ARTICLE

Endocrinological Issues and Hormonal Manipulation in Children and Men With Klinefelter Syndrome

MATTHEW S. WOSNITZER AND DARIUS A. PADUCH*
[1]

47, XXY or Klinefelter syndrome (KS), the most common chromosomal aberration in males, is characterized by either absolute or relative hypogonadism with frequent decline in serum testosterone (T) following the onset of puberty. Decreased T levels are the result of testicular dysfunction with decrease in size of Leydig cells, and loss of germs and Sertoli cells leading to tubular hyalinization. Increase in estradiol results from over-expression of aromatase CYP19. Deficient androgen production and observed varied response of end-organs to T leads to delayed progression of puberty with decreased facial/body hair, poor muscle development, osteoporosis, and gynecomastia. It is possible that hypogonadism and excessive estradiol production contribute to emotional and social immaturity, and specific learning disabilities in KS. Based on the authors' experience and literature review, early fertility preservation and hormonal supplementation may normalize pubertal development, prevent metabolic sequelae of hypogonadism, and have a positive effect on academic and social development. No randomized clinical trials are available studying the effects of T supplementation on reproductive or cognitive issues in KS. Aggressive T supplementation (topical gel) and selective use of aromatase inhibitors may be considered at the onset of puberty with careful follow-up and titration to reach age-specific high-normal physiologic serum values. The decision to institute hormonal therapy should be part of a multidisciplinary approach including physical, speech, behavioral, and occupational therapy.

KEY WORDS: Klinefelter syndrome; hypogonadism; testosterone surge; testosterone replacement therapy; aromatase inhibitors; nonobstructive azoospermia; fertility; meiosis; spermatogenesis; Leydig cells; Sertoli cells; germ cells

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INTRODUCTION

Klinefelter syndrome (KS) is the most common cause of male hypogonadism and chromosomal aberration occurring in 0.2% of the general population, comprising up to 4% of patients in male reproductive practices and 15% of azoospermic males [Bojesen et al., 2003; Ghorbel et al., 2012]. KS genotype is caused by meiotic nondisjunction, most commonly resulting in the 47, XXY karyotype (X disomy), with variable phenotype often indistinguishable from boys with normal karyotypes on physical examination. Men with more than two X chromosomes (48,XXXY) are more affected than men with 47,XXY karyotype [Samango-Sprouse, 2001]. Given the wide phenotypic spectrum, less than 10% of men are diagnosed before puberty and many men with KS remain undiagnosed. Variation in phenotype may be explained by hormonal and genetic background differences, including androgen receptor polymorphism in the CAG_n repeat and skewed inactivation of additional genetic material on the X chromosome [Zechner et al., 2001; Bojesen et al., 2011]. Classic KS phenotype typically includes micropenis, small, hard testes with adolescence-onset testicular failure (spermatogenic and steroidogenic), hypergonadotropic hypogonadism with low testosterone, infertility, tall

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eunuchoid stature (over 50% of males exceeding the 97th centile of height for their age), sparse facial and pubic hair, atypical motor function, behavioral issues, and specific mild to moderate deficits in language based skills with decreased verbal intelligence quotient, attention, and auditory processing [Klinefelter et al., 1942; Ross et al., 2008; Zahn-Waxler et al., 2008]. KS is associated with obesity and hyperestrogenism throughout life as well as increased risk of cancer (breast/germ cell), endocrine complications (diabetes mellitus, growth hormone deficiency, hypothyroidism, hypoparathyroidism), autoimmune diseases, and decreased bone density.

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Early diagnosis of 47, XXY and proactive testosterone replacement along with multidisciplinary approach for physical, speech, behavioral, and occupational therapy promotes effective developmental, social, and academic progress [Paduch et al., 2009; Radicioni et al., 2010]. It is important to remember that most descriptions of the phenotype and associated comorbidities are derived from studies of older patients who were not treated during puberty and early adulthood.

MATERIALS AND METHODS

Systematic review was conducted of the relevant literature using the Pubmed NLM database to search for primary and review articles using keywords "Klinefelter syndrome" and "testosterone," "testosterone replacement," "aromatase inhibitors," "spermatogenesis," "Leydig cell dysfunction," "partial androgen resistance". In addition data based on 200 children, adolescents, and young adults seen at our center's specialized KS clinic was used.

RESULTS

Diagnosis of 47, XXY

Cytogenetic diagnosis is completed by karyotyping of typically 20 mitotic spreads from peripheral blood. Historically the presence of Barr body in mucosal scraping was used. More recently fluorescence in situ hybridization (FISH), or molecular techniques like methylation-specific polymerase chain reaction (PCR) based on inactivation pattern differences of genes on the X chromosome: familial mental retardation gene 1 (*FMR1*) and X chromosome inactivating transcript (*XIST*) are being used to overcome the high cost of cytogenetics and the limited sensitivity of detecting low levels of mosaicism with cytogenetics [Mehta et al., 2012]. Peripheral blood cytogenetics in children diagnosed in utero should be performed to confirm prenatal diagnosis. Y chromosome microdeletion analysis is performed in azoospermic men.

