Taylor & Francis
Taylor & Francis Group

Expert Review of Endocrinology & Metabolism

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iere20

A current perspective into young female sex hormone replacement: a review

Miriam Giordano Imbroll & Mark Gruppetta

To cite this article: Miriam Giordano Imbroll & Mark Gruppetta (2020): A current perspective into young female sex hormone replacement: a review, Expert Review of Endocrinology & Metabolism, DOI: 10.1080/17446651.2020.1816820

To link to this article: https://doi.org/10.1080/17446651.2020.1816820

Published online: 06 Sep 2020.

EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM
https://doi.org/10.1080/17446651.2020.1816820

Taylor & Francis
Taylor & Francis Group

REVIEW

A current perspective into young female sex hormone replacement: a review

Miriam Giordano Imbroll [a,b] and Mark Gruppetta[a,b]

[a]Department of Medicine, Faculty of Medicine and Surgery, University of Malta, Mater Dei Hospital, Msida, Malta; [b]Department of Medicine, Mater Dei Hospital, Msida, Malta

ABSTRACT

Introduction: Hormone replacement in females with hypogonadism is advocated to address the various clinical aspects of estrogen deficiency.

Areas covered: This article focuses on hormone replacement in young females with hypogonadism, including a rationale as to why hormone replacement in such patients differs from treatment in postmenopausal females, a summary of symptoms encountered by females with hypogonadism and a comprehensive discussion of the various treatment options available, specifically focusing on the latest advances in the subject. A Medline search was conducted using different combinations of relevant keywords, giving preference to recent publications.

Expert opinion: Whilst traditionally oral contraceptive pills (containing ethynyl estradiol) were commonly used as a form of hormone replacement, it is now increasingly recognized that this is not the optimal treatment option. Physiological hormone replacement with transdermal estradiol is found to be superior. Evidence suggests that micronized progesterone may be associated with fewer side effects, although its effect on endometrial protection is not yet proven. Synthetic progestins confer varying degrees of androgenic and thromboembolic properties which should be kept in mind when prescribing individualized treatment. Further studies in different sub-cohorts of female patients with hypogonadism might help address the specific needs of individual patients.

ARTICLE HISTORY
Received 8 June 2020
Accepted 27 August 2020

KEYWORDS
Hormone replacement; female hypogonadism; premature ovarian insufficiency; estrogen; progestogen

1. Introduction

Female hypogonadism is defined as hypothalamic-pituitary-adrenal axis dysfunction leading to an estrogen deficient state and consequently menstrual cycle dysregulation [1]. Hypogonadism may be classified as premature ovarian insufficiency (POI) (failure arising from the gonads themselves) or hypogonadotropic hypogonadism (secondary gonadal failure); the result of inadequate gonadotropin stimulation [2].

Female hypogonadism due to POI can be acquired or congenital. Acquired causes can be related to sudden destruction of follicles by chemotherapy, irradiation, or infections such as mumps oophoritis. Congenital causes of POI include an autoimmune process, occasionally associated with an autoimmune polyendocrine syndrome, and rarely genetic syndromes. Secondary hypogonadism (hypogonadotropic hypogonadism) may result from a dysfunction at a hypothalamic level, at a pituitary level or both [3]. This may be functional, resulting from excessive stress (psychogenic or physical), vigorous exercise, dieting, or chronic illness (such as chronic hepatic or renal insufficiency and AIDS), medication-related (antipsychotics and opiates), secondary to anatomically defined pathologic conditions of the hypothalamic-pituitary unit (including pituitary tumors, hemorrhagic pituitary destruction, infiltrative diseases of the pituitary, empty sella syndrome, head injury, infection), irradiation of the head or genetically defined conditions such as isolated gonadotrophin deficiency [1,3].

The average age of natural menopause in females is approximately 50 years. One percent of women continue menstruating until the age of 60 years and beyond and another 1% stop menstruating before the age of 40 years [4]. Women exhibiting features of gonadal failure prior to 50 years of age, especially before the age of 40 should be considered for sex hormone replacement therapy [5,6]. This consideration stems from the fact that many of the complications associated with hypogonadism, irrespective of the cause, are primarily attributed to estrogen deficiency, underscoring the importance of physiological hormonal replacement in such patients.

This review aims to explore the rationale behind hormonal replacement in young females and to highlight the challenges in their management. It aims to construct a holistic, comprehensive, evidence-based account whilst providing practical and salient points for practice. It also intends to integrate various inputs arising from different sources; including clinical, pharmacological, and physiological matters. Furthermore, this review aims to discuss the various hormonal replacement options available for these patients, outlining recent arguments and developments in this field; including the benefits and risks of specific treatments.

CONTACT Miriam Giordano Imbroll giordanomiriam@yahoo.com Diabetes and Endocrine Centre, Department of Medicine, Mater Dei Hospital, Msida MSD2090, Malta

Article highlights

- The etiology of female hypogonadism is varied and may be classified as premature ovarian insufficiency (failure arising from the ovaries themselves) or secondary gonadal failure, also known as hypogonadotropic hypogonadism; the result of inadequate gonadotropin stimulation.
- Women exhibiting features of gonadal failure prior to 50 years of age, especially prior to the age of 40, should be considered for sex hormone replacement therapy in order to avoid the complications of early menopause (menopausal symptoms, increased mortality mainly related to cardiovascular disease, bone health, and neurological sequelae).
- By prescribing sex hormone replacement, one aims to restore normal physiological states, therefore in such a context the term 'replacement' is indeed pertinent as opposed to the concept of 'extension' of hormone therapy in the post-menopausal age group.
- Hormonal replacement consists of an estrogen component as well as a progestogen component, in females possessing a uterus.
- Oestradiol is superior to ethinyloestradiol in terms of cardiovascular parameters, thromboembolic risk, and bone health. Furthermore, the use of transdermal or transvaginal estrogen therapy has been associated with a decreased risk of thromboembolism and possibly stroke, when compared to the classical oral formulation.
- Different progestogens have a varying affinity to the progesterone receptor and other steroid receptors: mineralocorticoid, glucocorticoid, and androgen receptors. These differing actions, together with other factors including route of administration, pharmacokinetics, and protein-binding strength, explains the differing androgenic and thromboembolic profiles.
- Treatment with testosterone was found to have positive effects on cardiometabolic risk factors, quality of life, and neurocognitive functions but long-term studies confirming safety and efficacy are lacking.
- With regards to follow up, a multidisciplinary setting is advisable and aims to address specific patients' needs according to the varied aetiology of female hypogonadism.

