# Predictors of Sperm Recovery and Azoospermia Relapse in Men With Nonobstructive Azoospermia After Varicocele Repair

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**Abbreviations and Acronyms**

FSH = follicle-stimulating hormone

HS = hypospermatogenesis

ICSI = intracytoplasmic sperm injection

IVF = in vitro fertilization

MA = maturation arrest

NOA = nonobstructive azoospermia

SCO = Sertoli-cell-only

TESE = testicular sperm extraction

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**Purpose:** In this study we determined the recoverability and sustainability of motile sperm in semen of men with nonobstructive azoospermia after varicocelectomy as related to different variables.

**Materials and Methods:** Men with documented infertility for more than 1 year, with nonobstructive azoospermia and clinically palpable varicoceles were included in this prospective noncontrolled study. Participants underwent simultaneous subinguinal microsurgical varicocelectomy and testicular biopsies. Preoperative as well as initial and late followup semen analyses were performed. Outcomes of sperm recovery and relapse of azoospermia were correlated with the variables of patient age, infertility duration, varicocele grade, laterality, follicle-stimulating hormone, testicular volume and testicular histology.

**Results:** The study included 31 men with a mean ± SD age of 34.9 ± 8.7 years and mean followup of 19.3 ± 3.3 months. Hypospermatogenesis, late maturation arrest, early maturation arrest and Sertoli-cell-only were observed in 13, 6, 2 and 10 patients, respectively. Overall, sperm recovery was evident in 10 of 31 (32.3%) patients (persistent recovery 19.4%, intermittent recovery 6.5%, relapse 6.5%). Sperm were recovered in patients with hypospermatogenesis (7 of 13, 53.8%) and late maturation arrest (3 of 6, 50%). No sperm were recovered in those with early maturation arrest or Sertoli-cell-only. Among the variables only histological patterns demonstrated a significant correlation with recovery (rho = 0.504, $p = 0.004$). None of variables was significantly correlated with relapse. Bilateral varicocele repair demonstrated a strong yet nonsignificant negative correlation with relapse (rho = −0.612, $p = 0.06$).

**Conclusions:** Varicocelectomy could recover motile sperm in men with nonobstructive azoospermia, palpable varicoceles and hypospermatogenesis or late maturation arrest. No sperm was recovered with early maturation arrest or Sertoli-cell-only. Recovery might be persistent or intermittent, or involve relapse of azoospermia. Testicular histology was the sole parameter significantly correlated with recovery and no predictors of relapse could be identified. This prognostic role of testicular biopsy is imperative in couple counseling.

**Key Words:** azoospermia; infertility, male; varicocele

NONOBSTRUCTIVE azoospermia refers to the repeated detection of no spermatozoa in the semen due to testicular dysfunction with production of minimal or no fully developed spermatozoa.[1,2] Approximately 1% of all men and 10% of infertile men are affected by testicular dysfunction resulting in NOA.[3] Clinical varicoceles have been reported in 4.3% to 13.3% of infertile men with NOA,[4] and are implicated as a main cause of male infertility and testicular failure.[5,6]



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Previous literature reports varying success rates after varicocele repair in patients with NOA with semen parameter improvement from 0% to 57%.[4] Since the advent of IVF-ICSI in early 1990s[7] there has been renewed interest in varicocele repair in men with NOA, adding to several reports in the literature on the recoverability of motile sperm in semen following varicocele repair.[8–17] Nevertheless, the reports on sperm recovery are conflicting. The success rates are variable and the predictors of success have not been definitively identified. In particular, the literature lacks compelling data on the sustainability of sperm recovery.[9–12]

To our knowledge there have been no studies evaluating the predictors of sustainability of sperm in semen after varicocele repair in men with NOA. In this prospective observational study we evaluated the effect of varicocele repair on patients with NOA, and determined the recoverability and sustainability of motile sperm in semen after varicocelectomy as related to different variables.

## MATERIALS AND METHODS

### Study Design and Setting

This prospective, noncontrolled, open label, observational study was conducted at the author's institution from August 2004 to November 2009. The study received ethical committee approval and informed consent was obtained from each patient.

### Inclusion-Exclusion Criteria

Men with documented infertility for more than 1 year, NOA and clinically palpable unilateral or bilateral varicoceles were considered eligible for the study. Patients with obstructive azoospermia, subclinical varicoceles, recurrent varicoceles, cryptorchidism, a history of exposure to gonadotoxins or known genetic abnormalities were excluded from the study.

