Klinefelter Syndrome. The Effects of Early Androgen Therapy on Competence and Behavioral Phenotype

Ryan Flannigan, MD,1 Premal Patel, MD,2 and Darius A. Paduch, MD, PhD1,3

ABSTRACT

Introduction: Klinefelter syndrome (KS) is the result of sex chromosome aneuploidy most often characterized as 47,XXY. The typical features of KS include tall stature, gynecomastia, small firm testicles, hypergonadotropic hypogonadism, and infertility. However, abnormalities in neurodevelopment, cognition, and social and behavioral functioning also can be present. The abnormalities in neurodevelopment are believed to be due in part to androgen deficiency during early development and puberty.

Aim: To discuss the role of androgens in normal adolescent development; discuss the cognitive, behavioral, and social functioning of children with KS; evaluate the evidence for early androgen therapy in men with KS; and discuss management strategies in the development of boys with KS.

Methods: A systematic review of early androgen therapy and KS was performed using PubMed-Medline and Scopus databases. Relevant articles commenting on social, behavioral, cognitive, and physical outcomes among infants, children, and adolescents were included for reporting and discussion.

Main Outcome Measures: Social and behavioral functioning; cognitive outcomes; adverse effects associated with androgen therapy.

Results: 3 retrospective articles and 2 randomized controlled trials addressing early androgen therapy in boys with KS were reviewed. These studies showed an improvement in several aspects of social and cognitive functioning based on validated questionnaires. Treatment strategies, potential negative effects, and limitations of the literature on early androgen therapy in boys with KS are discussed.

Conclusion: Our findings indicate that early androgen supplementation in children with KS combined with specific educational, familial, and social support improves behavioral functioning. The optimal timing of hormonal therapy might require prospective studies, but based on our data and review of the literature, the benefit of early hormonal and therapeutic intervention in KS is very encouraging. 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.

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Key Words: Klinefelter Syndrome; 47,XXY; Testosterone; Neurodevelopment; Behavioral Phenotype; Androgen

INTRODUCTION

Klinefelter syndrome (KS) refers to the genetic diagnosis of an X chromosome polyplody with at least 1 additional X chromosome present and a clinical phenotype of tall stature, small testicles, androgen deficiency, infertility, and gynecomastia. The syndrome was first described by Klinefelter et al,1 when they reported on a series of 9 men in 1942; these men were found to have azoospermia, small hard testicles, limited hair growth to the face and body, and gynecomastia. However, it wasn’t until 1959 when patients presented with this phenotype and were found to have an additional X chromosome.2 KS has since become the most common genetic X chromosome abnormality. KS is identified in 0.1% to 0.2% of newborn boys and is the most common genetic cause of male infertility, with an incidence of 3% to 4% in infertile men, attributed to oligozoospermia in 0.6% and azoospermia in 10% to 12%.3–6 Most diagnoses of KS are made through prenatal diagnosis in mothers older than 35 years.
Genetics of KS

In KS, non-dysjunction of the sex chromosomes results in at least 1 additional X chromosome. 80% to 90% of men with KS have a 47,XXY karyotype. Several variant karyotypes also have been described such as 47,iXq,Y, 48,XXX, and 48,XXXX or mosaicisms 47,XXY and 46,XY. In these cases, non-dysjunction occurs most frequently during meiosis I in oogenesis (50%) and spermatogenesis (40%) or in meiosis II during oogenesis (10%). Rarely, non-disjunction occurs in early embryogenesis (3%). It is important to discuss with the patient and parents that it is the Y chromosome that determines the sex of an individual; hence, regardless of the number of X chromosomes, boys and men with KS are phenotypically male. Genes derived from the X chromosome are predominantly expressed in the brain, testes, and ovaries. Most of the genetic material on 1 X chromosome in women undergoes inactivation; hence, in 46,XX female and 46,XY male individuals, there is only 1 functional X chromosome. Inactivation of additional X chromosomes occurs by epigenetic regulation through non-coding RNAs called XIST, which is expressed on the X chromosome to be inactivated. Unfortunately, the process of X chromosome inactivation is promiscuous and not complete; hence, the entire additional X chromosome is not always inactivated.

