

Title: Klinefelter Syndrome: What should we tell prospective parents?

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Abstract

Klinefelter syndrome (KS) or 47,XXY is the most common sex chromosome aneuploidy (SCA), occurring at a prevalence of 1 in 600 male pregnancies. Historically, only 25% of individuals with KS came to medical attention, for a range of issues across the life course including under-virilisation at birth, developmental and social concerns in childhood, absence, delay or arrest of puberty in adolescence or infertility in adulthood. Our understanding of the phenotypic spectrum of KS has been largely influenced by this ascertainment bias. With increasing uptake of antenatal non-invasive prenatal testing (NIPT) a corresponding increase in identification of KS has been documented. Population-based longitudinal data from infancy to adulthood on these individuals is lacking, which impedes balanced antenatal genetic counselling and raises issues for prospective parents and clinicians alike.

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Key points

What is already known about this topic?

- Prior to the widespread availability of NIPT, only 25% of individuals with Klinefelter Syndrome were detected on the basis of postnatal clinical features
- With increasing uptake of NIPT, increasing numbers of sex chromosome aneuploidy will be detected in countries where sex chromosomes are included in this test
- Antenatal counselling for prospective parents after a presumptive or confirmed case of Klinefelter Syndrome is challenging due to ascertainment bias of existing data

What does this study add?

- An awareness of the limitations of current data is crucial to allow a balanced approach to antenatal counselling
- Involvement of paediatric endocrinologists or paediatricians in the antenatal counselling process will facilitate this balanced approach
- The role of peer support and advocacy networks in this process should be explored
- Highlights a need for high quality longitudinal data to report on pregnancy outcomes and phenotypes of infants born with antenatally diagnosed SCA

Introduction

Klinefelter Syndrome (KS) or 47,XXY is the most common sex chromosome aneuploidy (SCA), occurring at a rate of approximately 1 in 500-600 male pregnancies (1, 2). These figures are derived from published population data extracted from a Danish cytogenetic central registry(3) and from similar United Kingdom registries (4). The clinical phenotype cannot be predicted on the basis of chromosomal findings alone, with a broad range of health issues, only some resulting in presentation for medical care. As a result, historically it is estimated that up to 75% remain undetected throughout life(5, 6). Contemporary practice with a shift towards non-invasive prenatal testing (NIPT) for chromosomal disorders has resulted in an increasing number of KS males being identified antenatally (7, 8). Sex chromosome analysis is not included as part of NIPT screening in many countries (9) for reasons including concerns around the potential for sex selection(10). Professional bodies worldwide have cautioned against its routine use. A joint position paper compiled by the European Society of Human Genetics and the American Society of Human Genetics recommends against routine screening for SCA including KS with NIPT(11), and both the International Society of Prenatal Diagnosis and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommend that SCA screening should be optional and only performed with informed consent(12, 13). This consent should extend beyond a discussion around the ability of NIPT to identify chromosomal sex of a foetus (14) and should include explicit information about the possibility of identification of an SCA, including KS and the range of phenotype associated with these conditions.

While many excellent and comprehensive reviews have outlined the genetic, clinical and neurodevelopment aspects of KS in detail (15, 16), in this paper, we briefly discuss the range of possible outcomes to be considered, identify and outline a comprehensive plan for counselling of prospective parents, when a foetus has been either identified as being at risk of (on NIPT) or confirmed as having KS, in order to address common questions.

What is Klinefelter Syndrome and how common is it? Epidemiology and risk factors

KS was initially described in 1942 as a condition commencing in adolescence ‘characterised by gynaecomastia and a specific type of hypogonadism’ and was thought to relate almost entirely to the function of Sertoli cells (17). A supernumerary X chromosome was subsequently identified as the underlying explanation for KS in 1959 (18), with the additional X chromosome of maternal origin in ~50% of cases (19). Overall, 90% of individuals are non-mosaic where all cells contain this chromosomal configuration. The remaining 10% demonstrate mosaic or rare variants (2). KS occurs as a random event and results from nondisjunction, which can occur in meiosis or during the early

stages of post-zygotic development. An effect of increasing maternal age is weaker in KS compared to other chromosomal disorders (20, 21). The clinical spectrum of KS is highly variable. Historically timing of clinical presentation has varied across the life course, related to specific, age related clinical disorders or problems (12). Absence of presentation for medical care is estimated at 68-75% of all KS, with non-identification of cases, resulting in ascertainment bias in terms of the reported frequency at which clinical features are observed (5). This bias has made accurate, complete and balanced antenatal counselling challenging. There are limited but emerging data on clinical outcomes in males who have remained undiagnosed for the majority of their lives as reported by Zhao et al (6). What remains unclear the difference in severity of phenotype between those who had and had not presented for medical attention prior to identification of KS as part of this biobank initiative. Without systematic longitudinal data into adulthood, it is unknown whether any male with KS can be considered truly 'unaffected', regardless of their level of contact with medical professionals.

Attempts to explain the wide variation in phenotype have not to date provided clinicians with an ability to 'predict' postnatal outcomes and complications on the basis of genetic testing. In a study of 70 KS, X chromosome inactivation (skew X) was found in 12/70 (26%) and CAG repeat length heterozygosity for both short and long alleles in 46/70. Height, arm span, bone density gynaecomastia and testis size correlated with these, while X inactivation correlated with lipid status and response to testosterone (16, 22, 23). Additionally, DNA methylation profiling and RNA sequence transcription and profiling showed transcription of both autosomes and X chromosomes in the pseudoautosomal region (PAR) 1 and PAR2 regions to be altered in white cells in KS, with both hyper and hypomethylation and epigenetic instability or changes which may alter transcription and phenotypic traits. (12,24). Five to 15% of X chromosome genes escape inactivation in KS and are expressed from both chromosomes (24, 25) which may also account for some of the phenotypic variability in KS (26).

