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Understanding premature ovarian insufficiency: A barrier to fertility

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Abstract
Premature ovarian insufficiency is a multifaceted condition with an array of etiologies and sequelae that emerge due to premature loss of ovarian activity in women before the age of 40 years. It is a hypoestrogenic state characterized by elevated gonadotrophin levels and menstrual irregularities attributable to cessation of ovulation with possible implications on fertility. The premature interruption of normal ovarian function at such a young age makes the patient susceptible to a range of immediate and enduring health repercussions that can have a detrimental impact on the physical and psychological well-being of these individuals. It is essential to diagnose the condition promptly and have a comprehensive understanding of the potential accompanying health issues resulting from the lack of estrogen. While there is a substantial availability of literature on premature ovarian insufficiency, there remain numerous facets of this condition that require further exploration. These areas of study include the early identification of at-risk populations to prevent catastrophic events and the development of strategies and interventions aimed at delaying the premature cessation of ovarian function. The cornerstone of management is estrogen therapy, which is administered to alleviate symptoms resulting from estrogen deficiency. This review provides an overview of the comprehension and management of this intricate condition.

Keywords: Premature ovarian insufficiency, hormone replacement therapy, estradiol, estrogen deficiency, menstrual irregularities

Introduction
Premature ovarian insufficiency (POI), commonly referred to as "ovarian failure," is marked by a rapid disruption of ovarian function, occurring well before the usual expected timeline in the typical female human [1, 2]. A reduction in the count of remaining ovarian follicles and the subsequent shortfall in ovarian sex hormones are distinctive features of POI. This condition results in reduced fertility and an estrogen deficiency, often occurring many years or even decades before the typical age of menopause [3]. The clinical presentation of POI can vary, but it often includes menstrual irregularities, missed periods leading to amenorrhea, the abrupt onset of secondary amenorrhea, primary amenorrhea, subfertility or infertility, and estrogen deficiency symptoms of menopause [4].

POI affects approximately 1 in 100 women under 40 years of age and there has been a gradual increase in the occurrence. While a significant proportion of cases lack an identifiable cause, various etiological factors are linked to POI such as genetic anomalies, autoimmune damage to the ovaries, iatrogenic factors, infections, toxins, and environmental influences [2, 4-7].

While different terms such as POI or premature ovarian failure (POF) have been used to describe this condition, the European Society of Human Reproduction and Embryology (ESHRE) consensus recently adopted the term POI instead of “failure” because is describes the nature of this condition more accurately, whereas POF is considered as the final stage of POI [8].

To gain a deeper insight into the mechanisms responsible for early ovarian dysfunction, it is advisable to categorize POI based on its onset. This categorization can distinguish between cases that occur spontaneously and those that are a result of a known insult, such as surgery (e.g., bilateral oophorectomy), chemotherapy, or radiation exposure [9]. While both categories ultimately lead to a premature and significant reduction in ovarian reserve and a deficiency in circulating sex hormones, their onset differs.

Spontaneous POI typically presents insidiously, and there is often a delay in diagnosis, whereas in cases consequent to a recognized insult, the onset is more abrupt [10]. Conversely, iatrogenic POI is usually expected by both the patients and clinicians. This anticipation allows for the initiation of interventions to manage symptoms and mitigate the long-term health risks associated with hypoestrogenemia at an earlier stage in the process [11]. It is essential to begin therapy promptly to alleviate the distressing menopausal and other hypoestrogenic symptoms and enhance the quality of life for patients facing these issues [12].

Methodology

This review aimed to investigate the latest developments in the assessment and treatment of POI via a review of the literature using search keywords, such as "POI", "management", "hormone replacement therapy", "estradiol". Virtual focus-group discussions involving the author and 11 Indian gynecology experts were conducted. The objective of the discussions was to enhance the readiness of healthcare providers to deliver the best possible care to women affected by such an intricate yet frequently encountered condition like POI.

