

TRANSITION IN ENDOCRINOLOGY

Induction of puberty

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Abstract

Puberty is the period during which we attain adult secondary sexual characteristics and reproductive capability. Its onset depends upon reactivation of pulsative GnRH, secretion from its relative quiescence during childhood, on the background of intact potential for pituitary–gonadal function. This review is intended: to highlight those current practices in diagnosis and management that are evidence based and those that are not; to help clinicians deal with areas of uncertainty with reference to physiologic first principles; by sign-posting relevant data arising from other patient groups with shared issues; to illustrate how recent scientific advances are (or should be) altering clinician perceptions of pubertal delay; and finally, to emphasise that the management of men and women presenting in advanced adult life with absent puberty cannot simply be extrapolated from paediatric practice. There is a broad spectrum of pubertal timing that varies among different populations, separated in time and space. Delayed puberty usually represents an extreme of the normal, a developmental pattern referred to as constitutional delay of growth and puberty (CDGP), but organic defects of the hypothalamo–pituitary–gonadal axis predisposing to hypogonadism may not always be initially distinguishable from it. CDGP and organic, or congenital hypogonadotropic hypogonadism are both significantly more common in boys than girls. Moreover, around 1/3 of adults with organic hypogonadotropic hypogonadism had evidence of partial puberty at presentation and, confusingly, some 5–10% of these subsequently may exhibit recovery of endogenous gonadotrophin secretion, including men with Kallmann syndrome. However, the distinction is crucial as expectative ('watch-and-wait') management is inappropriate in the context of hypogonadism. The probability of pubertal delay being caused by organic hypogonadism rises exponentially both with increasing age at presentation and the presence of associated 'red flag' clinical features. These 'red flags' comprise findings indicating lack of prior 'mini-puberty' (such as cryptorchidism or micropenis), or the presence of non-reproductive congenital defects known to be associated with specific hypogonadal syndromes, e.g. anosmia, deafness, mirror movements, renal agenesis, dental/digital anomalies, clefting or coloboma would be compatible with Kallmann (or perhaps CHARGE) syndrome. In children, interventions (whether in the form of treatment or simple reassurance) have been historically

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Dr Richard Quinton graduated in medicine from the University of Cambridge, which awarded him an entrance exhibition in 1983 and the Ralph Noble Prize for his MD thesis on Kallmann's. He was appointed Consultant Endocrinologist at the Royal Victoria Infirmary and Senior Lecturer at the University of Newcastle-upon-Tyne, where he is a full member of the Institute of Genetic Medicine. He is Vice Chair of the EU-funded COST consortium on diseases affecting the neuroendocrine control of human reproduction and is the UK representative to the Endocrine Section of the European association of Medical Specialists (UEMS).



Professor Leo Dunkel worked at the University of Kuopio as Chair of Paediatrics, Department of Clinical Medicine, University of Kuopio, Finland. In 2012, he was appointed, alongside Professor Marta Korbonits, the Centre Lead for Endocrinology, School of Medicine and Dentistry, Queen Mary University of London. Professor Dunkel has served on the Editorial Boards of many prestigious peer-reviewed journals. He is also a Member of the EU-funded COST consortium (BM1105) on diseases affecting the neuroendocrine control of human reproduction (www.gnrhnetwork.eu).



directed at maximising height potential and minimising psychosocial morbidity, though issues of future fertility and bone density potential are now increasingly 'in the mix'. Pubertal adults almost invariably harbour organic hypogonadism, requiring sensitive acknowledgement of underlying personal issues and the timely introduction of sex hormone replacement therapy at more physiological doses.

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Introduction

Puberty is a period during which children attain adult secondary sexual characteristics and reproductive capability. The onset of puberty requires an intact hypothalamic–pituitary–gonadal (HPG) axis. Reactivation of the secretion of gonadotrophin-releasing hormone (GnRH) from its stage of childhood quiescence stimulates luteinising hormone (LH) and follicle-stimulating hormone (FSH) secretion, which in turn activates the production of gonadal sex steroids.

The first external sign of puberty in girls is usually the initiation of breast development, designated as change from Tanner stage B1 to B2 (B2; also called breast budding) and, in boys, change from Tanner's genital stage G1 to G2 including enlargement of the testes (i.e. achievement of volume > 3 ml or testicular length \geq 25 mm) (1, 2, 3, 4). Development of pubic hair is usually not regarded as a marker for pubertal onset because pubarche may result from maturation of the adrenal glands (adrenarche) and onset of pubic hair can thus be independent of HPG axis activation.