The increased rate of antenatal SCA diagnoses as a result of NIPT in some countries (7) presents an opportunity to establish longitudinal follow up of a more complete cohort(27).

How is KS diagnosed prenatally?

Prenatal features

The majority of fetuses with KS do not present with any ultrasound abnormalities that prompt diagnostic testing. Abnormalities detected on foetal ultrasound such as nuchal thickness, heart or brain abnormality are likely to lead to further investigation with amniocentesis which in turn may

lead to a diagnosis of KS(28), again with an ascertainment bias . Features such as undescended testes or micropenis, although detected in a minority of fetuses with KS, are unlikely to imply KS per se, and diagnosis is most frequently confirmed after a high risk NIPT result in countries where SCA are tested (7, 29).

Will KS impact on the timing and mode of birth?

While the majority of KS cases are undetected before birth, an increased risk of preterm delivery, Caesarean delivery, respiratory distress syndrome and infant mortality have been reported in small cohorts of prenatally diagnosed KS (30). There is insufficient evidence to support recommendations around changes to prenatal management of known KS fetuses.

Prenatal diagnosis

NIPT is considered a good screening test for SCA, where the positive predictive value for 47,XXX, 47,XXY and 47,XYY is up to 90%(31). However, abnormal results require definitive confirmation. This should occur via prenatal diagnostic procedures (amniocentesis/chorionic villous sampling) in a situation where interruption of pregnancy is being considered or by post-natal testing of the baby, facilitating confirmation of the nature of the SCA and associated phenotype. This information should be provided at the first point of contact following an increased risk NIPT. It has been demonstrated that in some jurisdictions, invasive confirmatory testing only occurred in 36% of those identified at high risk on NIPT(32), raising concerns that NIPT is not being utilized as intended within a screening and diagnostic pathway. This low rate of diagnostic confirmation suggests that some children remain undiagnosed or decisions regarding termination are being made based on screening results alone. Genetic counselling plays a key role at all stages of the diagnostic pathway. Ideally, parents should be made aware that SCA may be suspected if NIPT is performed , and of need for further testing to confirm result if high risk is identified on NIPT. However this is not always the case. Hence the potential diagnosis can be highly unexpected, confronting and anxiety-provoking. Genetic counselling should be offered to all families following either a suspected or confirmed diagnosis of KS, ideally at both timepoints, by a clinician familiar with the issues and complexities discussed herein and should be provided in a timely manner by a multidisciplinary team which may include obstetricians, genetic counsellors, paediatric endocrinologists and peer-support/advocacy teams.

Key counselling point

Genetic counselling by a clinician familiar with the issues and complexities of KS should be offered to all families following a suspected prenatal diagnosis. After a confirmed diagnosis, timely access to a

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multidisciplinary team may include obstetricians, genetic counsellors, paediatric endocrinologists and peer-support.

Post-natal issues in confirmed KS

Counselling of confirmed KS must include a comprehensive understanding of an expected range of outcomes in KS. The wide variability in clinical presentation of KS has resulted in possible bias in the ability to provide a balanced discussion of a range of short and long term outcomes, impeding the ability of genetic counselling to provide a balanced view to prospective parents. In many cases, antenatal counselling for KS occurs after a positive antenatal genetic test which has been undertaken for another reason i.e. the pregnancy is asymptomatic and the result is unexpected. A balanced discussion needs to focus on clinical problems that might present at different ages and how they may affect a male with KS(29), acknowledging the fact that a majority of males who have KS remain undiagnosed through the life course, where a complete understanding of their medical and psychosocial is not fully understood.

Testosterone deficiency: Neonatal presentation and treatment

At birth, testosterone levels are typically high in male infants, falling over the first week of life (33). Thereafter, a postnatal surge of pituitary hormones including gonadotrophins (Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH)) results in 'mini-puberty' where testosterone levels peak 1-3 months and decline by 6 months (34, 35) after which testosterone levels are typically undetectable until the onset of puberty.

A key feature of KS is the presence of hypergonadotropic hypogonadism, testosterone deficiency and Sertoli cell deficiency, resulting in infertility. Given that micropenis and cryptorchidism (bilateral undescended testes) may comprise part of the clinical spectrum of KS, although uncommon, it has been postulated that all boys with KS have a degree of deficiency in testosterone production in infancy. While the proportion of boys with KS who have cryptorchidism is quoted as 27-37% (15), these data have an ascertainment bias, based on clinical studies conducted prior to the introduction of NIPT and subsequent ascertainment of otherwise asymptomatic cases. Antenatal testosterone levels have been shown to be normal in 47,XXY and 47,XYY compared to 46,XY infants at 16-20 weeks gestation (36). These reports regarding testosterone levels during mini-puberty in boys with KS have varied (37), with interpretation confounded by variance in what constitutes timing of the normal neonatal surge, making comparisons between studies difficult. In a retrospective review, Spaziani et al found no hormonal signs of tubular or interstitial damage in 145 KS infants at <6 months (38) with testosterone levels higher than in controls, and Johannesen et al reported that

testosterone levels in 47,XXY (n=27) males to be within male reference ranges (39). Conversely, Lahlou 2004 reported that testosterone levels were lower in boys diagnosed with KS in the antenatal period than in controls during infancy, from 1- 18 months (although more correctly these were at the lower end of the normal limit and were taken at various timepoints) (40) and Bastida et al reports evidence of testicular endocrine function impairment during childhood and puberty in 20 boys with KS in a retrospective chart review (41).

