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REPRODUCTIVE MEDICINE

Genetic aspects of premature ovarian failure: a literature review

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Abstract
Background The diagnosis of premature ovarian failure (POF) is based on the finding of amenorrhea before the age of 40 years associated with follicle-stimulating hormone levels in the menopausal range. It is a heterogeneous disorder affecting approximately 1% of women <40 years, 1:10,000 women by age 20 years and 1:1,000 women by age 30 years. POF is generally characterized by low levels of gonadal hormones (estrogens and inhibins) and high levels of gonadotropins (LH and FSH) (hypergonadotropic amenorrhea).
Methods Review of significant articles regarding genetic causes that are associated with POF.
Results Heterogeneity of POF is reflected by a variety of possible causes, including autoimmunity, toxics, drugs, as well as genetic defects. Changes at a single autosomal locus and many X-linked loci have been implicated in women with POF. X chromosome abnormalities (e.g., Turner syndrome) represent the major cause of primary amenorrhea associated with ovarian dysgenesis. Many genes have been involved in POF development, among them *BMP15*, *FMR1*, *FMR2*, *LHR*, *FSHR*, *INHA*, *FOXL2*, *FOXO3*, *ERα*, *SF1*, *ERβ* and *CYP19A1* genes.
Conclusion Despite the description of several candidate genes, the cause of POF remains undetermined in the vast majority of cases.

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Introduction

Premature ovarian failure (POF) (MIM—311360), or premature ovarian insufficiency, is an early ovarian dysfunction clinically defined as the cessation of ovarian function with elevated gonadotrophin and low estrogen level before or at the age of 40 years [1]. This condition is characterized by the presence of primary or secondary amenorrhea for at least 4 months, hypoestrogenism and elevated serum gonadotropin concentrations. The diagnosis is confirmed by two blood tests at least 1 month apart to measure FSH [2–4].

POF incidence in patients with 46, XX karyotype was estimated in around 1:1,000 women under 30 years old, 1:250 around 35 years old and 1:100 at 40 years old [5].

Multiple causes of POF can be defined and result in follicle reduction and/or defects in the follicular development stimulus mechanism [5]. Ovarian dysfunction can be secondary to autoimmune diseases, infections (e.g., mumps), chemotherapy and radiation treatment and metabolic diseases (e.g., galactosemia), but for most of the cases, the etiology is idiopathic and probably genetic [6]. The genetic basis to the disease is supported by the occurrence of families with several affected women [3, 7–9].

Regarding the genetic causes of POF, they can be chromosomal or caused by single genes, involving the X chromosome or autosomes [10]. The X chromosome abnormalities represent 13% of the cases, followed by the *FMR1* premutation that represents 6% of the cases [11, 12]. Besides, there are many reports of mutations and polymorphisms in genes related to the sporadic form of