2. Methods

To address these aspects, a thorough and comprehensive review of the relevant guidelines and literature has been undertaken. A Medline search was conducted using different combinations of relevant keywords: 'female hormone replacement therapy,' 'menopausal hormone therapy,' 'female hypogonadism,' 'premature ovarian failure/insufficiency,' 'premature menopause' 'estrogen,' 'progestogen.' The literature search was subsequently expanded to focus on relevant important aspects in this field. Relevant guidelines, position statements, and review articles were also researched. Furthermore, to ensure a comprehensive and wide-ranging analysis of the literature relevant to the area being reviewed, pertinent publications were subsequently manually pursued from other cited papers in retrieved articles. A preference to recent publications was made.

3. Background to hormone replacement

Most evidence related to hormone replacement therapy results from studies performed in post-menopausal females. The Women's Health initiative (WHI) trial was one of the largest US prevention studies of its kind and the original study design was to follow-up patients over a period of 9 years. The type of hormone replacement used in the treatment arm was 0.625 mg conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) in patients with an intact uterus. Interim monitoring indicated an increased risk of coronary heart disease (CHD), breast cancer, stroke, and pulmonary embolism in the treatment group as opposed to the placebo group. This was reflected in the initial reports [7]. Consequently, the part of the study using a fixed combination of CEE and MPA was halted after an average follow-up period of 5.2 years. These initial results had dissuaded various patients and clinicians from utilizing hormonal replacement therapy in the post-menopausal age group [8].

Subsequent analysis of the WHI [9] was carried out on the 10,739 postmenopausal women with a previous hysterectomy that had been randomized to CEE or placebo. Over a 6.8 year period, there was an increased risk of stroke, decreased risk of hip fracture, no effect on CHD, and possibly a reduction in breast cancer incidence. The latter was eventually confirmed on further extended follow up [10,11]. Another secondary analysis of the WHI [12] was carried out on the 10,739 postmenopausal women on CEE alone together with 16,608 women with an intact uterus who were given CEE and MPA or placebo. An interesting finding in this analysis was that women who initiated hormone therapy closer to menopause (less than 10 years since menopausal onset) tended to have reduced CHD risk when compared to the increased risk in women starting hormone replacement at a later stage (between 10 and 19 years since menopause and after 20 years since menopause), although this trend did not reach statistical significance. A similar trend was observed for total mortality. Risk of stroke on the other hand was elevated irrespective of years after menopause [12].

Other studies highlighting the diverging risks in different age groups, were the Early versus Late Intervention Trial with Estradiol (ELITE) and the Kronos Early Estrogen Prevention Study (KEEPS) study. The ELITE study, randomizing patients to either receiving 1 mg 17β estradiol plus vaginal progesterone for 10 days every 30 days (in women with a uterus) or placebo, showed that carotid intima media thickness was less over 5 years in those taking estradiol. This finding was noted in those patients who started treatment less than 6 years from onset of menopause and was not seen in those who were randomized to treatment more than 10 years after menopause [13]. In the KEEPS study, hormone therapy in the form of either CEE or transdermal 17β-estradiol started in recently menopausal women had no adverse effect on the rate of carotid intima media thickness and no increase in venous thrombosis. Ancillary studies demonstrated a positive effect on mood in those taking CEE and an improvement in hot flushes, sleep patterns, and maintenance of bone mineral density in both groups receiving the different estrogens [14].

Moreover, one must be mindful and acknowledge that these trials were carried out specifically in post-menopausal females. Specific research regarding hormone replacement therapy in young patients (less than 50 years) exhibiting female hypogonadism (including those with early menopause) is scanty. Such patients are recognized to exhibit a pathological state of estrogen deficiency when compared to their peers with normal ovarian function. By prescribing sex hormone replacement, one aims to restore normal physiological states, thus predicting that adverse effects would be even less than in those starting treatments after natural

menopause has occurred. In the former group, the term 'replacement' is indeed pertinent, as opposed to the concept of 'extension' of hormone therapy as is in post-menopausal women [2,15,16].

4. Symptoms of estrogen deficiency in young females

Early menopause is associated with increased mortality [17–22] mainly related to cardiovascular disease. They also have increased morbidity related to bone health and neurological sequelae [2,16].

4.1. Cardiovascular consequences

Menopause is considered to be an independent risk factor for cardiovascular disease as evidenced by its inclusion in the Framingham model of cardiovascular risk [23]. It is uncommon for females under the age of 60 to suffer from coronary heart disease [24]; however, females with untreated early menopause tend to lose this protectivity [25–27]. Furthermore, in a study by Ossewaarde et al. (2005), ischemic heart disease mortality was found to be 2% lower with each increasing year of age at menopause [22].

Studies supporting this association between menopause and mortality include the Study of Women's Health Across the Nation (SWAN) [28] where an increase in low-density lipoprotein cholesterol, total cholesterol and apolipoprotein B were found to be related directly to the last menstrual period date. Significantly less carotid atherosclerosis was documented in women with late menopause or women making use of postmenopausal estrogens as opposed to women with early menopause and no estrogen use [29].

In patients with early menopause, treatment with hormone replacement may potentially offset this adverse cardiovascular effect. In a study by Elsheikh et al., 21 women with Turner's syndrome were studied prospectively, and treatment with hormone replacement therapy had a favorable effect on central arterial hemodynamics [30]. Similarly, in another study, endothelial function was restored in females with premature ovarian insufficiency when treated with hormone replacement therapy [31].

4.2. Bone related consequences

Early menopause, irrespective of the cause, is clearly associated with reduced bone mineral density (BMD) [32–39]. Although this has not yet been adequately demonstrated, it is very likely to be associated with an increased risk of fracture later on in life [6]. This is of prime concern in young females with premature menopause, more so in patients who have not attained peak bone mass (around age 30 years) due to prolonged estrogen deficiency prior to this age [34,40,41].

