PREMATURE OVARIAN FAILURE

The loss of function of the ovaries before age 40.

Diagnosis  Female

Related Diagnoses:
Anovulation  Menstrual cycle disorders  Autoimmune disorders  Turner syndrome  Vaginismus
Menopause  Poor ovarian reserve  Hyperprolactinemia  Hypergonadotropism
Gonadal dysgenesis  Fragile X syndrome  Hypoestrogenism  Heart disease

About Premature ovarian failure

Premature ovarian failure is defined as a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles/arrested folliculogenesis before the age of 40 years (secondary amenorrhea).

Hormonally, POF is defined by abnormally low levels of estrogen and high levels of FSH, which demonstrate that the ovaries are no longer responding to circulating FSH by producing estrogen and developing fertile eggs. The ovaries will likely appear shrunken.

It has been estimated that POF affects 1% of the female population. The age of onset can be as early as the teenage years, or can even exist from birth, but varies widely. POF is not the same as a natural menopause, in that the dysfunction of the ovaries, loss of eggs, or removal of the ovaries at a young age is not a normal physiological occurrence. Women suffering from POF usually experience menopausal symptoms that are more severe than the symptoms found in older menopausal women.

The cause of POF is usually unknown (idiopathic). Some cases of POF are attributed to autoimmune disorders, others to genetic disorders such as Turner syndrome and Fragile X syndrome. If it has a genetic cause, it may be called
gonadal dysgenesis. Also, chemotherapy and radiation treatments for cancer can sometimes cause ovarian failure. In natural menopause, the ovaries usually continue to produce low levels of hormones, but in chemotherapy or radiation-induced POF, the ovaries will often cease all functioning and hormone levels will be similar to those of a woman whose ovaries have been removed. Family history and ovarian or other pelvic surgery earlier in life are also implicated as risk factors for POF.

Mechanisms involved in premature ovarian failure inducing chemotherapeutic agents.

Chemotherapeutic agents are classified into five classes according to their mode of action: alkylating agents, antimetabolites, aneuploidy inducers, radiomimetics and topoisomerase II inhibitors. Antitumour effects of these drugs are often accompanied by their damage on other organs, especially the reproductive system. There are several hypotheses for POF induction by chemotherapy (Pic. 1). First, chemically agents can impair follicular stock by driving ovarian cell apoptosis, leading to a finite number of primordial follicles and ensuing POF. Second, some chemical agents interfere with local hormonal regulation related to either follicular recruitment or rest. Third, some chemical agents may interrupt interactions between the oocytes and GCs, which are crucial for follicular growth and maturation. For the above reasons, follicular storage decreases or the follicles do not fully mature, increasing the POF risk.

There are two basic types of premature ovarian failure:

1. POF where there are few to no remaining follicles (caused by genetic disorders, autoimmune damage, chemotherapy, radiation to the pelvic region, surgery, endometriosis and infection)
2. POF where there are an abundant number of follicles (one frequent cause is autoimmune ovarian disease which damages maturing follicles, but leaves the primordial follicles intact)

Diagnosis

1. Ultrasound frequently reveals small ovaries without evidence of growing follicles. In the cases with primary amenorrhea, gonadal dysgenesis is documented by the finding of streak ovaries.
2. The evaluation of other peptide factors of ovarian origin, such as inhibin B and anti-mullerian hormone (AMH), is very useful to determine the follicular reserve when POF is suspected.
3. Histological examination of biopsies performed during pelvic laparoscopy in the case of hypoplastic ovaries (0.20–0.30 ml on ultrasound) may reveal the presence of primary follicles.
4. Karyotype evaluation and other cytogenetic investigations are useful to identify major X chromosome abnormalities.

POF with possible ovarian failure is a devastating diagnosis for a young woman’s health and hopes of motherhood. The condition is important to identify and its
causes are important to investigate and research for the preservation of future well-being. The physical, psychological, reproductive, and social impact is significant and will be greater when the condition develops in very young women and adolescents. Life expectancy may be reduced because of skeletal and organ effects. This impact will increase where diagnosis is delayed or the condition and its causes inadequately treated.

**Associated diseases**

Osteoporosis or decreased bone density affects almost all women with POF due to an insufficiency of estrogen. There is also an increased risk of heart disease, hypothyroidism in the form of Hashimoto's thyroiditis, Addison's disease, and other auto-immune disorders.