Life-Long Principles of Evaluation and Management of 47, XXY (KS) Patients

Perinatal evaluation with testosterone treatment from 3 to 6 months after birth is the accepted standard of care. Fifty milligrams of Depo-testosterone (intramuscular injection once/month) for 3 months has been used. Alternatively 1 pump of Androgel 1% (1.25 g/day; 37.5 g/month) may be used for older infants with attention to any skin reaction. Response to T treatment measured as increase in penile length is a good indicator of overall tissue sensitivity to testosterone. During the prepubertal period, focus on physical, occupational, and speech therapy is critical for normal academic progress. Between birth and 10 years of age, androgen treatment is used only for very short periods in children who did not receive the 3-month treatment after birth or if the initial response was not adequate. In our practice we limit the 3-month treatment in prepubertal boys to age 8 to avoid initiation of early puberty. During puberty, physical examination with measurement of testicular volume is performed every 6 months. All men with KS should undergo a complete hormonal profile which includes follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol, prolactin, inhibin-B, insulin-like growth factor-1 (IGF-1), and cortisol levels every 6 months starting prior to the predicted start of puberty. Thyroid and lipid profiles are obtained once a year. When FSH and LH increase, a multidisciplinary discussion with patient and parents is completed to discuss fertility management options. Morning urine samples can be used to identify sperm, but in adolescents who ejaculate spontaneously, analysis of a semen sample may be considered following discussion with parents and patient. If sperm are identified in semen, semen cryopreservation is offered. Anastrozole 1 mg once a day is used for 6 months, and additional semen samples are obtained for cryopreservation to store at least 4–6 vials of

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ejaculated sperm. For adolescents without sperm in ejaculate, the option of testicular sperm retrieval during puberty or in adulthood should be discussed. Bone density testing (dual-energy X-ray absorptiometry, DEXA) should also be completed routinely given the risk of osteopenia and osteoporosis with low testosterone. If decreased bone density is identified, additional calcium, phosphorus, parathyroid hormone, and vitamin D3 are obtained. Despite conflicting evidence for increased breast carcinoma risk, patients are taught early regarding self-examination to identify abnormal breast nodules or nipple discharge.

Postnatal Testosterone Surge

Testosterone is secreted at adult levels during three periods of male life including transiently during the first trimester of pregnancy (male genital tract differentiation) and during early neonatal life as a perinatal androgen surge (minipuberty) between 2 and 6 months of age. The third period starts during puberty and continues throughout the male life span with varied efficiency. It is postulated that decreased testosterone production occurs during all three periods in males with KS, although there are studies both in favor and against this in the 47,XXY fetus, during infancy, and during pre-puberty [Salbenblatt et al., 1985; Ratcliffe et al., 1994; Lahlou et al., 2004; Cabrol et al., 2011]. Testosterone levels normally increase up to 10 nmol/L during the first months of life and some studies show that the spike in T production within the first 3 months is decreased in boys with KS. This may be related to the inappropriate function of fetal Leydig cells, but the reason for lower T levels in newborns with KS is not completely understood. In KS patients, confirmatory postnatal karyotype, early evaluation by a physician experienced with management of KS, and measurement of penile size and testosterone level are critical. Failure to exhibit the dramatic changes that occur during normal puberty (approximately 30-fold increase in testosterone levels) is due to testicular abnormalities affecting Leydig cell function. In most KS males, testosterone rises during puberty and subsequently plateaus [Salbenblatt et al., 1985]. However despite the increase, rate of progression and testosterone levels achieved seem to be less prominent than in non-KS adolescents.

Sexual Development

In 47, XXY (KS), testosterone levels characteristically decline during late adolescence and early adulthood. Onset of puberty in KS patients occurs at a predicable time, but decreased androgen production and hyperestrogenism results in delayed progression of puberty with decreased facial/body hair, muscle development, eunuchoid features, and gynecomastia [Smyth and Bremner, 1998]. Based on our experience it seems that men with KS have varied degrees of partial androgen resistance. This manifests as attenuated suppression of SHBG during TRT as compared to non-KS men, and poor androgenization despite high–normal levels of T achieved with TRT. The pubertal growth spurt is the same as in 46,XY boys, and prepubertal males with KS have similar testosterone, LH, FSH, inhibin B, and anti-Mullerian hormone (AMH) until the initiation of puberty. Based on our observations (Paduch DA, unpublished work), penile girth may be decreased in some adolescents, and boys with 48,XXXY may have thickening of penile skin with circumference exceeding length. Scrotal development is normal, but testicular size is significantly decreased during puberty (occurs between Tanner stages II–III) secondary to progressive deterioration of germinal epithelium, Sertoli cells, and peritubular fibrosis while the epididymis is spared. In addition to testicular dysfunction, some boys may also demonstrate growth hormone deficiency which further impairs muscle development and peak pubertal bone mineral density [Rossodivita and Colabucci, 1994; van den Bergh et al., 2001; Bahillo-Curieses et al., 2011].

