

Clinical presentation of patients with premature ovarian failure in an outpatient clinic

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Abstract

Introduction: Premature ovarian failure (P.O.F.) refers to the cessation of ovarian function at an early age (<40 years). This is more common with secondary than with primary amenorrhea. POI affects one in 10000 women by the age of 20 years and one in 100 by the age of 40 years. In the majority of women, the etiology of POF is unknown. Other etiological factors may be Genetic or chromosomal, Autoimmune, defective gonadotropic factor, Infection (Mumps oophoritis), and Iatrogenic. The first symptom of POI is usually irregular or missed periods. Later, the symptoms may mimic those of Hypoestrogenism. If a woman is diagnosed with POI and wishes to become pregnant, she may consider trying IVF with a donor oocyte.

Material and Method: The study aimed to identify the pattern of clinical presentation of POI. This is a retrospective study of 29 patients (Diagnosed cases of >25 mIU/mL FSH) who attended the OPD clinic of obstetrics

of gynecology in District Shivpuri with age <40 years from 1st January 2019 to 30 June 2021 data was collected about clinical presentation and investigations from OPD record.

Results: The most common age group affected was 35-40 years 48.27%. The most common presenting complaint of the patient was infertility 44.82%, patients with a history of delayed menses were 27.58%, patients with secondary amenorrhea were 31.03% and primary amenorrhea was 24.13%, Other patients presented with symptoms due to Hypoestrogenism.

Conclusion: In our study patients presented with various clinical features like delayed menses, primary and secondary amenorrhea, infertility symptoms due to hypoestrogenism, and decreased self-confidence. These patients of POI were found to have intermitted ovulation to complete cessation of ovulation and menses. Hormone replacement therapy should be given wherever it is

needed. Psychological support and counseling of these patients should be done.

Keywords: Premature ovarian failure, Hypoestrogenism, Delayed menses.

Introduction

Premature ovarian failure (P.O.F.) refers to the cessation of ovarian function at an early age. P.O.F. is a heterogeneous condition. There are three types of P.O.F. Type 1 POF (Prepubertal) that occurs before puberty where there is a lack of pubertal development and primary amenorrhea. Patients in type 2 POF (Postpubertal) present with secondary amenorrhea where ovarian failure occurs at an early age (< 40 years), before the age for natural menopause. Premature cessation of ovarian function also occurs with certain treatments offered for other conditions like chemotherapy/radiotherapy for cancers, or surgical menopause with bilateral oophorectomy. This Type 3 is iatrogenic POF. These conditions are characterized by amenorrhea and hypergonadotropic Hypoestrogenism¹.

One percent of all women in reproductive years will experience premature ovarian failure. Of all amenorrheic women, the incidence of POF is 10 percent.^{2,3} This is more common with secondary than with primary amenorrhea. POI affects one in 10000 women by the age of 20 years and one in 100 by the age of 40 years.⁴

In the majority of women, the etiology of POF is unknown. This is probably a genetic disorder with an increased risk of accelerated follicular atresia. The following etiological factors have been suggested.

Genetic or chromosomal^{5,6,7}. There are many reasons involved in the causation of POI. Over 50 genes are found to be causally related to POI⁸ and the disease course of some cases has been clarified, but in most cases, the genetic background remains unexplained, suggesting that more genes may be associated with the etiology of POI

and they need to be discovered. Most of the abnormalities discovered were of the X chromosome, although a few autosomal abnormalities were also observed. Monosomy X is well known to be manifested as Turner's syndrome and is associated with primary amenorrhea, but recent studies have shown that some women with numerical abnormalities of the X chromosome can have spontaneous menstruation up to their twenties and thirties, and some can even conceive.⁹

Genetic studies in premature ovarian insufficiency are mostly on folliculogenesis (NR5A1, NOBOX, FIGLA, and FOXL2), in ovarian steroidogenesis (FSHR, FSH, LHR, and LH) or on folliculogenesis growth factors (inhibin A, GDF9, and BMP15),^{10,11,12}. The disease course of POI differs remarkably among the causative genes, the types of mutations, or possibly combinations of mutated genes that are mostly unknown at present. Despite numerous genes implicated in the etiology of POI, most women with isolated POI do not undergo genetic testing mainly because of the cost of sequencing individual genes, and the fact that most genes account only for a small portion of POI patients.¹³

Autoimmune **Blumenfeld et al** (1991)¹⁴, suggested autoimmune disorder as an etiology of premature ovarian failure. The incidence has been reported as high as 40 percent. The frequent association of four different endocrinopathies namely, premature ovarian failure, Graves disease, Hashimoto's thyroiditis, and Addison's disease suggest that they are different manifestations of a single immunologic disorder. POI of adrenal origin is the most common type, observed in 60–80% of patients with autoimmune POI.