Current scenario of primary ovarian insufficiency

POI represents a spectrum of conditions that impact not only female fertility, but also contribute to health issues and potential mortality due to the prolonged absence of estrogen [2, 13, 14]. POI typically occurs in women under the age of 40 years and is diagnosed when there is a history of amenorrhea lasting 4-6 months along with consistently elevated levels of follicle stimulating hormone (FSH) as well as reduced estradiol levels, as determined by tests taken one month apart [15, 16]. It is imperative to rule out POI in women who exhibit amenorrhea, oligomenorrhea, or symptoms of estrogen deficiency when they are under the age of 40 years [8]. Based on the age of onset, POI can present itself as primary amenorrhea, without the onset of menarche, or secondary amenorrhea after puberty [17]. Secondary amenorrhea can result from various factors, including but not limited to pregnancy, hypothyroidism, and genetic abnormalities [13, 18]. POI is distinct from menopause because it is characterized by some residual variability in ovarian function and the presence of primordial follicles. In contrast, menopause occurs when the primordial follicles are depleted, leading to a complete cessation of menstruation [16].

POI is relatively prevalent in the general population, with an estimated incidence of 1 in 100 by the age of 40 years, 1 in 1000 by the age of 30 years, and 1 in 10,000 by 20 years of age [19]. Around 10%-28% women with POI experience primary amenorrhea and 4%-18% experience secondary amenorrhea [20]. By ethnicity, 1.0% of Caucasian, 1.4% of African American, 1.4% of Hispanics, 0.5% of Chinese and 0.1% of Japanese women have been reported to experience POF [21].

Understanding of symptomatology, etiology, and risk factors of POI

Symptoms

Women with POI are typically observed with secondary amenorrhea/menopause, many a time preceded by irregular menstrual cycle at age <40 years [22]. In some cases of primary amenorrhea, the underlying cause may be a chromosomal abnormality. Other common symptoms include hot flushes and night sweats [19], which are primarily attributed to estrogen deficiency [23]. Vaginal symptoms include dyspareunia and dryness, which can be distressing for women [17, 24]. In addition to these, women also suffer from sleep disturbances, mood swings, lack of concentration, depression, loss of libido, dry eyes, altered urinary frequency, and lack of energy [25]. These symptoms are usually transient and are mainly due to changes in ovarian functions (estrogen withdrawal rather than deficiency) that result from spontaneous onset of POI [26].

Etiology

POI is believed to originate from either dysfunction or depletion of ovarian follicles. Beginning at the ovarian level, infrequent mutations in the genes responsible for regulation of FSH and luteinizing hormone (LH) receptors can disrupt the ovaries' ability to respond to these circulating gonadotropins, ultimately resulting in non-functional ovarian tissue [13, 27]. Iatrogenic factors leading to POI, such as oophorectomy, chemotherapy, or radiation, along with certain infections, like malaria, varicella, shigella, mumps, and tuberculosis, have the potential to significantly damage healthy ovarian tissue and reduce the amount of remaining functional tissue [4, 6, 13, 15, 27, 28]. Chromosomal abnormalities, such as Turner Syndrome (X, 0), can result in premature oocyte apoptosis during fetal development and accelerate oocyte depletion early in life, often before the age of 10 years [13]. A premutation in the fragile X mental retardation 1 (FMR1) gene (59-199 CGG trinucleotide repeats) significantly elevates the risk for developing POI. Autoimmune diseases such as adrenal insufficiency (Addison's disease), rheumatoid arthritis, hypothyroidism (Hashimoto's thyroiditis), systemic lupus erythematosus, non-typical congenital adrenal hyperplasia, and type 1 diabetes mellitus have also been linked to POI [13, 27].

Genetic mutations, autosomal recessive conditions like galactosemia (Characterized by a reduction of galactose-1-phosphate), ataxia-telangiectasia (Associated with mutations in the ATM gene), and blepharophimosis-ptosis-epicanthus-inversus syndrome (referred to as BPES, caused by mutations in the FOXL2 gene) have effects on POI that are not yet fully understood [13, 15]. Environmental exposures, including factors like smoking, nicotine, and certain substances like dimethylbenzanthracene, are theorized to play a role in the development of POI. These substances may bind to receptors on ovarian granulosa cells, triggering the activation of proapoptotic genes and inhibiting aromatase activity, resulting in decreased levels of circulating estradiol [15]. Other environmental factors, such as substances used in plastic production (phthalates and bisphenol-A), might also have a role in POI, but the exact mechanisms involved remain unclear [27].