Associations between exogenous testosterone administration in infancy and developmental benefits during childhood have been reported (42). It is suggested that consideration of this treatment should be given to all infants with KS, based on an assumed testosterone deficiency. It should be noted that this has not been tested in a randomised controlled setting and despite being included in a recent report as recommended clinical care this approach has not been or endorsed in existing clinical guidelines for (43). It is however an important clinical question to address as there is increasing interest in this area among clinician, parent and advocacy groups(44). A small randomised controlled trial of 20 infants with KS noted that when 3 testosterone injections were given 4 weeks apart (age 6-15 weeks) adiposity was 15% less in treated infants and increases in growth velocity and stretched penile length were also seen (45). The latter two effects would be expected in any infant in whom exogenous testosterone is given (in the absence of a disorder of androgen action). It would seem counter-intuitive to strive for supra-physiological levels of testosterone and a recent review on this topic identified that further studies are required to clarify whether infants with KS present with impaired testosterone production during mini-puberty (46). It is likely that there is a spectrum of testosterone deficiency, which should be evaluated, assessed and managed on an individual basis.

Further work in this area is underway but need be considered in the context of a conflicting movement within the Differences in Sexual Development (DSD) community and advocacy groups to move away from the administration of testosterone under any circumstance to an individual who has no capacity to provide consent. This is based on the premise that such treatment is a violation of basic human rights. An enquiry into this very issue is ongoing in Australia at present by the Australian Human Rights Commission(47).

Key counselling point

A review by a paediatric endocrinologist during the mini-puberty stage is recommended to assess the clinical +/- biochemical profile of each infant. Testosterone replacement in infants is controversial. Care should be individualised according to clinical need.

II. Testosterone Deficiency: Puberty

Puberty in males is driven by gonadotrophin (LH and FSH) release from the pituitary gland. The action of LH on testicular Leydig cells triggers testosterone production in the testes and FSH acts to increase Sertoli cell numbers and eventually sperm production. The majority of boys with KS will enter puberty at a normal time, between ages 12- 14 years, and will progress normally without testosterone supplementation(48) indicating adequate Leydig function during those early years. Given that expansion of the Sertoli cell population with consequent spermatogenesis is the reason for testicular enlargement during puberty, it follows that Sertoli cell dysfunction leads to a lack of corresponding increase in testicular size through puberty. Almost without exception, men with KS have reduced testicular volumes compared to the general population(15).

Indications that puberty is not progressing adequately include reduced growth velocity, development of gynaecomastia (breast tissue), and a lack of appropriate virilisation. Rising LH levels without increasing testosterone over time can be monitored for, detected and managed once an individual has access to regular endocrinology follow up during adolescence. From mid-puberty onwards, FSH and LH levels rise to well above normal adolescent levels in most males with KS, inhibin B becomes undetectable and testosterone frequently falls to low or low-normal levels(49). Hence, many post-pubertal KS males display a varying degree of androgen deficiency. Consequently, testosterone substitution therapy is widely used to prevent the symptoms and sequelae of hypogonadism such as fatigue, low mood, central adiposity and reduced muscle mass.

Key counselling point

Testosterone replacement therapy during adolescence is standard treatment for prevention of the sequelae of hypogonadotropic hypogonadism in individuals with KS.

III. Fertility

Small testes and complete azoospermia (lack of sperm) are universal features of adult males with KS(50). Only a single case report outlines a natural conception with a man with KS (51) but it is unknown if further cases exist in un-diagnosed KS cases. Although males with KS have traditionally been described as infertile, evolving in-vitro fertilisation (IVF) techniques of intra-cytoplasmic sperm injection (ICSI) and micro-testicular sperm extraction (micro-TESE) have been associated with successful sperm retrieval in up to 75% of men(52, 53) with an increasing number of successful pregnancies over time (54, 55) without risk of KS transmission to the foetus (55). Fertility in KS should be discussed in the context of infertility rates in the general population which approximate 15% (56, 57).

Although it is not fully understood how the additional X-chromosome impacts on sperm production, progressive fibrosis and hyalinisation of seminiferous tubules (58) occurs from childhood (59). With this in mind, consideration of fertility preservation in adolescence has been postulated. Controversy surrounds recommendations for timing and method for possible sperm retrieval for storage in adolescents. Spermatogenic cell lines have been retrieved (59) but attempted sperm retrieval in adolescents with KS has been unsuccessful (61) with little evidence for utilization of this technique and no clear guidelines on which to base clinical practice (60,61). There is evidence to support consideration of sperm retrieval before the age of 30 years, but overall there is less evidence for effective sperm retrieval during adolescence (60), and it could be argued that fertility preservation should only be pursued in adulthood (61). In adolescence the testicular architecture is already abnormal and the number of potential sperm which can be harvested is extremely small or absent at that time(62). Freeze thaw cycle losses of up to 50% of stored sperm further lessen chance of effective biopsy salvage (63). Furthermore, testicular biopsy during adolescence may have the effect of damaging an already abnormal testis thereby reducing the chances of future success at a time when fertility is actually desired. Given the relatively high success rate for sperm retrieval for adults with KS, current evidence suggests that delaying invasive procedures is still to be recommended (53, 64). Discussion in late adolescence around potential options for sperm retrieval and consultation with an endocrinologist or andrologist should be offered, to allow for planning for future fertility preservation. However, it must be emphasised that even with evolving IVF techniques, the chances that these procedures will result in successful pregnancy for males with KS are low(65).

Key counselling point.

Discussions on fertility preserving options should be introduced in late adolescence, depending on the individual maturity and wishes of the young person.

IV. Neurodevelopment

Cognitive, language, and learning disabilities, attention and executive functioning difficulties, internalizing and externalizing behavioural and mental health disorders, are described in many children, adolescents and adults with KS, with marked variability in the presence and severity of these features between individuals (66-69). Lack of population-based longitudinal data into adulthood should moderate any commentary in this area, particularly as many men with KS are identified only at the time of consultation regarding infertility, and have not formally been assessed for adverse neurodevelopmental or psychologic difficulties. Cohort studies of 47,XXY indicate that QoL and the personal impact of the diagnosis may be under-recognised (70) and emerging data relating to males identified as having KS in adulthood suggests that compared to 46,XY males, KS

males diagnosed in adulthood were less likely to have attained a university degree and more likely to have lower intelligence scores and poor overall health(6).

