

Klinefelter syndrome: going beyond the diagnosis

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ABSTRACT

Although Klinefelter syndrome (KS) is common, it is rarely recognised in childhood, sometimes being identified with speech or developmental delay or incidental antenatal diagnosis. The only regular feature is testicular dysfunction. Postnatal gonadotropin surge (mini-puberty) may be lower, but treatment with testosterone needs prospective studies. The onset of puberty is at the normal age and biochemical hypogonadism does not typically occur until late puberty. Testosterone supplementation can be considered then or earlier for clinical hypogonadism. The size at birth is normal, but growth acceleration is more rapid in early and mid-childhood, with adult height greater than mid-parental height. Extreme tall stature is unusual. The incidence of adolescent gynaecomastia (35.6%) is not increased compared with typically developing boys and can be reduced or resolved by testosterone supplementation, potentially preventing the need for surgery. Around two-thirds require speech and language therapy or developmental support and early institution of therapy is important. Provision of psychological support may be helpful in ameliorating these experiences and provide opportunities to develop strategies to recognise, process and express feelings and thoughts. Boys with KS are at increased risk of impairment in social cognition and less accurate perceptions of social emotional cues. The concept of likely fertility problems needs introduction alongside regular reviews of puberty and sexual function in adolescents. Although there is now greater success in harvesting sperm through techniques such as testicular sperm extraction, it is more successful in later than in early adolescence. In vitro maturation of germ cells is still experimental.

INTRODUCTION

This review presents the contemporary approach to the provision of support for boys and adolescents with Klinefelter syndrome (KS) and their parents by practitioners who have a special interest in their clinical care and research.

GETTING THE DIAGNOSIS

Although KS is common, with 47,XXY being present in around 1 in 600 males, not only is it rarely recognised in childhood and adolescence, the majority are actually never diagnosed. Major congenital abnormalities are unusual. Some boys are identified by antenatal diagnosis, usually unexpectedly, but others may not present until later on account of developmental, speech and language delay, or sometimes unusual behavioural patterns. Much has been written about the effect on speech and development and about growth and puberty

variations from follow-up studies of newborn-identified individuals from the 1970s to 1990s, which provide an unbiased overview on account of recruitment by population screening.^{1–4} A recent review is available with more specific information.⁵

COMMUNICATING THE DIAGNOSIS

On first encounter with the parents it is important to establish rapport and set out a balanced overview of the condition, ideally using the genetic shortcut 'XXY' or the abbreviation 'KS', which families prefer. Use of the term 'variant' rather than 'abnormality' acknowledges that the majority of boys and men with KS function pretty normally. Reassurance that their son will not necessarily develop all the features of the syndrome is really valuable. Many parents worry about explaining the diagnosis to the wider network of family, friends, nursery and school as most people have never heard of KS. Discussions around the diagnosis of KS outwith the immediate family are not usually necessary or helpful, unless relevant for medical or educational purposes. Most boys with KS grow up happily within the family environment and do not look or behave differently. Guiding the parents in including their son in the family routines and doing normal things on a day-to-day basis without constantly referring to KS is important, and as potentially socially vulnerable individuals, encouragement, love, care and individual attention from a supportive family are the most important elements of their upbringing.

INFANCY AND EARLY CHILDHOOD

Growth

The size at birth of boys with KS is not different from the population, but growth acceleration is more rapid in early and mid-childhood, resulting in upward height centile shifts, and by mid-childhood many boys end up on a centile greater than mid-parental height.¹ Extreme tall stature is unusual, and if not present by school entry then it is not going to be an issue and thus parents can be reassured. Boys with other X aneuploidy variants of KS (48,XXXY, 48,XXYY) may grow even taller, but this may depend on the presence of other congenital skeletal variations. 49,XXXXY and its variants may also be associated with reduced height.⁶

Testicular function

Hypogonadism in KS may start as early as fetal life or infancy due to the higher prevalence of under-developed genitalia and cryptorchidism, reduced germ cell number on testicular biopsies, and smaller testicular size, and studies have also suggested a blunted testosterone surge during mini-puberty