Risk Factors

Pelvic surgery, mumps and exposure to chemical agents were identified as risk factors for POF. A family history of POI and smoking are widely acknowledged as risk factors for the onset of POI. Additionally, bilateral ovarian surgery for endometriomas has been associated with a reported 2.3% of women developing POI [29, 30]. Nulliparity, a history of lifelong irregular menstrual cycles, hysterectomy, illicit drug use, viral infections, chemotherapy, autoimmune diseases, and radiation therapy are also potential factors that may be

implicated in the development of POI [8, 21]. It is crucial to note that the use of the combined oral contraceptive pill (COCP), fertility drugs, and previous hormone replacement therapy (HRT) does not lead to the development of POI. However, discontinuing these treatments may reveal previously undiagnosed POI [30-32].

Expert Opinion

The experts opined that POI impacts many organ systems due to reduced estrogen levels, resulting in a wide range of cutaneous, vasomotor, genitourinary, and psychosomatic menopausal symptoms. Though the exact mechanism for the development of POI is not known, it can be due to preliminary decrease in the primordial follicle pool; accelerated atresia of follicles; or defective maturation/recruitment of primordial follicles. Long-term health risks associated with POI include accelerated cognitive impairment, cardiovascular risks, including impaired endothelial function, elevated triglycerides, cholesterol, and low-density lipoprotein cholesterol, impact on bone health, and fertility problems, resulting in a lower chance of natural ovulation and spontaneous pregnancy. POI has a profound impact on various aspects of a woman's health, and understanding these risks is crucial for effective diagnosis and management.

Diagnostic workup for POI

Diagnosis of POI can be easily made on clinical presentation with two measurements of elevated FSH levels in women <40 years of age with amenorrhea or oligomenorrhea for 4-6 months. Final diagnosis can be made on certain investigations, which include assessment of gonadotropin hormone levels. Both FSH and LH are elevated in women with POI (Hypergonadotropic amenorrhea) [33, 34]. The diagnosis of POI should be confirmed after a minimum of two elevated FSH test results (>40 IU/l) at least 4–6 weeks apart [7]. Low estradiol levels, along with elevated FSH and LH levels, are indicative of a diagnosis of POI [8, 33]. Anti-Mullerian hormone (AMH) is produced by granulosa cells of growing follicles. It regulates early follicular recruitment from the primordial pool and is a good reflector of ovarian reserve [35-38]. AMH levels are usually very low or undetectable in women with POI [39]. A comprehensive diagnostic workup for POI including investigations like AMH, FSH levels, thyroid function tests, karyotyping, FMR1 premutation analysis, and anti-ovarian and anti-adrenal antibody testing is recommended. These tests can help uncover the potential underlying causes of POI [4, 40].

Expert Opinion

The experts recommended that an early diagnosis of POI is necessary in order to monitor and support follicular growth and chances of ovulation, when ovarian function still exists. They typically diagnose a patient as having POI based on low estradiol (E2) levels and elevated FSH levels. Additional diagnostic tests may include a transvaginal ultrasound scan of the ovaries. When this scan reveals normal ovarian size/volume and a high antral ovarian follicle count, it can make the diagnosis of POI less likely. It is important to note that some physicians do not recommend antibodies and FMR1 gene testing due to a negligible incidence of fragile X syndrome in their clinic. Physicians aim to tailor their diagnostic approach to each patient's unique circumstances. The experts' recommendation for all patients with POI was to undergo at least one bone mineral density (BMD) scan as it is crucial for assessing bone health.

Role of hormone replacement therapy in poi management

Estrogen is responsible for bone remodeling and hence its deficiency is associated with bone loss, decreased mineral density and fracture risk, as seen after natural menopause [41, 42]. Depending on the extent and duration of estrogen deficiency, women with POI tend to experience a reduction in BMD at an earlier stage compared to women with typical ovarian function [25, 43]. Estrogen is also known to have cardioprotective effects, and its early depletion increases the risk of cardiovascular mortality. As a result, women with POI are at a heightened risk of cardiovascular mortality [39, 44, 45].

