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Sex Hormone Replacement in Disorders of Sex Development

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Abstract

People with disorders of sex development (DSD) may have impaired sex steroid production or their gonads removed before, during or after adolescence, thus requiring hormone replacement therapy (HRT) to induce puberty and/or maintain secondary sexual characteristics, to optimize bone health, and to promote physical and social well-being. Oestrogens are usually used for this purpose in persons reared as females (eventually combined with progestins if a uterus is present) and androgens in those reared as males. An alternative therapy for women with ascertained complete androgen insensitivity syndrome could be testosterone, because this is the main sex steroid hormone secreted by their gonads, but this approach remains to be better explored. Few sound evidence-based data are available to guide HRT administration at puberty and in adulthood in individuals with DSD, but recent data and new formulations may give better perspectives for the future.

Hormone replacement therapy (HRT) is a major aspect of the clinical management of people with disorders or differences of sex development (DSD). Objectives of sex steroid administration vary dependent on the age and developmental stage of persons with DSD [1–3].

Early supplementation within the first years of life to promote phallic growth in boys with micropenis [4], to assess in vivo sensitivity to androgens in babies with ambiguous genitalia [5], or to increase urethral tissue before surgery for hypospadias [6] remains largely experimental or based on data in small samples with poor follow-up or absence of adequate control groups.

The main indication for HRT is induction of puberty and substitutive therapy in adulthood [1, 7, 8]. HRT should attempt to replicate the normal 'tempo' of puberty – i.e. the velocity of the progression from one stage of pubertal maturation to the following one [9], to establish and maintain secondary sexual characteristics in adult-

hood, to achieve adult height and adult body proportions, to optimize bone health and sexual maturation, including a satisfying quality of sexual life and psychosocial well-being [1, 7, 8]. Although no evidence-based data on the optimal hormone formulations, route of administration, doses and monitoring parameters are available to guide clinical practice in subjects with DSD [1, 2, 8, 10–12], recent data and the availability of new formulations may lead to more physiological approaches instead of empirical treatments largely used in the past. At any rate, the above complex objectives can only be achieved by individually tailored HRT, long-term monitoring and, hopefully, management close to tertiary centres with documented experience in this field.

Three aspects have to be taken into account regarding HRT in DSD. Firstly, no therapy should be initiated without the fully informed assent/consent of both the adolescent patient and her/his parents [2, 13]. This implies that each child needs to be informed fully, but gently, on his/her condition by increasing age (at least by the age of 10/11 years), according to his/her neuro-psychological development. In addition, the commencement of HRT provides an opportunity to discuss (or rediscuss) the condition with the adolescent and his/her parents, and set a foundation for long-term adherence to treatment by explaining all its objectives [2]. A survey carried out in Italy demonstrated that the start of HRT is a much more troubled passage for young women with 46,XY DSD than physicians usually consider [unpubl. data]. Secondly, sex assignment should be re-evaluated before initiating HRT, if needed. Any uncertainty about sex of rearing has to be ruled out before implementing sex steroid treatment with relevant physical and psychological consequences. In case of opposite HRT in individuals with intact gonads (i.e. oestrogen therapy in 46,XY girls with 5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency, partial androgen resistance syndrome) the administration of gonadotropin-releasing hormone analogues should be considered, possibly delaying gonadectomy till the achievement of adult age and full responsibility for medical and surgical treatments. Yet reports on this matter and its consequences remain anecdotal [14]. Finally, compliance is of utmost importance to optimize treatment and long-term outcome; thus, patients, and their parents before legal age, need to be involved in the selection among the required sex steroids and the type of administration.

Oestrogen Replacement Therapy in Disorders of Sex Development

Oestrogens are a group of steroid hormones produced by the ovary and adrenal cortex, as well as by peripheral conversion from androgens, mainly in adipose tissue. The primary circulating oestrogen in premenopausal women is 17β-oestradiol (E2) produced by conversion of testosterone in the ovary, while oestrone (E1) is a less potent metabolite, produced by conversion of E2 or androstenedione (fig. 1). The two products are in a physiological ratio of 1:1, which should be reproduced in an optimal oestrogen replacement therapy (ERT) [7].

