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RECOVERY OF SPERMATOGENESIS AFTER MICROSURGICAL SUBINGUINAL VARICOCELE REPAIR IN AZOOSPERMIC MEN BASED ON TESTICULAR HISTOLOGY

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ABSTRACT

Objective: Analyze whether testicular histologic patterns from a group of azoospermic men with varicocele is predictive of treatment outcome after subinguinal microsurgical varicocele repair.

Materials and Methods: Seventeen azoospermic men underwent bilateral open single testis biopsy and microsurgical subinguinal repair of clinical varicoceles.

Results: Histopathology of testicular biopsies revealed hypospermatogenesis (HYPO) in 6 men, maturation arrest (MA) in 5, and Sertoli cell-only (SCO) in 6. Overall, presence of spermatozoa in the ejaculates was achieved in 47% (8/17) of men after varicocele repair, but only 35% (6/17) of them had motile sperm in their ejaculates. Only men with testicular histology revealing HYPO (5/6) or maturation arrest (3/5) had improvement after surgery. Median (25% - 75% percentile) postoperative motile sperm count for both groups were 0.9 X 10^6/mL (0.1-1.8 X 10^6/mL) and 0.7 X 10^6/mL (0.1-1.1), respectively (p = 0.87). The mean time for appearance of spermatozoa in the ejaculates was 5 months (3 to 9 months). One (HYPO) of 8 (12.5%) men who improved after surgery contributed to an unassisted pregnancy. Postoperative testicular biopsies obtained from patients who had no improvement after surgery revealed that testicular histology diagnosis remained unchanged. Successful testicular sperm retrieval for intracytoplasmic sperm injection (ICSI) was achieved in 4 of 9 (44.4%) individuals who did not improve after surgery, including 1 man with testicular histology exhibiting SCO.

Conclusions: Microsurgical varicocele repair in nonobstructive azoospermic men with clinical varicoceles can result in sperm appearance in the ejaculate when hypospermatogenesis or maturation arrest is found on testicular histology diagnosis.

Key words: varicocele; microsurgery; azoospermia; testis; histology
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INTRODUCTION

Azoospermia and severe oligozoospermia in association with varicocele is reported to range from 4.3% to 13.3% (1). Testicular histopathology in severe oligozoospermic and azoospermic patients are often bilateral and range from various degrees of hypospermatogenesis to Sertoli cell-only pattern (2,3). Although few controlled studies have evaluated the outcome of varicocele repair in infertile men, most of them support a favorable effect of surgical correction on general sperm quality and fertility (4-6). The beneficial effect of varicocele repair in azoospermic patients, on the other hand, remains controversial.

While some studies have documented recovery of spermatogenesis and unassisted pregnancies after surgery (1,7-11), others associated the presence of varicoceles as incidental findings (12) or with a limited role in azoospermia (13).

For azoospermic men with varicoceles, even modest induction of spermatogenesis leading to the presence of motile sperm in the ejaculate after varicocele repair could allow these men to establish a pregnancy on their partners, either unassisted or assisted, thus expanding the couple's reproductive options. Identification of who will benefit from surgery may have profound clinical impact, since induction of spermatogenesis is not achieved in all individuals after varicocelectomy. The purpose of this study was to evaluate treatment outcome after subinguinal microsurgical varicocele repair in relation to testicular histopathology in a group of nonobstructed azoospermic men with clinical varicoceles.