Leydig Cell Dysfunction in Klinefelter Syndrome

Testicular degeneration in KS patients may occur from spatially and ontogenically incorrect gene expression from an additional X chromosome or failure in cell divisions. During meiosis, abnormal paring of sex chromosomes leads to meiotic arrest and subsequent germ cells apoptosis. It is fascinating to notice that most somatic cells proceed through normal mitotic divisions despite of presence of additional X chromosome. However, spermatogonial stem cells, Sertoli cells, and Leydig cells undergo varied degrees of degeneration leading to infertility and hormonal abnormalities [De Sanctis and Ciccone, 2010]. There is conflicting information about timing of degeneration with some studies describing loss of spermatogonia beginning in infancy [Mikamo et al., 1968]. Diminished spermatogonia with normal Leydig and Sertoli cells have also been reported to first occur in pre-pubertal boys with KS [Muller et al., 1995], although the majority of boys have spermatogonia identified in early adolescence [Wikstrom et al., 2007]. Patients with KS demonstrate reduced adult dark spermatogonia, with gradual loss mediated by massive apoptosis preceding hypergonadotropic hypogonadism with elevated gonadotropin levels and decreased testosterone levels [Wikstrom et al., 2004, 2007]. *TEX11*, an X-chromosome derived germ-cell-specific protein expressed in spermatgonia and spermatocytes may lead to spermatogenic defects in KS [Yu et al., 2012]. Germ cells in patients with KS are also characterized by maturational arrest occurring either at early stages with type A spermatogonia before meiotic division or during later stages [Lanfranco et al., 2004; Wikstrom et al., 2004; Sciurano et al., 2009]. Studies of INSL3 indicate that Leydig cells in male infants with nonmosaic KS are sensitive to LH and such sensitivity is not diminished during the first year of life [Cabrol et al., 2011]. However, studies which use very short periods of injections of hCG to test steroidogenic activity of Leydig cells fail to measure Leydig cell activity under pulsatile and continuous release of LH occurring from puberty forward. Therefore, results of hCG stimulation tests have to be carefully interpreted. It is clearly established that T production is

regulated by acute response to LH and chronically regulated at the level of gene transcription. Most studies show that irrespective of age, median T values in men with KS are lower; thus defective Leydig cell function or excessive conversion of T to estradiol within the testis is a paramount characteristic of KS.

Steroidogenesis is initiated by activation of the LH receptor leading to an increase in cAMP, phosphorylation of cAMP-dependent kinase and activation of steroidogenic acute regulatory protein (StAR) and peripheral-type benzodiazepine (PBR) receptor, a rate-limiting step in steroidogenesis. Cholesterol is transported by StAR and PBR to mitochondria where cholesterol is converted to pregnenolone by CYP11A1 (a precursor for steroidogenic activity in Leydig cells). Current evidence suggests that hormonal regulation in Leydig cells is also mediated by multiple signal cascades including cAMP-protein kinase A (PKA), serine/threonine AKT kinase (AKT, also called protein kinase B or PKB), phosphatidylinositol 3-kinase (PI-3K), protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and intracellular Ca^{2+} signaling proteins. In addition, other biologically active agents including growth factors, steroids, prostaglandins, and cytokines can influence Leydig cell response through endocrine, autocrine, or paracrine regulation. This is clinically important since improved understanding of steroidogenic defects in men with KS will enable identification of specific treatment options [Azhar and Reaven, 2007]. In adult human Leydig cell culture, the steroidogenic activity after LH stimulation is decreased (Fig. 1). Experiments performed in our laboratory indicate that the decrease in steroid synthesis occurs downstream from CYP11A1 regulated conversion of cholesterol to pregnenolone. Adult KS testes are characterized by tubular hyalinization with most of the testicular space occupied by Leydig cells often called "Leydig cell hyperplasia" or "hypertrophy." Based on morphometric studies performed in our lab, Leydig cell size is decreased and there is no evidence that Leydig cells undergo active cell division or that their total number is higher than in non-KS testis (Fig. 2; Paduch DA, unpublished work). The majority of Leydig cells in KS have normal morphology [Regadera et al., 1991; Aksglaede et al., 2011]. Studies of isolated Leydig cells illustrate

