



## Testicular Sperm Sampling by Subcapsular Orchiectomy in Klinefelter Patients: A New Simplified Treatment Approach

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<b>OBJECTIVE</b>	To evaluate subcapsular orchiectomy as a method to retrieve spermatozoa from minute testicular foci in men with Klinefelter syndrome (KS).
<b>METHODS</b>	Fourteen men with KS were consecutively recruited to unilateral subcapsular orchiectomy. Testicular tissue was dissected mechanically and enzymatically to identify possible sperm. Previous testosterone replacement therapy was interrupted for 10 months (range: 9-12 months) to minimize a possible effect on the spermatogenesis. Two men with high estrogen/testosterone ratios were treated with aromatase inhibitor (letrozol, 2.5 mg/d for 3 months) before operation.
<b>RESULTS</b>	Testicular sperm were detected in 5 of 14 KS men giving an overall success rate of 36%. The success rate was 50% (5 of 10 men) after exclusion of the 4 men previous treated with androgen substitution. So far, 3 (21%) clinical pregnancies and 2 live births or ongoing pregnancies (14%) have been obtained. Testicular sperm could not be detected in the 2 men treated with aromatase inhibitor before operation. The maximum operative time was 20 minutes, and none had surgical complications such as pain, fever, or hematomas. The mean testosterone level, measured 1-4 months after orchiectomy, decreased to 72% ( $7.9 \pm 2.4$ nmol/L) of the preoperative level.
<b>CONCLUSION</b>	Subcapsular orchiectomy appears to be easy and quick compared with conventional microtesticular sperm extraction. However, in this pilot study, it has not been possible to demonstrate pregnancy and live birth rates as high as that reported with microtesticular sperm extraction, and further studies are needed before the procedure should be used routinely for sperm retrieval in patients with KS. UROLOGY 86: 744–750, 2015. © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license ( <a href="http://creativecommons.org/licenses/by-nc-nd/4.0/">http://creativecommons.org/licenses/by-nc-nd/4.0/</a> ).

Men with Klinefelter syndrome (KS) usually present with germ cells until puberty but generally show azoospermia in adult life.<sup>1</sup> Thus, onset of puberty in KS is associated with accelerated germ cell depletion.<sup>2</sup> However, focal spermatogenesis may originate in euploid germ cell lines in such patients, although seminiferous tubules with full spermatogenesis usually appear in only very few foci.<sup>3,4</sup>

The ability to father children is often an important question to many KS patients. Using new techniques of

microtesticular sperm extraction (micro-TESE), a number of studies have shown the possibility of extracting sperm for assisted reproduction in KS men, and to date, more than 100 healthy children have been born using sperm from KS men.<sup>5</sup> In a large study including 115 men with nonmosaic KS, it was possible to find sperm in only 12 (10.3%) men by micro-TESE. However, because spermatids were detected in 50 (43.5%) of the men in this study, spermatid injections were performed.<sup>6</sup> Conversely, 2 recent reviews reported mean TESE rates of 44% in 373

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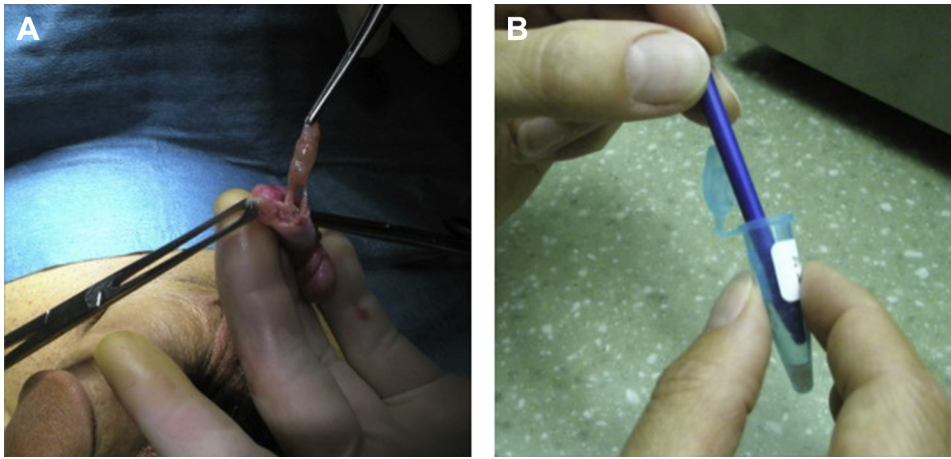
**Study Approval:** The study has been approved by the Danish Scientific Ethics Committee of Middle Jutland (M–20100041) and the Danish Data Protection Agency (2010-41-4539) and registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT 01750632).

