Fertility in Adolescents With Klinefelter Syndrome: A Survey of Current Clinical Practice

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Context: Progress has been made in determining the fertility timeline and potential in adolescents with Klinefelter syndrome; however, medical professionals are currently without protocols to guide treatment.

Objective: To evaluate the current practices regarding fertility and andrology care in adolescent males with Klinefelter syndrome.

Design: A 24-question survey was developed to elicit practitioner background/expertise and management practices. This was distributed to members of the Society for the Study of Male Reproduction, the Pediatric Endocrine Society, and the Endocrine Society.

Setting: N/A.

Patients: Adolescent males with Klinefelter syndrome.

Intervention: None.

Main Outcome Measured: Current practices regarding fertility and andrology care.

Results: 232 responses were received from 133 (57%) adult endocrinologists, 60 (26%) pediatric endocrinologists, and 39 (17%) urologists. Among these, 69% of respondents were in academics, 62% practiced for > 10 years, and 65% received formal training in Klinefelter syndrome. All specialties encouraged sperm banking in late puberty, however most disagreed with the practice in early puberty. Seventy-eight percent agreed that testicular biopsy should be offered if no sperm was found in the ejaculate. The perceived optimal age for testicular biopsy varied among specialists. Clinical symptoms of hypogonadism (28%), rising gonadotropin levels (15%), and testosterone levels (15%) were the most commonly cited reasons for initiation of testosterone replacement therapy.

Conclusion: Fertility preservation practices in adolescents with Klinefelter syndrome vary greatly within and among the specialties caring for these patients. These findings should guide future research and highlight the importance of establishing clinical practice guidelines. **(*J Clin Endocrinol Metab* 105: 1–9, 2019)**

Key Words: Klinefelter syndrome, fertility preservation, andrology, infertility, sperm

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Abbreviations: FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; KS, Klinefelter syndrome; LH, luteinizing hormone; TESE, testicular sperm extraction.

Males with Klinefelter syndrome (KS) typically have elevated gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH]), low-normal testosterone, eunuchoid body habitus, small hyalinized testes, gynecomastia, and azoospermia, with the majority having the 47,XXY chromosomal abnormality (1). KS is the most common karyotypic anomaly diagnosed in infertile men and 11% to 15% of azoospermic men are ultimately found to have KS (2). One in every 600 newborn males are diagnosed with KS, and there is often a delay in diagnosis, with < 10% being diagnosed before puberty (3).

The appropriate management of adolescent males with KS remains controversial, particularly with respect to testosterone replacement therapy and fertility preservation. This is because the underlying mechanisms causing the disruption of gonadal development and spermatogenesis in patients with KS are poorly understood, although this is an area of active research. The testicular degenerative process has been found to start in the fetal period, with a decreased number of germ cells on testicular biopsies from 47,XXY midterm fetuses. This histologic pattern persists into the prepubertal period. From early puberty to midpuberty, there are observed testicular histological changes that coincide with activation of the pituitary–gonadal axis. Namely, progressive and extensive seminiferous tubule fibrosis and hyalinization, germ cell depletion, Sertoli cell degeneration, and Leydig cell hyperplasia are seen. Adult males with KS demonstrate hypergonadotropic hypogonadism with high FSH and LH levels, low/low-normal levels of testosterone, and undetectable levels of inhibin B (4).

Nonmosaic 47,XXY patients with KS have traditionally been considered sterile. More recent data shows that sperm is found in the ejaculate of approximately 8% of nonmosaic adult males with KS. Natural conception rarely occurs for males with KS (5), but fortunately, sperm will be found in 45% to 50% of men undergoing microscopic testicular sperm extraction (micro-TESE) for use with intracytoplasmic sperm injection (ICSI) (6). Limited data exist regarding the optimal timing and techniques for fertility preservation in patients with KS or about the effects of hormonal manipulation on sperm retrieval rates in adolescents (7). There is some evidence to support adolescent germ cell depletion in males with KS, leading many to advocate for freezing of semen samples or testicular tissue in boys with KS in early puberty, and even micro-TESE before starting testosterone supplementation (8, 9). However, some have questioned the rationale for testis surgery and sperm freezing in adolescent patients with KS and have instead advocated to delay the decision into adulthood, when the patient and his partner can make an informed choice (10).

