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MICRODISSECTION TESTICULAR SPERM EXTRACTION IN MEN WITH KLINEFELTER SYNDROME AND AZOOSPERMIA

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Abstract

Objective. To review evidence on surgical sperm retrieval in Klinefelter syndrome and describe microdissection testicular sperm extraction (micro-TESE) outcomes in 62 men treated at two reproductive centers in Tashkent, Uzbekistan.

Methods. A narrative review was combined with a two-center retrospective case series of 62 men aged 24–31 years treated over a five-year period in Tashkent, Uzbekistan: 30 at “ERAMED EKO” and 32 at “SIZ ONA BO’LASIZ”. All had a genetically confirmed 47,XXY karyotype and azoospermia documented on at least four semen analyses. All were diagnosed with hypergonadotropic hypogonadism. Follicle-stimulating hormone (FSH) ranged from 35 to 61 mIU/mL, and testicular volumes ranged from 0.8 to 2.2 cm³. Patients underwent micro-TESE without preoperative hormonal stimulation. Retrieved tissue was transferred to embryologists for sperm examination. Informed consent for surgery was obtained.

Results. Spermatozoa were identified in 2 of 62 men, giving a patient-level retrieval rate of 3.2% (exact 95% confidence interval [CI] 0.4–11.2%). Only rare spermatozoa were recovered; these were

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cryopreserved for planned in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI). In the remaining 60 men (96.8%), retrieval was unsuccessful and reported Johnsen scores ranged from 2 to 4. Published international syntheses report estimates around 44%, although their populations, procedures and outcome denominators differ.

Conclusion. This series documents a low sperm retrieval rate despite occasional recovery of spermatozoa for cryopreservation. The data do not establish why retrieval differed from published estimates. In particular, they cannot determine whether hormonal pretreatment would have improved the outcome. Post-thaw survival and subsequent reproductive outcomes were not evaluated.

Keywords: Klinefelter syndrome; azoospermia; micro-TESE; FSH; Johnsen score; cryopreservation; ICSI.

Introduction

Narrative review

Clinical rationale for surgical sperm retrieval

Klinefelter syndrome is a genetic cause of male infertility characterized by variable testicular dysfunction. Azoospermia, impaired spermatogenesis and hypergonadotropic hypogonadism are common reproductive manifestations. Nevertheless, the extent of residual spermatogenesis differs between individuals, creating uncertainty when counseling patients about surgical sperm retrieval [1]. Azoospermia does not exclude focal sperm production within the testes. This focal distribution provides the rationale for surgical retrieval even in men with marked testicular dysfunction. Small testes and elevated FSH describe the clinical phenotype but do not reliably establish whether sperm-containing foci remain [1,3].

Micro-TESE involves examination of testicular tissue under an operating microscope and selective sampling of potentially productive seminiferous tubules. Schlegel's original description emphasized identification of regions containing spermatozoa while limiting the amount of tissue removed compared with conventional biopsy sampling [2]. This approach is intended to identify foci that may be missed by nonselective sampling.

The original study of microdissection included men with nonobstructive azoospermia rather than an exclusively Klinefelter population [2]. Syndrome-specific estimates are therefore more appropriate for counseling. European Academy of Andrology guidance recommends considering TESE and sperm cryopreservation in men with Klinefelter syndrome, confirmed azoospermia and a current or potential future wish for paternity [1].

Scope of the review

This narrative review draws on selected guidelines, meta-analyses and clinical studies addressing sperm retrieval, candidate predictors, endocrine pretreatment and use of retrieved sperm for ICSI. It provides context for the clinical series rather than a new systematic synthesis. No pooled estimate was recalculated, and published cohorts were not treated as matched controls.

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International sperm retrieval outcomes

Corona and colleagues included 37 studies and 1,248 men with Klinefelter syndrome in their 2017 meta-analysis. The pooled retrieval rate was 44% per TESE cycle (95% CI 39–48%) [3]. Because extraction methods varied, this is neither a micro-TESE-specific rate nor an upper limit for individual centers.

In 2025, Momtazi-Mar and colleagues reviewed 48 studies involving 2,815 men with nonmosaic Klinefelter syndrome and reported a median retrieval rate of 44% [6]. This median and the earlier pooled estimate are different summary measures despite their numerical agreement. Both indicate that sperm retrieval is achievable in a substantial proportion of selected patients, with considerable variation between series.

Contemporary clinical cohorts also demonstrate variation. Feng and colleagues retrieved sperm suitable for ICSI in 124 of 260 men undergoing micro-TESE, corresponding to 47.7% [7]. Pelit and colleagues reported a retrieval rate of 32.6% in 43 men undergoing micro-TESE after hormonal pretreatment [8].

