

# Premature Ovarian Failure

Svetlana Vujović<sup>1,2</sup>, Miomira Ivović<sup>2</sup>, Milina Tančić-Gajić<sup>2</sup>, Ljiljana Marina<sup>2</sup>, Marija Barać<sup>2</sup>, Zorana Arizanović<sup>2</sup>, Ana Nenezić<sup>2</sup>, Maja Ivanišević<sup>3</sup>, Jelena Micić<sup>3</sup>, Silvija Sajić<sup>1,4</sup>, Dragan Micić<sup>1,2</sup>

<sup>1</sup>School of Medicine, University of Belgrade, Belgrade, Serbia;

<sup>2</sup>Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia;

<sup>3</sup>Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia;

<sup>4</sup>University Children's Hospital, Belgrade, Serbia

## SUMMARY

Premature ovarian failure (POF) is the occurrence of hypergonadotropic hypogonadal amenorrhea in women under the age of forty years. It is idiopathic in 74-90% patients. Known cases can be divided into primary and secondary POF. In primary POF genetic aberrations can involve the X chromosome (monosomy, trisomy, translocations, deletions) or autosomes. Genetic mechanisms include reduced gene dosage and non-specific chromosome effects impairing meiosis, decreasing the pool of primordial follicles and increasing atresia due to apoptosis or failure of follicle maturation. Autoimmune ovarian damage is caused by alteration of T-cell subsets and T-cell mediated injury, increase of autoantibody producing B-cells, a low number of effector/cytotoxic lymphocyte, which decreases the number and activity of natural killer cells. Bilateral oophorectomy, chemotherapy, radiotherapy and infections cause the secondary POF. Symptoms of POF include irritability, nervousness, loss of libido, depression, lack of concentration, hot flushes, weight gaining, dry skin, vaginal dryness, frequent infections etc. The diagnosis is confirmed by the level of FSH of over 40 IU/L and estradiol below 50 pmol/L in women aged below 40 years. Biochemical and other hormonal analysis (free thyroxin, TSH, prolactin, testosterone), karyotype (<30 years of age), ultrasound of the breasts and pelvis are advisable. Optimal therapy is combined estrogen progestagen therapy given in a sequential rhythm, after excluding absolute contraindications. Testosterone can be added to adnexectomized women and those with a low libido. Sequential estrogen progestagen replacement therapy is the first line therapy for ovulation induction in those looking for pregnancy and after that oocyte donation will be advised. Appropriate estrogen-progestagen therapy improves the quality of life and prevents complications such as cardiovascular diseases, osteoporosis, stroke etc.

**Keywords:** premature ovarian failure; etiology; therapy

## INTRODUCTION

Premature ovarian failure (POF) is a heterogeneous disorder of multifactorial origin defined as the occurrence of secondary amenorrhea, hypergonadotropism and hypogonadism in women under the age of 40 years. The incidence is 1:10,000 women at the age of 20, 1:1,000 at the age of 30 and 1:100 at the age of 40 years [1]. It can be sporadic or familial (4-33%) [2, 3].

decreased number of follicles being found during the ovarian development or increased rate of follicle loss or accelerated atresia. Proposed etiological factors of POF are shown in Table 1.

## PRIMARY POF

Primary POF represents a group of disorders induced by changes in some specific genes or autoimmune process or enzymatic disorder.

## ETIOLOGY

Most cases of POF are idiopathic [4]. Abnormal pairing in meiosis resulting in oocyte apoptosis at a check point has been suggested as an etiological factor [5]. POF may result from a

## Genetic aberrations

Genetic mechanism of POF includes reduced gene dosage and non-specific chromosome effects that impair meiosis. These can lead to

**Table 1.** Etiology of premature ovarian failure (POF)

Primary POF	Genetic aberrations	X-linked (monosomy, trisomy, deletions, translocations, fragile X)
		Autosomal dominant (FSH receptor gene polymorphism, inhibin B mutation, etc.)
	Enzyme deficiency	Metabolic
	Autoimmune disease	
Secondary POF	Surgical	Bilateral oophorectomy
		Hysterectomy without oophorectomy /uterine artery embolisation
	Chemotherapy or radiotherapy	
	Infections	

