Fertility Guidelines for Klinefelter Syndrome

Consensus-based treatment recommendations from the AXYS Clinic & Research Consortium

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Introduction

Klinefelter syndrome (KS) is identified at a frequency of 1:600 males among the general population. The classic—and by far the most common—karyotype is 47,XXY. Mosaic karyotypes include 46,XY and 47,XXY.

Klinefelter Syndrome can be diagnosed at 3 different stages of an individual's life:

1. The fetal stage, during prenatal genetic diagnosis
2. Childhood or adolescence, during investigation for abnormal-feeling testes, delayed puberty, or behavioral and/or learning problems
3. Adulthood, during evaluation for infertility and/or sexual dysfunction (hypoandrogenism)

While there is a phenotypic spectrum for KS, all men with KS demonstrate testicular dysfunction. This is evidenced by impaired spermatogenesis and testosterone production. The phenotype varies largely due to mosaicism within the peripheral blood, the testes, or both along with differences in androgen receptor sensitivity.

Reproductive health considerations are relevant at all ages of diagnosis. However, controversy exists around the need for, timing of, and approach to fertility preservation and treatment.

Since germ cell loss is believed to progress with age,[1] preventive cryopreservation of ejaculated or intratesticular spermatozoa has been proposed to preserve fertility.[2] Rarely, spermatozoa can be found in the ejaculate of some men with mosaic KS or of younger males with non-mosaic KS.[3]

Among experts treating pubertal and post-pubertal adolescent males with KS, there is debate over whether to conduct testicular sperm extraction (TESE) upon diagnosis to "preserve" fertility or to wait until a man with KS is ready for fatherhood.

Recent studies demonstrating chromosomal mosaicism not only among peripheral blood, but also within the testis, further fuel this debate. In other words, normal 46, XY germ cells are thought to give rise to sperm that demonstrate near baseline rates of euploid sperm

(94 to 99%). These euploid germ cells may persist later into life, allowing surgical sperm retrieval for use in *in vitro* fertilization (IVF)/Intracytoplasmic Sperm Injection (ICSI). This allows men with KS to have their own non-KS biological children.[4,5]

This guide will discuss and provide recommendations on the following:

1. Fertility evaluation of adults with KS
2. Infertility treatments for adults with KS
3. Risk of genetic abnormalities in the biological children of adults with Klinefelter Syndrome
4. Effect of long-term testosterone replacement therapy (TRT) on fertility
5. Fertility preservation consultation for peri-pubertal and adolescent males
6. Experimental options to support biological fatherhood

Section 1 of 6: Fertility evaluation of adult men with Klinefelter Syndrome

Men with KS who are seeking fertility should receive a full medical history, physical examination, and appropriate laboratory investigations.

The medical history should include a comprehensive review of:

- Fertility in the man and his partner
- Past surgeries and medical procedures
- Medications (with special attention to endocrine disruptors)
- Potential lifestyle factors (including smoking, recreational drugs, weight loss, and exercise)
- Environmental and work-related exposures

The physical examination should include an assessment of:

- General stature and body habitus
- Presence of gynecomastia
- Secondary sexual characteristics and masculinization (including facial hair, muscular development, and penile and testes growth)

During physical examination, pay specific attention to Tanner staging, presence and characterization of the epididymis, vas deferens, and spermatic cord for varicocele. Consider an orchidometer or scrotal ultrasound for estimating testes size.

The table below shows Tanner staging specific to pubic hair and testes size in boys with normal 46,XY karyotype vs. those with KS.[6,7]

Tanner staging specific to public hair and testes size in boys with normal 46,XY karyotype vs. KS[6,7]						
Karyotype	**Symptom**	**Tanner stage 1**	**Tanner stage 2**	**Tanner stage 3**	**Tanner stage 4**	**Tanner stage 5**
Normal (46,XY)	**Testis size**	2.5mL	5.5mL	15mL	20mL	22.5mL
	Pubic hair	None	Sparse to base of penis	Hair to pubis, darker and coarser	Dark, course and curly hair similar to adult length over limited area	Mature adult distribution
KS (47,XXY, 46,XY, or 47,XXY)	**Testis size**	<2.5mL	2.5 to 4mL	4 to 10mL	4 to 10mL	4 to 10mL
	Pubic hair	None	Sparse to base of penis	Hair to pubis, darker and coarser	Dark, course and curly hair similar to adult length over limited area	Mature adult distribution

Most men with KS present with azoospermia or severe oligospermia (mostly less than 1 million sperm per milliliter of semen). Given this, as part of evaluation:

- Perform at least 2 semen analyses with extended search of the centrifuged specimen.
- Obtain a hormone profile consisting of an early morning (8:00 to 10:00 a.m.) testosterone, estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH).
- Consider Y-chromosome microdeletion testing.[8] While Y-chromosome microdeletions are not more common in men with KS than in the general population, we recommend these screening tests to complete the diagnostic workup and prior to invasive procedures such as TESE.

