International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Amber QJ et al. Int J Reprod Contracept Obstet Gynecol. 2019 Oct;8(10):3926-3930
www.ijrcog.org

pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20194356

Original Research Article

Study of incidence of premature ovarian failure in patient attending outpatient department for infertility in a tertiary care centre

Qazi Jaweria Amber*, Tushar Tatyaba Palve

Department of Obstetrics and Gynecology, Grant Medical College and J. J. Group of Hospitals, Mumbai, Maharashtra, India

Received: 21 June 2019
Revised: 04 September 2019
Accepted: 11 September 2019

***Correspondence:**
Dr. Qazi Jaweria Amber,
E-mail: jawerianaved@gmail.com

ABSTRACT

Background: To assess the incidence of premature ovarian failure in cases attending infertility outpatient Department of Obstetrics and Gynecology in a tertiary care centre. A total of 350 patients attending infertility opd were screened over period of 150 days from which authors observed premature menopause in 10 cases accounting for an incidence of 2.8%. POF affects approximately one in 10,000 women by age 20; one in 1,000 women by age 30; one in 100 women by age 40. Premature ovarian failure is a common cause of infertility in women.
Methods: Patient attending outpatient Department of Obstetrics and Gynecology with age less than 40 years and infertility, symptoms of menopause were enrolled for the study for duration of 150 days.
Results: Present study authors found a total of 2.8% of patient presenting in our outpatient department for infertility had Premature ovarian failure.80% of them were symptomatic suffering with symptoms of hormonal deficiencies .100% of patient with infertility diagnosed as premature ovarian failure had low AMH and High FSH and LH levels indicating poor prognosis.
Conclusions: Patient presenting with infertility and amenorrhoea can be cases of premature menopause. Here it is essential to investigate and treat the patient. Infertility might be one of the early presenting symptoms if not the first one. These patients if treated and diagnosed early can have a better living. Considering the wide spectrum of functional derangements in patient with early menopause and benefits of early hormone replacements these patients should be diagnosed and treated early.

Keywords: AMH low, High FSH, High LH, Infertility, Premature menopause, Premature ovarian failure, Secondary amenorrhoea

INTRODUCTION

Premature ovarian failure is defined as a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles/ arrested folliculogenisis before the age of 40 years (secondary amenorrhea).[1,2]

Epidemiology

POF affects approximately one in 10,000 women by age 20; one in 1,000 women by age 30; one in 100 women by age 40.[3] The familial form of POF is rare, representing 4 to 31% of all cases of POF.[4-6]

Etiology

The causes of POF are extremely heterogeneous. Acquired forms such as those occurring after treatments for neoplastic diseases or autoimmune diseases account for many cases.[1] POF has a strong genetic component with X chromosome abnormalities playing a primary role mainly in the cases with ovarian dysgenesis.[7,8] Despite the description of several candidate genes the cause of POF still remains undetermined in the majority of the cases (idiopathic). This idiopathic form of POF can show sporadic and familial forms.

The different causes of POF are illustrated as follows:[9-11]

- Iatrogenic origin (surgery, chemotherapy, radiations)
- Autoimmune, including polyglandular autoimmune syndrome, as well as autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy (APECED) due to mutations in AIRE gene)
- Infections (e.g. herpes zoster, cytomegalovirus)
- Chromosome X defects;
  - Turner syndrome
  - Fragile X syndrome (FMR1 gene premutation)
- Syndromic defects:
  - Congenital disorders of glycosylation (CDG, formerly named carbohydrate-deficient glycoprotein syndromes) (recessive)
  - Galactosemia (recessive)
  - Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) (female-limited, dominant)
  - Pseudohypoparathyroidism (PHP) type Ia
- Isolated defects:
  - Follicle stimulating hormone (FSH) receptor mutations (FSHR), (recessive)
  - Luteinizing hormone (LH) receptor mutations (LHR), (recessive)
  - FOXL2 (transcription factor involved in BPES) mutations (female-limited defect, dominant)
  - Bone morphogenetic protein 15 (BMP15) mutations (female-limited defect, heterozygous mutation)
- Idiopathic.

Symptoms

The symptoms can vary considerably from patient to patient and the disorder may occur abruptly or spontaneously or it may develop gradually over several years. About half of the cases of primary amenorrhea are due to ovarian dysgenesis, which is revealed by the finding OF streak ovaries accompanied by uterus hypoplasia at ultrasound. In the other patients, follicles (10mm) may be found at histological evaluation such as in the case of FSHR mutations.[12] In these cases, almost normal pubertal development may be seen. Post-pubertal onset of ovarian failure represents the large majority of the cases.[1] This is characterized by secondary amenorrhea associated with premature follicular depletion or arrested folliculogenisis. As in the case of physiological menopause, POF is clinically characterized by typical manifestations of climacterium such as palpitations, heat intolerance, flushes, night sweats, irritability, anxiety, depression, sleep disturbance, decreased libido, hair coarseness, vaginal dryness, fatigue. Female infertility is an obvious and presently irreversible consequence of POF.

