Outcomes of operative sperm retrieval strategies for fertility preservation among males scheduled to undergo cancer treatment

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Objective: To describe the outcomes of electroejaculation (EEJ) and testicular sperm extraction (TESE) performed for fertility preservation among male patients who are unable to ejaculate or have nonobstructive azoospermia/severe oligospermia before definitive cancer therapy.
Design: Retrospective cohort study.
Setting: Tertiary cancer referral center.
Patient(s): Forty-nine patients seeking fertility preservation before definitive cancer therapy, with anejaculation, religious or cultural objections to masturbation, azoospermia, or severe oligospermia requiring either EEJ or TESE.
Intervention(s): EEJ and TESE.
Main Outcome Measure(s): Sperm retrieval rates.
Result(s): Fifty-nine percent of patients overall and 60% of adolescents/young adults had sperm retrieved for cryopreservation. EEJ was successful in retrieving sperm in 60% of adolescents. Of all adolescents and young adults undergoing TESE, 33% had sperm retrieved for cryopreservation. No complications were reported. Chemotherapy was commenced without delay in all patients requiring it, frequently on the same day as the sperm retrieval.
Conclusion(s): EEJ and TESE can be safely and successfully used for fertility preservation before cancer therapy among boys and young adult men who are unable to provide a semen specimen or have nonobstructive azoospermia, and they should be considered in all men meeting this patient profile. (Fertil Steril® 2014;101:805–11. ©2014 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, adolescent, electroejaculation, testicular sperm extraction, cancer

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Infertility, particularly nonobstructive azoospermia, is a well recognized effect of chemotherapeutic regimens for the treatment of male patients with cancer (1–3). In the United States, ~60% of male patients aged 15–29 years experience 20-year survival after diagnosis of invasive cancer, with an almost 50% 20-year survival rate in the 30–44-year-old age group (4). Increasing survival rates are expected in the future as oncologic care continues to improve, making the likelihood of future fertility an important component of the treatment of these patients. Given these survival rates, fertility preservation among patients with newly diagnosed cancer is gaining increasing clinical attention. In addition, 43%–71% of adolescent patients and their parents, across cancer risk groups, report a concern regarding fertility potential after cancer diagnosis (5). Despite this, referral rates for fertility preservation among oncologists remain low, with recent surveys reporting only 38%–47% of oncologists providing in-depth material or referring patients to fertility specialists for patients of "child-bearing" age (6, 7).

Among post-pubertal males, fertility preservation before the use of potentially gonadotoxic chemotherapeutic and radiotherapy agents is

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frequently a straightforward procedure, consisting of cryopreservation of masturbation-assisted ejaculated semen. Obtaining semen samples by masturbation poses a clinical dilemma in some of these patients, who report having never masturbated secondary to young age, religious or cultural objections, severe pain limiting the ability to ejaculate, or anatomic derangements due to tumor mass leading to anejaculation.

Additionally, recent literature confirms that some men with cancer are already oligospermic/azoospermic before any therapeutic intervention (8, 9). The mechanism of this tumor-induced impairment in spermatogenesis is not fully understood at this time; it may be caused by local effects of testicular tumors on nearby seminiferous tubules owing to paracrine action of secretory substances of the tumor, disruption of the blood-testis barrier, endocrine effects from production of β-hCG and α-fetoprotein (AFP), and systemic responses from cytokines, including interleukins and tumor necrosis factors (10). Patients with testicular cancer may in fact be presenting along a spectrum of disease known as the testicular dysgenesis syndrome, supported by epidemiologic and histologic links between cryptorchidism, hypospadias, male infertility, and testicular cancer (11). It should be noted, however, that patients presenting with these factors are frequently normospermic, highlighting a lack of true understanding of the factors leading to subfertility in these men.