Addressing modifiable risk factors such as smoking cessation, restoration of vitamin D levels, exercise, weight management, and calcium supplementation, may be helpful in contributing to restoring bone mineral density [34,42,43]. However, hormone replacement therapy is recommended to maintain bone health and prevent osteoporosis [44–47].

4.3. Cognitive function

Estrogen replacement in postmenopausal females has been found to be neuroprotective and associated with a decreased risk of Alzheimer's disease [48] and dementia [49]. Studies have also shown cognitive decline and Parkinsonism in patients with early menopause [50,51].

4.4. Other symptoms

Women with hypogonadism due to primary ovarian insufficiency may experience symptoms identical to those experienced by women who proceed through menopause naturally. These include vasomotor symptoms (hot flushes and night sweats) and features of sexual dysfunction (vaginal dryness, dyspareunia, and decreased libido) [15]. These symptoms can sometimes be quite severe and together with fertility issues inherent in these conditions may contribute to the psychological distress associated in such cases [52,53]. Patients should be offered psychological support and lifestyle interventions [52]. In a study by Smith et al., females with premature ovarian insufficiency had a higher preponderance for dry eye syndrome than age-matched controls [54] however no study to date has explored whether treatment with androgens or estrogen ameliorated these symptoms.

5. Hormone replacement therapy (HRT)

Hormonal replacement consists of an estrogen component as well as a progestogen component, in females possessing a uterus. Replacement aims to promote and maintain secondary sexual characteristics and, as already alluded to, to reduce the risk of developing long-term complications such as cardiovascular disease and osteoporosis [4]. Both estrogen and progestogen can be administered via multiple different formulations. Recently, the management of female patients with hypogonadism is moving away from the conventional oral contraceptive pill and post-menopausal hormone replacement therapy, toward a more physiological hormonal mode of replacement [2,6,45,55,56].

5.1. Estrogen replacement

Estrogen replacement comes in different formulations (Table 1). Recent evidence indicates that the use of transdermal or transvaginal estrogen therapy is the preferred route when compared to the classical oral formulation, either alone or

Table 1. Common estrogen options available.

- Natural estrogens
  - Oral micronized estradiol 0.5–2 mg (estradiol valerate)
  - 17β-estradiol transdermal patches 100–200 µg
  - Estrogen transdermal gel 1–2 mg
- Synthetic estrogens
  - Oral ethynyl estradiol 20–35 µg
- Conjugated equine estrogen 0.625–1.25 mg

combined with a progestogen as first-line hormone replacement for women in menopause [57]. The advantages associated with the former two options of delivery are related to the fact that they bypass the first-pass effect on the liver that occurs and is inevitable when estrogen is administered orally [15]. Evidence suggests that the risk of thromboembolism and cardiovascular events (including stroke) is decreased with the transdermal route, as opposed to oral estrogens [15,57–61].

The 'type' of estrogen also plays a role on the risk of thromboembolism. Most oral contraceptive pills (OCPs) contain the synthetic ethynyl estradiol (EE). Over the years, formulations of OCPs containing EE have reduced the dose of EE with the aim of reducing the risk of VTE. Most oral formulations currently contain 10–35ug of EE [62]. HRT preparations containing 'more' physiological estrogens in the form of estradiol valerate and 17β-estradiol are preferred [45,56,63]. These seem to be safer than the synthetic EE [6]. EE was initially used as the estrogen component in OCPs because of the low bioavailability of estradiol (5%) as opposed to EE (38–48%) [64,65]. Eventually, micronization and esterification of estradiol enhanced its bioavailability. This also facilitated its use for contraceptive purposes [66]. The affinity of estradiol valerate for the estrogen receptor is 50 times less that of 17β-estradiol [67]. Therefore, it is essentially inactive and acts solely as a prodrug of 17β-estradiol, the active drug. The conversion of estradiol valerate to 17β-estradiol occurs in the gut and liver [68]. Furthermore, the enzyme 11β-hydroxylase converts 17β-estradiol to estrone which in turn can be reconverted to its original state. Thus, estrone acts as a reservoir for 17β-estradiol. This pharmacokinetic equilibrium provides for a fairly stable estradiol level following oral estradiol valerate administration [69].

The systematic review by Mohammed et al., (2015) included 15 observational studies with follow-up of 3 to 20.15 years comparing transdermal estrogen therapy with oral estrogen in the postmenopausal age group. There was an increased risk of first episode of venous thromboembolism, deep vein thrombosis, and possibly stroke but not MI [57]. A preceding systematic review [60], investigating the effect of non-oral hormonal therapy with oral formulations on cardiovascular markers found potentially unfavorable changes in CRP and activated protein C, in the arm prescribed oral hormone therapy. The latter study was again carried out in postmenopausal women. More importantly, a study comparing the effects of hormone replacement on multiple parameters in women with premature ovarian failure, physiological hormone replacement with transdermal estradiol and vaginal progesterone was superior to standard OCP (EE and norethisterone). Although both arms caused similar luteinizing hormone and follicle-stimulating hormone suppression and symptom relief, the former group had less activation of the renin-angiotensin system, enhanced blood pressure control and a positive effect on renal function; all contributing to the crucial long-term role in cardiovascular health in females requiring long-term hormone replacement [56].

In the study by Cartwright [55], patients with spontaneous premature ovarian failure were randomized to no hormonal treatment for 2 years, COCP (EE/levonorgestrel), or hormonal treatment in the form of oral estradiol hemihydrate and norethisterone acetate. Lumbar bone density was superior in those receiving the latter combination as opposed to those receiving COCP, whereas in those patients off treatment there was a drop in bone density. Bone turnover markers showed similar reductions in the two treatment arms [55]. Furthermore, in another study, transdermal estradiol and vaginal progesterone were found to be superior to standard hormone replacement with EE and norethisterone on lumbar bone mass and bone formation markers over a 12-month period [45].

In postmenopausal women, the thromboembolic risk was found to be increased by up to 5–8 times in patients taking oral estrogen, especially those with underlying obesity or clotting disorders, but not in patients making use of transdermal estrogens [58,59,70,71]. Similarly, in another meta-analysis, thromboembolic risk, and possibly the risk of stroke was increased with oral as opposed to transdermal estrogen [57].