## Correspondence to:

Svetlana VUJOVIĆ  
Clinic of Endocrinology, Diabetes  
and Metabolic Diseases  
Clinical Center of Serbia  
Dr Subotića 13, 11000 Belgrade  
Serbia  
vujovics@eunet.rs

**Table 2.** Genes implicated in premature ovarian failure

Categories	Chromosomes	Gene
Identified mutations	X	FMR1, 2, BMP15
	Autosomal genes	FOXL2, FSHR, LHR, FSH $\beta$ , LH $\beta$ , inhibin A, GALT, AIRE, NOGGIN, POLG
Unidentified mutations	X	AT2, c-kit, sox 3
	Autosomal genes	MIS
Candidate genes	X	DIAPH2, DFFRX, XPNPEP2, 2FX, FSHPRH1, XIST
	Autosomal genes	WT1, ATM

ovarian failure by causing decrease in the pool of primordial follicles, increased atresia of the follicles due to apoptosis or failure of follicle maturation (Table 2).

### **X-linked**

#### *X monosomy – Turner syndrome*

Ovarian follicles degenerate at birth as a result of the lack of a diploid dosage of one or more vital genes, both alleles of which are active in oogenesis. Oogenesis proceeds normally in these individuals until diplotene oocytes begin to be incorporated into nascent follicles. There is a subsequent block of production of complete follicles manifesting as fetal follicular atresia. Loughlin et al. [6] found that in 80% of cases the paternally derived X is lost. Turner syndrome is characterized by primary amenorrhea, short stature and characteristic phenotypic features. Cytogenetic data indicate that most Turner syndrome features map to the short arms of the X (Xp) and Y (Yp) chromosomes [7].

#### *Trisomy X*

It occurs in 1:900 women and does not influence the fertility rate significantly. Jacobs et al. [8] described a woman with XXX and POF. According to Goswami et al. [9] 3.8% patients with POF had the triple X.

#### *Mosaicism*

Women having mosaicism (45X/46XX and 45X/47XXX) carry mixed germ lines and manifest phenotypic abnormalities and POF. Simpson and Rajkovic [10] found that 12% of them menstruate.

#### *Deletions*

They are more common than translocations. Deleted X chromosome necessarily leave a portion of normal unpaired X and isodentric probably interfere with pairing, resulting in atresia of oocytes. Ovarian function is preserved when distal deletions occur. Proximal deletions induce ovarian failure. Deletion at Xp11 results in 50% primary and 50% secondary amenorrhea, while the deletion of Xq13 induces primary amenorrhea. Merry et al. [11] found that a large deletion that removes the whole critical region for POF in Xq21 is not associated with ovarian failure.

### *Translocations*

In the X short arm the proximal region is of the greatest importance for normal ovarian functioning. Women with deletions in Xp11.1 to Xp21 usually show either complete or premature POF. The critical region for normal ovarian function has been proposed for Xq13-26 [12, 13]. Within this region the most frequent breakpoints involve POF1 loci Xq26-qter [14] and POF2 loci Xq13.3-21.1 [15].

Distal deletions involving POF1 loci are associated with POF at ages 24-39 years, and translocations involving the POF2 locus cause POF at an earlier age of 16-21 years. Chromosome dynamics in this region is sensitive to structural changes and unpaired chromosomes provoke oocyte apoptosis.

### *Fragile X*

Normal length of CGG repeats in 5'-UTR is <50 repeats, premutation occurs in 50-200 repeats and full mutation >200 repeats. FMR1 is expressed in the granulosa cells of the primary follicles but only in a part of the preantral-antral follicles [16]. The premutation allele of the FMR1 gene is at the FRAXA locus in Xq27.3. The FMR1 premutation is found in 5% of all POF [16]. They have 50-200 copies of the CGG repeats in the 5' untranslated region of the FMR1 gene. Fragile X sy is due to CGG expansion >55 repeats resulting in POF in female carriers and in mental retardation in males.