The spectrum of concerns in antenatally diagnosed KS is under current investigation. Prospective studies of children with KS diagnosed by newborn screening have identified speech-language delays in up to 75%, motor skills delays in 50% (16) and autism spectrum disorder at a prevalence rate of 5-11% in small cohort studies (71, 72) compared to <1% in the general population(73). Evidence that early identification of other SCAs results in improved neurodevelopmental outcomes (74) indicates that appropriate review and assessment throughout childhood will ensure that any evolving issues are identified and managed proactively to optimise QOL, social skills and educational outcomes of the child with KS.

As most males with KS remain undiagnosed throughout the life-course and many only come to the attention of medical professionals during investigation for infertility, the full neurodevelopmental spectrum of KS will only fully be realised once population-based longitudinal studies of males with an antenatal diagnosis of KS are established.

Key counselling point.

KS is be associated with cognitive, language, and learning disabilities, attention and executive functioning difficulties, as well as internalizing and externalizing behavioural and psychological disorders. However, the rate of these neurodevelopmental outcomes may be over-reported due to ascertainment bias. Early diagnosis and intervention may improve outcomes.

V. Other known associations

In addition to assessment, monitoring and management of the potential hormonal and neurodevelopment issues as described above, increased risk for auto immune disorders has been described(15). Reduced bone health in men with KS has been associated with inadequate testosterone replacement and is reversible with appropriate treatment(75). Rare tumours of male breast cancer risk is reported at 20-30 times that of the normal male, and mediastinal germ cell tumours are seen at 1.5/1000 KS or 50 times the population risk(76, 77) . As suggested by data described in a study of the UK Biobank population, males (aged 40-70 years) with KS are at 3-fold risk of developing type 2 diabetes, 3.3-fold risk of thromboembolism and 4.4-fold increase in chronic pulmonary disease compared to unaffected males (6). These reported risk increases suggest a need for awareness , counselling and routine, intermittent surveillance in all KS. Lifelong medical follow up

is required to facilitate early identification of dysglycemia, autoimmune) disease and bone health issues(15).

Key counselling point

The focus of antenatal counselling with parents emphasises the role of appropriate screening and early management of evolving issues as the key to improved clinical outcomes.

What options for postnatal therapy are available in KS?

Discussion is not recommended in routine clinical care around associations between exogenous testosterone administration in infancy and developmental benefits during childhood(42) as this treatment remains controversial (43). At present, early review and assessment by a paediatric endocrinologist with individualised intervention on the basis of clinical need is recommended. It is also advised that planning for proactive review and screening for evolving developmental concerns and screening for known comorbidities should begin at the time of identification of SCA.

What are the recommendations for the timing and frequency of follow up and screening of individuals with antenatally diagnosed KS during childhood?

Recommendations for screening and follow up of individuals with KS vary(43, 78). Given significant variation in advice, we have also included our expert opinion and suggestions for comparison below, Table 1. As clinical variability is broad, lifelong care of an individual with antenatally diagnosed KS will likely involve input from a multidisciplinary team of genetic counsellors, paediatric endocrinologists, urologists, general/behavioural paediatricians, andrologists and fertility specialists. Outside of the medical system, school and peer supports are also of vital importance for both parents and children

Do individuals with KS experience gender diversity?

The majority of individuals with KS identify as male (79). Gender diversity is not a prominent feature of the phenotype but KS has been reported in approximately 1% of transgender individuals(80) where the population prevalence of gender dysphoria is thought to be in the order of 0.5-1.3%(81). An underlying diagnosis of autism spectrum disorder in case reports of gender diversity may be subject to ascertainment bias rather than the chromosomal complement per se (82, 83).

Future recurrence risk

The risk of recurrence of KS in future pregnancies is not increased after an index case.

Conclusion

With increasing uptake of NIPT worldwide, there will be a corresponding increase in the numbers of referrals for genetic counselling following antenatally identified KS. Antenatal genetic counselling following identification of either suspected (on NIPT) or confirmed KS presents unique challenges for the clinician, often complicated by time pressure on parents to make decisions around continuation of a pregnancy. A crucial first step that prospective parents are aware of the limitations of NIPT tests performed, so that confirmatory testing may be expedited. A balance is required, between describing known associations and risks of KS, whilst acknowledging variations related to paucity of long term population data for this condition, with current information skewed or biased by description of the 25% who have presented for medical care. Combined antenatal counselling with genetic and paediatric endocrine input may be of benefit and provides a clinical perspective on this complex and variable clinical spectrum. Emphasis should be placed on the value of early and regular post-natal care to identify, treat and monitor any identified concerns so that interventions can be implemented early. Referral to peer support groups can provide valuable insights into the adult lived experience of KS.

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Ethics committee approval not indicated for this study as it is a literature review and no original experimental or clinical data are presented.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

AUTHOR CONTRIBUTIONS

MW drafted the manuscript and is responsible for the final submitted version. All authors contributed to the final draft.