Progress has been made in determining the fertility timeline and potential in these males; however, medical professionals are currently without guidelines to counsel patients and families regarding the optimal fertility preservation protocols. Our objectives were to determine which specialties are primarily treating adolescents with KS, what the the current attitudes/practices towards fertility and andrology care are in these patients, and on which areas of care variability we should focus education efforts and practice guidelines. Additionally, we sought to provide a thorough review of the current literature to highlight the gaps within the literature and provide additional context for our survey questions.

Materials and Methods

A 24-question anonymous survey was designed by the authors to elicit practitioner training background, expertise, management strategies/practices, and attitudes regarding fertility preservation in adolescent patients with KS. A review of the current literature was used to formulate the specific questions in the survey regarding sperm banking, testicular biopsy, and testosterone supplementation (11). The entire survey (question content, phrasing, order of questions) was reviewed and approved by each author prior to being distributed. After institutional review board (IRB) exemption, the survey was distributed via email to all members of the Society for the Study of Male Reproduction, the Pediatric Endocrine Society, and the Endocrine Society. These societies were chosen to include most of the potential providers who treat patients with KS at different ages. The survey was sent via email twice to each society, approximately 1 month apart and providers were given 1 additional month to complete the survey. All questions required a response prior to submitting the survey.

The responses for each survey question were collected and a data set was formed using simple descriptive statistics. A relative frequency distribution table was created for each question based on the possible responses. Additional relative frequency distribution tables were calculated for each question based on the providers' "field of practice" (ie, pediatric endocrinology, adult urology, etc.). All free-text responses (eg, "Other [Please specify]") were analyzed to determine whether they should be classified as one of the other categorical options or analyzed individually.

Results

We received a total of 232 survey responses over a 1-month period, from 60 (26%) pediatric endocrinologists, 133 (57%) adult endocrinologists, and 39 (17%)

urologists. Overall response rates for the Society for the Study of Male Reproduction, the Pediatric Endocrine Society, and the Endocrine Society were 4.7%, 5%, and 1%, respectively.

Table 1 represents the overall response rate and specialty-specific response rates for questions designed to evaluate practitioner training, background, and expertise. Sixty-nine percent (159/232) of physicians practiced in an academic setting, with 8% (19/232) having both private and academic components to their practice. The majority of providers (62%, 145/232) had been in practice for more than 10 years, and 65% (150/232) had formal training in the care of patients with KS. "Post-residency training" was the most commonly cited time for formal training; however, 40% (34/85) of adult endocrinologists listed residency as their formal training time. Most practitioners (72%, 166/232) cared for fewer than 10 patients with KS per year, and urologists were more likely to estimate 10 to 20 patients per year. "Past clinical experience" and "current literature" guided management decisions for most providers, and urologists were more inclined than other specialties to base their decisions on "future fertility potential."

Table 2 contains the responses for questions regarding sperm banking and testicular biopsy in patients with KS. There was almost a 50:50 split in pediatric endocrinologists and urologists with respect to sperm banking in the early puberty window (10–13 years of age), while 75% (99/133) of adult endocrinologists disagreed with the practice. The majority of providers (74%, 172/232) encouraged sperm banking in the late puberty window (14–16 years of age), and this was consistent among all specialties. 78% (180/232) of respondents agreed that testicular biopsy should be offered to patients with KS if no sperm was found in the ejaculate. While the optimal age for the procedure varied widely among specialists, most providers (93%, 215/232) agreed that testicular exploration/biopsy should not be performed in boys younger than 8 years of age.

There was variation seen among specialists when asked if patients with KS should be under the care of a psychotherapist prior to undergoing any invasive fertility treatments: Pediatric endocrinologists were split 50:50, most adult endocrinologists (74%, 99/133) believed they should, whereas only 22% (8/39) urologists supported the idea. All groups were split 50:50 on if the decision for if a testicular biopsy for sperm identification and freezing in prepubertal boys with KS should be made solely by their parents; however, all groups did agree (91%, 211/232) that the decision should be made in consultation with the patient.

