Surgery for Male Infertility

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1. Introduction

Male reproductive health has become an important issue in current assisted reproduction. During recent years the perception of the “male factor” contributing to infertility has undergone a number of revisions, realizing that >50% of infertility is entirely or in part due to a male factor [1]. Outcomes of assisted reproduction are primarily dependent on the availability of viable sperm and age of the female member of the couple being treated. In azoospermic men intracytoplasmic sperm injection (ICSI) has become the standard therapy [2–4]. Nevertheless, the treatment of obstructive and nonobstructive azoospermia (NOA) will often include a surgical intervention. For men with NOA, surgical sperm retrieval is required to allow successful treatment with ICSI. For men with obstructive azoospermia sperm retrieval rates approach 100% and microsurgical vasectomy reversal provides a very high chance of resulting in delivery of a child. Additionally, surgical treatment is more cost effective than alternative forms of treatment such as assisted reproduction procedures alone [5,6]. The aim of this article is to provide updated information regarding surgical treatment options for male infertility and to present current literature and data.

2. Testis biopsy

A testis biopsy is a diagnostic technique to assess spermatogenesis. It is most useful to determine whether obstruction is the cause of azoospermia. In men with NOA testis biopsy can provide some, but not absolute, diagnostic information. It can also rule
out the unlikely possibility of testicular intratubular germ cell neoplasia (carcinoma in situ) that is more common in men with unexplained unilateral testicular atrophy or with a history of cryptorchidism [7]. Infertile men with abnormal semen analyses have a 20-fold greater incidence of testicular cancer compared to the general population [8]. Furthermore, it is possible to take additional tissue during this diagnostic procedure that can be frozen for subsequent therapeutic trials of assisted reproduction. Cytologic evaluation, when performed concurrently with standard testicular biopsy, may provide important adjunctive information. Cytospin and touch prep techniques allow for the detection of late maturation arrest, which is not evaluable on fixed permanent sections. Additionally, cytospin and touch prep techniques allow the evaluation of the presence of sperm within the seminiferous tubule without the removal of an additional piece of testicular parenchyma. The wet prep technique allows the evaluation of sperm motility. The presence of sperm motility appears to be highly indicative of the presence of obstruction. Further information regarding the frequency of late maturation arrest and the endurance of the predictive value of wet prep sperm motility is needed. At present, cytologic techniques should best be considered adjuncts to, but not replacements of, careful evaluation of fixed permanent testicular biopsy specimens [9].

Adequate specimens for tissue evaluation can be obtained by open biopsy, needle biopsy, or, occasionally, fine-needle aspiration [10–12]. Given the potential inadequacy of needle biopsy or fine-needle aspiration, with the attendant risks to the vasculature of the testis, the open biopsy technique is preferable [13,14]. The biopsy should be performed prior to reconstruction (rather than simultaneous to vasoepididymostomy), so that a definitive analysis of sperm production is possible on fixed sections prior to further exploration. Diagnostic information on the status of spermatogenesis is most reliably determined on evaluation of a thin-sectioned, stained, fixed tissue specimen. In testicular biopsies the most advanced spermatogenic pattern, as opposed to the predominant pattern, appears to affect the results of sperm retrieval. For men who had at least one area of hypospermatogenesis present on diagnostic testis biopsy, spermatozoa were retrieved in 57 of 73 attempts (81%), whereas for men with maturation arrest as the most advanced pattern, spermatozoa were retrieved in only 27 of 62 attempts (44%). If the entire diagnostic biopsy had a Sertoli cell-only pattern, our most recent data found that sperm could be retrieved for 41% (98 of 257) of testicular sperm extraction (TESE) attempts [15]. Although no finding absolutely determined sperm retrieval or negated the possibility of successful TESE, the findings of diagnostic biopsy were helpful in evaluating the chance of success with testicular sperm extraction [16].

In the authors’ experience a diagnostic testis biopsy is not required prior to TESE-ICSI for NOA. A diagnostic biopsy should be performed if the etiology of azoospermia is not clear, if the risk of carcinoma in situ is high (rare), or if the results of biopsy will affect the couple’s choice to undergo TESE-ICSI [17].

