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REVIEW AND UPDATE ON PRIMARY OVARIAN INSUFFICIENCY

Gynaecology

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ABSTRACT

Primary ovarian insufficiency (POI) previously known as premature menopause or primary ovarian failure. It is defined as menstrual disturbances either amenorrhoea or oligomenorrhoea before 40yrs of age due to depletion or dysfunction of ovarian follicles. It is characterised by high levels of gonadotropins and low estradiol. The most common presenting symptom of POI is primary or secondary amenorrhoea. POI is caused by mostly chromosomal abnormalities or damage due to chemotherapy or radiotherapy and less frequently by infection or infiltrative disorder. Approximately 4% of women with POI will have adrenal and ovarian antibodies. In many of the cases cause is unknown. Chromosomal abnormalities need to be tested in women with POI. Fragile X permutation testing is indicated in these women. Women with POI or unknown cause anticortical antibodies or 21 OH antibodies screening should be considered. Family history of early menopause is a risk factor for POI. POI after chemotherapy or radiotherapy is termed as "Acute ovarian failure" which is transient. The highest incidence of acute ovarian failure is seen with alkylating agents or procarbazine and with pelvic irradiation more than 10cGy. Anti Mullerian hormone assessment is done to know the status of ovarian reserve in women before and after ovarian surgery or chemotherapy. 5 % - 10% chance of pregnancy in women with POI, so contraception is advised with COC or barrier methods. Fertility is mainly by donor oocyte. Decreased life expectancy in these women is due to an increased risk of cardiovascular diseases. Counselling is required for both patients and family, regarding effects on future fertility.

KEYWORDS

Primary ovarian insufficiency, Premature ovarian failure, Fragile X premutation, Ovarian autoimmunity

DEFINITION:

Primary ovarian insufficiency (POI) previously referred to as primary ovarian failure or premature menopause[1]. This is due to either dysfunction or depletion of ovarian follicles[2,3]. POI is defined as disordered menses (amenorrhoea, oligomenorrhoea, polymenorrhoea, or metrorrhagia) before 40 years of age with raised gonadotropin levels and reduced estradiol [1,3]. The term premature ovarian failure is troubling to young women and family, so the appropriate term is "Insufficiency" rather than "failure" as it reflects the possibility of resumption of function and does not carry the negative conation of the word "Failure"[2,3].

SYMPTOMS of POI:

Most of the women with POI experience intermittent ovarian function rather than a complete cessation of ovarian function[1-4]**.** Menstrual irregularities such as amenorrhoea, polymenorrhoea are seen in these women. The most common presenting symptom is primary or secondary amenorrhoea. Other symptoms are suggestive of estrogen deficiency such as hot flushes, vaginal dryness, sleep disturbances, dyspareunia, loss of libido, altered urinary frequency[1-3]. The incidence of POI among women with amenorrhoea ranges from 2% to 10%[2]. Family history plays a significant role regarding early menopause, as females from these families are at risk for POI[2]. These women also experience infertility and psychological problems which have a significant impact on their quality of life. Some women may not experience the symptoms. In some women, symptoms may be fluctuating due to ovarian activity [1,3].

Diagnostic Criteria:

As per ESHRE guidelines, POI is diagnosed by 1. Age less than 40yrs 2. Oligomenorrhoea or amenorrhoea for at least 4 months 3. An elevated FSH levels > 25 IU/L on two occasions more than 4 weeks apart [3,4]. Period of complete amenorrhoea is not required to make the diagnosis as most of the women have fluctuating ovarian function [4].

MECHANISMS:

The two major mechanisms involved in POI are 1. Follicular dysfunction 2. Follicular depletion [1]. In follicular dysfunction, though there is a normal number of follicles in the ovary, they are unable to function due to mutation in FSH or LH receptor, G protein mutation, enzyme deficiency, ovarian autoimmunity, development of luteinized graffian follicles related to low follicle cohort size[4]. Follicular depletion due to inadequate pool of primordial follicles in utero, spontaneous accelerated follicular loss as in Turner syndrome, or exposure to environmental toxins[1,4].