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References

1. Herlihy AS, Halliday JL, Cock ML, McLachlan RI. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. *Med J Aust.* 2011;194(1):24-8.
2. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab.* 2003;88(2):622-6.
3. Nielsen J, Wohler M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Aarhus, Denmark. *Hum Genet.* 1991;87(1):81-3.
4. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn.* 1997;17(4):363-8.
5. Nieschlag E. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. *Dtsch Arztebl Int.* 2013;110(20):347-53.
6. Zhao Y, Gardner EJ, Tuke MA, Zhang H, Pietzner M, Koprulu M, et al. Detection and characterization of male sex chromosome abnormalities in the UK Biobank study. *Genet Med.* 2022.
7. Howard-Bath A, Poulton A, Halliday J, Hui L. Population-based trends in the prenatal diagnosis of sex chromosome aneuploidy before and after non-invasive prenatal testing. *Prenat Diagn.* 2018;38(13):1062-8.
8. Loughry L, Pynaker C, White M, Halliday J, Hui L. State-wide increase in prenatal diagnosis of klinefelter syndrome on amniocentesis and chorionic villus sampling: Impact of non-invasive prenatal testing for sex chromosome conditions. *Prenat Diagn.* 2022.
9. Gadsbøll K, Petersen OB, Gatinois V, Strange H, Jacobsson B, Wapner R, et al. Current use of noninvasive prenatal testing in Europe, Australia and the USA: A graphical presentation. *Acta Obstet Gynecol Scand.* 2020;99(6):722-30.
10. Bowman-Smart H, Savulescu J, Gyngell C, Mand C, Delatycki MB. Sex selection and non-invasive prenatal testing: A review of current practices, evidence, and ethical issues. *Prenat Diagn.* 2020;40(4):398-407.
11. Dondorp W, de Wert G, Bombard Y, Bianchi DW, Bergmann C, Borry P, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. *Eur J Hum Genet.* 2015;23(11):1592.
12. RANZCOG Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions https://ranzcoг.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Prenatal-screening_1.pdf?ext=.pdf2018 [Accessed 2022]
13. Benn P, Borrell A, Chiu RW, Cuckle H, Dugoff L, Faas B, et al. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. *Prenat Diagn.* 2015;35(8):725-34.
14. Bowman-Smart H, Savulescu J, Mand C, Gyngell C, Pertile MD, Lewis S, et al. 'Is it better not to know certain things?': views of women who have undergone non-invasive prenatal testing on its possible future applications. *J Med Ethics.* 2019;45(4):231-8.
15. Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P, Skakkebaek A. Klinefelter Syndrome: Integrating Genetics, Neuropsychology, and Endocrinology. *Endocr Rev.* 2018;39(4):389-423.
16. Davis S, Howell S, Wilson R, Tanda T, Ross J, Zeitler P, et al. Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome. *Adv Pediatr.* 2016;63(1):15-46.
17. KLINEFELTER HF, JR., REIFENSTEIN EC, JR., ALBRIGHT F, JR. Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone1. *The Journal of Clinical Endocrinology & Metabolism.* 1942;2(11):615-27.
18. Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature.* 1959;183(4657):302-3.
19. Thomas NS, Hassold TJ. Aberrant recombination and the origin of Klinefelter syndrome. *Hum Reprod Update.* 2003;9(4):309-17.

20. Visootsak J, Aylstock M, Graham JM, Jr. Klinefelter syndrome and its variants: an update and review for the primary pediatrician. *Clin Pediatr (Phila)*. 2001;40(12):639-51.
21. Hook EB. Rates of chromosome abnormalities at different maternal ages. *Obstet Gynecol*. 1981;58(3):282-5.
22. Bojesen A, Hertz JM, Gravholt CH. Genotype and phenotype in Klinefelter syndrome - impact of androgen receptor polymorphism and skewed X inactivation. *Int J Androl*. 2011;34(6 Pt 2):e642-8.
23. Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E. X-chromosome inactivation patterns and androgen receptor functionality influence phenotype and social characteristics as well as pharmacogenetics of testosterone therapy in Klinefelter patients. *J Clin Endocrinol Metab*. 2004;89(12):6208-17.
24. Berletch JB, Yang F, Disteche CM. Escape from X inactivation in mice and humans. *Genome Biol*. 2010;11(6):213.
25. Berletch JB, Yang F, Xu J, Carrel L, Disteche CM. Genes that escape from X inactivation. *Hum Genet*. 2011;130(2):237-45.
26. Navarro-Cobos MJ, Balaton BP, Brown CJ. Genes that escape from X-chromosome inactivation: Potential contributors to Klinefelter syndrome. *Am J Med Genet C Semin Med Genet*. 2020;184(2):226-38.
27. Howell S, Davis SM, Thompson T, Brown M, Tanda T, Kowal K, et al. Non-Invasive Prenatal Testing (NIPT) Results for Participants of the eXtraordinary Babies Study: Screening, Counseling, Diagnosis, and Discordance. 2021:2021.11.03.21265829.
28. Swanson K, Bishop JC, Al-Kouatly HB, Makhamreh M, Felton T, Vora NL, et al. Prenatal phenotype of 47, XXY (Klinefelter syndrome). *Prenat Diagn*. 2021.
29. Jo DG, Seo JT, Lee JS, Park SY, Kim JW. Klinefelter syndrome diagnosed by prenatal screening tests in high-risk groups. *Korean J Urol*. 2013;54(4):263-5.
30. Dotters-Katz SK, Humphrey WM, Senz KL, Lee VR, Shaffer BL, Caughey AB. The impact of prenatally diagnosed Klinefelter Syndrome on obstetric and neonatal outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:173-6.
31. Wang Y, Li S, Wang W, Dong Y, Zhang M, Wang X, et al. Cell-free DNA screening for sex chromosome aneuploidies by non-invasive prenatal testing in maternal plasma. *Mol Cytogenet*. 2020;13:10.
32. Lindquist A, Hui L, Poulton A, Kluckow E, Hutchinson B, Pertile MD, et al. State-wide utilization and performance of traditional and cell-free DNA-based prenatal testing pathways: the Victorian Perinatal Record Linkage (PeRL) study. *Ultrasound Obstet Gynecol*. 2020;56(2):215-24.
33. Tomlinson C, Macintyre H, Dorrian CA, Ahmed SF, Wallace AM. Testosterone measurements in early infancy. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(6):F558-9.
34. Rey RA. Mini-puberty and true puberty: differences in testicular function. *Ann Endocrinol (Paris)*. 2014;75(2):58-63.
35. Grumbach MM. A window of opportunity: the diagnosis of gonadotropin deficiency in the male infant. *J Clin Endocrinol Metab*. 2005;90(5):3122-7.
36. Ratcliffe SG, Read G, Pan H, Fear C, Lindenbaum R, Crossley J. Prenatal testosterone levels in XXY and XYY males. *Horm Res*. 1994;42(3):106-9.
37. Fennoy I. Testosterone and the child (0-12 years) with Klinefelter syndrome (47XXY): a review. *Acta Paediatr*. 2011;100(6):846-50.
38. Spaziani M, Granato S, Liberati N, Rossi FM, Tahani N, Pozza C, et al. From mini-puberty to pre-puberty: early impairment of the hypothalamus–pituitary–gonadal axis with normal testicular function in children with non-mosaic Klinefelter syndrome. *Journal of Endocrinological Investigation*. 2020.
39. Johannsen TH, Main KM, Ljubicic ML, Jensen TK, Andersen HR, Andersen MS, et al. Sex Differences in Reproductive Hormones During Mini-Puberty in Infants With Normal and Disordered Sex Development. *J Clin Endocrinol Metab*. 2018;103(8):3028-37.