3. Genetic abnormalities and testing

Genetic disorders are associated with spermatogenic failure. These abnormalities include chromosomal abnormalities, detectable with routine karyotype testing, Y chromosome microdeletions, so-called “AZF defects” and mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is apparent that assisted reproduction and in particular ICSI may skew the natural selection process and that a potential risk associated with its use is the transfer of genetic defects from one generation to the next. Therefore, karyotype evaluation and Y chromosome microdeletion analysis is recommended for men with severe male factor infertility, including sperm concentrations <10 × 10^6/cc and NOA, before treatment with assisted reproduction [17].

3.1. Karyotype evaluation

The most common karyotypic abnormality in men with severe male factor infertility is Klinefelter’s syndrome, affecting up to 7–13% of azoospermic men. Almost all men with the “classic form” (47,XXY) of Klinefelter’s syndrome will be azoospermic, whereas limited sperm production is commonly found in men with a mosaic pattern of Klinefelter’s syndrome. Other karyotypic abnormalities identified include Robertsonian translocations, chromosomal inversions, and sex chromosome abnormalities.

3.2. Y chromosome (AZF) microdeletions

Microdeletions on the long arm of the Y chromosome have been demonstrated to disrupt spermatogenesis in 5–15% of men with azoospermia or severe oligospermia. Y chromosome microdeletions affecting fertility usually involve deletion of one or more of the entire AZFa, AZFb, or AZFc regions. The
specific region that is missing on the Y chromosome may provide prognostic significance. Approximately two thirds of men with deletions involving only AZFc have sperm present in the ejaculate. In azoospermic men with AZFc deletions, sperm production is commonly present within the testicle, and TESE is as successful as for other men with NOA. For men with deletions involving the AZFb region, the chance of having sperm in the ejaculate or finding sperm with TESE is severely decreased. Deletions involving the entire AZFa region are also commonly associated with a Sertoli cell-only pattern on diagnostic biopsy [17].

3.3. Cystic fibrosis gene mutation

A strong association exists between congenital bilateral absence of the vas deferens (CBAVD) and mutations of the CFTR gene. About two thirds of men with CBAVD but no other clinical signs of cystic fibrosis have mutations of the CFTR gene. Therefore, it is important to test the partner for CFTR gene abnormalities before applying a treatment that uses his sperm. Genetic testing for CFTR mutations in the female partner should be offered before proceeding with treatments that use the sperm of men with CBAVD [18].

4. Sperm retrieval for assisted reproduction

Sperm retrieval for use with the advanced form of assisted reproduction, ICSI, is possible for many men with obstructive azoospermia and NOA [19]. In obstructive azoospermia, several techniques exist to allow for sperm retrieval rates approaching 100%. In NOA, TESE is essential for subsequent ICSI. However, in patients with defective spermatogenesis sperm retrieval is less certain [20]. Some couples will not have sperm retrieved with TESE. Therefore, the use of frozen donor spermatozoa as back-up should be discussed prior to simultaneous TESE-ICSI attempts.

4.1. Obstructive azoospermia

It had long been thought that sperm exiting the testis lack maturity, motility, and fertilizing capability and that transit through the epididymis is essential to the acquisition of these features. In the unobstructed setting, sperm quality improves as the spermatozoa travel from caput to cauda; this is not true, however, in the obstructed setting. In reproductive tract obstruction, improved motility is seen in sperm retrieved from the caput epididymis compared to the cauda, as sperm extracted from the tail of an obstructed epididymis are in advanced stages of degeneration and necrosis. Thus, in the case of obstruction, better quality sperm can be found proximally: in the rete testis, vasa efferentia, or caput epididymis; the more distal cauda epididymis is the site of sperm degeneration. These factors should be taken into account during any attempt at sperm removal [9].

