Mini Review

HORMONE RESEARCH IN PÆDIATRICS

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Use of Hormone Replacement in Females with Endocrine Disorders

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Abstract
Hormone replacement therapy (HRT) is necessary in adolescents with primary ovarian insufficiency (POI) in order to avoid estrogen deficiency. The goal of this minirewiew is to present the different types of estrogens (17β-estradiol, estradiol valerate, ethinyl estradiol, and combined equine estrogens) as well as the different types of progestins available. In order to choose among the different types of HRTs, the features of each regimen are being discussed as well as their risks and their respective benefits. The differences between oral combined contraceptive pills and a dissociated regimen containing estrogen and progestins are emphasized. The different effects of HRTs, mainly on feminization, growth spurt, bone mass as well as cardiovascular risk, and the follow-up of these young patients are presented. HRT in adolescents and young adults with estrogen deficiency is necessary and should be continued until the age of natural menopause. Studies have so far essentially included children or adolescents with Turner syndrome. Therefore, studies on HRT including patients with POI and a normal karyotype are necessary.
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A 17-year-old patient was referred because of secondary amenorrhea. Her first menses occurred at the age of 13 years, they have occurred regularly every 30 days for 3 years and stopped when she was 16 years old. Her weight was 55 kg and her height 1.70 m. Her hormonal levels, checked twice, showed elevated gonadotropins and low estradiol (E2) levels. Her last hormonal evaluation was follicle-stimulating hormone (50 IU/L [normal 2–10]), luteinizing hormone (30 IU/L [normal 2–10]), and E2 = 30 pmol/L (normal: 70–120). She had no history of surgery. She had not received any chemotherapy or radiotherapy. There was no familial history of primary ovarian insufficiency (POI). Her karyotype was 46,XX, and no fragile X mental retardation 1 gene (*FMR1*) premutation was identified; 21-hydroxylase antibodies were negative. She had been smoking for the previous 4 months and was at the time smoking 5 cigarettes per day.

Below we are going to address the following questions: What type of hormone replacement therapy can be prescribed to this adolescent? What doses and what route are optimal? What are the goals of this treatment? What follow-up is necessary? For how long should this treatment be prescribed?

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Table 1. Different routes and dosages of estrogens

17β-E2	–Oral: 1, 1.5, 2 mg per pill once a day –TD patches: 25, 50, 75, 100 μg per day twice weekly –TD gel: 0.52, 0.75, 1.5 mg per spray daily –Vaginal ring: 0.05–0.1 mg/day –Oral: 1.5 mg in combined pill with nomegestrol acetate
EV	–Oral: 1, 2, 3 mg per pill in COCP with dienogest –Oral: 1 and 2 mg per pill with progestins in noncontraceptive pill –Intramuscular 10–20 mg every 4 weeks
EE	–Oral: 10–50 μg per COCP with different progestins –TD patches with gestodene 13–20 μg –Vaginal contraceptive rings with etonogestrel 15 μg
CEE	–Oral: 0.3, 0.625, 0.9, 1.25, 2.5 mg

17β-E2, 17β-estradiol; EV, estradiol valerate; EE, ethinyl estradiol; CEE, conjugated ethinyl estradiol.

Table 2. Different origins of progestins

Derived from progesterone	Derived from testosterone
17-OH progesterone	Estranes
Medroxyprogesterone acetate	Norethisterone (1st generation)
Cyproterone acetate	Dienogest
Chlormadinone acetate	Gonanes
Megestrol acetate	Norgestrel (2nd generation)
Drospirenone	Desogestrel (etonogestrel) (3rd generation)
19-Norprogesterone	Gestodene (3rd generation)
Nestorone	Norgestimate (norelgestromin) (3rd generation)
Nomegestrol acetate	
Trimegestone	

