Journal of Pediatric Urology (xxxx) xxx xxx

Review Article

Androgenization in Klinefelter syndrome: Clinical spectrum from infancy through young adulthood

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Keywords
Klinefelter syndrome; Testosterone; Androgenization; Hypergonadotrophic hypogonadism

Received 5 November 2020
Revised 2 February 2021
Accepted 19 February 2021
Available online xxx

Summary
Klinefelter syndrome (KS) is an uncommon chromosomal disorder in males that has a variable clinical appearance. Classic KS involves an extra X chromosome, (47, XXY), although other variations may exist, including a milder mosaic form as well as multiple extra sex chromosomes with more dramatic phenotypes. KS is underdiagnosed, especially prepubertally, owing to a paucity of concrete clinical signs; however, diagnostic rates increase during and after puberty, as the consequences of hypergonadotropic hypogonadism begin to manifest. Testicular failure causing decreased circulating testosterone (T) and germ cell depletion, a hallmark feature in KS, commonly begins shortly after the onset of puberty and leads to the most commonly recognized KS traits: small testes, azoospermia, gynecomastia, decreased facial and pubic hair.

While many KS men maintain adequate T levels leading up to young adulthood, some may have lower T levels at an earlier age leading to varied levels of androgenization and clinical KS features. At certain critical time points, absent or decreased T may alter the development of normal male reproductive organs, external genitalia, development of secondary sexual characteristics and spermatogenesis. Testicular failure in utero may lead to ambiguous genitalia, cryptorchidism and/or hypospadias, all of which depend on fetal T production. In the neonatal period and childhood, decreased T levels during the mini-puberty of infancy may negatively impact germ cell differentiation and male neuropsychological development. Finally, decreased T during pubertal and young adulthood can lead to decreased virilization during puberty, eunuchoid skeleton and decreased spermatogenesis. Depending on the timing of the testicular failure, a reproductive window of sperm production may exist to achieve paternity for KS men. The presence or absence of clinical characteristics reflecting decreased androgenization provides an insight to the relative testicular function during these developmental time points for those with KS and contributes to variability within the syndrome.

Introduction

Klinefelter syndrome (KS), the most common chromosomal aberration in males, occurs in roughly 1 in 600 births and may be underestimated due to variability in clinical features. Previous studies approximate a KS diagnosis rate of only 25%, with only 10% of patients diagnosed before puberty [1]. Males born with at least two X chromosomes and at least one Y chromosome meet the diagnostic criteria, and the classical syndrome including tall stature, small testes, hypergonadotropic hypogonadism and azoospermia, are based on the most common 47, XXY karyotype; however, phenotypic variation still exists within the classical genotype. Multiple genetic aberrations of varying clinical severity have also been described, including a mosaic (46,XY/47,XXY) form with milder features. Furthermore, the rarer, non-classic KS karyotypes with multiple aneuploidies (48, XXXY; 49, XXXYY, 48, XXYY) are associated with dramatic phenotypes that make childhood diagnosis more attainable [2]. The combination of variability and minimal early syndromic signs makes childhood diagnosis difficult. Early diagnosis may be essential, as it may allow clinicians to appropriately manage the decreased androgen production and worsening spermatogenesis that occurs over time for those with KS [3].

Physiologic circulating testosterone (T) levels play a crucial role at critical developmental stages and throughout the male lifespan. Early in the neonatal period, T is elevated and critical for male sexual differentiation, notably contributing to testicular descent into the scrotum and, after being converted to dihydrotestosterone (DHT), normal penile development and urethra [4,5]. After the "mini-puberty of infancy" between 3

https://doi.org/10.1016/j.jpurol.2021.02.021
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and 6 months of age, T levels remain low throughout childhood until the onset of puberty, when T influences the development of secondary sexual characteristics [6]. Into adulthood, normal T levels are involved in health maintenance of multiple organ systems, and intratesticular T fosters spermatogenesis and male fertility.