Endometrial thickness and to a lesser extent uterine volume were more favorable with physiological replacement (transdermal estradiol and vaginal progesterone) as opposed to the standard OCP (EE 30 mg and norethisterone 1.5 mg daily) [72].

Another justification for hormone replacement moving away from the classical OCP is the fact that OCPs provide supraphysiological doses of synthetic estrogen, aiming to suppress ovulation in a female with normal menstrual cycles, rather than just 'replacing' ovarian function [15]. Furthermore, most OCPs have a typical 1-week 'pill-free' interval each month, resulting in an 'oestrogen-deficient' state. Over a one-year period, this adds up to a significant amount of time over a period of a year where the body is not exposed to estrogen. Some patients may also develop menopausal symptoms during these 'pill-free' intervals [15].

5.2. Progestogen replacement

In females possessing a uterus, hormone replacement should include both an estrogen and a progestogen. A cyclical progestogen provides endometrial protection and acts against endometrial hyperplasia resulting from the sustained use of unbalanced estrogens [6,73,74]. There are various modes of progestogen administration, including oral or transdermal formulations as well as continuous/combined single estrogen and progestogen regimens. The progestogen component in HRT may be natural or synthetic (Table 2). Natural progesterone has a molecular structure that is bioidentical to endogenous progesterone, as opposed to synthetic progestogens (progestins) which embrace a different structure. The latter harbor similar effects to endogenous progesterone but may have differing progesterone receptor actions. Biological and physiological effects of progestogens are elicited through their binding with the nuclear progesterone receptors. Different progestins bind with a high, though varied affinity, to the progesterone receptors. Additionally, progestogens have varying affinity to other steroid receptors: mineralocorticoid, glucocorticoid, and androgen receptors. The differing actions, resulting from the degree of binding of these receptors, together with

Table 2. Classification of most commonly used Progestins.

- Natural
- Synthetic
  - Semi-synthetic
    - Medroxyprogesterone acetate
    - Dydrogesterone
  - Testosterone derived
    - Norethisterone
    - Norgestrel
    - Levonorgestrel
  - Newer less androgenic
    - Desogestrel
    - Norgestimate
    - Gestodene
  - Anti-androgenic
    - Drospirenone
    - Dienogest
    - Cyproterone acetate

(Adapted from [62,92])

other factors including route of administration, pharmacokinetics, and protein-binding strength, explains the differing bioavailability and activity of various progestogens [62,63,75,76].

Micronization of natural progesterone increases its half-life, decreases particle size and enhances the dissolution leading to enhanced bioavailability [77]. Whilst it is not widely prescribed, micronized progesterone is suggested to have no effect on mood, it does not decrease HDL cholesterol and does not adversely affect pregnancy outcomes as opposed to synthetic progestins [78]. Data regarding postmenopausal females, suggest that micronized progesterone does not seem to have an effect breast cancer risk, has no effect on blood pressure, reduces the incidence of new onset diabetes [79,80] and improves the quality of life [81]. In the Kronos Early Estrogen Prevention study (KEEPS), a study carried out in postmenopausal women, micronized progesterone added to estrogen replacement had no effect on coronary artery calcium scores, carotid intima media thickness, insulin resistance, lipids and blood pressure [82]. However, there is a paucity of evidence for its effectiveness in its use as HRT for endometrial protection [15,83]. This may be attributed to the fact that the recommended dose of micronized progesterone with full estrogen replacement is inadequate to provide full endometrial maturation, making this an unattractive choice in young women with POI who need long-term treatment [15]. Transdermal natural progesterone cream use was also studied. Complex pharmacokinetics were evident, and it was concluded that inconsistent and unreliable results regarding its absorption and clinical effects rendered its use unsupported by evidence [84,85].

There is paucity of data on the use of progesterone secreting intrauterine devices in patients with POI, since most studies have been carried out in postmenopausal women. There are diverging views with some advocating its safety (conceptual less exposure to systemic progestogen), efficacy (higher protection against endometrial hyperplasia), contraception, and compliance [86–88]. On the other hand, the cessation of regular menses, might be an undesirable effect in young females seeking to 'normalize' their reproductive lives [15].

Dydrogesterone (Table 2), is a stereoisomer of progesterone and a highly selective synthetic progestin, considered more 'natural' than most. It binds almost exclusively to the progesterone receptor and has no estrogenic, androgenic, antiandrogenic, or glucocorticoid activity [89]. In one of the few long-term controlled studies published on HRT in young women with early menopause, the NIH Intramural Research Program Study, medroxyprogesterone was the progesterone used [90]. Medroxyprogesterone is a non-testosterone derived 21-carbon progestin that has proven to be capable of inducing a fully secretory endometrium when given with appropriate doses of estrogen in regular monthly cycles [15,91]. It also exhibits significant glucocorticoid activity [62].

On the other hand, other available synthetic progestins can be testosterone-related, including norethisterone, levonorgestrel and norgestrel, and its derivatives desogestrel, norgestimate, and gestodene. Levonorgestrel; a potent progestogen, and norethisterone have no glucocorticoid and antimineralocorticoid activity but have some androgenic activity [92,93]. Interestingly, norethisterone was noted to be minimally aromatized to EE in the liver. This, however, does not seem to be clinically relevant at standard doses (1 mg) but might be clinically significant at higher doses (5 mg) [94,95]. Regarding transdermal systems, formulations containing norethisterone acetate and levonorgestrel in combination with transdermal estradiol are available and have been found to provide effective endometrial protection. Either sequential transdermal systems with a progestogen component added to estradiol in the second phase of the menstrual cycle (where regular cyclical bleeding is expected) or a continuous combined system with both estradiol and the progestogen delivered throughout, are available. Most of these transdermal systems use norethisterone acetate in a 4-day delivery system whilst a 7-day levonorgestrel delivery system is also available [96–99].

Newer compounds of synthetic progestins are less androgenic and in instances, antiandrogenic. Table 3 depicts the relative androgenicity and thromboembolic risk of the respective progestins. The older generation progestins; such as norethindrone, norethisterone, and levonorgestrel have relatively high androgenicity, however, venous thromboembolic risk is relatively lower than that of the newer generation progestins. The latter progestins include norgestimate, gestodene, and desogestrel [92,100,101].

Table 3. Relative androgenicity and thromboembolic risk of the different progestins.

