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;102:199–205. ©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 39×10^6/ejaculate, sperm concentration of 15×10^6/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 (39×10^6/ejaculate and 15×10^6/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

Dutch language. After removing duplicates, the authors screened titles and abstracts to select eligible studies. Full text papers were obtained of the selected abstracts and were excluded if studies did not meet the inclusion criteria. If not included initially, cross-references picked up during the review procedure were also selected. The complete search strategy is available on request.

RESULTS

Between 1998 and 2013, semen cryopreservation was offered to 114 boys diagnosed with cancer. Cryopreservation attempts by masturbation were reported in 106 boys with cancer (93%) before treatment. Of these boys, 57 patients had one attempt, 46 had two attempts, and three patients had three attempts. However, not all attempts were adequate for cryopreservation. In total, 78/106 (68%) patients had semen samples that were adequate for cryopreservation, while 18 patients (16%) had immotile spermatozoa or absent spermatozoa and 10 patients (9%) were not able to produce an ejaculate by masturbation (Table 1). None of the eight patients with an unsuccessful first attempt were able to produce an adequate consecutive semen sample at a new attempt. 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.

Electroejaculation was offered to a selection of 11 patients (10%). Of these, eight patients were offered electroejaculation primarily because of, for example, motor disabilities or early puberty (≥genital development [G] 2 pubic hair development [P] 2 but small testicular volume and no nocturnal ejaculations); three patients were offered electroejaculation secondarily because they initially failed to produce adequate semen by masturbation after at least two attempts. Patient characteristics are listed in Table 1. Of the eight patients who received electroejaculation primarily, two (25%) produced a semen sample adequate for cryopreservation. In the selected three cases with secondary electroejaculation, one case produced an adequate semen sample.

Patients with adequate sperm yield retrieved by masturbation or electroejaculation were significantly older at time of diagnosis compared with patients without adequate sperm yield (median, 16.6 years [10.8–18.9] vs. median, 16.0 years [12.0–18.3]; $P=.02$).

Levels of FSH, LH, inhibin B, and T from patients with adequate sperm yield retrieved by masturbation did not significantly differ from those of patients with no adequate sperm yield.

Literature Review

The literature search on electroejaculation in children with cancer identified 1,979 articles. After removing duplicates, 1,112 reports were screened for title and abstract. Eighteen reports met the inclusion criteria and were retrieved for further assessment. Of the selected studies, a cross-reference of related articles, references, and citing articles was performed; this yielded no further manuscripts for inclusion (Supplemental Fig. 1). Ultimately, the literature search revealed four manuscripts (Table 2). Including our 11 cases, in total 29 cases were evaluable.

The median age at diagnosis of the boys who underwent electroejaculation was 14.0 years (12.0–18.0), median Tanner stage was 3.0 (range 2.0–5.0), and median testicular volume of cases with available information (n = 13) was 10.0 mL (6.0–20.0). The 29 patients were diagnosed with leukemia/NHL (5/9 successful), HL (2/9 successful), sarcoma/PNET (4/9 successful), and testicular tumors (2/2 successful). In total, 13/29 (48%) of these selected patients produced semen samples that fulfilled the criteria required for cryopreservation.

Hormone levels at time of cryopreservation were measured in 20/29 patients. Median FSH level was 2.1 (0.01–6.7) UI/L, median LH level was 1.45 (0.01–4.9) UI/L, median inhibin B level was 249.0 (56.0–320.0) ng/L, and median T level was 4.7 (0.01–42.4) nmol/L. Median semen volume was 0.4 (0.02–6.1) × 10^6 mL, median sperm concentration

TABLE 1

Characteristics of boys referred for cryopreservation of semen.