The Different Types of Estrogens and Progestins

Our patient has POI and therefore needs hormone replacement therapy (HRT) containing estrogens in order to compensate her estrogen deficiency. Estrogens can be administered as 17β-E2, estradiol valerate (EV), conjugated estrogens, or ethinyl estradiol (EE) (Table 1). E2 is the endogenous estrogen. In Europe, it is available in the form of a pill, transdermal (TD) patches and gel. In some countries E2 is available as a vaginal ring. EV is a synthetic prodrug of 17β-E2. After oral administration it is rapidly hydrolyzed to E2 by intestinal enzymes. Conjugated equine estrogens (CEE) are extracted from equine urine and contain more than 100 estrogenic compounds of different potencies [1]. The main estrogens contained in CEE are E2, estrone (E1) and estriol (E3). CEE is used mainly in the United States for postmenopausal treatment. Historically, it has been the most widely used form of estrogen for the induction of puberty in the United States. EE is a synthetic estrogen. It is also named 17α-E2 It was first synthetized in Berlin in 1938 and was commercialized in 1943. It is the main estrogen used in combined oral contraceptive pills (COCPs). Formulations of COCPs have dramatically changed over the past 50 years, as the EE concentration has decreased in order to reduce the risk of venous thromboembolism [2]. The most recent contraceptive pills contain 10–35 μg of EE instead of an equivalent of 100–150 μg in the initial pills which were available during the 1960s. Some COCPs containing EV or 17β-E2 have been available for some years [3]. EE is available not only in oral COCPs but in contraceptive patches as well as in contraceptive rings.

As our patient has a uterus, progesterone or progestin needs to be associated with estrogens, in order to avoid endometrial hyperplasia and potential endometrial carcinoma [4]. Studies performed in postmenopausal women, on hormonal menopausal replacement therapy, have shown that at least 12 days of progestin per month are necessary to avoid the risk of endometrial carcinoma [3]. However, data are extrapolated from postmenopausal women since no data have been available so far in young patients using HRT. Natural progesterone can be administered orally or transvaginally. Rings containing natural progesterone are used for contraception in breastfeeding women [5]. Vaginal gel (8% of progesterone) is used for infertility treatments [6]. Progestins are

Table 3. Different routes and dosages of progesterone and progestins

Progesterone (P4)	–Oral: 100 and 200 mg per pill –Vaginal ring: 10 mg/day –Vaginal gel: 8%
Dydrogesterone	–Oral: 10 mg per pill
Levonorgestrel	–Oral: 0.03 mg (microprogestin pill) –Oral: 1.5 mg (emergency pill) –IUD: 52 or 13.5 mg –Implant
Desogestrel	–Oral: 75 μg per pill
Etonogestrel	–Implant: 68 mg
Medroxyprogesterone acetate	–Injectable every 3 months: 150 mg –Oral
Combined with estrogens	
1st, 2nd, 3rd and new generation progestins	–Oral in combined pill with EE, E2, EV –Transvaginal in ring with EE –Patches with EE

synthetic molecules. They can be classified according to their origin, whether they are derived from progesterone or testosterone [7] (Table 2). Among progestins derived from progesterone, some are derived from 17-OH progesterone and some from 19-norprogesterone. Progestins derived from testosterone are levonorgestrel, desogestrel, gestodene, and norgestimate. They are the most frequent progestins contained in combined contraceptive pills. Progestins are also available in microprogestin pills. These pills are devoid of estrogens. Medroxyprogesterone is used as tablets in the United States. Progestins are also available as implants. Furthermore, they are contained in some intrauterine device (IUD). Finally, injectable progestins are available as contraceptives, such as medroxyprogesterone acetate given every 3 months (Table 3).

The Different Routes and Doses of Estrogen Administration

Concerning the route of E2 administration, pharmacokinetics and pharmacodynamics of oral and TD 17β-E2 have been evaluated mainly in girls and adolescents with Turner syndrome (TS). Taboada et al. [8] recruited 10 girls with TS, mean age (±SE) 17.7 ± 0.4 years, and 20 normally menstruating controls. TS were randomized 2 weeks each to oral 0.5 mg and biweekly TD E2 (37.5 μg) with 2 weeks' washout in between or oral 2.0 mg and TD E2 (75 μg). E2, E1, and a recombinant cell bioassay were used to evaluate steroid serum concentration as well as bioactive hormonal levels. The high-dose (75 μg) TD E2 group concentrations were the closest to serum levels of normally menstruating girls. A longer duration of treatment has been evaluated by the same group [9]. Forty girls with TS, with a mean age of 16.7 ± 1.7 years, were randomized to 17β-E2 orally or 17β-E2 TD [9]. Doses were titrated using mean E2 concentrations of normally menstruating girls. The mean oral dose was 2 mg, and the TD dose was 100 μg. The range of doses of E2 is, however, not mentioned in the paper. Evaluation was performed after 6 and 12 months on HRT. Total estrogen exposure was significantly higher after oral 17β-E2. The potential impact of this higher exposure in the long term remains unknown. This study illustrates that TD 17β-E2 is more physiological than oral 17β-E2.