Defective gonadotropic factor^{15,16} defective gonadotropic factors, which might interfere with the functions of bioactive gonadotropins.

Hypergonadotropic hypogonadism and infertility/subfertility in women are the results of gonadotropin resistance caused by inactivating mutations in receptors of the two gonadotropins, LH and FSH.

1. Infection Mumps oophoritis, like mumps orchitis, has been suggested as an aetiological factor. Viral infection may cause follicular destruction. mumps and oophoritis have been considered to be a cause of POI, accounting for 3–7% of total POI cases.¹⁷
2. Iatrogenic- Physical insult to ovaries Irradiation or chemotherapy. 64% occurred following ovarian surgeries (i.e., except for bilateral oophorectomy). Patients who underwent surgery for benign ovarian cysts before the onset of ovarian insufficiency were also found prone to POI.¹⁸

It is a condition involving medical, psychological, and reproductive implications. It causes menstrual disturbances and infertility, as well as various health problems, mainly due to estrogen deficiency, throughout a women's life. After a diagnosis of POI, fertility treatment has been considered to be of no or very little value.

The first symptom of POI is usually **irregular or missed periods**. Later, the symptoms may mimic those of natural menopause:

- Hot flashes
- Night sweats
- Irritability
- Poor concentration
- Decreased sex drive
- Pain during sex
- Vaginal dryness

For many women with POI, trouble in getting pregnant or infertility is the main reason they go to their health care provider.¹⁹

The diagnosis of premature ovarian insufficiency (POI) is a grievous event in a woman's life. Diagnosis of POI can be reached upon by taking a thorough medical history of the patient including asking whether you have relatives with POI. A pregnancy test is also conducted to make sure that the patient is not pregnant. A physical examination of the patient is performed to look for signs of other disorders which could be causing the symptoms. Blood tests are conducted to check for certain hormone levels. Patients may also have a blood test to do a chromosome analysis. A pelvic ultrasound is done to see whether or not the ovaries are enlarged or have multiple follicles.

Follicle-stimulating hormone (FSH) levels have been chiefly used in making the diagnosis of POI, but precise cut-off levels have not been determined. The most relevant diagnostic criteria proposed so far are those of the European Society of Human Reproduction and Embryology (ESHRE) POI guideline development group's guideline, which are as follows: oligo/amenorrhea for at least 4 months and elevated FSH levels >25 mIU/ml on two occasions >4 weeks apart.²⁰

However, only Another most common reason associated with POI is hypergonadotrophic hypogonadism. Low sex hormone levels are accompanied by elevated gonadotropin levels. In girls with delayed puberty, if gonadotropin levels are elevated, the laboratory investigation must include a Karyotype to rule out genetic disorders of gonadal development.²¹

POI is associated, in the **long term**, with an increased risk of osteoporosis and cardiovascular disorders and with some degree of cognitive deterioration. In addition to these complications, POI is reported to be associated with earlier mortality.

Hormone replacement therapy (HRT):^{5,7} HRT is the most common treatment of POI. It gives the body enough estrogen and other hormones that the ovaries are not making. HRT improves sexual health and decreases the risks for osteoporosis and heart disease. It can be taken until about age 50; that's about the age when menopause usually begins. In prepubertal POF, HRT is targeted for induction of puberty, maintenance of menstrual and sexual function. However, the mode of induction of pubertal growth and development varies with the type of cytogenetic abnormality, e.g. in Turner syndrome patients with predicted adult short stature a delay in initiation of HRT is required. Those who had completed their childbearing before their POF should be informed about the possible restoration of ovulation and conception while they are on Combined Oral Contraceptive (COC) of HRT.

