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High serum FSH levels in men with nonobstructive azoospermia does not affect success of microdissection testicular sperm extraction

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Objective: To evaluate the outcomes of microdissection testicular sperm extraction (micro-TESE) in patients with high FSH.
Design: Clinical retrospective study.
Setting: Department of urology at a tertiary university hospital.
Patient(s): Seven hundred ninety-two men with nonobstructive azoospermia.
Intervention(s): Micro-TESE followed by intracytoplasmic sperm injection was performed. The men were classified into four groups based on serum FSH levels: <15, 15–30, 31–45, and >45 IU/mL.
Main Outcome Measure(s): Sperm retrieval, clinical pregnancy, and live birth rates.
Result(s): Testicular sperm were successfully retrieved in 60% of the men. Sperm retrieval rates in the groups of men with FSH values 15–30, 31–45, and >45 IU/mL was 60%, 67%, and 60% respectively; this was higher than the group of men with FSH < 15 (51%). Of those men who had sperm retrieved, clinical pregnancy and live birth rates were similar in the four groups (46%, 50%, 52%, 46% and 38%, 45%, 44%, 36%, respectively).
Conclusion(s): The chances of sperm retrieval using micro-TESE is just as common, if not better for men with elevated FSH levels than for men with lower FSH. Micro-TESE results appear to differ from earlier series that report low retrieval rates with random biopsies for men with elevated FSH. High FSH is not a contraindication for micro-TESE. (Fertil Steril® 2009;92:590–3. ©2009 by American Society for Reproductive Medicine.)

Key Words: Azoospermia, testis, biopsy, FSH, microdissection, TESE, predictors, pregnancy

Microdissection testicular sperm extraction (micro-TESE) has become a recognized procedure for men with nonobstructive azoospermia (NOA). Simultaneous TESE–intracytoplasmic sperm injection cycles expose the couple to an emotional and financial burden, so it would be beneficial to predict the success of sperm retrieval using noninvasive parameters before attempted treatment. An important preoperative serum parameter studied in the first years of TESE was FSH. In general, the serum concentration of FSH is inversely correlated with impairment of spermatogenesis. Recent studies have shown that elevated FSH levels have been associated with a low probability for the retrieval of spermatozoa in men (1) and lower pregnancy rates in their female partners (2) using random biopsy TESE techniques. These studies propose that patients be counseled against undergoing TESE if they have abnormal FSH values, because their chances of sperm retrieval will be lower.

Serum FSH is an indirect reflection of the global (spermatogenic) function and histology of the testis as a whole. Therefore, FSH may predict the presence of sperm at random biopsy using conventional TESE techniques (3–6). In distinction, microscopic dissection TESE (micro-TESE) is based on the principle of identifying the most advanced pattern, not necessarily the predominant pattern, of spermatogenesis in the testis. Although FSH reflects the predominant pattern of spermatogenesis, it may not reflect isolated areas of spermatogenesis within the testis. Thus, micro-TESE has been shown to be more successful in sperm retrieval than a single biopsy or multiple random biopsies (7, 8). The primary aim of the present study was to evaluate the outcomes of micro-TESE, primarily the sperm retrieval, clinical pregnancy, and live birth rates in patients with elevated serum FSH. We also analyzed the predictive value of FSH, biopsy histology, testicular volume, and male age for retrieving testicular sperm by micro-TESE in NOA men.

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MATERIALS AND METHODS

Patients

The study group consisted of 792 men with NOA who underwent micro-TESE by a single urologist over a 9-year period between 1997 and 2006. Azoospermia was confirmed by

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analysis of two different specimens according to World Health Organization guidelines (9). An additional centrifuged semen sample was confirmed to be azoospermic on the day of the planned TESE. Testicular volume was measured by physical examination using an orchidometer and the volume of the larger testis was used for analysis. FSH was measured by Access chemiluminescent immunoassay with detection limits of 0.05 IU/L and intraassay and interassay coefficients of variation of <3% and <5%, respectively. The reference range of FSH levels is 1.3 to 19.4 IU/mL. The men were classified into four groups based on FSH values in increments of 15 IU/mL. Clinical pregnancy in their female partners was defined by identification of gestational sac in which a fetal heartbeat could be seen on transvaginal ultrasound examination 6 weeks after embryo transfer. Confirmation of live birth was obtained by telephone interviews of couples who were identified with clinical pregnancy. The study protocol was exempt from review at the Institutional Review Board of Weill Cornell Medical College.

Microdissection TESE

The procedure has been described previously (10). Briefly, a midline incision was made in the scrotum, and the scrotal content was pushed out preferentially from the side of the larger testis. The tunica vaginalis was opened and the testis covered with the tunica albuginea was visualized. The remainder of the procedure was performed under an operative microscope.

