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[1]Department of Obstetrics and Gynecology, University Clinical Hospital Center Split,
[2]Department of Obstetrics and Gynecology, University Clinical Hospital Center Zagreb,
[3]School of Medicine, University of Split, [4]School of Medicine, University of Zagreb

PREMATURE OVARIAN INSUFFICIENCY

Jelena Marušić[1,3], Marina Šprem Goldštajn[2,4], Damir Roje[1,3], Indira Kosović[1], Jasminka Rešić Karara[1]

Review article

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Summary. Premature ovarian insufficiency (POI) is a clinical syndrome defined as the loss of ovarian activity before the age of 40. POI is a life-changing diagnosis, with profound physical and psychological consequences. Spontaneous POI affects approximately 1% of women under the age of 40. However, the rising incidence of iatrogenic POI is of increasing concern. POI is a heterogeneous, multifactorial disorder, and in the majority of cases the etiology is unknown. The diagnosis of POI is based on the presence of amenorrhea and of an elevated gonadotropin level. Hormone replacement therapy should be used at least until the average age of menopause to alleviate the symptoms of hypoestrogenism and to prevent severe long term consequences especially those of cardiovascular diseases and osteoporosis. The treatment of these women should be coordinated by a multidisciplinary team. Women with POI should be informed that there is a small chance of spontaneous pregnancy. IVF with donor oocytes represents the highest chance for pregnancy in these patients. Further research is needed to identify the population in risk in a timely manner and to find mechanisms that can prolong, recover, or preserve ovarian function.

Introduction

Premature ovarian insufficiency (POI) is a clinical syndrome defined as the loss of ovarian activity before the age of 40, characterized by elevated gonadotropin levels, hypoestrogenism and amenorrhea. The syndrome was first described in 1942 by Fuller Albright, who used the term "primary ovarian insufficiency" to suggest that the primary defect lying within the ovary (1). There has been a long-standing lack of consensus about the nomenclature of the syndrome with a variety of other terms in use, such as primary ovarian insufficiency, premature ovarian failure, premature menopause, gonadal dysgenesis, hypergonadotropic hypogonadism etc. It was necessary to reach the consensus about the use of standard terminology to clarify the information given to women, to improve communication between professionals, to facilitate data collection and to help further research. European Society of Human Reproduction and Embryology (ESHRE) guidelines propose the term "premature ovarian insufficiency" as the one to be used in research and in clinical practice (2). The use of the term premature refers to the timeline rather than the etiology; it defines ovarian insufficiency which occurs before the age of 40 caused by any cause. The term insufficiency, instead of the term failure, is thought to reflect the unpredictable nature of ovarian function in the syndrome more accurately, and it does not carry the negative connotation of failure. Despite our ongoing efforts to improve our understanding of the mechanisms involved, POI is still a poorly understood entity with a heterogeneous and extremely complex etiology. The knowledge of the syndrome and the understanding of the various sequels of POI are vital to early diagnosis, appropriate counsel and optimal treatment of these patients. In addition to causing infertility, POI is associated with multiple sequels, such as vasomotor symptoms, urogenital symptoms, neurological dysfunction, cognitive impairment, bone loss and increased risk of cardiovascular diseases (3).

Epidemiology

POI is not an uncommon syndrome and it affects 1% of women under the age of 40, 0.1% of women under the age of 30 and 1 in 3000 adolescents (4). The incidence of spontaneous POI appears to have remained stable. However, in the last decades there has been an increasing incidence of iatrogenic POI caused by oophorectomy, chemotherapy and radiotherapy (5, 6).

POI is related to familial occurrence in about 15% of cases, which suggests a genetic background (7). Statistically significant differences in the prevalence were observed across different ethnic groups, ranging from 0.1% in Japanese to 1% in Caucasian and 1.4% in African American and Hispanic group (8).