To date, sperm obtained by electroejaculation (EEJ) for cryopreservation among teenagers has been reported in only three case series, all with small patient cohorts (12–14). Similarly, testicular sperm extraction (TESE) before cancer treatment among azoospermic adults has been reported in a variety of case series, also all with small patient populations (15–20). We report our experience with surgical sperm retrieval, via EEJ and TESE, for patients unable to produce a semen specimen or with azoospermia who sought fertility preservation before definitive oncologic therapy. Additionally, we performed a subset analysis to report outcomes of surgical sperm retrieval for fertility preservation in adolescents and young adults aged 11–19 years.

MATERIALS AND METHODS

Patient Population

A retrospective review was performed of all male patients referred for evaluation for surgical sperm retrieval for fertility preservation before definitive cancer therapy at a tertiary referral cancer center. Males were referred for evaluation at a single center for surgical sperm retrieval because of inability to ejaculate (anejaculation), religious or cultural objections to masturbation, azoospermia, or severe oligospermia (<1 million sperm/mL of semen) before cancer treatment. The database was registered with, and the study approved by, the Institutional Ethics Committee.

Owing to the tertiary referral center nature of the institution, patients are frequently referred for definitive treatment on an urgent or emergent basis, rendering a complete preoperative work-up for nonobstructive azoospermia difficult to complete in all patients. Patients who were able to provide a semen specimen had at least a single semen analysis reviewed. Azoospermic and severely oligospermic patients were additionally evaluated with a karyotype and analysis for Y chromosome microdeletions when time permitted. All patients had a complete physical examination performed with assessment of Tanner pubertal stage and use of a Prader orchidometer to evaluate testicular volumes. Hormonal evaluation including total serum testosterone and FSH was obtained, when possible, before sperm retrieval. Surgical sperm retrieval was generally scheduled at the time of other surgical procedures in all patients scheduled for adjunctive procedures for cancer therapy (radical orchiectomy, insertion of a central venous access infusion device, bone marrow biopsies).

Electroejaculation

Among patients who were either anejaculatory or could not otherwise produce a semen specimen, EEJ was performed under general anesthesia. In some cases, especially among Orthodox Jewish patients, consultation was held with the patient's rabbi in an effort to define what was rabbinically permitted regarding semen retrieval. When EEJ was permitted, the procedure commenced with bladder catheterization and instillation of 30 mL sperm transport medium into the bladder. The patient was then placed in the lateral decubitus position, and a digital rectal examination and anoscopy were performed. EEJ was performed with the use of the Seager Model 14 Electroejaculator (Dalzell USA Medical Systems), by inserting a 1.25-inch transrectal probe (with longitudinally oriented electrodes). The probe was inserted and the electrodes were oriented anteriorly to be placed in contact with the rectal mucosa in the region of the prostate and seminal vesicles. A pulsatile pattern of electrical stimulation was administered with 20–25 V and 0.4–0.6 A until ejaculation occurred. Stimulations were administered in cycles of five stimulations while attention was paid to the rectal temperature. If the temperature were to rise above 37°C the procedure would be aborted. The ejaculate was collected in a sterile plastic cup with a wide mouth. This was mixed with sperm transport medium and was then evaluated for the presence of sperm with the use of phase-contrast microscopy at $\times$400 magnification. Wet preparation of the semen sample was performed by the operating surgeon at the time of EEJ to evaluate semen quality. The number of sperm and their motility were recorded. Total number of vials cryopreserved was ultimately decided by the embryologist at the local sperm bank, with a recommendation by the operating surgeon to maximize number of vials cryopreserved whenever possible. The patient was then returned to the supine position, the bladder was catheterized, and the resulting urine sample was collected. Both antegrade and retrograde specimens were sent to the sperm bank for evaluation.

Testicular Sperm Extraction

In patients in whom EEJ was not permitted for religious reasons, or in whom EEJ procured an inadequate specimen (azoospermia, or <1 sperm per 10 high-power fields,or absence of motility), or who were azoospermic or severely