	Cohort (n = 114)	Conservative cryopreservation (n = 106)	Electroejaculation		
			Total (n = 11)	Successful (n = 3)	Unsuccessful (n = 8)
Age	16.3 (10.8–18.9)	16.5 (10.8–18.9)	13.7 (12.0–16.0)	13.8 (12.6–16.0)	13.3 (12.0–16.0)
Tanner					
Genital development	4 (2–5)	4.5 (3–5)	3 (2–5)	3 (2–5)	3 (3–5)
Pubic hair development	4 (2–5)	4.5 (3–5)	3 (2–5)	3 (2–5)	3 (2–5)
Testicular volume (mL)					
Left	13.5 (6.0–20.0)	14.3 (8.0–20.0)	9.5 (6.0–15.0)		9.5 (6.0–15.0)
Right	12.8 (6.0–20.0)	13.5 (8.0–20.0)	9.5 (6.0–15.0)		9.5 (6.0–15.0)
Semen analysis					
Volume (×10^6 mL)	1.1 (0.0–4.5)	1.1 (0.0–4.5)	0.4 (0.02–3.0)	0.4 (0.4–0.4)	0.4 (0.02–3.0)
Concentration (×10^6/mL)	14.0 (0.0–323.0)	15.0 (0.0–323.0)	2.0 (0.1–14.5)	2.0 (0.1–5.5)	2.0 (0.1–14.5)
Motility (%)	29.0 (0.0–69.0)	29.0 (0.0–69.0)	1.0 (0.0–4.0)	3.0 (2.0–4.0)	0
pH	7.6 (6.4–8.0)	7.7 (7.1–8.0)	7.3 (6.4–8.0)	7.9	7.0 (6.4–8.0)

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TABLE 2

Case series and reports of EE in boys with cancer preceding treatment.

Author and year	Study design	Age at EE	Diagnosis	Tanner stage	Testis V	T (UI/L)	Semen analysis	Adequate yield
Schmiegelow et al. (5) 1998	Case report	14	Relapse of pre-B ALL	G3P3	20–25 mL	NA	A: V 0.7 mL; M 1%; R: C 1.6 × 10^6/mL; M 5%	+
Muller et al. (6) 2000	Cohort study	13	NHL	>3	NA	NA	V 0.8 mL; C 75 × 10^6/mL; M 38%	+
		14	ALL relapse	>3	NA	NA	V 3.2 mL; C 4.0 × 10^6/mL; M 10%	+
Hovav et al. (4) 2001	Cohort study	15	Ewing sarcoma	NA	NA	NA	R: C 15 × 10^6/mL; M 6%	+
		15	Osteosarcoma	NA	NA	NA	R: C 24 × 10^6/mL; M 53%	+
		17	Osteogenic sarcoma	NA	NA	NA	A: C 0.65 × 10^6/mL; M 0%; R: C 9 × 10^6/mL; M 0%	–
		18	TGCT	NA	NA	NA	A: C 35 × 10^6/mL; M 33%	+
Hagenas et al. (7) 2010	Cohort study	12.7	HL	G5P4	8 mL	0.0	V 0.1 mL; C 0 × 10^6/mL; M 0%	–
		12.9	HL	P3	15 mL	8.0	V 1.3 mL; C 5.5 × 10^6/mL; M 15%	+
		13.8	Ewing sarcoma	G4	NA	4.1	V 0.1 mL; C 0 × 10^6/mL; M 0%	–
		13.9	Lymphoma	G3P4	8 mL	NA	V 0.1 mL; C 0 × 10^6/mL; M 0%	–
		14	Lymphoma	P5	20 mL	12.5	V 0.8 mL; C 99 × 10^6/mL; M 27%	+
		14.3	RMS	G4	15 mL	5.2	V 0.5 mL; C 0.3 × 10^6/mL; M 14%	+
		14.4	Osteosarcoma	P4	10 mL	13.1	V 6.1 mL; C 0.1 × 10^6/mL; M 0%	–
		14.5	Osteosarcoma	G3P3	10 mL	NA	V 0.03 mL; C 0 × 10^6/mL; M 0%	–
		15	HL	NA	NA	1.4	V 0.4 mL; C 0.24 × 10^6/mL; M 0%	–
		15.3	RMS	P5	15 mL	1.6	V 2.6 mL; C 0.8 × 10^6/mL; M 0%	–
		17.3	Testicular cancer	NA	8 mL	42.4	V 1.8 mL; C 0.1 × 10^6/mL; M 10%	+
This study	Retrospective cohort study	12.7	HL	G3P3	NA	3.1	V 0.4 mL; C 0 × 10^6/mL; M 0%	–
		13.0	HL	NA	6 mL	0.6	C 0 × 10^6/mL; M 0%	–
		14.6	HL	P2-3	10 mL	1.7	C 14.5 × 10^6/mL; M 0%	–
		15.9	HL	G3P3	9 mL	1.4	V 0.3 mL; C 0.1 × 10^6/mL; M 0%	–
		16.0	B-NHL	G5P5	NA	20.1	V 0.4 mL; C 2.0 × 10^6/mL; M 4%	+
		12.0	T-ALL	NA	NA	17.9	C 0 × 10^6/mL; M 0%	–
		13.7	B-NHL	NA	15 mL	3.4	V 1.9 mL; C 2.0 × 10^6/mL; M 0%	–
		12.5	Osteosarcoma	G3–4 P3–4	NA	7.4	V 0.4 mL; C 0.1 × 10^6/mL	+
		15.0	ALL	G5P5	NA	6.0	V 0.02 mL; C 0 × 10^6/mL; M 0%	–
		13.8	HL	G2P2	NA	8.3	V 0.4 mL; C 5.5 × 10^6/mL; M 2%	+
		12.0	HL	NA	NA	0.4	V 3.0 mL; C 0 × 10^6/mL; M 0%	–
Total		14.3						13/29