MATERIALS AND METHODS

Patients

We reviewed the charts of 256 infertile men who underwent surgical repair of clinical varicoceles from August 1996 to September 2003. Seventeen of 256 (6.6%) men, with a median of 32 years-old (19 - 45 years), who presented with clinical varicoceles and nonobstructive azoospermia, were included in this retrospective study. All men had a history of primary infertility of at least 1 year duration (median 23.6 months, range 13-96 months). Other causes of azoospermia were ruled out. Varicoceles were identified on physical examination and graded as large (grade 3, visible when standing), moderate-sized (grade 2, visible with Valsalva's maneuver when standing) and small (grade 1, palpable with Valsalva's maneuver when standing). Only men with clinical unilateral or bilateral varicoceles were included. Testicular volume was assessed using the Prader orchidometer. A testicular volume < 20 mL was considered diminished. At least 2 preoperative semen analyses were obtained and evaluated according to the WHO criteria (14). All semen analyses confirmed the absence of sperm in the centrifuged pellet. All men had ejaculate volumes > 1.5 cc, alkaline seminal fluid pH, and reproductive ductal structures palpably normal. Hormonal profile included serum testing for follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin. Thirty G-banded metaphases were analyzed by high-resolution Giemsa karyotype in 15 men. All of them were cytogenetically normal. Polymerase chain Yq microdeletion screening for AZFa, AZFb and AZFc was done in 12 individuals. Deletions of Yq were not observed in any of them.

The median preoperative hormone levels were: FSH = 14.0 mUI/mL (25% - 75% percentile, range 6.5 - 34.6 mUI/mL), LH = 5.8 mUI/mL (25% - 75% percentile, range 3.5 - 14.5 mUI/mL), prolactin = 7.4 ng/mL (25% - 75% percentile, range 4.2 - 16.0 ng/mL), and testosterone = 544.3 ng/dL (25% - 75% percentile, range 285.0 - 864.0 ng/dL). Ten men (59%) had elevated serum FSH levels (normal range: 1.0 - 10.0 mUI/mL). Bilateral and unilateral left-sided procedures have been done in 11 (65%) and 6 men respectively. Varicoceles were large in 9 (53%) men and moderate-sized in 8. Diminished testicular volume has been found bilaterally in 6 (35%) men and unilaterally in 7.

Microsurgical Varicocele Repair

All subjects underwent testicular artery and lymphatic-sparing subinguinal varicocele repair. Briefly, a 2.5-cm skin incision was made over the external inguinal ring. The subcutaneous tissue was separated until the exposure of spermatic cord. The cord was elevated with a Babcock clamp and the posterior cremasteric veins were ligated and transected. A Penrose drain was placed behind the cord without tension. The cremasteric fascia was then opened to expose the cord structures and the dissection proceeded using either operating microscope with 6-16X magnification (15 patients) or loupes with 2.5X magnification (2 patients). Dilated cremasteric veins within the fascia were ligated and transected. Lymphatics and arteries were identified and preserved. Whenever necessary, the cord structures were sprayed with papaverine hydrochloride to increase the arterial beat. All dilated veins of the spermatic cord were identified, tagged with vessel loops, then ligated and transected. Vasal veins were ligated only if they ex-

ceed 2 mm in diameter. Sclerosis of additional veins was not used. The incision was closed with absorbable sutures. Procedures were performed on an outpatient basis using either regional or local anesthesia in combination with short-acting sedation. The surgical technique used in this study was nearly identical to that described previously (15). After surgery, semen samples were obtained at 2 - 4 month intervals and evaluated according to the WHO criteria (14). The mean postoperative follow-up duration was 18.9 ± 5.3 months. An average was computed for each seminal parameter, and then used for statistical purposes.

Testis Biopsy

Open bilateral diagnostic testis biopsies were performed in all subjects at the same time of varicocele repair. For this, a 1-cm transverse incision was made at the anterior scrotal skin. The scrotal tunics were incised until identification of the tunica albuginea. The testis was manipulated to expose a relatively avascular area, where a 5-mm incision was made over the tunica. By producing counter pressure on the posterior surface of the testis, testicular tissue was evaginated into the incision, and a single piece measuring approximately 3 x 3 x 3 mm was excised with a wet and sharp Iris scissors using a no-touch method. The specimens were transferred to the Bouin's solution and afterwards stained with hematoxylin and eosin, and histologically sectioned. Testicular biopsies were classified as follows: (a) Sertoli cell-only (SCO), (b) maturation arrest and (c) hypospermatogenesis (HYPO). At least 50 seminiferous tubules were evaluated on each testis. Sertoli cell-only category indicated that germinative cells were absent. Maturation arrest (MA) category was defined as absence of mature spermatozoa, despite normal early stages of spermatogenesis. Hypospermatogenesis indicated that all stages of the spermatogenic cycle were present, including mature sperm, but there was a proportional reduction in the number of all germ cells at each level.