Etiology

POI is a heterogeneous, multifactorial disorder and its etiology remains poorly understood. In the majority of cases, POI etiology is unknown and it is termed as idiopathic POI. The pathogenesis of idiopathic POI can be explained by three mechanisms: congenital reduction in the number of primordial follicles, follicle dysfunction, or accelerated follicular apoptosis. POI can be caused by chromosomal or genetic defects. Abnormalities in the X chromosome have been estimated to occur in 12–14% of women with POI, and in about 50% of patients with primary amenorrhoea (9–11). Chromosomal analysis should be performed in all women with non-iatrogenic idiopathic POI. The most frequently identified single gene mutation associated with POI is the fragile X mental retardation 1 (FMR1) gene premutation. The full mutation (more than 200 CGG trinucleotide repeats) results in intellectual and developmental disability in men who carry the mutation. Approximately 23% of women with premutation (55–200 CGG repeats) will develop POI (12). Women with full mutation or with an intermediate sized CGG repeats are not in risk of developing POI. Based on its prevalence and severe clinical implications for women and their families, fragile -X testing is recommended in all women with non-iatrogenic POI (2, 13). Numerous autosomal genetic mutations have been associated with POI. The primary mutation genes are those involved in folliculogenesis, genes of sex hormone receptors or genes involved in ovarian steroidogenesis (14, 15). Routine screening for autosomal gene mutation in women with POI is not recommended. Autoimmune etiology has been found in about 30% of POI cases and it may present itself separately or with some autoimmune diseases like adrenal insufficiency, Hashimoto's and diabetes mellitus type 1. POI of adrenal autoimmune origin is the most frequent type in patients with autoimmune POI (16, 17). Screening for 21-hydroxylase auto antibodies should be performed in women with POI of an unknown cause. POI is also associated with thyroid autoimmunity and screening for thyroid peroxidase autoantibodies should be performed. Some associations have been reported between POI and infections, such as parotitis virus, human immunodeficiency virus, tuberculosis, varicella virus, cytomegalovirus, shigella and malaria (18). However, their contribution to pathogenesis remains unclear. Some recent meta-analyses warn of the potential impact of environmental pollutants and toxins in the pathogenesis of POI but there is no clear evidence of the impact of environmental factors on POI (19). Cigarette smoking is toxic for ovarian function and there is a connection between smoking and earlier menopause, but it is not a direct cause of POI (20). POI may also occur after iatrogenic procedures like surgical interventions (bilateral ovarian cystectomies), chemo or radiotherapy treatment or pelvic vessel embolization and it is termed as iatrogenic POI (21, 22).

Clinical presentation and diagnosis

The spectrum of the symptomatology of POI is highly variable. Women usually present with menstrual irregularity or amenorrhea, with or without symptoms of estrogen deficiency. They may present with primary (10% of cases of POI) or secondary amenorrhea depending on the etiology of POI (23). Women with primary amenorrhea may never experience menopausal symptoms. Hot flushes, night sweats, dyspareunia, vaginal dryness, sleep disturbance, mood changes, dry eyes, low libido and the lack of energy are typical of POI with secondary amenorrhea and may be the reason for an initial medical consultation (24). For some women, POI may be diagnosed only during an evaluation of infertility.

There are no ideal markers for the diagnosis of POI. At first, it is necessary to exclude pregnancy, in any reproductive-age women, with secondary amenorrhea. The criteria for POI diagnosis are the occurrence of amenorrhea for at least four months and increased FSH levels > 25 IU/l on two occasions repeated at a four-week interval (2). The FSH serum level is the gold standard test in POI diagnosis. Anti-Mullerian hormone (AMH), as a biomarker of the ovarian reserve, could be very low not only in POI patients, but also in women with regular menstrual cycles with a diminished ovarian reserve (DOR) and it should not be routinely used to diagnose POI syndrome (25).

Fertility

Infertility issues are the most dramatic problem for POI women, with an extremely negative impact on the psychological status and the quality of life. Women with POI have up to 5% chance of spontaneous conceiving after confirming the diagnosis (26). Intermittent ovarian activity may occur in women with POI, although this is likely to decrease with the increasing duration of amenorrhea. Artificial reproduction techniques are unsuccessful in women with POI due to their exhausted pool of oocytes. A range of treatments including exogenous estrogen administration, corticosteroids, combined oral contraceptives, dehydroepiandrosterone have been explored as potential treatments for increasing ovarian activity but without any significant results on ovulation rate or the possibility of conception (27, 28). At present, the oocyte donation remains the only proven method and the treatment of choice for infertility in women with POI. (2). However, oocyte donation pregnancies are associated with a higher risk of obstetric complications. Nowadays, new methods of infertility treatment in POI patients are

being developed. This new treatment was named as in vitro activation (IVA) of dominant follicles (29). IVA implements chemical stimulation of the ovarian tissue with phosphatidylinositol-3-kinase stimulator to activate primordial, secondary and preantral follicles. A cycle of IVA includes laparoscopic surgery in order to remove the ovary, cutting the ovary into cortical strips and vitrifying. After thawing, the ovarian strips are incubated with stimulators and then autografted under laparoscopic surgery. After that, patients start ovarian stimulation protocol and IVF procedures. There have been two healthy delivered babies and two additional pregnancies after IVA procedures. Moreover, Stimpfel et al. differentiated in vitro stem cells from an adult human ovarian cortex. Stem cells have self-renewal and regeneration potential and this may open a new opportunity in the treatment of premature ovarian insufficiency (30, 31).