Responses to survey questions regarding testosterone replacement in patients with KS are found in Table 3. There was no consensus on when to start boys with KS on testosterone replacement among the different specialists. Rising gonadotropin levels (16%, 38/232),

Table 1. Overall and Specialty-Specific Rates Results From Questions Related to Practitioner Training and Expertise in KS

		Overall (n = 232)	Adult Endocrine (n = 133)	Peds Endocrine (n = 60)	Urologists (n = 39)
Nature of practice	Academic	159 (69%)	85 (64%)	47 (78%)	27 (69%)
	Private	54 (23%)	34 (26%)	10 (17%)	10 (25%)
Years in practice	<3 years	30 (13%)	19 (14%)	8 (13%)	3 (8%)
	3–6 years	27 (12%)	15 (11%)	6 (10%)	6 (15%)
	6–10 years	30 (13%)	12 (9%)	11 (18)	7 (18%)
	>10 years	145 (62%)	87 (66%)	35 (59%)	23 (59%)
Formal training in patients with KS	Yes	150 (65%)	82 (62%)	40 (67%)	28 (72%)
	No	82 (35%)	51 (38%)	20 (33%)	11 (28%)
Number of patients with KS seen per year	<10	166 (72%)	99 (75%)	50 (83%)	17 (44%)
	10–20	44 (19%)	20 (15%)	7 (12%)	17 (44%)
	20–40	17 (7%)	12 (9%)	3 (5%)	2 (5%)
	>40	5 (2%)	2 (1%)	0	3 (7%)
Age of most patients	Adults	144 (62%)	122 (92%)	1 (2%)	21 (54%)
	Pediatrics	60 (25%)	0	59 (98%)	1 (2%)
	All ages	28 (12%)	11 (8%)	0	17 (44%)
Basis of treatment approach to patients with KS (select all)	Clinical experience	150 (65%)	82 (62%)	43 (72%)	25 (64%)
	Current literature	168 (72%)	92 (69%)	47 (78%)	29 (74%)
	Future fertility potential	51 (22%)	29 (29%)	6 (10%)	16 (41%)
	Current clinical status	77 (33%)	38 (29%)	21 (35%)	18 (46%)

Abbreviation: KS, Klinefelter syndrome.

Table 2. Overall and Specialty-Specific Results From Questions Regarding Sperm Banking and Testicular Biopsy in Patients with KS

		Overall (n = 232)	Adult Endocrine (n = 133)	Peds Endocrine (n = 60)	Urologists (n = 39)
Sperm banking in patients 10–13 years of age with KS	Yes	83 (36%)	34 (25%)	29 (48%)	20 (51%)
	No	149 (64%)	99 (75%)	31 (52%)	19 (49%)
Sperm banking in patients 14–16 years of age with KS	Yes	172 (74%)	88 (66%)	50 (83%)	34 (87%)
	No	60 (26%)	45 (34%)	10 (17%)	5 (13%)
Age to begin counseling patients with KS on sperm banking	8–10 years	9 (4%)	5 (4%)	3 (5%)	1 (2%)
	10–13 years	73 (31%)	29 (22%)	30 (50%)	14 (36%)
	14–16 years	94 (41%)	55 (41%)	18 (30%)	21 (54%)
	>16 years	56 (24%)	44 (33%)	9 (15%)	3 (8%)
Testicular biopsy in boys with KS if no sperm found in ejaculate	Yes	180 (78%)	105 (79%)	46 (76%)	29 (74%)
	No	52 (22%)	28 (21%)	14 (24%)	10 (26%)
Sperm extraction in boys with KS <8 years of age	Yes	17 (7%)	12 (9%)	4 (7%)	1 (2%)
	No	215 (93%)	121 (91%)	56 (93%)	38 (98%)
What age is appropriate for testicular biopsy/sperm freezing	8–10 years	8 (4%)	5 (4%)	3 (5%)	0
	10–13 years	52 (22%)	28 (21%)	15 (25%)	9 (23%)
	14–16 years	75 (32%)	41 (31%)	22 (37%)	12 (31%)
	>16 years	97 (42%)	59 (44%)	20 (33%)	18 (46%)

Abbreviation: KS, Klinefelter syndrome.

declining testosterone levels (15%, 37/232), and clinical symptoms of hypogonadism (28%, 65/232) were commonly cited indications. The optimal timing for testosterone replacement was commonly believed to be from 10 to 13 years (30%, 69/232), or 14 to 16 years (37%, 86/232), with topical (50%, 117/232) and injections (69%, 161/232) being the preferred replacement modalities. All specialties agreed that testosterone replacement in adolescent males should be managed by pediatric endocrinologists. The majority of adult endocrinologists (61%, 81/133) and urologists (64%, 25/39) did not agree with starting infants with KS on testosterone, however most (65%, 39/60) pediatric endocrinologists believed it was indicated if the patient had a micropenis.