### Intervention and Outcomes Measures

The patients underwent simultaneous subinguinal microsurgical varicocele repair and testicular biopsies. The main outcomes following varicocelectomy were the recoverability of motile sperm in the semen and the relapse to azoospermic status. Preoperative semen analyses were performed at least twice, 2 to 4 weeks apart, and were preceded by 3 to 5 days of abstinence. Initial followup semen analysis was done 3 to 4 months after varicocelectomy. An additional 3 late consecutive semen analyses, separated by a minimum of 3 months, were repeated afterward. Preoperative azoospermia was identified as detection of no sperm in the centrifuged pellets of preoperative semen analyses. Persistent sperm recovery was defined as the recoverability of motile sperm consistently in all post-varicocelectomy semen analyses, whereas intermittent sperm recovery referred to the recoverability of motile sperm intermittently in 3 late consecutive semen analyses. Relapse to azoospermic status was defined as the consistent detection of no sperm in the centrifuged pellets of the 3 late consecutive semen analyses after successful sperm recovery in initial followup semen analysis.

### Sample Size Calculation

A motile sperm recovery rate of 39.1% was postulated after varicocele repair based on previous meta-analysis data.[8] Since men with NOA may occasionally demonstrate sperm in the ejaculate without treatment, we suggested a 5% recovery rate without varicocele repair based on that assumption. To accomplish a statistical power of 80% and by setting the alpha level at 5%, 25 patients was the sample size required in a double-sided pairwise continuity correction analysis.

### Statistical Analysis

The data were analyzed with SPSS® 16.0 software and the paired t test was used for changes in semen parameters. The outcomes of sperm recovery and relapse to azoospermic status were correlated with the variables of patient age, infertility duration, varicocele grade and laterality, FSH, testicular volume and testicular histological patterns to identify the predictors. Correlations were examined using the nonparametric Spearman's correlation coefficient (rho), with 2-tailed $p < 0.05$ considered statistically significant.

## RESULTS

The study included 31 men with a mean age of 34.9 ± 8.7 years at varicocelectomy. Table 1 presents the preoperative demographics and characteristics of the study sample. The patients were followed for 14 to 27 months (mean 19.3 ± 3.3) after varicocele repair.

Motile sperm recovery was evident in 10 of 31 (32.3%) patients, including 9 of 31 (29%) who demonstrated sperm recovery in the initial followup semen analysis. Overall, 6 of 31 (19.4%) patients achieved persistent sperm recovery in all post-varicocelectomy semen analyses, 2 of 31 (6.5%) showed intermittent sperm recovery, whereas an additional 2 of 31 (6.5%) had relapse to a complete azoospermic

**Table 1.** *Demographics and characteristics of study population*

| | | |
|---|---|---|
| Mean ± SD pt age (range) | 34.9 ± 8.7 | (23–51) |
| Mean ± SD yrs infertility (range) | 9.2 ± 6.7 | (2–23) |
| No./total No. laterality (%):* | | |
| Rt | 0 | |
| Lt | 12/31 | (38.7) |
| Bilat | 19/31 | (61.3) |
| No./total No. grade (%):* | | |
| 1 | 20/50 | (40) |
| 2 | 17/50 | (34) |
| 3 | 13/50 | (26) |
| Mean ± SD cc testicular vol (range): | | |
| Rt | 18.6 ± 4.1 (8.5–25.3) | |
| Lt | 18.0 ± 6.3 (8.2–27.1) | |
| Mean ± SD ml U/ml FSH (range) | 18.1 ± 7.3 (7.3–39.1) | |

* A total of 50 varicoceles were treated in 31 men.

**Table 2.** *Improvements in semen parameters in patients demonstrating sperm recovery*

| | Mean ± SD Postop (range) | p Value |
|---|---|---|
| Concentration ($10^6$/ml) | 2.3 ± 1.7 (0.4–5.7) | 0.0019 |
| Motility (%) | 15.3 ± 8.5 (2–32.6) | 0.0003 |
| Normal morphology (%) | 7.75 ± 2.7 (2.1–10.5) | 0.0001 |

All preoperative values.

state after initial successful sperm recovery. In the subset of patients demonstrating initial successful sperm recovery 2 of 9 (22.2%) had relapse of azoospermia. Semen parameters (sperm concentration, motility and normal morphology) improved significantly in the subset of patients who achieved sperm recovery (table 2).

The histological patterns of hypospermatogenesis, late MA at spermatid stage, early MA at secondary spermatocyte stage and SCO were observed in 13, 6, 2 and 10 patients, respectively. Sperm were recovered in patients with HS (7 of 13, 53.8%) and late MA (3 of 6, 50%), while no sperm could be recovered from ejaculate of patients with early MA or SCO. Table 3 illustrates the recoverability of motile sperm and relapse of azoospermia in patients with different testicular histological patterns.