Generation	Names	Relative androgenicity	Relative Venous thromboembolic risk (compared to no oral contraceptive)
	Medroxyprogesterone acetate	Medium	
1	Norethindrone	Medium	+
1–2	Norethisterone	High	+
2	Levonorgestrel	High	+
2–3	Norgestimate	Low	+
3	Gestodene	Low	++
3	Desogestrel	Low	+++
4	Drosperinone	Antiandrogenic	+++
4	Dienogest	Antiandrogenic	++/+++
	Cyproterone acetate	Antiandrogenic	+++

(Adapted from [62,100,101])

Other progestins found in certain OCPs include drospirenone and dienogest. Drospirenone has antiandrogenic and antimineralocorticoid properties but a relatively higher thrombotic risk [92,100] (Table 3). It is structurally related to spironolactone with weak diuretic activity resulting in water and sodium excretion and a slight decrease in blood pressure. 3 mg drospirenone is equivalent to about 9–10 mg spironolactone. On the other hand, 2 mg cyproterone acetate exerts a diuretic effect equivalent to 50 mg spironolactone [92,102]. Trials comparing OCP containing 3 mg of drospirenone with 2 mg cyproterone acetate showed similar reductions in hirsutism scores, suggesting an effect possibly related to ovarian suppression [103]. Dienogest is another progestin that has high bioavailability and absorption rates, an antiandrogenic effect with no glucocorticoid, mineralocorticoid, and estrogenic activity [76,92].

Various studies evaluating the thromboembolic risk noted that second-generation androgenic progestins conferred the lowest increased VTE risk (2–3 fold increased risk compared to the general population) as opposed to the later generation nonandrogenic progestins (5–7 fold increase risk) [62,104–106]. Interestingly, studies investigating progesterone-only contraceptives did not seem to confer increased VTE risk [106,107]. Hence, it was suggested that the increased VTE risk of combined contraceptives seems to be related to the interplay between the estrogen and progestin component, suggesting that some progestins might actually be mitigating the increased VTE risk to some extent. The results in a number of studies may suggest that the risk of VTE associated with EE was more antagonized with the use of some progestins particularly those which are more androgenic (second generation progestins) [101,108]. This implies that factors that determine the VTE risk in a particular formulation include; the type of estrogen and its mode of administration, the type of progestin and the interplay between the two. In a recent large international prospective-controlled surveillance study (INAS-SCORE), the use of estradiol valerate with dienogest was compared to other EE containing oral contraceptives pills, and the rate of VTEs was significantly lower when compared to all patients on other OCP but similar in comparison to those on EE/levonorgestrel (the latter group having the lowest increased VTE risk) [109]. In another recent study on 80,396 women predominantly postmenopausal diagnosed with VTE, in comparison to women with no exposure, CEE and MPA was found to confer the highest VTE risk, whilst estradiol with dydrogesterone the lowest risk [71].

5.3. Testosterone treatment

Around 50% of endogenous testosterone in females is produced by the ovaries [110]. Therefore conceptually, there is an element of androgen deficiency in patients with premature ovarian insufficiency which may play a role in some of the symptoms experienced by these patients [15].

In postmenopausal females, testosterone treatment may be effective in improving sexual function [111]; however, long-term effects may not be clear [112]. In a randomized placebo-controlled trial in patients with bilateral salpingo-oophorectomy and hysterectomy, patients treated with 300ug of testosterone were found to have an improvement in the sexual activity score and treatment was well tolerated over a 24 week period [113]. Androgen replacement, in patients with Turner's syndrome having POI, was found to be safe and provided beneficial effects on body composition, neurocognition, and quality of life [114]. Treatment with androgens in patients with POI should be considered only after obtaining comprehensive-informed consent, which includes information about the emerging evidence regarding androgen treatment and its beneficial outcomes, but also information about the paucity of data regarding long-term health effects [6].

6. Follow up of patients

Clinical assessment in patients started on hormone replacement therapy should minimally occur on a yearly basis. Issues regarding compliance should be reinforced [6] and any issue related to the practical aspect of treatment should be addressed. Management should ideally take place in a multidisciplinary setting, with particular attention given to prevention of potential morbidities including bone health and cardiovascular disease [2]. No evidence associates hormone replacement therapy with a greater risk of breast cancer than the normal menstruating women, so if no other risk factors coexist, patient with POI do not need mammographic screening earlier than that recommended for the general population [2]. On a case by case basis, breast ultrasonography might be considered before commencement of HRT. Special attention should also be given to reproductive health, including contraception and fertility, together with the emotional support this entails [2].

Although the mean age of natural menopause is 50 ± 4 years [115], clinicians should embark on attempting individualized judgment regarding when and how to discontinue treatment with HRT, depending on one's individual clinical scenario [15]. Patients with a strong family history of osteoporosis or ischemic heart disease might consider treatment for a longer period of time, whereas women with a strong family history of breast cancer might consider stopping treatment at an earlier age [15].

7. Conclusion

In premenopausal females, hormonal replacement of ovarian sex steroids is truly replacing hormones that would normally be present in this age group. It is in fact paramount to prevent the morbidity and mortality associated without treatment. Recent advances and studies have shown that some of the more recently available drugs can better mimic normal ovarian physiology, in such a way to reduce menopausal symptoms, whilst maintaining bone health and cardiovascular protectivity. In this review, we have highlighted the latest approaches to replacement whilst discussing the various options available.

8. Expert opinion

Currently, one finds extensive literature available regarding hormonal replacement in postmenopausal females, and even though the place and use of HRT in this age group has gone through various phases, recently the pendulum seems to be swinging back to favoring treatment, especially in the early postmenopausal years [8]. Conversely, the place of hormone replacement in the hypogonadal females in premenopausal age group has never been disputed and lately, there have been major developments in research focusing on this area. Hormone replacement therapy in premenopausal women is deemed to be truly 'replacing' hormones which physiologically are deficient, as opposed to 'prolongation' of hormone treatment in the post-menopausal age group [6]. Therefore, inferences emerging from studies carried out in postmenopausal settings, especially in the older age group might not necessarily translate to women in a younger age group. Recent reports have addressed the specific clinical needs for this group of patients.