ETIOLOGY:

In 90% of cases cause is unknown i.e, idiopathic[1,2,5]. POI is caused by chromosomal defects and genetic defects. When POI presents as primary amenorrhoea, 50% due to abnormal karyotype[6]. Other causes are autoimmune disorders, infections, iatrogenic causes such as radiation, chemotherapy, and surgery[3]. Spontaneous POI is the condition where POI is not induced by radiation, chemotherapy, or surgery, so in these cases, karyotype is 46 XX i.e,normal[5]. FMR1 gene mutation and steroidogenic cell autoimmunity is the mechanism for POI in 6% and 4% of women with spontaneous POI i.e, with normal karyotype respectively [2,5].

Chromosomal abnormalities:

Based on clinical evidence the incidence of chromosomal abnormalities in women with POI is 10%-12%, more in primary amenorrhoeic women than secondary amenorrhoea[7,8]. Among these 90% are X chromosome abnormalities[7,8]. In the presence of Y chromosome there is an increased risk of gonadal neoplasia i.e, around 45%, so gonadectomy is indicated in these women[3,9]. Turner syndrome 45XO, usually due to X chromosome deletion also one of the causes of POI in premenarchal girls.

Fragile X syndrome and POI:

Fragile X syndrome is inherited as an X-linked dominant pattern. The gene which undergoes mutation in this syndrome is Fragile X mental retardation 1 gene (FMR1) gene. FMRP protein produced by FMR1 gene expressed in the female reproductive tract is primordial germ cells in the fetus and in the granulosa cells of developing follicles in adults. Individuals with premutation carriers (55- 200 CGG repeats) are at risk for POI than full mutation carriers (>200 CGG repeats)for FXS[10,11]. Pre mutation carrier women are not at increased risk for intellectual disability[10]. The incidence of POI in premutation carriers is 21% compared to the general population is around 1%[12]. Women who carry premutation gene for FXS requires genetic and fertility counselling both and these women are advised not to postpone pregnancy as they are at risk for POI[12].

Autosomal gene mutations[3]:

Mutations in the genes involved in folliculogenesis (NR5A1, NOBOX, FIGLA, and FOXL2), folliculogenesis growth factor (BMP15, GDF9, inhibin A), ovarian steroidogenesis (FSH, FSHR, LH, LHR), or genes identified in syndromes are associated with POI(BLM, WRN, RTS). However autosomal gene mutation testing is not recommended in women with POI unless there is evidence suggesting mutation of specific gene[3].

Autoimmune disorders:

POI is most commonly seen in women with autoimmune disorders. Individuals with celiac disease, Addison's disease, Autoimmune polyendocrine syndrome type 2 are more predisposed to POI. POI due to adrenal autoimmunity is the most frequent type among autoimmune POI approximately 60% to 80%[13]. Women with adrenal autoimmunity will have circulating adrenal or ovary autoantibodies directed against steroidogenic enzymes known as steroid cells antibodies (SCA), therefore women with POI to be tested for adrenocortical antibodies or 21 OH antibodies because of the possibility of subclinical or latent Addison's disease[3,14]. Diagnosis of POI due to autoimmune ovarian damage can be done by identifying the presence of SCA. SCA is against autoantigens present on adrenal cortex, ovary, placenta, and testis[3].

Thyroid autoimmunity:

In the absence of adrenal autoimmunity, POI is most commonly associated with thyroid autoimmunity [15,16]. All the women with non-iatrogenic POI, with clinical features suggestive of an autoimmune disorder or unknown etiology to be screened for thyroid peroxidase antibodies. Once TPO- ab is positive, annual TSH measurements are recommended, if the women are negative for TPO-ab, screening is recommended like normal population[3,14].