4.2. NOA

Human testicular histology is heterogeneous. Small foci of abnormal spermatogenesis can be adjacent to normal seminiferous tubules. This formerly casual observation is now the cornerstone of treatment for men with NOA. Successful sperm retrieval is possible in most testicular sperm retrieval attempts in men with NOA, despite diagnostic testis biopsy specimens showing predominantly maturation arrest. The ability to retrieve sperm from the testes of men with NOA is independent of testicular size and follicle-stimulating hormone (FSH) level, but dependent on the most advanced level of spermatogenesis identified. All standard parameters of testicular evaluation (testicular volume, FSH, inhibin B levels) evaluate overall function of the testis. Because sperm retrieval and pregnancy depend on finding sperm in just one small focus of the testis, the only predictor of successful treatment is the most developed region of the testis, not the predominant pattern of testicular histology, overall testicular volume, or FSH level. These observations suggest that nearly all cases of male factor infertility can potentially be treated [9].

4.3. TESE

Scrotal exploration is performed through a median raphe or transverse scrotal incision under local or general anesthesia. Sperm are retrieved using an open testicular biopsy technique. To confirm accurate identification of the testis and to avoid any injury to the epididymis, delivery of the testis is routinely performed. Testicular blood vessels in the tunica albuginea are identified. An avascular region near the midpoint of the medial, lateral, or anterior surface of the testis is chosen, and a generous incision in the tunica albuginea, avoiding any capsular testicular vessels, is created to directly examine a wide area of testicular parenchyma.

4.4. Microdissection TESE

The technique that we developed allows the removal of tiny volumes (2–3 mg) of testicular tissue
with improved sperm yield [21]. This technique requires use of an operating microscope and there is a brief learning curve to identify which tubules contain spermatogenesis. The tubules containing sperm can often be visually identified under an operating microscope after opening the testis, when \( \times 15-25 \) magnification is used to assist the biopsies. This approach (1) improves the yield of sperm per biopsy, (2) reduces tissue removal, (3) makes the embryologist’s job easier in finding sperm because less tissue has to be examined, and (4) allows identification of blood vessels within the testicle, minimizing the risk of vascular injury and loss of other areas of the testis [22,23]. Our observations of better sperm yield when using microdissection TESE (vs. multiple random biopsies) has been confirmed by several other investigators [24–26]. The benefit of microdissection TESE over standard testis biopsies has been demonstrated in multiple controlled surgical series. Amer et al compared microdissection TESE with open surgical biopsy in the same patient. In this randomized, controlled trial the microsurgical approach was found to be relatively safer than the conventional technique with significantly improved sperm yield [24]. Also Okada et al demonstrated a higher sperm recovery rate combined with a significantly lower complication rate for microdissection than for conventional TESE [25].

Encouraging experience has been obtained at Weill-Cornell with TESE-ICSI in the past 684 attempted treatment cycles for couples in whom the man had NOA. The mean age of patients entering treatment was 36.1 yr for men and 32.1 yr for women. In men, the initial mean serum FSH level was 22.7 IU/l (normal, 1–8 IU/l), and average testis volume 9.6 cc. During the past 684 attempted TESE-ICSI cycles, sperm were retrieved for injection in 406 cycles (59% retrieval rate). For those cycles in which sperm were retrieved, the fertilization rate per injected oocyte was 59% (2299 of 4136), and embryo transfer occurred in 92% of cycles. Clinical pregnancies (fetal heartbeat on ultrasound) were established in 48% (194 of 406) of evaluable cycles and live deliveries occurred in 42% of cycles for which sufficient time had passed for completed gestation. A total of 228 children have been born from our center. Twin deliveries occurred in 11% of cases, triplets in <1%, and singleton deliveries for the remainder. No etiology ofazoospermia provided an absolute predictor for the presence or absence of sperm within the testes, except for deletions of the entire AZFa and AZFb region. Testicular volume and serum FSH levels did not predict sperm retrieval.

