A clinical algorithm for management of fertility in adolescents with the Klinefelter syndrome

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Purpose of review
The review presents a clinical algorithm for the evaluation and treatment for adolescents with Klinefelter's syndrome who desire fertility preservation.

Recent findings
Sperm is present in the ejaculate in around 8% of men with Klinefelter's syndrome. Although most are severely oligospermic/azoospermic, 43–45% of men will have sperm found during a testicular sperm extraction, reaching up to 70% in adolescents.

Summary
Klinefelter's syndrome (47, XXY) causes hypogonadotophic hypogonadism and severe oligospermia/azoospermia rendering natural conception rare. During puberty, boys often require testosterone replacement therapy to develop secondary sexual characteristics, which can further decrease spermatogenesis. There is a progressive decrease of testicular germ cells after the onset of puberty, suggesting that fertility evaluation and preservation should begin shortly thereafter. In adolescents desiring fertility evaluation, any testosterone therapy should be discontinued, hormones and gonadotrophins measured, and a semen analysis obtained. Adolescents with low testosterone are administered aromatase inhibitors, selective estrogen receptors modulators and/or human chorionic gonadotropin to increase endogenous testosterone production. After testosterone levels are normalized, semen analysis is performed, and cryopreservation encouraged if sperm is present. For those without sperm in the ejaculate, a testicular sperm extraction is offered.

Keywords
fertility preservation, Klinefelter's syndrome, male infertility, testosterone therapy

INTRODUCTION

Klinefelter's syndrome is a relatively uncommon genetic disorder of sex chromosomes affecting nearly 1 in 500–600 newborn males [1]. Diagnosis is made by karyotype analysis revealing an extra X chromosome (47, XXY). The classic phenotype of Klinefelter's syndrome is tall stature, gynecomastia, and small testes; however, in clinical practice, many men go undiagnosed because of heterogeneous and mild physical symptoms [2]. Unfortunately, 95–99% of men with Klinefelter's syndrome are infertile because of poor sperm production associated with germ cell loss and hyalinization of seminiferous tubules. Prior to the introduction of intracytoplasmic sperm injection (ICSI) in 1993, Klinefelter's syndrome was considered an untreatable cause of infertility. If sperm is not recoverable in the ejaculate of Klinefelter's syndrome men, testicular sperm can be successfully obtained in 43% [3] of attempts by conventional testicular sperm extraction (c-TESE) or 45% [3] by microscopic testicular sperm extraction (m-TESE) for ICSI, as there are often isolated foci of spermatogenesis within the testis. Live births from TESE-ICSI are as high as 50% for men with Klinefelter's syndrome [4]. Therefore, it appears that up to 25% of men with Klinefelter's syndrome can obtain paternity.

Owing to the often-profound hypogonadism in Klinefelter's syndrome, pediatric endocrinologists commonly initiate testosterone replacement therapy (TRT) at the start of puberty when the follicle-

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KEY POINTS

- Most men with Klinefelter's syndrome (47, XXY) are severely oligospermic or azoospermic and natural conception is rare.
- Owing to profound hypogonadism, testosterone replacement therapy may be needed to improve the timing of puberty or establish secondary sexual characteristics; however, negative feedback of testosterone on the hypothalamic–pituitary axis can further decrease spermatogenesis.
- Decreasing populations of germ cells are observed shortly after the onset of puberty, suggesting that adolescence may be the optimal time to consider fertility preservation, although current literature demonstrates similar or better sperm retrieval rates in adults.
- For adolescents seeking fertility evaluation, we discontinue any testosterone replacement therapy, evaluate testosterone and gonadotrophin levels and administer aromatase inhibitors, selective estrogen receptor modulators and/or hCG to increase endogenous testosterone if needed.
- At the initial evaluation and/or after optimization of testosterone levels we obtain a semen analysis and cryopreserve sperm if present and recommend a testicular sperm extraction if sperm is absent at the time of desired fertility.

stimulating hormone (FSH) and luteinizing hormone begin to rise. TRT helps develop masculine sexual characteristics and increase bone mineral density [5]. Once started, TRT is lifelong to prevent osteoporosis, metabolic syndrome, obesity, and diabetes [5]. Unfortunately, a side-effect of TRT is infertility from suppression of luteinizing hormone, FSH, and intratesticular testosterone. As boys with Klinefelter's syndrome are already infertile, this second potential insult from exogenous testosterone therapy led many authors to pursue fertility preservation prior to initiation of TRT.