Management

POI is a serious condition, and patients with POI diagnosis are a high risk group, which is due to the lack of the ovarian hormone, primarily estrogen, exposed to an increased risk of cardiovascular diseases, osteoporosis, neurological diseases, genitourinary disorders, psychological dysfunction etc. In consequence, these patients have a higher morbidity and greater mortality than their healthy peers. It is for this reason that all the leading gynecological societies recommend hormonal replacement therapy (HNL), in the case of POI patients, with the purpose of helping induce secondary sexual characteristics in adolescents and of preventing a series of serious illnesses that may result from a deficiency of estrogen in adults (2, 32, 33) HNL is the first choice in treating these patients, and the treatment should be continued until the age of the expected natural menopause. COC pill containing ethinyl-estradiol could also be a suitable option for POI patients who need contraception, but HRT is more beneficial to improving bone health and cardiovascular markers (34, 35). HNL, along with other supportive measures, such as general lifestyle and dietary measures with increased calcium and vitamin D intake, smoking cessation and alcohol intake cessation can significantly improve the quality of life of POI patients.

Vasomotor symptoms are the main reason for taking HNL in women with POI. Numerous studies of women with POI, especially with the iatrogenic form, indicate a rapid improvement in vasomotor problems after the introduction of HNL (36). Estrogen has an important role in regulating and maintaining bone structure, and estrogen deficiency, associated with POI. has been shown to result in a reduction in bone density and in an increased risk of fractures. Estrogens activate osteoblasts and have an inhibitory effect on osteoclast activity. Furthermore, they favorably affect the cortical and trabecular bone. The presence of osteoporosis among POI patients is as high as 8–14%, and the use of HNL suggests an improvement in the bone density of the patients (37).

Reduced life expectancy, due to cardiovascular diseases, is observed among women with untreated POI, and despite the lack of longitudinal outcome data, HRT is strongly recommended to prevent cardiovascular morbidity and mortality risk in this population. The risk of mortality from ischemic heart disease is said to be approximately 80% increased among women with POI, in comparison to women with natural menopause (38). Vaginal dryness, dyspareunia and incontinence are directly associated with the lack of estrogen. Therefore, systemic or local therapy is advised in the prevention and treatment of genitourinary problems in POI patients (39).

POI is associated with a higher risk of neurological dysfunction, cognitive impairment, and dementia, especially iatrogenic POI (40). There is no clear evidence, from prospective controlled studies, that the use of HNL reduces the risk of cognitive decline or dementia in women with POI.

It is known that the risk of breast cancer increases with the later age of menopause it is thus assumed that the risk is lower in patients with POI. This was confirmed by the research by Wu et al. they showed that the incidence of breast cancer is significantly lower in a patient with POI in comparison to women with natural menopause (41). There is no evidence that HRT increases the risk of breast cancer before the age of natural menopause (42). Recent studies also suggest the association of various types of progesterone with breast cancer, and, with limited evidence, they support the use of micronized progesterone (43).

There is an irresistible association between prolonged estrogen-only HRT and endometrial cancer, so any in all POI patients with uterus only combined estrogen-progesterone therapy should be used (44). In older postmenopausal women, a higher incidence of venous thromboembolism with HNL was demonstrated, but there is no evidence of a greater incidence of the same in women with POI (45). Only a smaller branch of the WHI (Women's Health Initiative) study showed an increased risk of developing VTE in POI patients taking HNL (46). Transdermal route should be considered in women with POI who are at the increased risk of venous thromboembolism.

There are many routes of administration, doses, and various types of estrogen and progesterone preparations that can be used for POI treatment. There are three types of estrogens for HNL: 17β-estradiol, ethinyl-estradiol and estradiol valerate. There are no studies comparing the use of a particular type of estrogen preparation in a POI patient. There is very little evidence of the benefits of a particular preparation but in the opinion of experts, it is recommended to use 17β- estradiol which has more physiological effects (47). Estrogens can be administrated systemically, in oral or transdermal form, or locally. Transdermal route of administration deliver hormone directly into the circulation, which avoids

complications associated with first pass effect on the liver when estrogen is given orally. Avoiding the first passage through the liver, it achieves higher plasma concentrations with a lower treatment dose and shows significantly less negative effects (inflammatory factors, blood pressure, lipid profile, and renin) than oral administration (48). However, data for women with POI does not exist, so we also take the decision of the application regime upon their wishes. In women with POI who have uterus, it is necessary to add progesterone to prevent endometrial cancer. Progesterone can be administrated orally, vaginally or in the form of intrauterine device system. Again, there are no studies on the type of progesterone preparation. However, due to fewer side effects on cardiovascular health and due to lower risk of endometrium cancer, the recommendation is to use natural micronized progesterone instead of synthetic progesterone (49). The cyclic mode of application of HNL has been shown to reduce the occurrence of endometriosis of the ovary and is a highly preferable regimen for the patients planning pregnancy by oocyte donation. In regard to progesterone, there is currently no evidence that a vaginal progesterone gel or a transdermal application of progesterone is sufficient to protect the endometrium from cancer. Therefore, oral administration is still recommended.