- **Calcium and vitamin D supplements:-** Because women with POI are at higher risk for osteoporosis, they should take calcium and vitamin D every day.
- **In vitro fertilization (IVF):-** If a woman is diagnosed with POI and wishes to become pregnant, she may consider trying IVF with a donor oocyte.
- **Fertility preservation techniques**^{22,5} - The patient should be counseled about various fertility preservation techniques such as like oocyte or embryo cryopreservation or GnRH against ovarian (suppression) and adoption of other methods.
- **Regular physical activity and healthy body weight:-** Getting regular exercise and controlling body weight can lower the risk for osteoporosis and heart disease.
- **Treatments for associated conditions:-** Patients with POF who have an autoimmune basis should be also assessed for other endocrine autoimmune disorders. They have to be offered respective replacement therapies

accordingly besides HRT in case of associated disorders. If any other associated condition is present related to POI, it is important to treat that as well. Treatments may involve medicines and hormones.¹²

POI increases the risk of bone loss, cardiovascular diseases, and endocrine disorders. Health care providers also should be aware of the potential psychological effects of primary ovarian insufficiency and should counsel the family members and patients on the risk of associated comorbidities.

Material and Method

The study aimed to identify the pattern of clinical presentation of premature ovarian insufficiency POI.

This is a retrospective study of 29 patients attending the OPD clinic of obstetrics of gynecology in District Shivpuri with age <40 years from 1st January 2019 to 30 June 2021. These 29 patients were documented patients of primary ovarian insufficiency (patients with FSH >25 mIU/mL at 2/3 menstrual cycle).

Detailed information was collected from the record of the clinic regarding age, BMI, Medical, Surgical, obstetrics, and fertility history. Various presenting symptoms:- Menstrual problem (Primary amenorrhea, secondary amenorrhea, Oligo amenorrhea, and other menstrual problem) Infertility, hot flushes, irritability, mood changes, Sexual dysfunction, bony pain, and other problems. General and examination and gynecological examination:- (Per abdomen, Per speculum, per vaginal) was done and findings were noted. All investigations report:- CBC, ESR, Hormonal profile (LH, FSH, TSH, PRL), and others were studied. Imaging reports and other tests were also studied. patients karyotyping and diagnostic hysterolaparoscopy can be done only in a few patients because of financial constraints.

Inclusion criteria: Patients of primary amenorrhea and all patients >40 years with symptoms suggesting premature ovarian failure.

Exclusion Criteria

- Women >40 years.
- Other causes of a menstrual problem like DUB and organic causes.
- Chemotherapy and radiotherapy and surgery (Hysterectomy and adnexal surgery) and Iatrogenic cause of POI.

All the data were analyzed using IBM, SPSS Ver. 20 software. Cross Tabulation and frequency distribution were used to prepare tables. Data are expressed as numbers, percentages, and mean.

Results

Table 1: An sociodemographic factor affecting the quality of life of women with primary ovarian insufficiency.

Characteristics	Number	Percentage
Age (year)		
<20	7	24.13
20-24	1	3.44
25-29	2	6.89
30-34	5	17.24
35-40	14	48.27
Total	29	100
Education		
Primary	3	10.34
HSC	16	55.17
Graduate	8	27.58
Post Graduate	2	6.89
Total	29	100
Occupation		
Housewife	15	51.72
Employed	7	24.13

Student	7	24.13
Total	29	100
Marital status		
Unmarried	10	34.48
Married	19	65.51
Total	29	100
Have children		
Yes	16	55.17
No	13	44.82
Total	29	100
Type of pregnancy		
Natural	15	51.72
Donor Egg	1	3.44
Total	16	55.16
POI Family History		
Yes	5	17.24
No	24	82.75
Total	29	100

The most common age group affected was 35-40 years 48.27%. 55.17% of patients were HSC educated, Most of the 51.72% were housewives, and with a history of natural conception only in 17.24% of patients, family history of POI was there.

Table 2: Distribution of cases according to symptoms many patients had multiple complaints.

Menstrual symptoms	Case (29)		
	No.	%	
Irregular menses	6	20.68	
Delayed menses	8	27.58	
Amenorrhoea	Primary	7	24.13
	Secondary	9	31.03
Infertility	13	44.82	
Vasomotor	10	34.48	

(Hot flashes, night sweats)			
Anxiety depression or mood swings		8	27.58
Concentration or memory problem		5	17.24
Decreased sex drive		7	24.13
Vaginal dryness		14	48.27

The most common presenting complaint of the patient was infertility 44.82%, patients with a history of delayed menses were 27.58%, patients with secondary amenorrhea were 31.03% and primary amenorrhea was 24.13%, Other patients presented with symptoms due to Hypoestrogenism.

Table 3: Value of serum FSH above 25 IU.