There are clear differences in pubertal timing among ethnic groups, but in most populations the average ages at attainment of the first signs of puberty are around ten for girls and 12 in boys (5, 6). Puberty is delayed if there is no breast development by 13 years in girls or absence of testicular enlargement by 14 years in boys (4). Because of the secular change towards earlier onset of puberty in the USA (7, 8) and some other countries (5, 6), different age limits may be more appropriate in some ethnic groups. Even the latest-developing girls seem to start their puberty 1 year earlier than two decades ago (5, 6).

Evaluation of delayed puberty

Constitutional delay of growth and puberty (CDGP) represents the commonest cause of delayed puberty in both sexes. At least 30% of girls and up to 65% of boys with delayed puberty have CDGP (9). Autosomal dominant mode of inheritance (with or without complete

penetrance) is the commonest inheritance pattern (10). Although CDGP does seem to be more frequent than might be expected among first-degree relatives of probands with hypogonadotrophic hypogonadism, the genetic basis of this observation remains elusive. In the study population, 50–75% of subjects with CDGP have a family history of delayed puberty. As much as 80% of all variation in the timing of puberty is due to genetic factors (11, 12).

CDGP can be considered an extreme of the normal spectrum of pubertal timing, but can be diagnosed only after exclusion of other underlying conditions. The differential diagnosis of CDGP is divided into three main categories (4, 9): hypergonadotrophic hypogonadism (characterised by elevated gonadotrophin levels due to lack of negative feedback from the gonads), congenital hypogonadotrophic hypogonadism (CHH-characterised by low LH and FSH levels due to organic hypothalamic or pituitary disorders) and transient (or functional) hypogonadotrophic hypogonadism (FHH), where pubertal delay is due to maturational delay in the HPG axis secondary to an underlying non-reproductive condition.

One of the most difficult distinctions is that between CDGP and CHH in teenage years. Subjects with CDGP are typically short, because their skeletal maturation is delayed and their height is compatible with the bone age. In about half of adolescents with CDGP, linear growth has already begun to falter in the years before the expected onset of puberty, and it has been shown that these children with poor growth in childhood do not fully exploit their genetic height potential and will ultimately have adult height significantly below their mid-parental target height (13). By contrast, patients with CHH have steady linear growth during childhood and only become short for their age with absence of the pubertal growth spurt. In a typical case, the diagnosis of CHH is made during the second or third decade of life, but the diagnosis is sometimes only made much later in life. Common presenting signs are delayed onset of puberty, primary amenorrhoea,

poorly developed secondary sexual characteristics, eunuchoid body proportions, or infertility, though the diagnosis can sometimes be suspected before the age of pubertal onset (indeed, in the first 6 months of life it can actually be confirmed on the basis of low testosterone and gonadotrophin levels). This is a crucial distinction as expectative ('watch-and-wait') management is inappropriate in the context of teenage CHH. For the differential diagnosis of the two conditions, a variety of physiological and stimulation tests have been proposed, such as assessment of LH pulsatility by frequent sampling (14), prolactin response to various provocations (15), gonadotrophin response to GNRH (16), testosterone response to human chorionic gonadotrophin (hCG) (17, 18, 19) and first morning-voided urine FSH and LH (20). Most recently, a single measurement of inhibin B level has been shown to discriminate complete CHH from CDGP with specificity of 100% at inhibin B concentration of 35 pg/ml in pre-pubertal boys (21). However, the presence or absence of 'red flag' features remains the strongest differentiator. These 'red flags' comprise findings indicating lack of prior 'mini-puberty' (such as cryptorchidism or micropenis), or the presence of non-reproductive congenital defects known to be associated with specific hypogonadal syndromes, e.g. anosmia, deafness, mirror movements, renal agenesis, dental/digital anomalies, clefting or coloboma would be compatible with Kallmann syndrome (KS), or conceivably CHARGE syndrome. Nevertheless, around 1/3 of adults with organic hypogonadotropic hypogonadism have evidence of partial puberty at presentation, with correspondingly higher levels of Inhibin B. Moreover, some 5–10% of CHH men may subsequently exhibit recovery of endogenous gonadotropin secretion, including some with KS (22, 23).