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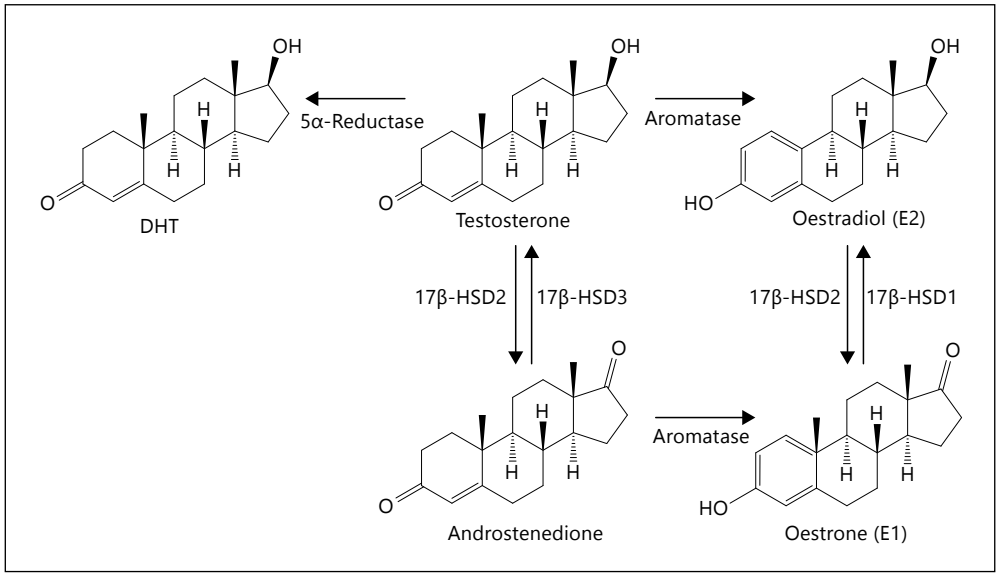

Fig. 1. Pathways of oestrogen and androgen metabolism.

Oral or transdermal oestrogens are used both for pubertal induction and ERT in adulthood (table 1). Treatment should be started with low doses and slowly increased on the basis of pubertal stage progression and bone age maturation until the achievement of adult doses (table 1). At the start of ERT, too high oestrogen doses should be avoided, since they lead to premature closure of the epiphyses and impaired adult height [1, 7, 8, 10–12]. Progestins need to be added after 12–24 months of oestrogen mono treatment or at the occurrence of menarche in girls with a uterus for 10–14 days/month to induce menses and avoid endometrial hyperplasia (table 1) [1, 7, 8].

Large differences persist among paediatric endocrinologists regarding the preferred oestrogen formulation and the route of administration, but oral oestrogens are often used instead of transdermal oestrogens to induce puberty in Europe as well in the USA [15, 16]. Oral ethinyl oestradiol, now substantially used in Europe since this compound is no longer available in the USA as a single drug, has been described as able to produce a better body contour and breast shape in adolescents than 'natural' oestrogens [17], but this statement is poorly substantiated. Low doses of depot E2 have been employed in the USA to induce puberty in girls with sex chromosome DSD (Turner's syndrome) [18], but this practice is poorly diffused.

Equivalence among different oestrogen formulations and some characteristiscs are summarized in table 2. The more physiological formulations are oral micronized or transdermal (patch or gel) bio-identical E2 [7]. Two general types of patches exist: the reservoir system and the matrix (or drug-in-adhesive) system. The latter one can be cut and partially applied to deliver lower doses [7]. Gel formulations are usually in fixed formulations, but a recent product dispenses 0.5 mg/puff (Estreva© gel 0.1%); in our expe-

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Table 1. Oestrogen and progestin doses and formulations for pubertal induction and ERT in adult females

