Different approaches to Hormone Replacement Therapy in women with premature ovarian insufficiency

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ABSTRACT

Premature ovarian insufficiency (POI) is a major burden in the lives of affected women, many of whom are still very young. In addition to the resulting infertility, the consequences of estrogen deficiency represent a long-term challenge for both the patient and the attending physician. This article summarizes the current recommendations on hormonal treatment of POI, discusses pros and cons of the various hormone preparations, sets out the beneficial effects of the different estrogen and progesterone preparations, and draws attention to possible disadvantages of certain preparations.

KEYWORDS

Premature ovarian insufficiency, hormone replacement therapy, recommendations.

Introduction

Premature ovarian insufficiency (POI) refers to a decrease in ovarian function before the age of 40 and it affects approximately 1% of all women [1]. Estradiol is frequently decreased (below 50 pmol/L) in affected women, while gonadotropins are elevated; women report menstrual changes ranging from irregular cycles to amenorrhea [2]. In the literature, various terms are used synonymously with POI. However, the European Society for Human Reproduction and Embryology (ESHRE) Guideline as well as other international recommendations uniformly advocate the use of the term POI. This term is intended to emphasize that "premature" includes both spontaneous and iatrogenic conditions, while "insufficiency" includes the possible intermittent cessation of ovarian activity, as is frequently observed in affected women, especially shortly after the onset of symptoms [3]. The loss of primordial follicles in the ovary resulting in the development of POI may be due to genetic, autoimmune, or iatrogenic causes. In most cases, however, no cause for the loss of primordial follicles can be found. About 30% of affected women show a familial cluster. At diagnosis, most women present with secondary amenorrhea or oligomenorrhea. Most patients report menopausal symptoms, among which subfertility is the main concern at first contact with the physician. Unlike women with a natural menopause, women with POI may still have residual ovarian function. If POI is suspected, follicle-stimulating hormone (FSH) should be determined twice at an interval of 4-6 weeks. If the FSH value exceeds 25 U/l, POI can be diagnosed according to current ESHRE recommendations, although a variety of threshold limits are stated in other recommendations [4-7]. The most commonly recommended threshold however is >40 IU/l [3]. Furthermore, it is important to note that POI is not diagnosed in women without menstrual irregularities. If some menstrual bleeding still occurs, blood tests should be done on the second or third day of the menstrual cycle [3].

Menopausal complaints

Patients with POI can suffer from a variety of menopausal symptoms, just as women with natural menopause can. Typical symptoms include hot flashes, sweats, sleep disturbances, hair loss, mood swings, and decreased libido. These symptoms are due to the decrease in ovarian estradiol production; furthermore, decreased ovarian testosterone production might also lead to adverse effects on sexual desire and general well-being [3,8]. In the case of women with intermittent cessation of ovarian activity, symptoms can occur for a period of time and can cease when ovarian function resumes.

Systemic hormone replacement is necessary to reduce these symptoms. Furthermore, if local symptoms such as vaginal atrophy and dyspareunia are present, additional topical estrogen administration may be indicated.

Comorbidities in POI

Women diagnosed with POI are at increased risk of cardiovascular disease, leading to reduced life expectancy in affected women [9]. Endothelial function is impaired in women experiencing ovarian insufficiency before the age of 45 compared with premenopausal women, but can be improved with hormone therapy [10]. In addition, women with POI should be educated about other cardiovascular risk factors, such as hyper-

tension, nicotine abuse, and obesity, and efforts should be made to minimize these modifiable risk factors.