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and an increase in gonadotropins over the first 2–3 months of infancy.^{7,8} However, due to lack of general understanding about mini-puberty in infants, it is unclear if any hypogonadism in boys with KS has management implications. Studies on this area are few. Davis *et al*⁹ reported improved body composition in infants randomly assigned to early testosterone treatment. Samango-Sprouse *et al* reported higher scores on standardised developmental assessments in multiple cognitive domains at 3 and 6 years of age in boys who received a course of testosterone for treatment of micropenis.¹⁰ However, this retrospective study lacked blinding and randomisation, thereby limiting the generalisability of the findings. Reports of cognitive and behavioural benefits in boys with KS treated with testosterone need to be replicated in prospective studies. Hence, the current evidence is insufficient to support the routine use of testosterone in KS during infancy.¹¹ Referral to a paediatric endocrinologist should be considered if micropenis is present. The British Society for Paediatric Endocrinology and Diabetes guidelines recommend three injections of testosterone 25 mg (0.1 mL) at monthly intervals or topical 1%–2% testosterone cream as the usual choices for treatment.¹² If cryptorchidism is noted, the infant should be referred to paediatric urology.

Speech and developmental delay

Around two-thirds of boys with KS will require speech and language therapy or developmental support, but it is important to be aware of their needs and to institute therapy as early as possible.^{1–5} For boys who require help, the amount of input required is entirely dependent on the level of need and is of the same extent as would be required for chromosomally typical children; thus, no treatment approaches are unique to boys with KS. This is important to stress as some therapists may cite inexperience and lack of knowledge about specific treatments for KS.

MID-CHILDHOOD

Hypogonadism

Studies of gonadal function in mid-childhood have not shown any abnormality so there is no clear rationale for testosterone supplementation (figure 1).^{1,13–16}

Education and behaviour

Most boys with KS do not fall into the category of requiring significant educational support, but the subtleties of specific learning defects, particularly in receptive and expressive language, may cause frustration, and the inability of a boy to explain himself clearly and as quickly as others may lead to temper tantrums and anger outbursts. Clear parenting guidelines and professional support are valuable at this age. Social skills often take longer to develop, with boys feeling isolated, preferring their own company. Family guidance and encouragement is key here. Those with more severe difficulties and associated comorbidities will benefit with input from multidisciplinary community paediatric and child and adolescent mental health services.

ADOLESCENCE

Hypogonadism

The principal concerns in the second decade are around the treatment of hypogonadism, if present, with testosterone and assessment of fertility prospects and possibly its preservation.

The clinical onset of puberty is not delayed in boys with KS, which is a frequent misunderstanding. Early testicular enlargement occurs at the same age and to the same initial extent as chromosomally typical boys. Although the gonadotropins follicle