In adults, the diagnostic value of the GNRH test is limited (24) and assessment of baseline gonadotrophin levels is usually sufficient. Similarly, other hormones of the pituitary should be first evaluated by basal hormonal levels (measured by ultrasensitive assays), with provocation tests reserved for situations in which the basal hormone measurements are insufficiently informative, or in cases where there is strong clinical evidence of a multiple pituitary hormone deficiency.

Anosmia can often be diagnosed by simply asking the patient, but only semi-quantitative olfactometry (e.g. UPSIT) (25) can reliably distinguish between normal or partially defective olfaction. Accurate olfactory phenotyping can support more directed genetic testing (26). Magnetic resonance imaging (MRI) of the olfactory tract (especially T2-weighted coronal views) can readily

demonstrate hypoplastic or absent olfactory bulbs, which are pathognomonic of KS. MRI should also be used in suspicion of pituitary and/or hypothalamic tumours, in patients with persistent hyperprolactinaemia, multiple pituitary hormone deficiency or neurological signs of a tumour clinical (visual field defects and headache). However, according to a recent clinical practice guideline, the cost effectiveness of MRI to exclude pituitary and/or hypothalamic tumours has not been established (27). In contrast, MRI is seldom indicated for suspected FHH. We also recommend assessment of bone mineral density of the lumbar spine, femoral neck and hip at the initial diagnosis of HH and after 1–3 years of sex steroid therapy in hypogonadal patients (though if resources limit the number of scans, then obviously the key time point at which to scan would be after the first few years of treatment).

At present, several things limit our ability to integrate genetic mutational analysis into everyday clinical practice. First, our knowledge of the spectrum of genes involved is incomplete. Second, so is our knowledge of adult phenotypes associated even with sequence variants of known genes. Third, the timelines for turnaround of genetic data from research labs are generally longer than clinicians have available to make decisions. However, there are circumstances where clinical genetics can play a key role, such as where there is already a known high-penetrance genetic variant (e.g. *KAL1* and *FGFR1*) segregating within a given kindred.

Another diagnostic challenge with slim gonadotrophin-deficient women is that between organic CHH and functional hypothalamic amenorrhoea (HA), relating to bioenergetic stress and/or occult underlying non-gonadal disease. Indeed, with particularly severe stress, gonadotrophin levels can even become suppressed in women with primary ovarian failure. Pragmatically, however, the endocrine aspects to treatment are the same (oestrogen for induction/maintenance of post-adrenarchial secondary sexual characteristics and bone health; ovulation induction with gonadotrophin for infertility). Moreover, there is now known to be genetic overlap between organic and functional gonadotrophin deficiency syndromes, such that HA is now more usefully considered as resulting from genetic–environmental interactions (28).

Considerations in different diagnostic groups

Induction of puberty is commonly considered for adolescents who either have delayed puberty or have been

Table 1 Common causes of delayed puberty other than constitutional delay of growth and puberty. Table modified and reprinted with permission from Palmert *et al.* (6).

Hypergonadotrophic hypogonadism	Hypogonadotrophic hypogonadism	Functional hypogonadotrophic hypogonadism
Common causes: Turner syndrome Gonadal dysgenesis Chemotherapy/radiation therapy	CNS tumours/infiltrative diseases Isolated hypogonadotrophic hypogonadism Kallmann syndrome Combined pituitary hormone deficiency Chemotherapy/radiation therapy	Systemic illness/conditions Inflammatory bowel disease Celiac disease Anorexia nervosa/bulimia Hypothyroidism Excessive exercise

diagnosed with hypogonadism. Appropriate treatment modalities vary by the diagnosis. Commonest causes of hypogonadism causing delayed puberty are listed in Table 1.

For men and women presenting with absent or partial puberty and biochemical hypogonadotrophic hypogonadism beyond the teenage years, the diagnostics and treatment aims are straightforward. CDGP is no longer a likely diagnosis and, as these individuals have generally already attained normal adult stature, this i) makes it improbable that they should harbour broader hypopituitarism beyond isolated gonadotrophin deficiency (though serum screening for hyperprolactinaemia, iron overload and, possibly, coeliac disease is essential) and ii) removes any potential therapeutic conflicts between the goals of maximising final height and promptness of pubertal induction. Sex hormone replacement in hitherto apubertal adults can result in dramatic improvements in bone density, even when this treatment has only been initiated in middle age.

