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Age, Sperm Retrieval, and Testicular Histology in Klinefelter Syndrome

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Study Need and Importance: Males with Klinefelter syndrome (KS) are typically infertile due to primary testicular failure and suffer from hypergonadotropic hypogonadism. Biologic paternity may be an option with surgical sperm retrieval using microdissection testicular sperm extraction which may identify small pockets of seminiferous tubules with mature sperm. The concern for progressive germ cell loss and initiation of exogenous testosterone therapy in KS males, both of which may put future sperm production at risk, has been used to recommend early sperm retrieval in adolescence. However, the optimal timing for surgical sperm retrieval in KS males has not been defined.

What We Found: We examined testis histology patterns and sperm retrieval rates in adolescent (<20 years) and adult (≥20 years) KS males who underwent microdissection testicular sperm extraction from 1995 to 2020 at our institution. Adult patients were further stratified into decades of age (20-29 years, 30-39 years, and ≥40 years). We found that the proportion of patients with germ cell–containing histology patterns in testis biopsy samples decreased with increasing age, and no males greater than 40 years had any foci of germ cell–containing histology. The sperm retrieval rate in adolescent KS males was 53% and was significantly higher in the 20 to 29–year cohort (71%) and lower in the ≥40-year cohort (13%; Figure). Multivariable analysis demonstrated hypospermatogenesis histology pattern on testis biopsy was associated with increased odds of successful sperm retrieval.

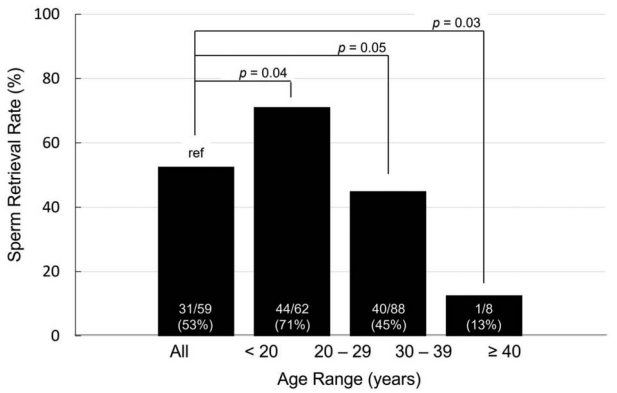

Figure. Sperm retrieval rates in males with Klinefelter syndrome. Sperm retrieval rates (%) from microdissection testicular sperm extraction by age in deciles (adolescent [<20 years] and adults [20-29 years, 30-39 years, ≥40 years]) are shown. Chi-square statistics were used to determine differences in sperm retrieval rates between each group. Adult cohorts were compared to the adolescent group (referent group).

Limitations: Our study was limited by its retrospective nature, limited sample size of the oldest age cohort, and the fact that the vast majority of adolescent KS males were taking testosterone-related medications.

Interpretation for Patient Care: KS males in their twenties have the highest chance of sperm retrieval, not adolescent males. There is no clear benefit to attempted sperm retrieval in adolescent KS males unless exogenous testosterone supplementation is planned.

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Age, Sperm Retrieval, and Testicular Histology in Klinefelter Syndrome

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Conflict of Interest Disclosures: The Authors have no conflicts of interest to disclose.

Ethics Statement: This study received Institutional Review Board approval (IRB no. 20-04021763).

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Purpose: We sought to examine sperm retrieval and testicular histology in males of different ages with Klinefelter syndrome.

Materials and Methods: We identified all males with Klinefelter syndrome who underwent microdissection testicular sperm extraction at our institution from 1995 to 2020. Patients were divided into adolescent (<20 years) and adult (≥20 years) cohorts. Histology and sperm retrieval were compared using chi-square statistics. Multivariable logistic regression models were used to examine factors associated with successful sperm retrieval.

Results: We identified 217 males with Klinefelter syndrome, of whom 59 were adolescents and 158 were adults. Adults were stratified into 10-year groupings (20-29 years, n = 62; 30-39 years, n = 88; ≥40 years, n = 8). Approximately 17% of adolescents had testis histology containing germ cells compared with 15% of the 20 to 29−year cohort, 14% of the 30 to 39−year cohort, and 0% over 40 years. In comparison to adolescents (53%), the sperm retrieval rate was significantly higher in the 20 to 29−year cohort (71%, $P = .04$) and lower in the ≥40-year cohort (13%, $P = .03$). In multivariable analysis, the presence of hypospermatogenesis on testis biopsy (OR 5.8, $P = .03$) was associated with higher odds of successful sperm retrieval.