**Complications**

Infertility as the result of this condition.

**Risk factors**

- Genetic disorders
- Autoimmune diseases
- Tuberculosis of the genital tract
- Smoking
- Radiation and/or chemotherapy
- Ovarian failure following hysterectomy
- Prolonged GnRH (Gonadotrophin Releasing Hormone) therapy
- Enzyme defects
- Resistant ovary
- Induction of multiple ovulation in infertility

**Impact on fertility**

Women suffering from POF experience similar symptoms to natural menopause; however, these symptoms are also accompanied by an earlier loss of fertility. Therefore, women at risk of POF who delay childbearing until after their 30s may experience problems conceiving and carrying a pregnancy to full term. This loss of fertility can be due to an accelerated loss of follicles, an inability of the remaining follicles to respond to ovulatory signals, an initially reduced ovarian reserve at the time of birth, or a combination of all.

**Prevention**

Avoiding exposure of toxins, such as cigarette, chemicals, pesticides and viruses. Genetic screening test for those with family history of premature ovarian
failure. Important for those, who want to find out if they carry a gene for the disease and might pass it to their children.

### Symptoms

Usual signs and symptoms of premature ovarian failure include the following:

- irregular or skipped periods (amenorrhea)
- hot flashes and night sweats
- irritability, poor concentration
- vaginal dryness
- decreased sexual desire
- infertility
- osteoporosis
- low thyroid function, such as muscle hypotonia, fatigue and cold intolerance
- Addison's disease, such as fatigue, muscle weakness, loss of appetite and weight loss.
- heart diseases, such as palpitation and chest pain

### Therapies

#### Self therapy

**Acupuncture**

Acupuncture has been used in eastern Asian countries for thousands of years and suggested as an effective approach to managing vasomotor symptoms. It has been found effective in reducing the hot flush severity in perimenopausal and postmenopausal women.

#### Conventional medicine

**Pharmacotherapy**

**Hormone replacement therapy**

HRT is based on the idea that the treatment may prevent discomfort caused by diminished circulating estrogen and progesterone hormones. The main types of hormones involved are estrogens, progesterone or progestins, and sometimes testosterone. According to the association on hormone replacement therapy and cardiovascular diseases and breast...
cancer incidence, doctors prefer that the benefits of hormone replacement therapy usually outweigh the potential risks in young women with premature ovarian failure. It is often referred to as "treatment" rather than therapy.

**Calcium and vitamin D supplements:** These treatments are important for bone health and help decrease the risk of development of osteoporosis.

**Surgical therapy**

Damaged ovarian function can be rescued after stem cell transplantation. There are several stem cell types that have been investigated in POF treatment. Their recovery of ovary function demonstrates some significant differences from other techniques, some of which are listed in Table 1.

Clinical applications of stem cell therapy have become popular for treating premature ovarian failure. Oocyte and granulosa cells regeneration along with the re-establishment of hormone or cytokine profiles supporting stem cell follicular development may be involved in the improvement of both the damaged ovary function and fertility recovery. Nevertheless, the mechanism behind this still remains unclear. Although these stem cells may potentially differentiate into oocytes or granulosa cells, studies have proved they could not develop into fully functional follicles in vivo. Both the proliferation and apoptosis (programmed cell death) of granulosa cells are critical in the development of follicles. Greater numbers of studies have revealed stem cells transplanted into the damaged ovary are more inclined to differentiate into granulosa cell-like cells to replenish the lost granulosa cells. Additionally, factors produced by stem cells could inhibit stromal cell apoptosis, thereby playing a part in rescuing damaged ovarian function.

**Assisted reproduction**

Infertility is a common complication of premature ovarian failure. The only solution presently available for the fertility defect in women with absent follicular reserve is egg donation.

