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Electroejaculation as a method of fertility preservation in boys diagnosed with cancer: a single-center experience and review of the literature

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Objective: To evaluate the feasibility of electroejaculation to perform semen cryopreservation in pubertal boys before gonadotoxic therapy and to review the literature on this topic.
Design: Retrospective cohort study and review of the literature.
Setting: Academic children's hospital.
Patient(s): Boys diagnosed with cancer to whom sperm cryopreservation was offered before the start of gonadotoxic therapy.
Intervention(s): We studied the outcome of electroejaculation, including patient characteristics, hormone levels, and pretreatment semen parameters.
Main Outcome Measure(s): Semen cryopreservation.
Result(s): Pretreatment semen samples were obtained by masturbation in 106/114 boys with cancer, of which 78/106 were adequate for preservation. Electroejaculation was offered to 11 boys, of which three of 11 samples appeared adequate for preservation. Reviewing all reported electroejaculation cases in children with cancer in the literature, 13/29 (45%) cases were successful. Testosterone levels were higher in patients with successful sperm yield obtained by electroejaculation (median, 8.3 nmol/L [5.2–42.4] in successful harvests, vs. median 1.7 nmol/L [0.01–17.9] in unsuccessful harvests).
Conclusion(s): Semen cryopreservation should be offered to all pubertal boys diagnosed with cancer. If masturbation fails, electroejaculation can be considered as a useful option for semen cryopreservation and leads to adequate material for cryopreservation in about half of the cases. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Sperm cryopreservation, electroejaculation, infertility, childhood cancer

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The survival rates of childhood cancer have considerably increased over the last decades (1). Because of this prolonged survival, long-term effects of treatment have become more apparent. One of these effects is infertility (2). Treatment with high doses of alkylating agents, testicle irradiation with doses >1.2 Gy, and total body irradiation before hematopoietic stem cell transplantation are risk factors for infertility later in life (3).

To preserve fertility, pretreatment sperm cryopreservation can be offered to boys diagnosed with cancer to give these boys the chance to father their own offspring. However, young patients are especially frequently unable to produce sperm by masturbation. In

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adults diagnosed with cancer, neurological diseases, and paraplegia, electroejaculation has been found to be a useful alternative (4, 5). In children diagnosed with cancer, only limited information on the feasibility and efficacy of electroejaculation is available (4–7). Here we provide an overview of semen cryopreservation after the introduction of electroejaculation in boys with cancer. Second, we present a narrative literature review on outcome of electroejaculation in childhood cancer patients.

MATERIALS AND METHODS

Subjects

From January 1998 to March 2013 semen cryopreservation was offered to boys above the age of 10 years with a Tanner stage $\geq$G2P2 before the start of their anticancer treatment at the Erasmus-MC Sophia Children's Hospital. The electroejaculation procedure was offered from 2003 onward if sperm production by masturbation was not possible because of motor disabilities or early puberty (primarily) or if no ejaculation was obtained by masturbation after multiple attempts owing to, for example, stress or early puberty (secondary). For the current analysis, patients with previous gonadotoxic therapy as well as patients diagnosed with a brain tumor were excluded. Patients were categorized into five diagnosis groups: leukemia/non-Hodgkin lymphoma, Hodgkin lymphoma, sarcoma/primitive neuroectodermal tumor (PNET), testicular tumors, and other tumors. Part of the described cohort of childhood cancer patients (diagnosed from 1995 to 2005) was described elsewhere (8). Data described in the current retrospective study were assessed using the standard guidelines following good clinical practice in our center. This study is exempt from requiring formal ethical approval according to the local Institutional Review Board. Informed consent for registration of all clinical data from every patient who visited the outpatient clinic were obtained according to Institutional Review Board standards.

Methods

Retrospectively, clinical data were retrieved from patient record files. Data were collected on age at diagnosis, type and stage of disease, therapeutic modalities, B-symptoms (fever for 3 consecutive days, drenching night sweats, and weight loss exceeding 10% of body weight in 6 months), feasibility of ejaculation and masturbation at diagnosis, Tanner stage, testicular volume, and reproductive hormone levels. Tanner stage was assessed clinically at diagnosis and classified as prepubertal (Tanner stage 1), midpubertal (Tanner stage 2–3), or late pubertal (Tanner stage 4–5) (9).

Endpoints were type and quality of ejaculate, semen volume, concentration, sperm count, morphology, progressive motility, pH, vitality, leukocytes (present or not), number of round cells, as defined by the 5th World Health Organization (WHO) manual for semen analysis (10), and number of straws cryopreserved. Semen volume of 1.5 mL, total sperm number of 39 $\times$ 10^6/ejaculate, sperm concentration of 15 $\times$ 10^6/mL, total motility of 40%, progressive motility of 32%, vitality (live spermatozoa) of 58%, sperm morphology (normal forms) of 4%, and pH $\geq$7.2 are considered normal values (10). Oligospermia was defined as the total number or concentration of spermatozoa below the lower reference limit (39 $\times$ 10^6/ejaculate and 15 $\times$ 10^6/mL, respectively). Azoospermia was defined as absence of spermatozoa in the ejaculate (10). Regardless of meeting the WHO criteria, semen samples were defined to be adequate for cryopreservation if any motile spermatozoa were identified, since ultimately only a few motile spermatozoa are needed for assisted reproductive techniques (ART). To compare our results with previous studies and because none of the patients appeared to produce an adequate semen sample after an unsuccessful first attempt, the endpoint "successful semen cryopreservation" was based on the first attempt.

The electroejaculation procedure was commenced under general anesthesia as previously described by inserting a transrectal probe in contact with the prostate and seminal vesicles (4, 5, 7). The procedure was combined with other procedures for oncological treatment that needed to be performed under general anesthesia, such as insertion of a central venous access line.

Serum Hormone Levels

During the diagnostic phase, before the start of anticancer therapy, peripheral blood samples were obtained for analysis of serum hormone levels. Inhibin B levels were measured using kits purchased from Serotec Ltd. Within-assay and between-assay coefficients of variation (CV) were $<$9%, and $<$15%, respectively. Serum FSH and LH were determined with the Immulite assay (Diagnostic Products Corporation [DPC]). Reference values of LH, FSH, inhibin B, and testosterone (T) are 1.5–8.0 U/L, 2.0–7.0 U/L, 150–400 ng/L, and 10.0–30.0 nmol/L, respectively (11). Within-assay and between-assay CVs were $<$6% and $<$9%, and $<$5% and 11% for FSH and LH, respectively. Serum T levels were determined using coated tube radioimmunoassays (DPC). Intra-assay and inter-assay CVs were 3% and 4.5%.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 20.0. Data were presented as median, range, or percentages. Mann-Whitney *U* nonparametric test was used to compare the characteristics of patients with and without successful cryopreservation (masturbation only). $P<.05$ was considered statistically significant.

Literature Review

A literature search on electroejaculation was conducted in July 2013 using Embase, PubMed, Medline Ovid SP, Cochrane, Web of Science, and Google Scholar. The following key words and their synonyms were used: male, neoplasms, child, fertility, sperm, electric stimulation, and cryopreservation. Studies were eligible for selection if cryopreservation by electroejaculation was described, patients were aged between 10 and 19 years at diagnosis, individual data of the described cases were included, and the manuscript was published in a peer-reviewed scientific journal written in the English or