Conclusions: Younger males more frequently had germ cell−containing testis histology, however this finding was not associated with a higher odds of sperm retrieval. Reproductive urologists should counsel azoospermic males with Klinefelter syndrome that sperm retrieval during adolescence for fertility preservation is not required and can be performed in young adulthood.

Key Words: Klinefelter syndrome, male infertility, testicular sperm retrieval

Klinefelter syndrome (KS) is the most common chromosomal abnormality associated with male infertility, affecting approximately 1 in 500 to 1000 neonatal males.[1] KS is defined by a male karyotype with more than 1 X chromosome, most commonly 47,XXY. KS males typically have primary testicular failure resulting in hypergonadotropic hypogonadism, small firm testes, nonobstructive azoospermia, and gynecomastia.[1] The vast majority of KS males are infertile, however assisted reproductive technology and surgical sperm retrieval have permitted biologic paternity.[2] However, the optimal timing of sperm retrieval for in KS males has been controversial.

Fertility in azoospermic KS males can be achieved by surgical sperm retrieval due to the presence of small pockets of seminiferous tubules that contain mature sperm.[1,3,4] Two hypotheses exist to explain the presence of mature sperm in the atrophic

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testes of KS males. First, XXY spermatogonial stem cells may be capable of completing meiosis producing functional sperm.[1,5] Alternatively, XY spermatogonial stem cells may be present as a result of mitotic errors during expansion of this cell population.[6] Despite these hypotheses, postpubertal KS males typically have hyalinized seminiferous tubules and Leydig cell hyperplasia with a lack of germ cells.[7] Sperm retrieval rates (SRRs) in adolescent KS males are reported to range from 0% to 70%, whereas the SRR in adult KS males ranges from 20% to 72%.[1,4,8-10] Consideration for sperm retrieval in adolescents is led by the concern for progressive germ cell loss, as well as the use of testosterone supplementation which may suppress spermatogenesis and fertility.[1,9,11]

Although sperm retrieval in adolescent KS males is not commonly performed, the optimal age at which surgery should be performed to increase the chance of sperm retrieval has not been defined. Furthermore, there is encouragement from the pediatric endocrine community to perform sperm retrieval in adolescents for fertility preservation. Therefore, we sought to evaluate germ cell histology on testis biopsy and surgical SRRs with microdissection testicular sperm extraction (microTESE), along with factors associated with successful sperm retrieval, in adolescent and adult KS males. Our hope is that these data may aid in counseling KS males regarding timing of sperm retrieval.

MATERIALS AND METHODS

Study Population

Data from the electronic medical record (EMR) of KS males undergoing microTESE from 1995 to 2020 at a tertiary male infertility referral center were retrospectively reviewed. Patients were identified by ICD-9 (758.7) or ICD-10 (Q98.4) diagnosis codes, and confirmation was made by reviewing karyotype data. The microTESE procedures were performed by 3 high-volume reproductive urologists. Patients were excluded if they had[1] normal karyotype,[2] mosaic KS,[3] prior sperm retrieval attempts, or[4] no histologic data in the EMR. Adult KS males (n = 8) on or with recent history of testosterone supplementation at time of microTESE also were excluded. The majority of adolescent KS males (56/59, 95%) were receiving testosterone therapy, either in the form of topical testosterone and/or aromatase inhibitor or selective estrogen receptor modulator, at the time of microTESE. Study approval was obtained from the Weill Cornell Institutional Review Board (IRB No. 20-04021763).

Demographic and Clinical Data

Data retrieved from the EMR included patient age (years) at time of microTESE, BMI (kg/m^2), baseline serum hormone (testosterone, estradiol, and follicle-stimulating hormone [FSH]) levels within 6 months of microTESE, and mean testis volume (mL), based on physical exam by the attending surgeon or scrotal sonogram.

Patient data were stratified by age to allow analysis of demographic, histopathologic, and sperm retrieval data. Adolescents were defined as less than 20 years of age per World Health Organization definitions.[12] Adults were stratified by decade of age (ie, 20-29 years, 30-39 years, and $\geq$40 years).

