CME

Elevated follicle-stimulating hormone levels and the chances for azoospermic men to become fathers after retrieval of elongated spermatids from cryopreserved testicular tissue

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Objective: To assess individual chances for a live-born child in azoospermic men by performance of testicular sperm extraction (TESE) followed by intracytoplasmatic sperm injection (ICSI).
Design: A retrospective cohort study.
Setting: An academic fertility care center and research unit.
Patient(s): Two hundred three couples who wished to have a child; all men had azoospermia.
Intervention(s): All men were operated for TESE; 112 men were found to have elongated spermatids (ES), and 209 ICSI cycles were performed in these men using cryopreserved tissue.
Main Outcome Measure(s): Predictors for the chances to obtain live sperm and for probabilities of fertilization, clinical pregnancies, and live births.
Result(s): Testicular volume, FSH, and inhibin B levels were predictors for the presence of ES. Intracytoplasmic sperm injection resulted in 23 pregnancies, leading to 20 live births. Despite the presence of ES and performance of ICSI in cases of FSH levels ≥20 IU/L, no pregnancy resulted in these men (n = 21). Receiver operating characteristics revealed FSH levels of ≥20 IU/L as cutoff for treatment success. The number of testicular tubuli containing ES served as a predictor for clinical pregnancy as well as for live birth. Cigarette smoking by the male partner exerted a significant negative influence on treatment success.
Conclusion(s): The degree of completely maintained spermatogenesis within the biopsy appears to reflect intrinsic abilities of spermatozoa to induce normal embryo development. Charts based on regression models are presented for counseling patients before TESE; these explain chances of finding ES and probability of successful ICSI. Obtaining offspring is unlikely in cases of azoospermia and of FSH levels of ≥20 IU/L. (Fertil Steril® 2006;86: 339–47. ©2006 by American Society for Reproductive Medicine.)

Key Words: Intracytoplasmic sperm injection, ICSI, testicular sperm extraction, TESE, assisted reproduction, success rate, predictors, FSH

The first child conceived by intracytoplasmic sperm injection (ICSI) after testicular sperm extraction (TESE) was born in 1995 (1). This achievement offered patients with azoospermia a reasonable chance for a child of their own (2–6). However, accurate estimation of chances for such a successful procedure remains elusive, as does prediction of the presence of elongated spermatids in testicular tissue by noninvasive parameters, thus making reasonable assessment and counseling before the operation difficult.

Several studies relate the outcome of ICSI to testicular sperm from patients with either obstructive or nonobstructive azoospermia. Although some investigators found significantly reduced fertilization rates and also found reduced pregnancy rates in nonobstructive cases (7–9), other investigators described a lower fertilization rate without effect on the pregnancy rate (6, 10, 11) or no significance in fertilization or pregnancy rates at all (12).

The definition of azoospermia as obstructive is clear-cut in clinical terms: normal testicular volume, normal FSH levels, and reduced seminal markers of the accessory glands. These requirements are met most often in cases of postvasectomy or congenital bilateral aplasia of the vasa deferentes (CBAVD). Nevertheless, not every patient presenting with azoospermia can have his disorder designated definitely as obstructive or nonobstructive, because clinical and histological pictures often exhibit a mixed pattern. Thus, dividing patients into two groups may impede data evaluation. Azoospermic men with deletions of genes in the AZF regions of the Y chromosome may be considered nonobstruc-

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tive, but can, nevertheless, exhibit clinical features such as normal FSH concentrations and normal testis size, thus mimicking an obstructive cause (13).

Also, vasectomy, the most obvious cause of obstructive azoospermia, can be accompanied by a significant impairment of spermatogenic efficacy. This time-dependent effect also can cause FSH levels of vasectomized men to increase with the duration of the obstructive interval, even into the supernormal range (14). Rather, parameters describing azoospermia, such as histological findings, as well as noninvasive measures such as testicular volume and FSH levels, constitute a continuous spectrum comprising the diagnosis of azoospermia. We have demonstrated elsewhere that noninvasive parameters are associated with histological findings in testicular tissue (15).

In contrast to the use of descriptive terms, we examined how a histologically confirmed degree of spermatogenic impairment (representing a continuous variable) relates to the outcome of ICSI that is performed with TESE samples. The hypothesis of our study was that the outcome of ICSI with spermatids from tissue samples with poor spermatogenesis would be worse than would results from samples with more effective spermatogenesis; this would confirm that impaired fertilization abilities and aberrant embryo development are a function of the quality and degree of spermatogenesis. Endpoints of this investigation were presence of elongated spermatids, fertilization rate of oocytes, and clinical pregnancies and live births.

MATERIALS AND METHODS

Patients

Two hundred three azoospermic men underwent testicular biopsies for histology and TESE, if possible. In 91 men, no elongated spermatids were found. In the remaining 112 couples, 209 TESE-ICSI cycles were performed. Testicular tissue was cryopreserved in all cases, and in the TESE cycles, only elongated spermatids were used. The use of fresh testicular material for ICSI implies the preoperation hormonal stimulation of the female partner, with all its financial burdens and physical risks.

Because only about 50% of our patients have elongated spermatids and we cannot completely predict the presence of these cells, we refrain from using fresh biopsy material. We only perform such a procedure in men who have sperm previously present in the ejaculate but have no useful sperm found at the time of ovum pickup. Only then would an emergency TESE be performed and fresh biopsy material be used. Such patients are rare and are not included in this analysis. Earlier, all male patients underwent a clinical examination that included ultrasonography of scrotal contents, hormones, and semen parameters (16). Female partners had provided blood for hormone analysis in previous cycles and underwent a physical examination; all women had apparently normal reproductive functions.

All couples were counseled by human geneticists. All patients gave written informed consent for the use of their data for scientific evaluation as approved by the ethics committee (local institutional review board) of the University of Münster and by the State Medical Board, Münster, Germany.

Considering the success rates, it has to be kept in mind that in Germany, a maximum of three embryos can be produced, and embryo selection is against the federal embryo protection law.

Levels of FSH

Serum levels of FSH were determined by highly specific time-resolved fluoroimmunoassays (Autodelfia, Perkin-Elmer,

TABLE 1

Diagnostic overview of the 203 azoospermic men involved in this study, data as median and (range; not normally distributed values).

Diagnosis	No. of elongated spermatids present/total	% of Tubuli with complete spermatogenesis in the more intact testis	FSH in IU/L	Inhibin B in pg/mL
Idiopathic azoospermia	95/179	26 (0–100)	11.4 (1.2–47.8)	81 (7.8–273)
AZFc deletion of the Y chromosome	0/5	0 (0–0)	15.1 (4.5–28.6)	50 (22–100)
Klinefelter's syndrome	0/2	0 (0–0)	14.7 (14.5–14.8)	30 (13–47)
CBAVD	7/7	87 (7–98)	3.3 (1.7–4.9)	142 (49–199)
Ejaculation disorders	6/6	42 (29–94)	4.5 (2.0–12.7)	115 (25–154)
Postvasectomy	4/4	88 (66–93)	6.1 (3.7–8.8)	98 (40–199)
All	112/203	29 (0–100)	9.4 (1.2–47.8)	83 (7.8–273)

Note: AZFc = ; ejac = ejaculate.

Zitzmann. Chances for fatherhood in azoospermia. Fertil Steril 2006.

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