

Premature ovarian insufficiency – hormone replacement therapy and management of long-term consequences

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Abstract

Premature ovarian insufficiency (POI) correlates with increased risk of cardiovascular diseases, osteoporosis, genitourinary syndrome, and other symptoms of prolonged oestrogen deprivation. Properly selected therapy improves the quality of women's lives and reduces the risk of mortality. There is a wide spectrum of available oestrogen and progestogen formulations restoring proper levels of serum sex steroid hormones. The treatment should be implemented at recognition of the POI and continued to at least the age of natural menopause. Transdermal oestradiol and oral or vaginal progesterone administration provide the most physiological sex steroid replacement therapy. Patients' views and individual preference according to the route, dose, and regimen of hormonal treatment have to be taken into consideration in order to achieve high compliance rates. Women with POI should be managed by a multidisciplinary team, such as a gynaecologist, endocrinologist, dietitian, and psychologist.

Key words: hormone replacement therapy, premature ovarian insufficiency.

Introduction

Premature ovarian insufficiency (POI) is defined as the syndrome of ovarian function depletion before the age of 40 years, with oligo/amenorrhoea and increased follicle-stimulating hormone (FSH) concentration (> 25 IU/l), recorded at least twice, four weeks apart [1]. This problem affects about 1% of women before 40 years of age [2]. Premature loss of primordial follicles results in a significant reduction in the production of sex hormones by the ovaries. Causes of POI may be genetic, autoimmune, enzymatic, or iatrogenic. For women at reproductive age, infertility and consequences of hypoestrogenism are particularly important. Women with POI may suffer from hot flushes, night sweats, insomnia, depression, vaginal dryness, dyspareunia, and diminished libido [3]. Long-term consequences of POI are cardiovascular diseases, lipid disorders, osteoporosis, urogenital symptoms, psychological problems, and sexual and cognitive dysfunction [4].

Hormone replacement therapy

The goal of hormone replacement therapy (HRT) in patients with POI is to restore normal serum oestrogen concentrations according to age. In prepubertal girls, substitution of oestrogens is necessary to induce puber-

ty and achieve maximal bone density. Hormonal therapy takes part in prevention of cardiovascular diseases and osteoporosis, and reduces the risk of long-term morbidity. HRT should be introduced at the time of diagnosis of POI and continued to the average age of menopause [1].

Puberty induction

In young women with prepubertal POI, sex steroid replacement is necessary to achieve complete secondary sexual characteristics, adequate growth, optimal bone mineral density, and sufficient uterine development for future reproduction [5]. The recommended age for the beginning of oestrogen therapy is approximately 12-13 years [1]. According to the physiology of puberty, in which the oestrogen concentration is gradually increasing, HRT should be started from very low doses (6.25 µg/day via patch; 0.25 mg/day orally) [4]. Various types of oestrogen can be used in the induction of puberty: oral ethinylestradiol, micronised oestradiol, and transdermal 17β-oestradiol. The preferred therapeutic option is transdermal 17β-oestradiol, providing a profile of concentration most similar to physiological levels of oestradiol in the blood serum. Oestrogen doses should be increased every 6-12 months, over a period of 2-3 years, up to the doses used in adult wom-

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en with POI (50-100 µg/day via patch or 1-2 mg/day orally). After 2-3 years of oestrogen therapy or when breakthrough bleeding occurs, progestogen should be added for endometrial protection, regular withdrawal bleeding, and normal breast and uterine development. The recommended progestogens are: micronised progesterone (100-200 mg/day) or dydrogesterone (5-10 mg/day) for 12-14 days of the cycle [1].

Bone health consequences

One of the long-term consequences of POI is loss of bone mineral density (BMD) and increased risk of fractures, which is associated with the lack of protective effect of oestrogens on the bone [6]. The BMD loss after menopause is associated with bone remodelling [7]. There is significant reduction of BMD in the lumbar spine and femur in patients with POI [4]. Sex steroid replacement therapy restores bone density in young patients with ovarian function depletion [3]. The results of the study by Bachelot *et al.* revealed significant reduction in femur BMD and an increased incidence of osteopaenia and osteoporosis in the group of women with POI, who discontinued HRT after one year of treatment, compared to women who continued it for at least five years [8]. Treatment with transdermal oestradiol and vaginal progesterone has a more beneficial effect on the bone mass in the lumbar spine than standard HTM [9]. 1200 mg of calcium and 800-1000 IU of vitamin D per day is recommended in addition to hormonal replacement in women with POI [10].

Cardiovascular disease

The main reason for increased risk of early mortality in POI is cardiovascular disease, caused by vascular endothelial dysfunction, unfavourable lipid profile, and metabolic disorders [3, 11]. It has been shown that hormonal therapy restores endothelial function in women with POI within six months of treatment [12]. Despite the large number of studies on perimenopausal women, there is a relative lack of accurate data assessing the impact of POI and sex steroid treatment on the cardiovascular system of young women. Nevertheless, oestrogen therapy is recommended in POI patients in order to prevent possible adverse changes in the cardiovascular system [1]. Additionally, to reduce the risk of cardiovascular disease, patients should be educated about modification of the lifestyle, balanced diet, and regular physical activity and advised against smoking.

Neurological dysfunction

POI is associated with higher risk of neurological dysfunction, cognitive impairment, and dementia [13, 14].

There are no explicit data on the impact of HRT on verbal and memory function improvement. However, according to the European Society of Human Reproduction and Embryology (ESHRE) recommendations, oestrogen replacement should be used to reduce the risk of cognitive impairment [1]. It seems that HRT, mainly with oestrogens, diminishes mood disorders, including depressive symptoms [15]. The effect of physiological testosterone replacement on quality of life, self-esteem, and mood in women with primary ovarian insufficiency remains controversial [16].