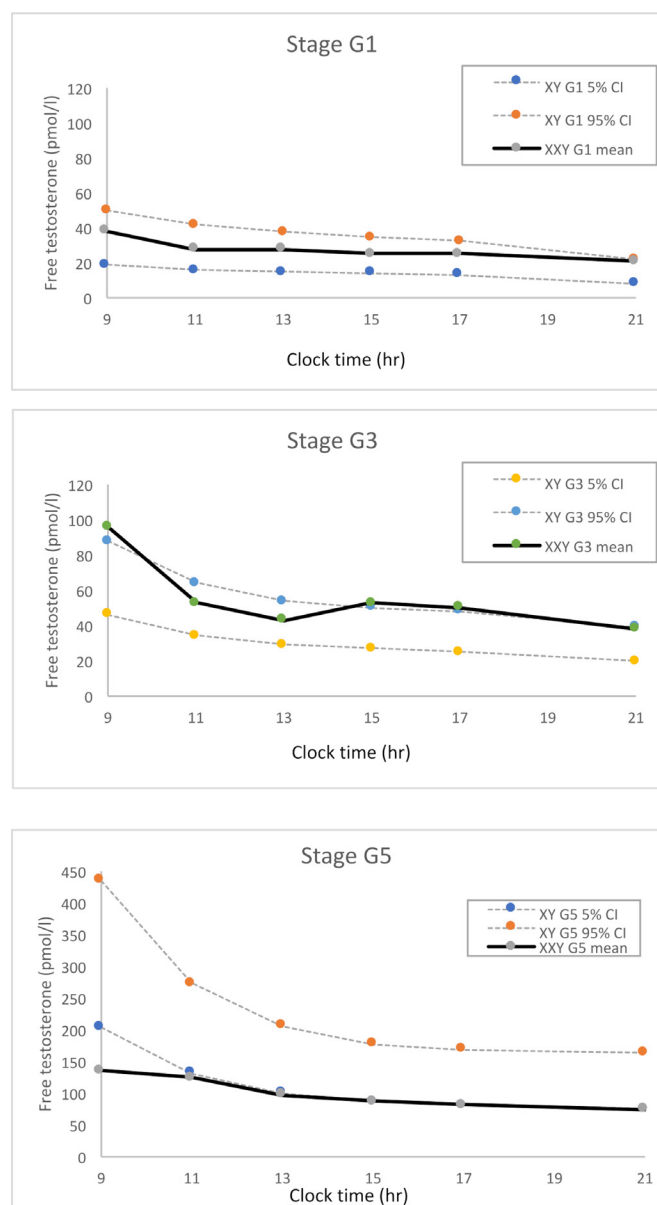


Figure 1 Diurnal variation profiles (09:00–21:00) of free testosterone concentrations measured in saliva. Unpublished data from 10 XXY boys (mean of 52 diurnal profiles) and 13 XY boys at Tanner stage G1, 6 XXY boys (mean of 10 diurnal profiles) and 25 XY boys at Tanner stage G3, and 11 XXY boys (mean of 20 diurnal profiles) and 13 XY boys at Tanner stage G5. XXY and XY boys were recruited by newborn population screening¹ and the mean testosterone concentrations in XXY boys are compared with the 95% CI from the XY controls by pubertal stage based on data from Butler *et al*.⁴⁰ The plasma testosterone equivalent is approximately 10 times higher (regression equation for conversion: salivary free testosterone (pmol/L)=9.8 plasma testosterone (nmol/L)+34.5).⁴⁰

stimulating hormone (FSH) and luteinising hormone (LH) increase at the start of puberty, testosterone is usually within the pubertal stage-related range (figure 1).^{1,5,13–16}

Hypogonadism can be defined biochemically or clinically (box 1). Biochemical hypogonadism (box 2) does not normally occur until later on in puberty, from around 14 years of age and over, and at Tanner stage 5.¹ Here the usual accelerated nocturnal rise in testosterone is blunted (figure 1). Thus, assessment of hypogonadism can only be made accurately by measuring the

Box 1 Classification of hypogonadism in Klinefelter syndrome

Biochemical hypogonadism

- ⇒ Low testosterone.
- During mini-puberty.
- During main puberty: usually not before puberty stage G5.

Clinical hypogonadism

- ⇒ Micropenis.
- ⇒ Slow virilisation, that is, delayed pubertal *progress*.
- ⇒ Gynaecomastia.
- ⇒ High body mass index: obesity.
- ⇒ Poor muscle development or tone?
- ⇒ Lethargy?

testosterone concentration in the morning (08:00–09:00), when it is at its highest on account of the significant diurnal variation in late puberty (figure 1). Therefore, afternoon blood samples are not useful diagnostically.

Clinical hypogonadism (box 1) is also a reason to consider testosterone supplementation in boys with KS as typical full virilisation may not occur. One manifestation and reason for intervention include increasing adiposity and the occurrence of a central deposition of fat particularly on the hips and abdomen, often described as a ‘beer-belly’.¹ Low muscle tone and reduced power may be subjectively improved by testosterone substitution. It can be difficult to determine whether symptoms of lethargy and lack of motivation are due to testosterone insufficiency, or just part of the syndrome. In such cases a trial of testosterone supplementation can be considered.