### **Autosomal dominant genes**

Autosomal translocations are uncommon in women with POF. Most reports of translocations document X/autosomal balanced translocations with no common autosomal breakpoint. Follicle stimulating hormone and luteinizing hormone receptor gene polymorphism were reported.

FOXL2 (forkhead transcription factor) is associated with blepharophimosis, ptosis and epicanthus inversus syndrome. EIF2B (mutant in the eukaryotic translation), the initiation factor 2B, is a family of genes associated with CNS leukodystrophy and ovarian failure.

### **Enzyme deficiency (metabolic)**

Deficiency of 17 hydroxylase and galactosae-1-phosphate uridylyl transferase (GALT) can induce POF.

According to Waggoner et al. [17] a study of 81% affected women developed ovarian failure with primary amenorrhea or secondary amenorrhea shortly after puberty. Typical characteristics of women with 17 OH deficiency includes primary amenorrhea, high levels of FSH, LH, progesterone, deoxycorticosteron, hypertension and hyperkalemic alkalosis. Intracellular accumulation of metabolites of galactose or glycolization deficiency induce disturbance of germinal cell migration leading to deficiency of the germinal cell pool [18].

### Autoimmune disease

Autoimmune mechanism is involved in the pathogenesis of up to 30% of cases of POF [19]. Evidence of oophoritis is rare (<3%) in POF in the absence of adrenal involvement [20].

Alterations of T cell subsets and T cell mediated injury is likely to play an important role in the pathogenesis of autoimmune POF. A statistically significant increase in CD8 density on T cells [21], an increase of antibodies producing B cells and a low number of effector suppressor/cytotoxic lymphocytes, reduced natural killer (NK) cell number and impaired NK cell activity have been documented. Oophoritis can be transferred by cells with a T helper phenotype. The role of cytokines has also been described in causing follicular atresia in POF.

POF can be associated with endocrine and non-endocrine diseases (Table 3).

The AIRE gene is responsible for autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy (APECED) leading to ovarian insufficiency. It is assigned to the chromosome 21q22.3 and more than 40 mutations are reported [22].

Positive adrenal antibodies can be found in some cases of POF. About 2-10% of POF cases are known to be associated with adrenal autoimmunity [23].

Autoimmune polyglandular syndrome (APS) can be divided into APS 1, 2 and 3 (Table 4).

## SECONDARY POF

### Surgical

Secondary POF is caused by some interventions (oophorectomy or chemo and radiotherapy, infections); bilateral oophorectomy or surgical menopause, hysterectomy without oophorectomy/uterine artery embolization. Uterine artery embolization has also a potential to result in POF by compromising the vascular supply to the ovary [24].

### Chemotherapy and radiotherapy

Before therapy of malignancy it is necessary to take care of preserving fertility by conserving the ovarian tissue or oocytes. Ovarian radiation of 9 Gy renders humans infertile. Complete ovarian failure occurs with a dose of 20 Gy. Therefore, ovariopexy (transposition of ovaries from the radiation field) preserves ovarian function in 60-100% patients [25].

POF can be sequellae of cytotoxic chemotherapy which is gonadotoxic in drug- and dose-dependent way.

Thus, POF can be caused by the therapy for myeloid leukemia, in non-Hodgkin lymphoma, Hodgkin disease and breast cancer in 50% of women. The use of gonadotrophin releasing analogue to suppress ovarian activity in order to protect it is as yet not supported by randomized controlled trials [26].

### Infections

Ovaries can be exposed to viruses and toxins. Mumps oophoritis occurs in 2-8% of women with POF [27]. Other causes include TBC, malaria, varicella, shigella, CMV, herpes simplex, etc. The mechanism by which chemicals (heavy metals, solvents, pesticides, plastics, cigarette smoke etc.) affects ovarian function may involve hormonal and immune disruption, DNA adduct formation, altered cellular proliferation or inappropriate cellular death [28].

