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REVIEW PAPER

Premature ovarian failure

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Abstract

Premature ovarian failure (POF) is the term usually used to describe women aged younger than 40 years, who present with amenorrhoea, hypergonadotropic hypogonadism, and infertility. POF is a devastating diagnosis for reproductive-aged women. The clinical presentation is diverse, and several different disorders can lead to premature ovarian failure. POF has serious health consequences, including psychological distress, infertility, osteoporosis, autoimmune disorders, ischaemic heart disease, and increased risk of mortality. Hashimoto's disease is the most frequent autoimmune disorder associated with premature ovarian failure. Management should be initiated immediately to prevent long-term consequences. Oestrogen therapy is the mainstay of management. Hormone therapy should be provided to eliminate symptoms of oestrogen deficiency.

Key words: premature ovarian failure, infertility, menstrual disorders.

Definition

Premature ovarian failure (POF) is the cessation of ovarian function before 40 years of age. The term refers to the condition when the ovaries have lost their germinative and hormonal functions because of the exhaustion of the number of ovarian follicles prior to the typical age for physiological menopause, which in Poland averages 51 years [1].

Most probably, POF occurs when the exhaustion of the number of ovarian follicles is concurrent with autoimmune ovarian damage and occurs in association with genetic predisposition.

POF develops in about 1% of women [2]. The incidence of POF is 1 in 100 women before 40 years of age and 1 in 1000 women before 30 years of age.

First case reports

POF was defined by de Moraes-Ruehsen and Jones in 1967 [3] as non-physiological amenorrhoea before the age of 40 years, but after puberty. In 1939, the hormone profile in women with POF was described as hypergonadotropic hypoestrogenism [4]. In 1950, the clinical features of POF were discussed in detail by Atria [5]. The author reported on the cases of 20 young women before 35 years of age with secondary loss of menses, hot flashes, infertility, and endometrial atrophy.

Diagnosis

The physician may encounter this condition when examining a young female patient who is struggling to get pregnant or is experiencing secondary amenorrhoea. In order to make a diagnosis in the case of a young female, it might be helpful to determine if there are any menopausal symptoms. The medical history of patients with POF usually reveals a normal age of menarche [6, 7] and regular menstrual cycles, followed by oligomenorrhoea or sudden amenorrhoea. In some cases, secondary loss of menses is diagnosed after stopping contraceptive pills [8-10]. Most frequently, women suffer from hot flushes, excessive sweating, hair loss, as well as skin and mucous membrane dryness.

Tests reveal a hypergonadotropic-hypogonadic hormone profile

Tests reveal a hypergonadotropic-hypogonadic hormone profile (also referred to as primary hypogonadism), which is characterised by low oestradiol (E_2) levels (< 20 pg/ml), elevated gonadotropin levels (follicle-stimulating hormone [FSH] > 20 IU/l), low anti-Müllerian hormone (AMH) levels – < 0.5 ng/ml (< 1 ng/ml), and low inhibin B levels [1, 11, 12].

FSH levels > 40 IU/l, recorded at least twice at an internal of 4-6 weeks, call for a diagnosis of premature

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ovarian failure [13, 14]. The diagnosis should not be made on the basis of a single FSH test because this causes a great deal of mental strain for young women. Also, the patient should be informed that a transient return of ovarian function (intermittent ovarian failure) is possible [15, 16]. This seldom happens, but some pregnancy cases in women with POF have been reported.

Low E_2 levels result from ovarian disorders in cases where the feedback mechanism stimulates the pituitary gland to secrete gonadotropic hormone (high FSH levels). The more dismal the ovarian failure, the higher the FSH levels.

AMH is a glycoprotein produced by the granulosa cells of the preantral and small antral follicles. AMH belongs to the group of peptide growth and growth differentiation factors. AMH levels do not hinge on the day of the cycle. Its concentrations decrease with age, which makes it a very good marker for fertility decline, including premature ovarian failure. In patients with POF, AMH levels are very low or negligible. In women affected by polycystic ovary syndrome (PCOS) the levels of AMH are considerably elevated because this condition is characterised by an excessive number of ovarian follicles (however, there is no folliculogenesis).

