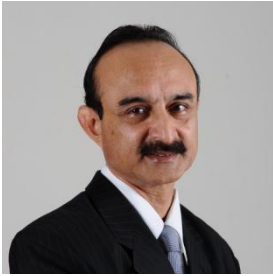


Aetiology and Patho physiology of Premature Ovarian Failure (POF)



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Introduction

Premature ovarian failure (POF) is defined as occurrence of amenorrhoea, hypergonadotropinemia and estrogen deficiency in women under the age of 40 years.¹ It is a term more widely used than ever before, as more young women are found to have elevated follicular stimulating hormone and decreased level of oestrogen, when they present with absent or irregular menses or infertility. Nearly 50% of women with premature ovarian failure have intermittent ovarian function and approximately 5% to 10% of these women subsequently conceive without medical intervention, often many years after diagnosis,² hence it may be appropriate to refer it as primary ovarian insufficiency.³

Often used as synonyms to premature menopause or early menopause, POF is not equivalent to menopause. Premature menopause is a complete cessation of menses before 40 years of age, characterized by amenorrhea associated with hypo-estrogenaemia & elevated gonadotrophin levels.

POF is a “hypergonadotrophic hypogonadism” or “primary hypogonadism” or “primary ovarian insufficiency”.

Method

This article is prepared by a search of English literature from 1967-2009, using key words of premature ovarian failure and premature menopause from The Cochrane library database and internet. A hand search of the references of these articles was also performed.

Epidemiology and prevalence

There are no actual estimates of the prevalence of premature ovarian failure. Approximately it affects 1 in 10,000 women by age 20, 1 in 1000 by age 30, and 1 in 100 by age 40 years.⁴ There are ethnic differences ranging from 1.4% in women of African-American and Hispanic descent to 1% in Caucasian, 0.5% in Chinese and 0.1% in Japanese women.⁵

POF occurs in 10-28% of the women with primary amenorrhea and 4-18% in those with secondary amenorrhea.⁶ Most cases of POI are sporadic. However, approximately 10% to 15% of women with POI have a family history of the disorder.⁷

Biology of ovarian ageing

Women are born with a fixed number of primordial follicles, which are reduced over the time. Primordial germ cells proliferate in female fetuses until about 4 month of gestation, when a peak store of about 7 million primordial follicles is established. The number declines from that point forward, reaching approximately 1- 2 million primordial follicles at birth and about 0.5 million at puberty. Thereafter exponential decay occurs over the reproductive years. Decline of follicles occurs in two phases. Up to 37 years following puberty, steady follicular depletion occurs by

atresia or apoptosis. Acceleration of follicular depletion by more than two fold occurs after 37 years when approximately 25,000 follicles remain. Menopause occurs on the basis of a depletion of potentially functional primordial follicles. At the time of menopause threshold number of 1000 follicles reached which has been shown to be refractory to gonadotropin stimulation, the so called “endocrinologically occult” follicle.⁸

Pathophysiology

The human ovary functions both as a reproductive and an endocrine organ. Cyclical menses and ovulation are the hallmark of healthy ovary. Reproductive failure and endocrine failure occurs as a result of ovarian function disruption. Three hypotheses proposed for etiology of premature ovarian failure are:

- Low initial number of ovarian follicle (low reserve)
- Acceleration of the atretic process
- Follicular dysfunction

Classification of premature ovarian failure

Premature ovarian failure is divided into two major pathogenic categories:

1. Spontaneous ovarian failure
2. Induced ovarian failure

On cytogenetic findings, two distinct groups are made as

1. Chromosomally incompetent ovarian failure
2. Chromosomally competent ovarian failure.⁸

Spontaneous POF

The pathogenesis of spontaneous POF in majority of the cases is unknown. However, the number of the known causes and genetic factors for POF continues to increase. Mechanisms involved are follicle depletion and follicle dysfunction.

Ovarian follicle depletion occurs as a result of disruption in any step of germ cell proliferation/migration or disruption in oogonia proliferation/migration leading to low ovarian follicle reserve as seen in pure gonadal dysgenesis, thymic aplasia/hypoplasia, autosomal recessive and idiopathic conditions. Low follicle number may support pubertal development, menstruation initiation & even fertility.⁹

Accelerated follicle atresia is seen in X chromosome related condition and infections. Autoimmune diseases and idiopathic etiology are also responsible for accelerated follicular atresia.¹⁰

Ovarian follicle dysfunction occurs as a result of gonadotropin molecule defect or defective gonadotropin receptor¹¹. Other causes are Steroidogenic enzyme defects (17-alpha-hydroxylase, 17-20-desmolase, or aromatase enzyme deficiency), Autoimmune condition, Signal defects (Abnormal gonadotropin (GnRH) receptor, Abnormality in the G-protein signaling pathway), Idiopathic (resistant ovary syndrome).¹⁰