Smoking is a risk factor for early menopause but not for POI, women at risk for POI are advised to stop smoking [3]. Hysterectomy with bilateral salpingo-oophorectomy, surgery for ovarian disease such as endometriosis, chemotherapy among cancer survivors, use of cyclophosphamide in autoimmune disorders such as SLE, etc all these contributing to the iatrogenic POI[3]. Therefore clinicians should make an effort to reduce the incidence of iatrogenic POI by modifying gynaecological surgical practice, treatment regimens for malignant and chronic diseases, and also educating the women regarding the risk of POI associated with smoking[3,7]. Infective etiology of POI is mostly due to mumps oophoritis, seen in 3%-7% of POI cases[17].

Table 1. Causes Of Premature Ovarian Insufficiency[18]:

Spontaneous Idiopathic
1. Genetic Turner syndrome (45XO) or mosaic Turner (45X/46XX)
2. Trisomy X (47XXX or mosaic)
3. Fragile X permutation
4. Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
5. Autoimmune polyglandular syndrome (types 1 and 2)
6. Follicle-stimulating hormone receptor mutations
7. 17α-hydroxylase deficiency Aromatase deficiency
8. Blepharophimosis, ptosis, epicanthus inversus syndrome Bloom syndrome
9. Ataxia telangiectasia
10. Fanconi anemia
11. Autoimmune
12. Infections Mumps oophoritis Tuberculosis, malaria, cytomegalovirus, varicella, and shigella
Induced
13. Bilateral oophorectomy, bilateral ovarian cystectomies
14. Chemotherapy-primarily, alkylating agents and anthracyclines
15. Radiation-external beam or intracavitary
16. Environmental toxins
17. Pelvic vessel embolization

Table 2.chemotherapuetic Agents And Class Are Known To Cause Gonadotoxi city And Premature Ovarian Insufficiency Risk[18]

Alkylating agent
1. Nitrogen mustard
2. Chlorambucil
3. Cyclophosphamide
4. Busulfan
5. Melphalan
6. Dacarbazine
Anthracycline
7. Doxorubicin
Substituted hydrazine
8. Procarbazine

Table 3.Radiation dose and age at exposure as determinants of permanent ovarian damage and premature ovarian insufficiency risk

20.3 Gy at birth
18.4 Gy at age 10 years
16.5 Gy at age 20 years
14.3 Gy at age 30 years
6.0 Gy at age 40 or more years

EVALUATION:

Primary amenorrhoea is seen in 10% of cases with POI[1]. Chromosomal analysis is recommended in all women with non-iatrogenic POI[3]. In women with secondary amenorrhoea, pregnancy is to be ruled out first. Women with menstrual irregularities to be evaluated for polycystic ovaries, thyroid disorder, hyperprolactinemia, hypogonadotropic hypogonadism, and POI[2]. Detailed history to be taken regarding other conditions such as celiac disease, uncontrolled diabetes mellitus, any emotional stress, reduced calorie intake, any prior radiation or chemotherapy, any pelvic surgeries [1,4]. Serum FSH measurement is the gold standard for the diagnosis of POI[3]. According to ESHRE, FSH levels > 25 IU /L on two occasions 4 weeks apart is confirmatory for the diagnosis of POI. Serum estradiol levels < 50 pg/ml is indicative of hypoestrogenism [2]. Anti Mullerian hormone should not be used for the diagnosis of POI, however, it can be used to assess the ovarian reserve [2,3]. Progesterone withdrawal is not advised in women with POI, as one-half of the women with POI will respond to progesterone withdrawal due to intermittent ovarian function and this test results will be misleading[6]. All women with non-iatrogenic POI should undergo chromosomal analysis[3]. Women with personal or family history POI are advised to get Fragile x premutation carrier testing and the implications of the testing to be discussed before the testing is performed[2,3]. Women with POI of unknown or any suspected autoimmune disorder cause to be tested for adrenal cortical antibodies or 21 OH antibodies[3]. In the absence of clinical signs and symptoms and negative for adrenocortical antibodies, and TP-ab future testing for these antibodies is not recommended, unless symptoms of these disorders develop. Screening for diabetes mellitus is not routinely recommended in women with POI. Screening for infections in women with POI is not recommended[3].Initial assessment and investigation in POI