Note: EE = electroejaculation; A = antegrade ejaculation; R = retrograde ejaculation; V = volume; C = concentration; M = motility %; pre-B ALL = precursor B-cell acute lymphoblastic leukemia; NHL = non-Hodgkin lymphoma; TGCT = testicular germ cell tumor; HL = Hodgkin lymphoma; RMS = rhabdomyosarcoma; T-ALL = T-cell acute lymphoblastic leukemia; G = genital development; P = pubic hair development; NA = not available.

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TABLE 3

Characteristics of semen cryopreservation of patients who underwent electroejaculation (n = 29).

	n	Successful yield (n = 13) (range)	n	No successful yield (n = 16) (range)
Age (y)	13	14.0 (12.5–18.0)	16	14.2 (12.0–17.0)
Tanner stage G	7	3 (2–5)	8	3.5 (3–5)
Tanner stage P	8	3 (2–5)	8	3.5 (2–5)
Testicular volume (mL)	4	15.0 (8.0–20.0)	9	10.0 (6.0–15.0)
FSH (UI/L)	7	2.1 (0.01–5.2)	12	1.9 (0.5–6.7)
LH (UI/L)	7	1.6 (0.01–4.9)	13	1.2 (0.5–4.1)
Inhibin B (ng/L)	7	277.0 (56.0–299.0)	13	194.0 (72.0–320.0)
T (nmol/L)	7	8.3 (5.2–42.4)	13	1.7 (0.01–17.9)

Note: Semen cryopreservation was defined to be successful if motile spermatozoa were found and subsequently banked.

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was 0.3 (0–99.0) × 10^6 mL, and median sperm motility was 0% (0.0%–53.0%). Electroejaculation was successful in 2/8 cases (25%) to whom it was offered primarily and in 11/21 cases (52%) to whom it was offered secondarily (Table 3).

