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ORIGINAL ARTICLE

Male Fertility

Microsurgical vasoepididymostomy for patients with infectious obstructive azoospermia: cause, outcome, and associated factors

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Azoospermia is of great importance to male infertility. Obstructive azoospermia (OA) due to infection is the most prevalent form of OA in China and has been less studied. We aim to observe the treatment outcome of microsurgical vasoepididymostomy (VE) and also to identify the factors relative to the result after reconstructive surgery. Two hundred and eight men presenting with OA due to infection during the study period from July 2010 to July 2013 were prospectively evaluated. Clinical examination, semen analysis, serum follicle stimulating hormone (FSH), and scrotal ultrasound were done before surgical exploration. Among the 198 men who were selected for surgical procedures, 159 candidates underwent microsurgical VE with sperm detected in the epididymal fluid. As for the other 39 cases, reconstruction was not feasible. The average age was 28.5 ± 3.9 years (range 22–38), with average follow-up being 16.5 ± 5.9 months (range 4–28). According to the 150 cases being followed after VE procedures, the total patency rate was 72% (108/150). During follow-up, 38.7% (58/150) natural pregnancies occurred, with overall live birth rate being 32.7% (49/150). Our data suggested that microsurgical VE is an effective therapy for postinfectious epididymal OA. Individualized counseling with prognosis based on etiology should be offered to patients to select optimal therapy.

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INTRODUCTION

The prevalence of azoospermia is <1% among all men and approximately 10%–15% among infertile men. Obstructive azoospermia (OA) due to an anatomical block in the epididymis or the vas deferens can be surgically corrected with a good outcome. Vasectomy is a frequent cause of OA in the Western countries;¹ however, other etiologies such as infection (mainly after sexually transmitted diseases) is a main cause for patients undergoing surgical exploration for OA in China.² Some of these patients are curable by reconstructive surgeries and even restore the ability to conceive naturally,³ whereas others will require sperm retrieval from testis or epididymis combined with intracytoplasmic sperm injection (ICSI) for fatherhood.⁴

Epididymitis and orchitis are common genitourinary conditions, which may lead to eternal epididymal and vasal obstruction.⁵ Gonorrhea, chlamydia, *Ureaplasma*, *Mycoplasma*, coliforms bacteria, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, blastomyces albicans, adenovirus, and enterovirus have all been reported as infectious etiology.⁶ These pathogens can induce not only intense inflammatory reaction, but also secondary scarring and obstruction of the epididymis and vas deferens.⁷

Nowadays, it is possible to accurately predict if the patient has normal spermatogenesis or not. To evaluate the obstructive site of suspected OA, different noninvasive and invasive tests can be

approached. Scrotal exploration and microsurgical reconstruction is a viable option for postinfectious epididymal obstruction. The site of obstruction may occur at any point of the male excurrent ductal system, which is constituted by the efferent ductules, epididymis, vas deferens, and the ejaculatory ducts. Treatment strategy and outcome differ a lot according to the obstructive site and etiology. For example, epididymal obstruction can be corrected by microsurgical reconstruction with vasoepididymostomy.⁸ If OA is caused by genitourinary tuberculosis, the outcome of surgical reconstruction is particularly poor due to scarring at multiple levels along reproductive tract.⁹ In this condition, sperm retrieval paired with IVF/ICSI should be considered as the first choice.

Due to the complexity and diversity of postinfectious OA, we report our clinical observation and treating outcome, and aim to assess our results obtained by microsurgical vasoepididymostomy (VE) and to identify the factors associated with patency after the procedures.

MATERIALS AND METHODS

Study design and patients

This was a prospective, single-center study approved by the Ethics Committee of Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University (China). All consecutive patients with suspected epididymal OA secondary to infection fulfilling all the inclusion criteria between July 2010 and July 2013 were included in our study. A detailed history

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review and clinical examination were done to note the infection and pathogen, testicular size, presence of the vas, epididymal fullness, and presence of varicocele. At least three semen samples, 4 weeks apart, were obtained from each patient to confirm normal semen volume, presence of fructose and absolute azoospermia.¹⁰ Scrotal ultrasonography and transrectal ultrasound (TRUS) were applied to access testicular size and integrity of testicular seminal tract (epididymis and scrotal portions of the vas deferens) and abdominal seminal tract (inguinal, pelvic portions of the vas deferens, and ejaculatory ducts). Hormonal evaluation included measuring the serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone using microparticle enzyme immunoassay.