Despite the variable clinical presentation, the often profound hypergonadotropic hypogonadism contributes to the commonly observed KS features in adulthood: infertility, small testes, gynecomastia, and decreased facial and pubic hair [7]. Although hypogonadism in general is recognized as a disease of older men, it is important to recognize that a relative T deficiency worsening throughout life, as in those with KS, can have profound impact starting as early as the neonatal period [8]. A lower frequency of childhood manifestations may exist, contributing to difficulty in early KS diagnosis, due to the observed decrease of testicular function that may begin in mid-puberty, with germ cell depletion and hyalinization of seminiferous tubules [3]. Clinician recognition of diagnoses that may result from lower T levels, such as cryptorchidism, or an attenuated increase at critical developmental time points, such as puberty, may help identify young boys who are at-risk for KS. In this review, we investigate what is known about conditions associated with decreased androgenization and the relative frequencies in which they exist from the neonatal period until young adulthood in order to describe the developmental clinical spectrum of KS.

Fetal and neonatal period

Development of normal male external genitalia and reproductive organs is a complex process beginning early in utero. During the first trimester, signaling from the SRY region of the Y chromosome drives the undifferentiated gonad towards testicular development. During embryonic week 9—10, Leydig cells form and begin to secrete T, which influences Wolffian duct persistence and differentiation into the epididymis, vas deferens, and seminal vesicles [9]. Fetal Sertoli cells play a complementary role by producing Mullerian inhibiting substance (MIS), in order to regress the female internal reproductive organs. Both T and its converted form, DHT are pivotal to the developing male external genitalia, including genital tubule elongation into the phallus, development of the urethra, and abdominal fetal testicular descent into the scrotum [9]. There are multiple factors that could lead to disruption of the pathway, including decreased androgens. Low androgen levels, in turn, may lead to aberrant development of the normal male phenotype, including ambiguous genitalia, cryptorchidism or hypospadias.

Diagnosis of KS during the fetal and neonatal period is difficult given the relatively normal phenotypic appearance, which would be especially difficult to detect via ultrasound; resulting in roughly 10—13% of prenatal diagnosis of KS [10]. The more recent increase in utilization of serum screening and cell free DNA have resulted in an increased diagnosis, however this is still not routinely done to screen for KS [11]. Incidental prenatal diagnosis is more common since there is no reason to have suspicion early on given the subtilty of the clinical presentation of KS. Despite not having a need for any intervention until adolescence, early diagnosis of KS would help to capture these patients so appropriate counseling and follow-up can be established.

Ambiguous genitalia

Disorders of sex development are a classification of conditions with a known genetic molecular cause for an infant to be born with ambiguous genitalia and an inability for clinicians to assign a birth sex on genital appearance alone [12]. While KS is included within this framework as a sex chromosome disorder of sexual differentiation, ambiguous genitalia is not a common feature of classic KS and occurs rarely. Any infant born with ambiguous genitalia promptly undergoes karyotype testing to help determine the genetic sex, and KS would be readily identified if it was present. Overall, KS is an uncommon diagnosis of children born with ambiguous genitalia, and only sporadic cases are reported. Unfortunately, the true prevalence remains unknown.

Many KS patients born with ambiguous genitalia have been found to have a concomitant genetic insult along the sexual developmental pathway, including mutations leading to androgen receptor (AR) dysfunction, SRY deletions, non-47, XXY karyotypes, and additional forms of mosaicism/non-disjunction (46XX/47XXY, 46,XX/47XXY/48XXYY, 47XXY/48,XXY,+21)[13]. These mosaic karyotypes are estimated to be present in less than 15% of KS patients.

Interestingly, in some KS patients born with ambiguous genitalia, the only identified genetic abnormality is the 47, XXY karyotype. Although the underlying cause for normal sexual dysfunction is unknown, low T production in utero by a KS fetus with eventual ambiguous genitalia has been described [14]. One hypothesis revolves around the DAX 1 locus, located on the X-chromosome that may have an anti-testis effect when there is presence of two X chromosomes. The DAX-1 locus, or dosage sensitive sex reversal gene, may suppress the SRY region on the Y chromosome in utero, therefore altering normal male genital development [13]. This may explain, in part, why non-classic KS karyotypes carry a higher incidence of ambiguous genitalia compared to the classic type; however, it does not explain why such a low frequency exists in classic KS, since there are always at least two X chromosomes present [30].