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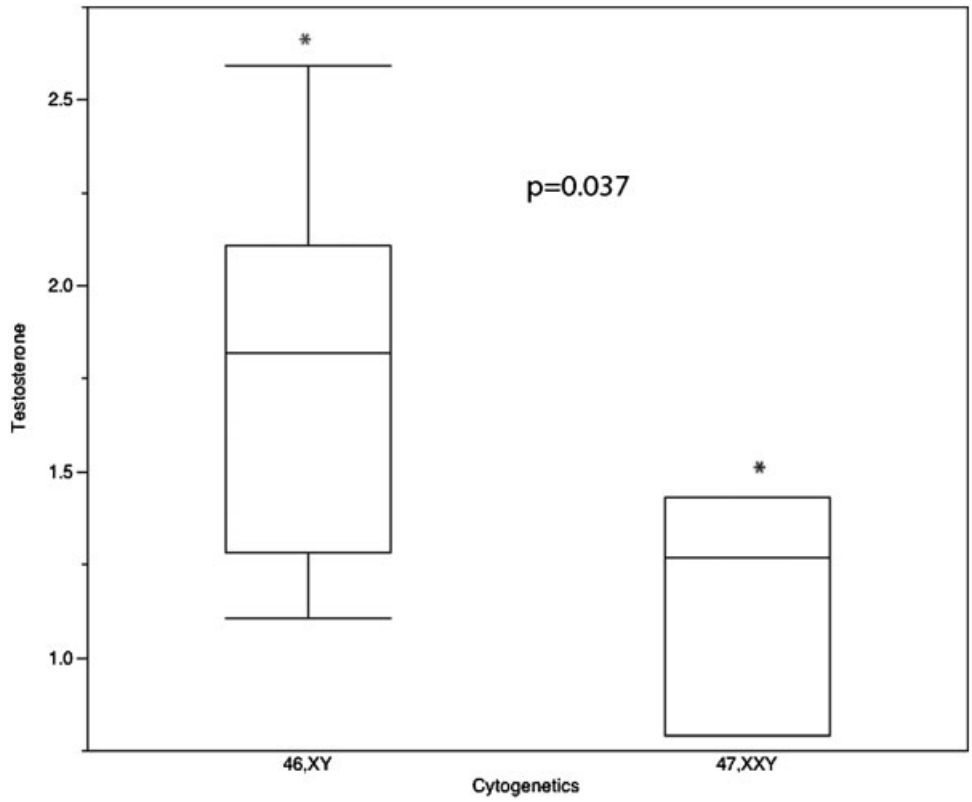

Figure 1. Steroidogenic activity after LH stimulation is decreased in adult human Leydig cell culture.

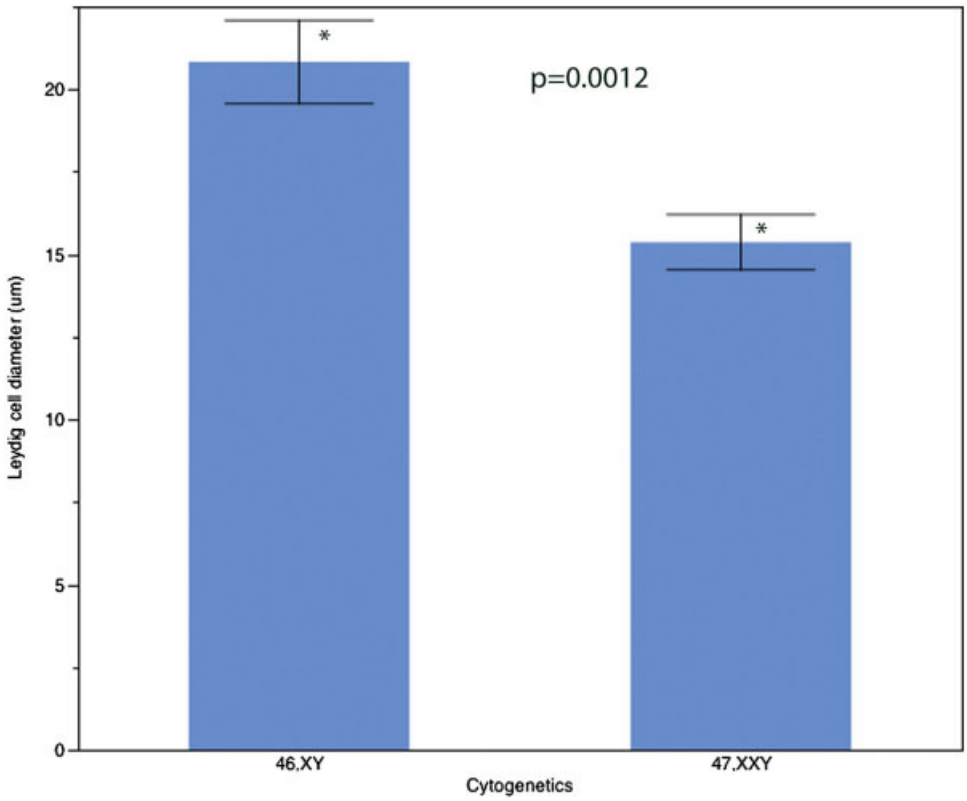

Figure 2. Morphometric analysis: Leydig cell size is decreased.

