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## Premature ovarian insufficiency: an augmenting disorder in the growing female population

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### Abstract

A primary ovarian abnormality such as absent menarche (primary amenorrhea) or early depletion of ovarian follicles/arrested folliculogenesis before the age of 40 is described as premature ovarian insufficiency (secondary amenorrhea). Its prevalence is 1% and 0.1 % in women under 40 and 30 respectively. Common Symptoms include palpitations, excessive sweating, flushes, anxiety, depression, and fatigue. There could be a variety of causes, including chromosomal abnormalities, autoimmune diseases, infections, idiopathic diseases, iatrogenic diseases, and so on. Diagnosis is usually done based on the level of hormones like estradiol, Follicle Stimulating Hormone, and Luteinizing Hormone. Considering the complications of premature ovarian failure, it is necessary to educate the female population about this disorder. Hence, the Present review focuses on the etiology, symptoms, complications, diagnosis, and treatment of premature ovarian failure.

**Keywords:** ovarian abnormality, premature ovarian failure.

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### Introduction

A primary ovarian abnormality such as absent menarche (primary amenorrhea) or early depletion of ovarian follicles/arrested folliculogenesis before the age of 40 is described as premature ovarian insufficiency (secondary amenorrhea) [1].

Most probably, Premature Ovarian Insufficiency (POI) occurs when the exhaustion of the number of ovarian follicles is concurrent with autoimmune ovarian damage and occurs in association with a genetic predisposition [2]. Women in Western populations typically reach menopause at the age of 51. The diagnosis is based on increased menopausal-range FSH levels (often > 40 IU/l) seen at least twice within a few weeks of one another. In addition to primary or secondary amenorrhoea,

infertility, sex steroid insufficiency, and high gonadotrophin levels, women with POI experience anovulation and hypoestrogenism. About 1% of women are affected by the disorder, which is present in 4–18% of women with secondary amenorrhoea and 10–28% of women with primary amenorrhoea. Early loss of ovarian function has been linked to considerable psychosocial effects and serious physical consequences, including a nearly 2-fold age-specific increase in mortality risk. Numerous pathogenic factors, such as chromosomal, genetic, autoimmune, metabolic (galactosemia), infectious (mumps), and iatrogenic (anticancer therapies) reasons, may contribute to the development of POI(3). De Moraes-Ruehsen and Jones classified the first case reports of POI as non-physiological amenorrhea before age 40 but after puberty in 1967. Hyper gonadotropic hypoestrogenism was employed to describe the hormone profile in women with POI in 1939. Atria provided a detailed discussion of the clinical characteristics of POI in 1950. Twenty young women under 35 who experienced

secondary menstrual loss, hot flushes, infertility, and endometrial degeneration were the subjects of the author's report [2].

### Symptoms and complications

Menopausal symptoms may be present in women with POI, sometimes even before menstrual irregularities begin. Before fulfilling the above diagnostic criteria, irregular menstrual cycles or infertility are typically present. Patients with secondary amenorrhea may suffer a sudden onset of the condition, but it can also be preceded by irregularities in the menstrual cycle (oligomenorrhea or polymenorrhea). Although the alteration is irreversible, there is frequently a brief remission. palpitations, excessive sweating, flushes, anxiety, depression, and fatigue are some of the symptoms (1). A study of 358 women with idiopathic POI found that 24% of all spontaneous ovarian function remission cases happened within a year of the diagnosis. In a more recent study, 117 (23 spontaneous ovarian function remission cases signs) of ovarian function recovery. There aren't any sensitive biochemical biomarkers for evaluating the patient population with POI's remaining follicle pool, hence the decrease in ovarian reserve is still most likely continuous rather than progressive [4].

### Etiology

#### Chromosomal abnormalities

POI is caused by a wide variety of factors. Many cases are acquired forms, such as those that appear following therapies for neoplastic or autoimmune illnesses. Strong genetic factors contribute to POI, with X chromosomal abnormalities being the main factor, especially in cases of ovarian dysgenesis. POI may be caused by genes including Turner syndrome, fragile X syndrome (FMR1 gene), or pseudohypoparathyroidism type 1a (GNAS1 gene).

#### Autoimmunity

POI is more commonly connected with autoimmune illnesses than the general population, and autoimmune disorders are observed in POI patients more frequently than in the general population.

As per the report, POI Patients are diagnosed for obtaining data on the correlation between POI and autoimmunity. A total of 16 autoantibody tests (antinuclear antibody, anti-DNA antibody, anti-centromere antibody, anti-SSA antibody, anti-SSB antibody, anti-SM antibody, anti-SCL-70 antibody, anti-RNP antibody, anti-Jo-1 antibody, anti-cytoperoxidase an antibody, microsome test, thyroid test, anti-

cardiolipin antibody, anti-CL/b2GP1 antibody) have been conducted. As per the result, 15% of Screened POI patients had clinical autoimmune disorders.

On cryostat slices, indirect immunofluorescence was used to demonstrate the presence of ovarian autoantibodies. Although autoimmune diseases and autoimmunity are frequently linked to POI, Hoek et al found that only patients with circulating adrenal or ovarian autoantibodies can show histological evidence of oophoritis [4].

#### Infections:

Numerous illnesses, including mumps, tuberculosis, malaria, varicella, cytomegalovirus, and herpes simplex virus, have been linked to POI, but the majority of these infections lack confirmed direct causative relationships. Although it is typically temporary, ovarian insufficiency has been observed to occur in 2-8% of women after mumps or oophoritis. According to current research, HIV infection may be linked to signs of a diminished ovarian reserve. Data relating HIV infection to age at menopause, however, are contradictory. According to research by de Pommerol et al., a cohort of 404 HIV-positive women in a French hospital had a 12% prevalence of POI. However, a recent systematic assessment of six research revealed conflicting findings, making it difficult to make firm conclusions. The authors acknowledged serious methodological limitations with the data that were available(5).