Induced ovarian failure

The mechanism of induced ovarian failure includes damage to proliferative ovarian granulosa cell and/or oocytes leading to follicular depletion and increased risk of POF. It

may be temporary and spontaneous return of ovarian function may occur. POF is seen in cases following hysterectomy with conservation of ovaries, drugs like tamoxifen, high dose chemotherapy, infradiaphragmatic radiation, smoking, occupational exposure to toxins and with increased use of GnRH stimulation. However, the anovulation associated with elevated basal concentrations of FSH and reduced levels of estrogen may be transitory and pregnancies have been reported in women with such histories. Bilateral oophorectomy results in acute development of symptoms in induced POF.¹⁰

Chromosomally incompetent ovarian failure

POF with abnormal constitution of chromosomes is referred as chromosomally incompetent ovarian failure (CIOF). This reflects to an atypical number of chromosomes or structural abnormality to one or more chromosomes. As ovarian determinants are present on both sex chromosomes as well as on autosomes, X chromosomal related conditions such as Turner's syndrome (45XO), fragile X syndrome, pure gonadal dysgenesis, Trisomy X, mutation involving X chromosomes and autosomal conditions such as Trisomy 13,18, mutation of FOXL2 gene and other autosomal mutation leading to Galactosemia, deficiency of 17- alpha hydroxylase, reproductive hormone inactivity, GnRH receptor abnormality, autoimmune polyglandular syndrome type 1 etc leads to POF.

Chromosomally competent ovarian failure

POF with normal constitution of chromosomes is referred as chromosomally competent ovarian failure (CCOF). POF as a result of environmental exposure to toxic agents,

infections and certain autoimmune conditions are associated with normal chromosomal constitution.

Causes of premature ovarian failure

Most of the times, POF is idiopathic. Diverse etiological factors adversely influence follicular depletion and rate of follicular atresia causing exhaustion of follicular stock. No one cause seems to predominate and represent for large percentage of the cases.

With widespread use of radiotherapy and chemotherapy for young age malignancies, cancer treatment is the most common cause for diminish ovarian reserve and thus increased incidence of POF. The risk of POF is more with treatment of cancer after puberty, high dose of chemotherapy or radiotherapy(9 Grays or higher) regimens, with combined chemo and radiation therapy and when the field of radiation involves pelvis. Evidence has suggested that co-treatment with GnRH agonists may reduce the gonadotoxic effects of chemotherapy.¹²

It is clear that there are several genetic causes for POF. Approximately 15-20% of women with POF have affected relatives, suggesting that the inherited predisposition to POF is common.⁷ It is likely that POF is a heterogeneous disorder caused by multiple gene mutation.

For the oogenesis to be complete, it is essential for both X chromosomes to be present, hence in Turners syndrome, ovarian function is defective.¹³ Prevalence of POF in Trisomy X is unknown, but association has been reported.¹⁴ The incidence of fragile X premutation has been reported to be as high as 20%.¹⁵ Paternally acquired premutation is more

associated than maternally acquired premutation.¹⁶ Deletion, rearrangement, deficiencies and excesses in either short arm or long arm of X chromosome are associated with POF.

Prevalence of POF in women with Galactosemia is 70-80%.¹⁷ Possible mechanism include the toxic effect of galactose or its metabolite on follicular structures and oogonia during fetal life and glycosylation of gonadotropin subunits leading to biological inactivity.¹⁷

Development of ovarian failure in 17-alpha hydroxylase deficiency is due to defective ovarian steroid synthesis.¹⁸

Autoimmune oophoritis may occur alone or in addition to other autoimmune endocrine disorder resulting in POF. Approximately 4% of cases of spontaneous POF are associated with adrenal autoimmunity. Approximately 60% of women with type 1 autoimmune polyglandular syndrome and 10% of women with type 2 have POF.¹⁹⁻²⁰

Type 1 polyglandular autoimmune syndrome is a autosomal recessive disorder characterized by Hypoparathyroidism, adrenal insufficiency, chronic mucocutaneous candidiasis, chronic hepatitis, POF and hypothyroidism. It is caused by mutation of gene located on chromosome 21q22. Type 2 polyglandular autoimmune syndrome is less defined, characterized by adrenal insufficiency, autoimmune thyroid disease, Type 1 diabetes mellitus and POF. It is associated with human leukocyte antigen subtypes.