Gynaecomastia

From a review by Butler¹⁷ of all the 191 published cases, the incidence of gynaecomastia in boys with KS (35.6%) is not increased compared with typically developing boys, and the breast enlarges to the same extent, but the persistence of gynaecomastia into adulthood may result from the absence of the morning rise of testosterone during later puberty and adulthood and the ensuing hypogonadism. Consequently, testosterone supplementation in a physiological incremental approach starting with transdermal

Box 2 Assessment of hypogonadism and testosterone replacement at each time point

Infancy (4–8 weeks)

- ⇒ Testosterone, follicle stimulating hormone (FSH) and luteinising hormone (LH).

Mid-puberty (age 13+ years)

- ⇒ Testosterone, FSH and LH at 08:00.

Later puberty (age 14+ years)

- ⇒ Testosterone, FSH, LH and inhibin at 08:00.

On testosterone gel

- ⇒ 4–6 hours after application.
- ⇒ Testosterone, FBC, FSH and LH.

On Sustanon/testosterone enantate injections

- ⇒ Preinjection (trough) level.
- ⇒ Testosterone, FSH, LH, FBC and LFT.

On Testosterone undecanoate (Nebido) injections

- ⇒ Peak level at 4 weeks after injection *and* preinjection (trough) level.
- ⇒ Testosterone, FSH, LH, FBC and LFT.

gel 10–20 mg each morning has been shown to reduce or resolve the development of gynaecomastia, potentially preventing the need for surgical intervention later on.¹⁷ It is most effective when treatment is started at the first appearance of breast tissue enlargement.

Growth spurt

The magnitude of the adolescent growth spurt in height is the same in boys with KS as in typically growing boys.¹⁵ Thus it is possible to predict with confidence that the adult height of a boy whose height is within the normal centile range at the start of puberty will not become excessive. Those with tall parents and whose heights are above 3 SD in late childhood, if concerned about extreme tall stature, may benefit from rapidly escalating doses of intramuscular testosterone (Sustanon or testosterone enantate) once the clinical onset of puberty is documented, monitoring height and bone age.³

Psychological support

The constellation of the developmental variations in KS can have implications for clinical care. Language problems can disrupt understanding of content and meaning and may impact on outcomes of clinical discussions. Confusion can lead to misunderstandings of information, increased anxiety and non-compliance with treatment. Provision of psychological support is important as part of a multidisciplinary approach to promoting lifespan health and well-being, and importantly supporting endocrine and fertility discussions.

Boys with KS are reported to be at increased risk of impairments in social cognition and less accurate perceptions of social emotional cues, while simultaneously experiencing increased emotional arousal, in parallel with decreased ability to identify and verbalise their emotions.^{18 19} This array of difficulties may affect management of, coping with and verbalising feelings and concerns, with a potential to be exacerbated by receptive and expressive language problems.

These features, often in parallel with literal interpretation of language and problems with social communication, may impede understanding and may be a barrier to externalising and discussion with family and partners. This can, in turn, contribute to feelings of panic and misunderstandings during interactions, with significant impact on relationships, and can extend to clinical encounters.

Provision of psychological support may be helpful in ameliorating these experiences and provide opportunities to develop strategies to recognise, process and express feelings and thoughts.²⁰ This may aid understanding, may be beneficial in reducing stress and anxiety, and promote understanding of clinical discussions, treatment and informed decision making.

Gender incongruence

The incidence of gender incongruence and gender dysphoria is not increased in males with KS.²¹

Education

KS can have a significant impact on cognitive, social and emotional development and well-being. The generalised breadth and range of subjects in the high school years may be particularly challenging, and social communication problems may cause upset and difficulties ‘joining in’ with peers.

Short-term working auditory memory and auditory processing difficulties have been reported in KS and may significantly impact access of curriculum, particularly with traditional forms

of teaching, such as speaking, listening and writing, where more time to process and record information may be required.¹⁸ Written support from paediatricians and psychologists can be valuable at this point, providing anticipatory and advisory guidance, including provision of one-to-one support, small group settings and extra time during examinations. Additional guidance from educators to aid learning and memory can be valuable: provision of tailored materials such as visuals, bullet points, shorter sentences and practical experiences.