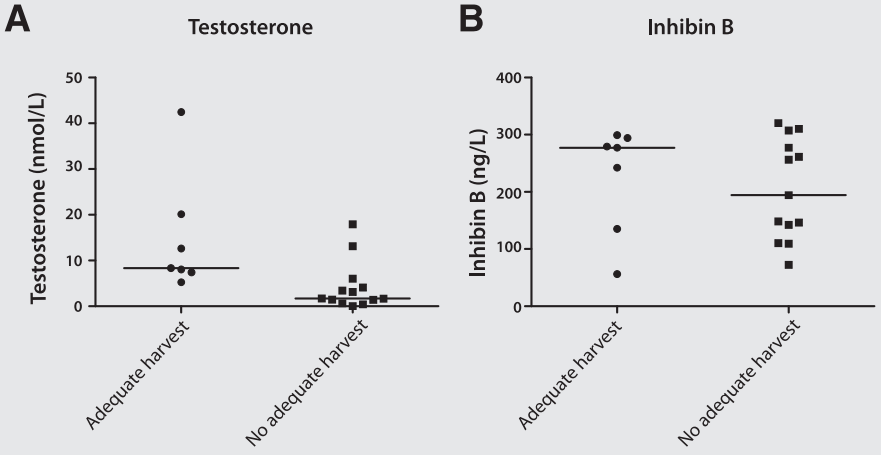
No differences in age, Tanner stage, and testicular volume between cases with and without adequate sperm yield were found (Table 3). In addition, hormone levels were similar in the two groups, except for T, which seems higher in patients with an adequate sperm yield by electroejaculation, that is, respectively, median, 8.3 nmol/L (5.2–42.4) versus 1.7 nmol/L (0.01–17.9; Fig. 1). FSH, LH, and inhibin B levels were not different in cases with and without adequate sperm yield (Table 3).

DISCUSSION

It has become good clinical practice to offer cryopreservation of semen in pubertal boys with cancer before starting gonadotoxic treatment to allow them the possibility to father their own genetic child. Adolescent males with cancer have been reported to be good candidates for sperm banking (12–14). Currently, according to the literature, approximately 77% of boys aged 12–18 years with new or relapsed cancer are offered sperm banking before start of therapy (15), and 28%–69% of these patients attempt to cryopreserve semen (15, 16), of which approximately 65% are successful (15, 17). In our cohort of 106 cases who were able to produce a semen sample by masturbation, a similar success rate of 74% was found.

Electroejaculation is an alternative technique to cryopreserve semen, but so far, information on the success of electroejaculation procedures in children is scarce. Summarizing all available information on reported cases, including the present study, 45% of the procedures resulted in a yield that was sufficient for banking. Although this represents a selected series, this illustrates that electroejaculation is a meaningful sperm harvest alternative for young boys who are not able to produce a semen sample by masturbation. It has to be emphasized, however, that only one out of 29 cases produced a sufficient semen sample according to the WHO criteria. Nevertheless, 13/29 patients had semen samples stored, as motile spermatozoa were present and, currently, potential pregnancies can be achieved in intracytoplasmic sperm

FIGURE 1



Hormone levels of patients who underwent electroejaculation (n = 20/29). Lines indicate median values. Mann-Whitney *U*-test showed a significant difference for T between the two groups. Semen cryopreservation was defined to be successful if motile spermatozoa were found and subsequently banked.

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injection programs with only a few functional spermatozoa (18, 19). However, the cryopreserved semen of our study has not yet been used for ART because of the young age of the patients. To our knowledge, it is not known whether such programs will ultimately be of help in childhood cancer survivors, since no data on pregnancy outcome of the cryopreserved semen of childhood cancer patients are available, but this would be very interesting to study. In survivors of adult males with cancer, approximately 18%–46% of ART cycles resulted in pregnancy (20–22) and 75% of the pregnancies resulted in a living birth (20, 22). A registry documenting sperm banking in childhood cancer patients as well as follow-up data on the usage of cryopreserved sperm and pregnancy outcome of these patients would be of utmost value.

In the selection of children to whom electroejaculation should be offered, the efficacy, costs, and medical and psychological burden of electroejaculation should be carefully weighed. For that reason, identifying predictive factors for a successful yield would be of great value. It is obvious that, based on current knowledge in this small series, evidence-based guidelines cannot be provided. Although numbers are too small to draw firm conclusions, our study suggests that T may be a valuable predictor for a successful sperm yield retrieved by electroejaculation. In addition, Tanner stage and age may be used as useful parameters for considering electroejaculation. We show that even in cases with early puberty (G2P2), electroejaculation may be feasible, and especially in these patients, T may guide the decision. Additionally, the patients' emotional and sexual development should also play an important role in the decision to offer cryopreservation by electroejaculation.