40. Lahlou N, Fennoy I, Carel JC, Roger M. Inhibin B and anti-Müllerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. *J Clin Endocrinol Metab.* 2004;89(4):1864-8.
41. Bastida MG, Rey RA, Bergadá I, Bedecarrás P, Andreone L, del Rey G, et al. Establishment of testicular endocrine function impairment during childhood and puberty in boys with Klinefelter syndrome. *Clin Endocrinol (Oxf).* 2007;67(6):863-70.
42. Samango-Sprouse CA, Tran SL, Lasutschinkow PC, Sadeghin T, Powell S, Mitchell FL, et al. Neurodevelopmental outcome of prenatally diagnosed boys with 47,XXY (Klinefelter syndrome) and the potential influence of early hormonal therapy. *Am J Med Genet A.* 2020;182(8):1881-9.
43. Zitzmann M, Aksglaede L, Corona G, Isidori AM, Juul A, T'Sjoen G, et al. European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology. *Andrology.* 2021;9(1):145-67.
44. The Focus Foundation 47, XXY <https://thefocusfoundation.org/x-y-chromosomal-variations/xyy/> [Accessed 12/01/2022].
45. Davis SM, Reynolds RM, Dabelea DM, Zeitler PS, Tartaglia NR. Testosterone Treatment in Infants With 47,XXY: Effects on Body Composition. *Journal of the Endocrine Society.* 2019;3(12):2276-85.
46. Aksglaede L, Davis SM, Ross JL, Juul A. Minipuberty in Klinefelter syndrome: Current status and future directions. *Am J Med Genet C Semin Med Genet.* 2020;184(2):320-6.
47. Australian Human Rights Commission. Protecting the Human Rights of People Born with Variations in Sex Characteristics in the context of Medical Interventions. https://humanrights.gov.au/sites/default/files/AHRC_Consultation%20paper_2018_2.pdf?_ga=2.229062428.1078827859.1609983373-132411671.16099833732018.
48. Tanner M, Miettinen PJ, Hero M, Toppari J, Raivio T. Onset and progression of puberty in Klinefelter syndrome. *Clin Endocrinol (Oxf).* 2021.
49. Wikström AM, Dunkel L. Testicular function in Klinefelter syndrome. *Horm Res.* 2008;69(6):317-26.
50. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet.* 2004;364(9430):273-83.
51. Laron Z, Dickerman Z, Zamir R, Galatzer A. Paternity in Klinefelter's syndrome--a case report. *Arch Androl.* 1982;8(2):149-51.
52. Corona G, Pizzocaro A, Lanfranco F, Garolla A, Pelliccione F, Vignozzi L, et al. Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. *Hum Reprod Update.* 2017;23(3):265-75.
53. Lantsberg D, Mizrahi Y, Katz DJ. Micro-testicular sperm extraction outcomes for non-obstructive azoospermia in a single large clinic in Victoria. *Aust N Z J Obstet Gynaecol.* 2022.
54. Ramasamy R, Ricci JA, Palermo GD, Gosden LV, Rosenwaks Z, Schlegel PN. Successful fertility treatment for Klinefelter's syndrome. *J Urol.* 2009;182(3):1108-13.
55. Greco E, Scarselli F, Minasi MG, Casciani V, Zavaglia D, Dente D, et al. Birth of 16 healthy children after ICSI in cases of nonmosaic Klinefelter syndrome. *Hum Reprod.* 2013;28(5):1155-60.
56. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertil Steril.* 2013;99(5):1324-31.e1.
57. Petraglia F, Serour GI, Chapron C. The changing prevalence of infertility. *Int J Gynaecol Obstet.* 2013;123 Suppl 2:S4-8.
58. Aksglaede L, Wikström AM, Rajpert-De Meyts E, Dunkel L, Skakkebaek NE, Juul A. Natural history of seminiferous tubule degeneration in Klinefelter syndrome. *Hum Reprod Update.* 2006;12(1):39-48.
59. Wikström AM, Raivio T, Hadziselimovic F, Wikström S, Tuuri T, Dunkel L. Klinefelter syndrome in adolescence: onset of puberty is associated with accelerated germ cell depletion. *J Clin Endocrinol Metab.* 2004;89(5):2263-70.