In the same study, metabolic effects of oral versus TD 17β-E2 have been studied [9]. Changes in body composition and lipid oxidation were evaluated after 6 and 12 months of treatment. After 12 months, the route of delivery of 17β-E2 did not affect body composition, bone mineral content accrual, lipoprotein profiles, markers of inflammation, blood glucose, and insulin concentrations.

Studies performed in postmenopausal women and women with hypopituitarism have raised some concerns about the impact of the oral route of 17β-E2 on IGF-1

levels. However, Mauras et al. [10] tested the effects of oral versus TD estrogen in growth hormone-treated girls with TS. Eleven girls, mean age (±SE) 13.4 ± 0.5 years, were randomized and received 17β-E2 orally (0.5, 1, and 2 mg for 2 weeks each) and 17β-E2 TD (25, 37.5, and 50 μg for 2 weeks each). No clinically significant change was observed in this study in IGF-1 concentrations after either form of estrogen. Although the duration of each treatment was short, this study illustrates the fact that the route of 17β-E2 administration does not seem to have a major impact on IGF-1 concentrations.

A major issue concerning estrogens relies on their impact on coagulation factors and therefore thromboembolic diseases. When administered orally, estrogens are metabolized by the liver; this phenomenon is called the hepatic first pass. Oral estrogens increase several coagulation factors and hepatic proteins such as angiotensinogen or sex hormone binding globulin (SHBG). SHBG represents the best marker in order to evaluate the hepatic impact of an estrogen molecule [11]. EE has a stronger hepatic impact than E2 as it is not metabolized in the liver because of its ethinyl group. Furthermore, EE is involved in several hepatic passes, and it does not bind to SHBG. Therefore, its bioavailability is higher than the bioavailability of E2. Concerning the route of administration of E2, oral versus TD E2 have been tested in postmenopausal women, in order to avoid interference with endogenous E2 [12]. The ESTHER trial has shown that TD E2 has less impact on the liver than oral E2 and induces fewer thromboembolic events [12]. Concerning the route of administration of EE, Sitruk-Ware et al. [13] compared a daily dose of 15 μg of EE delivered by oral tablet or vaginal ring for 21 days in postmenopausal women. Angiotensinogen increased similarly with oral or vaginal delivery. This study illustrates the fact that the transvaginal route for EE has a similar impact on hemostatic factors and hepatic proteins than oral EE.

Separate Regimen or Combined HRT in Young Patients

Estrogens and progestins can be administered in a separate regimen or can be combined. Guidelines concerning the treatment of women with POI have recently been published by the European Society of Human Reproduction (ESHRE) [14]. When estrogens and progestins are given separately, estrogens are usually administered from day 1 to day 25 of the month and progestins from day 12–14 to day 25 in order to recreate the physiology of the menstrual cycle. In this sequential regimen, no treatment is given between day 25 and the end of the month. Withdrawal bleedings usually occur within a few days after stopping the treatment. The main goal of HRT is to substitute estrogen deficiency and so to obtain physiological serum levels of E2. In hypogonadal adolescents, daily doses of 2–3 mg of oral E2 or biweekly 50–100 μg E2 patches have been tested [8, 9]. As our patient has already reached puberty, there is no need to progressively increase the dose of estrogens. Nowadays, CEE are rarely used during puberty in Europe. The E2 vaginal ring delivers a dose of E2 for local estrogen therapy. It is only indicated for women after the menopause [15], and its dosage is too low for HRT in young patients.

Concerning progesterone, the average daily dose tested in HRT is 200 mg of natural progesterone or 20 mg of dydrogesterone (Table 3) [14].

Although TD 17β-E2 with oral progesterone probably represents the most physiological route for HRT, compliance is often an issue, especially in adolescents. They may prefer to take a combined daily pill. Combined treatments are contraceptives where the progestin contained in the pill has strong antigonadotropic effects. In these combinations, estrogens are present in order to compensate for estrogen deficiency and to regulate vaginal bleedings [16]. However, some combined treatments are not contraceptive since the progestin contained in the pill is not antigonadotropic. Most of them contain 17β-E2 or EV. Their marketing was initially intended for postmenopausal women, and this point should be explained to an adolescent when prescribing this type of molecule.