Fifty-one men with classic, non-mosaic Klinefelter’s syndrome (47,XXY, or mosaic patterns that do not include 46,XY) underwent attempted sperm retrieval during simultaneous 69 ICSI cycles at our institution. An additional three in vitro fertilization (IVF) cycles were done in which cryopreserved sperm from previous TESE procedures were used. Sperm were found in 71% (49 of 69) of the fresh retrieval attempts. Of the cycles in which sperm were retrieved by TESE, the fertilization rate per injected oocyte was 60%, embryo transfer occurred in 88%, and clinical pregnancy was achieved in 41% (20 of 49), with 28 children born to date. A multiple gestation rate of 39% has been seen in these pregnancies (3 triplets, 5 twins). All children have been healthy (all 46,XX girls and 46,XY boys). Pretreatment testicular biopsy histology was not helpful in distinguishing who would succeed with microdissection TESE for patients with Klinefelter’s syndrome. Although a majority of men had Sertoli cell-only on diagnostic biopsy, 70% of these patients had sperm found on subsequent microdissection TESE. Even though two of the patients treated had previously undergone multiple random biopsy TESE with no sperm found, sperm were retrieved in a subsequent procedure using the microdissection technique [27]. These findings illustrate the potential for TESE-ICSI to provide fertility despite underlying genetic abnormalities [28].

5. Varicocelectomy

Varicoceles occur in 15% of men in the general population, in 35% of men with primary infertility [29], and in 81% of men with secondary infertility [30]. The role of the varicocele in male infertility, however, continues to be controversial. Several uncontrolled studies of varicocelectomy have suggested that patients who undergo varicocelectomy repair will have demonstrable improvement in semen parameters. However, few randomized controlled studies have documented a beneficial effect [17].

Surgical approaches to varicocele correction include inguinal, retroperitoneal, and laparoscopic techniques. Transvenous embolization as well as antegrade and retrograde sclerotherapy are also highly successful with minimal morbidity, but their application is limited to those with significant experience in these techniques. Laparoscopic approaches appear to be fairly successful. Laparoscopy, however, takes the subcutaneous procedure of inguinal varicocelectomy and converts it into an intra-abdominal approach, which is of higher risk. Unfortunately, only few controlled studies have
compared the different treatment options for varicocele. Cayan et al prospectively evaluated the difference in sperm parameters, pregnancy and recurrence rates, and complications after high ligation surgery versus microsurgical high inguinal varicocelectomy. His results showed significantly lower recurrence and hydrocele rates, a higher increase in sperm motility, and higher pregnancy rates in patients undergoing a microsurgical varicocelectomy [31]. Zucchi et al analyzed the outcome following conventional open surgery with inguinal approach versus antegrade sclerotherapy. He demonstrated that sclerotherapy combines shorter surgical time and faster recovery with comparable other parameters [32]. No prospective randomized study comparing outcome and complications of microsurgical approach with antegrade or retrograde sclerotherapy exits.

Varicocelectomy involves ligation of all internal spermatic veins to prevent the retrograde flow of blood in this system that is pathognomonic of a varicocele. To effectively and safely correct a varicocele, one should: (1) leave the vas deferens and its associated vessels intact, (2) divide all internal spermatic veins (and external spermatic veins if the inguinal approach is used), and (3) leave the lymphatic vessels and testicular arteries intact. Difficulty in visualizing any small internal spermatic vessels in the retroperitoneum explains the 10% clinical recurrence/persistence rate after a “Palomo varicocelectomy.” Even with a muscle-splitting approach, more morbidity occurs with this approach than an inguinal approach.

The optimal surgical approach to varicocelectomy is an inguinal or subinguinal one, with at least ×6–8 optical magnification. If it is readily available, an operating microscope provides the ability to use variable magnification during the procedure. In the authors’ experience with both approaches, the use of an operating microscope clearly provides better visualization of the lymphatics and the testicular arteries during varicocelectomy. Although it is tedious to perform a microsurgical dissection, the advantages are that significant: testicular arteries can be identified and preserved in >99.5% of cases, the varicocele recurrence/persistence rate is <0.5%, and hydroceles occur postoperatively in <0.5% of cases. It is highly upsetting to both patient and physician when painful testicular atrophy occurs because of inadvertent injury to the testicular artery or when a massive, symptomatic hydrocele is present postoperatively. Considering the gravity of these postoperative complications, it certainly seems worth extending the intraoperative case time by 15 or 20 min to decrease the postoperative complication rate from 10% to approximately 1%. Therefore, there is little rationale for performance of varicocele repair without optical magnification [9].