60. Gies I, De Schepper J, Goossens E, Van Saen D, Pennings G, Tournaye H. Spermatogonial stem cell preservation in boys with Klinefelter syndrome: to bank or not to bank, that's the question. *Fertil Steril*. 2012;98(2):284-9.
61. Pook CJ, Cocca A, Grandone A, Al-Hussini M, Lam W. The Evidence for Fertility Preservation in Pediatric Klinefelter Syndrome. *Frontiers in Reproductive Health*. 2021;3.
62. Gies I, De Schepper J, Van Saen D, Anckaert E, Goossens E, Tournaye H. Failure of a combined clinical- and hormonal-based strategy to detect early spermatogenesis and retrieve spermatogonial stem cells in 47,XXY boys by single testicular biopsy. *Hum Reprod*. 2012;27(4):998-1004.
63. Ozkavukcu S, Erdemli E, Isik A, Oztuna D, Karahuseyinoglu S. Effects of cryopreservation on sperm parameters and ultrastructural morphology of human spermatozoa. *Journal of assisted reproduction and genetics*. 2008;25(8):403-11.
64. Franik S, Hoeijmakers Y, D'Hauwers K, Braat DD, Nelen WL, Smeets D, et al. Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. *Hum Reprod*. 2016;31(9):1952-9.
65. Vloeberghs V, Verheyen G, Santos-Ribeiro S, Staessen C, Verpoest W, Gies I, et al. Is genetic fatherhood within reach for all azoospermic Klinefelter men? *PLoS One*. 2018;13(7):e0200300.
66. Tartaglia N, Howell S, Davis S, Kowal K, Tanda T, Brown M, et al. Early neurodevelopmental and medical profile in children with sex chromosome trisomies: Background for the prospective eXtraordinary babies study to identify early risk factors and targets for intervention. *Am J Med Genet C Semin Med Genet*. 2020;184(2):428-43.
67. Skakkebaek A, Moore PJ, Chang S, Fedder J, Gravholt CH. Quality of life in men with Klinefelter syndrome: the impact of genotype, health, socioeconomics, and sexual function. *Genet Med*. 2018;20(2):214-22.
68. Skakkebaek A, Moore PJ, Pedersen AD, Bojesen A, Kristensen MK, Fedder J, et al. Anxiety and depression in Klinefelter syndrome: The impact of personality and social engagement. *PLoS One*. 2018;13(11):e0206932.
69. 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(1):228-38.
70. Herlihy AS, McLachlan RI, Gillam L, Cock ML, Collins V, Halliday JL. The psychosocial impact of Klinefelter syndrome and factors influencing quality of life. *Genet Med*. 2011;13(7):632-42.
71. Tartaglia NR, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S, et al. Autism Spectrum Disorder in Males with Sex Chromosome Aneuploidy: XXY/Klinefelter Syndrome, XYY, and XXYY. *Journal of developmental and behavioral pediatrics : JDBP*. 2017;38(3):197-207.
72. Bishop DV, Jacobs PA, Lachlan K, Wellesley D, Barnicoat A, Boyd PA, et al. Autism, language and communication in children with sex chromosome trisomies. *Arch Dis Child*. 2011;96(10):954-9.
73. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Res*. 2012;5(3):160-79.
74. Wigby K, D'Epagnier C, Howell S, Reicks A, Wilson R, Cordeiro L, et al. Expanding the phenotype of Triple X syndrome: A comparison of prenatal versus postnatal diagnosis. *Am J Med Genet A*. 2016;170(11):2870-81.
75. Piot A, Ploton I, Boutroy S, Bacchetta J, Ailloud S, Lejeune H, et al. Klinefelter Bone Microarchitecture Evolution with Testosterone Replacement Therapy. *Calcif Tissue Int*. 2022.
76. Bonouvrie K, van der Werff Ten Bosch J, van den Akker M. Klinefelter syndrome and germ cell tumors: review of the literature. *Int J Pediatr Endocrinol*. 2020;2020:18.
77. De Sanctis V, Fiscina B, Soliman A, Giovannini M, Yassin M. Klinefelter syndrome and cancer: from childhood to adulthood. *Pediatr Endocrinol Rev*. 2013;11(1):44-50.
78. Samango-Sprouse CA, Counts DR, Tran SL, Lasutschinkow PC, Porter GF, Gropman AL. Update On The Clinical Perspectives And Care Of The Child With 47,XXY (Klinefelter Syndrome). *The application of clinical genetics*. 2019;12:191-202.

79. Groth KA, Skakkebaek A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. *J Clin Endocrinol Metab.* 2013;98(1):20-30.
80. Liang B, Cheung AS, Nolan BJ. Clinical features and prevalence of Klinefelter syndrome in transgender individuals: A systematic review. *Clin Endocrinol (Oxf).* 2022.
81. Zucker KJ. Epidemiology of gender dysphoria and transgender identity. *Sex Health.* 2017;14(5):404-11.
82. Davies GW, Parkinson J. Gender dysphoria in Klinefelter's syndrome: three cases. *Australas Psychiatry.* 2018;26(3):313-4.
83. Fisher AD, Castellini G, Casale H, Fanni E, Bandini E, Campone B, et al. Hypersexuality, Paraphilic Behaviors, and Gender Dysphoria in Individuals with Klinefelter's Syndrome. *J Sex Med.* 2015;12(12):2413-24.

Table 1. Clinical recommendations for the management and screening of individuals identified with Klinefelter Syndrome