The inclusion criteria were as the following: (1) all of the patients had a history of definitely diagnosed orchitis, epididymitis or urethritis, or had the history of swollen and painful testicle. (2) Azoospermia diagnosed on at least three semen analyses after centrifugation (1500 g, 15 min); (3) Seminal fructose present; (4) Normal serum level of FSH, LH, and testosterone; (5) At least one testicle volume ≥ 10 ml, presence of the vas, epididymis, and seminal vesicle measured by ultrasound. The patients who had ejaculatory duct obstruction/congenital bilateral absence of vas deferens as a cause of obstructive azoospermia and those who had a history of previous vasoepididymal reconstructive surgery were excluded. Patient selection is demonstrated in **Figure 1**. The study ended when a natural pregnancy occurred and the follow-up of patients with no sperm detected was at least 12 months.

Surgical procedures

Reconstructive surgery was done under general anesthesia after taking informed consent. Through a scrotal incision, the epididymis was examined under an operating microscope to look for dilated tubules.¹¹ Epididymal fluid was examined under a light microscope by the sequence from cauda, corpus to caput until the detection of complete sperm. Motile sperm is preferred, which is in accordance with other reports for higher patency and better semen parameters. However, if the exploration is near caput, and even immotile sperms are found, we will choose it and do the anastomosis. After sperms were found in epididymal fluid and the vas was patent proven by vasography, the vas was transected transversally close to the testicle in its straight part. Then, VE was performed using a single-armed two-suture microsurgical intussusception technique with longitudinal suture placement.¹² If no sperm was detected in the epididymal fluid even up to the caput, a biopsy of the testis was taken and preserved in Bouin's fluid for histopathological examination (HPE), and no further exploration of the vas deferens was performed. Sperm retrieval and cryopreservation may be performed at the time of microsurgical reconstruction to avoid a second procedure if the microsurgical reconstruction is not successful.

Postoperative follow-up

The first postoperative follow-up was 1 week after the operation to examine wound and other possible complications such as scrotal edema and hematoma. Semen analyses were initiated at 8 weeks, followed by 3, 6, 9, and 12 months until no sperm was found at 12 months or until pregnancy was achieved. The patency was defined as a concentration of more than 10 000 sperms per ml. If patency was achieved, the follow-up of natural pregnancy will be prolonged to 18 months.

Statistics

The results were presented as mean \pm standard deviation (s.d.). Statistical analyses were performed with paired *t*-tests using SPSS program version 13.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Clinical characteristics

All the 208 patients diagnosed as postinfectious OA in the study were assessed serum sexual hormone (FSH, LH, PRL, T, E2), scrotal ultrasonography, and transrectal ultrasound (TRUS) with the appearance of epididymal duct ectasia, which was further classified into thin net-like ectasia (0.3–1.0 mm in inner diameter) and tubular ectasia (>1.0 mm in inner diameter).¹³ A total of 198 patients underwent scrotal exploration and/or microsurgical VE. The average age was 28.5 years, with average follow-up of 16.5 months. Among all the cases, a history of orchitis, epididymitis, or urethritis was given by 149 men, whereas 59 men reported signs and/or symptoms such as swollen and painful testicle consistent with acute infection without further diagnosis and treatment. Forty-five patients presented they were previously fertile.

Overall outcome

About 80.3% (159/198) of candidate patients underwent VE, among which bilateral VE were 132 and unilateral VE were 27. There were 150 patients being followed with complete data, with the patency rate of 72% (108/150). During the follow-up, 58 (58/150, 38.7%) achieved natural pregnancy with live birth of 49 (49/150, 32.7%). About 39 patients underwent only scrotal exploration, among which no sperm was detected in epididymal fluid of eight patients, and multiple vasal obstruction or pelvic vasal obstruction existed in the other 31 patients. Follow-up data are shown in **Figure 1**.