A recent meta-analysis evaluated whether treatment of varicocele improves pregnancy rates in couples with male or unexplained subfertility associated with a varicocele [33]. In a systematic review of seven randomized controlled studies, Evers and Collins found 61 pregnancies among 281 treated couples and 50 pregnancies among 259 controls. The authors reported an overall relative benefit of treatment of 1.01 (95%CI, 0.73–1.40) by the fixed effects model and 1.04 (95%CI, 0.62–1.75) by the random effects model. Performing a subgroup analyses, no beneficial effect of varicocele treatment was found in trials restricted to male subfertility with clinical varicocele, or in those that included men with subclinical varicocele or normal semen analysis. Unfortunately, this review included studies in which patients had normal semen parameters or were treated for “subclinical varicoceles,” a practice that is not supported by even the most ardent supporters of varicocele repair.

Of further relevant interest is the increasing practice of varicocele repair for men with NOA. One recent study found a return of sperm to the ejaculate in 12 of 28 men (43%) men with NOA at an average follow-up of 24 mo. A second study found spermatogenesis adequate to produce sperm in the ejaculate of 12 of 22 men (55%) with NOA. Other smaller and older studies have conflicting results. A recent analysis of a series of patients with varicoceles and NOA who were evaluated and treated at Weill-Cornell revealed little benefit for that practice. Of 31 men who underwent varicocele repair for documented NOA, 20% (7 of 31) had sperm on at least one postoperative semen analysis. However, after varicocele repair, only 3 of 31 men (0.6%) had adequate motile sperm in the ejaculate for ICSI (without TESE). A history of prior varicocele repair did not affect the results of TESE for men with NOA and varicoceles. Retrospective analysis of patients with clinical varicoceles identified before TESE shows that the rate of sperm retrieval was identical in those who had their varicoceles repaired before TESE as compared with those who did not have them repaired before TESE, 60% (41 of 68) and 60% (42 of 70), respectively [34]. Based on these data, varicocele repair is of limited value for men with NOA and varicoceles.

In the authors’ opinion, surgical repair should probably be reserved for men who are very young and have large varicoceles, and possibly for those with testicular atrophy associated with a varicocele.
6. Vasectomy reversal

Reversal of vasectomy is technically possible and highly successful for a majority of men. The modern techniques for vasovasostomy are modifications of the microsurgical approaches described in the mid-1970s by Drs. Owens and Silber. Microsurgical techniques generally have high postoperative patency rates in experienced hands. Yet, only 50–70% of couples actually achieve a pregnancy after vasovasostomy [35]. The duration of time after vasectomy is important. Secondary obstruction of the epididymis becomes increasingly more common when >10 yr have passed after vasectomy. Although the duration of time after vasectomy has an impact on pregnancy rate, Silber and Grotjan suggested that the age of the female partner has the greatest impact. A review of 4010 cases performed by the same surgeon showed that among female partners under age 30 yr at the time of vasectomy reversal, 94.2% established a pregnancy, whereas only 61.1% of female partners aged ≥40 yr became pregnant. Regarding antisperm antibodies there is no clear evidence that they account for failure to conceive after vasectomy reversal [36]. Rather, it is likely that female infertility, secondary obstruction in the epididymis, or recurrent obstruction at the anastomotic site contribute to the inability to achieve pregnancies in partners of men with established patency after vasovasostomy.