The big question for adolescents with Klinefelter's syndrome is when to pursue fertility preservation. Authors pose concerns of decreased sperm number and quality as boys with Klinefelter's syndrome complete puberty and advance into adulthood [4]. It is postulated that puberty, and the rise in luteinizing hormone and FSH, may lead to progressive decline of germ cells and testicular function; however, germ cell loss may already begin to decline in childhood [6▪]. Testis volume in Klinefelter's syndrome boys will increase to an average of 6 cc in childhood with a subsequent degeneration and atrophy to an average adult size of 2–4 cc [7,8]. Compounding the problem, treatment with testosterone may decrease the success of future sperm retrieval [9]. Success rates for TESE in adolescent and young adults with Klinefelter's syndrome ranges from 0 to 70%, with most authors unable to identify sperm in boys 10–16 years old [10]. Therefore, some experts believe there is window for optimal fertility preservation between the ages of 16–18 and advocate for TESE at this time. Others feel that early m-TESE is too aggressive as adult m-TESE success on average 50%, and patients become profoundly hypogonadal in the recovery [11▪▪]. Additionally, adolescents are not of the age of consent and parents are making the treatment decisions. Klinefelter's syndrome patients may ultimately decide later in life that they do not have an interest in fathering children. Therefore, determining fertility preservation, initiation of testosterone replacement, and when to consider TESE in Klinefelter's syndrome adolescents presents a challenge.

In this review, we will discuss contemporary management of adolescents with Klinefelter's syndrome, with a specific focus on fertility preservation and management of hypogonadism. As urologists often see these children after evaluation by an endocrinologist, we simplify our treatment strategy by creating case scenarios and present a treatment algorithm (Fig. 1).

NO PRIOR HORMONAL THERAPY

Boys with Klinefelter's syndrome have normal for age levels of testosterone. It is not until puberty and the subsequent rise in luteinizing hormone and FSH, that hypogonadism is noticed. A typical scenario in our clinic is adolescents with Klinefelter's syndrome presenting without ever initiating testosterone replacement, generally between the ages of 14–18. We begin our workup by obtaining baseline testosterone, luteinizing hormone, FSH and estrogen levels. If the patient is able to ejaculate, we obtain a semen analysis. Despite almost uniform infertility, systematic literature review indicates that about 8% will have sperm in the ejaculate [10]. If the patient is not able to ejaculate and has not reached tanner 5, we repeat yearly semen analysis. If sperm is found, we offer cryopreservation. If sperm is not found we may offer TESE. As the child ages through puberty, the need for hormone replacement will be continuously evaluated.

NORMAL TESTOSTERONE, NO PRIOR TESTOSTERONE REPLACEMENT

Boys with normal testosterone levels (testosterone > 300) generally will not require testosterone supplementation to advance through puberty. We will