POF and infertility

Fertility of women with POI is severely diminished, but unlike menopause, POI may be accompanied with spontaneous ovarian activity and natural pregnancies. The major causes of POI include autoimmunity, genetic and environmental factors. At the same increased prevalence of gynecological and other cancers, improvement in the treatment procedures has led to better survival rates but increased incidence of POI in women during reproductive age during the past few decades.[13]

Management of infertility in POF

The rapid and unanticipated truncation in a woman's reproductive life span is among the most distressful sequela of POI diagnosis, particularly for those women who have yet to embark on planning a family. Whereas fertility is markedly compromised, infertility in the setting of POI may not be absolute. Up to 25% of women with POI may spontaneously ovulate, and 5% to 10% will conceive and deliver after being diagnosed with POI.[14,15] Despite marked advances in the field of reproductive medicine in recent years, there are no interventions that can reliably improve residual ovarian reserve parameters or any treatment other than use of donor eggs which can improve conception rates in women with POI.[16] Women with POI should be reassured that spontaneous pregnancies from idiopathic POI do not show any higher obstetric morbidity or neonatal risk as compared with the general population.[16,17] Conversely, those not interested in future fertility should be made aware that, despite the recognized reproductive compromise, spontaneous resumption of ovarian activity and thus unwanted conceptions can occur. Therefore, contraceptive strategies should be recommended in those women who wish to avoid pregnancy. For women with diagnosed or suspected POI for whom fertility is a priority, prompt referral to a reproductive endocrinologist is recommended. For those with established POI, while the opportunity for fertility preservation is missed, assisted conception by IVF using donor gametes or embryos provides the patient with the best option for biological parenting. Oocyte donation cycles generally result in high pregnancy rates given that the success rates are attributed to the age of the preselected and young oocyte donor. Alternatively, some couples prefer to pursue adoption to complete their families. All options should be offered to couples with a clear appreciation that this topic is sensitive and decisions should be individualized.

Recent advances in treatment of infertility in POF

In vitro maturation (IVM) and in vitro fertilization (IVF) technologies are facing with growing demands of low ovarian reserve women to conceive. Although ovarian stem cells (OSCs) of older women are capable of producing in vitro fresh oocyte-like cells (OLCs), such cells cannot respond to IVM and IVF due to the lack of granulosa cells required for their maturation. Follicular renewal is also dependent on support of circulating blood mononuclear cells. They induce intermediary stages of meiosis (metaphase I chromosomal duplication and crossover, anaphase, telophase, and cytokinesis) in newly emerging ovarian germ cells, as for the first time demonstrated here, induce formation of granulosa cells, and stimulate follicular growth and development. A pretreatment of OSC culture with mononuclear cells collected from blood of a young healthy fertile woman may cause differentiation of bipotential OSCs into both developing germ and granulosa cells.[18]

METHODS

Patient attending outpatient Department of Obstetrics and Gynecology with age less than 40 years and infertility, symptoms of menopause were enrolled for the study for duration of 150 days. This study is planned to calculate the incidence of premature ovarian failure in patient presenting with infertility attending outpatient department at our Cama and Albeless Hospital under Grant Medical College and J. J. Group of Hospital, Mumbai. Patient presenting with complains of infertility and amenorrhoea for 6 months were enrolled. FSH levels were send for all the patients and those with FSH level more than 20 IU done 2 times 4 week apart were included. Further these patient were screened for serum LH other endocrine derangements including serum thyroid prolactin serum vitamin D3. An ultrasound abdomen and pelvis was done for these patients. Serum Anti mullerian hormone was done for all of them which is an indicator of ovarian reserve. As per the limitation and compliance issue authors could get endocrine opinion karyotyping and diagnostic hysterolaproscopy for few of them. The current study has also mentions the histopathology of uterine endometrium from the previous investigation like dilatation and curette or endometrial biopsy or hysteroscopy if patient has done before attending our institute and has a valid report.

Exclusion criteria

- Women more than 40 years
- Primary amenorrhoea
- Dysfunctional and organic causes of menstrual disturbances
- Secondary amenorrhoea due to chemotherapy and radiotherapy. In order to avoid bias authors restrained from including iatrogenic cases like post chemotherapy post radiotherapy post surgical cases like hysterectomy adnexal surgeries oophorectomy and tubal surgeries.