The reasons for highly delayed presentations beyond the teenage years in some patients with CHH/KS have not been subject to any formal analysis, but recurrent themes emerge from both physician personal experience, and from patient experiences shared at focus groups and/or in online electronic traffic on the various support group-hosted sites. These include general shyness (of patient and/or parents), constitutional reluctance or financial constraints inhibiting engagement with healthcare systems, strongly held beliefs expressed by friends, family or physicians that 'everything will be alright in the end' and, frankly, overt errors of omission or procrastination made by physicians they encountered in earlier life. The association of pubertal delay with a history of any reproductive or non-reproductive defect associated with 'red flag markers' of permanent hypogonadism (micropenis, cryptorchidism, anosmia, deafness, clefting, etc.) should be a diagnostic 'game changer', but all too often is not (29). Some patients have pointed to intensive and, perhaps, overenthusiastic investigation at

their initial presentation as having induced them to miss follow-up visits and disengage with endocrine follow-up for many years thereafter. Patients from cultures favouring arranged marriage and/or 'modesty' in clothing coverage can also occasionally remain undiagnosed until the outcome of infertility investigations. The case histories contained in the online supplementary data from Santhakumar *et al.* (2013) illustrate most of these issues (30).

In CDGP, where pubertal delay is transient, the patient should make the decision regarding whether the treatment is initiated, but if there are 'red flag' markers of permanent hypogonadism there is no reason to defer treatment; the goal of such therapy is to accelerate growth and/or to induce secondary sexual characteristics and, potentially, to alleviate psychosocial difficulties. Late puberty can affect psychosocial well-being and, as late-developing adolescents are often short compared with their peers, patients and families are often concerned that delayed puberty may also affect adult stature. Many adolescents present with delayed puberty combined with relative familial short stature, compounding these concerns and leading to more subspeciality referrals than would either condition alone; however, adult height only slightly below the genetic height potential (target height) is usually reached (31). If stature is not a major concern, reassurance with accurate adult height prediction is frequently sufficient, especially if puberty has already started. Hormonal therapy can be beneficial, especially for those who have decreased self-esteem, if there is clear anxiety about growth rate and/or delayed pubertal characteristics, or if there are psychosocial difficulties that may derive from negative interactions with peers (32, 33, 34, 35).

If endogenous gonadotrophin-dependent puberty has not started after 1 year of treatment, then permanent hypogonadotrophic hypogonadism and other diagnoses should be reconsidered and an MRI of the brain is indicated.

For the treatment of ovarian failure in girls with Turner syndrome, there is significant uncertainty about

the appropriate timing and dosage for oestrogen-replacement therapy (30, 36, 37). Elevated gonadotrophin levels and slow skeletal maturation suggest that oestrogen deficiency in Turner girls begins already in infancy (38, 39). Oestrogen may also have positive behavioural and neurocognitive effects in the developing brain (40, 41). Despite this evidence, until recently a common clinical practice has been to postpone oestrogen-replacement therapy until the mid-teens. This practice was based on the widely held view that too-early onset of oestrogen therapy might reduce adult height by accelerating epiphyseal fusion (42). This view has been revised by studies showing that postponing oestrogen replacement in adolescent girls with Turner syndrome may compromise self-esteem and social adjustment and does not provide any beneficial effect on adult height (37). Indeed, recent data from a placebo-controlled study suggest that combining ultra-low doses of ethinyl oestradiol (EE; as low as 25 ng/kg daily for children from 5.0 to 8.0 years of age; 50 ng/kg daily for those aged 8.0–12.0 years of age) with growth hormone (GH), may improve growth and provide other potential benefits (ClinicalTrials.gov number, NCT00001221) (43). Obviously, this study would bear repeating using tiny doses of 17 β -oestradiol, given the illogicality inherent in using EE as 'oestrogen replacement' for patients on GH (*q.v.*). Moreover, there are also data linking a history of late introduction of oestrogen therapy with incomplete uterine maturation in adult Turner women, which could impact adversely on egg-donation outcomes (44).

How to treat

Constitutional delay of growth and puberty

The options for management of CDGP include expectant observation or therapy with low dose testosterone (in boys) or oestrogen (in girls) (Table 2). Numerous studies of treatment of CDGP in boys have been reported. These are largely observational and some randomised-controlled trials (carried out with small numbers of subjects), which involve low doses of androgens given in short courses (31, 33, 35). Such therapy expedites growth but does not advance bone age over calendar age, advances sexual maturation and often improves psychosocial well-being. For girls, similar outcomes are likely although published data are scarce. For girls, therapy is initiated with appropriately low doses of oestrogen (Table 2). CDGP is an overlapping condition with idiopathic short stature (ISS) and, for a subset of patients, short stature can be more concerning than delayed puberty. Although the US FDA

has approved GH for the treatment of ISS and height SDS ≤ 2.25 for age, this therapy increases adult height only modestly in CDGP and its use is not recommended.