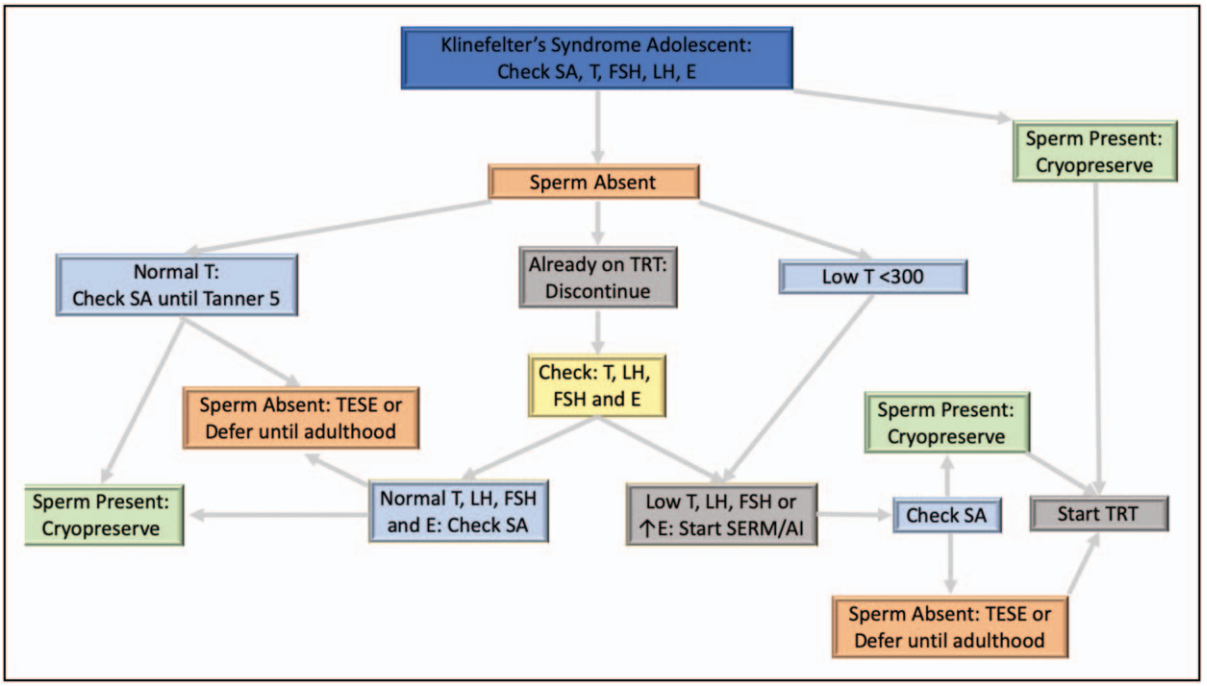

FIGURE 1. Evaluation and treatment algorithm for fertility preservation in adolescents with Klinefelter's syndrome. FSH, Follicle stimulating hormone; SERM, selective estrogen receptor modulator; TESE, testicular sperm extraction; TRT, testosterone replacement therapy. Adapted permission from [12].

evaluate semen analysis for sperm and offer cryopreservation if present. If the semen analysis does not show sperm, as testosterone replacement is not planned, we do not usually advocate for adolescents to undergo TESE in this scenario. Successful sperm retrievals in adult males with Klinefelter's syndrome are successful approximately 86% of the time in those not requiring medical optimization to increase serum testosterone [9]. Therefore, adolescents with normal testosterone level through puberty may postpone TESE until adulthood when they are ready to have children.

LOW TESTOSTERONE, NO PRIOR TESTOSTERONE REPLACEMENT

We often see boys who are referred for fertility preservation prior to initiation of TRT by their endocrinologist. As always, evaluation begins with baseline hormonal levels. If the patient is able to ejaculate, we obtain a semen analysis to evaluate for sperm. If present, we offer cryopreservation, and initiation of TRT. If absent, we repeat semen analysis yearly until tanner 5 or predicted onset of puberty. At this time, we recommend hormonal optimization with an aromatase inhibitor such as anastrozole if the testosterone:estrogen ratio is less than 10, or a selective estrogen receptor modulator (SERM) such as clomiphene citrate if luteinizing hormone and FSH are low. Anastrozole decreases serum estradiol levels by preventing the conversion of testosterone to estrogen. As a result, there is decreased negative feedback to the hypothalamus and a subsequent increase in FSH and luteinizing hormone. Therefore, treatment with anastrozole can increase endogenous production of testosterone and increase intratesticular testosterone which may benefit sperm production. After one month, we recheck the hormones. If testosterone remains below 250 ng/dl, we may add hCG 1500 IU twice weekly and increase dosage if there is no response. In men whose testosterone level rose above 250 ng/dl, subsequent mTESE found sperm 75% of the time [9]. In those that remained less than 250 mg/dl, sperm was found 55% [9]. Other strategies have been proposed regarding androgen replacement at this time. Mehta *et al.* [13] propose starting TRT with topical gel for serum testosterone less than 350 ng/dl with simultaneous initiation of anastrozole 1 mg daily for 6–24 months. If sperm is not found in the ejaculate, we will offer a TESE. If the patient currently does not currently desire paternity or cryopreservation and TESE is deferred, we will discuss with their endocrinologist about initiating TRT or continuing their current hormonal therapy.