The choice between these two treatments should rely on the contraceptive need. Indeed, although fertility is greatly reduced in patients with POI, studies have shown a rate of spontaneous pregnancies reaching 4–6% [17]. Therefore, when contraception is needed, combined contraception containing estrogens and progestins represents the best choice. Implants or IUD, which are currently available, do not contain estrogens; therefore, they should not be given alone to adolescents or women with POI. Combined contraception is available as a pill, a patch, or a vaginal ring. Obviously, the latest route can only be offered to adolescents with previous sexual activity. COCPs are classified into generations depending on the type of progestin contained in the pill. First-generation pills contain norethisterone acetate, lynestrenol, and norethynodrel. Very few of them are currently used. Most of the contraceptive pills available are second-, third-, or new-generation pills. Second-generation pills contain norgestrel or levonorgestrel. Third-generation COCPs contain dienogest, gestodene, or

norgestimate. In the past years, some pills have been developed containing "new" progestins, such as drospirenone, chlormadinone acetate, and dienogest [18]. Over the years, progestins with less androgenic effects have been used in contraceptive pills. However, all COCPs have antiandrogenic properties due to the antigonadotropic effect of the progestin and due to the elevation of SHBG induced by the estrogenic component of the COCP.

When prescribing a combined contraception, the balance between benefits and risks should be evaluated. The US Medical Eligibility Criteria for Contraceptive Use (US MEC) comprises recommendations for the use of specific contraceptive methods by women and men who have certain characteristics or medical conditions. These recommendations for health-care providers were updated and have recently been published [18]. First of all, the familial history of venous thromboembolism (VTE) should be established. As recommended by the World Health Organization, when initiating COCPs, clinical examination should include blood pressure measurement [18]. No gynecological examination is necessary. Many controversies concerning contraceptive pills have arisen, especially in England in 1995 [19]. All combined oral contraceptives are associated with an increased risk of VTE. However, their absolute risk remains low. The VTE risk depends on the estrogen concentration as well as the type of progestin contained in COCP. The thromboembolic risk is higher when EE is higher than 35 μg [20]. It is not statistically different between pills containing less than 35 μg EE [20]. Data from studies evaluating thromboembolic events in women taking pills containing EV or 17β-E2 have not been available so far. According to the progestin, the absolute thromboembolic risk reaches 4–6/10,000 women-year with pills containing second-generation progestins and 6–8/10,000 women-year with third-generation progestins or new progestins [21]. In other words, the VTE risk with 30–35 μg EE and gestodene, desogestrel, cyproterone acetate, and drospirenone is similar. It is 50–80% higher than with levonorgestrel [20]. The venous risk with vaginal rings and patches containing EE is equivalent to third-generation progestins. Lidegaard et al. [22] studied a national Danish cohort of women on COCP between 1995 and 2005. In this study, compared to nonusers, the rate of VTE in current users decreased with the duration of use (<1 year 4.17, 95% confidence interval [CI] 3.73–4.66, 1–4 years 2.98, 95% CI 2.73–3.26, and >4 years 2.76, 95% CI 2.53–3.02; $p < 0.001$) [22]. These data have been confirmed in a population case-control study from the Netherlands called MEGA study [23]. This increased risk during the first year, called starter effect, is due to the fact that when starting the COCP, coagulation abnormalities may be revealed, the most frequent ones being Leiden and prothrombin mutations [24]. Interestingly, the absolute thromboembolic risk during pregnancy ranges from 5–20/10,000 to 40–65/10,000 during the postpartum period [25]. Therefore, thromboembolic risks of COCPs should be put in perspective with the risk of unwanted pregnancies.

The arterial risk, including stroke and myocardial infarction, is extremely low in adolescents and young women. A recent Cochrane review has included observational studies of women aged 18–50 years and has compared the arterial risk between users and nonusers of COCPs [26]. This network meta-analysis showed that the risk of myocardial infarction or ischemic stroke was only increased in women using COCPs containing ≥50 μg of EE. Therefore, although our patient was smoking, COCPs containing 30 μg or less seem to be safe.

Furthermore, when choosing the type of HRT, noncontraceptive benefits of the COCPs should be taken into account. For instance, if the adolescent does not wish to have menses on a monthly basis, extended regimens can be advised [27]. In such cases, COCPs are given continuously for 3–6 months. Durations of more than 6 months usually induce spotting. Among the noncontraceptive benefits, most COCPs decrease menstrual flow and reduce dysmenorrhea [28]. Another possibility in order to avoid menses, even in adolescents, is to use an IUD containing levonorgestrel, as small IUDs are now available. In a small study, 60% of adolescents with this type of IUD achieved amenorrhea, including adolescent girls with heavy menstrual bleeding [29]. However, estrogens need to be added in case of POI, in order to compensate for the lack of estrogens.