that estradiol suppresses testosterone production in up to 40%, and inhibition of estradiol by selective estrogen receptor antagonist reverses this process. Additionally our group has shown that expression of aromatase CYP19, which converts T to estradiol, is four times higher in the testes of KS males (Fig. 3). Abnormalities of Sertoli cells with failure to mature, and fewer androgen receptors with cytoplasmic rather than cell surface location have been demonstrated [Wikstrom et al., 2004, 2007]. Sertoli cell marker secretion and expression are dramatically decreased by the completion of puberty [Wikstrom et al., 2007]. Additional study is required to determine whether impaired spermatogenesis in KS results from these changes in germ cells, Sertoli cells, Leydig cells, elevated intratesticular estradiol, or due to interaction between these constituents. Small testicular size is the only consistent physical feature in 47,XXY, but the difference in size of testes between 46,XY and 47,XXY boys does not become evident until at least Tanner stage II.

KS and Infertility

Men with KS are commonly infertile because of primary testicular failure. While infertility affects 97% of KS patients, KS adolescents (Tanner stages II–III) have few sperm identified in 70% of cases, and less than 10% have adequate sperm in ejaculate (cryptozoospermia or oligospermia) for cryopreservation. There is likely a specific time period in early puberty during which ejaculated sperm or sperm from testicular biopsy may be obtained for cryopreservation (Fig. 4). Although most adult men are azoospermic, rarely KS mosaic cases have had successful pregnancy without assisted medical technology [Terzoli et al., 1992]. Adolescents with KS start masturbation at the same age as 46 XY males, but have delayed ability for ejaculation (mean difference between first masturbation and first ejaculation 2 months in 46 XY vs. 9 months in KS patients) likely secondary to relative testosterone deficiency and delayed development of the spinal cord motor generator, a sexually dimorphic S2–S4

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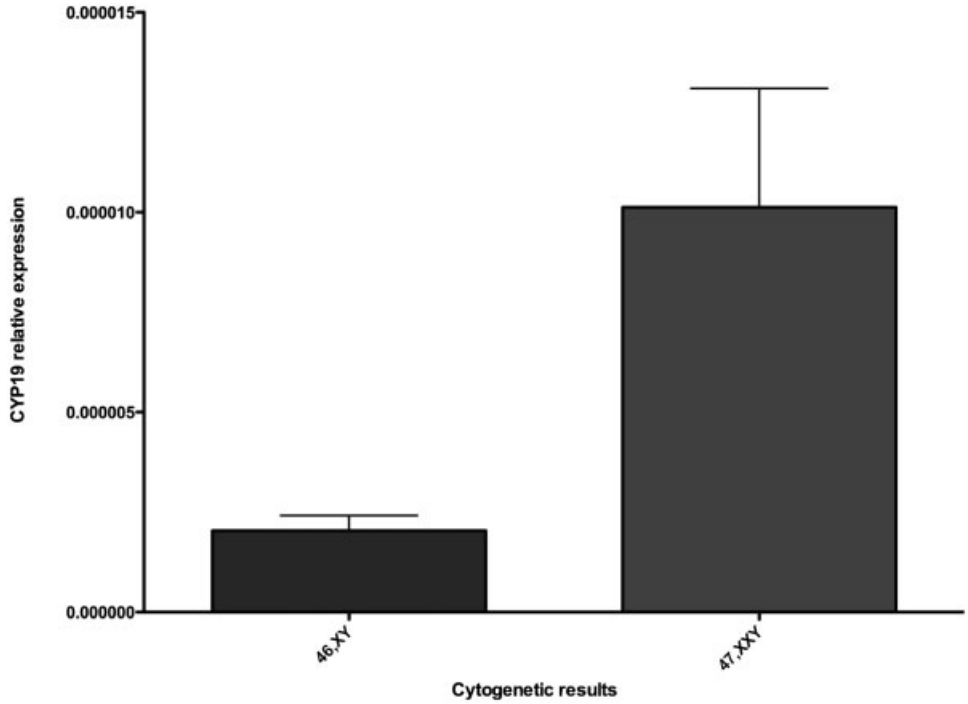

Figure 3. Aromatase CYP19 expression is higher in the testes of KS males.