**Table 3.** Endocrine and non-endocrine diseases associated with premature ovarian failure

Endocrine	Hypo/hyperthyroidism, hypoparathyroidism, diabetes mellitus type II, hypophysitis, Addison's disease
Non-endocrine	Idiopathic thrombocytopenic purpura, chronic candidiasis, vitiligo, alopecia, hemolytic or pernicious anemia, systemic lupus erythematoses, rheumatoid arthritis, cirrhosis, Sjogren's sy, primary biliary cirrhosis, chronic hepatitis etc.

**Table 4.** Type, inheritance, involvement and age of appearance of autoimmune polyglandular syndromes

Type	Inheritance	Autoimmune involvement	Age
I	Autosomal recessive mutation in AIRE gene	Candidiasis + Addison's disease + hypoparathyroidism	3-5 years
II	Polygenic dominant HLADR3	Addison's disease + Autoimmune thyroiditis (Schmidt's sy) and/or diabetes mellitus type I (Carpenter's sy)	3rd or 4th decade
III	Apart from the absence of adrenal failure, no clinical differences compared to type II	Hypothyroidism and other immune syndromes with EXCLUSION of Addison's disease	Adults

## PRESENTATION AND ASSESSMENT

Young women who experience loss of menstrual regularity for three or more consecutive months should have appropriate evaluation of POF at their first visit [29]. Most of women do not have any symptoms. However, in untreated POF, typical symptoms of estrogen deprivation may be present. They include nervousness, irritability, hot flushes, restlessness, insomnia, depression, loss of libido, loss of concentration, etc. Physical examination may reveal thinness of the skin or weight gain, painful bones, stiffness, etc. After history taking and physical examination, blood samples have to be taken for the biochemical analysis [30]. Hormone analysis (FSH, LH, prolactin, estradiol, progesterone, testosterone, free thyroxin, TSH) is necessary, as is autoimmune screening for polyendocrinopathy. FSH of over 40 IU/L and estradiol below 50 pmol/L in women aged below 40 years confirm the diagnosis. Adrenocorticotropic hormone stimulation test is optional if Addison's disease is suspected. Chromosome analysis is advised in women with POF younger than 30 years. There is no role for a routine ovarian biopsy. Pelvic and breast ultrasounds are advisable. Co-existing diseases must be detected. Dual X-ray absorptiometry (DXA) is optional.

## MANAGEMENT

Patients must be provided with adequate information (education, understanding and counseling). Management includes hormone replacement therapy for the prevention of long term complications and therapy for fertility [31].

## HORMONE REPLACEMENT THERAPY

Sequential estrogen progestogen replacement therapy is the mainstay of treatment for women with POF. Proposed combination of estrogen-progestogens are Ethynilestradiol 0.03 mg and Drospirenone 3 mg or estradiol valerat 2 mg and norgestrel 0.5 mg or estradiol valerat 2 mg and noretisteron acetate 1 mg. It is recommended until the average age of natural menopause. The dose of estrogen therapy should be higher than the average dose for the menopausal therapy. There is no evidence to show that ERT increases the risk of breast cancer in women with POF. Hence, women with POF do not need to start mammography screening early. Additional treatment with testosterone is advised in adnexectomized women and

those with a low libido [32]. It is necessary to exclude the contraindications of hormone therapy; gynecological carcinomas and carcinoma of the breast, liver and kidney failure, pregnancy, thromboembolism, porphiria and meningioma.

## FERTILITY

Women with POF have a 5-15% chance of conceiving spontaneously. The first line therapy is a trial with estradiol replacement with close monitoring of ovulation. Exogenous estrogens could act by sensitizing the granulosa cells to the effect of FSH leading to ovulation. Estroprogestogens may act similarly by down-regulation of the LH and FSH receptors. They can be advised until the age of 55 years [33]. Therapy with gonadotrophin releasing hormone is not successful. Only IVF and embryo transfer using donor oocytes have demonstrated high success rates and is considered to be the fertility treatment of choice. In cases where ovarian failure is foreseeable, as in women undergoing carcinoma treatment, embryo freezing or freezing the mature eggs prior to treatment currently offers the highest likelihood of future pregnancy. Cryopreservation is still largely experimental and would be the option or prepubertal girls.