Oral oestrogen formulations Ethinyl oestradiol: 2.5–5 μg/daily (= 50–100 ng/kg/day), the doses should be gradually increased to adult dose (20–25 μg/day)[1]
Micronized E2: 5 μg/kg/day orally; the doses should be gradually increased to adult dose (minimum effective adult dose 2 mg/day)
Conjugated equine oestrogens: ~0.3 mg/day, then 0.625–1.25 mg/day[1]
Transdermal oestrogen formulations (adult dose) E2 patch: 6–25 μg/2 times per week; the doses should be gradually increased to adult dose (50–200 μg/24 h)
E2 gel: 50–200 μg/24 h
Depot oestrogen formulations Depot E2: 0.2 mg/month, increasing 0.2 mg every 6 months till 1.0 mg, then 0.5 mg every 6 months (max 3.0 mg/month)[1]
Progestin[2] formulations: Medroxyprogesterone acetate: tablet 10–20 mg
Micronized progesterone: tablet 100–200 mg (oral or vaginal)

[1] Unavailable in some countries.
[2] Progestins should be added to HRT after 12–24 months of oestrogen-only treatment for 10–14 days/month to induce menses in women with DSD and uterus.

Table 2. Equivalence among different oestrogen formulations

Drug	mg	Note
Oral micronized E2	1.0	Natural form and natural binder for oestrogen receptors in humans
Transdermal E2	0.05	More physiologic mode of delivery leading to more constant plasma levels and lower side-effects
Ethinyl oestradiol	0.05	Synthetic analogue, it binds oestrogen receptors such as E2, but it is retained for a longer time; protected from hepatic inactivation
Conjugated oestrogens	0.625	Mixture of oestrogens derived from pregnant mares' urine (~50% E1 sulphate); protected from hepatic inactivation

rience, this compound can be advantageously used from mid-adolescence onward, permitting a better personalisation of E2 dose. Benefits of transdermal oestrogen over oral formulations include a more physiologic delivery with controlled absorption, more constant plasma levels, improved bioavailability, reduced side effects, and a painless and simple mode of administration. In addition, they show decreased first pass effect, less

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variability in markers of hepatic metabolism and less inferences with IGF-I levels [7, 19, 20]. In adolescents with Turner syndrome, transdermal oestrogens resulted in a significantly greater increase in bone density compared with oral conjugated oestrogen [21], while benefits on other biological systems have not been found [21, 22]. An interesting trial in Turner syndrome showed that when E2 concentrations are titrated to normal adolescent range, micronized oral or transdermal E2 administration did not differentially affect body composition, lipid oxidation and lipid concentrations, but E1 levels and total bio-oestrogen activity were significantly higher after oral than transdermal E2 [23]. In addition, a tendency for lower IGF1 serum levels was found with oral E2 [23]. The authors concluded that transdermal administration results in a more physiological oestrogen milieu than micronized oral E2 administration in adolescent girls [23].

The optimal dose of oestrogen for substitutive therapy in young adulthood is not well known [1], thus doses and formulations often rely on the individual specialist's experience. In postmenopausal women, a transdermal oestrogen dose as low as 14 μg/day is able to maintain bone mineral density [20], but this finding cannot be adequate for young premenopausal women and, mainly, 46,XY females with complete androgen insensitivity syndrome (AIS) [10].

There is no clear evidence of adverse events related to oestrogen treatment in young women with DSD. A small increase of the risk in myocardial infarction, stroke, breast cancer and thromboembolic disease with oral HRT has been reported in adult menopausal women [24]. However, the absolute risk is likely small and these results must be considered in the appropriate context. In fact, data in ageing women should not be extrapolated to adolescent and young adult subjects and the new transdermal and micronized formulations present lower cardiovascular risk, if any, in comparison with the conjugate oestrogens [7, 20, 25]. In addition, some recent evidence indicates that micronized progesterone may be safer than synthetic medroxiprogesterone acetate used in the past. The bio-identical compound does not increase breast cell proliferation and is devoid of any androgenic as well as glucocorticoid activities, being slightly hypotensive and likely representing the optimal progestogen in terms of cardiovascular effects, risk of venous thromboembolism, gall bladder disease, stroke and even breast cancer, at least in postmenopausal women [26, 27]. A trial is in progress to assess if micronized progesterone has a better safety profile when compared to its synthetic counterparts and may result in a different risk profile in women aged 18–45 years with premature ovarian failure [28]. While similar experiences in individuals with DSD are lacking, results of such trials may also contribute to improve HRT in females with DSD.

