Outcomes of microdissection testicular sperm extraction in men with nonobstructive azoospermia due to maturation arrest

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Objective: To evaluate sperm retrieval in men with nonobstructive azoospermia and maturation arrest (MA) undergoing microdissection testicular sperm extraction (micro-TESE).
Design: Retrospective chart review.
Setting: Tertiary referral center.
Patient(s): Men with nonobstructive azoospermia and MA who underwent micro-TESE.
Intervention(s): Microdissection TESE.
Main Outcome Measure(s): Sperm retrieval rate (SRR).
Result(s): A total of 211 patients (13%) had a histologic finding of MA at the most advanced level. The overall SRR was 52%. A total of 146 patients were classified as having early MA (arrest at the primary spermatocyte stage), and 65 as having late MA (early spermatid stage). The SRR in men with early, vs. late, MA was 40% vs. 78%. Of the 211 men with MA, 51 had diffuse MA (100% of tubules showed MA). The SRR was significantly lower in men with diffuse vs. focal MA (35% vs. 57%). On multivariable analysis, late MA and higher follicle-stimulating hormone levels were positively associated with successful sperm retrieval.
Conclusion(s): Sperm were successfully identified in up to one half of the men with MA after micro-TESE. Among men with MA, late MA seems to be the best predictor of successful sperm retrieval with micro-TESE. (Fertil Steril® 2015;104:569–73. ©2015 by American Society for Reproductive Medicine.)
Key Words: Microdissection testicular sperm extraction, maturation arrest, nonobstructive azoospermia

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Nonobstructive azoospermia (NOA), or testicular failure, affects 1% of males and 10% of those who seek fertility assistance (1). Three histopathological patterns are typically described in the biopsies of men who have NOA: reduced spermatogenesis with all germ cell types present (hypospermatogenesis); premature arrest of spermatogenesis (maturation arrest [MA]); and complete absence of germ cells (Sertoli-cell-only syndrome) (2). Limited biopsies may fail to identify focal areas of sperm production that may otherwise be found with a detailed micro–testicular sperm extraction (TESE) search. Clinically, the histologic classification on a diagnostic biopsy can provide value in predicting the chance of success with TESE. For instance, the average sperm retrieval rate (SRR) is 94% in patients with hypospermatogenesis, compared with 40% in patients with Sertoli-cell-only syndrome, even with micro-TESE (3, 4).

Maturation arrest is defined as an absence of mature spermatozoa as a result of an early arrest in germ cell development in the seminiferous tubules. It is further delineated into early and late MA, based on the most-mature cell type noted on histology. In early MA, spermatogenic arrest occurs at the spermatogonia or spermatocyte stage; in late MA, arrest occurs at the spermatid stage (5–7). Late MA is

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distinguished from hypospermatogenesis in that no condensed, oval spermatids are seen in late MA. The underlying genetic causes that result in the phenotypes of early vs. late MA remain undetermined. On biopsy, MA can also vary in its heterogeneity, from focal to diffuse, further complicating prediction of SRR with TESE.

In men with MA, studies show a highly variable SRR of 23%–50% (6, 7). Both Tsai et al. (6) and Weedin et al. (7) found that, compared with men with late MA, those diagnosed with early MA had a decreased probability of successful sperm retrieval. Due to the limited number of cases in prior publications, histopathology could not be used to predict successful TESE. Therefore, we present a series of patients with NOA who underwent micro-TESE, performed by a single surgeon at our center, and were diagnosed with MA. We classified men with MA as either early or late, and focal or diffuse, and evaluated sperm SRR.

METHODS

After receiving approval from the Weill Cornell Medical College Institutional Review Board, we retrospectively reviewed the charts of 1,686 consecutive patients who had NOA, confirmed by analysis of 2 centrifuged semen samples, from November 1995 through June 2014. All patients who were reviewed underwent micro-TESE at a single center, performed by a single surgeon. The NOA was confirmed via repeat semen analysis on the day of micro-TESE. Men with complete azoospermia factor (AZF)a or AZFb microdeletions were excluded from our analysis: no men with AZFa or AZFb underwent micro-TESE.