Only testicular histological patterns demonstrated a significant correlation with recovery of motile sperm after varicocelectomy (Spearman's rho = 0.504, p = 0.004). None of the variables of patient age, infertility duration, varicocele grade, varicocele laterality, FSH or testicular volume showed a significant correlation with sperm recovery. In a subset analysis of patients who achieved initial sperm recovery, none of the examined variables demonstrated a significant correlation with relapse of azoospermia. Bilateral varicocele repair demonstrated a strong, although nonsignificant, negative correlation with relapse (Spearman's rho = −0.612, p = 0.06).

## DISCUSSION

Historically NOA has been deemed the most difficult condition to treat in infertile men. The introduction of ICSI 2 decades ago, coupled with TESE, revolutionized the management of NOA and resulted in many pregnancies using testicular sperm.[7,8] However, several concerns have been raised regarding TESE and ICSI. Testicular sperm are successfully retrievable in only approximately 50% to 60% of men,[8,18] with ICSI having lower success rates compared to ejaculated sperm.[19] Additionally, pregnancies achieved from such techniques result in higher rates of multiple gestations, prematurity, congenital anomalies and long-term implications.[20]

Varicocele repair has been reported to recover motile sperm in the ejaculate of some men with NOA, obviating the need for inconvenient TESE and enhancing the chance of spontaneous pregnancy through intercourse. Matthews et al reported motile sperm recovery in the ejaculate of 12 of 22 (54.5%) men with NOA following inguinal microsurgical varicocelectomy, from which 2 resulted in natural pregnancies.[16] Kim et al further demonstrated the recovery of motile sperm in 43% of 28 men with NOA after microsurgical inguinal varicocele repair.[15] In their series 55% of men with HS and 50% with late MA at spermatid stage achieved recovery of sperm in ejaculate, whereas none of the patients with SCO or early MA at spermatocyte stage showed sperm recovery. Likewise, Esteves and Glina reported recovery of sperm in the ejaculate of 47% of men after varicocele repair.[13] Only men with HS or MA patterns demonstrated improvement after surgery while all patients with SCO continued to be azoospermic.[13] Moreover, Pasqualotto et al reported improvement in semen quality after varicocelectomy, even in men with NOA demonstrating germ cell aplasia in a single large testis biopsy.[11] A meta-analysis of studies addressing varicocele repair in patients with NOA has further endorsed the improvements in semen quality after varicocele repair.[8] Of 233 patients 39.1% had motile sperm in the postoperative ejaculate with a mean sperm density of $1.6 \times 10^6 \pm 1.2 \times 10^6$ and mean sperm motility of 20.1% ± 18.5%. In addition to sperm recovery in the ejaculate, varicocele repair may also increase the TESE retrieval rate, improve ICSI clinical pregnancy/live birth rates and decrease the likelihood of miscarriage in infertile couples with male partner NOA and clinical varicocele.[8,21,22]

Testicular histology has proved to be the most important predictor of sperm recovery in men with NOA with varicoceles.[8, 12–17,23] The histological patterns of HS and late MA have been reported to correlate positively and significantly with favorable treatment outcomes, whereas the value of varicocele repair in men with early MA or SCO pattern is uncertain. In the meta-analysis by Weedin et al success rates in patients with HS (54.5%) or MA (42.1%) were significantly higher (p <0.001 in both

**Table 3.** *Recoverability of sperm and relapse to azoospermia in different testicular histological patterns*

| | No./Total No. (%) | | | |
|---|---|---|---|---|
| Testicular Histology | Overall Sperm Recovery | Persistent Sperm Recovery | Intermittent Sperm Recovery | Relapse |
| HS | 7/13 (53.8) | 5/13 (38.5) | 1/13 (7.7) | 1/13 (7.7) |
| MA | | | | |
| Late | 3/6 (50) | 1/6 (16.7) | 1/6 (16.7) | 1/6 (16.7) |
| Early | 0/2 (0) | 0/2 (0) | 0/2 (0) | Not applicable |
| SCO | 0/10 (0) | 0/10 (0) | 0/10 (0) | Not applicable |
| Totals | 10/31 (32.3) | 6/31 (19.4) | 2/31 (6.5) | 2/31 (6.5) |

groups) than in those with SCO (11.3%).[8] Late MA had a higher probability ($p < 0.007$) of sperm recovery (45.8%) compared to early MA (0%).