Intraoperative finding

In 159 men, sperm was present in the epididymal fluid, and microscopic VE was performed using our previously described technique.¹⁴ Among them, normally appearing motile sperms ranging from progressive to simply twitching in place were detected in milky epididymal fluid in some patients, and no motile sperm was detected in others with the epididymal fluid being pasty. The site of anastomosis was above where sperms were present in the epididymis. As for the exploration procedures ($n = 39$), reconstruction could not be performed due to void epididymis in 8 patients, while the examination of testicular biopsy showed normal spermatogenesis. In the other 31 patients, VE could not be performed because the bilateral vas was proven blocked in the pelvic part or multiple vasal obstruction existed.

Clinical characteristics and treatment outcome of various infectious organisms

In the group of patients who had the history of *Neisseria gonorrhoeae* infection, 27.0% (10/37) of patients only underwent scrotal exploration due to multiple level obstruction of vas, which was significantly higher than that of other groups. The treatments and outcomes of various pathogens were summarized in **Table 1**.

DISCUSSION

Postinfectious epididymal obstruction may account for a large percentage of OA in China in nonvasectomized patients. Acute epididymitis is usually due to retrograde ascent of urethral pathogens and sexually transmitted bacterial infections: notably, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, but also *Ureaplasma urealyticum*, *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. The incidence of postinfectious OA is disproportionately higher in the developing countries compared with that in the developed countries due to relatively higher incidence of genital tract infection and improper treatment. The symptoms and consequences

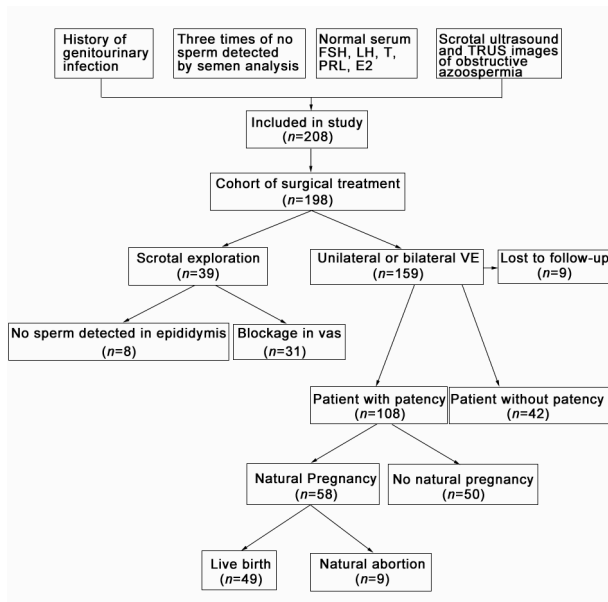


Figure 1: Patient selection, treatment procedure, and follow-up data.

Table 1: Clinical characteristics and surgical treatment outcome of various categories of male genital duct infection

Pathogen	Patients (n)	VE procedures (n=159*)			Exploration procedures (n=39)	
		Patency	Natural pregnancy	Live birth	No sperm in epididymal fluid	Blockage in distal vas
Mycoplasma	35	20 (71.4)	10 (35.7)	9 (32.1)	2	3
Chlamydia	10	6 (75)	4 (50)	3 (37.5)	0	1
Gonorrhoeae	37	17 (73.9)	8 (34.8)	7 (30.4)	2	10
Nonspecific	116	65 (71.4)	36 (39.6)	30 (33.0)	4	17
Total	198	108 (72)	58 (38.7)	49 (32.7)	8	31

*There were 150 VE procedures with complete follow-up data; Data in parenthesis are percentages. VE: vasoepididymostomy

of epididymitis include pain, nodules, edema, urinary difficulties, fever, urethral discharge, and infertility. However, epididymitis can also be asymptomatic, meaning that it is also underestimated in clinical practice.¹⁵ In Peng's report, it is an idiopathic factor, but infection that is the most common cause of epididymal obstruction in the Chinese populations.¹⁶ From our investigation, we found that patients could clearly recall the history of epididymo-orchitis if he has been definitely diagnosed and treated. Patients may not always report or recall a remote epididymal infection or they may have mistaken it as a simple urinary tract infection. Hence, there exists the possibility that patients of so-called idiopathic primary epididymal obstruction may have a history of lower urinary tract infection. The category of pathogens may be relative to the severity of inflammatory damage, the extent of epididymitis, and the obstructive site.¹⁷ Gonorrhoea was the common cause of correctable epididymal obstruction with higher rate (up to 25%) of complete blockage of reproductive ducts, compared to other pathogens.¹⁵ This was same to our results.