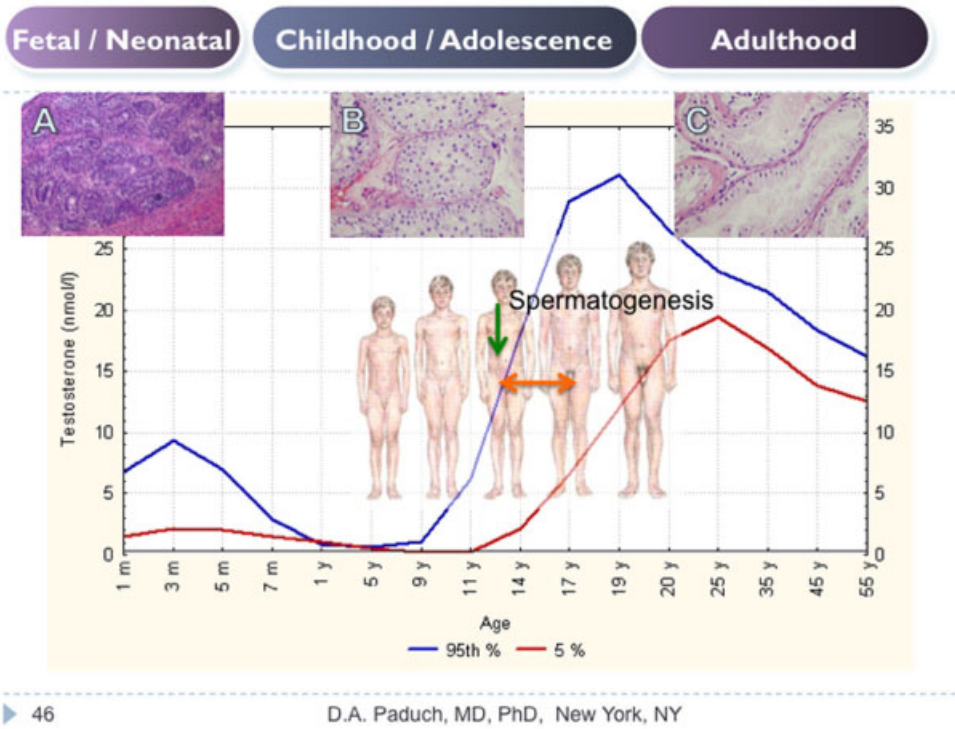

Figure 4. Spermatogenesis in KS males.

center which is dependent on testosterone. With the widespread use of microdissection testicular sperm extraction (TESE) and intracytoplasmic sperm injection for nonmosaic KS, patients with KS have increased chances of successful sperm recovery (≥50%) and subsequent reproduction considered equivalent to men with nonobstructive azoospermia of other causes [Palermo et al., 1998; Schiff et al., 2005; Ramasamy et al., 2009]. Men with normal baseline testosterone had the highest sperm retrieval rate (86%), while those requiring medical therapy who responded with a testosterone of 250 ng/dl or greater had increased sperm retrieval rate (77%) than those who had less optimal testosterone response (55%). This finding indicates that optimal spermatogenesis requires an optimal intratesticular hormonal environment. Serum FSH at baseline did not affect sperm retrieval. Successful TESE has been completed with cryopreservation of rare sperm in 75% of adolescents (Paduch, DA, unpublished work). While some groups recommend more conservative approaches, our group recommends discussion of microsurgical testicular sperm extraction and cryopreservation during puberty and young adulthood [Oates, 2012]. To the best of our knowledge, the effects of hormonal manipulation on sperm retrieval rates in adolescents have not been studied outside of our center. When sperm was identified, all adolescents were on testosterone supplementation using topical testosterone and most of them used anastrozole 1 mg a day for 6 months prior to retrieval. The hormonal manipulation in adolescents should result in catch-up in progression of puberty, normal strength, agility, muscle mass, and bone mineral density—a goal which can be achieved in most adolescents if treated early. The improvements in academic and social development noted in boys with KS treated with T may be a direct result of normalization of hormonal profile on brain development or secondary to increased attention to academic progress, gain in self-confidence, and selection bias. These three goals of normal academic progress, age adequate psychosocial development, and physical maturity take priority over any effects of hormonal manipulation on fertility. It is critical to recognize that there is a significant difference in FSH and LH suppression between injectable testosterone and topical testosterone. Injectable testosterone suppresses FSH and LH and therapy with injectable testosterone must be stopped prior to any infertility treatment. Topical testosterone, however, may be used as long as there is no significant suppression of FSH and LH. The incorporation of nontestosterone hormonal therapy (clomiphene citrate, aromatase inhibitors, hCG) may be beneficial in circumstances requiring increased testosterone prior to sperm retrieval. The impact of testicular dissection for sperm extraction has been identified to result in serum T decline with recovery in 12–18 months postoperatively, with rare testicular atrophy or persistent hypogonadism [Ramasamy et al., 2005; Takada et al., 2008].