Discussion

By including pediatric endocrinologists, adult endocrinologists, and urologists in our survey audience we sought to present a comprehensive estimation of the current management strategies/practices, and attitudes towards fertility preservation in adolescent males with KS.

The management of these patients continues to evolve. It is critical that practitioners treating pediatric or adolescent patients with KS be familiar with the current literature to optimally manage these patients (7, 10). However, this can be challenging, because the current literature is limited by relatively small numbers of patients, the experimental interventions studied, and at times conflicting results (or interpretations of results). Because of the complex potential ethical, legal, and logistical issues surrounding the treatment of these patients, many have argued that fertility preservation should be limited to large academic centers (12).

Practitioner training, background, and expertise

The majority of providers who were surveyed in this study reported that they practice in an academic setting, had been in practice for more than 10 years, and had formal training in the care of patients with KS. While the number of patients with KS seen by most physicians remains low (fewer than 10 per year), this is consistent with the reported incidence and significant delay in diagnosis (3), and it further emphasizes the need for early referral to large academic centers. "Past clinical experience" and "current literature" guided management decisions for most providers, likely in part because the literature regarding testosterone replacement, sperm banking, and testicular biopsy in adolescent patients with KS is extremely variable, further indicating a vital need for consensus guidelines.

Testosterone replacement therapy

There are 3 physiologic peaks of testosterone during the normal male development: prenatal period, "mini-puberty," and during adolescence. It is unclear whether testosterone deficiency occurs for patients with KS at all 3 peaks, and there is currently no consensus on when to start boys with KS on testosterone replacement. Some studies have demonstrated lower testosterone levels in infants with KS (13), while other studies have shown normal/high normal testosterone levels in the same population (14). Additionally, boys with KS often have

Table 3. Overall and Specialty-Specific Results From Questions Regarding Testosterone Replacement Therapy (TRT) in Patients with KS

		Overall (n = 232)	Adult Endocrine (n = 133)	Peds Endocrine (n = 60)	Urologists (n = 39)
When should boys with KS be started on TRT	Delayed puberty	31 (13%)	22 (17%)	4 (7%)	5 (13%)
	After testicular biopsy/banking	37 (15%)	23 (17%)	4 (7%)	10 (26%)
	Based on testosterone levels	37 (15%)	25 (19%)	8 (13%)	4 (10%)
	Rising gonadotropins	38 (16%)	19 (14%)	17 (28%)	0
	Signs of hypogonadism	65 (28%)	32 (24%)	17 (28%)	16 (41%)
	Not at all	3 (1%)	2 (1%)	0	1 (3%)
Optimal timing for TRT in boys with KS	<8 years	1 (0.4%)	1 (1%)	0	0
	8–10 years	8 (4%)	4 (3%)	3 (5%)	1 (3%)
	10–13 years	69 (30%)	42 (32%)	20 (33%)	7 (18%)
	14–16 years	86 (37%)	49 (37%)	23 (38%)	14 (36%)
	>16 years	36 (15%)	23 (17%)	2 (3%)	11 (28%)
Should infants with KS be started on TRT?	Yes	15 (6%)	8 (6%)	7 (12%)	0
	Only with micropenis	97 (42%)	44 (33%)	39 (65%)	14 (36%)
	No	120 (52%)	81 (61%)	14 (23%)	25 (64%)
Optimal modality for TRT (mark all that apply)	Topical	117 (50%)	78 (59%)	18 (30%)	21 (54%)
	Injection	161 (69%)	89 (67%)	54 (90%)	18 (46%)
	Pellets	26 (11%)	15 (11%)	2 (3%)	9 (23%)
	Estrogen receptor blockers	7 (3%)	0	1 (2%)	6 (15%)
	hCG	24 (10%)	15 (11%)	0	9 (23%)
	Aromatase inhibitor	16 (7%)	2 (2%)	2 (3%)	12 (31%)
Who should manage TRT in boys with KS?	Pediatric Endocrinology	161 (69%)	83 (62%)	58 (97%)	20 (51%)
	Endocrinology	54 (23%)	48 (36%)	2 (3%)	4 (10%)
	Urology	10 (4%)	0	0	10 (25%)
	Family Medicine	1 (.04%)	1 (0.8%)	0	0
Should asymptomatic adolescent boys with KS be treated prior to symptoms?	Yes	104 (45%)	71 (53%)	23 (38%)	10 (26%)
	No	128 (55%)	62 (47%)	37 (62%)	29 (74%)