Women with ovarian insufficiency under the age of 45 show significantly decreased bone density compared with women who experience a normal menopause [11]. The risk of osteoporosis is increased in women with POI. To promote their bone health, affected women should also substitute vitamin D and calcium and engage in weight-bearing exercises in addition to receiving hormone replacement therapy (HRT) [12]. HRT with physiological estrogen substitution and cyclic oral medroxyprogesterone can improve bone density in patients with POI, and after three years of therapy, bone density can be raised to the point where there is no difference between patients with POI and premenopausal women, as demonstrated by a randomized controlled trial [13]. There are also studies that have shown HRT to have a more positive effect on bone density than conventional combined oral contraception using ethinyl estradiol [14, 15]. Bone densitometry should be performed at diagnosis [16]. If osteoporosis is present, bone densitometry should be repeated after no more than three years to allow for adjustment of the HRT if bone density continues to decline.

Women with POI might also be at increased risk of neurological disease patterns, as a neuroprotective effect of estrogen on brain function has been described [17]. To date, there are no data on the effect of HRT in improving cognitive health in women with POI. Nevertheless, the ESHRE advocates HRT to reduce the potential risks to neurological health [4].

Fertility and the desire to have children

At diagnosis, infertility is usually the most impactful feature of the disease for affected women. Although approximately 25% of women still have residual ovarian function at diagnosis, natural pregnancy can be achieved in only about 5-10% of women [18,19]. For infertile women with POI, there are currently no reliable treatment options to increase pregnancy rates by means of assisted reproductive techniques [20]. Nevertheless, women with no desire to have children should still be informed about contraceptive methods in order to prevent an unwanted pregnancy.

Therapy

HRT is recommended in POI to control symptoms and prevent subsequent consequences of ovarian hormone insufficiency. The term hormone replacement therapy is highly appropriate, as the hormones used replace what would be present physiologically.

Hormone replacement therapy

HRT has multifactorial significance for affected patients. In contrast to hormone administration after natural menopause, POI patients are treated for true hormone deficiency. In addition to treating estrogen deprivation symptoms, the therapy is also an effective primary preventive measure against long-term

risks of POI, such as cardiovascular events and osteoporosis [21].

For this purpose, HRT should be provided from the time of diagnosis until at least the age of natural menopause, and can be prescribed thereafter based on the individual wishes of the patient [20].

Unfortunately, there is currently no uniform standard for the optimal HRT regimen. Table 1 gives an overview of the different recommendations given by recent reviews and guidelines.

In addition to HRT, which is recommended for all women without contraindications to hormonal therapy, women with POI should substitute vitamin D3 and maintain a calcium- and vitamin D-rich diet [12].

There are few studies that address the optimal dosage of HRT for women with POI. Although all guidelines are in agreement that HRT should be continued until the natural age of the menopause, different therapy proposals are made.

On the one hand, estrogen substitution should aim to achieve symptom control; on the other, the estrogen concentration should also be sufficient to provide effective cardiovascular protection and protection against osteoporosis.

Therefore, it seems reasonable to choose dosages that achieve physiological estrogen concentrations. Estradiol can be administered both transdermally and orally.

Three different types of estrogens are available for HRT: 17ß-estradiol, ethinyl estradiol, and conjugated equine estrogens (CEEs). 17ß-estradiol has been found in some studies to be preferable to ethinyl estradiol, due to its cardiovascular and osteoprotective effects [14, 22]. CEEs are less frequently used since they have been associated with a higher risk of thrombosis, strokes and myocardial infarctions compared with 17ß-estradiol HRT in postmenopausal women [23]. More recently CEEs have also been linked to an increased risk of hypertension in older postmenopausal women when compared with placebo [24].

Transdermal application of estrogens avoids the hepatic first-path mechanism and achieves higher plasma levels at lower doses. In older postmenopausal women, transdermal application is associated with a lower risk of stroke, myocardial infarction, and also breast cancer compared with systemic administration [25-28]. However, whether these effects translate to young women with POI is not clear [4].