Inhibin B is also useful to assess the ovarian reserve. However, its measurement depends on the phase of the cycle since it is produced by the granulosa cells of the early antral follicles mainly in the follicular phase of the menstrual cycle. In the early follicular phase, the levels of inhibin B reflect the number and quality of ovarian follicles. Consequently, patients with POF have decreased levels of inhibin B.

What affects the ovarian follicular maturation?

In human females, the process of ovarian follicular maturation, or folliculogenesis, is a highly organised and complex process [17]. Folliculogenesis is the progressive maturation of small primordial follicles that progress to become large ovulatory follicles. The follicle consists of the gamete itself, or oocyte, surrounded by supporting somatic cells, the granulosa and thecal cells that are important for the growth and development of the follicles. When follicles eventually mature, the oocytes are released from the surface of the ovary, collected by the uterine tube, and either proceed to become fertilised and implanted in the uterus or are lost. The process of follicular maturation occurs continuously, and it can take as long as a year to proceed from the initiation of growth of a primordial follicle to become an ovulatory follicle. Human females begin life with a fixed number of primordial follicles, but only a few hundred follicles completely develop, and the oocyte is released during ovulation. The granulosa and thecal somatic cells synthesise and secrete various hormones and growth factors, including inhibin, FOXL2, IGF-1, melatonin, steroid hormones and other growth and differentiation factors (such as bone morphogenetic protein 15 [BMP15], and growth differentiation factor 9 [GDF9]), and are in turn regulated by the gonadotrophins, FSH, and luteinizing hormone (LH). The outcome of folliculogenesis is either ovulation or follicular atresia.

Histopathological diagnosis

Two histopathological types of POF have been described. In type 1 (afollicular), there is a complete depletion of ovarian follicles. This form is found in patients with POF that is associated with gonadal dysgenesis, chromosome aberrations, and disorders of sex development. The lack of ovarian follicles results from the fact that the germinal cells either fail to develop or are not present [18]. In type 2 (follicular), follicular structures are preserved in the ovary, so either an induced or spontaneous return of ovarian function is still possible. Type 2 of POF can have one of the three forms: 1) oophoritis, or an inflammation of the ovarian follicles; 2) ovaries with very few follicles present; or 3) ovaries with numerous primordial follicles (resistant ovary syndrome – ROS). The follicular form can progress into the afollicular form (in galactosaemia, in an animal model of autoimmune oophoritis).

The occurrence of ROS seems to have a different pathogenesis. In 1969, Jones and de Moraes-Ruehsen were the first to report on three female patients with ROS; based on the first patient's surname, they called it "Savage syndrome" [19]. Other authors have also described a similar combination of symptoms, such as numerous primordial follicles present in the ovary, hypergonadotropic hypoestrogenism, and decreased sensitivity even to high-dose gonadotropin used in patients both with primary and secondary lack of menses, in order to induce ovulation [20, 21]. Clinically, patients with ROS have manifested POF symptoms. Some studies conducted in patients with ROS have demonstrated the lack of gonadotropin receptors or the presence of antibodies to these receptors that interfere with their activity; whereas, other studies have shown that the gonadotropin molecule might be abnormally structured (FSH and LH are biologically inactive) or that there might be pathological lesions of the thymus [22].

Causes

Genetic

Premature ovarian failure may have genetic causes, such as Turner syndrome, fragile X syndrome (FMR1 gene) or pseudohypoparathyroidism type 1a (GNAS1 gene). POF can be associated with other non-endocrine and endocrine diseases. The mutations of *AIRE* gene are responsible for polyendocrinopathies (APS I-III). Inhibin

is a potential candidate gene for POF based on its dual actions on FSH secretion by the pituitary and gametogenesis in the gonads [23] (Table I).