- Consider confirmatory X and Y chromosomal fluorescence in situ hybridization (FISH) on peripheral lymphocytes. While a karyotype is the gold standard for KS diagnosis, FISH can detect and characterize low-percentage mosaicism, which may confer a higher likelihood of sperm retrieval.

Recommendation

When evaluating an individual who presents with KS and azoospermia or severe oligospermia and desires fertility (clinical principle), conduct a thorough medical history, physical exam, and laboratory tests. Lab tests should include a serum hormone profile, 2 semen analyses with extended search following centrifugation, and Y-chromosome microdeletion testing.

Section 2 of 6: Current infertility treatments for adults with KS

Medical treatment

Normal testosterone levels are critical for sperm development, and normalizing testosterone levels is a goal of medical management in men with KS, particularly in preparation for fertility surgeries.

Several medical therapies have been evaluated in individuals with non-obstructive azoospermia (NOA) and KS. These include antiestrogens (such as clomiphene citrate or tamoxifen), aromatase inhibitors (such as anastrozole or testolactone), and gonadotropins (such as recombinant FSH or hCG).

- **Non-steroidal antiestrogens** block the inhibitory feedback of estrogen on the pituitary gland, resulting in increased levels of LH and FSH and a subsequent rise in testosterone.

  Clomiphene citrate has been used in severely oligospermic men and thus far, only 2 series have evaluated its use in men with NOA. One of these demonstrated detection of ejaculated sperm among two-thirds of non-KS men using clomiphene citrate who were originally NOA and diagnosed with either maturation arrest or hypo-spermatogenesis on initial testicular biopsy. The other retrospective series

did not demonstrate an improvement in testicular sperm retrieval with hormonal optimization.[9,10] However, we must emphasize that men with KS often have elevated FSH values at baseline, and further raising the LH and FSH levels likely won't make a clinically meaningful difference.

- **Exogenous gonadotropins** decrease endogenous gonadotropin levels through negative feedback. This reduction of gonadotropins from hyper-gonadotrophic levels to a more controlled administration reduces the over-stimulation of FSH and LH receptors in the Sertoli and Leydig cells. This "re-set" may ultimately result in the improved function of Sertoli and Leydig cells.[11]

  Ramasamy and colleagues reported improved TESE outcomes in men with NOA and KS who received exogenous gonadotropin therapy.[12] Testosterone and other androgens are converted into estradiol (E_2) by the enzyme aromatase, which is present in the liver, adipose tissue, and testes. Elevated E_2 levels suppress LH and FSH secretion from the pituitary and inhibit testosterone biosynthesis. Aromatase inhibitors are designed to block the conversion of testosterone to E_2 and thus further re-establish an ideal testosterone and E_2 (T/E) balance (greater than 10).

  Although significant improvements in sperm counts were noted in men with severe oligozoospermia, men with NOA experienced no such benefit. Expert opinion, however, holds that use of non-steroidal aromatase inhibitors remains the best option in improving intra-testicular testosterone levels and normalizing the T/E balance that may further improve surgical sperm recovery rate.

Surgical treatment

Providers must address each man with KS as an individual, while also managing treatment within the context of the couple who desires fertility. Surgical sperm retrieval can be approached via a conventional testicular sperm extraction (cTESE) or with an expanded search using the microdissection testicular sperm extraction (mTESE) approach. Expert opinion states that epididymal sperm aspirations should not be performed to search for sperm.

A recent meta-analysis comparing cTESE to mTESE sperm retrieval rates in men with KS showed a sperm retrieval rate of 43% (95% confidence interval [CI] 35 to 50%) for cTESE vs 45% (95% CI 38 to 52%) for mTESE.[4] However, due to the focal nature of spermatogenesis with KS, experts recommend the mTESE approach to extract the focally

dilated seminiferous tubules while identifying and minimizing damage to intratesticular blood vessels.

A urologist and IVF team with expertise in sperm retrieval and tissue processing should perform mTESE to optimize recovery of extremely rare sperm. During the procedure, the team extracts favorable seminiferous tubules until they identify spermatozoa. If the team finds no mature spermatozoa in the first testis, they perfect an additional search on the contralateral testis.

If the team identifies spermatozoa, they then process the specimen and either use it immediately for IVF/ICSI or cryopreserve it for later use. Thanks to the advances in mTESE techniques, sperm can be detected with cTESE or mTESE in approximately 43% of men with KS[13] and used for ICSI.

Assisted Reproductive Technology (ART)

For KS couples desiring fertility, ICSI is an important adjunct of fertility care. The partner of the man with KS should be referred to a reproductive endocrinologist (REI) for a female fertility evaluation and coordination of oocyte retrieval.