Microdissection testicular sperm extraction (micro-TESE) (16) for procurement of spermatozoa within the testis has been performed bilaterally at least 6 months postoperatively (median: 9 months; range: 6-15 months) in all men who showed no improvement after surgery. Concomitantly, a single piece measuring approximately 3 x 3 x 3 mm was excised without using microsurgery from a surrounding area of the microdissected samples for testicular histology diagnosis. Testicular sperm extraction with microdissection has been chosen in such cases because of its concept, i.e., a microscope-guided testis biopsy that has been shown to significantly improve sperm yield with minimal tissue excision (16).

Statistical Analysis

Preoperative hormone levels and testicular size were compared among the groups and between the patients who did and did not improve after varicocele repair. After varicocelectomy, sperm parameters were compared between the groups with testicular histology diagnosis of hypospermatogenesis and maturation arrest. Due to the large variation observed in clinical and sperm parameters, our data are presented as median and percentiles 25% and 75%, which better describes our patient population. Nonparametric tests were used for statistical analysis because our data were drawn from not normally distributed population (17). Kruskal-Wallis test was used to compare FSH levels and total testicular volume among groups. Mann-Whitney rank-sum test was used to compare sperm count, total number of motile sperm, sperm viability and normal forms between hypospermatogenesis and maturation arrest groups. The Mann-Whitney test was also used to compare FSH levels between patients who improved or not after surgery. Although nonparametric tests are not as powerful as parametric methods for statistical evaluation, they are more reliable when analyzing data from not normally distributed populations (17).

Pairwise comparisons using the Fisher exact test were performed to analyze statistical differences between spermatogenesis recovery rates. The Fisher exact test was used instead of the Chi-square test due to the small number of patients in each group (17).

Sperm retrieval success rates were not compared due to the extremely low number of subjects in each group. A value of < 0.05 was considered statistically significant. Statistical calculations were performed using computer software (Statistica®, Stasoft, Tulsa, OK).

RESULTS

Hypospermatogenesis (HYPO) was identified on diagnostic testis biopsy in 6 men, maturation arrest (MA) in 5 and Sertoli cell-only (SCO) in 6. Overall, presence of spermatozoa in the ejaculates was achieved in 47% (8/17) of men after varicocele repair, but only 35% (6/17) of them had motile sperm in their ejaculates. Only men with testicular histology revealing HYPO (5/6) or maturation arrest (3/5) had improvement after surgery. Median (25% - 75% percentile) motile sperm count for both groups were 0.9 X 10^6/mL (0.1 - 1.8 X 10^6/mL) and 0.7 X 10^6/mL (0.1 - 1.1), respectively (p = 0.87), Table-1. The mean time for appearance of spermatozoa in the ejaculates was 5 months (range 3 - 6 months). One (HYPO) of 8 men who improved after surgery contributed to an unassisted pregnancy which occurred 6 months after surgery. Median (25% - 75% percentile) motile sperm count for this man during the follow-up period was 1.5 X 10^6/mL (1.1 - 1.8 X 10^6/mL). None of the patients who had sperm in the ejaculates after varicocele repair returned to be azoospermic during the follow-up period.

Preoperative serum FSH levels were 10.9 (3.2 - 21.2) mUI/mL and 19.5 (7.5 - 31.8) mUI/mL in men who did and did not show recovery of spermatogenesis after varicocele repair (p = 0.22). FSH levels in men with HYPO, MA and SCO were not significantly different (Table-1). Appearance of sperm in the ejaculates was observed in 6 (46%) of 13 men with testes of reduced volume and in 2 (50%) of 4 men with normal-sized testes (p = 0.99). Combined testicular volume (right plus left sides) in men with HYPO, MA and SCO were not significantly different (Table-1).