Furthermore, the specific drugs and formulations used as hormone replacement have been shown to impact important long-term outcomes. While traditionally oral contraceptive pills (containing ethynyl estradiol) were commonly used as a form of hormone replacement, it is now increasingly recognized that even though this might be effective in treating some of the symptoms arising from estrogen deficiency, this would not have been achieved through a physiological approach leading to poorer long-term outcomes. Studies using physiological hormone replacement via transdermal estradiol preparations had better cardiovascular [56] and bone-related outcomes [45,55] compared to standard OCP (EE containing). The route of estrogen administration has also been found to impact long-term morbidity. Transdermal estradiol was found to have more favorable effects on blood pressure control [56] endometrial thickness [72], lumbar bone mass [45], and thromboembolic risk [58,59,70].

Micronized progesterone, the more 'natural' type, is suggested to be associated with fewer side effects [79,80,82], although its effect on endometrial protection is not yet proven [15]. Synthetic progestins confer varying degrees of androgenic and thromboembolic properties. The increased thromboembolic risk of combined formulations seems to be related to the interplay between the estrogen and progestogen component, with a possibility that certain progestogens can mitigate the increased thrombotic risk to some extent [92,104–106]. Therefore, these factors must be kept in mind when choosing the type of progesterone for the individual patient.

While the role of testosterone replacement in a group of patients with early menopause has shown some benefits on cardiometabolic risk factors, quality of life, and neurocognitive functions [114] from initial studies, long-term studies confirming safety and efficacy are needed to address these queries and provide a platform for its routine use [6].

Considering the multifaceted clinical needs that such patients encounter, a multidisciplinary approach to research in this area is required emphasizing a holistic approach including input from specialties such as psychology, oncology, and fertility management. Furthermore, the etiology of these hypogonadal patients varies significantly (Ex hypogonadotropic hypogonadism, Turner's syndrome, radiotherapy or chemotherapy induced POI, etc. This variation in etiology may play a role in the various responses seen with specific treatments. The study of patient sub cohorts to understand the particular needs for treatment depending on one's etiology would be a welcoming development in this field. Patient's preference should also be taken into consideration when deciding on which treatment option to offer. Moreover, personalized prescription approaches based on women's genotype might be made available in the future, making hormone therapy prescribing safer and more effective [8].

Acknowledgments

The authors would like to thank Dr. Lianne Camilleri for her assistance in manuscript editing.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

ORCID

Miriam Giordano Imbroll http://orcid.org/0000-0002-7022-3520

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Rothman MS, Wierman ME. Female hypogonadism: evaluation of the hypothalamic–pituitary–ovarian axis. Pituitary. 2008;11 (2):163–169.
2. Sassarini J, Lumsden MA, Critchley HO. Sex hormone replacement in ovarian failure–new treatment concepts. Best Pract Res Clin Endocrinol Metab. 2015;29(1):105–114.
   • **An engaging narrative review highlighting important novel aspects of treating patients with POI.**
3. Bulun SE. Physiology and pathology of the female reproductive axis. In: Melmed S, Auchus RJ, Goldfine AB, et al., editors. Williams Textbook of Endocrinology. 14 ed. Philadelphia:Elsevier; 2020. p.622–623.
4. Conway GS. Premature ovarian failure. Br Med Bull. 2000;56 (3):643–649.
5. Vujovic S, Brincat M, Erel T, et al. EMAS position statement: managing women with premature ovarian failure. Maturitas. 2010;67 (1):91–93.
6. Webber L, Davies M, Anderson R, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926–937.
   • **Comprehensive guideline on the management of POI.**

7. Rossouw JE, Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–333.
8. Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017; 13 (4):220–231.
9. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291:1701–1712.
10. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 2012;13(5):476–486.
11. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310(13):1353–1368.
12. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297(13):1465–1477.
13. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016;374(13):1221–1231.
14. Miller VM, Naftolin F, Asthana S, et al. The Kronos early estrogen prevention study (KEEPS): what have we learned? Menopause. 2019;26(9):1071–1084.
15. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril. 2016;106(7):1588–1599.
    - **Noteworthy narrative review on the multiple health risks associated with premature ovarian insufficiency and treatment options.**
16. Faubion SS, Kuhle CL, Shuster LT, et al. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015;18(4):483–491.
17. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1(7):767–776.
18. Tao XY, Zuo AZ, Wang JQ, et al. Effect of primary ovarian insufficiency and early natural menopause on mortality: a meta-analysis. Climacteric. 2016;19(1):27–36.
19. Wu X, Cai H, Kallianpur A, et al. Age at menarche and natural menopause and number of reproductive years in association with mortality: results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. PloS One. 2014;9(8): e103673.
20. Hong JS, Yi SW, Kang HC, et al. Age at menopause and cause-specific mortality in South Korean women: kangwha Cohort Study. Maturitas. 2007;56(4):411–419.
21. Amagai Y, Ishikawa S, Gotoh T, et al. Age at menopause and mortality in Japan: the Jichi Medical School cohort study. J Epidemiol. 2006;16(4):161–166.
22. Ossewaarde ME, Bots ML, Verbeek AL, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005;16(4):556–562.
23. Kannel WB, Hjortland MC, McNamara PM, et al. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med. 1976;85(4):447–452.
24. Scarborough PA, Bhatnagar P, Wickramasinghe K, et al. Coronary heart disease statistics 2010 edition. British Health Foundation Health Promotion research group, Department of Public Health, University of Oxford. 2010 Nov 27.
25. Lobo RA. Surgical menopause and cardiovascular risks. Menopause. 2007;14(3):562–566.
26. Løkkegaard E, Jovanovic Z, Heitmann BL, et al. The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. Maturitas. 2006 20;53(2):226–233.
27. Yorgun H, Tokgözoğlu L, Canpolat U, et al. The cardiovascular effects of premature ovarian failure. Int J Cardiol. 2013;168 (1):506–510.
28. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009;54 (25):2366–2373.
29. Joakimsen O, Bønaa KH, Stensland-Bugge E, et al. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: the Tromsø Study. J Clin Epidemiol. 2000;53(5):525–530.
30. Elsheikh M, Bird R, Casadei B, et al. The effect of hormone replacement therapy on cardiovascular hemodynamics in women with Turner's syndrome. J Clin Endocrinol Metab. 2000;85(2):614–618.
31. Kalantaridou SN, Naka KK, Bechlioulis A, et al. Premature ovarian failure, endothelial dysfunction and estrogen–progestogen replacement. Trends Endocrinol Metab. 2006;17(3):101–109.
32. Freriks K, Timmermans J, Beerendonk CC, et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. J Clin Endocrinol Metab. 2011;96(9):E1517–E1526.
33. Bachelot A, Rouxel A, Massin N, et al. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. Eur J Endocrinol. 2009;161(1):179–187.
34. Popat VB, Calis KA, Vanderhoof VH, et al. Bone mineral density in estrogen-deficient young women. J Clin Endocrinol Metab. 2009;94 (7):2277–2283.
35. Han TS, Goswami D, Trikudanathan S, et al. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 2008;159(2):179–186.
36. Gallagher JC. Effect of early menopause on bone mineral density and fractures. Menopause. 2007;14(3):567–571.
37. van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. Osteoporos Int. 2003;14 (6):525–530.
38. Bakalov VK, Axelrod L, Baron J, et al. Selective reduction in cortical bone mineral density in turner syndrome independent of ovarian hormone deficiency. J Clin Endocrinol Metab. 2003;88 (12):5717–5722.
39. Conway GS, Kaltsas G, Patel A, et al. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;65(2):337–341.
40. Nelson LM. Primary ovarian insufficiency. N Engl J Med. 2009;360 (6):606–614.
41. Ohta H, Sugimoto I, Masuda A, et al. Decreased bone mineral density associated with early menopause progresses for at least ten years: cross-sectional comparisons between early and normal menopausal women. Bone. 1996;18(3):227–231.
42. Bours SP, van Geel TA, Geusens PP, et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. J Clin Endocrinol Metab. 2011;96 (5):1360–1367.
43. Challoumas D, Cobbold C, Dimitrakakis G. Effects of calcium intake on the cardiovascular system in postmenopausal women. Atherosclerosis. 2013;231(1):1–7.
44. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23–57.
45. Crofton PM, Evans N, Bath LE, et al. Physiological versus standard sex steroid replacement in young women with premature ovarian