Cryptorchidism

Cryptorchidism, or failure of one or both testes to descend into the scrotum, is the most common disorder of male sexual development, occurring in approximately 2—4% of full-term male births [15]. Testicular descent is a complex process reliant on complex local signaling between the testis and the gubernaculum in which T plays a pivotal role. Unlike ambiguous genitalia, increased cryptorchidism rates are observed in KS compared to non-syndromic full-term male births; however here too, the true prevalence remains unknown. Cryptorchidism has been reported as a common clinical finding of KS patients in the literature [1], and previous studies have reported prevalence of up to 17.6% in patients who were diagnosed with KS as a child [16]. Unfortunately, this may be misleadingly low as only 10% of KS patients are diagnosed before puberty [1]. A large cross-

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sectional analysis performed at an andrology clinic revealed that 27% of KS patients reported a history of cryptorchidism compared to 8% of the total patients attending the clinic [2]. Again, it is difficult to determine the true prevalence of cryptorchidism compared to the general population given that the penetrance of infertility is also higher in KS patients compared to the general population. Despite the limitations of these studies, the true incidence probably lies between 17.6 and 27%, which is significantly higher than in non-syndromic boys.

Conversely, KS rates are low when evaluating boys born with cryptorchidism. Ferlin et al. found that of 600 boys with unilateral or bilateral cryptorchidism who were followed for 2–3 years, only 8 (1.3%) also had KS, 7 classic (47, XXY) and 1 mosaic (46 XY/47 XXY). Of these 8 cases of cryptorchidism in KS, 5 were bilateral, 3 were unilateral and none of the testes showed spontaneous descent prior to surgical repair [17]. Even with assuming an underreporting of KS cases, the low rates of KS within cryptorchidism cohorts should keep clinicians from performing karyotype analysis for all boys with KS. Instead, clinicians should maintain a high index of suspicion, or evaluate, for other signs consistent with KS throughout childhood.

Hypospadias

Hypospadias, another common sexual development disorder, may also result from decreased fetal T production, notably DHT, which influences urethral and external genitalia development [18]. In KS patients, hypospadias rates have been reported as high as between 7 and 13% [19,20]. Karyotyping is not a routine workup for hypospadias unless there are other syndromic findings and it is possible that these numbers are over-estimates given the rarity of prepubertal KS diagnosis. Inversely, there are varying degrees of hypospadias from mild, which may be under-reported, to severe which might be defined as ambiguous genitalia. Although little is known about the embryonic levels of T or the effect of supernumerary X chromosomes on penile and urethral development in KS patients, there likely is a higher incidence of hypospadias, suggesting attenuated androgenization during sexual development in some KS neonates.

Mini-puberty of infancy

In KS, conflicting data exists regarding the gonadotropin and hormone levels during the mini-puberty of infancy. In small case series, T levels during this period have been shown to range between low [21,22] and high-normal [23,24], compared to controls. In the largest study from Cabrol et al., 68 prenatally diagnosed KS infants found no difference in T levels compared to controls but did show an increase of FSH in about 25% of patients, despite normal LH, inhibin B, and anti-Mullerian hormone levels. The group also found normal levels of insulin-like 3 protein (INSL3), which in adults correlates with quantity and quality of Leydig cells, compared to controls, seemingly signaling adequate testicular function during this time period [24]. A different study with 10 kS patients described significantly higher gonadotropin levels compared to controls, albeit the T concentration was also elevated [23]. Although this was a smaller cohort, it is interesting to note findings of elevated FSH or LH, given that a hallmark of KS in adolescence and adulthood is worsening testicular function and failure of both sperm and T production. It is unclear if larger studies are needed to determine if this phenomenon is consistent in KS infants, as it could be a sign of early compensated testicular failure, which predisposes patients to testicular burnout later in life. Further studies would be needed to determine if an intervention, such as T replacement therapy (TRT), during this time period could delay testicular degeneration in adolescence.