Clinical Phenotype and Endocrinology of KS

The clinical manifestation has been further characterized since its initial inception. The clinical phenotype classically includes tall stature, gynecomastia (Figure 1), gynoid hips, sparsity of body hair, firm hypotrophic testes (<4 mL; Figure 2), hypergonadotrophic hypogonadism, infertility, and a propensity toward obesity. Infertility is typically associated with progressive hyalinization, fibrosis, Leydig cell hyperplasia, and depletion of germ cells among the seminiferous tubules. This typically results in Sertoli cell only syndrome and is believed to worsen immediately after puberty. Most often results in azoospermia and requires surgical sperm retrieval by microdissection testicular sperm extraction. Boys with KS also might have abnormal physical features including a small or micropenis, truncal hypotonia (68%), joint laxity (50%), hand tremors in children after 5 years of age (20–50%), clinodactyly or curved 5th digit (26%), pectus excavatum, delayed puberty (50%), gynecomastia (30%), mirror movements (40%), infantile cherubic faces, and disproportionately long limbs. Other clinical features include developmental abnormalities in speech with decreased phoneme repertoire (50–75%), age-appropriate language comprehension (80%), delayed auditory memory (50–80%), enhanced visual memory (50–80%), normal IQ within 10 to 15 points of siblings (80%), reading deficiencies or dyslexia (50%), delayed balance skill acquisition (50–80%), sensory differences, pseudo-torticollis (20%), developmental dyspraxia (50–80%), and psychosocial functioning. The behavioral profile of boys with KS consists of poor self-esteem, shyness, increased anxiety, depression, and social difficulties. Because of androgen deficiency in infants and boys with KS, they can exhibit, albeit less commonly, features of under-virilization such as microgenitocranium, bifid scrotum, cryptorchidism, and hypospadias. During adolescence 62% of boys can maintain serum testosterone (T) levels higher than 10 nmol/L through hypergonadotropinemic compensation, and most will enter puberty. However, relative androgen deficiency is progressive in most men in later stages of life; men with KS are at risk of sequelae of androgen deficiency such as osteoporosis, low libido, and erectile dysfunction (ED). It appears that ED is likely the result of androgen deficiency and not linked to the syndrome itself, because 1 study reported a comparable rate of ED in 40 men with KS compared with age- and T-matched controls; similarly, a study of 53 men with KS had a comparable rate of ED as 75 age-matched controls with a rate of 18.9% but significantly lower sexual desire. The severity of ED in young
men with KS varies by report, but 2.5% (mean age = 23.3 years) to 22.7% (mean age = 40 years) of men with KS were found to have severe ED. It also is important to acknowledge that these individuals most often do not have normal levels of androgen (65–85% of men with KS have total T levels < 12 nmol/L) and therefore typically have normal libido and sexual function even at minimally low serum levels. In fact, significant heterogeneity exists in the clinical phenotype of men with KS, and many of the features progressively worsen as the individual ages. This can be due to varying levels of androgens, T/estradiol ratios, androgen receptor sensitivity differences associated with variable CAG repeat lengths, or variation in X chromosome inactivation.

Examination of the testes during the 2nd trimester in fetuses with KS has demonstrated variable findings, with half reporting a smaller number of germ cells and the others finding normal histology. Androgen levels in infants and young children have been variable, with some studies finding a lower level of circulating androgens and a decreased postnatal surge. Others have reported diminished muscle tone and a smaller penis, which serves as a reflection of androgen deficiency. Based on our experience, it is rather clear that most, if not all, male individuals with KS exhibit a certain level of androgen resistance; hence, rather than focusing on absolute T levels, we use markers of androgenization such as muscle and penile development, strength, bone age, presence of acne, and hair distribution.

Early Diagnosis of KS

Diagnostic delay is a common feature of KS because of the wide variability in clinical presentation and often delayed onset of symptoms at or beyond puberty. Furthermore, the more mild forms tend to lack any obvious clinical signs other than small and firm testes. A study from the United Kingdom estimated that 64% of cases of KS might never be diagnosed, 10% are diagnosed prenatally, and the remaining 26% are diagnosed before puberty and at adulthood. A similar study from Denmark found comparable results with approximately 75% of cases undiagnosed and fewer than 10% identified before puberty when comparing postnatal prevalence with prenatal incidence in those undergoing prenatal cytogenetic studies. With increasing maternal ages, more diagnoses are being made in utero. Conventionally, KS is diagnosed by cytogenetic studies from peripheral blood lymphocytes evaluating the karyotype in GTG and RHG banding. However, fluorescence in situ hybridization can be performed on peripheral blood lymphocytes by using probes targeting DXZ1 and DYZ3 and aid in diagnosing individuals with mosaicism. There has been growing interest in the rationale for postnatal screening of KS to allow early identification to potentially implement beneficial interventions because many sequelae are related to a time-dependent exposure of low T. Because children with KS often possess neurodevelopmental delays and variable extents of cognitive deficits, neurologists and developmental pediatricians use cytogenetics in evaluation of children with developmental delay. These can present as language-based difficulties, executive dysfunction, learning disabilities, and speech delays. It is the myriad of these dysfunctions that is believed to contribute to the complex social and behavioral phenotypes commonly seen in children with KS. Children with KS also are at an increased risk for attention-deficit/hyperactivity disorder (ADHD) and other psychological conditions. Awareness about the association of these symptoms with KS among pediatricians and educators should lead to more common implementation of cytogenetic testing. Early identification allows implementation of treatment strategies for learning and/or emotional disorders, access to appropriate resources, and alleviation of parental distress. Implementing language therapy can help children develop more advanced language comprehension and expression skills, which can prevent social isolation. Medically, KS is associated with hypergonadotropic hypogonadism, which tends to manifest clinically by midpuberty. Early diagnosis can allow the initiation of androgen replacement therapy before signs and symptoms of hypogonadism develop. Early diagnosis also has the advantage of considering fertility preservation. Because KS is associated with a decline in spermatogenic capacity likely at birth and more convincingly during puberty, a study looking at pediatric and parental attitude toward neonatal screening and sperm preservation found a positive attitude and appreciation for these strategies.