Androgen Replacement Therapy in Disorders of Sex Development

Testosterone is the main androgen secreted by the testes; it can act on target tissues directly or indirectly via aromatization to E2 or conversion to dihydrotestosterone (DHT; fig. 1). Both testosterone and DHT bind to the androgen receptor, but with

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Table 3. Androgen formulations for pubertal induction and ART

Formulation	Pros	Cons
T enanthate 250 mg, i.m. Duration of action: 3–4 weeks	Most cost-effective method, safe, few side effects	wide swings of T levels, E2 may become excessive in some men, painful injections
T undecanoate 1,000 mg, i.m. Duration of action: 12–15 weeks	Extremely stable T levels for a prolonged period of time, excellent efficacy	Painful injections Not suitable for puberty induction
T pellets, s.c. implantation, six pellets, each of 200 ng Duration of action: 6 months	Favourable pharmacokinetic profile, uniform T levels	Local side effects, procedure of implantation
T undecanoate, per os 20–80 mg daily	Flexible, good for low-dose therapy	Has to be taken with dietary fat, few experience in adolescents
Oromucosal T, transbuccal, 10, 20, 30 mg Duration of action: 4–6 h	Avoids hepatic metabolisation	Very short acting, administration twice daily, not investigated in adolescents
T patch, transdermal 1.2–1.8–2.4 mg/24 h Duration of action: 24 h	Favourable pharmacokinetic behaviour, no negative effect on the prostate	Size 30–60 cm^2, high rate of skin irritations
Scrotal T patch, transdermal Duration of action: 22 h	Suitable to imitate physiological circadian rhythm, high conversion to DHT	On shaved skin, local skin reactions in 5–8%, not available in all European countries
T-Gel: 1/2%, transdermal 10–50–100 mg per day Duration of action: 24 h	Better compliance in comparison to T patch and injectable T with similar clinical effects, T, DHT, E2 levels within the normal range, flexibility in dosage	No long-term experience, local minor skin irritations in 5%
DHT 2% gel, transdermal 10–200 mg per day Duration of action: 24 h	No aromatizing to E2: prostate sparing, slowing closure of pubertal epiphysis, advantageous in gynaecomastia	Some clinical effects not very well investigated, not available in all European countries, has to be manufactured by an experienced pharmacy

T = Testosterone; i.m. = intramuscular; s.c. = subcutaneous; E2 = 17β-estradiol.

different affinity; the latter one is the most potent androgen without the possibility of being aromatized to E2 (fig. 1) [29, 30].

Testosterone is mainly used in androgen replacement therapy (ART) since it is the only product able to replace all the direct and indirect actions of the hormone [29]. The main formulations of androgens are summarized in table 3. No randomized clinical trials have proven that one of the listed testosterone preparations has clear advantages over any of the others in terms of better clinical outcome or more efficient substitution [29, 30]. The choice of which means of administration is used depends on practical concerns, such as the feasibility, the controllability and the patients' preference. At any rate, two testosterone products are most likely better: transdermal formulations (gel and patches) that show physiological pharmacokinetic properties and more flexibility in dosage, and intramuscular testosterone undecanoate that provides stable hormone levels for long-term substitution in adult patients [29, 30]. However, the majority of paediatric endocrinologists in the USA and in Italy still use the traditional testosterone esters, such as testosterone enanthate, mainly to induce puberty

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[16, 31]. DHT as a primary medication for substitution has very few clinical indications in DSD, mainly in patients with 5α-reductase deficiency (table 3). It is commercially available as 2.5% gel in France and can be manufactured by local pharmacies in Germany, but this is not commonly conducted in other countries (especially the USA). In some instances, import of DHT gel (Andractim®) means treatment at the patients' own expense without reimbursement.

The indication for ART is mostly seen with impaired gonadal function in people with DSD raised as males. Two main groups of patients with 46,XY DSD have to be distinguished, because they may require different approaches: hypogonadal individuals sensitive to androgens (as mixed or partial gonadal dysgenesis, 5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency) and those with impaired response to androgens (partial or complete AIS).