Histology Data

Testis biopsies were taken at the time of microTESE after samples were taken from initial dissection. Pathology reports were provided by a fellowship-trained genitourinary pathologist and documented at least 1 of 4 distinct histologic patterns, including Sertoli-cell only (SCO), tubular atrophy (TA), maturation arrest (MA), or hypospermatogenesis (HS). TA was defined as peritubular membrane thickening secondary to fibrosis with absence of Sertoli and intratubular germ cells.[13] The patterns were reported in percentages, with all 4 patterns contributing to a total of 100%. For further analysis, patients were classified as having at least 1 focus of germ cell–containing histology (MA and/or HS) or having nongerm cell–containing histology (SCO and/or TA).

Outcome Data

Sperm retrieval was defined as successful or unsuccessful based on identification of at least 1 spermatozoon. Sperm identification was retrieved from the surgeon's intraoperative report, intraoperative analysis by an embryologist present in the operating room, clinic note, or sperm cryopreservation report (if not mentioned in the operative or clinic note).

Statistical Analysis

Descriptive summary statistics were reported for the entire cohort and all age groups including medians as appropriate measures for central tendency. Absolute SRRs for each age cohort were compared using chi-square statistics. Multivariable logistic regression was completed to determine factors associated with increased odds of successful sperm retrieval using a priori selected variables including age groups (<20 years, 20-29 years, 30-39 years, and $\geq$40 years) and histopathologic patterns (SCO, TA, MA, HS). Sensitivity analysis was performed treating age as a continuous variable. Additional analyses were conducted examining the relationship between serum hormones (testosterone, estradiol, FSH) and sperm retrieval. Significance was considered at $P < .05$, and 95% confidence intervals were reported. All analysis was completed with Stata v17 (StataCorp LLC, College Station, Texas).

RESULTS

Patient Cohort

A total of 249 males with nonmosaic KS underwent microTESE between 1995 and 2010. Of these, 10 were excluded due to lack of histological data, 8 adults were excluded due to current or recent testosterone therapy, and 14 were excluded due to

Table 1. *Demographic Data (n = 217)*

	Age <20 y	Age 20-29 y	Age 30-39 y	Age ≥40 y	All ages
Total, No. (%)	59 (27)	62 (28)	88 (40)	8 (3.7)	217 (100)
BMI, median (IQR), kg/m^2	20 (17-22)	26 (22-30)	28 (24-30)	27 (23-30)	24 (21-29)
Race, No. (%)					
White	43 (73)	42 (68)	38 (43)	4 (50)	127 (59)
Asian	1 (1.7)	3 (4.8)	5 (5.7)	0 (0.0)	9 (4.1)
Hispanic	1 (1.7)	1 (1.6)	2 (2.3)	0 (0.0)	4 (1.8)
Black	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)	2 (0.9)
Native American	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.5)
Unknown	14 (24)	16 (26)	40 (46)	4 (50)	75 (34)
Testis size, median (IQR), mL	3.0 (2.0-3.0)	2.0 (1.5-3.0)	2.0 (1.5-2.9)	1.5 (1.0-2.0)	2.0 (1.5-3.0)
FSH, median (IQR), mIU/mL	8.4 (1.0-34)	32 (24-44)	35 (24-45)	30 (11-43)	31 (18-44)
Testosterone, median (IQR), ng/dL	179 (9.3-269)	238 (180-344)	199 (118-292)	188 (122-347)	212 (121-314)
Estradiol, median (IQR), pg/mL	14 (6.1-20)	26 (20-32)	27 (20-37)	24 (21-32)	24 (20-32)

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; IQR, interquartile range.

prior sperm extraction attempt. Therefore, a total of 217 patients were included in the final analysis.

Our adolescent cohort was comprised of individuals mostly on a combination of androgel and anastrozole (48/59, 81%). The remaining individuals were either on androgel alone (6/59, 10%), clomiphene alone (1/59, 1.7%), or on no hormonal therapy (4/59, 6.8%).

Demographics

Overall, median BMI was 24 kg/m^2 (IQR, 21-29) and median testis volume was 2 mL (IQR, 1.5–3.0; Table 1).

When stratified for age, there were 59 (27%) adolescents, and 158 (73%) adults. Adults were further separated by decade of age; there were 62 (39%) patients in the 20 to 29–year cohort, 88 (56%) patients in the 30 to 39–year cohort, and 8 (5.1%) patients in the ≥40-year cohort.

Regardless of age, White was the predominant race represented in our cohort. Overall, median serum testosterone levels prior to microTESE were 211 ng/dL (IQR, 121-314), median serum estradiol levels were 24 pg/mL (IQR, 20-32), and median serum FSH levels were 31 mIU/mL (IQR, 18-44; Table 1).