Post-16 education and higher education may provide opportunities to study fewer, specialised subjects, creating perhaps increased opportunities to demonstrate niche abilities during these later educational years. In these settings, psychological and educational guidance for provision of reasonable adjustments, access of appropriate assistance such as Disabled Students' Allowance, and career guidance are very valuable during positive transitions between school, college and beyond into employment, protecting self-esteem and building confidence. A choice of practical, non-academic careers can alleviate the pressure of standard learning processes. Similarly, written support and guidance for employers may be helpful in some workplace settings.

Fertility

Previous studies of infant and young testes have shown normal architecture and the presence of germ cells, although there appears to be a reduction in their number.²² When puberty commences, most of the developing tubules are Sertoli cells only, and in response presumably to the high gonadotropins a disordered testicular architecture develops with hyalinisation of the seminiferous tubules. It is possible to see a significant degree of initial testicular growth, in some boys with KS up to 12 mL, but subsequent involution and reduction in size occur, usually measuring 3–5 mL in older adolescents and adults. On account of the normal pubertal prostatic development, ejaculation occurs but the semen is azoospermic in over 90%.²³ For adolescents who are sexually active, contraception should still be advised.

It is wise to introduce the concept of likely fertility problems during the teenage years, alongside the need for regular reviews of puberty and sexual function.²⁴ Although there is now much greater success in sperm harvesting through newer techniques such as testicular sperm extraction or microscopic testicular sperm extraction (mTESE), the optimal timing of this process is unclear. The largest meta-analysis of sperm retrieval in patients with KS suggested a success rate of 44%, with age, testosterone, FSH and testicular volume having no significant relationship with outcome.²⁵ This contrasts initial studies which indicated that success was less likely in men aged over 35 years and which started an interest in attempting sperm retrieval in younger patients.²⁶ However, there is increasing evidence that fertility preservation should not be offered to adolescents younger than 16 years due to the lower retrieval rates of germ cells by mTESE compared with those for adolescents and adults between 16 and 30 years.^{26 27}

Many young adult men with KS are emotionally less mature than their counterparts and the concept of fertility estimation and the emotional consequences of knowing they are going to be infertile need very careful counselling and preparation. The balance of carrying out a surgical sperm retrieval at the right time must be measured against the potential psychological distress caused if no sperm is found. The counselling process is important as some men with KS may have a reduced capacity to understand complex explanations. Points for discussion are best presented in a simple structured way and backed up by a

written version. Once a young adult with KS is mature enough to make this decision, mTESE can be considered if azoospermia on a serial semen analysis is demonstrated.

Future experimental considerations

By mid-puberty most of the testicular damage has already occurred and germ cells are reduced or totally absent.²⁸ This is believed to be due to a massive loss of spermatogonial stem cells in the early pubertal period. However, the lack of longitudinal data makes it impossible to determine the trajectory of germ cell loss in individual patients. While cryopreservation of prepubertal testicular tissue to preserve spermatogonial stem cells is becoming more common (eg, those facing cancer treatment), this is not a straightforward option for boys with KS.²⁹ This is due to the uncertainties of whether germ cells are present within the tissue and their potential to undergo spermatogenesis. While they may be present in tissues obtained from prepubertal patients, the majority of these germ cells are likely to be aneuploid (XXY) and unlikely to be viable for subsequent use in transplantation or in vitro spermatogenesis. In addition, the potential for XX or XY spermatogonia to spontaneously lose the extra X chromosome resulting in focal spermatogenesis at puberty is unknown and removing testicular tissue in prepuberty may negatively impact on this.³⁰ As a result, current guidelines produced by the European Academy of Andrology recommend against performing a testicular biopsy in prepuberty, instead focusing on maximising the potential for obtaining viable sperm by performing mTESE in young adulthood.²⁴ This situation may change in the future should effective methods for in vitro spermatogenesis be developed that could be applied to germ cells obtained from patients with KS. At the time of writing, there is only experimental evidence in mouse models of chromosome loss.³¹