In the former group, experiences from hypogonadal boys of other origin have to be used to establish protocols for the induction of puberty. If normal height is present, ART can be started at the male 'normal' age of puberty onset [8, 32, 33], while it may be likely delayed in an adolescent with short stature to gain more height [32, 33]. As with ERT, ART must be started with low doses to mimic normal pubertal stage progression, to maintain androgens within the age-appropriate reference ranges and to avoid impairment of adult height or undesired therapy effects (e.g. occurrence or worsening of gynaecomastia). Although testosterone esters are still widely spread for pubertal induction (table 3) [16, 32], the unphysiological wide swings of testosterone levels and repeated painful injections pose disadvantages [33, 34]. Alternatively, Walvoord [33] proposed a scheme for transdermal replacement, based on data from a small series showing better physiological testosterone levels and clinical outcomes [35]. Then, Mayo et al. [36] reported that 8-hour overnight 5-mg testosterone patches are sufficient for pubertal induction and well tolerated. Another attempt to use 1% testosterone gel for pubertal induction was not promising: therapy started with 0.5 g of testosterone gel/day and was titrated up over 3 weeks based on serum hormone levels. Doses were then held stable (0.5–2.5 g gel/day), but no clear dose response emerged and only 40% of patients showed adequate clinical effects [37]. Recently, a 2% testosterone gel (Tostrex©; 10 mg/puff) has become commercially available in Europe. This might be a promising titratable transdermal formulation, but clinical trials in adolescents are lacking. Other formulations (transbuccal testosterone, long-acting intramuscular testosterone undecanoate) have not been investigated for pubertal induction [32]. In addition, residual functioning of the testes in some boys may permit some spontaneous virilisation and delay of ART. Although treatment with DHT could be supportive during puberty in boys with 5α-reductase deficiency, specific trials on this issue have not been done and it is not clear whether these male patients need additional androgen treatment at all.

In males with AIS, ART poses a great challenge. In partial AIS, impaired sensitivity to all androgens may require supraphysiological doses. Warne et al. [1] suggested high-dose testosterone treatment delivered by subcutaneous testosterone pellets. This

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approach likely needs to be combined with an aromatase inhibitor to prevent further progression of gynaecomastia [1]. In addition, adverse events related to high substitutive doses have to be strictly monitored and weighed against clinical benefits [1]. Postpubertal treatment has been reported using 250 mg/week of injectable testosterone enanthate with a good response [38], but it must be again underlined that this approach remains anecdotal. Clear genetic or clinical parameters as well as functional tests to predict response to ART in partial AIS are not available [2, 38]. In women with complete AIS, testosterone is the main sex steroid hormone secreted by their gonads; thus, this hormone might be used for HRT instead of E2 titrating the doses upon the sex steroid values reported in subjects with intact gonads [unpubl. data]. However, one trial in 4 patients did not demonstrate that ART is preferable to usual ERT in women with complete AIS without gonads with regard to psychosexual functioning [39]. A trial which is currently in progress promises to provide sound data to inform the need for ART [40].

Adverse reactions of ART are related to naturally occurring testosterone and DHT actions on target tissues. In adolescence, some boys experience unwanted effects (fluid retention, aggressiveness) during the first days after testosterone enanthate injections [1]. Premature closure of the epiphyses, aggressiveness, acne and gynaecomastia have to be mentioned, but they are unlikely with optimal ART [29, 30, 32, 33]. In adult men, side effects (as excessive stimulation of libido, priapism, polycythaemia, obstructive sleep apnoea, gynaecomastia, lower levels of high-density lipoprotein cholesterol) are rare, not severe and reversible [29, 30]. The impact of ART on the prostate in adult men with DSD is not known, but it should be taken into account during follow-up [1]. Contraindications, such as prostate carcinoma, unclear prostate findings and mammary carcinoma, are often not applicable to male patients with DSD.