Some individuals had undescended or retractile testes with subsequent orchiopexy, testis mass, and varicocele. There were 2 adolescents, 4 individuals in the 20 to 29–year cohort, 15 individuals in the 30 to 39–year cohort, and 1 individual in the ≥40-year cohort with undescended or retractile testes with subsequent orchiopexy. Only 1 patient had a history of benign testis mass, and he was over 40 years of age at the time of sperm retrieval. For those with varicocele, 4 were adolescent males (none repaired), 36 were in the 20 to 29–year cohort (7 underwent repair), 29 in the 30 to 39–year cohort (9 underwent repair), and 4 in the ≥40-year cohort (1 underwent repair).

Testis Biopsy Histology

Patients were categorized as having histologic patterns containing foci or germ cells (ie, MA and/or HS) or not (ie, SCO and/or TA; Table 2). Overall, the percentage of individuals with no germ cell histology patterns (ie, SCO and/or TA) at time of microTESE increased with age. Albeit minor increases between the different age cohorts, 83% (49/59) of adolescents had this histological pattern compared with 86% (53/62) of the 20 to 29–year and 86% (76/88) of the 30 to 39–year cohorts. All patients in the ≥40-year cohorts had no germ cell histology patterns. Correspondingly, the percentage of males with at least 1 focus of histology containing germ cells was highest in the adolescent group (10/59, 17%) and decreased with age, with no men over the age of 40 years with any germ cell–containing histological patterns noted on testis biopsy (0/8, 0%).

Sperm Retrieval Rates

Overall SRR was 54% for our cohort, and SRR per age group is shown in Figure 1. Compared to the adolescent group (SRR 53%), the 20 to 29–year cohort had a significantly higher SRR (71%, $P = .04$), whereas men older than 40-years had a significantly

Table 2. *Germ Cell Histology in Testis Biopsy at Time of Sperm Retrieval in Adolescent vs Adult Males with Klinefelter Syndrome*

	Age <20 y	Age 20-29 y	Age 30-39 y	Age ≥40 y
Total No.	59	62	88	8
No germ cells (SCO ± TA), No. (%)	49 (83)	53 (86)	76 (86)	8 (100)
Germ cells (MA ± HS), No. (%)	10 (17)	9 (15)	12 (14)	0 (0.0)

Abbreviations: HS, hypospermatogenesis; MA, maturation arrest; SCO, Sertoli-cell only; TA, tubular atrophy.

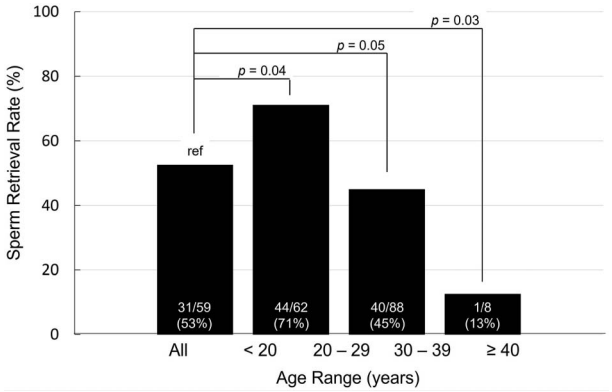

Figure 1. Sperm retrieval rates in males with Klinefelter syndrome. Sperm retrieval rates (%) from microdissection testicular sperm extraction by age in deciles (adolescent [<20 years] and adults [20-29 years, 30-39 years, ≥40 years]) are shown. Chi-square statistics were used to determine differences in sperm retrieval rates between each group. Adult cohorts were compared to the adolescent group (referent group).

lower SRR (13%, $P = .03$). The 30 to 39–year cohort SRR was similar to that seen in adolescents ($P = .5$).

Additional analysis of the adolescent cohort was performed to determine if SRRs were different in early (12-15 years) vs late (16-19 years) adolescents. We found that SRRs were not significantly different between the 2 groups (early: 16/34, 47% vs late: 15/25, 60%; $P = .3$; Figure 2), despite the majority of both groups being on testosterone therapy (early: 33/34, 97% vs late: 21/25, 84%; $P = .2$).

Factors Associated With Sperm Retrieval in KS Patients

Multivariable logistic regression models for successful sperm retrieval demonstrated that age between 20 to 29 years (OR 2.4, 95% CI [1.1, 5.3], $P = .02$) and presence of HS (OR 5.8, 95% CI [1.2, 27], $P = .03$) were associated with increased odds of sperm retrieval (Table 3). Sensitivity analysis examining age as a continuous variable demonstrated only the presence of HS (OR 5.8, 95% CI [1.3, 27], $P = .02$) being associated with increased odds of sperm retrieval (Supplemental Table 1, https://www.jurology.com).