LOW TESTOSTERONE WITH PREVIOUS TESTOSTERONE INITIATION

We often see boys who present for fertility preservation after initiation of TRT for puberty. These

patients can present a particular challenge. Evaluation begins with hormones and a semen analysis if possible. As always, if sperm is present, we offer cryopreservation. If luteinizing hormone and FSH are undetectable, we discontinue TRT. After an appropriate washout period, we recheck hormones. In the rare event that luteinizing hormone and FSH are within normal range, we will keep the patient off testosterone and check semen analysis for possible cryopreservation or offer TESE. If after washout of exogenous testosterone, if testosterone is low, FSH and luteinizing hormone are elevated or the testosterone:estrogen ratio is less than 10:1, we begin hormone optimization with an aromatase inhibitor or SERM similarly to TRT naïve patients (see above). We will then recheck hormones to monitor for response within a month. With appropriate response, we check semen analysis in three months for sperm, and offer TESE if desired. Once the fertility concern is managed, we begin TRT.

FUTURE TREATMENT OPTIONS

Unfortunately, not all attempts at obtaining sperm are successful. Prior to ICSI, Klinefelter's syndrome was considered an untreatable form of infertility. For Klinefelter's syndrome patients where sperm is not identified on TESE, future paternity may still be possible. Recently, spermatogonial stem cell autotransplantation led to successful spermatogenesis in macaques rendered infertile after alkylating chemotherapy [14]. In-vitro spermatogenesis using human spermatogonia has not been performed successfully in humans but has been successful in nonhuman primates [15]. As the science of fertility preservation evolves, more options will be available to Klinefelter's syndrome patients who do not have mature sperm at the time of fertility preservation.

CONCLUSION

Naturally conceived children have been reported for men with Klinefelter's syndrome; however, this is exceedingly rare [16]. In the era of mTESE, ICI and cryopreservation, Klinefelter's syndrome is no longer an absolute contraindication to paternity. We feel that cryopreservation in Klinefelter's syndrome adolescents is possible and TESE can be attempted after hormonal optimization and extensive counseling. We presented a simple algorithm to assist reproductive specialists in patient management.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Linden MG, Bender BG, Robinson A. Sex chromosome tetrasomy and pentasomy. Pediatrics 1995; 96:672–682.
2. Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Arch Dis Child 1999; 80:192–195.
3. Corona G, Pizzocaro A, Lanfranco F, *et al.* Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. Hum Reprod Update 2017; 23:265–275.
4. Plotton I, Brosse A, Cuzin B, Lejeune H. Klinefelter syndrome and TESE-ICSI. Ann Endocrinol (Paris) 2014; 75:118–125.
5. Groth KA, Skakkebæk A, Høst C, *et al.* Clinical review: Klinefelter syndrome: a clinical update. J Clin Endocrinol Metab 2013; 98:20–30.
6. ■ Van Saen D, Vloeberghs V, Gies I, *et al.* When does germ cell loss and fibrosis occur in patients with Klinefelter syndrome? Hum Reprod 2018; 33: 1009–1022.

Retrospective review examining sperm retrieval and germ cell presence in varying age groups of males with Klinefelter's syndrome.

7. Ratcliffe SG, Murray L, Teague P. Edinburgh study of growth and development of children with sex chromosome abnormalities. III. Birth Defects Orig Artic Ser 1986; 22:73–118.
8. Robinson A, Bender BG, Linden MG. Sex chromosomal aneuploidy: prospective and longitudinal studies. Birth Defects Orig Artic Ser 1986; 22:23–71.
9. Ramasamy R, Ricci JA, Palermo GD, *et al.* Successful fertility treatment for Klinefelter's syndrome. J Urol 2009; 182:1108–1113.
10. Franik S, Hoeijmakers Y, D'Hauwers K, *et al.* Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. Hum Reprod 2016; 31:1952–1959.
11. ■■ Fainberg J, Hayden RP, Schlegel PN. Fertility management of Klinefelter syndrome. Expert Rev Endocrinol Metab 2019; 14:369–380.

Recent critical expert review focused on identifying predictive factors for successful sperm retrieval in men with Klinefelter's syndrome.

12. Nassau DE, *et al.* The pediatric patient and future fertility: optimizing long-term male reproductive health outcomes. Fertil Steril 2020; 113:489–499.
13. Mehta A, Paduch DA, Schlegel PN. Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor. Fertil Steril 2013; 100:e27.
14. Frydman R, Grynberg M. Introduction: male fertility preservation: innovations and questions. Fertil Steril 2016; 105:247–248.
15. Hermann BP, Sukhwani M, Winkler F, *et al.* Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. Cell Stem Cell 2012; 11:715–726.
16. Laron Z, Dickerman Z, Zamir R, Galatzer A. Paternity in Klinefelter's syndrome: a case report. Arch Androl 1982; 8:149–151.