Childhood

Following the mini-puberty of infancy, T levels remain low during childhood until the onset of puberty [6]. In the absence of androgen-related changes, the predominant phenotypic finding during this time is developmental delay, learning disabilities, and neurocognitive behavioral issues. These cognitive issues are overwhelmingly present, estimated to occur in 68–75% of school age boys with KS, and predominately manifest as delays in early language development including difficulty with reading, spelling, proper syntax production, and word retrieval [7,25].

Several studies have reported positive improvements in behavior, learning capacity, and verbal fluency with T therapy [7,26]. Although the underlying mechanism for T's role during this time period is unknown, Patwardhan et al. demonstrated higher volumes of left temporal lobe grey matter for KS boys on exogenous T therapy starting at puberty compared to those who were not [26]. Since T levels are physiologically low during childhood, lower testosterone production earlier in life such as during fetal development or the mini-puberty of infancy, may play a role in neurocognitive and behavioral development. Learning disabilities in childhood may be another time period in which clinicians could intervene with an early KS diagnosis, and some experts recommend considering KS in boys with learning difficulties without a family history or other identifiable cause [7].

Adolescence and young adult

Diagnostic rates in KS increase after adolescence as the effects of hypogonadism become more recognizable [1]. The classic phenotype of tall stature, broad hips, bilateral gynecomastia, reduced muscle mass, sparse body hair, and small, firm testes has been characterized in only a minority of KS patients seeking evaluation [2,27]. Whereas many of these classic features are well known to result from decreased T, even morphological features can be attributed to decreased androgenization, notably from low estradiol (E_2) levels. A defining feature of KS is worsening testicular function that may begin soon after pubertal onset. Testicular decline involves both the depletion of germ cells, impairing spermatogenesis, and Leydig cell exhaustion, leading to hypergonadotrophic hypogonadism [3]. Variability in phenotypic traits for a KS individual are somewhat dependent on the timing of testicular decline. Whereas the testis may have maintained adequate function during fetal development,

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testicular failure can have profound impacts on pubertal development, body appearance, and fertility [1,7,28,29].

Puberty

During this critical developmental stage, increasing androgens in males induce secondary sexual characteristics and linear growth and fosters spermatogenesis initiation. Pubertal onset is dependent on hypothalamic signaling to the pituitary gland to secrete LH and FSH to induce Leydig cell production of T and Sertoli cells to initiate spermatogenesis. In adolescent boys with KS, the relative testicular function at this time point, and therefore response to pituitary signaling, can influence the pubertal outcome and secondary sexual characteristic development.

The majority of KS boys will initiate puberty around age 12, which is similar to the general population, but some may have a markedly delayed onset and not reach peak T levels by age 19 [30]. TRT may be needed for those who fail to either initiate puberty or progress to Tanner stage 5. Almost 85% of KS boys will have elevated gonadotropins during puberty, signifying early hypothalamic—pituitary—gonadal axis compensation. For the majority of boys with almost complete pubertal development, T levels are significantly lower compared to normal boys, indicating testicular burnout after the compensated period. Furthermore, in late Tanner stages, only 62% of KS boys were found to have T levels >290 ng/dL, compared to 85% of controls [29]. Variability in virilization influences identifiable male characteristics including muscle mass and facial and body hair and likely plays a role in abdominal adiposity. Gynecomastia, a sign of decreased T levels, often begins during adolescence and is experienced by 38—75% of KS adults [7]. Despite declining T levels, adolescents with KS may still have normal penile growth, body hair growth, voice maturation, and a typical adolescent augmented libido, further challenging diagnosis.

Skeletal features

Increased linear growth during puberty is also influenced by the increased androgen production. In men, T is converted into E_2 by aromatase in the peripheral tissues, and therefore E_2 concentration is dependent on circulating T levels. Interestingly, relative concentrations of E_2 have different effects on skeletal physiology. Lower E_2 levels, such as during the early pubertal period, drives longitudinal bone growth, whereas higher E_2 levels, such as during late puberty and early adulthood, induce epiphyseal plate closure and therefore growth arrest and final height [31].