Further analysis of hormone levels in adolescent KS males, both univariable and multivariable models, demonstrated baseline hormone levels in adolescent KS males were not associated with increased odds of successful sperm retrieval (Supplemental Table 2, https://www.jurology.com).

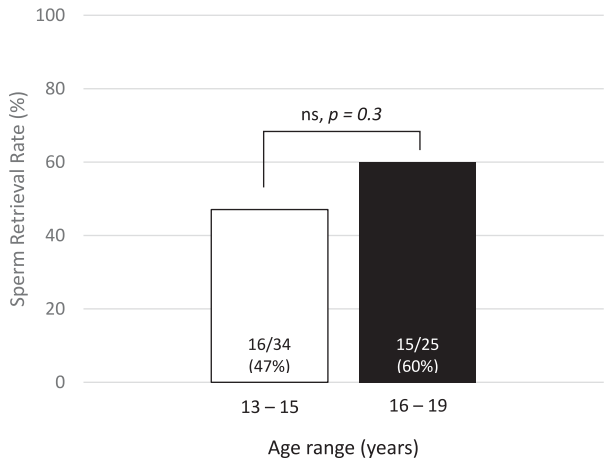

Figure 2. Sperm retrieval rates in adolescent males with Klinefelter syndrome. Sperm retrieval rates (%) from microdissection testicular sperm extraction in adolescent Klinefelter syndrome males is shown. The adolescent cohort was separated into early adolescence (age 13-15 years) and late adolescence (age 16-19 years). Chi-square statistics were used to determine differences in sperm retrieval rates between each group. ns indicates not significant.

DISCUSSION

The optimal timing for sperm retrieval in KS males has been widely debated with limited supportive data. Our data may be suggestive of the progressive loss of germ cells with increasing male age, however this was not correlated with a decrease in sperm retrieval in males with KS as they age. Although adolescent KS males more commonly had germ cell–containing histology (ie, MA or HS), SRR was the highest in the 20 to 29–year cohort. Not surprisingly, the presence of HS histology was associated with successful sperm retrieval.

Since germ cells are required for spermatogenesis, we divided our cohort into those with and without foci of germ cells on testis biopsy. We observed a subtle decrease in the percentage of patients with germ cell–containing histology with increasing age. This finding aligns with the concept that germ cell loss is progressive in KS males.[11] The precise timing at which germ cell loss begins in KS is not fully elucidated by our data. Some recent evidence suggests that this loss may begin in utero with decreased differentiation of gonocytes into prespermatogonia, and subsequently sperm, in

Table 3. *Factors Associated With Increased Odds of Successful Sperm Retrieval*

	Odds Ratio (95% CI)	*P* value
Age at microTESE		
Adolescent (<20 y)	(ref)	(ref)
Adult, 20-29 y	2.43 (1.1-5.3)	**.02**
Adult, 30-39 y	0.81 (0.4-1.6)	.5
Adult, ≥40 y	0.16 (0.2-1.4)	.1
Histology pattern present on testis biopsy[a]		
Sertoli-cell only	1.05 (0.2-1.9)	.9
Tubular atrophy	1.0 (0.8-5.3)	.1
Maturation arrest	1.1 (0.4-2.8)	.9
Hypospermatogenesis	5.8 (1.2-27.1)	**.03**

Abbreviations: CI, confidence interval; microTESE, microdissection testicular sperm extraction; ref, reference.
Bolded *P* values are statistically significant.
[a] Presence of testicular histology pattern in testis biopsy regardless of other patterns present.

KS.[14,15] Our observations suggest that germ cell loss continues as KS males age, as no males over the age of 40 years had any germ cell–containing histology, but this finding may be confounded by small sample size. Additional histologic studies are needed to definitively determine whether progressive loss of germ cells occurs in KS.

Overall SRRs for adolescent and adult KS males were similar. However, we found that the 20 to 29–year cohort had significantly higher SRR. These data are not surprising as conflicting SRRs in adolescent and adult KS males has been reported by various groups.[1,8-10] No significant difference in SRR was noted between early and late adolescents. In the 20 to 29–year-old cohort, sperm were isolated in 71% of cases, despite only approximately 15% exhibiting germ cell–containing histology on testis biopsy. Random testis biopsy may be unable to identify small foci of germ cells or mature sperm present in the testes of men who had sperm retrieved during microTESE.