Monitoring Hormonal Replacement Therapy

During puberty induction, each patient should be seen at 3- to 6-month intervals. A full clinical examination includes the assessment of clinical response (i.e. variations of somatic features in comparison with previous visits, including pubertal and sexual development and growth pattern). Intervals between visits can be stretched after attainment of full pubertal development and adult height [8]. Examination of the prostate gland should be included in adult males as well as an ultrasound scan of the uterus in females, if present [1]. The medical interview will comprise behavioural aspects, sexual functioning and performance and physical fitness. Laboratory findings [complete blood count, lipid metabolism, liver function, clotting parameters (females), prostate-specific antigen (males), bone densitometry] will be investigated to assess adequacy of therapy and to check for adverse reactions. Sex steroid profile and luteinizing hormone levels should be checked every 6–12 months [8]. The availability of new accurate methods for sex steroid assessment, as liquid chromatography/tandem

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mass spectrometry and cell bioassays, will permit better monitoring of therapy and titrate HRT according to normative values for age and pubertal stage [41–43]. Sex hormone-binding globulin levels have an impact on free and bioavailable steroids and should be included. Specific reference ranges should be established for any DSD without dysgenetic gonads, as the study in progress for complete AIS [unpubl. data].

Conclusions and Perspectives

ERT has greatly improved in the last years with the availability of bio-identical E2 and progesterone formulations. Currently, it seems reasonable to consider transdermal E2 as the gold standard for ERT in adolescent and young adult females with DSD and hypogonadism. The risks reported for postmenopausal women [24] are likely to poorly conform with the premenopausal age. Additionally, the fact that oral oestrogens are a heterogeneous group is confusing, and most statistics in the literature are based on experience with 'old' conjugated oral oestrogens, often combined with medroxyprogesterone acetate, and such data may not apply to recent oral or transdermal bio-identical products [20].

Regarding ART, boys and men with 46,XY DSD may have a variable level of sensitivity to androgens or a variable ability to metabolise androgens, stressing the need for a personalized therapeutical approach. The recent testosterone preparations, such as transdermal formulations, could be used more frequently to optimise outcome, but the evidence for this needs to be gathered. The response to androgen treatment in male patients with 46,XY DSD cannot be predicted and might be frustrating in some cases, mainly in those with partial AIS. In addition, optimization of HRT may require additional therapeutic intervention. For example, short boys with mixed gonadal dysgenesis may require early growth hormone treatment to normalize their growth pattern before puberty [44], allowing the beginning of HRT at a more appropriate chronological age, but this issue should also be evaluated in large multicentric studies.

Finally, specific trials for DSD people will be developed and doses and deliveries for pubertal induction and adult HRT should be optimized, a surveillance program to investigate specific long-term risks of HRT in persons with DSD should be developed and experiences in clinical practice among leading centres in DSD should be compared and shared, to better define indications, doses and limits of the various available treatment modalities. In addition, all patients, and in the early stage their parents, will need psychosocial support to cope with his/her individual condition as an integral part of the treatment protocol. To this regard, support groups can put forward the realities of living with such conditions. They can also serve as an informal communication interface with the medical profession, leading to better compliance and possibly to co-operation in developing specific therapeutic trials to address unresolved questions of HRT in DSD [45].

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References

1 Warne GL, Grover S, Zajac JD: Hormonal therapies for individuals with intersex conditions: protocol for use. Treat Endocrinol 2005;4:19–29.

2 Hughes IA, Houk C, Ahmed SF, Lee PA, LWPES/ESPE Consensus Group: Consensus statement on management of intersex disorders. Arch Dis Child 2006;91:554–563.

3 Ahmed FS, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, Elford S, Hughes IA, Izatt L, Krone N, Miles H, O'Toole S, Perry L, Sanders C, Simmonds M, Wallace AM, Watt A, Willis D: UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol (Oxf) 2011;75:12–26.

4 Wiygul J, Palmer LS: Micropenis. ScientificWorldJournal 2011;11:1462–1469.

5 Burstein S, Grumbach MM, Kaplan SL: Early determination of androgen-responsiveness is important in the management of microphallus. Lancet 1979;2:983–986.

6 Netto JM, Ferrarez CE, Schindler Leal AA, Tucci S Jr, Gomes CA, Barroso U Jr: Hormone therapy in hypospadias surgery: a systematic review. J Pediatr Urol 2013;9:971–979.