Neuroendocrinology of KS

With respect to the complex neurobehavioral deficits often seen in patients with KS, they could be a result of abnormal neurodevelopment. Findings of structural imaging studies have been varied, with most reporting a decrease in gray and white matter volume. The most pronounced effects have been on the frontal and temporal lobes. The neuroanatomic phenotype is just as variable as the clinical phenotype. What are paramount for appropriate neurodevelopment are androgens, specifically T, which plays an important role in mammalian brain development and exerts a wide array of influence on cognitive functioning and social behaviors in boys and men. Specifically, cognitive flexibility improves, decreases in perseverative behavior occur, and task switching, working memory, social cognition, and concept formation improve during the adolescent period corresponding to pubertal changes as we enter adulthood. Sex hormone influence begins in utero and continues through adulthood. These early androgens are believed to influence gray matter volume and cortical maturation leading to an organizational effect of social and cognitive behaviors. 2 surges were found to influence neurodevelopment before puberty, which include an intrauterine surge that happens at 8 to 24 weeks’ gestation and a neonatal surge, also known as “mini-puberty,” that occurs at 2 weeks after birth and continues until at least 24 weeks. Studies have identified thinning of the prefrontal cortex associated with progression of Tanner stages during puberty. However,
increased size of the subcortical white matter and corpus callosum has been correlated with T levels.\textsuperscript{37,38} Furthermore, in non-human primate studies, androgen receptors have been localized to numerous regions in the brain including several hypothalamic nuclei, lateral septum, stria terminalis, cortex, medial preoptic area, and amygdala.\textsuperscript{39} Thus, neurodevelopment and functioning could be largely influenced by the presence of adequate ligands for the naturally occurring androgen receptors among these areas. A multitude of studies have reported on those with androgen deficiency and the positive impact of T replacement in adolescents and adults with KS. However, little is known about T levels in children and whether early androgen replacement could lead to improvements in neurodevelopment.\textsuperscript{26} Different formulations of T replacement have been used, predominately T enanthate and oxandrolone. Aromatase inhibitors also are sometimes used in response to excessive estradiol levels.

METHODS

A systemic literature search of the PubMed-Medline and Scopus databases was performed on October 2017, including literature from 1999 through 2017. We included English-language articles only. The search strategy included broad terms in isolation or in combination: testosterone therapy, testosterone replacement, androgen therapy, androgen replacement, Klinefelter, Klinefelter syndrome, neurodevelopment, cognitive development, and cognitive development. Relevant articles on the effects of early androgen therapy on cognition, behavior, and social functioning of children with KS were sought. Review articles, editorials, case reports, comments, and meeting abstracts were excluded. Additional relevant articles were selected from authors’ bibliographies. All studies of interest were obtained as full-text articles. Study eligibility was determined by 2 authors (R.K.F. and P.P.).

RESULTS

7 studies specific to androgen replacement therapy in young male patients with KS were retrieved for our review. 3 of the studies were by the same author (Samango-Sprouse) with 1 of the studies evaluating children with 49,XXXXY and the impact of T therapy. The 2 randomized trials in the literature were published in 2017 by Ross et al and Davis et al and were derived from the same patient cohort. Ross et al reported improved social, behavior, and visuomotor performance in children receiving androgen supplementation. The studies and their findings are presented in Table 1.

DISCUSSION

Early Androgen Replacement

Androgen supplementation has been most commonly studied in postpubescent and adult men with KS and is commonly adopted to improve quality of life and prevent metabolic consequences and bone mineral density loss.\textsuperscript{40} However, only recently published reports are emerging concerning androgen supplementation in infants and young children.

A retrospective study of children with 49,XXXXY, a rare variant of KS, found a positive treatment effect in speech and language domains, gestural communication, and vocabulary development for those treated with early androgen replacement. Initiation of androgen replacement was based on phallus size, with 10 children receiving T enanthate 25 mg/month for 3 months and 1 child receiving 40 mg/month for 3 months. The 2 groups consisted of 11 children, with the mean age of T administration in the intervention group being 12 months. The 1st evaluation was conducted at 74 months in the treatment arm and 84 months in the control group. Limitations of the study as outlined by the investigators include that T administration was based on phallus size and androgen levels were not measured before initiation of therapy. Discrepancy in timing of evaluation after treatment was not discussed. Timing of androgen supplementation also varied substantially from newborn to 30 months of age.\textsuperscript{41}