One of the reasons for POF is a molecular defect in the *FMR1* gene (called a premutation). FMR1 testing makes it possible to discover predisposition to POF, and consequently to lower fertility or even infertility. The test result is of great importance to women who are postponing the decision about having children. Men who have inherited a defect in the FMR1 suffer from fragile X syndrome, which is the second most common cause of intellectual disability (mental retardation) after Down's syndrome.

Currently, it is even sometimes recommended that gene testing for POF be considered before starting hormonal contraception. The advocates claim that a woman may decide not to use contraception and bear a child earlier in her life if she is aware of a higher risk of developing POF due to the mutation. Indeed, it is sometimes the case that when a woman stops long-term contraceptive medication, it turns out that her ovarian function is no longer sufficient to become pregnant.

Table I. Genetically determined premature ovarian failure

Type	OMIM	Gen	Locus
POF1	311360	*FMR1*	Xq26-q28
POF2A	300511	*DIAPH2*	Xq13.3-q21.1
POF2B	300604	*POF1B*	Xq13.3-q21.1
POF3	608996	*FOXL2*	3q23
POF4	300510	*BMP15*	Xp11.2
POF5	611548	*NOBOX*	7q35
POF6	612310	*FIGLA*	2p12
POF7	612964	*NR5A1*	9q33

Autoimmune

Another cause may be an autoimmune process consisting in the production of anti-ovarian antibodies. Patients with POF can develop concomitant autoimmune diseases, such as autoimmune thyroiditis (Hashimoto's disease), autoimmune adrenal insufficiency (Addison's disease), diabetes type 1, coeliac disease, albinism, rheumatoid arthritis, systemic lupus erythematosus, and myasthenia gravis [24].

POF can be part of the autoimmune polyglandular syndrome (APS). For this reason, in order to diagnose the former, it is necessary to determine whether the patient presents with other autoimmune endocrine disorders [25-27] because as it has been proven that POF is likely develop 8-14 years before Addison's disease does [28-33].

The autoimmune pathogenesis is a multistage process. In this case, genetic and environmental factors must occur. The pathogenic mechanism has been thoroughly investigated in animal models of insulitis and thyroiditis [34]. First, abnormal amounts of dendritic cells accumulate in the endocrine tissue. Then, autoreactive CD4+ and CD8+ lymphocytes, which are a source of IgG autoantibodies, are produced in an uncontrolled manner. Autoreactive T lymphocytes cause damage to the gland tissue. Patients with autoimmune thyroid diseases (Graves' disease and Hashimoto's disease) have been shown to have increased amounts of macrophage cells and NK cells with MHC class II molecules (histocompatibility complex class II) in the thyroid gland [19, 20], and increased IgG levels in blood [35, 36].

Vaccination

Several years ago, cases of POS after anti-HPV vaccination were recorded. The patients developed secondary amenorrhea following HPV vaccinations, which did not resolve upon treatment with hormone replacement therapies. Serological evaluations showed low levels of E_2 and increased FSH and LH and specific auto-antibodies were detected (antiovarian and antithyroid), suggesting that the HPV vaccine triggered an autoimmune response.

The evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition was documented. Post-vaccination autoimmune phenomena are a major facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), and different vaccines, including HPV, have been identified as possible causes [37].

Enzymatic

Various congenital enzymatic deficiencies, such as galactosaemia, can also be the reason for POF.

Oncologic treatment

POF may be also the result of oncologic treatment (radio- or chemotherapy) as well as surgical treatment of ovaries. In case of radiotherapy, ovarian failure occurs at doses > 0.06 Gy, and permanent and irreversible damage to the ovaries occurs at doses > 8 G (Table II).