Abnormal pubertal T levels in KS contribute to the eunuchoid appearance with disproportional growth of long bones compared to the spine. Around 30% of KS men have this appearance, owing to delayed or prolonged early puberty, or the lower than expected T levels throughout the pubertal period, therefore increasing bone exposure to lower E_2 concentrations and increased long bone growth prior to plate closure [7]. Although a lower proportion of KS adults have this classic appearance, almost 90% will be taller than predicted based on mid-parental height and are an average of 4 cm taller than non-KS men at their final adult height [28,29]. Additionally, without TRT, KS men carry a 2—40 fold increased fracture risk with 5—40% rates of osteopenia and 10% rate of osteoporosis in adulthood due to lower E_2 levels throughout life and decreased bone mineralization.

Spermatogenesis

KS is a well-recognized cause of adult infertility. In fact, many men with absent or subtle KS features that have gone unnoticed by practitioners are diagnosed in adulthood after failing to conceive a natural pregnancy [32]. As part of the couple's infertility workup, a semen analysis (SA) showing absent (azoospermia) or severely low (oligospermia) sperm in the ejaculate would lead to a recommended karyotype analysis to reveal KS diagnosis [33]. Spermatogenesis and the presence of ejaculated sperm, which occurs typically by pubertal Tanner Stage 2 or 3, is dependent on testicular T production, which decreases during and after puberty in KS [34]. Compounding the negative impact of hypogonadism on sperm production is that testicular damage is not unique to Leydig cell dysfunction; there is also germ cell loss beginning in childhood, leading to infertility [3]. Despite a combination of insults to sperm production in KS, biological fatherhood can be attainable with sperm retrieval surgery and assisted reproductive technologies (ART).

Spermatogonia, the pluripotent germ cell that develops into sperm, decreases in KS patients throughout life. In a retrospective observational study, histological examination from testicular biopsies showed decreasing germ cells, starting between ages 4—9 years old. Germ cell decline peaked at puberty until adulthood, when only sporadic germ cells with few areas of spermatogenesis are observed. By adulthood, the majority of seminiferous tubules are hyalinized, but interestingly, Leydig and Sertoli cell hyperplasia is present, signifying maintained concentrations given the germ cell depletion [3]. Areas of spermatogenesis may be present in only 50% of KS males, and worsen to a rate of 30% for those with a concomitant history of cryptorchidism. The depletion of germ cells leads to decreased testicular size, another classic KS feature, following a predictable curve to the histological changes. In mid-puberty, the average testicular volume for a KS male is 5—8 ml, compared to 25 ml, considered to be the 50th percentile for non-KS 18-year-old males [29]. Testicle size decreases further after puberty to an average of 3 mls, likely because of worsening germ-cell loss [3].

It is estimated that 91—99% of KS men are azoospermic, and the roughly 8.4% of men with ejaculated sperm are so severely oligospermic (sperm concentration of <0.1 million/ml) that natural conception may be unattainable [7]. To achieve paternity via in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), microsurgical testicular sperm extraction (mTESE) can be performed with sperm retrieval rates (SRR) ranging between 44 and 68%. Age at mTESE has been shown to significantly impact SRR (Fig. 1). Interestingly, FSH and LH levels as well as testis volume have not been shown to impact SRR [35]. On the contrary, preoperative T levels >250, including those on treatment with either selective estrogen receptor