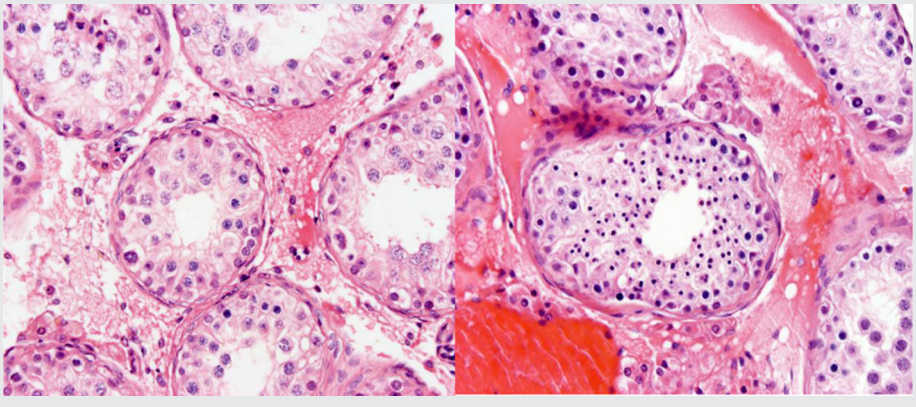
Preoperatively identifiable factors, including age, follicle-stimulating hormone (FSH), total serum testosterone (T), testis volume on physical exam, presence of a varicocele, history of cryptorchidism, history of testicular cancer, prior diagnosis of Klinefelter syndrome, and Y microdeletion (AZFc) were analyzed. Men with a history of varicocele underwent varicocelectomy before micro-TESE. Micro-TESE was performed as described previously (8). All men underwent initial unilateral micro-TESE, and if no sperm were retrieved, the contralateral testis was explored. Sperm retrieved were cryopreserved according to patient preference.

Although some patients were referred to our center with a previous diagnostic biopsy or TESE, we did not perform routine biopsies because a diagnostic biopsy does not predict the presence of focal areas of spermatogenesis that micro-TESE can identify (9). Given the limited information available from previous outside biopsies, and the small number of men who had them performed, histologic data from outside biopsies were not included in this analysis. The pathologic information used in this study was from a single random intraoperative biopsy taken at the time of micro-TESE.

Patients were considered to have MA if the most advanced pathologic pattern on either diagnostic or random intraoperative testis biopsy was consistent with MA. Biopsy slides were then re-reviewed by our uropathologist, who was blinded to the outcome of micro-TESE, and classified as either early or late MA. Early MA was defined as arrest of spermatogenesis at the primary spermatocyte stage (nuclei with filamentous chromatin, Fig. 1). Late MA was defined as arrest of spermatogenesis at the early spermatid phase (dark round nuclei, Fig. 1) and the absence of elongated spermatids/spermatozoa (elongated/oval nuclei).

Although previous studies have looked at men who have MA (6, 7, 10), no well-defined criteria have been established for determining if a patient is considered to have diffuse or focal MA. Thus, we established a classification scheme intended to delineate the 2 groups. Given that all pathology was from a single intraoperative biopsy taken during micro-TESE, we felt that if a biopsy showed 100% MA, i.e., all tubules examined had MA, then those patients likely had only MA in the remainder of the testis. In contrast, if a portion of the biopsy revealed an alternate pathology (i.e., Sertoli-cell-only syndrome or hypospermatogenesis), we classified those men as having focal MA. Successful sperm retrieval depends on having an area of the testis where complete

FIGURE 1



Early (*left*) and late maturation arrest (*right*).

Bernie. Micro-TESE in men with maturation arrest. Fertil Steril 2015.

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