Guidelines and reviews in recent years recommend suggested doses ranging between 1 mg and 4 mg for oral estradiol, and 50 and 200 µg for transdermal usage [3,4,12,20,29,30]. Most authors favor 2 mg estradiol for oral use or 100 µg for transdermal use as the initial dose, allowing for further adjustment over time. Only one recent review recommends adjusting doses of estradiol according to the patient's age [20]. Fruzzetti *et al*. suggest treating younger patients, up to 30 years of age, with high doses (50-200 µg/day for transdermal use and 2-4 mg/day for oral use). In patients aged between 30 and 45 years, the maximum dose of estradiol should not exceed 100 µg for transdermal or 2 mg for oral administration. Dose adjustment may be necessary for patients over 45, in which case the dose should be reduced to a maximum of 50 µg for transdermal use or 1 mg for oral use. The International Menopause Society (IMS) proposes adapting estradiol doses to achieve physiological levels of estradiol in a target range of 200-400 pmol/l [3].

Table 1 Recommendations on optimal doses of estrogen and progesterone for hormonal replacement therapy in women with premature ovarian insufficiency in reviews and guidelines since 2015.

ARTICLE	ESTROGEN		PROGESTERONE		COMBINED CONTRACEPTIVE PILL
	Oral	Transdermal	Cyclic	Continuous	
NICE guideline 2015	No advice on optimal dose is given		No advice on optimal dose is given		Can be used
Hamoda et al. 2017	2 mg estradiol 10 μg ethinyl estradiol	75-100 μg estradiol	12-14 days: - 200 mg micronized progesterone - 10 mg MPA	after two years without bleeding: 2.5 mg MPA	- limited use for women requiring contraception - 10 μg ethinyl estradiol corresponds to 1-2 mg of estradiol - Alternatively: contraceptive pills containing estradiol
Webber et al. 2017	2-4 mg estradiol	100 μg estradiol	10-12 days: - 200 mg oral micronized progesterone - 10 mg MPA	- 1 mg oral norethisterone - 2.5 mg MPA	- Might be preferred by young women with POI
Torrealday et al. 2017	- 1-2 mg estradiol - 0.625 to 1.25 mg CEE	100 μg estradiol	10-12 days: - 200 mg micronized progesterone 12 days: - 10 mg MPA	100 mg micronized progesterone, oral or vaginal	- COCs should not be used as a contraceptive - other contraception methods such as barrier contraceptives and intrauterine devices should be used
Machura et al. 2018	- Not recommended	100 μg estradiol	- Micronized progesterone for oral or vaginal use - No advice on optimal dose is given		- Might be recommended for patients desiring contraception
Fruzzetti et al. 2020	14-30 years: - 2-4 mg estradiol 30-45 years: - 1-2 mg estradiol >45 years: - 1 mg estradiol	14-30 years: - 50-200 μg estradiol 30-45 years: - 50-100 μg estradiol >45 years: - 50 μg estradiol	200 mg oral progesterone for 12-14 days	Not recommended	- COCs can be used but estradiol should be preferred
Panay et al. 2020	- 2-4 mg estradiol	- 75-100 μg estradiol - 3-4 metered 0.75 mg doses of estrogel	12 days: - 200 mg oral or vaginal micronized progesterone (higher doses are required if higher doses of estrogen are used) - Alternatively: norethisterone acetate or MPA	- No-bleed continuous combined regimens after > 1 year of amenorrhea	- Only initially as contraceptive but not for long-term use
Lambrinoudaki et al. 2021	- 2-4 mg estradiol - 0.625 – 1.25 mg CEE	- 50- 100 μg estradiol	- 200 mg natural progesterone - 10-20 mg dihydrogesterone - 1-5 mg norethisterone - 0.25 mg transdermal norethisterone	- Can be offered as well in lower doses (dose not specified)	- COCs should not be used
Abbreviations: **MPA** = medroxyprogesterone, **COCs** = combined oral contraceptive, **CEE** = conjugated equine estrogen.					

For the treatment of local estrogen deficiency symptoms, low-dose vaginal estrogen (or prasterone) may be used in addition to systemic administration. Patients can choose between creams, vaginal rings or tablets for local application, as the efficiency of these products appears to be similar [31].