A follow-up study was performed that included 101 boys with 47,XXY referred for a comprehensive neurodevelopmental assessment at the Neurodevelopmental Diagnostic Centre for Young Children (Davidsonville, MD, USA). 34 of these children received T injections as a treatment course for small phallus at a dose of 25 mg/month for 3 months as per their pediatric endocrinologist, with treatment age ranging from 4 to 15 months. At 36 and 72 months, standardized questionnaires were given to all participants. Their findings showed improved function in several aspects of neuromotor, speech and language, intellectual, and reading function. In accord with their prior retrospective study, limitations include that T was administered based on phallus size, which serves as a clinical surrogate of androgen deficiency.\textsuperscript{42} However, this could signify that androgen replacement has a positive impact on cognitive and behavioral outcomes in those with presumed androgen deficiency based on phallus size. A follow-up study of patients from the same cohort was published in 2015. 29 boys were administered T enanthate, as described previously, at a dose of 25 mg/month for 3 months when the boys were 4 to 15 months old. 57 children served as controls. Children were 9 to 11 years old. They found fewer behavioral problems and improved social behavioral skills of the boys who received T. Children who received early T also had fewer somatic complaints such as headaches and stomach aches, which have been reported to be higher in children with anxiety, language-based disabilities, and social communication difficulties. The most significant behavioral differences observed in this study were within social domains, including social cognition, communication, and overall social problems. The investigators did not identify any adverse outcomes in those receiving androgen supplementation.\textsuperscript{26}
decrease the prevalence of gynecomastia. Treatment with anastrozole seems to have been studied in other pediatric conditions such as constipation, obesity trended downward from 17% to 11% but was not statistically significant. They reported no adverse events with use of topical T or aromatase inhibitors.

Because of the high prevalence of gynecomastia in untreated KS in the past and documented hyperestrogenism in KS, many physicians including our group use aromatase inhibitors. Specifically, reversible aromatase inhibitors such as anastrozole have been studied in other pediatric conditions such as constitutional short stature. Treatment with anastrozole seems to decrease the prevalence of gynecomastia.

Most recently, a study evaluated 84 boys 4 to 12 years old with KS for a 24-month period. In double-blinded, randomized controlled fashion, these boys received oxandrolone (0.06 mg/kg) or placebo. Doses were lowered if the following events were noted: high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, abnormal liver enzymes, Tanner stage 2 in boys younger than 8 years, systolic or diastolic blood pressure increasing beyond the age-specific 95th percentile, or bone age advancement greater than 12 months in a 6-month interval and where the bone age was older than the chronologic age. Results demonstrated that early androgen therapy using oxandrolone improved visuomotor function compared with placebo and psychosocial functions such as anxiety, depression, and social interactions. However, no changes were noted for cognitive function and language, working memory, executive function, attention, and aggressive or hyperactive behaviors.

350 ng/dL. Topical formulations of T (AndroGel, AbbVie, North Chicago, IL, USA; and Axiron, Eli Lilly, Indianapolis, IN, USA) were used in 110 boys and an aromatase inhibitor (anastrozole 1 mg/day) was used in 75. 104 of the 110 boys receiving topical T therapy achieved serum T levels within the normal range, with an increase from 240 to 650 ng/dL. The rate of obesity trended downward from 17% to 11% but was not statistically significant. They reported no adverse events with use of topical T or aromatase inhibitors.

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### Table 1. Summary of articles relevant to early androgen therapy in KS included in this review