After the tunica albuginea was opened, direct examination of the testicular parenchyma was performed at ×12 to ×18 magnification. The examination included as much of the testicular parenchyma as possible. Small samples (5–10 mg) were excised from the larger, more opaque tubules. Each sample was examined immediately for the presence of the testicular spermatozoa by placing a small droplet of dispersed tissue suspension on a glass slide under a phase-contrast microscope at ×200 magnification. If no spermatozoa were identified in the initial sample, subsequent samples were taken from the same testis and, if needed, from the contralateral testis. Dissection was performed through all regions of testicular tissue, preserving the testicular blood supply. After the TESE procedure, the best testicular samples were pooled in 5 mL tubal fluid medium and subjected to centrifugation at 1800*g* and examined carefully for the presence of even a single spermatozoon. The procedure was terminated when spermatozoa were retrieved or when further dissection was thought likely to jeopardize the testicular blood supply.

Statistical Analysis

Data were analyzed using Stata version 9 (Stata Corp., College Station, TX). Student *t* test (unpaired) was used to compare mean log-transformed FSH levels for the outcome of sperm retrieval. Multiple logistic regression was used to assess the association between FSH and success of sperm retrieval, adjusting for potential confounding variables, including testicular volume, biopsy histology, and age. Confounding variables were included if they satisfied the criteria of changing the estimated association between FSH and sperm retrieval by at least 10%. This resulted in a final model that included biopsy histologic pattern and FSH level. Two-tailed *P* values of <.05 determined statistical significance. The area under the receiver operating curve (AUC) was generated to assess the predictive accuracy of selected predictors on likelihood of retrieving sperm, with a value of 0.5 indicating no predictive power and 1.0 indicating perfect prediction.

RESULTS

Testicular sperm was successfully retrieved in 60% of the men (ages 21–78). The mean FSH in the group that failed to retrieve sperm (20.0 IU/mL, 95% CI 17.5–20.3) was not significantly different (P=.24) from the group with successful retrieval (18.8 IU/mL, 95% CI 18.7–21.3). There was an inverse linear correlation between FSH and testicular volume ($r = -0.43$; P<.001). Men with with FSH <15 IU/mL had a larger (P<.05) testicular volume (12 ± 5 mL) than men

TABLE 1

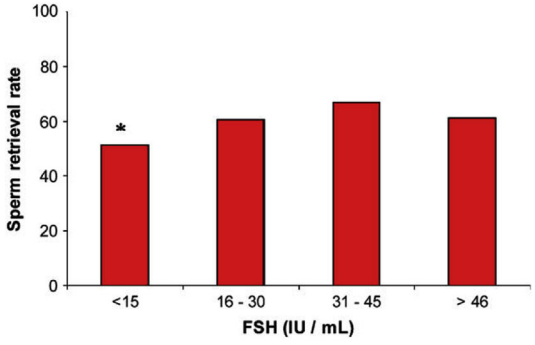
Baseline characteristics of men with nonobstructive azoospermia.

	Serum FSH (IU/mL)			
	< 15	15–30	31–45	> 45
n	245	360	124	63
Male age (yrs)	34 ± 7	36 ± 7	38 ± 7	37 ± 9
Female age (yrs)	31 ± 5	32 ± 5	32 ± 5	33 ± 6
Mean FSH (IU/mL)	9.0 ± 4.1	21.9 ± 4.0	36.5 ± 4	63.5 ± 22.8
Avg. vol. of larger testis (mL)	12 ± 5	9 ± 4	7 ± 4	6 ± 5
Histopathology (n)	127	314	102	58
Sertoli cell only (%)	34%	61%	68%	50%
Maturation arrest (%)	38%	16%	16%	28%
Hypospermatogenesis (%)	28%	23%	16%	22%

Ramasamy. Serum FSH and micro-TESE outcomes. Fertil Steril 2009.

FIGURE 1

Sperm retrieval rate in men with nonobstructive azoospermia. *$P<.05$.



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with FSH >15 IU/mL (8 ± 2 mL). Table 1 summarizes the baseline characteristics of the different subgroups of men with NOA based on FSH levels. The histology findings differed among different FSH groups. A greater percentage of maturation arrest (MA) histology was observed in the group with FSH<15 IU/mL compared with the group with FSH>15 IU/mL (38% vs. 17%; $P<.001$). Sperm retrieval rates in the groups of men with FSH values 15–30, 31–45, and >45 IU/mL were 60%, 67%, and 60%, respectively, and this was higher ($\chi^2 = 7.29$; $P=.006$) both individually and collectively than the group of men with FSH <15 IU/mL (51%) (Fig. 1). Of those men who had sperm retrieved, clinical pregnancy and live birth rates were similar (46%, 50%, 52%, 46% and 38%, 45%, 44%, 36%, respectively) in the four groups.

Adjusted associations from a multivariable model showed that the chance of retrieving sperm by micro-TESE is higher for men with FSH >15 IU/mL (Table 2). Using ROC analysis to evaluate the best combination of predictors for sperm retrieval, FSH and biopsy as combined predictors resulted only in a "fair" prediction model (AUC 0.71, 95% CI 0.67–0.74), but it is nonetheless significantly better than either FSH or biopsy histology alone. Neither male age nor testicular volume predicted presence of sperm with micro-TESE.