Abbreviations: hCG, human chorionic gonadotropin; KS, Klinefelter syndrome; TRT, testosterone replacement therapy.

normal levels of testosterone, FSH, LH, and inhibin B in the prepubertal period, and demonstrate a normal testosterone response to human chorionic gonadotropin (hCG) stimulation (15). Our findings reflected this, as there was no consensus among the differing specialists regarding when to start boys with KS on testosterone replacement.

With the currently available evidence, it is difficult to assess the impact of testosterone replacement in men with KS specifically, but it is known that exogenous testosterone will negatively impact spermatogenesis in all men. Previous studies have demonstrated a negative influence of exogenous testosterone on future fertility in patients with KS; however, most of these were small series (16). Subsequent larger studies have reported surgical sperm retrieval rates with TESE from 52% to 70% in patients with KS previously treated with testosterone replacement (17), and even those who continued topical testosterone replacement (18). Therefore, testosterone replacement may not have a permanent negative impact on future fertility in patients with KS; however, larger studies are needed to confirm these findings.

Some advocate for initiation of therapy in early-to-midpuberty, or at the onset of symptomatic hypogonadism, to ensure normal timing of puberty and prevent symptoms/sequelae of long-term androgen deficiency (19–21). In our survey, rising gonadotropin levels (16%, 38/232), declining testosterone (15%, 37/232), and clinical symptoms of hypogonadism (28%, 65/232) were commonly cited reasons for testosterone replacement. We found that the optimal timing for testosterone replacement was most commonly recommended from 10 to 13 years of age (30%, 69/232), or 14 to 16 years of age (37%, 86/232). In addition, the majority of pediatric endocrinologists believed it was appropriate to start testosterone replacement in infants with KS if the patient had a micropenis, while both adult endocrinologists and urologists generally disagreed with this practice. In general, penile length in boys with KS is often less than 46,XY boys, however it is usually not within the range of micropenis. Nevertheless, some physicians, as demonstrated in our cohort, may elect to treat infants with KS for micropenis (19–21).

Furthermore, there are no specific guidelines regarding the optimal modality of testosterone replacement for patients with KS. The route of administration in this patient population may have variable effects on the degree and duration of testicular function suppression. In

our study, the most commonly suggested routes of administration were topical (50%, 117/232) and injection (69%, 161/232). All specialties agreed that testosterone replacement should be managed primarily by pediatric endocrinologists. Some have advocated for cessation of maintenance injectable testosterone in men with KS prior to any consideration for subsequent treatment for infertility. Often, those with high levels of testosterone on injection therapy may be switched to topical therapy to achieve a more physiologic level of testosterone with suppression of FSH/LH until the patient decides on pursuing fertility (12). Some groups have also looked at using hCG +/- an aromatase inhibitor to stimulate testosterone production in males with KS (22). One study evaluated the use of implantable T pellets as a treatment option in nonadherent adolescents with KS (23); however, the requirement for repeat implantation every 3 months, increased cost of therapy/monitoring, and dramatic shifts in serum total and free testosterone concentrations may be undesirable for some patients with KS.

Sperm banking

In our survey, there was almost a 50:50 split between pediatric endocrinologists and urologists with respect to sperm banking in the early puberty window (10–13 years of age); in contrast, the majority of adult endocrinologists disagreed with the practice. The majority of providers encouraged sperm banking in the late puberty window (14–16 years of age), and this recommendation was consistent among all specialties.