Smoking, as containing polycyclic hydrocarbons leading to follicular exhaustion and POF.²¹ Incidence of POF with viral oophoritis is 3-7%.²² Pelvic surgery has potential to compromise blood supply and may cause inflammation leading to POF.

Causes of Premature ovarian failure include:

1. Genetic

- chromosomal: Turners, pure gonadal dysgenesis, Trisomy 18,13, fragile X
- familial
- metabolic: 17-alpha hydroxylase deficiency, ataxia telangiectasia, mucocutaneous and fungal infections

2. Autoimmune Disease

- Endocrinal Disease

Thyroid disease: Grave's disease, Hashimoto's disease

Adrenal failure

Hypoparathyroidism

Diabetes

- Non-endocrinal Disease

Pernicious anemia

Hemolytic anemia

Vitiligo

Rheumatoid arthritis

Glomerulonephritis

3. Infections

Pelvic infections – chlamydial, anaerobic

4. Environmental

Exposure to bromopropane

5. Iatrogenic

Surgical

Chemotherapy

Irradiation

Smoking

References

1. De Morale, Ruehsen M, Jons GS. Premature ovarian failure. *Fertil steril* 1967; 18:440-461.
2. Van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update*. 1999; 5: 483–492.
3. Welt CK. Primary ovarian insufficiency: more accurate term for premature ovarian failure. *Clin Endocrinol (oxf)* 2008; 68:499-509.
4. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol*.1986; 67: 604 –606 9.

5. Luborsky JL, Mayer P, Sower MF, Gold EB, Santoro N. premature menopause in multiethnic population study of menopause transition. *Hum Reprod.* 2002; 18:199-206.
6. Goswami D, Conway GS. Premature ovarian failure. *Hum Reprod Update.* 2005; 11:239-410.
7. Van Kasteren YM, Hundscheid RD, Smits AP et al. Familial idiopathic premature ovarian failure: an overrated and underestimated genetic disease? *Hum Reprod.* 1999; 14: 2455 –59.
8. Virkud A: Biology of ovarian aging and premature ovarian failure. *Progress in Reproductive Endocrinology –Nimesh Shelat, Jaypee Brothers* 2003; 93-99.
9. Stedman's Medical Dictionary. Philadelphia Lippincott Williams & Wilkins; 2000.
10. Rao K, Iqbal R. Premature ovarian failure. *Progress in Reproductive endocrinology- Nimesh Shelat, Jaypee Brothers.* 2003;125-138.
11. Aittomaki K, Lucena JLD, Pakarinen P. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. 1995; 82: 959 –968
12. Frank H, Smith W, Vermes I. Gonadal protection by a gonadotropin releasing hormone agonist depot in a young woman with Hodking's disease undergoing chemotherapy. *Gynecol Endocrinol* 2005; 20:274-78.
13. Zinn AR, Tonk VS, Chen Z et al. Evidence for a Turner's syndrome locus or loci at Xp112-p221. *Am J Hum Genet.* 1998; 63:1757-66.
14. Itu M, Neelam T, Ammini AC, Kucheria K. Primary amenorrhoea in triple X female. *Aust NZJ Obstet Gynecol.* 1990; 30:386-8.

15. Hagerman RJ, Hagerman PJ. The fragile X premutation: into the phenotypic fold. *Curr Opin Genet Dev.* 2002; 12: 278 –283
16. Hundscheid RDL, Sistermans EA, Thomas CMG. Imprinting effect in premature ovarian failure confined to paternally inherited fragile X premutation. *Am J Hum Genet.* 2000; 66:413-18.
17. Laml T, Preyer O, Umek W, Hengstschlager M, Hanzal E, Genetic disorder in premature ovarian failure. *Hum Rep Update.* 2002; 8:483-91.
18. Mallin SR. Congenital adrenal hyperplasia secondary to 17 hydroxylase deficiency : two sisters with amenorrhoea, hypokalamia, hypertension and cystic ovaries. *Ann Intern Med.*1969; 70:69-75.
19. Bakalov VK, Vanderhoof VH, Bondy CA , et al. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. *Hum Reprod.* 2002; 17: 2096 –2100.
20. Bakalov VK, Anasti JN, Calis KA, et al. Autoimmune oophoritis as a mechanism of follicular dysfunction in women with 46,XX spontaneous premature ovarian failure. *Fertil Steril.* 2005; 84: 958 –96518
21. Di Prospero F, Luzi S, Iacopini Z. Cigarette smoking damages women's reproductive life *Reprod Biomed Online.* 2000; 8:246-7.
22. Rebar RW, Coonolly HV. Clinical features of young women with hypergonadotropic amenorrhoea. *Fertil Steril* 1990; 53:804-810.