There are 3 different scenarios for oocyte and sperm retrieval timing:

1. Oocyte retrieval and cryopreservation prior to sperm retrieval with subsequent oocyte thawing on the day of sperm retrieval
2. Oocyte retrieval the day following surgical sperm retrieval
3. Sperm retrieval and cryopreservation prior to oocyte retrieval, subsequently using cryopreserved sperm.

Studies investigating the use of fresh or cryopreserved sperm for ART procedures have shown no difference between the cTESE vs. mTESE in pronuclear fertilization rates, embryo cleavage, and implantation rates.[13]

Studies investigating the pregnancy and live birth rates of KS couples using ICSI show a 43% pregnancy rate and of those pregnancies, a 43% live birth rate. Success rates in studies investigating ICSI outcomes show success independent of the age, mean testis volume, LH, FSH, or total testosterone levels of the man with KS.[4] A study by Sabbaghian et al showed a higher fertilization rate but no difference in live birth rate per embryo transfer when men with KS were compared to NOA men with normal karyotype.[14]

SECTION 3 of *6*: Risk of genetic abnormalities in the biological children of men with KS

A hypothetical fear exists that the children of men with KS could inherit numerical chromosomal anomalies. However, the literature reports no significant increase in aneuploidy in these children.[15] This is because either a few foci of 46, XY spermatogonia may be present in these individuals, reflecting gonosomal mosaicism, or only because euploid sperm survive. Therefore, with the help of ICSI, men with 47, XXY can achieve biologic fatherhood and children with a normal karyotype.

Although data on the children of fathers with KS who are born via ICSI is reassuring, a study based on ICSI combined with preimplantation genetic diagnosis (PGD) on 113 embryos showed that there is a reduction in the rate of euploid embryos for couples with KS when compared to controls (54% vs. 77.2%, no statistical data available). Due to the increase of sex chromosomal and autosomal abnormalities in the embryos of men with KS, consider PGD, and if it is not available, Non-Invasive Prenatal Testing (NIPT) after pregnancy as an appropriate preventive-diagnostic option.[16]

Recommendation

Perform preimplantation genetic diagnosis (PGD) and Non-Invasive Prenatal Testing (NIPT) in couples where the male partner has KS (expert opinion).

Section 4 of 6: Effect of long-term testosterone replacement therapy (TRT) on fertility

Indications to start TRT

The need for long-term TRT in men with KS complicates their fertility potential. At present, exogenous testosterone therapy is contraindicated in men with KS who are actively seeking fertility within the next 6 months. TRT can be considered in men with KS who do not desire fertility therapy for at least 6 to 12 months or who have significant hypogonadal symptoms despite treatment with other non-TRT options. Strategies exist to maintain spermatogenesis when TRT is necessary in the context of fertility therapy planning, including concomitant use of hCG.[17]

Infertility risk related to long-term TRT

Recovery of ejaculated sperm after TRT cessation occurs among 85% of non-KS men using long-term testosterone.[18] Since most men with KS are azoospermic, similar comparisons are not possible. Mehta et al[19] showed sperm recovery rates of 70% using mTESE following 1 year of combined topical testosterone replacement and aromatase inhibitor therapy in men with KS. These recovery rates have not been validated by other studies.

Recommendations

1. Caution men on the paucity of data espousing the safety of TRT in the midst of fertility therapy (strong recommendation).

2. Caution men about the uncertainty of sperm recovery after long-term TRT (expert opinion).

Section 5 of 6: Fertility preservation consultation for pre-pubertal boys and adolescents

Pediatric aspects of KS vary from those encountered in adults in many unique ways. This is especially true of the timing of initial diagnosis and approaches to fertility and hormonal management.

Timing of diagnosis

In the past, boys with KS were noted to have smaller and firmer than normal testes in the peri-pubertal age range, prompting suspicion and karyotype investigation that led to initial diagnosis. Previous reports indicate that this resulted in only 16% of boys with KS being diagnosed by the time of puberty.[20,21]

In recent years, genetic analysis at the time of amniocentesis, chorionic villus (CV) sampling, and maternal cell-free DNA testing have allowed for earlier diagnosis. Further, thanks to increased awareness of the prevalence of KS (1:600 male births), pediatricians now seek early genetic evaluation in boys with related conditions (such as cognitive disorders), resulting in a significant increase in childhood diagnosis.

This has led to the potential for beneficial interventions for this condition as well as increased early desire of parents to fully understand all aspects of their sons' futures, including the potential for biological fatherhood. As a result, parents are now seeking information about KS very early on, even prior to birth in some instances. There are both advantages and disadvantages of families knowing the potential sequelae of KS from a young age. However, providing information may equip families to better prepare for potential future implications associated with KS.