The possibility of surgical reconstruction depends on the presence of normal spermatogenesis in the testis, normal flow of sperms from testis to epididymis, and patency of distal vas duct. That is to say only obstructions situated at epididymis or in the vas at scrotal segment have the chance to be corrected. Therefore, it is vital to evaluate the

spermatogenesis of testis and obstructive site so as to choose the optimal treatment. Fine needle aspiration cytology (FNAC)¹⁸ is a minimally invasive procedure to evaluate accurately the testicular pathology, but there exist occasions when FNAC of azoospermic patients shows the presence of normal spermatogenesis, but no sperm is detected in epididymal fluid when intratesticular OA occurs. Although percutaneous epididymal sperm aspiration (PESA) shows the existence of sperm in epididymis accurately, it should not be recommended for those patients who primarily choose microsurgical reconstruction of the spermatic track because there exists the risk of subsequent scarring ending with secondary obstruction in caput. Besides the history of epididymitis or sexually transmitted disease, enlargement and fullness of epididymis by palpation are useful indications of epididymal obstruction, especially combined with another diagnostic assessment of ultrasonography. The degree of dilation of epididymal tube can be reliably identified.^{19,20} In the cohort of our research, sperms were much more easily detected in the patients showing thin net-like ectasia or tubular ectasia of epididymal duct, compared to the group with normal epididymal duct. Hence, patients unlikely to benefit from surgery could be excluded by preoperative ultrasonography assessment, which was in concordance with our previous reports.¹⁴

Under normal conditions, epididymal secretory factors are involved in the maturation of spermatozoa and its function can be evaluated by measuring L-carnitine, glycerylphosphoryl choline, and alpha-glucosidase in the seminal plasma. The secretion of alpha-glucosidase is used to evaluate epididymal function in an accurate way, and seminal plasma biochemical markers can indicate obstructive site. Epididymal neutral alpha-glucosidase is involved in the preparation of spermatozoa for storage.²¹ In our research, the average neutral alpha-glucosidase level was lower than normal, so its levels can be used as an additional indicator of OA.

Epididymitis can be caused by many pathogens such as bacteria, virus, mycoplasma, chlamydia, and fungus, which have a direct detrimental effect on sperm function and viability. In addition, leukocytes in the genital tract lead to immune response causing germinal epithelial damage with resultant fertility impairment.^{22,23}

In the epididymitis, it is of most frequency that the vas deferens encounters pathological conditions. The vas deferens is anatomically peculiar due to its thick muscular wall and extremely small lumen. Infection and inflammation may cause mucosal changes resulting in serious impedance of the free transmission of spermatozoa along its lumen. In the cases of tuberculosis, the vas deferens is blocked by granulomas or distorted by fibrosis surrounding the reproductive tract structures, and a low-volume ejaculate may be present when the disease involves the prostate and seminal vesicles. In that condition, ICSI may be preferred to reconstructive surgery.²⁴

The patency rate of the cohort is 72%, which is slightly lower than the best patency rate reported as 73%–92%.^{1,25} The possible reasons include patient characteristics, technical skills, and follow-up systems. Although it is difficult to compare the natural pregnancy rate of post-VE with that of ICSI because of the ages of the couple and female factors, the outcomes of VE for postinfectious OA are optimistic. After all, natural conception conforms to physiologic mechanisms and avoids the high cost, repeating invasive procedure of testis and epididymis, potential complications, and other risks associated with ICSI.

CONCLUSION

Infection is the frequent cause of epididymal obstruction. Some of these conditions are amenable to curative surgery, whereas others require sperm retrieval combined with ICSI. Data from this study

have shown that microsurgical vasoepididymostomy is an effective therapy for such azoospermic patients with epididymal obstruction. Obstructive site should be differentiated to select optimal therapy for patients before the final decision.

AUTHOR CONTRIBUTIONS

XFC and PP designed the study. XFC, WL, HXW, YPH, and PP carried out the clinical work. XFC and PP participated in drafting, collecting, and interpreting the data and critically revising the paper for key intellectual content. YRH and BC reviewed the paper. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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