Role and Effects of TRT and Aromatase Inhibitors

Testosterone supplementation in patients with 47, XXY (KS) promotes male phenotype development, increasing penile size, decreasing gynecomastia, abdominal obesity, and improving cognition [Ruvalcaba, 1989; Bojesen et al., 2010]. There are isolated reports of androgen therapy during infancy based on androgen therapy for micropenis data, but there is not enough data to draw significant conclusions. Samango-Sprouse (personal communication, 2012) report on significant increases in cognitive and speech and language development at 36 and 72 months in a cohort of infants with 47, XXY (KS) who were treated with testosterone ethanate once a month for 3 months. Randomized clinical trial data of TRT in patients with 47, XXY (KS) are not available [Mehta and Paduch, 2012]. Options for TRT for patients with 47 XXY (KS) include initiation early to mid puberty, or at the start of symptomatic hypogonadism [Lanfranco et al., 2004; Bojesen and Gravholt, 2007; Wikstrom and Dunkel, 2011]. While specific guidelines do not exist for TRT in KS patients, age-specific testosterone formulations and dosages may be obtained from the Endocrine Society's Clinical Practice Guidelines [Bhasin et al., 2010]. We advocate implementation starting at puberty (approximately age 11 years) with titration to maintain appropriate physiologic serum testosterone levels, gonadotropins (LH, FSH) and estradiol throughout puberty [Winter, 1990]. Such a regimen ensures normal completion of puberty and prevents well-established consequences of androgen deficiency. Males with KS may require increased doses of topical testosterone secondary to partial androgen resistance (see below). Topical

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testosterone is the preferable route of administration since physiologic levels of testosterone are achieved without complete suppression of LH and FSH (unlike injectable testosterone which is also painful and intimidating for children and adolescents). In pre-adolescent boys, topical testosterone (i.e., Androgel 1%, Abbott, Abbott Park, IL) is applied at one pump (1.25 g gel/day or 37.5 g/month) for 6–12 months, with progressive increase in dosing according to T levels and progression of puberty, assessed every 6 months. Pubic and axillary hairs are much more accurate measures of progression of puberty as many adolescents have poor facial hair development. Body odor, increase in penile size, nocturnal emissions, and acne are good indicators used to measure response to treatment. For adolescent males, two pumps (2.5 g gel/day) is the recommended starting topical testosterone (Androgel 1%). Once an adolescent starts using three pumps of Androgel 1% (3.75 g/day or 112 g/month) he can switch to more concentrated preparations to decrease the amount of gel applied. Patient preference and compliance are critical in selection of the specific preparation available on the market. Underarm testosterone preparations seem to be preferred in adolescents as it is similar to deodorant application—hence more familiar and less stigma-prone to adolescents. We start at 30 mg of Axiron (Eli Lilly, Indianapolis, IN) and increase every 6–12 months as needed (Table I). It is important to recognize that none of the available topical testosterone preparations in the United States are FDA-approved for use in men younger than 18. The goal is to have the serum testosterone level at the upper end of the normal age-specific range. Therapy should be monitored at 6 weeks following initiation and dose-adjusted every 6 months as determined by monitoring puberty and clinical response. Because KS adolescents frequently exhibit decreased response to TRT when compared to an age-matched cohort, vigilant follow-up is required to monitor testosterone response and medication titration to reach desired goal testosterone levels.

Given the elevation of circulating estrogens associated with increased adipose and aromatase CYP19 activity in KS, an alternative to exogenous testosterone therapy includes the use of aromatase inhibitors such as anastrazole (AstraZeneca, Wilmington DE) [Schlegel, 2012]. With decreased T/E ratio, anastrazole 1 mg daily for up to 2 years is helpful in KS adolescents with gynecomastia or central obesity who are nonresponders to maximal doses of topical testosterone (Androgel 1%, 10–12 g/day). This mechanism promotes bone health, and may alleviate the suppressive effects of exogenous testosterone on the hypothalamic–pituitary axis gonadotropins. Such therapy has been shown to have positive effects on intratesticular testosterone, testosterone production, and spermatogenesis in KS males [Raman and Schlegel, 2002]. Anastrazole has also been used without significant side effects in teenagers with short stature [Faglia et al., 2000]. Additional studies will be required in order to determine the ideal route and duration of TRT/aromatase inhibitors for 47, XXY (KS) patients. Prior to initiation of hormone supplementation, fertility preservation, ethical, and legal concerns should be discussed with the patient and his parents. Effects of anastrozole on cognition have been suggested by some groups, but there is currently insufficient data to support such a claim. From our experience, many adolescents report feeling worse after stopping anastrozole in terms of ability to concentrate and overall energy level. This clinical observation may explain that high circulation levels of estradiol affect CNS activity. Further research, however, is needed to make an evidence-based recommendation about optimal indications and duration of anti-estrogen therapy.

TABLE I. Recommended Testosterone Preparations for KS Patients

Testosterone formulation	Dosage	Pharmacokinetics	Monitoring	Side effects
Topical gel	Pre-pubertal: 1 pump (1.25 g gel/day)	High DHT:T ratio	Monitor T level 2 hr after application (after 2 weeks of treatment)	Skin irritation (rare)
Androgel 1% (12.5 mg T/1 pump) (metered-dose pump)	Adolescent: 2 pumps (2.5 g gel/day)			Risk of skin-to-skin transfer
	Once taking ≥3 pumps/day, consider switch to more concentrated form of T gel			
Axiron 2% (30 mg T/1.5 ml) (metered-dose pump with applicator)	30 mg daily (1 pump to axilla)	High DHT:T ratio	Monitor T level 2 hr after application (after two weeks of treatment)	Skin irritation (rare)
	Progressive increase in dosing according to T levels and progression of puberty, assessed every 6 months			Risk of skin-to-skin transfer

As hyperestrogenism in KS is well-accepted, we often recommend a diet low in naturally occurring phytoestrogens.