In short boys with CDGP, another potential therapeutic approach is the inhibition of oestrogen biosynthesis with aromatase inhibitors (AIs) (45, 46). AIs inhibit conversion of androgens to oestrogens, and because oestrogen is the predominant hormone needed for epiphyseal closure, AIs could prolong growth in height and thus potentially increase final adult height. In boys with short stature and/or delayed puberty, AIs are reported to delay bone maturation and appear to increase adult height in controlled trials (45, 46). However, the treatment efficacy in centimetres gained as well as the optimal dose, timing and duration of treatment remain uncertain. In particular, typical doses used for the treatment of ER+ breast cancers are almost certainly far too high for this putative indication. Moreover, potential adverse effects, especially impaired trabecular bone development and vertebral body deformities observed in boys with ISS treated with letrozole (47), must also be considered. Pending the outcome of ongoing clinical trials of these agents, therapy should be with testosterone alone unless stature is an overwhelming concern. We do not use GH or anabolic steroids, and believe that AIs are most appropriately used within clinical trials for the present time.

For boys with CDGP who elect to be treated, we initiate supplementation with 50 mg testosterone ester *i.m.* each month for 3–6 months, which can be repeated for another 3–6 months with dose escalation (Table 2).

For girls, we prefer oral or transdermal 17 β -oestradiol for several reasons. First, it is a precautionary principle to replace any given endocrine deficiency with the bio-identical hormone, whenever practical. Second, data from hypopituitary females receiving combined oestrogen and GH treatment indicate a markedly greater impairment of GH-mediated insulin-like growth factor 1 (IGF1) synthesis with EE than with 17 β -oestradiol (48), with a smaller inhibitory effect observed by taking 17 β -oestradiol transdermally vs orally (49). Finally, data from UK and Dutch registries of trans-women (male-to-female transsexuals) have highlighted a much greater risk of venous and/or arterial thrombosis with EE and conjugated equine oestrogens than with 17 β -oestradiol (50, 51, 52). Given that linear growth is an intrinsic concern in CDGP, it seems both unwise and unnecessary (despite longstanding habit and custom) to expose young girls to a synthetic molecule, with demonstrably higher thrombosis risk and the theoretical potential for growth impairment, when there is a better alternative.

Table 2 Medications used for the treatment of constitutional delay of growth and puberty and permanent hypogonadism. Table modified and reprinted with permission from Palmert *et al.* (6).

Drug and formulation	CDGP	Hypogonadism	Side effects and cautions
Induction of puberty in boys Testosterone ^a			
Testosterone enanthate, cypionate and propionate. Testosterone enanthate has longer duration of effect than testosterone propionate. i.m. injection	Not recommended before 14 years of age. Initial dose 50–100 mg every 4 weeks for 3–6 months. Repeated treatment with 25–50 mg increment in dose (not exceeding 100 mg)	Can initiate after age 12 years at 50 mg/month. Increase with 50 mg increments every 6–12 months. After reaching 100–150 mg monthly, decrease interval to every 2 weeks. Adult dose 200 mg every 2 weeks	Erythrocytosis, weight gain, prostate hyperplasia. High doses can cause premature epiphyseal closure. Not for use in boys with bone age <10 years All i.m. preparations: local side effects (pain, erythema, inflammatory reaction and sterile abscess). Priapism can occur in patients with sickle cell disease
Testosterone undecanoate i.m. injection	No data available	Adult dose is 1000 mg every 10–14 weeks	Very rarely, paroxysms of coughing and dyspnoea post injection, ascribed to lipid embolism from the vehicle; hence only recently licensed (with restrictions) in the USA
Testosterone gel. Transdermal preparations, applied topically at bedtime	No data available	Can be started when ~50% adult dose with i.m. testosterone has been achieved. Adult dose 50–80 mg daily	Local irritation. After applying, avoid close skin contact with others
Aromatase inhibitors ^b			Not yet approved for this indication. After onset of puberty, may increase gonadotrophin secretion and circulating testosterone levels (67)
Letrozole PO	2.5 mg daily	Not recommended	Decreased HDL cholesterol, erythrocytosis, vertebral deformities have been reported (47) Less potent than letrozole
Anastrozole PO	1.0 mg daily	Not recommended	
Treatment of fertility in boys and men Pulsatile GNRH s.c. pump	Not recommended routinely	Initial: 5–25 ng/kg per pulse every 90–120 min; increase to 25–600 ng/kg per pulse	Requires extensive experience. Most physiological form of replacement
hCG plus rFSH s.c. or i.m. hCG injections s.c. rhFSH injections	Not recommended routinely	hCG: dose 500–3000 IU twice weekly, increased to every 2 days. Dose adjusted based on serum testosterone levels. rhFSH: dose 75–225 IU 2–3 times weekly	hCG: inflammation locally in the testis, may induce apoptosis of germ cells. In hypogonadotrophic hypogonadism with prepubertal onset it is necessary to add FSH to induce testicular growth and spermatogenesis. No data on effects on future fertility
Induction of puberty in girls Oestrogen			
Ethinyl oestradiol (EE). Component of contraceptive pills. Lower dose EE PO preparations are available in Europe	Initial dose 2 µg daily. Increase after 6–12 months to 5 µg daily	Initial dose 2 µg daily. Increase every 6–12 months to 5, 10, and 20 µg daily (adult dose)	Liver toxicity, increased levels of some plasma binding proteins. Potentially greater risk of thromboembolism and arterial hypertension than natural human oestrogen 17β-oestradiol
17β-oestradiol PO tablets	Initial dose 5 µg/kg daily PO, increase after 6–12 months to 10 µg/kg daily	Initial dose 5 µg/kg daily PO, increase every 6–12 months to 10 µg/kg daily, then to 15 µg/kg and to 20 µg/kg daily. Adult dose 1–2 mg daily	Natural oestrogen, may be preferable to synthetic estrogens. Transdermal route may have advantages over oral administration