RESULTS

Present study authors found a total of 2.8% of patient presenting in our outpatient department for infertility had premature ovarian failure which was confirmed with their symptoms high FSH and low AMH levels. Infertility was the primary presenting symptom to outpatient department. 60% of patient belongs to 30-35 years age group. 80% of them were suffering from one or more symptom of ovarian insufficiency when specifically asked for. Five cases out of ten had never conceived before and presented as case of primary infertility rest five secondary infertility. All cases had high FHS and LH as per inclusion criteria also indicating peripheral oestrogen deficiency. All ten patients had lower than the reference serum AMH level indicating poor prognosis to treatment. Ultrasonography could diagnose around 50% cases only. Endometrial sampling showed atrophic endometrium as common finding.

Table 1: Distribution of cases according to age in different groups amongst cases studied.

Age group	Number of cases	Percentage
25-30	1	10%
30-35	6	60%
35-40	3	30%

Table 2: Distribution of cases according to symptoms except infertility.

Symptoms	Number of cases	Percentage
Symptoms	8	80%
No symptoms	2	20%

Authors categorised the patient presenting to our infertility OPD into above three age groups .Of the three groups major percentage, 6 out of 10 patients presenting with symptoms of premature ovarian failure belong to 30 to 35 yrs age group rest 30% belong to 35 to 40 years age group a single patient was 26 years old.

80% of patient agreed to be suffering from one or other symptoms inform of hot flushes, night sweat, irritability, vaginal dryness, and mood derangements. Some of them directly mentioned it few of them agreed of suffering from above symptoms when specifically inquired for. Infertility was the presenting symptom for all of them. Presence of these symptoms indicates decreased ovarian functions and requirement of hormonal replacement.

50% of patient has conceived before of which total three had previous living child and remaining two had previous history of abortions with no leaving child. The remaining 5 cases presented as a case of primary infertility.

Table 3: Distribution of cases according to primary or secondary infertility.

Type of infertility	Number of cases	Percentage
Primary	5	50%
Secondary	5	50%

Table 4: Value of serum FSH and LH above 20 IU.

Value above 20 IU	10	100%
Below 20 Iu	0	0%

All patient as per inclusion criteria had serum level above 20 IU ranging up to 120 IU these values were confirmed by repeat testing 4 week apart. These levels of FSH and LH are indication of low ovarian reserve and decreased ovarian functions requiring hormonal replacement. This was further established by confirming from their low AMH level.

Table 5: Serum antimullerian hormone level in ng/ml.

Lower then age specific reference value	10	100%
Normal to age specific reference value	0	0%

All patients had lower level of serum AMH level. Serum AMH is a reliable marker of ovarian reserve. Low AMH along with high FSH and LH indicated requirement of early and advanced technology for treatment of infertility also indicating further requirement of hormonal replacement.

Table 6: Ultrasonography pelvis findings.

USG findings	Number of cases	Percentage
Normal	5	50%
Abnormal (small uterus and or streak ovaries reduced endometrial thickness)	5	50%

50% patient has some findings in ultrasonography and another 50% with normal findings. A single case has uterine syneche but due to raised serum FSH and Low AMH with amenorrhoea included in this study.

Table 7: Type of endometrium on histopathology.

Type of endometrium	Number of cases out of 6	Percentage
Normal	2	33.33%
Atrophic	3	50%
Proliferative	1	16.66%

Endometrial sampling was possible in total 6 patients. 50% of patient in whom endometrial sampling was possible had an atrophic endometrium. Remaining 30% has normal endometrium and single patient (16%) had proliferative endometrium.

Table 8: Number of patient presenting as POF amongst total patient screened for infertility.

Total screened	Number of patient	Percentage
350	10	2.8%

Authors were able to screen total 350 patients for infertility during our study period of them there were total 10 cases that came out to be cases of premature ovarian failure. Thus Total 2.8% of patient presenting to opd for infertility had POF.

DISCUSSION

During 5 month study duration period of our study total 350 patients attended gynecology OPD with infertility. Out of which 10 were enrolled in the study with complains of amenorrhoea of more than 6 month. Their FSH levels were send, those with follicular stimulating hormone (FSH) more than 20 on two occasions 4 week apart were grouped as cases of premature ovarian failure (POF). Six out ten patients in the study were between 30-35 years age (Table 1). Another study conducted by Baheti S et al age group between 35-40 years has significant increase in risk of premature ovarian failure.[19] Baheti S et al, who studied general gynac patient found major percentage belonging to 35 to 40 years this difference can be understood by assuming POF presenting late after 35 years generally would have already conceived by this age.[19] Another study conducted by Coulam CB et al, they calculated the annual incidence rates of natural menopause per 100,000 person-years and found ten for ages 15 to 29 and 76 for ages 30 to 39.[3] In the age group 40 to 44, the incidence of natural menopause increased greatly to 881 per 100,000 person-years at risk.