The differing opinions may reflect the relatively poor understanding of the underlying mechanisms for the disruption of gonadal development and spermatogenesis in patients with KS. As mentioned earlier, there appears to be a lower number of germ cells on testicular biopsies from 47,XXY midterm fetuses, but the number and density of seminiferous tubules and Sertoli/Leydig cells appears normal (4, 24). In addition, while healthy neonates see a strong activation of the pituitary-gonadal axis between 3 weeks and 6 months of age ("mini-puberty") (25), infants with KS demonstrate lower testosterone levels during their "mini-puberty," possibly indicative of baseline Leydig cell dysfunction (13). Interestingly, prepubertal 47,XXY boys usually have normal levels of testosterone, FSH, LH, and inhibin B until the onset of puberty, but the number of spermatogonia are significantly reduced, possibly secondary to a massive apoptosis that may precede elevation in serum gonadotropin levels (4, 6). From early puberty to midpuberty, there are major histological changes seen within the testes that coincide with activation of the pituitary–gonadal axis. Initially, there is growth of the testicles from Sertoli and interstitial cell proliferation. This is followed by progressive and extensive fibrosis/hyalinization of the seminiferous tubules, germ cell depletion, Sertoli cell degeneration, and Leydig cell hyperplasia (8).

Patients with KS in early adolescence do have spermatogonia present in their testes (8). Therefore, it would reason that during early puberty, there is a period when spermatogenesis begins and sperm are present in ejaculate. Approximately 8% of nonmosaic adults with KS have been found to have sperm in the ejaculate (5, 19, 26). Conversely, sperm in the ejaculate of adolescents and young adults with KS has been shown to be exceedingly rare. In a review of adolescents and young men with KS, only 1/62 patients (2%) was found to have sperm in the ejaculate (27).

Certainly, there are some ethical concerns and challenges when obtaining sperm via masturbation from 12 to 14-year-old patients, which may influence providers. However, we know that the average age of onset of masturbation in the US is 12 years, and therefore most adolescents with KS should be able to produce a semen sample (28). In fact, a study evaluating patient and parent attitudes toward sperm preservation in boys undergoing chemotherapy found that 70% favored using masturbation or electrostimulation as a means of obtaining sperm for cryopreservation (29). In a 2013 retrospective study looking at the acceptability of fertility preservation by adolescents with KS and their parents, Revis et al found that adolescents with KS were not initially deeply concerned about their future fertility and only became involved in the process of fertility preservation after 3 medical consultations. However, the parents agreed immediately that fertility preservation should be attempted (30).

Similar to the mixed results of our survey, there have been numerous proposed management strategies with respect to the appropriate sperm banking age and even the practice of banking in general. Unfortunately, there is no well-accepted set of markers that allow us to determine the optimal timing for cryopreservation in these patients. Paduch et al suggest a strategy of monitoring FSH, LH, and testosterone levels every 6 months starting 2 years prior to predicted start of puberty. When FSH and LH begin to increase, sperm banking is initiated after discussion with the parents and child. If sperm is found in the ejaculate, the patient is started on an aromatase inhibitor (most commonly anastrozole) and additional samples collected over the next 6 months (12). The rationale behind this approach is that elevated estradiol levels, often seen in males

with KS are thought to impair spermatogonial division. However, impact of lowered estrogen levels on bone health remains a concern, as is the lack of supportive data for this regimen (31).

Because of the paucity of data, most investigators have proposed waiting to discuss fertility preservation in adolescents with KS until just after the onset of puberty when the patient is mature enough to be able to consider alternative options to become a father, and to accept the potential failure of germ cell retrieval. Clearly, more data are needed to determine the optimal age to offer sperm banking as an option for fertility preservation in adolescent patients with KS. In addition, randomized trials are needed to determine if and which hormonal therapy prior to sperm banking is the optimal treatment approach.