If the uterus is intact, administration of a progesterone is essential for endometrial protection. Endometrial protection is strongly recommended by all authors of recent publications, but there is wide range in terms of proposed dosages, time spans and compounds.

Some authors favor cyclic progesterone regimens, in particular shortly after diagnosis [3,12], and propose switching to a non-bleeding continuous therapy after one year [3] or alternatively two years [12].

To date, there are few evidence-based data on the effects of different types of progesterone for women with POI. Micronized progesterone and medroxyprogesterone acetate (MPA) are typically used. The dose of progesterone depends on the dose of estrogen chosen and should be increased when higher doses of estrogen are applied. Progesterone can be giv-

en either continuously or cyclically for at least 10-12 days per month. If sequential administration is chosen, the dose should be higher than for continuous treatment. Most authors recommend doses of 200 mg micronized progesterone or 10 mg MPA for cyclic administration [3,4,12]. Some authors also suggest endometrial protection using cyclic norethisterone [3] or dihydrogesterone [29]. Continuous progesterone treatment is a controversial topic in the literature. Some authors do not recommend continuous treatment at all [20] while others consider switching to a continuous regimen after more than one [3] or two years [12] of amenorrhea. Doses can then be lower in a continuous regimen, most guidelines recommending 2.5 mg MPA [4,12] or 100 mg micronized progesterone [30].

With regard to the advantages and disadvantages of the different progesterone preparations, micronized progesterone has shown more positive effects on breast cancer and metabolic risk in studies [32].

If desired by the patient, a levonorgestrel-containing intrauterine system that releases 20 μg of levonorgestrel daily can be used as an alternative. It is also important to keep in mind that HRT is not a contraceptive unless a levonorgestrel intrauterine system is used [29]. Usage of transdermal natural progesterone has been shown to be inadequate in a continuous treatment to compensate for the mitogenic impact of estrogen [33].

Combined oral contraceptives

The use of combined oral contraceptives (COCs) as an alternative to HRT is also controversial. COCs achieve supraphysiologic estrogen and progesterone concentrations that suppress ovulation. Since young women are generally more familiar with their use in comparison to HRT, which is more often used by older women, COCs might be preferred as a hormone therapy by some women with POI. An advantage of COCs, therefore, is that they also represent an additional contraceptive method compared with classical HRT. In most cases, ethinyl estradiol is used. However, ethinyl estradiol offers little osteoporosis and cardiovascular protection compared with estradiol, which is used in HRT [14]. A randomized controlled trial showed that HRT, when compared with COCs, resulted in significantly lower blood pressure values, better renal function, and reduced renin-angiotensin-aldosterone system activity at 12 months, improving cardiovascular health in patients with POI [22]. Ethinyl estradiol also shows adverse effects on lipid profile and coagulation factors and increases the risk of thromboembolic events in women with POI [3,34]. Women should be administered COCs without a hormone-free interval in order to prevent menopausal symptoms associated with pill-free intervals. Continuous estrogen administration will permanently prevent symptoms of estrogen deficiency [4].

When an effective contraceptive method is sought, the IMS, for example, recommends the use of COCs for two years after diagnosis [3]. After this time, spontaneous pregnancy is highly unlikely because intermittent resumption of ovarian activity usually ceases during the first two years after diagnosis. At this time, a switch to conventional HRT should be made to ensure optimal protection against long-term sequelae.

Androgen substitution

In premenopausal women, testosterone is produced both in the ovaries and in the adrenal cortex. Therefore, premenopausal ovarian insufficiency results in not only an estrogen deficit but also an androgen deficiency. However, based on current studies, there is no evidence to recommend androgen therapy in women with POI [3,35]. In a small cohort of women with Turner syndrome, improvement in bone density was shown with one year of methyltestosterone therapy, but in another cohort of patients with spontaneous POI, testosterone therapy administered in addition to HRT did not provide any benefit in terms of mood or quality of life [36,37].