Urogenital symptoms

Women with POI are more likely to suffer from genitourinary syndrome and sexual dysfunction [17]. Local treatment with lubricants and moisturisers does not always adequately ameliorate the symptoms. The most efficient treatment of genitourinary syndrome is oestrogen therapy. It restores vaginal epithelium and vasculature and lowers vaginal pH [18]. The most effective is local therapy with vaginal oestradiol, conjugated equine oestrogens, or estriol. All forms of vaginal oestrogens appear to be equally effective for the symptoms of vaginal atrophy [19]. Estriol seems to be safer because is less potent than oestradiol, clears more quickly, and is not inverted to oestradiol.

Choice of oestrogen/progestogen formulation

There are many routes of administration, doses, and various types of oestrogen and progestogen preparations that can be used to treat women with POI. The available oestrogens include: 17β-oestradiol, oestradiol valerate, ethinyloestradiol, and estriol. Oestrogens can be administered systemically in oral or transdermal form or locally (vaginal gels, creams, and rings). In women with POI with an intact uterus, it is necessary to add progestogen to prevent hyperplasia and endometrial cancer [20]. Progestogens can be given orally, vaginally and in an intrauterine device system. There are no data on the influence of progestogen administered by intramuscular injections and subcutaneous implants on endometrial protection during HRT in women with POI.

Currently available methods of POI therapy include HRT and combined oral contraceptive (COC). HRT, compared to COC, more closely mimics physiological concentrations of oestrogen and progesterone [11]. Oral contraception usually contains ethinyloestradiol, which results in supraphysiological doses of oestrogen and has an unfavourable effect on the serum lipid profile and increased production of coagulation factors. Nevertheless, COC is still a very common form of treatment of POI patients. It is especially dedicated for women

who express a strong need for effective contraception because there is a 5% risk of spontaneous pregnancy in POI [3]. Moreover, some patients often find the contraceptive pill to be a simpler and more peer-friendly method dedicated for young, non-postmenopausal women.

The transdermal route of administration of 17 β -oestradiol at a dose of 100 μ g per day seems to be the preferred one because it mimics the physiological serum oestradiol concentration and effectively reduces menopausal symptoms [15]. The advantage of this therapy is also a lack of the first-pass effect of the liver and on haemostatic factors [3]. It also has more beneficial effect on the lipid profile, markers of inflammation, and blood pressure. It has been shown that the use of transdermal HRT for 12 months, compared to COC, resulted in significantly lower blood pressure, better renal function, and less activation of the renin-angiotensin-aldosterone axis in POI patients [21]. 17 β -oestradiol is also more advantageous for bone mineral density and reduction of bone resorption compared to COC containing ethinylestradiol [9].

It seems that natural micronised progesterone, available in oral and vaginal form, has a more beneficial effect on the cardiovascular system and perhaps a reduced risk of breast cancer in comparison with synthetic progestogens [1]. Micronised progesterone and medroxyprogesterone acetate in HRT do not differ in thrombosis risk [22]. Although there are studies reassuring that micronised progesterone administration results in effective endometrial protection, still some authors express concerns regarding its potency in that aspect [15, 23].

It is recommended that therapy should be continued until the average age of menopause. However, the compliance among the POI patients is low. Around 40% of POI patients discontinue the therapy within the first year of treatment [8, 9]. The patient's preferences for optimal route, drug, and type of hormonal therapy should be key in the choice of treatment. Continuation of therapy is crucial in the prevention of long-term complications and general health of patients with POI.

Safety of hormone replacement therapy

The group of POI patients is under-researched. The results of studies assessing HRT safety in the population of postmenopausal women cannot be simply applied to young women with premature ovarian function depletion.

There is no evidence for increased risk of breast cancer associated with oestrogen therapy used by women with POI, compared to healthy women who do not receive such treatment. The necessity of earlier, preventive mammography or ultrasound scan has not been demonstrated [1, 24]. The review of current

studies showed a lower impact of micronised progesterone on the development of breast cancer than that of synthetic progestogens [25, 26].

Continuous oestrogen-progestogen HRT seems to be the most effective in the prevention of endometrial hyperplasia and cancer [25]. However, in young women with POI, regular withdrawal bleeding during sequential therapy gives a sense of normalcy with their peers.

The risk of venous thromboembolism (VTE) depends on the oestrogen formulation as well as the type of progestogen. Oral contraceptives containing synthetic ethinylestradiol express a first-pass effect on the liver, strongly influence haemostatic factors, and have an increased risk of thromboembolic events. Higher risk is associated with preparations with more than 35 μ g of ethinylestradiol and the newest generations of progestins. The second generation of synthetic progestogens, such as levonorgestrel, shows lower risk of VTE compared to recent generations (gestodene, desogestrel, cyproterone acetate, drospirenone). Physiological sex steroid replacement regimens (transdermal oestradiol with oral or vaginal micronised progesterone) are safer than COC in the context of VTE.

Conclusions

Premature ovarian insufficiency is associated with many long-term complications that adversely affect woman's health. Hormone replacement therapy is necessary to induce puberty, prevent the development of cardiovascular diseases, osteoporosis, and impaired cognitive functions, and relieve the symptoms of oestrogen deficiency. Various types and routes of administration of oestrogens and progestogens are available. Physiological sex steroid replacement therapy with transdermal oestradiol and oral or vaginal micronised progesterone seems to be most favourable from a metabolic point of view. However, in order to ensure compliance, the treatment should be adjusted to the individual needs of the patient.

Disclosure

The authors report no conflict of interest.

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