Jens Fedder, Claus H. Gravholt, and Claus Yding Andersen designed the study. Jens Fedder performed the infertility treatment including the orchiectomies. Ann Mains Milton handled the testicular biopsies in the IVF laboratory; Stine Gry Kristensen and Claus Yding Andersen cryopreserved the testicular tissue and made the slides for microscopy. Niels Marcussen and Birte Engvad performed the histologic evaluations. All authors contributed to the final article based on a draft written by Jens Fedder.

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**Figure 1. A, B.** Testicular sperm extraction by subcapsular orchietomy. **(A)** Macroscopic picture from the operation theater. The testis tissue is blunt released from the inside the *Tunica albuginea* and removed in toto, and **(B)** Sperm extraction kit.

nonmosaic KS men<sup>5</sup> and 50% in 741 KS men,<sup>7</sup> respectively, using TESE or micro-TESE.

The collection of seminiferous tubules with active spermatogenesis from KS men is, however, a time-consuming procedure with a duration of up to 7 hours.<sup>8</sup> TESE is usually performed on the day of, the day before, or some time before oocyte aspiration. In the last case, retrieved sperm are frozen until the ART procedure. Furthermore, if repeated sperm retrievals are required, including restitution intervals in between, the initiation of androgen treatment may be postponed. Therefore, we hypothesized that unilateral orchietomy would match or increase the success of other sperm retrieval procedures by optimizing the chances of finding useful sperm for treatment and cryopreservation in an effective way and allow the KS men to start androgen substitution therapy immediately. The primary outcome of this pilot study, which has run since 2010, is presence of testicular sperm, and a secondary outcome is clinical pregnancy.

## METHODS

### Patients

The 14 patients included in the project were recruited from the public fertility clinics in Odense, Brædstrup, Skive, and Holbæk. All KS men, aged 15-40 years, who wanted to have their own biological child and participate in the orchietomy project after being informed about its limitations and possible risks could be included. The only exclusion criterion was inability to understand the information given. They were usually referred for infertility treatment due to azoospermia. Determining the karyotype, which is an obligatory part of the examination program, revealed the diagnosis. In addition to karyotype, all non-vasectomized azoospermic men are examined for Y micro-deletions in the azoospermia factor region, cystic fibrosis transmembrane conductance regulator gene (CFTR) mutations, and as minimum levels of the hormones: follicle stimulating hormone (FSH), luteinizing hormone, testosterone fractions, and prolactin are determined.<sup>9,10</sup>

The study was approved by the Scientific Ethics Committee of Middle Jutland and by the Data Protection Agency and registered

in [ClinTrials.gov](http://ClinTrials.gov). All participants provided their written informed consent. Furthermore, inclusion of participants <18 years requires written informed consent from their parents.

### Clinical Characterization

Age, height, and weight of each patient were monitored, and a clinical examination performed. Because testicular microlithiasis may reflect defective spermatogenesis,<sup>11</sup> testicular microlithiasis and echogenicity were evaluated ultrasonographically, and the testicular volumes calculated.<sup>12</sup>

### Hormonal Pretreatment

Men substituted with testosterone undecanoate given as depots (Nebido, Bayer Schering, Berlin, Germany) had their treatment discontinued in average 10 months (range: 9-12 months) before sperm retrieval, and increased FSH and luteinizing hormone values after discontinuation was verified by analyses of blood samples. Two men with abnormally high estrogen/androgen ratio were given a 3-month pretreatment with letrozol, 2.5 mg/d (Femara, Novartis, Basel, Switzerland) to optimize the hormonal conditions before operation.

### Unilateral Orchietomy

The operations were performed under general anesthesia. Furthermore, 20 mL of Lidocain (5 mg/mL; Sysgehus Apoteket Danmark, Copenhagen, Denmark) was injected around the spermatic cord (18 mL) and under the scrotal skin (2 mL).

To avoid fragmentation of the testis tissue, a longitudinal cut was performed through the skin and *Tunica albuginea* as described by Desmond et al.<sup>13</sup> The testis tissue quelling out was removed in toto by blunt dissection (Fig. 1A), put into Sperm Preparation Medium (Product No. 1069; Origio, Måløv, Denmark), and transported to the laboratory. *Tunica albuginea* and the scrotal skin were closed with Vicryl 3-0 rapid continuous and knots, respectively (Ethicon Inc., a Johnson-Johnson company).

### Sperm Harvesting From Testicular Tissue

Little pieces of testis tissue (2 × 2 × 2 mm) were prepared in the in vitro fertilization (IVF) laboratory to facilitate sperm identification. Pieces of tissue were shredded with microscope slides in

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