Table 2 Continued

Drug and formulation	CDGP	Hypogonadism	Side effects and cautions
17 β -oestradiol. Transdermal patch or gel. Patches twice weekly, topical gel applied daily	Patch: initial 3.1–6.2 μ g/24 h (1/8–1/4 of 25 μ g/24 h patch). Increase by 3.1–6.2 μ g/24 h every 6 months	Patch: initial 3.1–6.2 μ g/24 h (1/8–1/4 of 25 μ g/24 h patch). Increase by 3.1–6.2 μ g/24 h every 6 months. Adult dose 50 (to 100) μ g/24 h	No dosage equivalent data between patches and gel available in younger patients
Conjugated equine estrogens (CEE) PO tablets	Initial dose 0.1625 mg daily for 6–12 months, and then titrating to 0.325 mg daily. Dosing depends on formulation	Initial dose 0.1625 mg for 6–12 months, increase every 6–12 months to 0.325, 0.45 and 0.625 mg daily. Common adult dose 0.625 mg	CEE are not oestradiol precursors. Use questioned by some as not physiological and because of reported increased cardiovascular risks in postmenopausal women
Progestogens/progestins Various options, usually PO	Usually necessary only if treatment continues longer than 12 months	5–10 mg of medroxyprogesterone acetate daily during the last 7 days of menstrual cycle. Alternative: micronized progesterone, dose 100–200 μ g daily	Progesterone added to induce endometrial cycling after 12–18 months of oestrogen therapy (later if oestrogen dose increased slowly; sooner if break-through bleeding)
Treatment of fertility in girls and women Pulsatile GnRH	Not recommended routinely	Used for fertility, as in male patients	See considerations above

^aTestosterone undecanoate PO tablets or anabolic steroids are not recommended for the induction of secondary sexual characteristics. Induction of fertility may be less successful in men who have lower baseline testicular volumes, have previously received testosterone treatment, and have not previously received treatment with GnRH (55, 56, 57, 58) or gonadotrophins.

^bRationale for the use of aromatase inhibitors in the induction of puberty in CDGP is to increase adult height.

When deciding whether to use oral or transdermal 17 β -oestradiol, the following factors should be considered. First, beyond the potential for better GH-mediated IGF1 synthesis, data from postmenopausal women suggest other advantages of the transdermal route in avoiding hepatic first-pass metabolism, both in respect of potentially lower thrombogenicity (53) and more neutral effect on lipids, with oral oestrogens tending to lower LDL-cholesterol and raise triglycerides (54). Second, it is usually easier to administer tiny doses of 17 β -oestradiol by cutting up a matrix patch or by using a metered-dose gel dispenser, than it is to split tablets. However, patient acceptability and product preference are crucial and, before getting too fixated on the minutiae of dosimetry, the huge individual variability in drug absorption needs to be recognised. Roughly speaking, similar plasma levels are achieved using 2 mg daily oral 17 β -oestradiol, 2 mg daily gel and 100 μ g patch, but with up to tenfold differences in 17 β -oestradiol levels between individual patients using the same preparation (e.g. (49)).

