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Review Article

Advances in Surgical Treatment of Male Infertility

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A male factor is the only cause of infertility in 30% to 40% of couples. Most causes of male infertility are treatable, and the goal of many treatments is to restore the ability to conceive naturally. Varicoceles are present in 15% of the normal male population and in approximately 40% of men with infertility. Varicocele is the most common cause of male infertility that can be corrected surgically. In males with azoospermia, the most common cause is post-vasectomy status. Approximately 6% of males who undergo vasectomy eventually seek reversal surgery. Success of vasectomy reversal decreases with the number of years between vasectomy and vasovasostomy. Other causes of obstructive azoospermia include epididymal, vasal or ejaculatory duct abnormalities. Epididymal obstruction is the most common cause of obstructive azoospermia. Patients with epididymal obstruction without other anatomical abnormalities can be considered as candidates for vasoepididymostomy. With microsurgical techniques, success of patency restoration can reach 70～90%. In case of surgically uncorrectable obstructive azoospermia, sperm extraction or aspiration for in vitro fertilization is needed. Nonobstructive azoospermia is the most challenging type of male infertility. However, microsurgical testicular sperm extraction may be an effective method for nonobstructive azoospermia patients.

Key Words: Infertility, Diagnosis

INTRODUCTION

Approximately 15% of couples cannot conceive a child after 1 year of regular, unprotected intercourse. A male factor is the only cause of infertility in 30% to 40% of couples.[1] For the treatment of male subfertility, the causative factor remains unknown in 40% of men presenting with a male factor. However, most causes of male infertility are treatable and the goal of many treatments is to restore the ability to conceive naturally. The dramatic recent improvements in the management of male infertility are largely attributable to improved surgical techniques and assisted reproductive technology (ART).[2] Specifically, *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) allow us to overcome even the most severe defects in spermatogenesis for which only a few treatments are available.[3] These advances have also added important reproductive options for men with non-ob-

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structive azoospermia (NOA), or testicular failure.[4]

Three related topics will now be addressed separately: 1. varicocelectomy, 2. management of obstructive azoospermia (OA), and 3. management of nonobstructive azoospermia.

VARICOCELECTOMY

Varicoceles are present in 15% of the normal male population and in approximately 40% of men with infertility.[5] The association between male subfertility and varicocele is unknown, but a meta-analysis showed that semen improvement is usually observed after surgical correction.[6] Varicocele repair may be considered the primary treatment option when a man with a varicocele has suboptimal semen quality and the female partner does not present any additional infertility factor.[7]

Repair of varicocele for treatment of male infertility is controversial;[8] however, any studies that have not shown an improved pregnancy rate after varicocele repair were small, were not stratified by grade of varicocele, and did not control for type of repair technique.[9] Varicocele repair can reverse a pathologic condition, halt further damage to testicular function, and improve spermatogenesis.[10,11] The pregnancy rates at 1 year after correction of varicocele were comparable for open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy.[12] The preferred approaches of most experts are microsurgical inguinal and subinguinal operations.[2]

The advantages of microsurgical techniques are the reliable identification and preservation of arterial and lymphatic vessels, while reducing the risk for persistence or recurrence of varicocele.[2,7] The application of microsurgical techniques to varicocele repair has resulted in a substantial reduction in the incidence of hydrocele formation because the lymphatic vessels can be more easily identified and preserved.[2,9] Studies have shown that varicocele repair can improve semen parameters, testicular function, and pregnancy rates in couples with male-factor infertility associated with varicocele.[13]

A previous study found that men with large varicoceles had a significantly lower sperm count than men with small varicoceles, and that those with small varicoceles had nearly the same total sperm count as that of expectant fathers.[14] Several groups have reported only a slight improvement in postoperative semen parameters without an increase in the pregnancy rate after removal of subclinical varicoceles.[15] Therefore, the role of subclinical varicocele in male infertility is still controversial. However, other studies[16,17] have found that patients treated for subclinical varicocele had the same probability of success as patients with larger varicoceles, especially in the natural pregnancy rate after surgical treatment (Table 1). These studies revealed that varicocelectomy may be the best option in subfertile men with subclinical varicocele resulted from improved semen quality and increased natural pregnancy rate.