Estrogens may only be administered alone, in the absence of progesterone or progestins, in adolescents or women without a uterus. These cases are mainly patients with complete androgen insensitivity syndrome after their gonadectomy [30]. Depending on the timing of the diagnosis and the surgery, estrogen replacement treatment may be introduced in order to induce breast development and puberty or after endogenous breast development.

Goals of HRT in Young Adolescents

The goals of HRT in adolescents are to develop and maintain secondary sexual characteristics, mainly breast development and feminization, to induce growth spurt, and to maintain bone mass.

HRT also decreases hot flushes although they are not always present in young patients with POI. If the patient is symptomatic on sequential treatment, a continuous regimen can be prescribed, in order to avoid hot flushes and night sweats during the week without HRT. No study in POI patients has so far evaluated the differences between a continuous regimen of estrogen versus a sequential treatment given for 3 weeks per month.

Bone health represents a major issue for adolescents. Research has shown that the highest velocity of bone mass accrual occurs 1 year before menarche and after the first 3 years of menses [31]. POI has been shown to be associated with decreased bone health, especially in the first years after diagnosis [32]. Although no data are available on the risk of fractures, estrogen treatment should be given in order to reduce the risk of osteoporosis, essentially in the spine region which is very sensitive to estrogens.

Furthermore, HRT protects against cardiovascular risk. Epidemiological studies performed in the Netherlands have shown that estrogen deficiency before the age of 40 is related to an increased cardiovascular risk [33]. In the Mayo Clinic cohort, increased mortality was seen mainly in women who had not taken estrogens up to the age of 45 years. It is important to distinguish cardiovascular effects of HRT in young patients from cardiovascular impacts of HRT described in postmenopausal women. Indeed, although HRT in both cases contain estrogen and progestin, the impacts of estrogens on vessels are different depending on the population treated. This illustrates the "timing theory of estrogens." They are beneficial in young patients and deleterious in women with atherosclerosis [34]. A very recent study [35] has compared the cardiovascular risk profile between women above 45 years of age previously diagnosed with POI and premenopausal controls of a comparable age. Women with POI had an increased waist circumference and a trend towards increased hypertension. However, no sign of increased subclinical atherosclerosis was observed in women with POI.

The impact of HRT on cognitive function, after long-term use in adolescents with POI, is currently not known. Data are only available in women who had bilateral oophorectomy before the age of natural menopause. Estrogen deficiency occurring too soon in these women is associated with an increased prevalence of dementia [36]. These data need to be confirmed in larger studies.

In the literature, so far, only 3 female cases with a loss of function mutation in the estrogen receptor ERα encoded by *ERS1* gene have been reported [37, 38]. They had extremely high E2 levels, and because of their estrogen resistance, they all lacked an estrogen-induced growth spurt at time of puberty. Their bone age was delayed, and bone density was low. Data on long-term effects of total estrogen deficiency are not available, as the patients are still too young. However, it will be interesting to follow these patients in order to illustrate the impacts of a complete estrogen deficiency on brain and cardiovascular system.

Follow-Up of HRT in Adolescents and Young Women

The duration of HRT is recommended up to the age of physiological menopause, on average at 50–51 years [14]. It is suggested that POI patients on HRT are followed up once a year. The main goal of each visit is to check compliance. In the follow-up of POI patients on HRT, E2 or follicle-stimulating hormone monitoring is not helpful as fluctuations may occur.

Several studies have evaluated the risk of breast cancer in women with POI. Wu et al. [39] have shown a decreased risk of breast cancer in POI women. Furthermore, Bösze et al. [40] have followed women with POI for 40 years. The risk of breast cancer is not increased in women taking HRT before the natural age of menopause. Therefore, mammography or breast ultrasound should not be performed on a routine basis before the age of 45. They should be performed earlier, but only in patients with familial cases of breast cancer diagnosed before the age of 50 in at least 2 first-degree relatives [14].

Bone evaluation by dual-energy x-ray absorptiometry is recommended in young patients when the diagnosis of POI has been established and then every 5 years [14]. Dual-energy x-ray absorptiometry can be used to evaluate HRT compliance and motivate patients to follow their treatment. As our patient was smoking, she definitely needs to be advised to stop smoking, since tobacco alters bone density. So far, only 1 study in a randomized controlled trial has compared the effect of HRT versus COCPs on bone mineral density in premature ovarian failure [41]. The COCP contained 30 μg of EE and 150 μg of levonorgestrel taken daily for 21 days followed by a 7-day break (Microgynon) and the HRT was Nuvelle® containing 2 mg of E2 daily and 75 μg of levonorgestrel for 12 days a month [41]. The results suggest that HRT is superior to COCP in increasing bone density. However, the dropout rate was very high in this study, with only 61% of women completing the trial.