## CONSEQUENCES OF ESTROGEN DEFICIENCY

Women with untreated POF are at increased risk of developing cardiovascular diseases [34], metabolic syndrome [35] osteoporosis, dementia, cognitive decline, parkinsonism. Untreated POF can induce specific increase in mortality rate due to the complications of the prolonged hypoestrogenic status.

## CONCLUSION

It is of primary importance to diagnose premature ovarian failure on time. The diagnosis is made by clinical signs and symptoms as well as by typical hormonal characteristics. It is necessary to investigate etiology, perform physical examination and treat women with sequential estrogen progestagen therapy. Duration of therapy is individual, but usually lasts until the normal menopausal time. Such treatment avoids long term complications and improves the quality of life.

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## Превремена инсуфицијенција јајника

Светлана Вујовић<sup>1,2</sup>, Миомира Ивовић<sup>2</sup>, Милина Танчић-Гајић<sup>2</sup>, Љиљана Марина<sup>2</sup>, Марија Бараћ<sup>2</sup>, Зорана Аризановић<sup>2</sup>, Ана Ненезић<sup>2</sup>, Маја Иванишевић<sup>3</sup>, Јелена Мицић<sup>3</sup>, Силвија Сајић<sup>1,4</sup>, Драган Мицић<sup>1,2</sup>

<sup>1</sup>Медицински факултет, Универзитет у Београду, Београд, Србија;

<sup>2</sup>Клиника за ендокринологију, дијабетес и болести метаболизма, Клинички центар Србије, Београд, Србија;

<sup>3</sup>Клиника за гинекологију и акушерство, Клинички центар Србије, Београд, Србија;

<sup>4</sup>Универзитетска дејча клиника, Београд, Србија

### КРАТАК САДРЖАЈ

Превремена инсуфицијенција јајника (ПИЈ) је хипергонадотропна хипоестрогена аменореја код жена млађих од 40 година. Идиопатска је код 74–90% пацијенткиња. Познати узроци деле ПИЈ на примарну и секундарну. Код примарне ПИЈ генске аберације могу укључити X-хромозом (монозомија, тризомија, транслокација, делеција) или аутозоми. Генетски механизам укључује смањено дозирање гена и неспецифичне хромозомске ефекте који оштећују мејозу, чиме доводе до смањења броја примордијалних фоликула и повећања атрезије због апоптозе или инсуфицијенције матурације фоликула. Аутоимунски узроци настају због алтерације Т-ћелија и њиховог оштећења, повећања аутоантитела која стварају Б-ћелије и малог броја ефектор-цитотоксичних лимфоцита, што смањује број ћелија природних убица. Секундарна ПИЈ настаје због обостране аднексектомије, хемитерапије, радиотерапије и инфекција. Симптоми и знаци ПИЈ су: иритабилност, нервоза, губитак либида, депресија, смањење концентрације, сувоћа коже и слузокожа (посеб-

но вагинална), повећање телесне тежине, главобоље, честе инфекције. Дијагноза се поставља на основу нивоа *FSH* већег од 40 IU/l и нивоа естрадиола мањег од 50 pmol/l код жена млађих од 40 година. Потребно је да се ураде биохемијске и хормонске анализе (*LH*, пролактин, слободни тестостерон, слободни тироксин, *TSH*, кортизол, *ACTH*). Одређивање кариотипа се врши женама које пре 30. године оболе од ПИЈ. Саветује се ултразвук мале карлице и дојки. Лечење естропрогестагенима се започиње одмах по постављању дијагнозе уколико нема контраиндикација. Тестостерон се додаје женама код којих је урађена обострана аднексектомија или имају низак либидо. Ради изазивања овулације дају се естропрогестагени, а уколико оно буде неуспешно, трудноћа се постиже донацијом јајне ћелије. Одговарајућа естропрогестагена терапија побољшава квалитет живота ових жена и спречава појаву касних компликација, као што су кардиоваскуларна обољења, психичке сметње, остеопороза итд.

**Кључне речи:** превремена инсуфицијенција јајника; етиологија; лечење

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