Varicoceles are found in 4.3% to 13.3% of men with azoospermia or severe oligospermia[18] and can result in sperm in the ejaculate of azoospermic men when severe

Table 1. Comparison of seminal parameters between the surgical group and drug group before and after treatment

	Surgical group (n=20)			Drug group* (n=55)		
	Before	After	p value	Before	After	p value
Volume (ml)	2.3±1.0	2.5±0.8	0.437	2.9±1.1	2.8±1.7	0.595
Count (10^6/ml)	39.3±36.0	57.5±46.9	0.005	54.6±33.4	55.8±46.7	0.853
Motility (%)	38.5±18.1	32.4±10.3	0.112	43.9±18.6	43.5±24.6	0.888
Morphology (%)	52.1±26.0	44.0±26.7	0.271	38.1±35.2	35.4±20.6	0.526
Viability (%)	46.0±21.8	41.9±26.6	0.561	33.5±31.9	32.1±19.0	0.717
Pregnancy, n (%)†		12 (60)			19 (19)	

Values are mean±standard deviation.
*L-carnitine (3 g/day orally, 3 times a day, for at least 6 months). †Number of natural pregnancies after treatment.
Adapted from Seo JT, Kim WT, et al.: The significance of microsurgical varicocelectomy in the treatment of subclinical varicocele, Fertil Steril, 2010;93:1907-10.

Table 2. Summary of articles of varicocele repair performed in men with NOA

Reference	Age (yr)	Follow-up (mo)	FSH, mean±SD (mIU/ml)	Approach	Patients (n)	With postop motile sperm	Bilateral repairs (%)	Success rate (%)	Relapse rate (%)	Postop sperm density, mean	Postop motility, mean (%)	Pregnancies (n)	Spontaneous pregnancies (n)
Mattews et al	35	10.3	19.6±4.5	Subinguinal	22	12	77	55	0	2.20×10^6	55	5	2
Kim et al	35	15.0	20.0±16.0	Inguinal	28	12	71	43	0	1.20×10^6	19	2	0
Kadioglu et al	30	13.4	12.3±7.1	Inguinal	24	5	71	21	0	0.04×10^6	14	0	0
Cakan and Altug	29	9.0	35.0±2.8	Inguinal	13	3	15	23	0	0.70×10^6	11	0	0
Schlegel and Kaufman	NA	14.7	NA	Subinguinal	31	7	94	22	0	NA	NA	0	0
Esteves and Glina	32	18.9	14.6	Subinguinal	17	8	65	47	0	0.80×10^6	NA	1	1
Gat et al	34	12.0	NA	Embolize	32	18	88	56	22	3.81×10^6	1	9	4
Poulakis et al	33	24.8	17.8±4.8	Embolize	14	7	87	50	0	3.10×10^6	2	2	2
Pasqualotto et al	30	12.0	17.0±12.4	Subinguinal	27	9	56	33	19	0.87×10^6	19	1	1
Ishikawa et al	NA	>6	14.6±10.5	Inguinal	6	2	17	33	0	0.20×10^6	NA	3	3
Lee et al	32	7.4	20.8±12.3	Inguinal	19	7	21	36	29	0.36×10^6	47	1	1

NOA: non-obstructine azoospermia, FSH: follicular stimulating hormone, SD: standard deviation, postop: post-operative, NA: not available.
Adapted from Weedin JW, et al. Varicocele repair in patients with nonobstructive azoospermia: a meta-analysis. J Urol 2010;183:2309-15.

hypospermatogenesis (HS) or maturation arrest at the spermatid stage is present.[4,13,19] Varicocele repair in patients with NOA can result in motile sperm in the ejaculate and even spontaneous pregnancy (Table 2). Repair can be performed successfully surgically or by percutaneous embolization of the internal spermatic vein. Motile sperm from the ejaculate can be used for IVF without the need for surgical retrieval. Favorable testicular histopathology can predict the appearance of sperm in the postoperative ejaculate. Patients with HS or late maturation arrest (MA) have a significantly higher probability of success than those with Sertoli cell-only syndrome or early MA. Testicular histopathology from testis biopsy can be used to determine whether patients with NOA might benefit from varicocele repair.[20] Therefore, varicocelectomy offers patients with NOA an opportunity to have sperm for undergoing ICSI in their ejaculate and even the possibility of natural conception.[4]

Treatment strategies for male infertility have changed dramatically over the past decade. These advances are largely attributable to microsurgical varicocelectomy and microsurgical techniques for surgical sperm retrieval and ART, specifically ICSI. Microsurgical varicocelectomy significantly increased the sperm retrieval rate in patients with clinical varicocele and NOA; it may also be the treatment option for subclinical varicocele. However, careful patient counseling is important for defining the relative risks and benefits of each approach. The recommendations must be individualized for each couple, and consideration of all the factors important to potential success, including age, must be reviewed.