7 Kenigsberg L, Balachandar S, Prasad K, Shah B: Exogenous pubertal induction by oral versus transdermal estrogen therapy. J Pediatr Adolesc Gynecol 2013;26:71–79.

8 Bertelloni S, Dati E, Baroncelli GI: Disorders of sex development: hormonal management in adolescence. Gynaecol Endocrinol 2008;24:339–346.

9 Tanner JM, Whitehouse RH: Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170–179.

10 Bertelloni S, Dati E, Baroncelli GI, Hiort O: Hormonal management of complete androgen insensitivity syndrome from adolescence onward. Horm Res Paediatr 2011;76:428–433.

11 Brain CE, Creighton SM, Mushtaq I, Carmichael PA, Barnicoat A, Honour JW, Larcher V, Achermann JC: Holistic management of DSD. Best Pract Res Clin Endocrinol Metab 2010;24:335–354.

12 Hiort O, Reinecke S, Thyen U, Jürgensen M, Holterhus PM, Schön D, Richter-Appelt H: Puberty in disorders of somatosexual differentiation. J Pediatr Endocrinol Metab 2003;16(suppl 2):297–306.

13 Wiesemann C: Ethical guidelines for the clinical management of intersex. Sex Dev 2010;4:300–303.

14 Bertelloni S, Balsamo A, Giordani L, Fischetto R, Russo G, Delvecchio M, Gennari M, Nicoletti A, Maggio MC, Concolino D, Cavallo L, Cicognani A, Chiumello G, Hiort O, Baroncelli GI, Faienza MF: 17β-Hydroxysteroid dehydrogenase-3 deficiency: from pregnancy to adolescence. J Endocrinol Invest 2009;32:666–670.

15 Kiess W, Conway G, Ritzen M, Rosenfield R, Bernasconi S, Juul A, van Pareren Y, de Muinck Keiser-Scharama SMPF, Bourguignon J-P: Induction of puberty in the hypogonadal girl: practices and attitudes of pediatric endocrinologists in Europe. Horm Res 2002;57:66–71.

16 Drobac S, Rubin K, Rogol AL, Rosenfield RL: A workshop on pubertal hormone replacement options in the United States. J Pediatr Endrcrinol Metab 2006;19:55–64.

17 Saenger P: Turner's syndrome. N Engl J Med 1996;335:1749–1754.

18 Rosenfield RL, Devine N, Hunold JJ, Mauras N, Moshang T Jr, Root AW: Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome. J Clin Endocrinol Metab 2005;90:6424–6430.

19 Kopper NW, Gudeman J, Thompson DJ: Transdermal hormone therapy in postmenopausal women: a review of metabolic effects and drug delivery technologies. Drug Des Devel Ther 2009;2:193–202.

20 Goodman MP: Are all estrogens created equal? A review of oral vs. transdermal therapy. J Womens Health (Larchmt) 2012;21:161–169.

21 Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA: Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. J Clin Endocrinol Metab 2009;94:2009–2014.

22 Mauras N, Shulman D, Hsiang HY, Balagopal P, Welch S: Metabolic effects of oral versus transdermal estrogen in growth hormone-treated girls with turner syndrome. J Clin Endocrinol Metab 2007;92:4154–4160.

23 Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein KO, Singh R, Hossain J, Santen RJ, Ross JL, Mauras N: Metabolic effects of oral versus transdermal 17β-estradiol (E_2): a randomized clinical trial in girls with Turner syndrome. J Clin Endocrinol Metab 2013;98:2716–2724.

24 Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, 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.

Hiort O, Ahmed SF (eds): Understanding Differences and Disorders of Sex Development (DSD).
Endocr Dev. Basel, Karger 2014, vol 27, pp 149–159 (DOI: 10.1159/000363640)

25 Renoux C, Dell'aniello S, Garbe E, Suissa S: Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ 2010;340:c2519.

26 Gompel A: Micronized progesterone and its impact on the endometrium and breast vs progestogens. Climacteric 2012;15(suppl 1):18–25.