**Find more about related issues**

**Diagnoses**
Anovulation
Failure of the ovaries to release an oocyte over a period of time generally exceeding 3 months. Learn more at: www.fertilitypedia.org/therapy/diag/anovulation

Menstrual cycle disorders
An abnormal condition in a woman’s menstrual cycle. Learn more at: www.fertilitypedia.org/therapy/diag/menstrual-cycle-disorders

Autoimmune disorders
A condition arising from an abnormal immune response to a normal body part. Learn more at: www.fertilitypedia.org/therapy/diag/autoimmune-disorders-1

Turner syndrome
Turner syndrome is a genetic disorder in which a female is partly or completely missing one X chromosome that results in ovarian dysgenesis. Learn more at: www.fertilitypedia.org/therapy/diag/turner-syndrome

Vaginismus
A physical or psychological condition in which woman cannot engage in any form of vaginal penetration. Learn more at: www.fertilitypedia.org/therapy/diag/vaginismus

Menopause
The time in most women’s lives when menstrual periods stop permanently, and the woman is no longer able to have children. Learn more at: www.fertilitypedia.org/therapy/diag/menopause

Poor ovarian reserve
A condition of low fertility characterized by low numbers of remaining oocytes in the ovaries or possibly impaired oocyte development or recruitment. Learn more at: www.fertilitypedia.org/therapy/diag/poor-ovarian-reserve

Hyperprolactinemia
The presence of abnormally high levels of prolactin in the blood. Learn more at: www.fertilitypedia.org/therapy/diag/hyperprolactinemia

Hypergonadotropism
The condition of elevated concentrations of gonadotropins within the blood. Learn more at: www.fertilitypedia.org/therapy/diag/hypergonadotropism
**Gonadal dysgenesis**
Any congenital developmental disorder of the reproductive system characterized by a progressive loss of germ cells on the developing gonads.
Learn more at: [www.fertilitypedia.org/therapy/diag/gonadal-dysgenesis](www.fertilitypedia.org/therapy/diag/gonadal-dysgenesis)

**Fragile X syndrome**
Genetic condition that is the most common inherited cause of intellectual disability, as well as the most frequent cause of autism spectrum disorder.
Learn more at: [www.fertilitypedia.org/therapy/diag/fragile-x-syndrome](www.fertilitypedia.org/therapy/diag/fragile-x-syndrome)

**Hypoestrogenism**
A lower than normal level of estrogen which is the primary sex hormone in women.
Learn more at: [www.fertilitypedia.org/therapy/diag/hypoestrogenism](www.fertilitypedia.org/therapy/diag/hypoestrogenism)

**Heart disease**
Various types of conditions that can affect the function of the heart or blood vessels, which may have the negative effect also to the infertility.
Learn more at: [www.fertilitypedia.org/therapy/diag/heart-disease](www.fertilitypedia.org/therapy/diag/heart-disease)

**Organs**

**Ovary**
The ovum-producing organs of the internal female reproductive system.
Learn more at: [www.fertilitypedia.org/edu/organs/ovary](www.fertilitypedia.org/edu/organs/ovary)

**Reproductive cells**

**Cumulus oophorus**
A group of granulosa cells that support the oocyte in an antral follicle.
Learn more at: [www.fertilitypedia.org/edu/reproductive-cells/cumulus-oophorus](www.fertilitypedia.org/edu/reproductive-cells/cumulus-oophorus)

**Oocyte**
A female germ cell involved in reproduction.
Learn more at: [www.fertilitypedia.org/edu/reproductive-cells/oocyte](www.fertilitypedia.org/edu/reproductive-cells/oocyte)

**Biological control**

**Anti-Müllerian hormone**
A hormone, that provokes the regression of male fetal Müllerian ducts.
Learn more at: [www.fertilitypedia.org/edu/biological-control/anti-mullerian-hormone](www.fertilitypedia.org/edu/biological-control/anti-mullerian-hormone)
Estradiol
A steroid and estrogen sex hormone produced in the ovaries of females.
Learn more at: www.fertilitypedia.org/edu/biological-control/estradiol

Follicle-stimulating hormone
FSH is a hormone secreted by the anterior pituitary gland. It regulates the development, growth, pubertal matur and reproductive functions of the body.
Learn more at: www.fertilitypedia.org/edu/biological-control/follicle-stimulating-hormone

Reproductive functions

Folliculogenesis
Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/folliculogenesis

Oogenesis
The process of the maturation of the female gametes through the meiotic division.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/oogenesis

Ovulation
The release of egg(s) from the ovaries.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/ovulation

Risk factors

Chemotherapy
A category of cancer treatment that uses one or more anti-cancer drugs.
Learn more at: www.fertilitypedia.org/therapy/rf/chemotherapy

