# Premature Ovarian Failure

## Clinical Presentation and Treatment

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**KEYWORDS**

• Infertility • Estrogen therapy • Ovarian failure • Autoimmune disorders
• Heart disease • Osteoporosis

**KEY POINTS**

- Long-term health consequences, including psychological distress, infertility, osteoporosis, heart disease, autoimmune disorders, and increased mortality, have a significant impact on the quality of life for the woman diagnosed with premature ovarian failure.
- Initiation of hormone replacement therapy (HRT) should be initiated immediately without considering the Women's Health Initiative findings.
- Donor oocyte in vitro fertilization has high pregnancy rates.

### INTRODUCTION AND TERMINOLOGY

Premature ovarian failure (POF) is defined as hypergonadotropic hypogonadism with the cessation of menses before age 40. About 1% to 3% of women experience POF before age 40.[1,2] The incidence is lower in younger women. A follicle stimulating hormone (FSH) concentration greater than 20 to 40 mIU/mL in the presence of amenorrhea has been proposed to define ovarian failure.[3] The presumption of ovarian failure is evidenced by the association between decreased natural fecundity and lowered assisted reproductive technology success rates with increased FSH concentrations and increased age. When the FSH concentrations are greater than 12 to 15 mIU/mL in women who are less than the age of 40 years with regular cycles, the ovaries are unlikely to respond to the stimulating agents, such as human menopausal gonadotropins and recombinant FSH. On the other hand, some women who are diagnosed with POF may become pregnant spontaneously albeit the likelihood is low. Therefore, the term "primary ovarian insufficiency" has been proposed as an alternative to POF by some investigators.[4,5] This new term sounds like it covers different spectrums of the disorder and, thus, may be more appropriate for clinical use. However, the term

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primary ovarian insufficiency may lead to phenotypic heterogeneity in translational studies. Recruitment of heterogeneous study populations may prevent finding significant associations between the disorder and the genotype. Even the current term POF includes a heterogeneous group of women as the various clinical presentations suggest. Manifestations of POF, defined as an FSH level greater than 40 mIU/mL with amenorrhea before age 40, include primary amenorrhea, secondary amenorrhea, presence or absence of autoimmune disorders, and association with chromosomal abnormalities such as Turner syndrome, all of which imply different causes. Moreover, the authors do not think insufficiency has a better connotation than failure, and these 2 words are actually synonyms. To prevent unnecessary confusion in the literature, the continued use of the term POF is suggested.

## CAUSE

It is well known that X chromosome abnormalities are the underlying cause in some cases of POF. The most common of these abnormalities is 45,X or Turner syndrome, which affects 1 in 2500 female newborns worldwide.[6] It is thought that 75% or more of conceptions affected by Turner syndrome result in spontaneous abortion.[7] Turner syndrome is characterized clinically by short stature, cardiovascular anomalies (especially coarctation of the aorta and aortic valvular abnormalities), webbed neck, lymphedema, and POF.

In addition to Turner syndrome, other X chromosome aberrations, such as deletions of the short or long arm of the X chromosome, have been shown to be associated with POF.[6] These deletions show variable phenotype depending on the location of the deletion. Proximal deletions of Xq are associated with primary amenorrhea especially if these originate more proximal than Xq21.[6] Similarly, the amount of remaining Xp also affects the phenotype.[6] The numerous cases of X chromosome abnormalities and POF have led to the identification of a "critical region" at Xq13.3-Xq27. Several candidate genes in this region have been suggested; however, the exact contributors remain elusive.

Autosomal chromosomal abnormalities and balanced autosomal reciprocal translocations can also be associated with POF. Necropsy examinations on fetuses with trisomy 13 and 18 revealed findings consistent with ovarian dysgenesis.[8] Numerous autosomal genes are known to affect ovarian development, and translocations involving a sex chromosome and autosome may affect autosomal gene expression, and/or meiosis I progression.[8]

POF can also be part of various phenotypic abnormalities that are seen in well-defined Mendelian disorders. Autoimmune polyendocrine syndrome (APS) type 1 and 2 show multiple endocrine organ failures including adrenal insufficiency, hypoparathyroidism, hypothyroidism, type 1 diabetes mellitus, and ovarian failure. APS type 1 is caused by mutations in the AIRE gene.[9] Perrault syndrome is an autosomal-recessive disorder involving POF and neurosensory deafness. The connexin 37 gene is an attractive candidate for this disorder because the connexin gene family is responsible for many congenital forms of deafness, and the null mice for connexin 37 develop ovarian failure.[10] Another Mendelian disorder associated with POF is ataxia telangiectasia. It involves cerebellar ataxia, telangiectesias, immunodeficiency, genomic instability, and malignancy.[11] The gene that has been found to be mutated in patients with ataxi-telangiectesia is named the ATM gene.[12] Women with type I blepharophimosis, ptosis, epicanthus inversus syndrome can present with POF.[13] FOXL2 mutations have been identified in these women. Fragile X syndrome is of note because not only does it have an intricate genetic origin but also it is one of the