 (±3.2)	50 (±3.6)	50 (±3.6)	NS	NS	NS
AFC (follicles)[a]	2.3 (±1.6)	2.5 (±2.1)	3.8 (±1.2)	NS	NS	NS
Ovarian volume (cm^3)[a]	6.3 (±2.4)	5.9 (±3.2)	7.2 (±4.6)	NS	NS	NS
Presence of ovarian atrophy[b]	19 (45%)	17 (47%)	26 (43%)	NS	NS	NS
FamilyPOI history[b]	2 (5%)	3 (8%)	3 (5%)	NS	NS	NS
BMI (kg/m^2)[a]	22.7 (±4.4)	23.3 (±5.9)	22.9 (±1.7)	NS	NS	NS
FSH_1 (IU/L) [a]	56.1 (±36.4)	45.1 (±28.3)	50.4 (±23.8)	NS	NS	NS
FSH_2 (IU/L) [a]	53.2 (±36.8)	58 (±32.2)	32.4 (±19.4)	NS	$p < .05$*	$p < .05$*
LH_1 (IU/L)[a]	33.5 (±23.4)	27.6 (±20.5)	29.5 (±18.3)	NS	NS	NS
LH_2 (IU/L) [a]	30.7 (±19.6)	33 (±16.3)	27.3 (±15.7)	NS	NS	NS
E_2 (pg/mL)[a]	38.7 (±36.3)	57.4 (±106.7)	27.1 (±19.7)	NS	NS	NS
PRL (ng/mL)[a]	14.5 (±7.8)	17.1 (±12.5)	18.2 (±17.8)	NS	NS	NS
AMH (ng/mL)[a]	0.28 (±0.5)	0.4 (±0.76)	0.05 (± 0.07)	NS	NS	NS
TSH (μIU/L)[a]	2.3 (±1.1)	2.3 (±1.9)	1.8 (±0.8)	NS	NS	NS

NS: no statistically significant ($p > .05$); AFC: atrial follicle count; POI: premature ovarian insufficiency; BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; AMH: antimüllerian hormone; TSH: thyroid stimulating hormone.
[a]Data are expressed as mean ± standard deviation.
[b]Data are expressed as count, percentage.
[c]Statistically significant when $p < .05$ (*).

Discussion

To our knowledge, this is the first study that audits POI patients and women with early menopause in Greece. Our aim was to research and record the age of POI and early menopause diagnosis to address the distinctive characteristics, clinical and hormonal, present in POI and early menopause which could lead to an early diagnosis.

In our study, the mean age of POI diagnosis was 33.8 years, five years later the age of menstrual disturbances onset. The causes of delay included the late referral of the patient to specialists and the delayed presentation of laboratory tests necessary for diagnosis. On the other hand, for women with early menopause the mean age of diagnosis and age of menstrual disturbances onset were approximately equal (∼43 years). Thus, patients with POI seem to be diagnosed later than women with early menopause. In the international database, there were no data demonstrating the age of diagnosis of POI patients compared to women with early menopause.

POI is a heterogeneous disorder. The majority of cases will be idiopathic (unexplained cause), followed by autoimmune, genetic, infectious, metabolic and environmental causes [15]. Particularly, POI can be detected exclusively or co-exist with autoimmune disorders (hypothyroidism, diabetes mellitus, Addison's disease, etc.) [16]. In our study, the majority of patients (77%) had idiopathic POI, followed by autoimmune (17%) and genetic (6%) POI. Hypothyroidism was the most common detected autoimmune disease in 16% of POI patients, followed by diabetes mellitus (1%) and Addison's disease (1%). Regarding the genetic background of our POI population, the premutation of FMR1 gene was the most common genetic factor (5%), followed by one Turner's syndrome case.

Seventy-six percent of POI patients have regular menstrual cycles in puberty and adulthood, followed by irregular menses later [17]. In our study, 3% of POI patients had primary amenorrhea and 97% secondary amenorrhea. Hot flushes, vaginal dryness, sleep disturbance, mood changes were referred only by the cases of secondary amenorrhea. Although it is believed that these symptoms are less frequent in primary amenorrhea due to estrogen withdrawal, we only reported two cases of primary amenorrhea to support this belief [18].

FSH levels are elevated in POI and early menopause [9]. In our study, FSH_1 and FSH_2 were elevated in both groups. FSH_2 was greater than FSH_1 in all POI patients whereas for women with early menopause, FSH_2 was lower than FSH_1. Moreover, all POI patients had statistically significant greater FSH_2 than women with early menopause. Despite the elevated FSH levels, there are studies showing an elevated FSH is not an indication for irreversible ovarian function [13,14]. The doctor should inform POI patients that for cases with temporary ovarian activity there is a chance of 5–10% for a spontaneous pregnancy [19].