The treatment of POI primarily revolves around estrogen replacement therapy. This approach aims to alleviate vasomotor symptoms, preserve bone density, reduce the risk of fractures, decrease the likelihood of cardiovascular and autoimmune-related health issues, safeguard cognitive function, and enhance the overall well-being of the affected patients [27, 46] Estradiol replacement therapy, can be administered via oral or transdermal route. Orally available estrogen types include 17-beta estradiol, ethinylestradiol and conjugated equine estrogens. Oral contraceptives contain synthetic estrogen–ethinylestradiol, which has shown unfavorable effects on lipid profile and an increased risk of venous thromboembolism (VTE). As a more physiological alternative, 17-beta estradiol is preferred over ethinylestradiol or conjugated equine estrogens. Transdermal estradiol is preferred in women with POI at an increased risk of VTE. For women with POI who have undergone a hysterectomy, it is appropriate to use estrogen therapy alone [14, 29].

In young women with POI and intact uterus, hormone replacement therapy containing estrogen and progesterone combination is crucial for uterine and ovarian function as it does not suppress remnant chances of ovulation unlike combined oral contraceptives [4, 47]. It regularizes menstrual cycles and normalizes elevated gonadotropin levels in patients with POI [48]. Progesterone has a protective effect on the endometrium and in premenopausal women, it is crucial to incorporate progestogen supplementation to prevent endometrial hyperplasia [49]. Progestogens are selected for use in clinical practice based on their other biological effects. Dydrogesterone comes from a natural source and is highly selective for progesterone receptors, thereby decreasing the risk of adverse effects. Dydrogesterone is a retroprogesterone that closely resembles endogenous progesterone and protects the endometrium with a well-tolerated bleeding pattern [50-54].

It's important to note that in premenopausal women with POI who wish to preserve fertility, using cyclic hormonal treatments to induce regular bleeding cycles is preferred. This approach can enhance their prospects of achieving a successful embryo transfer or even experiencing a naturally occurring pregnancy [27]. Although spontaneous ovulation is an extremely rare event in women with POI, it is possible to achieve a spontaneously achieved pregnancy with close monitoring. In fact, the greatest success in achieving pregnancy in these women has been through spontaneous

ovulation [27, 55, 56] Spontaneous pregnancy rate after POI diagnosis has been found to be 4.4%. In a cross-sectional study of 507 patients with idiopathic POI, 23% experienced spontaneous resumption of ovarian function and only 3.6% conceived spontaneously [56].

Because combined oral contraceptives achieve supratherapeutic levels of estrogen and progestogen, they may not be the optimal choice of treatment, given that the intent of the medication in normal, cycling woman is ovulation suppression. For women who are seeking pregnancy, the use of hormonal contraceptive regimen should be avoided [4].

Girls and women with POI due to Turner syndrome should be offered HRT throughout the normal reproductive lifespan [8]. Fibroids are not a contraindication for use of HRT in POI, and transdermal estradiol is the preferred delivery method for those who are obese or overweight [57].

For women with endometriosis who undergo oophorectomy, combined estrogen and progestogen therapy can be an effective treatment for vasomotor symptoms and may also lower the risk of disease reactivation [53]. For women undergoing chemotherapy or radiotherapy, *in vitro* fertilization (IVF) with embryo freezing before treatment initiation provides the highest likelihood of achieving a future pregnancy. Freezing mature eggs is typically less successful than embryo freezing. Moreover, cryopreservation (freezing) and transplantation of fresh ovarian tissue have led to an increasing number of successful pregnancies in these cases. This offers the possibility of restoring fertility after the completion of cancer treatment [7].

Safety Profile of HRT in POI

Several studies have shown that the progestogen choice rather than estrogen may affect breast safety profile of an HRT. A French cohort study involving 80,377 women confirmed that the risk of invasive breast cancer was significantly lower with MHTs containing progesterone or dydrogesterone than with MHTs containing other progestogens [58, 59]. An observational study using two largest UK primary care databases found that estradiol combined with dydrogesterone had the lowest risk of VTE among oral combined MHTs [60].