Appearance of spermatozoa in the ejaculate was not achieved in any men with testicular histology diagnosis of SCO. These individuals (n = 6) as well as the ones with testicular histology diagnosis of HYPO (n = 1) and MA (n = 2) underwent postoperative bilateral open single testis biopsy concomitant with microsurgical-guided sperm retrieval (Micro-TESE) for intracytoplasmic sperm injection (ICSI) (n = 6) or for diagnostic purposes only (n = 3). Postoperative testicular histology diagnosis was unchanged in comparison to preoperative ones. Successful testicular sperm retrieval using Micro-TESE was achieved in 4 of 9 (44.4%) individuals who did not improve after surgery, including one who had testicular histology diagnosis of SCO (Table-1).

COMMENTS

Recovery of spermatogenesis is possible after surgical repair of clinical varicoceles in men with nonobstructive azoospermia. Few studies have shown that nonobstructive azoospermic patients with clinical varicoceles can benefit from varicocelectomy (7-12). These studies reported improvement of semen parameters in up to 50%, including rare cases of spontaneous pregnancies. Matthews et al. (7), studying 22 men, found that 54% presented sperm in the ejaculate postoperatively. Although diagnostic testicular biopsy was not available for many of them, those men most likely to benefit had either hypospermatogenesis or maturation arrest. Kim et al., studying 28 patients, demonstrated that testicular histology was the most important predictive factor on outcome (8). In their study, patients with Sertoli cell-only pattern and maturation arrest at spermatocyte stage have not shown improvement; however, 50% of the individuals with maturation arrest at spermatid stage and 55% of them with hypospermatogenesis achieved postoperative improvement with appearance of sperm in their ejaculates (8). Pasqualotto et al., on the other hand, reported that improvement in semen quality after varicocelectomy may be possible even in azoospermic patients who present germ cell aplasia in a single large testis biopsy (10). In comparison, our series demonstrated postoperative return of sperm in the ejaculate in 47% of men after varicocele repair. We found that testicular histology diagnosis from a single large testis biopsy was the most important predictive factor on outcome. Only men with testicular histology revealing hypospermatogenesis or maturation arrest had improvement after surgery. All patients with Sertoli cell-only pattern still remained azoospermic after varicocelectomy. In our series, testicular volume and preoperative serum FSH levels were not predictive of treatment outcome, and these results were confirmed by others (9,11).

Table 1 – *Follicle-stimulating hormone levels (FSH), testicular volume, postoperative semen parameters, spermatogenesis recovery and sperm retrieval success rates in patients with testicular histology diagnosis of hypospermatogenesis (HYPO), maturation arrest (MA) and Sertoli-cell only (SCO).*

	Hypospermatogenesis (n = 6)	**Maturation Arrest (n = 5)**	**Sertoli Cell-Only (n = 6)**	**p Value §**	**p Value †**
FSH (mUI/mL)	7.9 (4.5-15.5)	9.3 (5.5-19.9)	12.9 (7.9-22.5)	0.16	-
Left + right testicle (mL)	35.0 (25.0-42.0)	30.0 (28.0-40.0)	27.0 (21.0-33.0)	0.07	-
Sperm count ($x10^6$/mL)	1.5 (0.1-2.0)	1.2 (0.1-1.9)	0.0	-	0.85
Total number of motile sperm ($x10^6$)	0.9 (0.1-1.8)	0.7 (0.1-1.1)	0.0	-	0.87
Sperm viability (%)	75.0 (61.0-86.0)	56.0 (40.0-63.0)	NA	-	0.06
Normal forms (%)*	7.5 (2.0-12.0)	4.2 (1.0-8.0)	NA	-	0.20
Spermatogenesis recovery rate (%)	5/6 (83.3%)	3/5 (75%)	0/6 (0%)	0.02	0.74
Sperm retrieval success rate (%)	1/1 (100%)	2/2 (100%)	1/6 (16.6%)	NA	NA