Partial Androgen Resistance and Compliance

Patients with KS manifest partial androgen insensitivity or resistance, which likely results from increased adipose tissue, aromatization from upregulation of aromatase CYP19 (with enhanced testosterone to estradiol conversion), and decreased activated androgen receptor trafficking from cytoplasm to nucleus. This resistance blunts the physiologic response of KS patients to TRT, and may lead to discouraged patients due to lack of rapid changes in physical appearance. For this reason, it is imperative that the urologist treating patients with KS set age-specific goals for patients regarding muscle strength, facial/sexual hair changes, and penile size changes. Attention to the concerns of the patient with KS is integral to their compliance with the treatment regimen and to ultimate outcome. Compliance must also be assessed by pill counting and weighing of the testosterone container weekly by parents to ensure that the adolescent is properly using the medication. Adolescents with KS, similar to any other group of young men with chronic conditions, have poor recognition of the negative consequences of medical noncompliance. Therefore, close interaction with parents, respect for adolescent autonomy, and regular serial follow-ups with serum blood measurements (T, SHBG, E, LH, FSH, CBC) are critical to achieve treatment objectives. During adolescence, more frequent patient visits may be necessary to maintain and assess compliance, to discuss safety, preventive measures, alcohol/drug use, bullying, depression, and anxiety. An alternative TRT regimen using implantable testosterone pellets for noncompliant patients has been utilized in rare occasions by our group and others [Khera et al., 2009].

Outcomes With TRT and Aromatase Inhibitors

TRT is accompanied by normalization of body proportions, decreased obesity, blood pressure, and improved behavior, work/academic performance, and musculoskeletal development. Additional long-term reduction in autoimmune disease, breast carcinoma, and osteoporosis risk occur [Mehta et al., 1993; Landin-Wilhelmsen et al., 1999]. The long-term consequences of TRT in KS patients and the extent of suppressive effects on the hypothalamic pituitary axis are difficult to assess from available literature. The first report of hormonal therapy outcomes in a large cohort of adolescents with KS was conducted by chart review from our center including 110 adolescent patients with KS treated between 2007 and 2012 (Mehta A, Paduch DA, unpublished work). Patients received hormone therapy (topical TRT ($n = 110$ patients) or aromatase inhibitors ($n = 75$ patients)) initiated at mean age of 13 years. Good clinical efficacy was achieved in all patients as defined by age-specific serum T levels. Following therapy, the percentage of obese patients decreased from 17% to 11% and mean serum T level improved from 240 to 650 ng/dl. Serum LH and FSH increased with puberty progression (2.6–16.6 mIU/ml, and 7–42 mIU/mL, respectively). No adverse outcomes related to TRT were reported. Topical TRT appears safe and efficacious in adolescents with 47, XXY (KS) and was not associated with suppression of serum LH or FSH.

It is unknown whether treatment with testosterone combined with an exercise program and dietary modifications will further lower the risk of developing childhood and adult obesity. Bone mineral density in patients with KS has been shown to correlate positively with serum testosterone, with benefits from testosterone treatment prior to age 20 but not after this age [Kubler et al., 1992; Wong et al., 1993]. The benefits of bisphosphonate therapy have also been demonstrated in decreasing markers of bone turnover in patients with KS [Stepan et al., 2003].

FUTURE DEVELOPMENTS

Gradual and consistent evidence accumulates indicating that early diagnosis and multidisciplinary management of children and adolescents with KS utilizing hormonal supplementation and manipulation to mimic the normal progression of puberty is not harmful and likely beneficial. Three major challenges exist in the endocrinological management of KS: overcoming partial androgen resistance, developing oral androgen receptor agonists, and enhancing understanding of ideal estrogen levels to facilitate optimal physical and neurobiological development. With improved understanding of the molecular defects leading to hypogonadism, and the tissue-specific requirements of sex steroids and growth factors, we will be able to plan and execute randomized prospective multicenter clinical trials which will lead our management of men with KS in the future.

CONCLUSION

KS is the most frequent chromosomal abnormality in infertile males. Physicians should be aware of the variety of issues associated with KS including testicular changes with seminiferous tubules degenerating during pubertal maturation leading to hypogonadism. Early fertility discussion with detection and appropriate management of low testosterone associated with KS has significant potential to avoid the perils of hypogonadism and to have somatic and behavioral benefits along with improvement of general health, pubertal progression, academic progress, and social integration.

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