		European Academy of Andrology Guidelines(71)	Update on the clinical perspective and care of the child with 47,XXY (42)	Author suggested practice
Antenatal	Confirmatory diagnosis of in utero suspected KS	<ul style="list-style-type: none"> Prenatal diagnosis of KS should be confirmed postnatally 	<ul style="list-style-type: none"> Positive NIPT results must be confirmed pre-or postnatally 	<ul style="list-style-type: none"> Positive NIPT results must be confirmed pre-or postnatally
	Antenatal counselling	<ul style="list-style-type: none"> Non-directive antenatal genetic counselling recommended 	<ul style="list-style-type: none"> Not described 	<ul style="list-style-type: none"> Non-directive counselling by genetic counsellor and paediatric endocrinologist
Infancy	Cryptorchidism	<ul style="list-style-type: none"> According to same treatment guidelines as children without KS 	<ul style="list-style-type: none"> Orchiopexy by age 1 year 	<ul style="list-style-type: none"> According to same treatment guidelines as children without KS
	Testicular development/function	<ul style="list-style-type: none"> Determination of LH and testosterone 2-3 months after birth in children with pre-natal diagnosis if testosterone is under consideration Recommend against testosterone supplementation except in cases of micro-penis 	<ul style="list-style-type: none"> Testosterone supplementation if lack of neonatal surge or smaller testicular/phallic size 	<ul style="list-style-type: none"> Assess genital development during mini-puberty Consider assessment of testicular function (LH/FSH/testosterone/Inhibin B) at between 2-4 months post term Recommend against universal testosterone supplementation
	Neurodevelopment	<ul style="list-style-type: none"> Not discussed 	<ul style="list-style-type: none"> Specific recommendations according to suspected issue 	<ul style="list-style-type: none"> Refer to a general paediatrician/developmental specialist for assessment and monitoring of potential issues from infancy
Childhood	Testicular development/function	<ul style="list-style-type: none"> Biennial physical examination pre-puberty Recommend against testosterone treatment in infants and pre-pubertal boys with KS 	<ul style="list-style-type: none"> Monitor for rise in LH/FSH starting at age 11 years 	<ul style="list-style-type: none"> Biennial physical examination pre-puberty Recommend against testosterone treatment in infants and pre-pubertal boys with KS
	Fertility preservation	<ul style="list-style-type: none"> Not during childhood 	<ul style="list-style-type: none"> Not during childhood 	<ul style="list-style-type: none"> Not during childhood
	Development/behaviour	<ul style="list-style-type: none"> Suspected neurological or psychiatric deficits should be assessed Recommend supports as needed 	<ul style="list-style-type: none"> Specific recommendations according to suspected issue 	<ul style="list-style-type: none"> As above, all children with KS should have regular assessment and monitoring of neurodevelopment throughout childhood with appropriate subspecialist referral and support when required.

	Growth	<ul style="list-style-type: none"> Suggest measurement of height and body proportions according to centiles or standard deviation scores Bone age in pre-pubertal children with KS depending on individual growth patterns 	<ul style="list-style-type: none"> Monitor (evaluate if small) 	<ul style="list-style-type: none"> Serial measurement of height and weight Investigation and management individualised according to clinical need.
	Vitamin D and calcium status	<ul style="list-style-type: none"> Determination of vitamin D blood levels and adequate vitamin D and calcium supplementation Biennial assessment of bone mineral status during childhood in case of vitamin D deficiency biennially in patients with KS (DXA scan) 	<ul style="list-style-type: none"> Not discussed 	<ul style="list-style-type: none"> As per current guidelines for general paediatric population
Adolescence	Testicular function	<ul style="list-style-type: none"> Assessment of Tanner stages, pubertal development, measurement of testosterone and gonadotropins, signs and symptoms of hypogonadism, prior to the predicted start of puberty Testosterone for delayed puberty and/or signs and symptoms of hypogonadism We suggest against testosterone therapy in compensated hypergonadotropic hypogonadism 	<ul style="list-style-type: none"> Monitor for rise in LH/FSH starting at age 11 years, begin testosterone replacement when levels rise Topical gel to preserve fertility 	<ul style="list-style-type: none"> Individualised approach to management depending on pubertal onset and progression. Emphasise requirement for post-pubertal monitoring for evolving hypogonadism
	Gynaecomastia	<ul style="list-style-type: none"> Not discussed 	<ul style="list-style-type: none"> Anastrozole 1 mg qd (if > Tanner 3 may need breast reduction surgery) 	<ul style="list-style-type: none"> Assessed at clinical encounters in the context of pubertal progression
	Neurodevelopment	<ul style="list-style-type: none"> Recommend speech therapist control, monitoring educational problems, social training and psychological support if needed 	<ul style="list-style-type: none"> Specific recommendations according to suspected issue 	<ul style="list-style-type: none"> Recommend continuation of regular specialist review and assessment
	Bone health	<ul style="list-style-type: none"> Not discussed 	<ul style="list-style-type: none"> Management as per that of hypogonadism 	<ul style="list-style-type: none"> Assess in the context of gonadal status, personal and family history of bony fragility and vitamin D status

	Autoimmune disorders	<ul style="list-style-type: none"> Suggest attention to possible autoimmune dysfunctions in patients with KS 	<ul style="list-style-type: none"> Monitor 	<ul style="list-style-type: none"> Bi-annual screening for coeliac disease, thyroid dysfunction and liver disease from the age of 10 years
	Germ cell tumours	<ul style="list-style-type: none"> Not discussed 	<ul style="list-style-type: none"> Monitor LDH, AFP, and HCG Serial examination 	<ul style="list-style-type: none"> Bi-annual screening of AFP and HCG from the age of 8 years
	Breast carcinoma	<ul style="list-style-type: none"> Advice relates to adulthood 	<ul style="list-style-type: none"> Serial examination 	<ul style="list-style-type: none"> Serial examination and investigation if warranted
	Spermatogenesis/fertility preservation	<ul style="list-style-type: none"> Information on fertility issues should be given to adolescent patients Semen collection in adolescents Cryopreservation if motile spermatozoa are present Consider a testicular biopsy for testicular sperm extraction (TESE) either 	<ul style="list-style-type: none"> Sperm collection age 16–20 years ideally 	<ul style="list-style-type: none"> If testicular volume is > 10ml and inhibin B levels during or after puberty suggest spermatogenesis, offer semen analysis and storage if sperm seen on centrifuged sample Advise adult men attend Andrology for management at time of desired fertility
	Cardiovascular risk	<ul style="list-style-type: none"> Advice relates to adulthood only 	<ul style="list-style-type: none"> Monitor 	<ul style="list-style-type: none"> Emphasise healthy lifestyle habits in keeping with the general population is recommended Additional testing/screening depending on the BMI, family history and specific clinical issues.