

# The Role of Varicocelectomy and Diagnostic Testis Biopsy in Men With Non-obstructive Azoospermia

*NYU Case of the Month, July 2020*

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**A** 37-year-old man presented with primary infertility of 12 months' duration. His wife was 30 years old and had not undergone a fertility evaluation. The couple had been having properly timed and unprotected intercourse for 12 months. The patient denied any sexual dysfunction. He had no past medical history, never had surgery, and did not take any medications. He denied smoking or using illicit drugs and had no relevant family history. He worked as a physician and denied genital trauma or exposure to toxic or radioactive agents.

## Evaluation, Treatment, and Management

The patient had a normal masculine hair distribution. His BMI was 23.7. No gynecomastia was present. Testes bilaterally were soft and approximately 7 cc on the right and 6 cc on the left (normal volume,  $\geq 18$  cc). He had a grade 3 left varicocele and no right varicocele. His epididymis and vas deferens were normal bilaterally.

The patient had 2 semen analyses that showed normal-volume azoospermia. He also had an endocrine evaluation that demonstrated normal testosterone of 426 ng/dL (normal range, 300–890 ng/dL) and elevated follicle stimulating hormone of 24.1 mIU/mL (normal range, 1.5–12.4 mIU/mL).

He had a genetic evaluation, which detected no Y chromosome microdeletions and showed a 46,XY karyotype.

The patient's wife was referred to a reproductive endocrinologist, and her evaluation was normal. The couple was counseled on their options, which included proceeding directly with microdissection testicular sperm extraction (mTESE) with in vitro fertility with intracytoplasmic sperm injection (IVF-ICSI), left varicocelectomy without diagnostic testis biopsy, or left varicocelectomy with diagnostic testis biopsy. The patient elected to undergo left microsurgical subinguinal varicocelectomy with a diagnostic testis biopsy. The diagnostic testis biopsy was done through the subinguinal incision by delivering the testis into the operative field; the histopathologic diagnosis was hypospermatogenesis. During the subsequent 12 months, the patient had semen analyses performed every 3 months, all of which remained azoospermic. Twelve months after the varicocele repair, the patient underwent a mTESE that successfully yielded sperm. The couple had a live birth after 2 rounds of IVF-ICSI.

## Comment

Varicocele, or dilation of the pampiniform plexus, occurs in 15% of young men.<sup>1</sup> Varicocelectomy is indicated in infertile men with a clinically palpable

varicocele, abnormal semen analyses, and a partner with normal fertility.<sup>2</sup> Azoospermia, or a lack of sperm in the ejaculate, occurs in about 1% of men, and 60% of these men will have non-obstructive azoospermia (NOA), or azoospermia due to a severe defect in spermatogenesis.<sup>3,4</sup> Although these men lack sperm in the ejaculate, mTESE enables a skilled surgeon to identify focal areas of spermatogenesis within the testes for use with IVF-ICSI. Diagnostic testis biopsy provides an estimate of the severity of spermatogenic dysfunction in men with NOA and can predict mTESE outcome. Varicocele repair and diagnostic testis biopsy should be considered in the management of men with NOA who have a clinical varicocele.

### *Return of Sperm to Ejaculate*

The ideal outcome for repairing a clinical varicocele in a patient with NOA is the return of sperm to the ejaculate.<sup>5</sup> Presence of sperm in the ejaculate will enable a patient to avoid undergoing a second procedure for sperm retrieval. In addition to avoiding the short-term morbidity of another surgery, the potential long-term complication of testosterone deficiency is also avoided in men who can forgo mTESE.<sup>6</sup>

In a brief 2020 literature review on the effectiveness of varicocele repair in men with NOA, 222 of 751 men (29.5%) experienced a return of sperm to their ejaculate.<sup>7</sup> In a more detailed meta-analysis in 2016, sperm was found in the postoperative ejaculate of 151 of 344 men (43.9%).<sup>8</sup> Return of sperm to the ejaculate ranged from 20.8% to 55.0% of men, depending on the study, and the average sperm concentration was  $1.8 \times 10^6/\text{mL}$ , with an average motility of 22.9%.

Although not indicated in most studies, the time from varicocele repair to return of sperm in the

ejaculate varied from 4.5 months to 11 months. Impressively, 13.6% of men with return of sperm to their ejaculate were able to conceive naturally. It should be noted, however, that the return of sperm to the ejaculate may not persist, so patients should always be advised to cryopreserve in case they experience an azoospermia relapse.

Most men with NOA and a clinical varicocele should not expect a return of sperm to their ejaculate after treatment of their varicocele. However, if female age does not preclude waiting a year for the benefits of varicocele repair to manifest, close to a third of these men will see sperm return to their ejaculate. The possibility of avoiding mTESE, or even of conceiving naturally, will make varicocele treatment appealing to many men with NOA and a varicocele.

### *Sperm Retrieval Rate*

Testicular sperm extraction with IVF-ICSI is the only mechanism by which most men with NOA will be able to father a child. Given that most men will not see a return of sperm to their ejaculate after a varicocele repair, the outcomes of mTESE are relevant to men with NOA and a varicocele.