Expert Opinion

The management of POI by experts encompasses various aspects, including hormone replacement therapy (HRT), fertility and obstetric risk management, comorbidity management, patient education, counselling, and psychological support. Available HRT options include estrogen, progesterone, tibolone, the combination of estrogen and progesterone, and selective estrogen receptor modulators (SERMs).

Experts suggested the use of sequential HRT, which combines both estrogen and progestogen, for the management of patients with POI. This therapeutic approach is typically continued until the individual reaches the average age of natural menopause, which is approximately 50 years. One of its crucial effects is the suppression of elevated FSH and LH levels, which help to restore hormonal balance in the body.

The experts opined that estrogen as well as progestogen will help in improving the uterine environment, increase endometrial thickness, restore endometrial blood flow, regularize the cycle, increase gonadotropin levels, and not suppress remnant chances of ovulation, unlike combined oral contraceptives. The focus group had a discussion on the available estradiol and progestogen combination formulation. The physicians recommended sequential HRT with combination of 2 mg of estradiol hemihydrate and 10 mg of dydrogesterone for the management estrogen deficiency symptoms in patients with POI until they reach menopausal age. This therapy can improve hot flushes and vaginal and urinary symptoms for women with POI and reduce the risk of osteoporosis, thus helping in preventing heart disease. When these women reach the time at which they would naturally attain menopause, at around 50 years of age, the clinician may decide whether, or how long, to continue treatment.

Summary of Guidelines and Recommendations

Given that POI has broader health implications beyond gynecological concerns, combined hormonal contraceptives are more effective at preventing ovulation and pregnancy compared with HRT. Although the odds of spontaneous pregnancy in women with POI are relatively low, this is an important consideration for those who prioritize pregnancy prevention. Treatment for all women with POI should continue until they reach the average age of natural menopause, which is typically around 50 to 51 years. Additionally, it is crucial to acknowledge the challenges that adolescents and young women may encounter when coping with the physical, reproductive, and social effects of primary ovarian insufficiency. Therefore, comprehensive, as well as long-term management of this condition is essential [61].

As per ESHRE recommendation, HRT is indicated for the treatment of symptoms of low estrogen in women with POI. Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus. 17-β estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement [8]. The American College of Obstetricians and Gynecologists recommends systemic HRT to treat the symptoms of hypoestrogenism and mitigate long-term health risks if there are no contraindications to treatment. As a first-line approach, HRT (Either orally or transdermally) that achieves replacement levels of estrogen is recommended. Treatment for all women with POI should continue until the average age of natural menopause is reached [61]. According to the Indian Menopause Society guidelines, HRT should be started as early as possible in women with POI and continued till the age of natural menopause [62].

An increased risk of breast cancer has been a concern for older postmenopausal women using HRT. However, studies have shown that the risk may be reduced in women with untreated POI due to reduced estrogen exposure. There is no evidence of increase in the chance of breast cancer development in women with POI who are taking HRT early in their lives, before the age of natural menopause [57].

Conclusion

Experts reached a consensus that a combination of 2 mg of estradiol hemihydrate and 10 mg of dydrogesterone can be employed for the management of patients with POI until they reach menopausal age. Women with POI who experience infertility have access to various assisted reproductive techniques and preventative measures to safeguard their fertility. The choice of a procreative

management strategy is tailored to the individual patient, taking into account the clinical context and the patient's current ovarian reserve. Despite inadequate or absent ovarian reserve, successful pregnancies and live births have been achieved through experimental fertility preservation methods. It is crucial to gain in depth understanding of the genetic factors contributing to POI and develop more sensitive markers for secondary/preantral follicles. Large, randomized controlled trials are necessary to assess the safety and effectiveness of various HRT options. In the absence of such trials, a multidisciplinary approach is essential in identifying these patients and providing them with optimal care and strong psychological support. Ongoing research on experimental methods is actively advancing, and the field of fertility preservation continues to grow.

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Conflicts of Interest
The author received speaker' honorarium from Abbott for participation in advisory board meetings.

Ethical Approval
Not required as this is a review article.

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