MANAGEMENT OF OBSTRUCTIVE AZOOSPERMIA

Approximately 20% of men visiting for infertility have azoospermia.[21] Of these patients, about 40% have post-testicular obstruction.[22] OA is the absence of both spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to the bilateral obstruction of the epididymis or the seminal or ejaculatory ducts. Men with OA present with normal follicular stimulating hormone (FSH) levels, normal testis size, and epididymal enlargement. Occasionally, the vas deferens is absent because of

congenital factors or previous surgery.

OA may result from previous vasectomy, epididymal, vassal, or ejaculatory duct abnormalities. Epididymal obstruction is the most common cause of OA, affecting 30～67% of obstructive azoospermic men with normal testicular spermatogenesis.[23-25] Epididymal obstruction may be caused by infection, trauma, or epididymal blowout breakage after vasectomy. Recently, many reports of epididymal obstruction with unknown etiology have emerged.[22,26,27] Microsurgical reconstruction remains the safest and most cost-effective treatment option for OA patients.[28-30]

1. Vasovasostomy

It has been estimated that up to 6% of males who undergo vasectomy eventually seek reversal surgery.[31] A literature review suggests that superior results are obtained when performing a microscopic rather than a macroscopic or loupe magnification vasovasostomy.[32] After vasovasostomy, 70% to 95% of patients have return of sperm to ejaculate, and pregnancies are obtained without ART in 30% to 75% couples.[7,33] The factor that influences the rate of sperm returning and pregnancy is the number of years between vasectomy and vasovasostomy.[33] Silber indicated that men with an obstructive interval of 5 years or less had a high likelihood of being fertile.[34] The pregnancy rate seemed to decrease with duration of obstruction although it was statistically insignificant, while the patency rate did not appear to obviously change. The age of the female partner also greatly influences the rate of pregnancy.

2. Vasoepididymostomy

Patients with epididymal obstruction without other anatomical abnormalities should be considered candidates for vasoepididymostomy. Given the expense and potential side effects from hormonal therapy for the female partner, microscopic vasoepididymostomy is considered to be the first choice for the epididymal obstructive azoospermic male. Following the development of microsurgical instruments and suture material, several techniques for successful anastomosis have been reported.

With microsurgical techniques, restoration of patency can be achieved in 70～90% of patients, although restoration of fertility is achieved only in 50%.[35] The surgical success rate was dependent on the pre- and intraoperative variables of individual patients. The success rate of unilateral vasoepididymostomy is low, but bilateral surgery is likely to enhance the overall patency rate.[36] The luminal diameters of the epidimymal tubules are smaller in the caput epididymis than the caudal epididymis. In some reports, the vasoepididymostomy site was associated with the patency rate. The diameter of epididymal tubules is smaller in the caput epididymis than the caudal epididymis. The patency rate of caudal vasoepididymostomy is higher than that of the caput.[37,38]

In men undergoing vasoepididymostomy, sperm retrieval and cryopreservation during an operation is recommended for surgical and pregnancy failure. Intraoperative sperm cryopreservation in men undergoing vasoepididymostomy will maximize postoperative fertility options.[39,40]

3. Sperm retrieval techniques in OA

It is controversial whether the technique of sperm retrieval (open or percutaneous) or the source of sperm (testicular, epididymal, vassal, or seminal vesicular) affects the pregnancy rate. Each technique and sperm source usually provides sufficient sperm for ICSI and may provide enough viable sperm for cryopreservation.[7,40]

Sperm extraction or aspiration for IVF via ICSI is needed to cure surgically uncorrectable azoospermia or failed microsurgical reconstruction[41] and the majority of patients with congenital bilateral absence of the vas deferens.[42,43] Sperm retrieval with IVF/ICSI is also preferred to surgical treatment when the female partner is advanced in age or has female infertility requiring IVF.[7]

MANAGEMENT OF NOA

NOA is the most challenging type, but no specific treatment has been available in the past. With the advent of ICSI in conjunction with sperm retrieval via testicular sperm extraction (TESE), many nonobstructive azoospermic patients are able to father children.[44] TESE/ICSI is also successful as an intervention for Klinefelter syndrome.[45]

However, 20～50% of NOA patients are not able to have sperm retrieved for ART.[46] Microsurgical TESE is an advanced type of TESE that applies microsurgical

techniques.[47] Microsurgical TESE is an effective form of sperm retrieval for ICSI from men with NOA. The advantages of this technique are that it is a minimally invasive technique, removes a minimal amount of testicular tissue, and minimizes the negative impact on testicular function. Microsurgical TESE is more effective in men with NOA than conventional TESE.[48]

CONCLUSIONS

Treatment strategies for male infertility have changed dramatically over the past decade. These advances are largely attributable to microsurgical varicocele repair, microsurgical reconstructive techniques, and microsurgical techniques for surgical sperm retrieval and ART, specifically ICSI.

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