*******Sperm morphology according to the Kruger's strict criteria; NA=not applicable; **§** Comparisons among the 3 groups using the Kruskal-Wallis test; **†** Comparison between HYPO and MA groups using the Mann-Whitney rank-sum test; Spermatogenesis recovery rates were compared using the Fisher exact test; P values < 0.05 were considered significant.*

Interestingly, in our series, despite the induction of spermatogenesis in men with hypospermatogenesis and maturation arrest, we found that semen parameters still remained severely abnormal after varicocele repair. Severe oligozoospermia and teratozoospermia have been observed in all individuals after repeated routine semen analyses. In addition, 25% (2/8) of men who improved after surgery presented with only immotile sperm in their ejaculates. Therefore, it is likely that advanced assisted reproductive techniques will be required for most couples to initiate a pregnancy, as shown in a recent study by Schlegel & Kaufmann who reported that only 9.6% men after varicocele repair had adequate motile sperm in the ejaculate for ICSI (13). The latter does not diminish the clinical impact of our findings because even modest improvements in semen quality after varicocele repair may expand the couple's reproductive options. Although our series is small, one couple achieved an unassisted pregnancy, which would have been otherwise impossible if the varicocelectomy had not been performed. Matthews et al. reported that 9% of azoospermic men who improved after varicocele repair contributed to unassisted pregnancies (7). Czaplicki et al. (1), Kim et al. (8) and Pasqualotto et al. (2) also reported

unassisted pregnancies after varicocelectomy in azoospermic patients.

Although spermatozoa have been consistently found in repeated semen analyses during the follow-up period, we have observed that appearance of sperm within the ejaculates may not be immediate. The clinician should be advised that it may take up to 6 months after varicocelectomy to consider that varicocele repair has not been able to recover spermatogenesis. Pasqualotto et al., on the other hand, reported that most of their patients relapsed into azoospermia 6 months after recovery of spermatogenesis; therefore, information of the possibility of sperm cryopreservation is also given for such individuals (10). In our series, none of our patients relapsed into azoospermia during the mean follow-up period of 18 months. However, patient population between studies may be distinct. While 4 out of 5 germ cell aplasia patients of the authors' study recovered spermatogenesis after surgery, none of ours with similar histology did. Most of our patients who recovered after surgery had hypospermatogenesis on testicular histology, and it is possible that these patients may have a better long-term prognosis in terms of sperm production maintenance than those with SCO who eventually improve after surgery.

The only possible option for nonobstructive azoospermic men to have their own biological children is invasive testicular sperm retrieval, such as testicular sperm extraction (TESE) associated with ICSI. Retrieval techniques fail to obtain sperm for ICSI in 25-50% of men with spermatogenic failure (18-19), and clinical parameters including testicular size and FSH levels do not accurately predict whether or not sperm will be recovered during testicular exploration (18). Schlegel et al. suggested that the ability to obtain sperm is dependent on the presence of at least one area of spermatogenic activity on a diagnostic testicular biopsy (18). Even when the procedure is successful, the number of sperm harvested is extremely low, thus limiting the feasibility of cryopreservation of exceeded spermatozoa from a TESE-ICSI cycle. In addition, some individuals have to undergo repeated biopsies that may injury testicular vascular supply, thereby causing loss of parenchyma (20).

As discussed previously, even though most nonobstructive azoospermic men who benefit from varicocele repair will still require in vitro fertilization in association with intracytoplasmic sperm injection (ICSI) to achieve pregnancy, the procedure can be performed using ejaculated sperm, which is technically easier and provides better results than using sperm harvested from testicular sperm extraction (TESE) (21,22). Furthermore, it avoids the risk of ICSI cycle cancellation by an unsuccessful TESE or the use of donor backup (21).