Hypogonadotrophic hypogonadism

In boys and girls with HH, initial sex steroid therapy is the same as for CDGP (indeed the two diagnoses may not always be initially distinguishable), but doses are gradually increased to full adult replacement levels over ~3 years (Table 2). Exogenous testosterone does not induce testicular growth or spermatogenesis in men with hypogonadotrophic hypogonadism. Equally, exogenous oestrogen does not induce ovulation (findings that clinch the diagnosis), and induction of fertility in both sexes requires treatment with either pulsatile GnRH (55, 56, 57) or exogenous gonadotrophins (57). Fertility outcomes with each regimen are variable, with poorer responses in patients with signs of absent mini-puberty (prepubertal testes, cryptorchidism and/or low IB) (56, 58).

Induction of puberty in adolescent males with either hCG monotherapy or with combinational therapy of hCG + recombinant FSH (rFSH) may result in better testicular growth and improvement in potential fertility compared with treatment with testosterone therapy (59). If the patient has spontaneous onset of pubertal development one can start with hCG monotherapy; FSH can be added in cases where azoospermia persists after 6–12 months of treatment. Early induction of spermatogenesis may increase sperm production capacity and reduce the time required for appearance of sperm once fertility is desired. Monotherapy of hCG alone is at least theoretically less efficacious in the induction of spermatogenesis induction than combinational therapy of hCG + FSH (59, 60).

The optimal regimen to maximise the potentiality for fertility in severe cases, i.e. those with testicular volume <4 ml, is unknown. FSH pretreatment may plausibly maximise the Sertoli cell population before exposure to hCG or GnRH-induced endogenous LH and thus has the potential to improve fertility outcomes (61). In girls with HH, treatment with oestrogen needs to be combined with progestin for endometrial cycling.

For older men and women presenting with IHH, pharmacologic treatment is potentially much simpler, though psychological support is a frequently unmet need that is only partly compensated for by help available from patient support groups. The only factors limiting the tempo and dosimetry of pubertal induction in men are the absolute requirements to avoid erythrocytosis and psychological destabilisation related to a late coming-to-terms with issues of libido and sexuality. Given that these patients delayed their presentations for so long, it may seem counter-intuitive that they should wish to 'get it all over with as soon and as simply as possible', but that is a commonly expressed wish, and they can easily become frustrated and disappointed with the apparent slowness of their progress on 'paediatric' doses of testosterone. A regime comprising stepwise incremental doses of testosterone gel via calibrated dispenser would appear to offer the best possibility of achieving physiological simulation of male puberty. However, when offered the choice, our older subpubertal men have almost universally chosen a less physiological, but for them much simpler regime, of 4 monthly i.m. depot injections of testosterone undecanoate 1 g, leading to full pubertal development after around 1 year, without any apparent excursions of haematocrit, or reported psychological difficulties or 'drop-outs' (62). Given the lack of an observed 'andropause' in normal men and the huge degree of overlap between the adverse consequences of untreated hypogonadism and those of normal male ageing (sarcopaenia, osteopaenia, anaemia, etc.), there is no plausible upper age limit beyond which pubertal induction should not generally be undertaken.

For older hypogonadal women, the factors limiting the tempo and dosimetry of oestrogen replacement are the need to optimise breast development and to minimise sensations of bloating and/or breast discomfort that can arise on initial exposure. These women may already have severe osteoporosis and/or sustained a low-trauma fracture, but we would encourage physicians not to reflexly initiate antiresorptive therapy with bisphosphonate right at the outset. These agents lack an evidence base in women (and men) who are totally naive to sex hormones and, moreover, also lack adequate safety and efficacy data much beyond

5–10 years anyway. So bisphosphonates are ideally kept in reserve for later life when discontinuation of oestrogen/progestogen replacement is being contemplated.