INTO ADULT LIFE

We know from population mortality and morbidity studies that there is no significant lowering of life expectancy in males with KS; however, higher risk areas include osteoporosis, cardiovascular disease and breast cancer.^{32 33} Lifelong follow-up is important not only from the endocrine and metabolic perspective but also for emotional, psychological and fertility support. Only recently have specialist services for adults with KS been established, such as our University College London Hospital KF-Xtra Clinic, a multidisciplinary team, co-authors of this paper, transitioning boys with KS seamlessly from childhood and adolescence to adult services to provide lifelong care. This approach can provide benefits both to quality of life and physical well-being and also research.

Testosterone treatment and metabolic care

Testosterone therapy is the mainstay of treatment for men with KS, with benefits including reduced fat mass and improved muscle strength, bone density, libido and mood.^{34 35} Current formulations of testosterone include testosterone gels (topical daily application), weekly to monthly mixed testosterone esters given either by subcutaneous or intramuscular injections, and 3 monthly testosterone undecanoate (box 3). No data exist to guide optimal formulation and dosing in adults with KS. Testosterone gels, in metered pumps, allow self-administration and easy dose titration, minimise fluctuation in testosterone levels, and can be helpful when introducing therapy. Intramuscular treatment requires administration by the healthcare staff, so patients often find the long-acting formulation convenient and can be

Box 3 Types and dosages of testosterone suitable at each age

Intramuscular or subcutaneous

Infancy or toddler (for micropenis)

⇒ Sustanon or testosterone enantate 25 mg (0.1 mL) for three injections at monthly intervals. Course can be repeated if required.

Puberty

⇒ Sustanon or testosterone enantate 50 mg (0.2 mL) intramuscularly/subcutaneously every 4 weeks once clinical signs of puberty are evident, then dose escalation at 6–12 monthly intervals to full dose of 250 mg 3–4 weekly (or 100 mg every 7–10 days subcutaneously).

Postpuberty

⇒ Sustanon or testosterone enantate 250 mg 3–4 weekly intramuscularly or 100 mg every 7–10 days subcutaneously.
⇒ Testosterone undecanoate (Nebido) 1000 mg intramuscularly 10–14 weekly.

Transdermal

Puberty

⇒ Testosterone 2% gel (Tostran) 10 mg daily once clinical signs of puberty are evident. May be more effective if administered in the morning if gynaecomastia is present.
⇒ Dose escalation at 6–12 monthly intervals to full dose (product-dependent).

Postpuberty

⇒ Adult dose (Tostran 60 mg, Testavan 69 mg, Testogel 40 mg), or locally available preparations titrated to clinical effect and to achieve 4–6 hours post administration a plasma testosterone concentration in the mid-upper male range.

useful where compliance is an issue. Three to four weekly injections lead to greater fluctuations in testosterone levels, which can be problematic particularly in mood variations and energy. More frequent, lower dose self-administered subcutaneous injections can be considered as well.³⁶ Monitoring of therapy includes an assessment of the testosterone concentration, full blood count, haematocrit and prostate-specific antigen in relevant subjects. Polycythaemia is the most frequent side effect encountered, particularly with long-acting testosterone.³⁵

KS is associated with an increased risk of metabolic syndrome, insulin resistance and type 2 diabetes mellitus, obesity, dyslipidaemia, and an approximate doubling of risk of cardiovascular disease.³⁷ While the exact mechanisms responsible for this remain to be elucidated, data on the modifying influence of testosterone therapy are conflicting in men with hypogonadism.^{35,38} Education on healthy lifestyle choices, and provision of careful surveillance and appropriate interventions to actively manage cardiovascular risk therefore remain essential.