Evaluations and interventions

Recent research indicates that KS testes appear histologically normal at birth and then undergo progressive fibrosis and abrupt loss of germ cells, leading to severe testicular atrophy, hypergonadotropic hypogonadism, and testicular failure. Experts believe that these changes mainly occur at and around the time of puberty, though the precise time of onset and mechanism(s) remain unknown. This observation potentially suggests a theoretical opportunity to harvest spermatogonia (diploid germ cells) as a precursor of

sperms (haploid germ cells) before deterioration occurs, which may offer a potential avenue for future fertility treatment. Since spermatogenesis and ability to produce sperm does not occur until puberty, this may be of benefit.

Current relevant fertility questions for children with KS include the optimal timing of sperm retrieval or whether pre-pubertal testis biopsy to bank spermatogonial stem cells (SSC) should be performed at all during adolescence. Proponents of testicular banking and cryopreservation argue that most KS testes will progressively fibrose and that peripubertal testis tissue banking for future fertility restoration is only mildly invasive and offers an "insurance policy", if needed, for the majority of individuals with KS who will be infertile. Detractors argue that sperm retrieval rates are comparable across ages and not all individuals will desire future fertility. These detractors also argue that waiting until a man with KS desires fertility may avoid an unnecessary procedure, and that spermatogonial stem cell cryopreservation, with subsequent transplantation is currently experimental in human populations.

Evaluation

Unique considerations are needed in the evaluation of a pre- or peri-pubertal boy with KS, beyond routine evaluation (previously mentioned above for adults). KS families almost always have a significant desire to fully understand the fertility aspects of this condition and "what happens at puberty".

If this diagnosis is made prenatally or perinatally, providers typically have a general discussion with the family about the natural history resulting in testicular failure . Discussions of fertility become much more pertinent and meaningful as the boy with KS reaches the pubertal period.

Providers must pay special attention to Tanner staging and serial hormonal evaluation to help guide fertility considerations. Determinations of when testosterone therapy to initiate puberty become important, as does balancing timing and initiation of hormonal treatments with their effects on spermatogenesis and fertility management. Coordination between the primary care pediatrician, pediatric geneticist, pediatric endocrinologist, and pediatric urology fertility specialist is especially essential in assessing and managing these boys at this point in development.

Preparation and knowledge of the fertility and puberty issues vary widely among boys with KS and their parents. Therefore, the counseling physician must be aware of the

complexities. It is important for families to understand that the KS condition leads to severe impairment of the testes that make testosterone and produce sperm.

Similarly, it is important to indicate that male puberty can fully occur, albeit with the assistance of exogenous testosterone in some cases. It is also important for families to know that the risk for recurrence of KS in children of men with KS is not significantly different from the general population. Boys with KS and their parents should also be aware of the potential for negative psychological effects associated with an infertility diagnosis and with a negative TESE outcome (no sperm identification at all).

In all of these discussions, the counseling physician must be aware of the sensitivities of both the parents and the boy with KS, as these may vary widely. With proper information and presentation, most boys with KS at pubertal ages will feel reassured and comfortable knowing about their condition as long as the counseling physician provides the information in a sensitive and positive manner.

Recommendations

1. Thanks to advances in genetic diagnosis, KS is now diagnosed much more frequently at early ages. This allows for earlier counseling and life planning for this condition. However, providers should not initiate testosterone treatment for induction of puberty without consideration of its potential negative effects on later fertility, taking into account an evaluation of an individual's overall fertility status.

2. Children with KS and their parents should have a consultation with a qualified reproductive specialist before puberty.

Section 6 of 6: Experimental options to support biological fatherhood

Most men with KS will need ART (TESE and ICSI) to become fathers (regular practice). If no sperm are identified in semen or through TESE procedure, using stem cell technology may help these men.[22]

Current treatment options are being investigated to potentially restore fertility through various mechanisms. These include:

- Banking pre- or peri-pubertal testicular tissue before progressive fibrosis and natural deterioration occurs
- Banking a portion of testis biopsies at the time of mTESE, when clinically indicated to obtain sperm for ICSI (regular practice). These tissues can then be used for spermatogonial stem cell transplantation (at any age), or *in vitro* differentiation of sperm (experimental).[23-25]

If no SSCs are detected in the testes, using skin fibroblasts and induced pluripotent stem cell technology could be another potential future option (experimental). This has been tested successfully in a mouse model, but not yet in humans.[26]

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The AXYS Clinical & Research Consortium was founded in 2015 and exists to:

- **Make life easier for those seeking evaluation and treatment.**
- **Bring consistency to treatment that is consensus and/or evidence-based.**
- **Advance the overall X&Y variation field through coordinated efforts including research.**
- **Bring clinical excellence to the field of X&Y variations.**

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