failure: effects on bone mass acquisition and turnover. Clin Endocrinol. 2010;73(6):707–714.
•• **An open-labelled randomised controlled crossover trial comparing the effect of physiological hormone replacement versus standard hormone replacement specifically in patients with premature ovarian insufficiency.**
46. Prior JC, Vigna YM, Wark JD, et al. Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. J Bone Miner Res. 1997;12(11):1851–1863.
47. Lindsay RD, Hart DM, Forrest C, et al. Prevention of spinal osteoporosis in oophorectomised women. Lancet. 1980;316 (8205):1151–1154.
48. Morrison JH, Brinton RD, Schmidt PJ, et al. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. J Neurosci. 2006;26(41):10332–10348.
49. Maki PM, Resnick SM. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. Neuroimage. 2001;14(4):789–801.
50. Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality following early bilateral oophorectomy. Menopause. 2009;16(1):15.
51. Rocca WA, Grossardt BR, De Andrade M, et al. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7 (10):821–828.
52. Mann E, Singer D, Pitkin J, et al. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. Climacteric. 2012 Oct 1;15(5):481–489.
53. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. J Psychosom Obstet Gynaecol. 2000;21 (3):167–174.
54. Smith JA, Vitale S, Reed GF, et al. Dry eye signs and symptoms in women with premature ovarian failure. Arch Ophthalmol. 2004;122 (2):151–156.
55. Cartwright B, Robinson J, Seed PT, et al. Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. J Clin Endocrinol Metab. 2016;101(9):3497–3505.
•• **An open randomized trial comparing HRT and COCP on the effect of bone density in patients with premature ovarian insufficiency.**
56. Langrish JP, Mills NL, Bath LE, et al. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. Hypertension. 2009;53(5):805–811.
•• **An open-label, randomised, controlled crossover trial investigating the effect of physiological hormone replacement versus standard hormone replacement specifically in patients with premature ovarian insufficiency.**
57. Mohammed K, Abu Dabrh AM, Benkhadra K, et al. Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100 (11):4012–4020.
58. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003;362(9382):428–432.
59. Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008;336 (7655):1227–1231.
60. Hemelaar M, van der Mooren MJ, Rad M, et al. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review. Fertil Steril. 2008;90(3):642–672.
61. Renoux C, Dell'Aniello S, Garbe E, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ. 2010;340:c2519.
62. Hugon-Rodin J, Gompel A, Plu-Bureau G. Mechanisms in endocrinology: epidemiology of hormonal contraceptives-related venous thromboembolism. Eur J Endocrinol. 2014;171(6):R221–R230.
63. Sitruk-Ware R, Nath A. Characteristics and metabolic effects of estrogen and progestins contained in oral contraceptive pills. Best Pract Res Clin Endocrinol Metab. 2013;27(1):13–24.
64. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005;8(sup1):3–63.
65. Kuhnz W, Gansau C, Mahler M. Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17 beta-estradiol. Arzneimittelforschung. 1993;43(9):966–973.
66. Kuhnz W, Blode H, Zimmermann H. Pharmacokinetics of exogenous natural and synthetic estrogens and antiestrogens. In: Oettel M, Schillinger E, editors. Handbook of Experimental Pharmacology, Estrogens and Antiestrogens II. Berlin: Springer Verlag; 1999. p. 261–322.
67. Ruggiero RJ, Likis FE. Estrogen: physiology, pharmacology, and formulations for replacement therapy. J Midwifery Womens Health. 2002;47(3):130–138.
68. Düsterberg B, Nishino Y. Pharmacokinetic and pharmacological features of oestradiol valerate. Maturitas. 1982;4(4):315–324.
69. Zeun S, Lu M, Uddin A. et al. Pharmacokinetics of an oral contraceptive containing oestradiol valerate and dienogest. Eur J Contracep Repr. 2009;14(3):221–232.
70. Canonico M, Oger E, Plu-Bureau G, et al. Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–845.
71. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.
72. O'donnell R, Warner P, Lee RJ, et al. Physiological sex steroid replacement in premature ovarian failure: randomized crossover trial of effect on uterine volume, endometrial thickness and blood flow, compared with a standard regimen. Hum Reprod. 2012;27 (4):1130–1138.
73. Roberts H, Hickey M, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia: A Cochrane review summary. Maturitas. 2014;77(1):4–6.
74. Schnatz PF. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24 (7):728–753.
75. Asi N, Mohammed K, Haydour Q, et al. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016;5(1):121.
76. Bińkowska M, Woroń J. Progestogens in menopausal hormone therapy. Menopause Rev. 2015;14(2):134–143.
77. Nahoul K, Dehennin L, Scholler R. Radioimmunoassay of plasma progesterone after oral administration of micronized progesterone. J Steroid Biochem. 1987;26(2):241–249.
78. Mirkin S, Amadio JM, Bernick BA, et al. 17β-Estradiol and natural progesterone for menopausal hormone therapy: REPLENISH phase 3 study design of a combination capsule and evidence review. Maturitas. 2015;81(1):28–35.
79. Mittal M, Savvas M, Arya R, et al. A randomised controlled trial comparing the effects of micronized progesterone to medroxyprogesterone acetate on cardiovascular health, lipid metabolism and the coagulation cascade in women with premature ovarian insufficiency: study protocol and review of the literature. Menopause Int. 2013;19(3):127–132.
80. Mueck A. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012;15(1):11–17.
81. Fitzpatrick LA, Pace C, Wiita B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. J Womens Health Gend Based Med. 2000;9(4):381–387.
82. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med. 2014;161(4):249–260.

83. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. Climacteric. 2016;19 (4):316–328.
84. Stanczyk FZ. Treatment of postmenopausal women with topical progesterone creams and gels: are they effective? Climacteric. 2014;17(sup2):8–11.
85. Elshafie MA, Ewies AA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. J Obstetrics Gynaecol. 2007;27(7):655–659.
86. Wildemeersch D, Andrade A, Goldstuck N. Femilis® 60 Levonorgestrel-Releasing Intrauterine System–A Review of 10 Years of Clinical Experience. Clin Med Insights Reprod Health. 2016;10:19–27.
87. Wildemeersch D, Janssens D, Weyers S. Continuous combined parenteral estrogen substitution and intrauterine progestogen delivery: the ideal HST combination? Maturitas. 2005;51(2):207–214.
88. Wildemeersch D. Why perimenopausal women should consider to use a levonorgestrel intrauterine system. Gynecological Endocrinol. 2016;32(8):659–661.
89. Mueck AO, Seeger H, Bühling KJ. Use of dydrogesterone in hormone replacement therapy. Maturitas. 2009;65:S51–S60.
90. Popat VB, Calis KA, Kalantaridou SN, et al. Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. J Clin Endocrinol Metab. 2014;99(9):3418–3426.
91. Gibbons WE, Moyer DL, Lobo RA, et al. Biochemical and histologic effects of sequential estrogen/progestin therapy on the endometrium of postmenopausal women. Am J Obstet Gynecol. 1986;154 (2):456–461.
92. Sitruk-Ware R, Nath A. The use of newer progestins for contraception. Contraception. 2010;82(5):410–417.
93. Stanczyk FZ, Roy S. Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. Contraception. 1990;42(1):67–96.
94. Klehr-Bathmann I, Kuhl H. Formation of ethinylestradiol in postmenopausal women during continuous treatment with a combination of estradiol, estriol and norethisterone acetate. Maturitas. 1995;21 (3):245–250.
95. Reed MJ, Ross MS, Lai LC, et al. In vivo conversion of norethisterone to ethynyloestradiol in perimenopausal women. J Steroid Biochem Mol Biol. 1990;37(2):301–303.
96. Sitruk-Ware R. New hormonal therapies and regimens in the postmenopause: routes of administration and timing of initiation. Climacteric. 2007;10(5):358–370.
97. Sturdee DW, Van de Weijer P, von Holst T. Endometrial safety of a transdermal sequential estradiol–levonorgestrel combination. Climacteric. 2002;5(2):170–177.
98. Wiseman LR, McTavish D. Transdermal estradiol/norethisterone. Drugs Aging. 1994;4(3):238–256.
99. Lindgren R, Risberg B, Hammar M, et al. Endometrial effects of transdermal estradiol/norethisterone acetate. Maturitas. 1992;15(1):71–78.
100. Plu-Bureau G, Maitrot-Mantelet L, Hugon-Rodin J, et al. Hormonal contraceptives and venous thromboembolism: an epidemiological update. Best Pract Res Clin Endocrinol Metab. 2013;27(1):25–34.
101. Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ. 2013;347: f5298.
102. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception. 2000;62(1):29–38.
103. Gerlinger C, Heithecker R. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis. 2002;69(4 Suppl):2–15.
104. Poulter NR, Chang CL, Farley TM, et al. Contraceptives: results of international multicentre case-control study. Lancet. 1995;346:1575–1582.
105. Spitzer WO, Lewis MA, Heinemann LA, et al. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. BMJ. 1996;312 (7023):83–88.
106. Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: danish cohort study, 2001-9. BMJ. 2011;343:d6423.
107. Tepper NK, Whiteman MK, Marchbanks PA, et al. Progestin-only contraception and thromboembolism: a systematic review. Contraception. 2016;94(6):678–700.
108. Fruzzetti F, Cagnacci A. Venous thrombosis and hormonal contraception: what's new with estradiol-based hormonal contraceptives? Open Access J Contracept. 2018;9:75–79.
109. Heinemann K, Franke C, Moehner S, et al. Cardiovascular safety in users of different combined oral contraceptives–Final results from the INAS-SCORE study. Eur J Contracep Repr. 2018;23:40.
110. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. J Clin Endocrinol Metab. 1974;39(2):340–346.
111. Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climacteric. 2010;13(2):121–131.
112. Tamimi RM, Hankinson SE, Chen WY, et al. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med. 2006;166(14):1483–1489.
113. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab. 2005;90(9):5226–5233.
114. Zuckerman-Levin N, Frolova-Bishara T, Militianu D, et al. Androgen replacement therapy in Turner syndrome: a pilot study. J Clin Endocrinol Metab. 2009;94(12):4820–4827.
115. van Noord PA, Dubas JS, Dorland M, et al. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. Fertil Steril. 1997;68 (1):95–102.