Nevertheless, patients with ongoing sexual dysfunction during HRT might benefit from androgen therapy [35].

If an androgen replacement therapy is desired, it should be applied as in postmenopausal women [35,38]. It remains to be seen whether further studies will provide clearer indications for or against additional androgen therapy.

Monitoring of hormone replacement therapy

No routine tests to monitor HRT in women with POI are established today, but occasional measurement of estradiol (minimum level of 200 pmol/l) might be indicated to ensure adequate response to hormone therapy and improve lasting compliance on the part of the patient. Neither ethinyl estradiol nor estrone is determined by assays. Measurement of FSH levels is not critical for HRT verification, since a decrease in FSH levels is not frequently observed even under effective hormone therapy [39]. Rather, regular follow up, e.g. annually, should take place to check the patient's satisfaction and the tolerability of the therapy [4]. Breast cancer screening as well as cervical cancer screening is recommended for women with POI as for the general population [4].

Risks of hormone replacement therapy after reaching natural menopause

To date, there is no evidence for an increased risk of breast cancer from HRT before the natural age of menopause in women with POI [40].

The risk of venous thromboembolism was shown in one study to be increased in women who started HRT at less than 40 years of age compared with older women [41]. If women affected by POI are at increased risk of thromboembolic events, transdermal application of estrogen should always be favored for this reason.

Hormone replacement therapy after reaching the age of natural menopause

The decision on when to stop HRT in women with POI should be made on an individual basis, depending on the patient's wishes and possible familial risk factors. Unfortunately,

there are currently no data on the recommended duration of HRT in women with POI [4].

When HRT is continued at lower post-menopausal doses, it is associated with a reduction in menopausal symptoms, cardiovascular disease, osteoporosis, and type II diabetes, thus reducing overall morbidity in these patients [21,42].

What do the guidelines say?

The ESHRE Guideline recommends cyclic combined HRT. An estrogen preparation of 17ß-estradiol with micronized natural progesterone is to be preferred. According to the ESHRE Guideline, combined cyclic HRT provides the highest endometrial protection [4], although other authors suggest greater endometrial safety by using a continuous combined regimen [43].

The current IMS white paper recommends a higher dose of estrogen than is intended for natural menopausal therapy. The goal of therapy should be to achieve physiologic estradiol levels of between 200 and 400 pmol/l [3]. In any case, a progesterone preparation should be used for endometrial protection. The progesterone used can be either 200 mg of micronized progesterone for 12 days of the cycle or noretheristerone acetate or MPA. A bleeding-free continuous hormone regimen may be chosen if women have already been experiencing amenorrhea for more than 1 year at the start of therapy, or after several years of sequential therapy [3]. Alternatively, the IMS recommends the use of a levonorgestrel-containing IUD for additional contraception, although studies assessing endometrial protection in women with POI are lacking. COCs containing ethinyl estradiol are inferior to HRT in terms of metabolic profile and osteoporosis protection, according to the IMS, and are recommended by the IMS only for initial therapy of POI in the first two years after diagnosis, when there is no desire to have children and safe contraception is desired.

Summary

Patients with POI benefit greatly from HRT. An HRT regimen that mimics natural ovarian hormone production and achieves physiologic estrogen levels should be chosen until the age of natural menopause. 17ß-estradiol should be preferred as the estrogen of choice and can be administered orally or transdermally. In addition, progesterone should be used if the patient has an intact uterus, preferably in a cyclic regimen for 10 to 12 days per month. Micronized progesterone, MPA and dydrogesterone are recommended. The patient should be informed that HRT is not a contraceptive and effective contraception should be discussed if necessary [44].

Studies to further characterize the optimum hormonal treatment of women suffering from POI with large numbers of included patients are needed, and patient registers, such as *https://poiregistry.net*, might help to aggregate a large data set and thus contribute to this effort.

HRT attenuates menopausal symptoms, maintains or increases bone density, alleviates psychological sequelae, and reduces the increased risk of cardiovascular disease.

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