DISCUSSION

The present study showed that sperm retrieval was higher in NOA men with FSH >15 IU/mL than those men with FSH <15 IU/mL. Also, sperm retrieval rates were maintained even when the FSH value was markedly elevated (Fig. 1). This is contrary to the results reported in earlier studies (1, 2, 11, 12). In trying to reconcile the conflicting evidence, it is important to distinguish the techniques used to obtain sperm in earlier studies as compared with the present study. Previous studies have used single biopsy and multiple random biopsies for sperm retrieval. Different areas of the testis can have varying histologies, and a single biopsy might miss areas of spermatogenesis and not be representative of the most advanced histology. Micro-TESE analyzes the testis thoroughly, looking for the most advanced stage of spermatogenesis. In addition, our previously published results indicate that micro-TESE has less effect on testicular function and that far less tissue is removed than random biopsies (10).

The relationship of FSH with spermatogenesis is not straightforward in men with NOA. This is manifest by the range of FSH levels seen in the present study; in particular, successful sperm retrieval was seen in three men with FSH >90 IU/mL. This may reflect the effectiveness of micro-TESE in finding small areas of sperm production. Surprisingly, a preoperative FSH level of ≥15 IU/L resulted in greater odds of finding sperm with micro-TESE compared with normal FSH values. This finding highlights azoospermic males with normal FSH as a distinct infertility subset, wherein relatively normal levels of hypothalamic-pituitary-gonadal

TABLE 2

Results of multivariable adjusted model of pertinent variables.

Variable	*P* value	Adjusted OR (95% CI)*
FSH (IU/mL)		
<15		Reference group
15–30	<.001	1.99 (1.37–2.88)
31–45	<.001	2.83 (1.72–4.67)
>45	.023	2.00 (1.10–3.64)
Biopsy histology		
Hypospermatogenesis		Reference group
Maturation arrest	<.001	0.09 (0.05,–0.19)
Sertoli cell only	<.001	0.05 (0.02–0.09)

* Adjusted OR represent estimates from full model adjusted for male age, testes size, biopsy histology, and FSH. CI = confidence interval; OR = odds ratio.

Ramasamy. Serum FSH and micro-TESE outcomes. Fertil Steril 2009.

feedback are apparently maintained (at least normal FSH levels) but spermatogenesis remains impaired. We have recently reported a subset of men with normal FSH, normal-sized testes, and diffuse MA, who had lower sperm retrieval rates (13). A significantly higher prevalence of chromosomal abnormalities and Y-chromosome microdeletions were found in this subgroup compared with other patients with NOA (45% vs. 17%; $P<.001$), and sperm retrieval success was lower (41% vs. 60%; $P=.05$). Therefore, in this subgroup of men with diffuse MA and normal FSH, the FSH level may reflect adequate control feedback from germ cells and Sertoli cells despite the absence of sperm production.

We have also seen that men with Sertoli cell–only and larger-volume testes will often have normal FSH levels (<15 IU/mL). This lower FSH may be a reflection of the larger number of Sertoli cells in a larger testis, providing more control feedback to suppress FSH production. The excellent findings with higher FSH may reflect the sensitivity of microdissection in finding small areas of sperm production.

Even the predominant testicular histology has limitations in predicting sperm retrieval, because, in essence, it is merely a random sampling that may not represent the inherent heterogeneity (and best area of spermatogenesis) in the testis. It further illustrates that neither FSH nor histology pattern is able to resolve spermatogenesis on an individual tubule level, and, therefore, they should not be used as predictors of sperm recovery. Fortunately, the micro-TESE technique using the operating microscope can visualize the most advanced pattern of spermatogenesis and optimize the chance of finding sperm despite high FSH levels or predominant histology patterns. We further conclude that at the present time there are no absolute predictors of sperm yield for micro-TESE.

Many studies have shown a relationship between testicular histopathologic findings and testicular sperm retrieval by TESE (12, 14–16). Histologic findings are generally the most useful predictive factor for successful TESE. However, it is still controversial whether invasive examination such as testicular biopsy should be performed, because it may cause inflammatory changes, hematoma, parenchymal fibrosis, or permanent devascularization of the testes (17, 18) and does not determine if sperm are present elsewhere in the testis. We do not recommend diagnostic testicular biopsy preoperatively, because FSH and biopsy as combined predictors resulted in only a "fair" prediction model of sperm retrieval (AUC 0.71).

Although nomograms have become valuable for the assessment of patient information in urologic oncology, we still lack a similar set of data in the field of infertility. Unfortunately, the candidate markers for spermatogenesis have proven to be imperfect, and efforts should continue to search for the optimal predictor or combination of predictors specifically for spermatogenesis. Whereas no model reliably predicts TESE outcomes in men with NOA, excluding patients based on FSH alone (even if FSH is >45 IU/mL) is no longer clinically appropriate. The best that we can offer to these patients at the present time is the unparalleled sensitivity and specificity of microscopically examining each and every tubule in the testis through micro-TESE.

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