Testicular biopsy

An even more controversial area in the management of patients with KS is the use of testicular biopsy to harvest sperm from patients with azoospermia for future use in assisted reproductive technology, possibly as early as prior to puberty. Damani et al published the first case report of a successful TESE in a 15-year-old patient with nonmosaic KS in 2001 (9). Subsequent studies have found sperm in TESE specimens in approximately 50% to 60% of adolescents with KS (8, 32, 33). Results for spermatozoa identification on TESE (using both needle biopsy and micro-TESE) have ranged from 0% to 70% (18, 34, 35). Greater success (40%–50%) has been reported with micro-TESE (34, 35) and after pretreatment with testosterone and anastrozole (18). Rohayem et al (34) found that at TESE in adolescents 13 to 14 years of age, the sperm retrieval rate was 10% (1/10), versus 45% (18/40) in 15- to 19-year-olds. They reported that a combination of total serum testosterone > 7.5 nmol/L and LH levels <17.5 U/L correlated with higher sperm retrieval rates at micro-TESE in patients with KS. The predictive value of these markers remains unclear.

The majority of responders in our survey agreed that testicular biopsy should be offered to patients with KS if no sperm was found in the ejaculate during sperm banking; however, the optimal age for the procedure varied widely among specialists. 74% (172/232) felt that > 14 years of age was an appropriate age for testicular biopsy, and 93% (215/232) agreed that sperm extraction should not be done in boys younger than 8 years of age.

Testicular tissue preservation should ideally be performed before hyalinization occurs, but it is important to remember that even in the prepubertal period only ~50% of males with KS will have germ cells in their testes (8). Currently there is no consensus regarding the optimal age for attempted sperm retrieval in males with KS (5, 32). While some data have shown that increasing age may have a negative impact on sperm retrieval (36), others have found no difference in sperm retrieval by TESE in patients from 15 to 33 years of age (5, 27). Additionally, for adolescents with KS younger than 15 years of age, the retrieval rate of germ cells by micro-TESE has been shown to be lower compared with adolescents aged 15 years and older (8, 30, 34, 37). Some suggest that the early initiation of testosterone replacement therapy and possibly adjuvant aromatase inhibitors prior to sperm harvesting will improve outcomes (18). However, these interventions may further compromise sperm retrieval rates both in the ejaculate and at micro-TESE.

Other experts suggest offering micro-TESE to patients with KS who have rising FSH/LH levels, if no sperm are found in the ejaculate, prior to the initiation of exogenous testosterone therapy (12) or performing TESE in adolescents with KS at the first sign of declining Sertoli cell function (38). Recent ongoing studies have focused on the cryopreservation of spermatogonial sperm cells for future fertility (32). It is unclear if early retrieval will increase the likelihood of successful sperm retrieval (32). The potential of restoration of spermatogenesis from cryopreserved spermatogonial stem cells is currently investigational (39).

Although these theories and therapeutic suggestions are intriguing, multiple authors (10, 27, 32) recommend a more conservative approach, emphasizing that prepubertal/pubertal TESE is experimental, that there are no clinical predictive parameters of success, and the procedure cannot guarantee future fertility. Clearly, more information is needed to answer even this most fundamental of questions.

This survey is limited by a comparatively small number of responses relative to the number of society members who were sent the survey. Overall response rates for the Society for the Study of Male Reproduction, the Pediatric Endocrine Society, and the Endocrine Society were 4.7%, 5%, and 1% respectively. The low response rates also limit our ability to evaluate statistically significant differences among the groups for each question. The restriction of the survey to these 3 academic societies may introduce bias and limit generalizability because of the type of practitioners who are more likely to respond to the survey. However, our main objective was to establish current practice patterns and highlight the areas where future research and guidelines are needed, and we believe that the body of gathered data does achieve this.

Conclusions

Clinical practices for fertility preservation in adolescents with KS vary greatly within and among the specialties caring for these patients. Most physicians see a relatively small number of patients with KS per year. Treatment decisions are based mainly on clinical experience and the current literature. Testosterone replacement is commonly part of the therapy recommended by pediatric endocrinologists for patients who have laboratory and clinical signs of hypogonadism. In general, most practitioners agree with sperm banking for patients with KS who are 14 years of age or older, and most agree with a testicular biopsy if no sperm is found in the ejaculate. These findings may help guide future research and highlight the importance of establishing clinical practice guidelines for this group of patients, in hopes of optimizing their chances of long-term paternity.

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