CONCLUSIONS

The approach to supporting boys and adolescents with KS is age-dependent and needs multiagency input. Provision of an accurate picture of the condition in contrast to internet search findings is important for reassurance. A report on this journal regarding the outcome of boys with KS identified in the Edinburgh newborn population screening study presents a balanced perspective on the range of functioning and lifestyle of adults with KS and this can help guide parents when KS is diagnosed.³⁹ Although the information in this review may benefit those in whom KS is already recognised, how do we address the issue of the 75%

of males with KS who remain unidentified? Discussion around population genetic screening and prospective identification continues, but this has many ethical and financial considerations.

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REFERENCES

- 1 Ratcliffe SG, Butler GE, Jones M. Edinburgh study of growth and development of children with sex chromosome abnormalities. IV. *Birth Defects Orig Artic Ser* 1990;26:1–44.
- 2 Nielsen J, Wohler M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Aarhus, Denmark. *Birth Defects Orig Artic Ser* 1990;26:209–23.
- 3 Stewart DA, Bailey JD, Netley CT, et al. Growth, development, and behavioral outcome from mid-adolescence to adulthood in subjects with chromosome aneuploidy: the Toronto study. *Birth Defects Orig Artic Ser* 1990;26:131–88.
- 4 Robinson A, Bender BG, Linden MG, et al. Sex chromosome aneuploidy: the Denver prospective study. *Birth Defects Orig Artic Ser* 1990;26:59–115.
- 5 Davis S, Howell S, Wilson R, et al. Advances in the interdisciplinary care of children with Klinefelter syndrome. *Adv Pediatr* 2016;63:15–46.
- 6 Ottesen AM, Aksglaede L, Garn I, et al. Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. *Am J Med Genet A* 2010;152A:1206–12.
- 7 Ross JL, Samango-Sprouse C, Lahlou N, et al. Early androgen deficiency in infants and young boys with 47,XXY Klinefelter syndrome. *Horm Res* 2005;64:39–45.
- 8 Aksglaede L, Davis SM, Ross JL, et al. Minipuberty in Klinefelter syndrome: current status and future directions. *Am J Med Genet C Semin Med Genet* 2020;184:320–6.
- 9 Davis SM, Reynolds RM, Dabelea DM, et al. Testosterone Treatment in Infants With 47,XXY: Effects on Body Composition. *J Endocr Soc* 2019;3:2276–85.
- 10 Samango-Sprouse C, Stapleton EJ, Lawson P. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. *American journal of medical genetics. Part C, Seminars in medical genetics* 2015;169:150–7.
- 11 Flannigan R, Patel P, Paduch DA. Klinefelter syndrome. The effects of early androgen therapy on competence and behavioral phenotype. *Sex Med Rev* 2018;6:595–606.
- 12 BSPED. BSPED guideline: testosterone therapy in infancy and adolescence. Available: <https://www.bsped.org.uk/media/1987/revised-bsped-testosterone-guideline-v3.pdf>
- 13 Salbenblatt JA, Bender BG, Puck MH, et al. Pituitary-gonadal function in Klinefelter syndrome before and during puberty. *Pediatr Res* 1985;19:82–6.
- 14 Topper E, Dickerman Z, Prager-Lewin R, et al. Puberty in 24 patients with Klinefelter syndrome. *Eur J Pediatr* 1982;139:8–12.
- 15 Aksglaede L, Skakkebaek NE, Almstrup K, et al. Clinical and biological parameters in 166 boys, adolescents and adults with nonmosaic Klinefelter syndrome: a Copenhagen experience. *Acta Paediatr* 2011;100:793–806.
- 16 Davis SM, Rogol AD, Ross JL. Testis development and fertility potential in boys with Klinefelter syndrome. *Endocrinol Metab Clin North Am* 2015;44:843–65.
- 17 Butler G. Incidence of gynaecomastia in Klinefelter syndrome adolescents and outcome of testosterone treatment. *Eur J Pediatr* 2021;180:3201–7.
- 18 van Rijn S, Swaab H, Aleman A, et al. X Chromosomal effects on social cognitive processing and emotion regulation: A study with Klinefelter men (47,XXY). *Schizophr Res* 2006;84:194–203.
- 19 van Rijn S, Swaab H. Emotion regulation in adults with Klinefelter syndrome (47,XXY): Neurocognitive underpinnings and associations with mental health problems. *J Clin Psychol* 2020;76:228–38.
- 20 van Rijn S, de Sonnevile L, Swaab H. The nature of social cognitive deficits in children and adults with Klinefelter syndrome (47,XXY). *Genes Brain Behav* 2018;17:e12465.
- 21 Kreukels BPC, Köhler B, Nordenström A, et al. Gender dysphoria and gender change in disorders of sex Development/Intersex conditions: results from the dsd-LIFE study. *J Sex Med* 2018;15:777–85.
- 22 Van Saen D, Vloeberghs V, Gies I, et al. When does germ cell loss and fibrosis occur in patients with Klinefelter syndrome? *Hum Reprod* 2018;33:1009–22.
- 23 Deebel NA, Bradshaw AW, Sadri-Ardekani H. Infertility considerations in Klinefelter syndrome: from origin to management. *Best Pract Res Clin Endocrinol Metab* 2020;34:101480.
- 24 Zitzmann M, Aksglaede L, Corona G, et al. European Academy of andrology guidelines on Klinefelter syndrome Endorsing organization: European Society of endocrinology. *Andrology* 2021;9:145–67.