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Cohort</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kubler et al.2014</td>
<td>KS</td>
<td>21 men with KS without T, 10 men with KS with T before 20 y of age, 11 men with KS with T after 20 y of age</td>
<td>Intramuscular injection of T 250 mg (Testosterone) every 4–6 wk</td>
<td>Men with KS &lt;20 y old received T for mean 5.7 ± 7.1 µg men with KS &gt;20 y old at T initiation received T for mean 5.4 ± 5.3 µg</td>
<td>BMD decrease those with no T treatment and those with KS treated beyond 20 y of age (P &lt; 0.001 and P = 0.04); BMD maintained in men with KS treated before 20 y of age (105% of normal controls)</td>
</tr>
<tr>
<td>Samango-Sprouse et al.2011</td>
<td>49,XXXY</td>
<td>22 children: 11 in treatment group (age range = 8 mo to 14 y), 11 in untreated group (age range = 27 mo to 19 y)</td>
<td>10 boys received T enanthate 25 mg for 3 mo, 1 boy received T enanthate 40 mg for 3 mo</td>
<td>Treatment arm 74 mo, control 84 mo</td>
<td>Positive treatment effect in speech and language domains, gestural communication, and vocabulary development</td>
</tr>
<tr>
<td>Samango-Sprouse et al.2015</td>
<td>47,XXY</td>
<td>101 children: 34 in treatment group (age range = 4–15 mo), 67 in untreated group (age range = 3 mo to 11 y)</td>
<td>34 boys received T enanthate 25 mg for 3 mo</td>
<td>Analyzed at 36 and 72 mo</td>
<td>Improved function in several aspects of neuromotor, speech, and language</td>
</tr>
<tr>
<td>Mehta et al.2014</td>
<td>KS</td>
<td>151 boys; mean age at T initiation = 11.6 y (range = 10–21 y); starting serum T &lt; 350 ng/dL.</td>
<td>Topical T therapy in all 110 boys titrated to high normal serum T levels, aromatase inhibitors added in 75 boys (anastrozole 1 mg/d)</td>
<td>3.4 office visits within 5-y period</td>
<td>Obesity rate trended down (17% to 11%; P = 0.25); serum T increased 240–650 ng/dL; 104 of 110 boys achieved serum T within normal range using T gels; serum LH and FSH increased during puberty (2.6–16.6 and 7–42 mIU/mL, respectively)</td>
</tr>
<tr>
<td>Samango-Sprouse et al.2015</td>
<td>47,XXY</td>
<td>86 children: 29 in treatment group (age range = 4–15 mo), 57 in untreated group (age range = 3 mo to 11 y)</td>
<td>29 boys received T enanthate 25 mg for 3 mo</td>
<td>Age range at evaluation: 9–11 y</td>
<td>Fewer behavioral problems, improved social behavioral skills</td>
</tr>
<tr>
<td>Ross et al.2017 (NCT00348946)</td>
<td>47,XXY</td>
<td>84 children: 43 in treatment group (age = 6.9 ± 2.2 y), 41 in untreated group (age = 8.2 ± 2.7 y)</td>
<td>Ox dose 0.06 mg/kg/d rounded to nearest 2.5 mg, or placebo, for 24 mo</td>
<td>Evaluated at baseline and then at 12 (n = 84) and 24 (n = 72) mo</td>
<td>Improved visual-motor performance, positive effects on several aspects of anxiety and depression and social functioning, not significant on most aspects of cognition</td>
</tr>
<tr>
<td>Davis et al.2017 (NCT00348946)</td>
<td>47,XXY: 47,XXY/46,XY; 48,XXY; 48,XXYY</td>
<td>93 children: 39 in treatment group (age = 8.2 ± 2.7 y), 41 in placebo group (age = 6.9 ± 2.2 y)</td>
<td>Ox dose 0.06 mg/kg/d rounded to nearest 2.5 mg, or placebo, for 24 mo</td>
<td>Evaluated at baseline and then at 12 (n = 84) and 24 (n = 72) mo</td>
<td>Decreased body fat, decreased triglycerides, decreased HDL cholesterol</td>
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</tbody>
</table>
Oxandrolone also decreased body fat during the study period, increased bone age, and lowered total cholesterol, high-density lipoprotein cholesterol, and triglycerides.45

**Timing of Androgen Therapy**

3 flares in physiologic T production occur naturally throughout life: during the 1st trimester for male genital tract development; during 2 to 6 months of age; and during adolescent puberty into adulthood.10 These physiologic T flares have been demonstrated in boys with KS, with some reports measuring lower T production than controls during these time points, although results are heterogeneous.24-38 This has developed the rationale for androgen supplementation during the neonatal and pubertal time points. No guidelines are available for the dose and timing of androgen supplementation. Based on the available literature published, the following time points have been reported.

3 to 15 Months of Age

Intramuscular injection of T enanthate 25 to 50 mg/month for 3 months has been described, corresponding to the normal postnatal T surge. AndroGel 1% (1 pump, 1.25 g of gel/day) also has been described in older children with close monitoring for skin reaction and minimizing risk of transference to siblings or other children. Penile length is monitored as a proxy for response to T therapy.10

Adolescents Before Puberty

Multiple groups have provided T therapy up to a 24-month duration during this period using topical T (ie, AndroGel 1%; 1 pump, 1.25 g/day), injectable T enanthate 25 to 50 mg/ingestion, and oxandrolone 0.06 mg/kg per day.

Puberty

One group reported on initiating at onset of puberty (~11 years of age). Before initiation of therapy, it was recommended to obtain serum T levels, gonadotropins, estradiol, prolactin, inhibin-B, insulin-like growth factor-1, and cortisol. These levels can be monitored starting before onset of puberty and then every 6 months throughout puberty. The clinician also should monitor secondary sexual characteristics relative to puberty including penile length and girth, testicular growth, and pubic and axillary hair every 6 months throughout puberty.10 T formulations reported during this period include AndroGel 1%, 2 pumps (2.5 g of gel/day) with titration up to 3 pumps (3.75 g of gel/day); and Axiron 2%, 1 pump (30 mg/day).53 Anastrazole 1 mg/day also has been reported for use in boys with high estradiol/T ratios.53

**Principles of Management of KS**

A multidisciplinary approach is essential in optimal management of patients with KS. Table 2 presents developmental factors, therapeutic considerations, and goals of therapy in boys with KS. Psychological and medical management are the mainstay components of management of boys with KS. Psychologically, behavioral and learning aids and direction are of benefit for these boys. Medically, early androgen therapy has been reported, with favorable results to date; however, despite the recently published randomized controlled trial of early androgen therapy with 24 months of follow-up and 5 retrospective series, no long-term randomized controlled trials are available to guide treatment approaches of KS. Surgical management is limited to sperm retrieval as part of fertility preservation or at the time of desired fertility when sperm is not available in the ejaculate.