High level of FSH
FSH levels above what an expected levels for one’s age and is indicator of proper ovarian function.
Learn more at: www.fertilitypedia.org/therapy/rf/high-level-of-fsh

Low level of AMH
Low blood levels of AMH (anti-Müllerian hormone) which may indicate poor ovarian reserve.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-amh
Low level of estrogen
A diminished level of blood estrogen level.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-estrogen

Radiation exposure
A damage to body caused by a large dose of radiation.
Learn more at: www.fertilitypedia.org/therapy/rf/radiation-exposure

Smoking
Long-lasting inhalation of the smoke of burning tobacco.
Learn more at: www.fertilitypedia.org/therapy/rf/smoking-1

Symptoms

Absence of menstrual periods
The absence of a menstrual period in a woman of reproductive age.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-menstrual-periods-1

Absence of ovulation
An anovulatory cycle is a menstrual cycle during which the ovaries do not release an oocyte.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-ovulation-1

Chest pain
A pain is felt anywhere in the chest area from the level of shoulders to the bottom of ribs.
Learn more at: www.fertilitypedia.org/edu/symptoms/chest-pain

Decreased level of AMH
Lower levels of Anti-Müllerian hormone according to the age.
Learn more at: www.fertilitypedia.org/edu/symptoms/decreased-level-of-amh

Heart defects
A defect in the structure of the heart and great vessels which is present at birth.
Learn more at: www.fertilitypedia.org/edu/symptoms/heart-defects

Increased level of FSH
A condition with high serum follicle–stimulating hormone (FSH) concentration.
Learn more at: www.fertilitypedia.org/edu/symptoms/increased-level-of-fsh
Infertility
The failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.
Learn more at: www.fertilitypedia.org/edu/symptoms/infertility

Lowered libido
The absence of sexual appetite.
Learn more at: www.fertilitypedia.org/edu/symptoms/lowered-libido

Osteoporosis
A chronic condition characterized by low bone mass and increased risk of fracture.
Learn more at: www.fertilitypedia.org/edu/symptoms/osteoporosis

Underweight
A term describing a person whose body weight is considered too low to be healthy.
Learn more at: www.fertilitypedia.org/edu/symptoms/underweight

Vaginal dryness
Decreased or missing lubrication of vagina.
Learn more at: www.fertilitypedia.org/edu/symptoms/vaginal-dryness

Therapies

Acupuncture
A form of alternative medicine and a key component of traditional Chinese medicine involving thin needles inserted into the body at acupuncture points
Learn more at: www.fertilitypedia.org/edu/therapies/acupuncture

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

Hormone replacement therapy
Learn more at: www.fertilitypedia.org/edu/therapies/hormone-replacement-therapy

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation
Pic. 1: The hypotheses for POF induction by chemotherapy and the stem cell therapy.

Table 1.: The stem cells used in POF therapy

There are several stem cell types that have been investigated in POF treatment. Their recovery of ovary function demonstrates some significant differences from other techniques, some of which are listed in Table 1.

<table>
<thead>
<tr>
<th>Stem cell type</th>
<th>Indications</th>
<th>Survival (days)</th>
<th>Neutrophil count</th>
<th>Morphological changes</th>
<th>Reprogramming</th>
<th>Recovery of ovarian function</th>
<th>Developmental potential</th>
<th>Summary Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow-derived</td>
<td>poor viability</td>
<td>0-14</td>
<td>0-3</td>
<td>0-2</td>
<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
<td>0-1</td>
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<tr>
<td>CB-MSCS</td>
<td>poor viability</td>
<td>0-14</td>
<td>0-3</td>
<td>0-2</td>
<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
<td>0-1</td>
</tr>
<tr>
<td>Adipose-derived</td>
<td>poor viability</td>
<td>0-14</td>
<td>0-3</td>
<td>0-2</td>
<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
<td>0-1</td>
</tr>
<tr>
<td>Endometrial stromal</td>
<td>poor viability</td>
<td>0-14</td>
<td>0-3</td>
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<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
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<tr>
<td>Mesenchymal</td>
<td>poor viability</td>
<td>0-14</td>
<td>0-3</td>
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<td>0-2</td>
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