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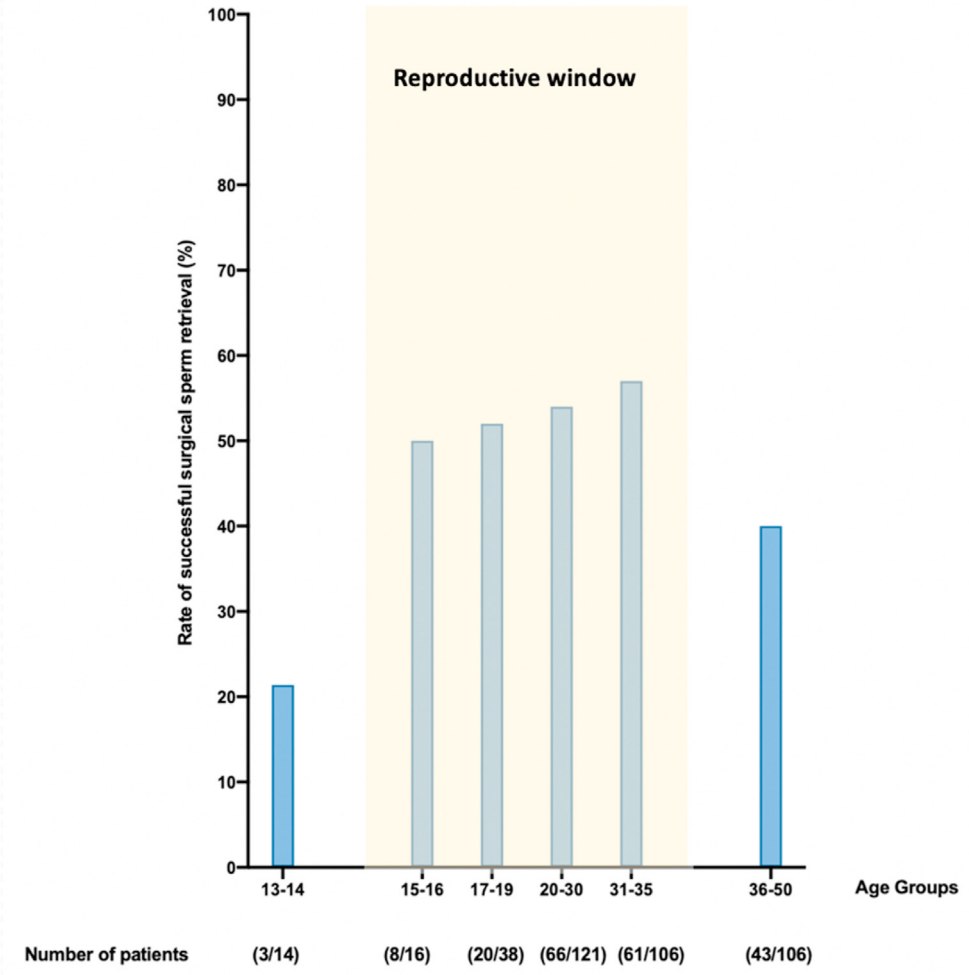

Fig. 1 Reproductive window of favorable SRR.

modulators (SERMs), aromatase inhibitors (AI), or hCG, are associated with higher SRR, and patients who had previously been on TRT had lower SRR, at around 25% [36]. Although the hypogonadism in KS is caused by germ cell depletion as well as Leydig cell failure, happening independently of each other, the relationship between T concentration and SRR illustrates the necessity of intratesticular T for spermatogenesis and suggests that T levels are the most important marker for evaluating global testicular function in KS patients.

The challenge for providers treating KS patients of reproductive age is balancing the timing of administering T therapy to mitigate the consequences of male hypogonadism against the spermatogenesis suppression that occurs with TRT. Unfortunately, owing to Leydig cell dysfunction, SERMs or LH analogues that upregulate natural T production and preserve fertility, may hasten testicular failure in the long-term. As illustrated in Fig. 1, a reproductive window of favorable SRRs are between ages 15—35, and it is important for patients to consider sperm cryopreservation during this time if they desire future paternity. We developed a clinical pathway for KS patients seeking fertility evaluation, outlined in Fig. 2, with the goal of offering and encouraging early sperm cryopreservation, including at the time of the first SA [32]. We discontinue any current TRT, and patients with low T are started on SERMs with or without aromatase inhibitors if E_2 is elevated. We continue to offer SA with sperm cryopreservation for any present ejaculated sperm after T optimization and/or after patients reach Tanner 5. For persistently azoospermic patients after medical optimization, we offer mTESE with the goal of cryopreserving sperm for patients not currently desiring a pregnancy and/or for use with for IVF/ICSI in couples seeking conception, with cryopreservation for any excess. We strongly advise fertility evaluation and specialist referral as early as possible so that sperm can be retrieved and cryopreserved within each individual patient's reproductive window.