The goal of management should be to allow each patient to reach his full potential and to function independently in society. As such, the approach to treatment should be holistic, individualized, multidisciplinary, and uniquely age dependent. Academic progress, social interactions, emotional maturity, physical development, sexual and pubertal progress, and preservation and management of infertility are key elements of management. For an additional review of KS management, see Wosnitzer and Paduch10 and Verri et al.49

**Academic Progress**

Most boys with KS have expressive language deficits (50–75%),51,52 expressive language dyspraxia, auditory delayed processing issues, and executive skills deficits, and many have problems with attention (ADHD). Speaking clearly, in a linear and focused manner, and finishing tasks are key elements of learning. Early introduction of speech therapy to overcome expressive language dyspraxia is a critical step for academic progress and success. Often the deficits in speech are not severe enough or the resources are difficult to obtain for in-school services, although 60% to 86% of boys with KS require special education services51,52; therefore, as a leading physician, one has to be proactive with directing parents to help the child with language and speech development. This can be done through online resources and paying close attention to appropriate articulation when the child communicates with his parents and peers. Other strategies include home exercises such as reading aloud with a concerted effort for crisp pronunciation.

Boys with KS have deficits in language and communication.51,52 Although the delay is often minimal, it can be significant to the point that parents and older siblings tend to answer questions for the patient; this approach is highly counterproductive because it prevents the boy from focusing on spoken language and auditory cues, thus impairing further normal development of communication skills in the child. It is important to emphasize to the educators that the child should be given time to answer the question when asked because boys with KS do not have global cognitive impairment but they do have selective deficits in language and communication.51,52 These limitations in language and communication have significant
<table>
<thead>
<tr>
<th>Developmental abnormalities</th>
<th>Therapeutic considerations</th>
<th>Goals of therapy</th>
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</thead>
<tbody>
<tr>
<td>Delayed expressive language and speech milestones</td>
<td>Early speech therapy and language evaluation</td>
<td>Improve impaired speech, language, voice, fluency</td>
</tr>
<tr>
<td></td>
<td>Encouragement for patient to speak for himself and answer questions</td>
<td>Improve communication and avoid social consequences of speech disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acquisition of strategies to enhance effectiveness of communication</td>
</tr>
<tr>
<td>Attention deficit, without hyperactivity during school</td>
<td>Classroom accommodations, communication to teacher, avoid distractions at home when doing homework, stimulant medications</td>
<td>Increase likelihood of academic success for boys with KS through behavioral interventions and environmental optimization</td>
</tr>
<tr>
<td>Deterioration in school performance in transition from elementary to middle school</td>
<td>Retest to identify disciplines requiring additional attention, consider at or before middle school entrance</td>
<td>Prompt identification and intervention for deficits</td>
</tr>
<tr>
<td>Math difficulties</td>
<td>Retest, identify deficits, and remediate</td>
<td>Improve mathematical knowledge, skillset, and concepts in numeracy</td>
</tr>
<tr>
<td>Identification of left-handedness</td>
<td>Consideration and accommodation with writing and sporting activities</td>
<td>Enhance gross and fine motor skills</td>
</tr>
<tr>
<td>Deficient complex language production and comprehension</td>
<td>Assess written and verbal language comprehension and communication; discuss performance with teachers; identify areas requiring additional attention</td>
<td>Improve written and verbal comprehension and communication</td>
</tr>
<tr>
<td>Decreased athleticism: running, agility, strength, and gross and fine motor coordination</td>
<td>Physical therapy, occupational therapy</td>
<td>Improved positive body self-perception through exercise, practice, and strategies for gross and fine motor skills, balance and coordination, strength and endurance, and cognitive and sensory processing and integration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choose sports that emphasize strengths</td>
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<td></td>
<td></td>
<td>Consider testosterone therapy</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td></td>
<td>Ensure timely progress through pubertal milestones, with adequate testosterone levels</td>
</tr>
<tr>
<td>Body image disorder</td>
<td>Group psychotherapy</td>
<td>Address sense of isolation and experience support from peers, improved body self-perception</td>
</tr>
<tr>
<td>Communication of KS diagnosis</td>
<td>Emotional support; address psychological, behavioral, and social factors that might influence the adaptive process to the KS condition</td>
<td>Improve comprehension, acceptance of diagnosis, and positive self-perception</td>
</tr>
<tr>
<td>Anxiety, depression, psychoses</td>
<td>Psychotherapy, cognitive-behavioral therapy ± medication when medically indicated</td>
<td>Alleviate dysfunctional emotions, behaviors, and cognitions through a goal-oriented, systematic procedure</td>
</tr>
<tr>
<td>Pharmacologic compliance</td>
<td>Teach strategies to improve compliance with medication</td>
<td>Decrease patient non-compliance by understanding the reasons for maintaining the behavior</td>
</tr>
<tr>
<td>Infertility</td>
<td>Referral to infertility specialist for evaluation and consideration of sperm retrieval if necessary, assessment of gonadotropin levels, semen analysis</td>
<td>Help patient achieve fertility preservation or pregnancy</td>
</tr>
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KS = Klinefelter syndrome.
*Adapted from Verri et al49 and Ross et al,50 with modifications.
impact on development of personality, behavior, and social adaptation.53