#### Idiopathic

Unexplained POI is commonly quoted as the most prevalent diagnosis, with incidence rates as high as 90%. Since 2003, a POI database of women who have been referred to Christchurch Women's Hospital and Southern Women's Health's gynecological endocrinology clinics had been documented. As per the reports, only 25% of the women had an unclear cause.

#### Iatrogenic

As most of the people have access to surgical management options, chemotherapy, and radiotherapy, iatrogenic causes of POI are becoming more prevalent. Before reaching 40, one in 49 women will receive a cancer diagnosis. The long-term overall survival for patients with pediatric cancer is 80%. Cancer survivors have a 13-fold higher risk of nonsurgical POI than their siblings who were not afflicted by the disease.

Risk factors for chemotherapy-induced ovarian failure.

Patient age (>40 years).

Familial ovarian history.

Ovarian follicle reserve.

Previous ovarian and pelvic surgery history.  
 Previous chemotherapy.  
 Previous pelvic and abdominal radiotherapy.  
 Persistent high level of follicle-stimulating hormone (FSH) (6).

### Diagnosis

#### Diagnostic criteria

Female patients usually experience secondary amenorrhea, irregular menstruation, or subfertility, together with or without symptoms of estrogen insufficiency. At least 25% of women do not suffer the typical menopausal symptoms like hot flashes, night sweats, mood swings, dry vagina, decreased libido, tiredness, and joint pains. Primary amenorrhea will be found in a smaller group of women. Due to the lack of defined diagnostic criteria for POI, prompt identification is essential to prevent chronic estrogen deficiency [7].

It is usually advised to assess gonadotrophin levels three to four months after amenorrhea or irregular menstruation. Estradiol should also be tested to confirm hypogonadism if FSH and LH levels are excessive. These tests should be repeated in at least 4 weeks. To rule up alternative pathology, prolactin, and thyroid function testing are also advised. Transvaginal ultrasound can be used to assess AFC and to rule out other illnesses.

The three main diagnostic procedures currently accessible to ascertain the underlying cause include testing for adrenal antibodies, karyotype, and the FMR1 gene premutation. Anti-adrenal and anti-thyroid autoantibody testing ought to be taken into consideration. Positive adrenal antibodies identify patients who are at risk of developing adrenal insufficiency and should thus undergo routine monitoring of adrenal function. These also suggest autoimmune oophoritis as the underlying mechanism. Furthermore, karyotyping and Fragile X testing should be carried out, particularly in patients who present at a young age or who have a family history of POI or learning disabilities [5].

### Therapy

#### Stem cell therapy

Under the right set of circumstances, stem cells can differentiate into any form of cell, making them distinct pluripotent cells. Researchers have looked into whether they can be utilized as precursors for new follicular units or to rouse the existing primordial follicles in the ovarian cortex so they can once again become fertile [8].

### Hormonal replacement therapy (HRT)

First-line treatment for POI involves replacing estrogen to reduce menopausal symptoms and improve bone, cardiovascular, and sexual health. Adolescents with POI may develop secondary sexual traits as a consequence of it. Before beginning progesterone therapy, estrogen therapy should be started at low dosages and gradually increased if breast development is incomplete or absent to prevent tubular breast formation [9].

### Fertility Regulation

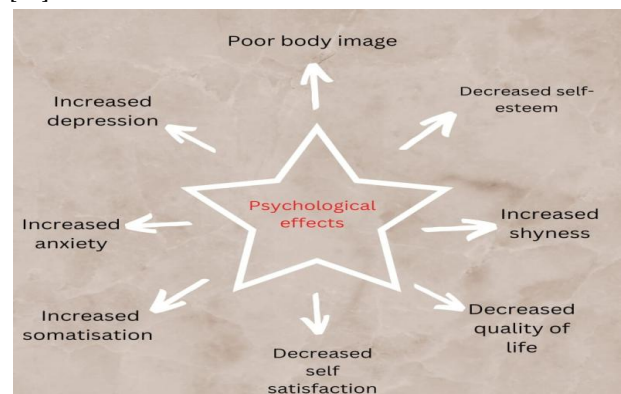
To improve these women's fertility, there are numerous therapeutic alternatives available. Ovulation can resume spontaneously in 5–10% of these women, which can result in pregnancy. As a result, women who are unwilling to have children in the future should be offered effective contraception [10].

### Social and Psychological Support

Many POI patients are dissatisfied with the amount of information their clinicians have given them (11).

When conveying unpleasant news, the family should be included. Patients will receive psychological support in the form of therapy and the proper medical care if they are experiencing depression or anxiety.

Their quality of life may change the outcome of the POI diagnosis and its implications. There are substantial support groups for these women, including the International Premature Ovarian Failure Association and the Daisy Network Premature Menopause Support Network. Patients should be gently informed of the diagnosis, making sure parental involvement is present, given the sensitive nature of diagnoses as well as their cultural significance. Teenagers with POI should also have their parents counseled about the repercussions and be prepared to assist their daughters emotionally [12].



**Figure 1:** Psychological Effects of POI

## Conclusion

POI is a common condition that has major consequences for a woman's emotional and physical well-being. It is caused by chromosomal abnormalities, autoimmune diseases, infections, idiopathic diseases, iatrogenic diseases. Common symptoms of POI include palpitations, excessive sweating, flushes, anxiety, depression, and fatigue. It is imperative to educate the female community about the problems of POI and the right treatment method. As a result, extensive information about POI is summarised in this review.

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