Table II. Drugs used in chemotherapy and the risk of fertility impairment

Risk of fertility impairment	Drugs
High	cyclophosphamide, melphalan, dacarbazine, busulfan, chlormethine (e.g. MOPP protocol)
Middle	cisplatin, carboplatin, doxorubicin, BEP, ABVD
Low	vincristine, methotrexate, bleomycin, mercaptopurine, vinblastine

Environmental

Most probably, some viral infections are the reason for POF (mumps virus, *Cytomegalovirus*, *Varicella* zoster virus). Other possible causes include tuberculosis, malaria, and shigella infection [38].

Smoking is also among the main factors that result in premature menopause. However, the occurrence of this particular cause depends on the woman herself [39].

Unknown

In most isolated defects the cause is still unknown. Several candidate genes have been identified, but causative mutations have been found in a strict minority of patients. The prevalence of some genetic defects remains to be determined (e.g. BMP15 mutations). Although one paper described auto-antibodies against FSHR in a series of women with POF, auto-antigens and specific auto-antibodies for the diagnosis of autoimmune forms of isolated POF remain to be determined.

The term reproductive autoimmune failure syndrome (RAFS) is being used more and more often. Anti-ovarian antibodies do not correlate with the presence or severity of oophoritis, so the measurement of these antibodies is not recommended. The measuring of CD8 density on T cells could provide a reliable indicator of the involvement of the immune system in POF [40, 41].

Premature ovarian failure symptoms and effects

Oestrogen deficiency leads to the first symptoms: hot flushes, excessive sweating, nervousness, diminished libido, weakness, skin, and mucous membrane dryness.

Also, premature oestrogen deficiency results in lower bone mineral density (osteopaenia, osteoporosis). Even young women with POF are likely to have a substantial decrease in bone mineral density, so densitometry testing is necessary in these cases. Patients with POF have been shown to have a higher risk of fractures than women who have developed osteoporosis for reasons other than POF (such as hyperthyroidism, steroid treatment, hyperparathyroidism).

These patients should also have vitamin $25OHD_3$ levels measured. By doing so, possible deficiency could be addressed and bone mass loss prevented.

Furthermore, insufficient oestrogen levels are associated with metabolic disorders, thus leading to cardiovascular diseases, such as atherosclerosis, hypercholesterolaemia, as well as urogenital atrophy, including vaginal dryness and infections.

However, lower fertility or even infertility are the most disturbing POF-related problems to every young woman.

Autoimmune hypothyroidism is the disease most commonly associated with POF, so screening by measurement of TSH, free T4, anti-thyroid-peroxidase, and anti-thyroglobulin antibody levels is recommended. The disease most commonly associated with POF is coeliac disease.

Autoimmunity against the adrenal gland has been shown in 2-10% of POF cases [42, 43].

Ovarian reserve

The ovarian reserve is assessed on cycle day 3 through AMH, FSH, antral follicle count (AFC), inhibin B, and E_2 testing. Patients with POF have elevated levels of FSH and E_2 (cycle day 3), considerably lower levels of AMH and inhibin B, as well as low AFC levels.

AMH is produced by the granulosa cells of the preantral follicles. Currently, it is believed that AMH is the best marker to be used to assess the ovarian reserve. FSH levels may vary from cycle to cycle.

It is commonly accepted that FSH levels > 15 IU/l are abnormal, and with FSH being > 20 IU/l the chances of getting pregnant are very unrealistic. According to some data, the ovarian reserve is thought to be diminished even at FSH levels > 10 IU/l. Women with a lower ovarian reserve quite often manifest normal FSH concentrations. For this reason, in order to assess the ovarian reserve, both FSH and AMH levels should be measured [44, 45].

Treatment

Casual treatment should be applied, if possible. A return of ovarian function has been reported in some patients with coeliac disease after introducing a gluten-free diet. Substitution treatment has also been attempted using hormone replacement therapy.

Apart from that, positive effects have been reported upon treatment for POF through immunomodulation therapy (in order to induce ovulation), including high-dose corticosteroid and intravenous immunoglobulin treatment [46-48]. Furthermore, a return of ovarian function has been observed in patients treated for myasthaenia gravis using thymectomy [49, 50]. Attempts have also been made to use monoclonal antibodies (e.g. etanercept) when treating POF caused by autoimmune ovarian damage [51, 52].