Most boys with KS do not have difficulties with arithmetic but do have problems with writing, comprehension, and languages.54 In the opinion of the senior author, the expressive language deficits are part of more global fine motor dysfunction and hypotonia. Because androgens stimulate growth of muscles, we believe that positive effects of early hormonal manipulation can be due to a direct effect of androgens on neuromotor function. This leads to not only increased muscle mass but also motor function50 and subsequently improved self-esteem.55–57 However, androgens are complementary treatment in addition to ongoing educational accommodation, speech, occupational, and physical therapy. Execution of tasks requires planning, gathering tools, finishing the product, and sharing the product. Executive skills deficits are extremely common in boys with KS.51

Executive skills often coincide with ADHD, one of the most common psychiatric diagnoses in men with KS, particularly the inattentive subtype of ADHD.58 Most, but not all, boys with KS respond to stimulants positively. Here, it is important to recognize that initiation of stimulants should be the last resort and not 1st-line therapy. In the senior author’s practice, androgen supplementation is initiated with educational and family support to help with concentration, stamina, and focus. Brain maturation occurs during adolescence, improving cognitive control and focus. A significant degree of brain maturity is related to the action of sex hormones.59 However, if despite hormonal supplementation, the boys continue to have issues with ADHD, then initiation of stimulants can be considered if meeting criteria for ADHD, initially at the lowest dose and titrate as required. Use of stimulants has shown positive effects in 79% of patients with sex chromosome aneuploidies including KS.58 Using a combination of educational interventions, androgen therapy, and family support, all our patients have graduated from high school and most patients enter college. An individualized multimodal therapeutic approach contributes to successful outcomes for boys with KS.60

Social Interactions and Emotional Maturity

Neurobiologically, sex hormones contribute to emotional stability and maturity, which are attained during and beyond puberty.61 Because boys with KS have a significant deficit in T production or partial resistance to androgens, there is no surprise that their emotional maturity lags significantly behind that of their peers. There are several aspects of KS that impair social interactions: language barriers described earlier, especially poor clarity of speech, shyness, lack of assertiveness, anxiety, and social immaturity.62 The barriers to being well understood often lead to frustration, marginalization, and avoidance of verbal contacts with peers. Here, there is no replacement for good parenting, providing explanation and guidance of appropriateness of verbal and non-verbal communications with peers. Often, involving a psychologist is helpful in overcoming the emotional immaturity and social anxiety faced by boys with KS.

Boys with KS also can have phenotypic abnormalities such as long arms and legs or gynecomastia, differentiating them from their peers, potentially leading to teasing, and further undermining their self-confidence.59 Poor physical performance and stamina can further alienate boys from their peer group. Similarly, clumsiness from poor development of fine motor skills51 lead to suboptimal performance in sports and daily activities. Considering our societal values of sport and physical prowess, it is conceivable that many boys with KS who were not treated early with androgens feel as outsiders, or alienated, and avoid social activities with peers. Hence, it is critical that in planning the treatment we as clinicians pay attention to keeping our patients at the front of the developmental curve when possible with respect to physical and pubertal development. There is no question in the view of the senior author that our patients do significantly better socially because they feel like they are on par or slightly ahead of other boys in their class with respect to their pubertal development. Helping boys with KS socially integrate with their peers is believed to be the most important factor in helping these boys graduate from high school.63

Potential Negative Effects of Androgen Supplementation in KS

The available evidence addressing early androgen supplementation in boys with KS is predominately limited to retrospective series and is subject to biases inherent to these types of studies. As such, clinicians must consider the evidence for potential benefit and the potential negative effects and harm in using this therapeutic strategy. Furthermore, the results are not easily quantifiable, and thus it is difficult to determine the number needed to treat to improve physiologic or psychological outcomes. Negative effects from androgen supplementation include penile pain from prolonged erections, development of pubic hair without progression of puberty, which could be embarrassing to the child and the parents, and excessive masturbation and penile length. During puberty, adverse events can include premature closure of epiphyses, possible down-regulation of androgen receptors, and exacerbation of acne. In our experience, the use of topical T applications with aromatase inhibitors seems to have minimal impact on lowering follicle-stimulating hormone and luteinizing hormone levels in adolescents with KS64; however, topical use must be prescribed in an appropriately selected population of reliable patients because of the potential risk of transference to others. Deep vein thrombosis and pulmonary embolism were reported at significantly higher rates in men with KS and should be considered and discussed when initiating therapy.65

Furthermore, oxandrolone (oral), T enanthate (injection), and topical T have been predominately reported in the literature for patients with KS. Oxandrolone is an anabolic steroid related to T. It is consumed orally, and relevant contraindications for men with KS as issued by the Food and Drug Administration (FDA) include nephrosis, hypercalcemia, and carcinoma of the breast or
prostate. Other side effects can include insomnia, depression, or libido changes, bleeding in patients with concomitant anticoagulation therapy, gynecomastia, body hair growth, acne, premature closure of epiphyses, edema through retention of sodium chloride, potassium, phosphate, and calcium, decreased glucose tolerance, increased renal creatinine excretion, inhibition of gonadotropin secretion, impaired spermatogenesis, and liver toxicity.