The technique for vasectomy reversal (i.e., vasovasostomy vs. vasoepididymostomy) depends on the intravasal findings at the time of surgical exploration. In addition, obstructive lesions may occur in the vas deferens at the inguinal level after hernia repair. Testis biopsy is not routinely indicated prior to vasectomy reversal. Optimal results with vasovasostomy (or vasoepididymostomy) are achieved when these principles are followed: (1) accurate mucosa-to-mucosa anastomosis to allow a leakproof anastomosis, (2) tension-free anastomosis, (3) adequate blood supply to the ends of the vas with healthy mucosa and muscularis, and (4) atraumatic technique. Adherence to these fundamental principles is far more important than the number of layers performed or the exact suture material used.

Using a microsurgical approach, sperm appear in the semen of 85–90% of men, and 50–70% of their wives become pregnant after vasovasostomy [35]. The Vasovasostomy Study Group found that results were progressively less favorable after microsurgical vasectomy reversal as the obstructive interval (time from vasectomy until its reversal) lengthened [37]. That group reported rates of return of sperm to the semen and pregnancy, respectively, in 1247 patients to be 97% and 76% if the obstructive interval was <3 yr, 88% and 53% if 3–8 yr, 79% and 44% if 9–14 yr, and 71% and 30% if ≥15 yr.

Besides being successful at providing high rates of pregnancy, microsurgery of obstructive azoospermia is typically more cost effective than alternative forms of treatment such as assisted reproduction procedures alone. Pavlovich and Schlegel evaluated the cost per delivery using two different initial approaches to the treatment of postvasectomy infertility. In their analysis the most cost-effective approach to treatment of postvasectomy infertility was microsurgical vasectomy reversal. This treatment also had the highest chance of resulting in delivery of a child for a single intervention [5].

Kolettis and Thomas compared vasoepididymostomy to microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection for treatment of epididymal obstruction secondary to vasectomy. They also concluded that vasoepididymostomy is more successful and more cost effective than microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection for vasectomy reversal [6].

7. Summary

Surgical treatment can be an effective approach for the diagnosis and treatment of male infertility, particularly in men with obstructive azoospermia or NOA. Accurate identification of the cause of infertility and microsurgical approaches to its management will often provide more effective treatment with lower morbidity. Appropriate training in microsurgery and overall experience with surgical techniques will produce the most effective treatment of the infertile man.

References

CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. In patients with obstructive azoospermia
   A. Nonmotile sperm can be found in the vasa efferentia or caput epididymis.
   B. Sperm cannot be found in the vasa efferentia or caput epididymis.
   C. Sperm quality improves as the spermatozoa travel from caput to cauda.
   D. Sperm quality declines as the spermatozoa travel from caput to cauda.

2. In testicular biopsies
   A. The results provide definitive proof of whether sperm will be found with testicular sperm extraction.
   B. The predominant pattern appears to affect the results of sperm retrieval.
   C. The most advanced spermatogenic pattern appears to affect the results of sperm retrieval.
   D. A Sertoli cell-only pattern negates the possibility of successful testicular sperm extraction.

3. Varicoceles occur in
   A. 15% of men with primary infertility.
   B. 35% of men with primary infertility.
   C. 53% of men with primary infertility.
   D. 81% of men with primary infertility.

4. To effectively and safely correct a varicocele, one should
   A. Leave the internal spermatic veins intact.
   B. Leave the external spermatic veins intact if the inguinal approach is used.
   C. Divide the lymphatic vessels and leave the testicular arteries intact.
   D. Leave the vas deferens and its associated vessels intact.

5. Which appears to be the least important principle in achieving optimal results with vasovasostomy?
   A. Accurate mucosa-to-mucosa anastomosis to allow a leak-proof anastomosis.
   B. Tension-free anastomosis.
   C. Adequate blood supply to the ends of the vas with healthy mucosa and muscularis.
   D. Number of layers performed.

6. Using a microsurgical approach for vasovasostomy,
   A. Sperm appear in the semen of 85–90% of men, and 70–80% of their wives become pregnant.
   B. Sperm appear in the semen of 50–60% of men, and 30–40% of their wives become pregnant.
   C. Sperm appear in the semen of 65–70% of men, and 40–50% of their wives become pregnant.
   D. Sperm appear in the semen of 85–90% of men, and 50–70% of their wives become pregnant.