1. Detailed history especially for family history of early menopause
2. Hormone profile Follicle-stimulating hormone(FSH) levels elevated >25 on two occasions >4 weeks apart with estradiol
3. Thyroid function and prolactin
4. Autoimmune screen antithyroid, antiadrenal, and anti ovarian antibodies
5. Karyotyping and genetic analysis especially in <30yrs or family history
6. An ultrasound scan to assess antral follicle count
7. Dual-energy X-ray absorptiometry (DXA) scan Estimation of baseline bone mineral density
8. Anti-Mullerian hormone (AMH) or Inhibin B Consider for assessment of ovarian reserve

Table 4. Summary Of Diagnostic Work Up[18]

Laboratory Tests	Rationale
Human chorionic gonadotropins	Exclude pregnancy
Follicle-stimulating hormone	Assess Hypothalamic-pituitary-ovarian axis
Anti-Mullerian hormone	Assess ovarian reserve
Karyotype, fragile X mental retardation 1 (FMR1) premutation	Evaluate for genetic etiology
Thyroid-stimulating hormone Thyroid peroxidase antibody 21 – Hydroxylase antibody	Evaluate for thyroid function Quantify risk for thyroid and adrenal dysfunction
Radiological tests Transvaginal ultrasonography	Evaluate antral follicle count to assess ovarian reserve
Dual Energy X-Ray absorptiometry scan	Assess bone density

Consequences of POI:

POI leads to serious health consequences such as premature death, cardiovascular disease, Neurological disease, and osteoporosis along with menopausal symptoms, psychiatric and impaired sexual functions[19,20]. These symptoms are more evident with iatrogenic rather than spontaneous[18,20]. Evidence suggests that premenopausal oophorectomy may lead to cognitive impairment, dementia, parkinsonism, depression, and anxiety. Therefore benefits should outweigh the risks associated with oophorectomy before taking a decision by gynaecologists[19,20]. Women with no genetic mutation and no family history of ovarian cancer, prophylactic oophorectomy is not

recommended if age is less than 40 years. In these women oophorectomy is recommended if age is more than 55 years, however, recommendations vary for oophorectomy between 40 years and 55 years[20]. Premature death in women with POI is mainly due to cardiovascular risk in both spontaneous or iatrogenic POI and is worsened by obesity. Therefore these women are advised to do regular exercise, to stop smoking, and maintaining a healthy weight to increase their life expectancy[3]. HRT to be given in these women to control menopausal symptoms and topical estrogen therapy for local symptoms such as dyspareunia and other genitourinary symptoms. As these women are at increased risk for osteoporosis, daily calcium supplementation is recommended[21].

Future Fertility:

These women to be counseled regarding the chances of future pregnancy around 5% to 10% and are advised to use contraception if needed[21]. Information to be given regarding that there are no interventions which will improve the ovarian activity and conception rates. Women who are desiring pregnancy, oocyte donation is the best option[3, 21]. Genetic counselling and preimplantation genetic testing are indicated in women with Fragile X premutation carriers. Adoption is advised in women with Turner's syndrome or gonadal dysgenesis as there is a risk of aortic rupture during pregnancy due to an abnormal aortic wall. Spontaneous pregnancies are seen in women with POI due to chemotherapy, however, women who underwent abdominopelvic irradiation are at risk for obstetric complications. Women with POI, who received anthracyclines should be taken care of its associated cardiac complications.

CONCLUSION:

Women with primary amenorrhoea need to be evaluated for primary ovarian insufficiency which includes chromosomal, genetic analysis, assessment of ovarian autoimmunity, adrenal antibodies, etc. Women with secondary amenorrhoea also need to be investigated for POI after ruling out pregnancy, other common disorders such as thyroid, hyperprolactinemia, etc. All women with POI needs counselling regarding mental health, fertility status, health consequences.

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