Varicocele, another common urologic condition that may decrease spermatogenesis, has been reported in 12.5% of KS patients, similar to the prevalence within the general population [37]. Varicocele management in KS men can be challenging, as the most well-accepted, non-pain indications for varicocelectomy are testicular size discrepancy in childhood or adolescence and abnormal sperm parameters in post-pubertal men. Owing to the low testis volume in KS, it would be difficult to determine a significant size difference for the patient to undergo repair. Furthermore, the updated joint infertility guideline from the

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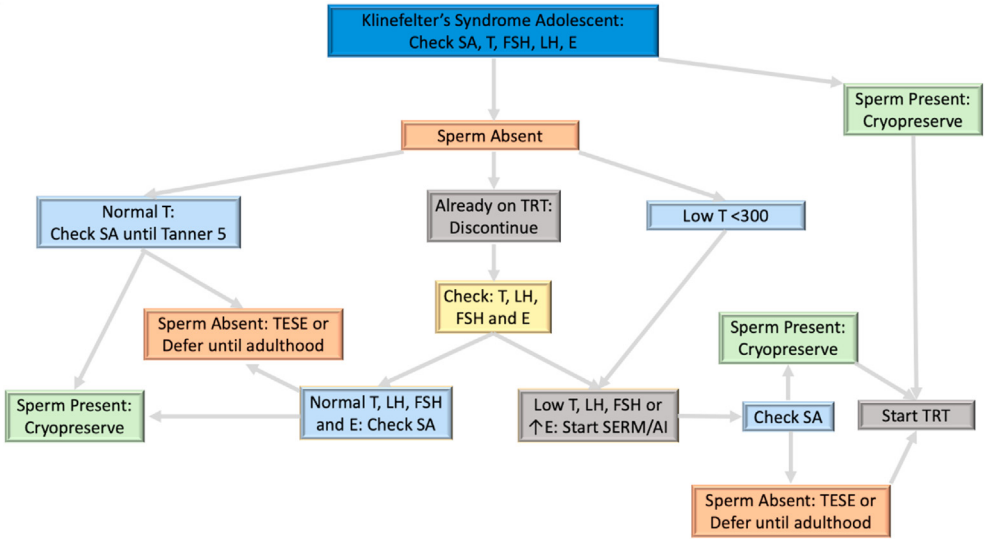

Fig. 2 Fertility evaluation and treatment pathway for KS men. * SA = semen analysis (2 semen analysis done at beginning of evaluation).

Table 1 Relative frequencies of decreased androgenization characteristics.

Features Accompanying KS	Frequencies
Cryptorchidism	17–27%
Hypospadias	7–13%
Learning disabilities/behavioral issues	68–75%
Gynecomastia	38–75%
Elevated gonadotropins	85%
Disproportional growth of long bones/Increased height	>90%
Decreased testicular volume	>95%
Decreased facial/public hair	30–80%
Azoospermia and associated infertility	91–99%

American Urological Association (AUA) and the American Society for Reproduction Medicine (ASRM) recommend against varicocelectomy in men with azoospermia, which is present in the overwhelming majority of KS men [38]. Given this new guideline statement, KS patients with varicocele(s) are unlikely to meet the criteria for varicocelectomy unless they are symptomatic.

Conclusion

KS is a complex genetic disorder with variable traits outlined in Table 1. The clinical spectrum in KS revolves around the timing of and relative T concentrations throughout the fetal, childhood, and pubertal years. The presence or absence of clinical characteristics reflecting decreased androgenization provides an insight to the relative testicular function during developmental time points for those with KS and contributes to variability within the syndrome. Although the frequency of identifiable KS features is lower during childhood, clinicians should consider the diagnosis when there is a presence of or combination of any of these traits. Early diagnosis in KS and directed therapy may successfully mitigate many of the consequences of hypogonadism during critical developmental steps as well as improve chance of paternity if fertility evaluation can occur before or during the reproductive window of favorable SRR. Furthermore, earlier diagnosis can not only help define the true prevalence of this disorder but also help elicit scientifically-derived treatments to improve quality of life for men with KS.

Funding

None.

Conflicts of interest statement

The authors have no relevant conflicts of interests to disclose.

Acknowledgements

None.

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Please cite this article as: Nassau DE et al., Androgenization in Klinefelter syndrome: Clinical spectrum from infancy through young adulthood, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2021.02.021