Monitoring the ovarian size and the number of follicles is not relevant in the follow-up of such patients, since

ovarian follicular activity is found in the majority of women with POI [42]. Even in patients with POI and primary amenorrhea, ultrasound identified follicles in 38% of them [43]. Uterine parameters have been studied by O'Donnell et al. [44]. They performed a randomized crossover study in 34 adult women, where the primary end points were uterine size and endometrial thickness. Women were for 12 months on 30 μg of oral EE and 1.5 mg of norethisterone followed by 12 months of 4-week cycles of TD E2 and vaginal progesterone or vice versa. The doses of TD E2 patches were 100 μg during the first week and 150 μg from week 2 to week 4 of treatment. Progesterone was administered using pessaries of 200 mg per day. There was a greater estimated endometrial thickness using TD E2 (4.8 mm) compared to that with the contraceptive pill (3 mm), with an estimated difference of 1.8 mm (95% CI 0.7–2.8; $p = 0.002$). The mean volume of the uterus was not statistically different between the two regimens. The impact of HRT on endometrial thickness is an issue mainly during egg donation cycles [45].

HRT in order to Induce Puberty

If our patient was 17 but had no breast development and primary amenorrhea, the goal of HRT would initially be to induce breast development. Recommendations have been established by several groups working on TS [46, 47] and by ESHRE [14]. Estrogens should initially be administered alone, and the dosage should be increased progressively, in order to mimic natural puberty. The preferred route of administration is TD, and the type of estrogen is 17β-E2. CEE or combined COCP is currently not recommended to induce breast development as the estrogen concentration is probably too high to start with. When starting estrogen at a mean age of 12 years, the recommended dose is one tenth to one eighth of the adult replacement dose. However, if the treatment is started at age 17, the initial dose of estrogen can be higher, i.e. between 0.5 and 1 mg of 17β-E2. In theory, progestins should be administered at least 2 years after beginning with estrogens or when spotting occurs. In adolescents, progestins can be added 1 instead of 2 years after starting estrogen. This is, however, based on expert practice and not on randomized studies [48].

When the diagnosis of hypogonadism is made in childhood, the optimal age at which to start has been the subject of controversy, i.e. between 12 and 13 or higher. Different societies actually recommend starting estrogen at the age of 12. When starting E2 around the age of 12, the initial dose of estrogen is 0.08–0.12 μg/kg. TD E2 is preferred. The patch is placed on the superior lateral glutea in the evening at bedtime and removed the following morning, resulting in approximately 10 h of treatment. Within 1–2 weeks of the start of treatment, physicians recommend to monitor the morning serum E2 with the patch still in situ, in order to adjust the dose if the target E2 range has not been reached [49]. A major problem is represented by the fact that low-dose patches are not currently available, but instructions for cutting them have been proposed [50]. Ankarberg-Lindgren et al. [50] have suggested to start the treatment by cutting the patch into 8 pieces and to use them progressively overnight. However, stability issues may occur. Percutaneous estrogen gel for induction of puberty in girls with TS has been suggested, with a starting dose of 0.1 mg and an increase to 0.2, 0.5, 1, and 1.5 mg every year [51].

Earlier estrogen treatments have been suggested by Ross and colleagues [52, 53]. This group suggests starting estrogens in TS patients as early as at 5 years of age. Low-dose estrogen replacement in childhood seems to normalize the onset and the tempo of puberty. These data have not been confirmed by other groups, and the methods can, therefore, not be recommended at the moment.

In conclusion, when treating a girl with hypogonadism using the optimal estrogen route, drug and dose have to be adjusted for every patient. In order to decide which type of treatment should be prescribed, the patient's preference for a combined or separate regimen, the need for contraception, and the preferred frequency of breakthrough bleedings should be taken into account. Although 1 in 4 adolescent females will be exposed to hormonal contraceptives by the age of 18, pediatric pharmaceutical testing of COCP is lacking. For instance, there are still no solid data about the impact of different COCPs on peak bone mass acquisition. So far, most studies available on HRT in young patients have included patients with TS. Therefore, studies need to be carried out on HRT in POI of other causes as well as in patients with hypogonadotropic hypogonadism.

Disclosure Statement

The author has no conflict of interest to declare.

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