As discussed earlier, the use of topical T therapy in children and adolescents must be appropriately selected because of the risk of transfERENCE and potential harm to other children. T enanthate is one of the most common forms of T replacement. It is injected intramuscularly, and relevant contraindications for men with KS as issued by the FDA include men with prostate cancer and those with a history of insensitivity to any of the drug components. Warnings of use have been issued for individuals with breast cancer, immobilization, and hypercalcemia from increased resorption of calcium among other electrolytes such as sodium, chloride, phosphate, and potassium; prolonged use has been reported in cases of cholestase and peliosis hepatitis and hepatic neoplasms; edema; gynecomastia; accelerated bone maturation and premature closure of epiphyses; impaired spermatogenesis from decreased gonadotropin release; and venous thromboembolic events and potential cardiovascular events in general in older men.

In cases of excessively increased estradiol levels, some clinicians will consider off-label use of aromatase inhibitors such as anastrozole to bring the levels within normal limits. Anastrozole is taken orally. Relevant warnings and precautions as issued by the FDA include decreased bone mineral density, increased cholesterol, and hypersensitivity reactions. Serious adverse reactions are rare, occurring in less than 1 in 10,000 patients, and include skin reactions, allergic reactions, and changes in serum liver function tests.

Disclosure and Initiation of Treatment

In our practice, managing androgen supplementation in individuals with KS requires an individualized and tailored approach to each boy according to his natural curve of pubertal development. Typically, we wait with initiation of androgens until 13 to 14 years of age, which corresponds to the time of pubertal onset among most boys in the United States. Other centers also prescribe androgen therapy in the infantile period (3–6 months). Adolescent interventions before puberty would be justified in cases of severe muscle loss and hypotonia and in boys with significant developmental concerns. The androgen doses are adjusted to mimic normal pubertal progression over 3 to 5 years. The best indicators of the appropriate titration of androgen supplementation are biological determinants such as development of armpit hair, pubic hair, increase in penile length and thickness, upper body muscle development, and increase in semen volume. In addition to using total T, we rely on signs and physical development during adolescence and titrate to appropriate progression of Tanner stages over 3 to 5 years during puberty. An objective measurement for age-specific strength parameters that can be used includes a digital hand dynamometer grip strength measuring device; age- and sex-stratified normative data in a population-based study have been published and can be used as a practical guide. Clinicians also can follow normative height and weight growth curves and penile growth curves during puberty. Some groups also have used weight-based dosing for oxandrolone and have rules to lower the dose if bone age advancement greater than 12 months occurs in a 6-month duration and bone age is older than chronologic age; progression of Tanner stage higher than 2 if younger than 8 years; systolic or diastolic blood pressure above the 95th percentile for age, height, and sex; low-density lipoprotein increasing above 159 mg/dL; high-density lipoprotein decreasing below 20 mg/dL; or alanine aminotransferase liver enzyme increasing beyond twice the upper limit of normal. Although other groups report T enanthate dosage to be individualistic and based on the pediatric endocrinologist’s clinical judgement, serum T levels are not typically measured before or after injections. Furthermore, response to androgen replacement is individualistic. Based on our clinical experience, boys with KS demonstrate a weaker response to T replacement therapy compared with boys without KS. Biologically, it has been shown that men with KS have impaired trafficking of androgen receptor from the cytoplasm to the nucleus, and thus boys with KS might require greater T replacement than those without KS.

It is also important to note that the FDA has not approved T administration to those younger than 18 years. In early adulthood, it is important to discuss and counsel these men regarding fertility potential and the possible role for fertility preservation through microdissection testicular sperm extraction. Reports have been shown that topical gel-based therapies have less effect of decreasing gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) and thus likely have less of a negative effect on spermatogenesis compared with injectable T, which typically has a higher peak level. In our practice, the senior author sees children, adolescents, and adults with KS. However, among institutions that have separate designations of pediatric or adult clinicians, it is essential to establish open communication of past, present, and future care needs for each patient at the transition from child to adult. A multidisciplinary transition program, when possible, can optimize clinical care and an effective transition to adulthood as their therapeutic goals evolve.

CONCLUSION

KS is commonly known for the classic constellation of features such as tall stature, gynecomastia, gynoid hips, small firm testes, hypergonadotropic hypogonadism, and infertility. However, many of these individuals have abnormal neurocognitive development and subsequently altered psychosocial functioning. Some of these abnormalities might be due in part to abnormal androgen
exposure in utero, infancy, and adolescence to promote normal neural development. Few studies have reported their experience using early androgen supplementation. Results suggest improved speech, language, reading, intellectual functioning, behavior, and social functioning in children treated with androgens. However, the evidence is currently limited to retrospective results and 1 prospective trial; further prospectively designed studies are necessary to make firm conclusions on the timing and intricacies of androgen supplementation in children with KS.

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