Table 1. International evidence on surgical sperm retrieval

Source	Sample and intervention	Retrieval rate
Corona et al., 2017 [3]	37 studies; 1,248 participants; TESE and micro-TESE	44%; pooled estimate
Momtazi-Mar et al., 2025 [6]	48 studies; 2,815 participants; nonmosaic KS	44%; median study rate
Feng et al., 2025 [7]	260 participants; micro-TESE	124/260 (47.7%)
Pelit et al., 2025 [8]	43 participants; micro-TESE after hormonal pretreatment	32.6%

The studies differ in case selection, extraction methods and pretreatment. The reviews may contain overlapping primary studies, so their sample sizes should not be summed. Retrieval rates must also be distinguished from pregnancy and live birth rates, which concern later treatment stages and different denominators.

Predictors and current research directions

Age and endocrine characteristics

The optimal age for retrieval remains uncertain. In the 2025 review, mean retrieval rates did not differ significantly between adolescent and adult cohorts (45% and 42%). Men with positive retrieval were younger on average, but the suggested decline after age 40 was not statistically conclusive [6]. These results do not establish a single preferred operative age for every patient.

The predictive value of hormonal measurements varies across studies. Rohayem and colleagues identified associations involving age and selected markers of Leydig cell function, whereas FSH and testicular volume were not associated with success in their cohort [5]. Corona and colleagues likewise did not identify associations for several baseline clinical and hormonal measures in study-level analyses [3]. These findings limit the use of any single laboratory measurement as an individual prognostic test.

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Hormonal pretreatment and cryopreservation

Pelit and colleagues compared choriogonadotropin alfa with anastrozole before micro-TESE. Retrieval did not differ significantly between groups, and the lack of an untreated comparator prevents estimation of the benefit of pretreatment itself [8]. European Association of Urology (EAU) guidance advises against routine hormonal stimulation to improve retrieval before TESE in men with nonobstructive azoospermia and hypergonadotropic hypogonadism; the recommendation is graded weak [9]. Klinefelter-specific guidance likewise considers the evidence insufficient for general use [1].

Feng and colleagues analyzed 170 ICSI cycles and found no statistically significant differences in pregnancy or live birth outcomes between fresh and cryopreserved testicular sperm [7]. The retrospective comparison supports feasibility but does not establish equivalence. For men with only rare spermatozoa, post-thaw recovery of usable cells remains a distinct outcome that must be documented.

The clinical questions therefore extend beyond whether spermatozoa can be found: they include the timing of retrieval, selection of candidates for endocrine treatment, preservation of rare cells and eventual reproductive outcomes. These distinctions are particularly relevant when interpreting a series with a low retrieval rate.

Patients and methods

Design and setting

This retrospective case series included 62 men who underwent micro-TESE over a five-year treatment period at two reproductive clinics in Tashkent, Uzbekistan. Thirty patients were treated at “ERAMED EKO” and 32 at “SIZ ONA BO’LASIZ”. Outcomes were analyzed at the patient level using aggregate clinical data. No untreated or hormonally pretreated comparison group was included.

Patients were aged 24–31 years. Klinefelter syndrome was confirmed by genetic testing showing a 47,XXY karyotype in every patient. Azoospermia was repeatedly documented: each patient had undergone at least four semen analyses showing no spermatozoa. All were diagnosed with hypergonadotropic hypogonadism. FSH values ranged from 35 to 61 mIU/mL, and reported testicular volumes ranged from 0.8 to 2.2 cm^3.

Intervention and outcomes

No preoperative hormonal treatment intended to stimulate spermatogenesis, including gonadotropin stimulation, was administered. All patients underwent micro-TESE. Following surgical sampling, testicular tissue was transferred to embryologists for examination for spermatozoa. A positive retrieval outcome was defined as identification of spermatozoa, without a specified minimum number or motility threshold. Spermatozoa recovered in the two positive cases were cryopreserved for planned in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

Histopathological findings in unsuccessful cases were summarized using the reported Johnsen score range. Individual score frequencies and the scoring method were unavailable. Age, FSH and testicular volume were summarized as ranges; means and medians could not be derived from the aggregate data.

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Statistical analysis

The retrieval proportion was calculated as the number of men with sperm identified divided by 62. A two-sided exact binomial 95% CI was computed using the Clopper–Pearson method. Outcomes were expressed as counts and percentages. No covariate adjustment, subgroup comparison or predictive modeling was undertaken because individual measurements were unavailable and only two outcomes were positive.

Consent and ethics reporting

All patients voluntarily provided informed consent for the surgical procedure. This report presents aggregate outcomes of clinical treatment without patient-identifying information. Ethics review of this analysis was not conducted.