Recently, melatonin supplementation has been described as a treatment modality in case of perimenopause [11, 12, 53]. It has been reported to have a positive effect on thyroid function and increasing gonadotropin levels. According to some data, melatonin is also useful to restore fertility and menstruation as well as to prevent menopause-related depression.

Melatonin is produced mainly by the pineal gland, but it is also secreted in many other body tissues, including retina, digestive tract, skin, bone marrow, and lymphocytes. Its paracrine function is generally accepted; however, its precise role still remains to be deter-

mined. Melatonin is produced in the dark because light has an adverse effect on its synthesis.

It has been confirmed that the pineal gland contains receptors for LH, FSH, androgens, and oestrogens. Moreover, melatonin has been shown to be present in the follicular fluid during ovulation. There, its concentrations are three times as high as they are in the blood serum, with its levels being higher during morning hours and in the seasons of the year when there is little sunlight. As the ovaries cannot produce this hormone, melatonin, which can be found in the follicular fluid, comes from blood, and the mature follicles are most probably able to accumulate it. It seems that melatonin can support ovulation.

Melatonin levels have been shown to be lower during perimenopause and after menopause. Administration of 3 mg melatonin daily for six months has resulted in lower LH levels in women 43-49 years of age (perimenopause), which has not been observed in women after menopause (aged 50-62 years). Lower FSH levels have been found in women with initially low concentrations of melatonin. In all the cases, administration of melatonin led to higher thyroid hormone concentrations. Melatonin is sometimes referred to as a time-keeping hormone because its regulates the secretion of pituitary gonadotropins.

Furthermore, melatonin regulates the immune system. Both *in vitro* and *in vivo*, it stimulates non-specific humoral and cell-mediated immunity, as well as antibody-mediated immunity. For this reason, it has been attempted to use melatonin for treatment of cancer. According to epidemiological studies, shift work may be a risk factor for the onset of breast cancer and colorectal cancer in women.

The question arises whether supplementation of melatonin could hinder adverse processes of the organism and cancerogenesis or improve circadian rhythms and fertility. The role of melatonin in the regulation of ovarian function still remains to be determined.

It has also been reported on positive effects of dehydroepiandrosterone (DHEA) supplementation in women with premature menopause [54, 55]. There have been cases of spontaneous pregnancies in infertile women with POF qualifying for donor-egg in vitro fertilisation (IVF) treatment. In these patients, low DHEA levels have been addressed with DHEA supplementation, thus leading to long-awaited pregnancy before IVF treatment. It has been shown that administration of DHEA in patients with premature ovarian failure increases the chances of getting pregnant, reduces the risk of miscarriages, and makes IVF treatment more successful. However, according to the latest recommendations of October 2014, DHEA supplementation should not be used in patients with POF, who have normal adrenal function.

In women with POF secondary to chemotherapy, using stem cell transplantation has been attempted in order to restore the germinative function of the ovary. In some studies, oogenesis has been successfully restored in the ovaries, but the ovarian follicles have neither maturated nor produced egg cells, and further research is needed [56, 57].

Conclusions

Premature ovarian failure means menopause before 40 years of age and affects about 1% of women. The main problems include lack of ovulation (infertility) and hypoestrogenism. The reasons for POF may vary, including genetic predisposition, autoimmune and enzymatic disorders, infections, and iatrogenic causes.

POF is a devastating diagnosis for reproductive-aged women. The diagnosis is relatively easy. However, it has serious health consequences, including psychological distress, infertility, osteoporosis, autoimmune disorders, ischaemic heart disease, and increased risk of mortality. Management should be initiated immediately to prevent long-term consequences. Oestrogen therapy is the mainstay of management. Postmenopausal oestrogen therapy studies should not be used to determine the risks of treatment in these young women [58].

Disclosure

Author reports no conflict of interest.

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