When using estrogen in POI patients, a dose is required to remove existing symptoms, preventing long-term risks to those who are exposed to estrogen deficiency while at the same time carrying the least risk since they will be taking them for years. An estrogen dose that will maintain a serum value of about 50–100 pg/ml, as found in healthy women, is achieved with 100 µg of estradiol transdermally (50). Similar concentrations are achieved by oral administration of 2 mg of estradiol but they result in supraphysiological concentrations of estrons whose clinical significance is unknown. There are no studies that prescribe the progesterone doses needed to protect the endometrium in these patients. It is recommended to apply oral for oral administration of 1mg norethisterone per day or 2.5mg medroxyprogesterone with continuous regimen or 10–12 days per month 10 mg medroxyprogesterone or 200 mg oral micronized progesterone (2, 44). The exact duration of the cycle and the use of progesterone may be individualized but it is certain that the period between the progesterone administrations should not be longer than 12 weeks.

There is no evidence of the ideal duration of HNL in these patients, but the recommendation is to apply it until the average age of menopause. There is also no specific strategy for monitoring these patients. The recommendation is to examine the patients once a year mostly for the purpose of checking the patients' satisfaction with the therapy and recording any possible side effects. The compliance among POI patients is very low, so their preferences in terms of route, drug and type of hormonal therapy should be respected in order to ensure greater compliance.

Conclusion

The diagnosis of premature ovarian insufficiency is extremely disturbing for women, especially if they have failed to reproduce. Women with POI have complex physical and psychological needs, and a multidisciplinary approach is recommended as standard practice to improve the quality of life after the loss of ovarian function. The early diagnosis and the treatment of these patients improve the quality and prolong life expectancy, and they are thus an unquestionable population for the application of HNL. Further research should focus on a better understanding of the disease, by exploring the possibility of early detection of the patients in risk and the possible prevention of the disease emergence in a timely and targeted treatment for the purpose of completely preventing or delaying the occurrence of POI.

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Address for correspondence: Jelena Marušić, Klinika za ženske bolesti i porode, Klinički bolnički centar Split

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[1]Klinika za ženske bolesti i porode, Klinički bolnički centar Split,
[2]Klinika za ženske bolesti i porode, Klinički bolnički centar Zagreb,
[3]Sveučilište u Splitu, Medicinski fakultet, [4]Sveučilište u Zagrebu, Medicinski fakultet

PRIJEVREMENA OVARIJSKA INSUFICIJENCIJA

Jelena Marušić[1,3], Marina Šprem Goldštajn[2,4], Damir Roje[1,3], Indira Kosović[1], Jasminka Rešić Karara[1]

Pregledni članak

Ključne riječi: prijevremena ovarijska insuficijencija, hormonsko nadomjesno liječenje

Sažetak. Prijevremena insuficijencija jajnika (eng. premature ovarian insufficiency – POI) klinički je sindrom definiran gubitkom aktivnosti jajnika prije 40. godine života. POI dijagnoza je koja mijenja život, s dubokim fizičkim i psihološkim posljedicama. Spontani oblik POI-a zahvaća približno 1% žena mlađih od 40 godina, ali sve je veća zabrinutost zbog porasta pojavnosti jatrogenog oblika POI. POI je heterogen, multifaktorski poremećaj i u većini slučajeva etiologija mu nije poznata. Dijagnoza POI-a temelji se na prisutnosti amenoreje i povišenoj razini FSH. Liječenje bi trebao koordinirati multidisciplinarni tim. Hormonsku nadomjesnu terapiju treba koristiti barem do prosječne dobi menopauze kako bi se ublažili simptomi hipoestrogenizma i spriječile neželjene dugoročne posljedice, posebno kardiovaskularne bolesti i osteoporoza. Žene s POI-em treba obavijestiti da postoji vrlo mala vjerojatnost spontane trudnoće. IVF s donorskim oocitima daje najveću šansu za trudnoću ovim pacijenticama. Potrebna su buduća istraživanja kako bi pravovremeno prepoznali rizičnu populaciju te pronašli mehanizme koji mogu produljiti, oporaviti ili očuvati funkciju jajnika.