We found that younger age and presence of HS were associated with increased odds of sperm retrieval. Younger age being associated with increased odds of sperm retrieval was driven by the significantly higher SRR in the 20 to 29–year cohort because, when using age as a continuous variable, age was no longer associated with increased odds of finding sperm. In both models, presence of HS, which is the actual presence of sperm, was expectedly associated with increased odds of finding sperm, similar to a prior study.[3,13]

Some adolescent KS males will be recommended to start exogenous testosterone therapy. It is imperative that these patients and their families are counseled regarding the negative effects of testosterone on sperm production. If one does decide to start exogenous testosterone therapy, early sperm retrieval (even in adolescence) should be considered. Patient preference and the importance of fertility to the patient should be carefully considered when counseling KS males regarding exogenous testosterone use and fertility preservation.

Our study includes the largest cohort of adolescent and adult KS patients to our knowledge allowing for specific observations in testis histology and sperm retrieval based on patient age. However, there are some important limitations to note, including the retrospective nature of the study. Furthermore, the number of males in the oldest (≥40 years of age) cohort was small. Additional multicenter studies should be performed so that SRRs from a larger cohort of older KS males may be studied. Another limitation was the majority of adolescent patients were taking testosterone therapy at the time of sperm retrieval, which may alter the actual SRR in this subset of KS males. Additionally, although this may increase generalizability of our study, 3 reproductive urologists performed sperm retrievals on our patient cohort. These surgeons performed microTESE based on their prior training, and sperm identification was performed per surgeon preference. Despite these limitations, our data strongly suggest that adolescent sperm retrieval in KS is unlikely to be of clinical benefit in preserving fertility, since men in their twenties were more likely to have sperm found. Our model, however, should be interpreted with caution as more robust analysis may provide additional insight into the true relationship between age and SRRs in KS males. Additionally, an exception to this recommendation is for the young KS male who is recommended to start exogenous testosterone, where earlier sperm retrieval for cryopreservation should be considered since testosterone therapy may suppress future sperm production. Finally, KS males desiring fertility should be counseled not to wait until later adulthood (ie, later thirties) to perform sperm retrieval. These data have strong implications for reproductive urologists in counseling KS males regarding sperm retrieval and fertility preservation.

CONCLUSIONS

Younger KS males, especially men in their twenties, have the highest chance of sperm retrieval and there is no added benefit for attempted sperm retrieval of adolescent KS males unless considering exogenous testosterone supplementation. These data should reinforce not encouraging sperm retrieval for attempted fertility preservation in adolescent KS males but to wait until these individuals reach the third decade of life or are ready to attempt conception. Future work should focus on optimizing future fertility for KS males using surgical sperm retrieval by microTESE and understanding the underlying mechanisms of germ cell loss that occur with age in KS males.

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EDITORIAL COMMENT

Identifying the optimal timing for microdissection testicular sperm extraction in Klinefelter syndrome (KS) requires balancing puberty, exogenous testosterone, and germ cell loss. Franik et al's 2016 meta-analysis recommended against sperm extraction under 16 years of age, citing a low sperm retrieval rate (SRR) and identified ages 16 to 30 as most promising, with a 40% to 70% SRR.[1] Kang et al echo these findings, with the highest SRR (71%) in those 20 to 29 years and the lowest in those $\geq$40 years (13%).[2] SRR in adolescents (53%) was similar to those 30to 39 years old (45%). It appears safe to wait until the patient can provide informed consent as an adult, though a decline in SRR is eventually noted. One important consideration is that most adolescents were on testosterone replacement therapy (TRT), potentially suppressing spermatogenesis, while all adults were TRT-naïve or TRT-free for over 2 years. Therefore, the lower SRR in adolescents should be interpreted with caution.

Kang et al report more favorable testicular histology in younger patients, with the greatest presence of germ cells in adolescents. This sparks a debate on a potential improvement of SRR rate in young adulthood or late adolescence by avoiding TRT in favor of alternative regimens including aromatase inhibitors, clomiphene citrate, or human chorionic gonadotropin. Current society guidelines favor TRT in adolescents with KS due to lack of data of other regimens, but management of these patients without TRT has been described.[3] Moreover, it remains to be answered if men who are diagnosed with KS in childhood vs adulthood have a phenotypic difference that could skew the findings of this and other studies. The greater use of testosterone in adolescents in this study could be indicative of that. Considering these findings, the conversation surrounding hormonal therapy for adolescents with KS is on the forefront.

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