Unfortunately, there are relatively few controlled studies of men undergoing mTESE after varicocele repair.<sup>9-11</sup> According to these studies, the sperm retrieval rate in men with NOA who underwent mTESE after varicocele repair was 57.2% (91/159) versus 36.5% (88/241) in men who underwent mTESE but did not undergo prior varicocele repair. The odds ratio for finding sperm at mTESE is 2.65 (95% confidence interval, 1.69-4.14;  $P < 0.0001$ ) in favor of men who underwent varicocele repair.<sup>8</sup> Unfortunately, there is significant heterogeneity among these studies, including

how the control groups were chosen. Furthermore, the duration of time between varicocele repair and mTESE varies from as little as 3 months to more than 2 years. Despite these limitations, the signal toward improved sperm retrieval rates in men with NOA after a varicocele is repaired is compelling.

### *The Role of Diagnostic Testis Biopsy at Time of Varicocelectomy*

An isolated diagnostic testis biopsy has a limited role in the modern management of men with a clear diagnosis of NOA.<sup>12</sup> Given the potentially focal nature of spermatogenesis in men with NOA, a significant portion of men undergoing mTESE will have a successful procedure, regardless of the histology shown on a diagnostic testis biopsy.<sup>13</sup> Even though a diagnostic testis biopsy will not often change the management of men with NOA, testicular histopathology remains the strongest predictor of mTESE outcome.<sup>14</sup> In men with NOA and clinical varicocele, the minimal added morbidity of a diagnostic testis biopsy at time of varicocelectomy may be worth the prognostic information gained.

As mentioned, testicular histopathology at the time of varicocelectomy is a strong predictor of the recovery of sperm to the ejaculate of men with NOA.<sup>8</sup> Although sperm was found in the postoperative ejaculate of 9.7% (6/62) of men with Sertoli cell-only histology, 35.3% (18/51) of men with maturation arrest had return of sperm to their ejaculate, and 56.2% (27/48) of men with hypospermatogenesis had return of sperm. When differentiating between early and late maturation arrest, 20% (2/10) of men with early maturation arrest will experience return of sperm to the ejaculate compared with 47%

(8/17) of men with later maturation arrest.<sup>15</sup> It is clear that the degree of spermatogenic impairment found on testis biopsy inversely correlates with the likelihood of return of sperm to the ejaculate.

The result of diagnostic testis biopsy at the time of varicolectomy is also highly correlated with the sperm retrieval results at the time of mTESE. Of men who did not have return of sperm to their ejaculate at least 1 year after varicocele repair, sperm retrieval was successful in 20% (7/35) with Sertoli cell-only histology, in 40% (2/5) with early maturation arrest, in 67% (6/9) with late maturation arrest, and in 100% (4/4) with hypospermatogenesis.<sup>15</sup> Although even a poor histopathology result should not dissuade a man with NOA from proceeding with mTESE, reducing the wide range of sperm retrieval rates into a more accurate individual percentage may be of benefit when counseling patients.

### *Sperm Retrieval After Varicocele Repair*

The method and timing of sperm retrieval after varicocele repair should be considered.<sup>16</sup> Testicular sperm aspiration (TESA) involves using a needle to percutaneously aspirate testicular tissue. Conventional testicular sperm extraction (cTESE) entails extracting testicular tissue through one or more small testicular incisions. Finally, mTESE involves making a large testicular incision that maximally exposes seminiferous tubules and using optical magnification to select larger seminiferous tubules. In a meta-analysis comparing sperm retrieval techniques, mTESE was 1.5-fold more successful than cTESE, and cTESE was 2.0-fold more successful than TESA.<sup>17</sup> Although all these

techniques are therapeutic options that can be offered to a patient with NOA, many reproductive surgeons will elect mTESE because of the focal nature of spermatogenesis in these men.

There is no defined optimal time duration between varicocele repair and mTESE. A minimum of 3 months is recommended, given that this is a typical cycle of spermatogenesis.<sup>16</sup> However, it can be helpful to be mindful of the velocity of improvement in semen analysis parameters after varicocele repair in men with severe oligospermia (sperm concentration <5 million/mL).<sup>18</sup> Although the time frame for most improvements is 3 to 6 months after varicocele repair, modest further improvements are also seen in 6 to 12 months. Generally, we perform mTESE 6 to 12 months after varicolectomy, depending on the female's age and the patient's preference.

### **Conclusions**

The management of varicocele in men with NOA is challenging because of the dearth of well-performed studies. However, there are multiple apparent benefits to varicolectomy in men with NOA. A significant number of these men will have a return of sperm to their ejaculate, mitigating the need for a surgical sperm retrieval. Even in treated men who still require mTESE, varicolectomy appears to improve the sperm retrieval rate. Diagnostic testis biopsy at the time of varicolectomy adds minimal morbidity while offering useful prognostic information both on the likelihood of return of sperm to the ejaculate and on mTESE outcome. The surgeon should wait at least 3 months after the patient's varicolectomy to perform a mTESE. ■

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