Unlike the careful dose titration typically carried out for hypogonadal men, oestrogen/progestogen replacement therapy in adult women has traditionally been entirely empirical, based upon the capacity of a preparation to induce withdrawal bleeds (short-term signal) or to improve/maintain bone density on serial DEXA scanning (ultra long-term signal). This is another area where the optimal management of hypogonadal women might usefully be informed by patient registry data held in relation to trans-women, for whom therapy titrated to achieve serum oestradiol levels in the 300–400 pmol/l range seems to give the best trade-off between benefits and risks (51). In women with impaired bone density at baseline, it is logical to defer bone-directed antiresorptive therapies at least until after maximum anabolic effect of oestrogen on bone has been achieved, as ascertained by serial DEXA scans. There are no data to inform an evidence-based decision on when to stop sex hormone replacement in a hypogonadal woman. However, if bone density is an issue (which it usually is), then it is logical to continue replacement therapy at least until the upper end of the age range for normal age at menopause.

Male hypergonadotrophic hypogonadism

Klinefelter syndrome is by far the commonest (0.1–0.2% birth prevalence) cause of hypergonadotrophic hypogonadism in males and comprises a wide spectrum of clinical and biochemical severity. Nevertheless, as virtually all affected boys manage to initiate puberty, the clinical picture of partial puberty that may be evident in later life may reflect secondary regression effect, more than primary failure of attainment. Only a minority of Klinefelter boys have come to the attention of an endocrinologist by the end of their teenage years, but such patients present potentially difficult management decisions in terms of optimising fertility outcomes.

These have already been extensively reviewed elsewhere (63, 64) but in essence relate to the following issues. First, although the techniques, success rates and general availability for testicular biopsy (or microdissection), sperm retrieval and sperm cryopreservation are continually advancing, this is counterbalanced by the rate of progressive seminiferous tubule degeneration occurring in the patients themselves. Second, the most invasive (and successful) sperm retrieval techniques have the potential to cause the most testicular damage and so would ideally be reserved

for those men actively desiring fertility, in whom this could be combined with superovulation induction, ICSI and embryo transfer into their partners. Yet, fertility is typically not at the forefront of the minds of Klinefelter adolescents, who are at the very peak of their fertility potential then. Finally, it has been suggested that early exposure to exogenous testosterone may reduce success rates of sperm retrieval. All these factors make for difficult conversations with vulnerable young men and their parents.

Regarding the appropriate time to commence androgen replacement in men with Klinefelter syndrome, the key parameters are serum testosterone level, haematocrit, bone density, patient well-being and sexual function. Even if these remain individually within the male reference range, the accumulation of longitudinal data showing a significant rate of decline indicates that the time has come to initiate treatment.

Areas of uncertainty and future research

Studies are needed to assess what impact sex steroid supplementation has on the psychosocial distress experienced by individuals with delayed puberty, and whether this distress has long-term consequences. It is not known whether pubertal delay adversely affects adult bone mass (65) and whether potentially compromised bone health is a reason to initiate sex-steroid replacement. Different oestrogen formulations, routes of administration (oral vs transdermal) and dosing regimens should be studied in controlled trials to develop optimal therapy for girls with delayed puberty.

Other areas for further evaluation include defining the optimal therapy for males with severe hypogonadotrophic hypogonadism, characterised by cryptorchidism, micropenis and lack of spontaneous increase in testicular size in puberty. For instance, should male neonates with bilateral cryptorchidism and/or micropenis be screened for hypogonadotrophic hypogonadism, by checking testosterone and gonadotrophin levels between 1 week and 6 months after birth? With advances in our knowledge of the genetics of IHH, we are also likely to be getting an increasing number of putative diagnoses made in pre-adolescent age, either as a result of family history or from recognition of IHH-associated clinical features (anosmia, history of cryptorchidism, etc.). Might their future fertility outcomes be enhanced by the earliest possible exposure to FSH, so as to 'catch up' on the minipuberty that they never had?

The minority of Turner girls who maintain normal ovarian function (evidenced by persistent menstrual cyclicity and normal levels of gonadotrophins and AMH), but who are not in a relationship will necessarily be concerned

about the possibility of early menopause. An increasing number are likely to turn to ovarian cryopreservation techniques, subject to financial constraints and local availability (66). Long-term outcome data for this in terms of live births will obviously take many years to accumulate.

Meanwhile, we have illustrated how recent scientific advances should already be altering clinician perceptions. We have also sought to support clinicians managing uncertainties in the evidence base, with reference both to physiologic first principles and to informative data arising from other relevant patient groups. Finally, we would emphasise that men and women presenting in advanced adult life with absent puberty cannot simply be 'shoe horned' into paediatric treatment algorithms.

Declaration of interest

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