Results

Spermatozoa were identified in 2 of 62 men (3.2%; exact 95% CI 0.4–11.2%). In each successful case, only rare spermatozoa were recovered and subsequently cryopreserved. No quantitative sperm count, motility assessment or post-thaw viability result was available.

Retrieval was unsuccessful in 60 men (96.8%). Reported Johnsen scores in this group ranged from 2 to 4. The number of patients at each score and histological findings in the two successful cases were unavailable, preventing comparison of histology by retrieval outcome.

Table 2. Clinical characteristics and micro-TESE outcomes

Characteristic	Value
Patients	62
ERAMED EKO	30 patients
SIZ ONA BO'LASIZ	32 patients
Genetic confirmation	47,XXY in all 62 patients
Confirmation of azoospermia	At least four semen analyses per patient
Age	24–31 years
Operative period	Five-year study period
Diagnosis	Klinefelter syndrome with azoospermia
Endocrine phenotype	Hypergonadotropic hypogonadism
FSH	35–61 mIU/mL
Testicular volume	0.8–2.2 cm^3
Intervention	Micro-TESE in all patients
Sperm retrieval	2/62 (3.2%)
Exact 95% CI	0.4–11.2%
Cryopreservation	Both patients with positive retrieval
No sperm retrieval	60/62 (96.8%)
Johnsen score in unsuccessful cases	2–4

The reported endpoints were sperm identification and cryopreservation. ICSI, fertilization, embryo development, pregnancy and live birth were not assessed. Perioperative complications and postoperative endocrine function were also not available; this does not establish their absence.

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Discussion

The principal finding was a patient-level retrieval rate of 3.2%, well below the approximately 44% reported in international syntheses [3,6]. This is a descriptive comparison rather than evidence of a treatment effect. The present denominator is patients, whereas the 2017 pooled estimate principally concerns TESE cycles, and extraction methods and case selection differ. The magnitude of the discrepancy warrants careful examination of the clinical and laboratory records.

Severe spermatogenic impairment is a plausible contributor, given the small reported testicular volumes, elevated FSH and low Johnsen scores in unsuccessful cases. However, these findings do not explain the discrepancy by themselves. Testicular dysfunction is also common in published Klinefelter cohorts, and neither high FSH nor small testes reliably excludes focal spermatogenesis [3,5]. Without individual data from successful and unsuccessful cases, their prognostic contribution cannot be estimated.

The Johnsen range of 2–4 describes heterogeneous histological patterns: Sertoli cells without germ cells, spermatogonia only, or a few spermatocytes without later stages [4]. It should not be collapsed into a uniform diagnosis of Sertoli-cell-only syndrome. Moreover, histology was available only for unsuccessful cases, and sampled sections may not reflect every region explored during surgery.

The absence of hormonal pretreatment cannot be assigned a causal role because there was no treated comparison group. Elevated FSH in primary testicular dysfunction does not indicate deficient gonadotropin drive, and benefit from additional FSH has not been established in this setting. Selected hypogonadal men may be considered individually for human chorionic gonadotropin (hCG) treatment, but Klinefelter-specific evidence remains limited [1,9]. The present findings therefore support neither mandatory pretreatment nor a conclusion that pretreatment is ineffective.

Limitations

The retrospective design and use of aggregate data limit assessment of selection bias and individual predictors. Although the 47, XXY karyotype and repeated azoospermia were confirmed in every patient, individual testosterone and luteinizing hormone (LH) values, testicular volume measurement methods and prior retrieval history were not available for comparative analysis. Surgical sampling and embryological search protocols were not described in sufficient detail to assess procedural variation. Only two positive outcomes preclude meaningful multivariable analysis.

The exact CI quantifies binomial uncertainty but does not address systematic differences between series. The cohort distribution by center is known, but center-specific and year-specific retrieval outcomes were unavailable. Complications and reproductive follow-up could not be assessed. The findings are specific to this cohort and cannot establish whether differences from international estimates reflect patient characteristics, hormonal management or procedural factors.

Conclusion

In this retrospective two-center series of 62 men with genetically confirmed Klinefelter syndrome and repeatedly documented azoospermia, micro-TESE identified rare spermatozoa in two patients (3.2%), permitting cryopreservation. This rate was lower than international summary estimates, but its determinants remain unresolved. The absence of a hormonal pretreatment group prevents

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conclusions about its benefit. Sperm retrieval and cryopreservation represent intermediate outcomes; subsequent reproductive success was not assessed.

AI assisted preparation

ChatGPT (OpenAI) assisted with literature synthesis, statistical calculation code, translation and manuscript drafting and editing. Patient observations were supplied independently of the AI system. Clinical interpretation and submission decisions remain the responsibility of the human authors.

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