Authors found majority of patient around 80% agreed suffering from one or more symptom of ovarian insufficiency when specifically asked for (Table 2). Baheti S et al, found 65% of patients with symptoms of premature ovarian failure.[19] Same study found 38% of patient of POF had infertility. Since our study was primarily conducted in infertility OPD 100% of patient in study had infertility as presenting symptom.

50% of patient had primary infertility and remaining 50% secondary (Table 3).

All patient as per inclusion criteria had serum level above 20 IU ranging up to 120 IU these values were confirmed by repeat testing 4 week apart. These levels of FSH and LH are indication of low ovarian reserve and decreased ovarian functions requiring hormonal replacement. (Table 4). Also this was an indicator towards oestrogen deficiency hence requirement of hormonal replacement.

Since our patients presented with infertility authors did serum AMH as a marker of ovarian reserve in these patients and found it to be lower than reference for that age group in all of them indicating low ovarian reserve (Table 5).

Ultrasound showed significant findings in form of small or atrophic uterus small ovaries and reduced endometrial thickness in just 50% (Table 6). Endometrial sampling was done for 6 out of 10 patients and it showed atrophic endometrium on histopathology in 50% (Table 7).

Incidence of premature ovarian failure came out to be 2.8%, (Table 8) there is no direct study conducted to find incidence of POF in patient presenting with infertility however Baheti S et al, calculated incidence of infertility as 38.46% amongst patient with premature ovarian failure.[19]

CONCLUSION

Patient presenting with infertility and amenorrhoea can be cases of premature ovarian failure. Here it is essential to investigate and treat the patient. Infertility might be one of the early presenting symptoms if not the first one. These patients if treated and diagnosed early can have a better living. Most of these patients suffer with symptoms of hormonal deficiency. Considering the wide spectrum of functional derangements in patient with early menopause and benefits of early hormone replacements these patients should be diagnosed and treated early. As per their low ovarian reserve as indicated by the level of Serum AMH and high FSH in these patient return of fertility will be a challenge with further requirements of advanced reproductive technology. However natural conception can still occur in few.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Santoro N. Mechanism of premature ovarian failure. Ann Endocrinol. 2003;64:87-92.
2. Timmreck RR. Contemporary issues in primary amenorrhea. Obs Gynecol Clin North Am. 2003;30:278-302.
3. Coulam CB, Adamson AJ. Incidence of premature ovarian failure. Obs Gynecol. 1986;67:604-6.
4. Conway GS, Kaltsas G, Patel A, Davies MC JH. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;(64):337-41.
5. Cramer DW, Xu H HB. Family history as a predictor of early menopause. Fertil Steril. 1995;(64):740-5.
6. Torgerson DJ, Thomas RD. Mothers and daughters menopausal ages: is there a link? Eur J Obs Gynecol. 1997;74:63-6.
7. Simpson RA. Ovarian differentiation and gonadal failure. Am J Med Genet. 1999;(89):186-200.
8. SL S. Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2000;97:189-94.
9. Achermann JC, Ozisik G, Meeks JJ JJ. Perspective: genetic causes of human reproductive diseases. Clin Endocrinol Metab. 2002;(87):2447-54.
10. Aittomaki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hyperonadotropic ovarian failure. Cell. 1995;(82):959-568.
11. Di Pasquale E, Beck-Peccoz PL. Hypergonadotropic ovarian failure associated with an inherited mutation of human bone morphogenetic protein-15 (BMP15) gene. Am J Hum. Genet. 2004;(75):106-11.
12. Meduri G, Touraine P, Beau I, Lahuna O, Desroches A, Vacher-Lavenu MC. Delayed puberty and primary amenorrhea associated with a novel mutation of the human follicle-stimulating hormone receptor: clinical, histological, and molecular studies. Clin Endocrinol Metab. 2003;88:3491-8.
13. Z. B. Fertility treatment in women with premature ovarian failure. Expert Rev Obs Gynecol. 2011;6(3):321-30.
14. Nelson LM, Anasti JN, Kimzey LM. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. J Clin Endocrinol Metab. 1994;79(5):1470-5.
15. RW R. Premature ovarian failure. 2009. Obs Gynecol. 2009;113(6):1355-63.
16. Webber L, Davies M. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926-37.
17. Van Kasteren SJ. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Updat. 1999;5(5):483-92.
18. Bukovsky A. Novel methods of treating ovarian infertility in older and POF women, testicular infertility, and other human functional diseases. Reprod Biol Endocrinol. 2015;25(13):10.
19. Baheti S, Verma A, Sharma M. Premature ovarian failure incidence, risk factors and its relation to BMI and infertility. Int J Reprod Contracept Obstet Gynecol. 2019;8:947-50.

Cite this article as: Amber QJ, Palve TT. Study of incidence of premature ovarian failure in patient attending outpatient department for infertility in a tertiary care centre. Int J Reprod Contracept Obstet Gynecol 2019;8:3926-30.