If both masturbation and electroejaculation fail to retrieve adequate semen for cryopreservation, it seems reasonable to perform testicular sperm extraction (TESE) under general anesthesia in pubertal patients. However, clinical experience of TESE in boys with newly diagnosed cancer is scarce. A recent study suggests that TESE can be safely and successfully used for fertility preservation (23). However, an adequate threshold for inclusion and the efficacy and safety of (more extensive) TESE in young mid- and postpubertal patients should be further evaluated in clinical trials before implementation in daily clinical practice.

There is a difference in banking percentage between the literature and our patients. Although this might be caused by the small numbers included in the studies, it may also be caused by a selection bias in patient selection and indication, the unknown threshold in particular. There is no clear threshold yet for the indication of electroejaculation. Patient diagnoses as well as the severity of the disease at presentation vary. In general, referral for semen cryopreservation is based on the doctor's opinion. These opinions may differ between doctors. Finally, all studies were not intended as cohort studies, and all but one previous study included less than five patients. Hagenas et al. (7) included 11 patients, of which semen quality was sufficient for cryopreservation in four cases, resulting in a success rate of 36%, which is in line with our results. Larger studies are needed to present a more accurate success rate.

Unfortunately, prepubertal boys with cancer are unable to produce an adequate ejaculate by masturbation or electroejaculation owing to immature spermatogenesis. TESE can be used in pubertal boys (23–25) but is still not an option for prepubertal boys. Retrieving spermatogonial stem cells by testis biopsies to preserve fertility in prepubertal boys needs to be further developed (25, 26). Issues such as tumor contamination, testis hemorrhage after biopsy, and the delay of starting treatment waiting for such procedures should be included in the further development of clinical practice guidelines by pediatric oncologists and fertility preservation experts.

We conclude that all pubertal boys with cancer should be offered semen cryopreservation before gonadotoxic therapy has started from Tanner stage G2P2 on. If masturbation fails, electroejaculation can be considered as a useful option for semen cryopreservation because it leads to adequate material for cryopreservation in about half of the cases.

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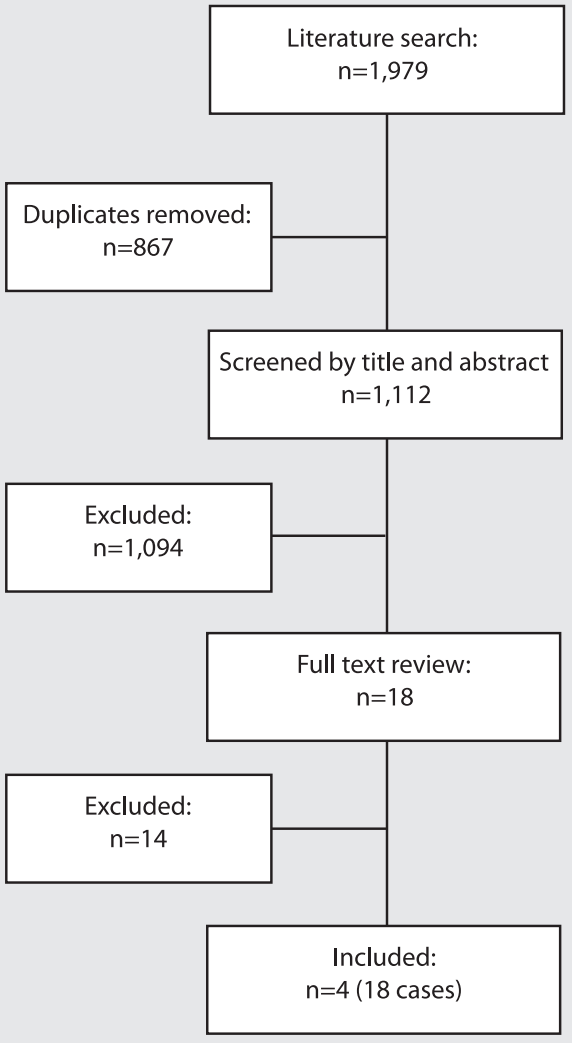
SUPPLEMENTAL FIGURE 1



Flowchart of literature search.

Adank. Electroejaculation in boys with cancer. Fertil Steril 2014.