- 25 Corona G, Pizzocaro A, Lanfranco F, *et al.* Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2017;23:265–75.
- 26 Ramasamy R, Fisher ES, Ricci JA, *et al.* Duration of microdissection testicular sperm extraction procedures: relationship to sperm retrieval success. *J Urol* 2011;185:1394–7.
- 27 Franik S, Hoeijmakers Y, D'Hauwers K, *et al.* Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. *Hum Reprod* 2016;31:1952–9.
- 28 Deebel NA, Galdon G, Zarandi NP, *et al.* Age-Related presence of spermatogonia in patients with Klinefelter syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2020;26:58–7.
- 29 Goossens E, Jahnukainen K, Mitchell RT, *et al.* Fertility preservation in boys: recent developments and new insights [†]. *Hum Reprod Open* 2020;2020:hoaa016.
- 30 Oates RD. The natural history of endocrine function and spermatogenesis in Klinefelter syndrome: what the data show. *Fertil Steril* 2012;98:266–73.
- 31 Galdon G, Deebel NA, Zarandi NP, *et al.* In vitro propagation of XXY undifferentiated mouse spermatogonia: model for fertility preservation in Klinefelter syndrome patients. *Int J Mol Sci* 2021;23:173.
- 32 Swerdlow AJ, Higgins CD, Schoemaker MJ, *et al.* Mortality in patients with Klinefelter syndrome in Britain: a cohort study. *J Clin Endocrinol Metab* 2005;90:6516–22.
- 33 Bojesen A, Juul S, Birkebaek NH, *et al.* Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. *J Clin Endocrinol Metab* 2006;91:1254–60.
- 34 Wang C, Cunningham G, Dobs A, *et al.* Long-Term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 2004;89:2085–98.
- 35 Fernández-Balsells MM, Murad MH, Lane M, *et al.* Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010;95:2560–75.
- 36 Figueiredo MG, Gagliano-Jucá T, Basaria S. Testosterone therapy with subcutaneous injections: a safe, practical, and reasonable option. *J Clin Endocrinol Metab* 2022;107:614–26.
- 37 Jiang-Feng M, Hong-Li X, Xue-Yan W, *et al.* Prevalence and risk factors of diabetes in patients with Klinefelter syndrome: a longitudinal observational study. *Fertil Steril* 2012;98:1331–5.
- 38 Jones DB, Higgins B, Billet JS, *et al.* The effect of testosterone replacement on plasma lipids and apolipoproteins. *Eur J Clin Invest* 1989;19:438–41.
- 39 Ratcliffe S. Long-Term outcome in children of sex chromosome abnormalities. *Arch Dis Child* 1999;80:192–5.
- 40 Butler GE, Walker RF, Walker RV, *et al.* Salivary testosterone levels and the progress of puberty in the normal boy. *Clin Endocrinol* 1989;30:587–96.