A value above 20 IU	29	100%
Below 20 IU	0	0%

All patients had FSH of about 25 IU.

Table 4: Ultrasonography pelvis findings.

USG findings	Number of cases	%
Normal	7	24.13
Small uterus with normal ovaries	7	24.13
Abnormal (small uterus and or streak ovaries, and/or reduced endometrial thickness)	15	51.72
Total	29	100

On USG findings- Normal USG was found in 24.13% of patients, a Small uterus with normal ovaries was found in 24.13% patients and Abnormal (small uterus and or streak ovaries, and/or reduced endometrial thickness) was found in 51.72% of patients.

Discussion

In this study, we addressed that POI is not just a medical issue. Unfortunately, in India, most medical staff pay attention only to medical problems in afflicted women. However, due to important problems such as infertility and early onset of menopausal symptoms due to premature ovarian failure are not taken care of, women are at risk for mental health problems. However, to provide better sexual and reproductive health services to these women early diagnosis and management should be there.

The present study was conducted to understand the clinical presentation of patients with premature ovarian failure in an outpatient clinic. It was observed that this disease has affected the women belonging to the age group between 20 to 40 years. The maximum number of patients were found to be of age group between 35 to 40 years (48.27%). It was also observed in our study that even women below the age of 20 years were also seen affected by this illness (24.13%) This data matches with the findings concluded by **Islam R et al**²³ who also stated that the age group comprises of young girls of less than 20 years to middle-aged women of 45 years.

In this study, it was observed that both married (65.61%) and unmarried (34.48%) women were suffering from POI. Out of the 19 married women, 16 had children (55.17%) and 13 (44.82%) women were childless. It was found in the study that there was a remarkable percentage of women who were trying to conceive but were not able to due to POI.

Another very important finding in our study was that out of 29 women, 24 women (82.75) were not having any family history of POI, which is very alarming. Due to the absence of any family history, it becomes difficult to conclude that the patient might have POI. Our results are in line with the results of another study done by **Alzubaidi NH et al.**²⁴

On the evaluation of symptoms presented in the outpatient clinic, we concluded that anxiety, depression, or mood swings were the most common complaint of the patients which were then followed by hot flashes, night sweats, vaginal dryness, infertility, amenorrhoea, reduced sex drive, and irregular menses. We can thus conclude that this disease has a wide range of symptoms that can disturb the overall health of women. The symptoms observed in our study are in accordance with the opinion of the **Committee**²⁵ on adolescent health care.

Pasquali EA et al²⁶ in his study concluded that amenorrhoea, vasomotor disorders like hot flashes and night sweats, and infertility were the most common symptoms like our study.

As far as the diagnostic criteria are concerned, serum FSH and LH play a very important role. In our study, we observed that 100% of the patients had the value of serum FSH above 20 IU. This finding of our study completely coincides with the European Society of Human Reproduction and Embryology (ESHRE)²⁷ POI guideline development group's guidelines, which are as follows: oligo/amenorrhea for at least 4 months and elevated FSH levels >25 mIU/mL on two occasions >4 weeks apart.

In our study, we also conducted ultrasonography of the pelvis region and concluded that 24.13% of women had normal findings and the same percentage of women had small uteri with normal ovaries. 51.27% of women showed small uterus and reduced endometrial thickness.

Thus we can conclude that USG also plays an important role in reaching the diagnosis of POI. This finding of our study goes in accordance with **Sarrel PM et al**²⁸ who also believe that USG may act as an adjunct to diagnose POI.

POI is a common condition that can have many far-reaching consequences on a woman's physical and mental health.

Conclusion

In our study patients presented with various clinical features like delayed menses, primary and secondary amenorrhea, infertility symptoms due to hypoestrogenism, and decreased self-confidence. These patients of POI were found to have intermitted ovulation to complete cessation of ovulation and menses. Psychological support and counseling of these patients should be done. Hormone replacement therapy, the importance of calcium and vitamin D3, future options for childbearing like IVF with donor oocyte, various fertility preservation techniques like oocyte or embryo cryopreservation, or GnRH agonist ovarian (suppression), and other methods should be discussed with all patients of premature ovarian failure if needed.

Long-term follow-up of these patients is a must to prevent various side effects of POI. Early diagnosis and proper treatment result in improvement in various symptoms and increased conception rate in patients of infertility. Stem cell Transplantations for malignancies in younger women have created newer challenges in this area of HRT for this special group of patients. Guidelines for this group need to be developed.

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