Primary Ovarian Insufficiency (POI; Premature Ovarian Failure; Early Menopause) — Symptoms and Treatment

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Primary ovarian insufficiency is a term that describes impaired ovarian function over a continuum and can include several disorders such as hypergonadotropic hypogonadism, ovarian dysgenesis, and premature ovarian failure. The endpoint of primary ovarian insufficiency is usually premature menopause. Premature menopause is defined as the onset of menopause in a woman before the age of 40 years. The diagnosis of premature menopause is confirmed by obtaining two serum follicle-stimulating hormone tests that are above 30 U/L and that are one month apart in a woman of 4 to 6 months’ history of amenorrhea.

Epidemiology of Primary Ovarian Insufficiency

Primary ovarian insufficiency is a common condition in middle-aged women. Approximately, 1 in 100 women who are 40 years or younger will develop primary ovarian insufficiency. On the other hand, only 1 in 10,000 women who are younger than 20 years will develop primary ovarian insufficiency.

Primary ovarian insufficiency is a condition that has been previously shown to be
associated with familial aggregation and genetic predisposition. X-linked modes of inheritance of primary ovarian insufficiency have been previously described. The most common example of an X-chromosome abnormality that is associated with primary ovarian insufficiency due to ovarian dysgenesis is Turner syndrome (45, XO). Fragile X syndrome which involves the FMR1 gene can be also associated with primary ovarian insufficiency.

**Etiology of Primary Ovarian Insufficiency**

The best-understood causes of primary ovarian insufficiency are those associated with ovarian dysgenesis. Turner syndrome is a condition that is characterized by the passing of a single X chromosome to the offspring instead of two. The patient is phenotypically a female who has primary amenorrhea. X isochromosome and Fragile X syndrome are other two conditions that can be associated with primary ovarian insufficiency. Translocation mutations in chromosomes 4, 6, 9, 12 and 18 have been also associated with primary ovarian insufficiency before.

Syndromic primary ovarian insufficiency is characterized by ovarian dysgenesis in addition to some syndromic features such as mental retardation, cataracts, neurosensory deafness, microcephaly, or cerebellar ataxia. XX gonadal dysgenesis that is associated with microcephaly, arachnodactyly, epibulbar dermoid, short stature, metabolic acidosis, blepharophimosis, ptosis, epicanthus and Malouf syndrome has been described before. Malouf syndrome is characterized by ectrodactyly, ectodermal dysplasia, and cleft lip or palate.

**17 alpha-hydroxylase/17,20 desmolase deficiency, aromatase mutations, and glycoprotein deficiencies** have been also reported to be associated with primary ovarian insufficiency. The destruction of the ovarian follicles by autoimmune processes can also cause primary ovarian insufficiency. Autoimmune thyroiditis is a condition that can be associated with primary ovarian insufficiency. Patients with hypothyroidism, adrenal insufficiency, hypoparathyroidism and type 1 diabetes mellitus are at an excessively increased risk of autoimmune primary ovarian insufficiency.

Other systemic conditions such as myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and thymic aplasia can also cause the condition.

Mumps and the human immunodeficiency virus have been also associated with an increased risk of primary ovarian insufficiency.

**Women who receive chemotherapy**, especially cyclophosphamide, are at a markedly increased risk of developing primary ovarian insufficiency. The administration of a gonadotropin-releasing hormone agonist prior to the administration of the chemotherapeutic agent appears to have a protective role against the induced ovarian damage. Radiotherapy can also induce accelerated ovarian follicle atresia and primary ovarian insufficiency.

The **surgical removal of both ovaries** will cause premature menopause. Isolated hysterectomies have been also associated with an increased risk of primary ovarian insufficiency most likely due to impaired blood supply to the ovaries post surgically.

**Clinical Presentation of Primary Ovarian**
Insufficiency

Women who develop primary ovarian insufficiency usually present with symptoms and signs suggestive of estrogen hormone deficiency. Symptoms of menopause such as **hot flushes, mood swings, and amenorrhea** occur before the age of 40 years. **Osteoporosis** is more common in women with premature menopause compared to women with normal-onset menopause.


Women with primary ovarian insufficiency might also present with **infertility**. The presence of other features of a syndromic condition such as mental retardation or certain facial features should be noted. Additionally, autoimmune conditions that are known to be associated with primary ovarian insufficiency should be excluded if possible. Women with primary ovarian insufficiency also have psychological issues and can develop neurocognitive deficits over time.
Diagnostic Workup for Primary Ovarian Insufficiency

The first test to be performed in a woman who is younger than 40 years old and who has developed amenorrhea for three months or more is a pregnancy test. Once pregnancy is excluded, further testing to establish an etiology and confirm the diagnosis is needed.

Serum thyroid stimulating hormone, follicle-stimulating hormone, prolactin, and estradiol are the main hormones that need to be checked in the patient. Patients with elevated follicle stimulating hormone levels and low estradiol should get the test repeated after one month. If the results are the same after one month, the diagnosis of primary ovarian insufficiency is confirmed.

Management of Primary Ovarian Insufficiency

The treatment of primary ovarian insufficiency can be subdivided into hormone replacement therapy, management of fertility issues, and psychological support of the affected woman.
The goal of hormone replacement therapy is to **prevent osteoporosis and ameliorate the symptoms and signs** of premature menopause. Transdermal estradiol can be used on a daily basis. Women who still have a uterus should also receive medroxyprogesterone for 12 days of the month to oppose the effects of estrogen on the uterus.

**Combined oral contraceptives** are usually used in women with primary ovarian insufficiency as a method of hormone replacement therapy. Pregnancy can still occur in some women who developed primary ovarian insufficiency, therefore, intrauterine devices or other methods of contraception might be used however combined oral contraceptives have the advantage of providing the benefits of hormone replacement therapy in addition to contraception.

Women who will receive chemotherapy for another indication should receive ovarian suppression therapy with gonadotropin releasing a hormone to lower the risk of primary ovarian insufficiency.

Fertility can be achieved in women who have developed primary ovarian insufficiency by **ovarian hyperstimulation** or by retrieving oocytes from a cryopreserved ovarian tissue. In vitro fertilization with donor, oocytes is another option.

Women who develop primary ovarian insufficiency might need psychological support because of the changes induced by menopause or because the etiology of the primary ovarian insufficiency is a mental disorder, i.e. anorexia nervosa.

**References**


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