Apart from testicular histological pattern, in several reports no other variable could predict successful varicocele repair.[12–18,23–28] In a meta-analysis the success rates for varicocele grades 1, 2 and 3 were 0%, 22% and 40%, respectively, yet the differences were not significant ($p = 0.07$).[8] Similarly success rates for patients with FSH less than 10 mIU/ml (25%) and FSH greater than 10 mIU/ml (21%) were not significantly different ($p = 0.79$). The rate of success for patients with normal size testes was 32% and for those with testicular hypotrophy was 25% ($p = 0.87$). A comparison of unilateral and bilateral repair was not addressed in any article included in the meta-analysis.[8]

In our study overall 32.3% of patients demonstrated motile sperm recovery, with 19.4% able to maintain persistent sperm recovery and 6.5% showing intermittent sperm recovery, whereas an additional 6.5% had relapse back to azoospermic status after successful sperm recovery on initial followup semen analysis. In patients demonstrating sperm recovery, mean sperm concentration, motility and normal morphology were $2.3 \pm 1.7$ ($\times 10^6$/ml), $15.3 \pm 8.5$ (%) and $7.75 \pm 2.7$ (%), respectively. Sperm were recovered in 53.8% and 50% of patients with HS and late MA patterns, respectively, while no sperm could be recovered in semen of patients with early MA or SCO. Testicular histological pattern was the only parameter correlating significantly with motile sperm recovery (rho = 0.504, $p = 0.004$), while patient age, infertility duration, varicocele grade, varicocele laterality, FSH and testicular volume did not correlate significantly with sperm recovery. These findings exhibit the important prognostic value of testicular histology and suggest that men with NOA should be counseled about undergoing testicular biopsy simultaneous to or before varicocelectomy. In particular, patients with early MA and SCO should be counseled about poor outcomes before undergoing varicocelectomy.

In contrast to numerous studies identifying predictors of sperm recovery, the literature is deficient regarding the predictors of relapse of azoospermia. Pasqualotto et al reported on 27 azoospermic men who underwent testis biopsy and microsurgical repair of clinical varicocele.[11] Induction of spermatogenesis was achieved in 9 men (33.3%) including 4 with germ cell aplasia. Of these 9 patients with improvement in semen quality 5 had relapse of azoospermia 6 months after the recovery of spermatogenesis (4 germ cell aplasia and 1 maturation arrest). Conversely Esteves and Glina found no relapse of azoospermia in 8 patients with sperm recovery.[13] Nevertheless, none of their patients had SCO. In the meta-analysis by Weedin et al, after demonstrating motile sperm in the ejaculate, 4.6% of patients had relapse of azoospermia within 2 to 6 months.[8]

In our study of the patients demonstrating initial sperm recovery 22.2% had relapse of azoospermia. The relapse to azoospermic status in our patients was observed in an unpredictable fashion given that no single parameter correlated significantly with relapse. Even testicular histology correlated nonsignificantly with relapse ($p = 0.545$). Bilateral varicocele repair exhibited a strong negative correlation with relapse of azoospermia (Spearman's rho = $-0.612$), yet it does not reach statistical significance ($p = 0.06$). This finding precluded the conclusion that relapse of azoospermia might be less with bilateral repair. A larger sample size should yield better evidence regarding the assumption that bilateral repair might decrease the likelihood of relapse.

Our findings have remarkable implications in the counseling of couples affected by NOA regarding reproductive options. For male partners even modest recovery of sperm resulting in the appearance of motile sperm in the ejaculate after varicocele repair could allow these men to contribute to pregnancy, unassisted or assisted.[8,12,13] Additionally, should men who recovered sperm require IVF-ICSI to achieve pregnancy, the procedure can be performed using ejaculated sperm, which is technically easier and provides better results compared to testicular sperm.[19,29] Moreover, considering the enormous psychological and financial burden of IVF-ICSI on the couple, the risks of ovulation hyperstimulation on the female partner and the uncertainty of recoverability or sustainability of sperm in the ejaculate, it is imperative to counsel the couple about sperm cryopreservation for possible future attempts of ICSI cycles. In particular, sperm cryopreservation is crucial for men with intermittent sperm recovery before commencing an ICSI cycle. The use of fresh sperm for ICSI might be considered in patients demonstrating persistent sperm recovery.

Our study was limited by the small sample size, short-term followup and noncontrolled design. Randomized controlled trials to examine the recoverability of sperm in ejaculate following varicocele repair vs no treatment should provide better evidence regarding the predictors.[30] However, it seems that randomized controlled trials examining relapse of azoospermia are impractical.

## CONCLUSIONS

Varicocele repair could allow the recovery of motile sperm in semen of infertile men with NOA and clinically palpable varicoceles in whom testicular histol-

ogy demonstrated HS or late MA. No sperm could be recovered in the semen of patients with early MA or SCO. Sperm recovery might be persistent or intermittent, or involve relapse of azoospermia. Testicular histological pattern was the sole parameter significantly correlated with sperm recovery, whereas no predictors of relapse of azoospermia could be identified. Based on our findings it is imperative to counsel couples about the potential of sperm recovery and relapse of azoospermia, the important prognostic role of testicular histology and the value of undergoing testicular biopsy simultaneously or before varicocelectomy.

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