In our study, postoperative testicular biopsy concomitant with microsurgical-guided sperm retrieval (Micro-TESE) have been performed in all individuals who remained azoospermic after varicocele repair. Although testicular histology diagnosis remained unchanged in comparison to preoperative ones, these findings must be taken into consideration with caution because single biopsies have the limitation to represent the predominant testicular pattern only. However, we cannot exclude that some degree of improvement in spermatogenesis may occur within the testis which are difficult to identify under standard pathology examination. In this regard, North et al. have recently demonstrated in a very elegant study using microthermic evaluation and histomorphometry that meiotic abnormalities can be reversible in azoospermic men with bilateral varicocele treated by microsurgical correction (23).

In our series, successful testicular sperm retrieval using Micro-TESE was achieved in all hypospermatogenesis and maturation arrest patients, and in 1 out of 6 SCO patients (44.4%) who did not improve after surgery. We believe that a possible explanation for these findings may be the fact that microdissected samples, which are guided-biopsies based on tubule diameter, were able to extract focal areas of complete spermatogenesis rather than the random parenchyma extraction obtained from standard biopsies. During microdissection, testicular parenchyma simultaneously extracted for diagnosis (single biopsies) and for sperm procurement may reflect distinct areas of spermatogenesis, based on the current knowledge on spermatogenesis heterogeneity. Although comparison within the same area would be preferable, in most of our cases microdissected

samples were extracted for sperm procurement during an ICSI cycle, and histological analyses of part of such material could limit the patient chance of having sperm found for ICSI, thus limiting the pregnancy success rate.

Therefore, testicular sperm retrieval for intracytoplasmic sperm injection can be successfully attempted in nonobstructive azoospermic men with clinical varicoceles who fail to improve after varicocelectomy. Ability to find spermatozoa within the testis of such individuals is related to the existence of focal areas of spermatogenesis, which may not be identified in a single testis biopsy (9,19). Schlegel et al. have demonstrated that testicular sperm retrieval using microsurgery-guided biopsies (Micro-TESE) optimizes the chance of finding the focal areas of normal spermatogenesis. Micro-TESE has also shown to provide better sperm yields with minimum tissue excision (16).

Of utmost importance is the fact that 15-20% of nonobstructive azoospermic patients have deletions of the Y chromosome (Yq) or karyotypic anomalies (24). In addition, 17% of men with varicoceles and severe oligozoospermia or azoospermia have deletions of Yq (25). It is possible that the presence of varicocele in men with germ cell aplasia is coincidental. Spermatogenic failure in such individuals may be related to an underlying genetic defect rather than varicocele-induced testicular damage. However, it is also possible that spermatogenic impairment related to genetic defects may be more serious if a varicocele is present. Therefore, genetic testing prior to considering varicocelectomy seems appropriate for a proper diagnosis and counseling. Repair of clinical varicoceles in men with testicular failure and genetic abnormalities, such as Yq microdeletions or Klinefelter karyotype, is currently controversial, and more data are needed to allow firm conclusions.

In our study, none of the patients who had genetic screening presented Y chromosome or karyotype abnormalities. In addition, no association between successful outcome and clinical parameters such as FSH levels, testicular volume, unilateral or bilateral varicocele repair were apparent. Novel methods are under investigation for their ability to predict the presence of testicular spermatozoa in azoospermic men with varicoceles, pre- and post-varicocelectomy, such as testicular tissue telomerase assay (25).

CONCLUSIONS

Our observations suggest that microsurgical varicocele repair in nonobstructive azoospermic men with clinical varicoceles can result in sperm appearance in the ejaculate when hypospermatogenesis or maturation arrest is present on testicular histology diagnosis. We believe that testicular histology may be helpful to select men who are candidates for varicocele repair, rather than resorting to testicular sperm extraction in preparation for assisted reproductive technology. Counseling is important for such individuals because poor sperm quality is expected when recovery of spermatogenesis is achieved after varicocele repair, and it is likely that assisted reproductive techniques will be required for such couples to initiate a pregnancy.

CONFLICT OF INTEREST

None declared.

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