27 L'Hermite M: HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. Climacteric 2013;16(suppl 1):44–53.

28 Mittal M, Savvas M, Arya R, McEniery C, Narvekar N, Cardozo L, Panay N, Hamoda H: 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;19:127–132.

29 Jockenhövel F: Testosterone supplementation: what and how to give. Aging Male 2003;6:200–206.

30 Gooren LJ, Bunck MC: Androgen replacement therapy: present and future. Drugs 2004;64:1861–1891.

31 Balsamo A, Bertelloni S: Trattamento dell'ipogonadismo in eta' evolutiva: indagine conoscitiva SIEDP; in Rappresentanza dei Gruppi di Studio SIEDP di Fisiopatologica della Puberta & Complicanze Endocrine nelle Malattie Croniche (abstract book). Parma, XVI Congresso Nazionale SIEDP, 2007, p 167.

32 Bertelloni S, Baroncelli GI, Garofalo P, Cianfarani S: Androgen therapy in hypogonadal adoescent males. Horm Res Paediatr 2010;74:292–296.

33 Walvoord E: Sex steroid replacement for induction of puberty in multiple pituitary hormone deficiency. Pediatr Endocrinol Rev 2009;6(suppl 2):298–305.

34 Rogol AD: New facets of androgen replacement therapy during childhood and adolescence. Expert Opin Pharmacother 2005;6:1319–1336.

35 de Sanctis V, Vullo C, Urso L, Rigolin F, Cavallini A, Caramelli K, Daugherty C, Mazer N: Clinical experience using the Androderm testosterone transdermal system in hypogonadal adolscents and young men with β-thalassemia major. J Pediatr Endocrinol Metab 1998;11(suppl 3):891–900.

36 Mayo A, Macintyre H, Wallace AM, Ahmed SF: Transdermal testosterone application: pharmacokinetics and effects on pubertal status, short-term growth, and bone turnover. J Clin Endocrinol Metab 2004;89:681–687.

37 Rogol A, Zum Brunnen TL, Pratt G, McWhirter C, Brennan JJ, Lagast H: Safety of and clinical response to transdermal testosterone gel 1% in boys with delayed pubertal development (abstract). Endocrine Society 89th Annual Meeting, 2007, pp 3–464.

38 Weidemann W, Peters B, Romalo G, Spindler K-D, Schweikert H-U: Response to androgen treatment in a patient with partial androgen insensitivity and a mutation in the deoxyribonucleic acid-binding domain of the androgen receptor. J Clin Endocrinol Metab 1998;83:1173–1176.

39 Slob AK, van der Werff ten Bosch JJ, van Hall EV, de Jong FH, Weijmar Schultz WC, Eikelboom FA: Psychosexual functioning in women with complete testicular feminization: is androgen replacement therapy preferable to estrogen? J Sex Marital Ther 1993;19:201–209.

40 Birnbaum W: CAIS-Studie. www.cais-studie.de.

41 Nelson RE, Grebe SK, O'Kane DJ, Singh RJ: Liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of estradiol and estrone in human plasma. Clin Chem 2004;50:373–384.

42 Kulle AE, Riepe FG, Melchior D, Hiort O, Holterhus PM: A novel ultrapressure liquid chromatography tandem mass spectrometry method for the simultaneous determination of androstenedione, testosterone, and dihydrotestosterone in pediatric blood samples: age- and sex-specific reference data. J Clin Endocrinol Metab 2010;95:2399–2409.

43 Klein KO, Baron J, Colli MJ, McDonnell DP, Cutler GB Jr: Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J Clin Invest 1994;94:2475–2480.

44 Bertelloni S, Dati E, Valetto A, Bertini V, Danti A, Baroncelli GI: Long-term growth hormone treatment in a boy with 45,X/46,X,idic(Yp) mixed gonadal dysgenesis: comparison with growth pattern of an untreated patient. Hormones (Athens) 2014;13:doi 10.14310/horm.2002.1498.

45 Cull ML, Simmonds M: Importance of support groups for intersex (disorders of sex development) patients, families and the medical profession. Sex Dev 2010;4:310–312.

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