Our study demonstrated that the age of menarche of POI patients was approximately 12 years in comparison to the early menopause group (13 years). Moreover, women with early menopause were statistically significantly older when menarche appeared than POI patients. Our findings verified studies which have presented the early menarche (<11 years) as a risk factor for POI or early menopause [20].

Regarding other hormonal and clinical characteristics, we found out that obesity did not seem to play an important role as BMI was under 25 kg/m^2 for all groups. Although an ovarian ultrasound is not required to establish the diagnosis, evidence of small ovarian volumes and low AFC (<5) are all consistent with a picture of POI [21]. In our study, we found that POI patients had ovarian volume < 6 mL and AFC ∼ 3. Regarding other investigations at the time of diagnosis, only 37% of POI patients and 51% of women with early menopause had a DEXA scan performed. The majority of patients in both groups had a normal bone density, followed by osteopenia. The fact that only few patients had a DEXA scan, implying an unawareness of the disorder.

HRT is considered as a cornerstone for the later management of POI and early menopause. Combinations of estrogens with progestogens are usually used to relieve patients from menopausal symptoms. After diagnosis, all POI and early menopause patients received transdermal estrogens and progestogens once or twice per week according to the case. The recommendation was the use of HRT till the age of natural menopause (∼51 years).

This is the first study about POI patients in Greece presenting data from two specialized departments. Due to the rarity of the disorder, more studies are necessary. Our findings are limited

but they aim to point the need for further investigations in this area, nationally and internationally.

Conclusion

To conclude, we found that the mean age of POI and early menopause diagnosis was 33.8 and 43 years, respectively. POI patients and women with early menopause were diagnosed, respectively, five years and four to six months later than the age of menstrual disturbances onset. It is estimated that in the future the prevalence of POI will increase due to the improved number of cancer survivors and the better knowledge of the disorder from the clinicians. In any case, the clinician should be suspicious when $a < 40$ years old woman refers oligomenorrhea (>4 months) with elevated gonadotrophins. In this case, the patient should be examined and repeat (>4 weeks apart) FSH to have a diagnosis. Further studies in this area are necessary.

Compliance with Ethical Standards

All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Luisi S, Orlandini C, Regini C, et al. Premature ovarian insufficiency: from pathogenesis to clinical management. J Endocrinol Invest. 2015; 38(6):597–603.
[2] Nelson LM, Anasti JN, Kimzey LM, et al. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. J Clin Endocrinol Metab. 1994;79: 1470–1475.
[3] Albright F, Smith PH, Fraser R. A syndrome characterized by primary ovarian insufficiency and decreased stature: report of 11 cases with a digression on hormonal control of axillary and pubic hair. Am J Med Sci. 1942;204(5):625–648.
[4] Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol. 1986;67(4):604–606.
[5] Shifren JL, Gass MLS. The North American Menopause Society recommendations for clinical care of midlife women. Menopause. 2014; 21(10):1038–1062.
[6] Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. Womens Health (Lond Engl). 2015;11:169–182.
[7] Anastasi JN. Premature ovarian failure: an update. Fertil Steril. 1998; 70:1–15.
[8] Shuster LT, Rhodes DJ, Gostout BS, et al. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010; 65(2):161–166.
[9] The Eshre Guideline Group on POI, Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926–937.
[10] Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(10):3489–3510.
[11] Gleicher N, Barad DH. Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR). Reprod Biol Endocrinol. 2011;9(1):67.
[12] Ben-Nagi J, Panay N. Premature ovarian insufficiency: how to improve reproductive outcome? Climacteric. 2012;17:342–346.
[13] Bidet M, Bachelot A, Bissauge E, et al. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J Clin Endocrinol Metab. 2011;96(12):3864–3872.
[14] Otero UB, Chor D, Carvalho MS, et al. Lack of association between age at menarche and age at menopause: Pró-Saúde study, Rio de Janeiro, Brazil. Maturitas. 2010;67(3):245–250.
[15] Nelson LM. Clinical practice, 2009 Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606–614.
[16] Cox L, Liu JH. Primary ovarian insufficiency: an update. Int J Womens Health. 2014;6:235–243.
[17] Rudnicka E, Kruszewska J, Klicka K, et al. Premature ovarian insufficiency – aetiopathology, epidemiology, and diagnostic evaluation. Prz Menopauzalny. 2018;17:105–108.
[18] Kovanci E, Schutt AK. Premature ovarian failure: clinical presentation and treatment. Obstet Gynecol Clin North Am. 2015;42(1):153–161.
[19] Rebar RW, Erickson GF, Yen SS. Idiopathic premature ovarian failure: clinical and endocrine characteristics. Fertil Steril. 1982;37(1): 35–41.
[20] Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. Hum Reprod. 2017;32(3):679–686.
[21] Torrealday S, Kodaman P, Pal L. Premature ovarian insufficiency – an update on recent advances in understanding and management. F1000 Res. 2017;6:2069.