Original Article

Intracytoplasmic sperm injection outcomes in patients with orgasmic dysfunction and anejaculation by percutaneous epididymal sperm aspiration (PESA)

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Background: Orgasmic dysfunction and anejaculation are two uncommon yet powerful factors of male infertility. The treatment of orgasmic dysfunction and anejaculation is especially important for men who desire paternity, who otherwise would have to undergo surgical sperm retrieval for use with intracytoplasmic sperm injection (ICSI). We evaluated the reproductive outcomes of percutaneous epididymal sperm aspiration (PESA) for ICSI in a cohort of infertile patients who had presented with orgasmic dysfunction and anejaculation in the past five years.

Methods: We conducted a retrospective study of 41 patients with orgasmic dysfunction and 55 patients with anejaculation who underwent surgical sperm retrieval for ICSI. The sperm was firstly aspirated from the cauda epididymis, and then from the caput of the epididymis. If aspiration attempts failed at both locations, testicular sperm aspiration (TESA) was performed. The ICSI outcomes following these collection methods were compared with those of patients with congenital bilateral absence of the vas deferens (CBAVD). The ICSI outcomes of PESA (fertilization rate, high-quality embryo rate, clinical pregnancy, and live birth rate) were recorded.

Results: Of all 96 participants, PESA was successfully performed in 91 patients (94.8%), and TESA was necessary for only 5 patients (5.2%). Of the 91 patients who received PESA, 90 succeeded in retrieving sperm from the cauda epididymis, and just 1 from the caput. Among the patients with anejaculation, there were 28 cases (28/55, 50.9%) of diabetes mellitus (DM). In 56 fresh transfer cycles, the clinical pregnancy rate and live birth rate were 57.1% and 51.8%, respectively, both similar to those of CBAVD (53.47% *vs.* 63.4%, P=0.483, 47.2% *vs.* 53.5%, P=0.393, respectively). The fertilization rate, transferable embryo rate, high-quality embryo rate, clinical pregnancy, early pregnancy loss, and the live birth rate did not show differences resulting from using fresh or frozen sperm in the two groups. The fertilization rate and high-quality embryo rate in patients with DM were lower than those of patients without DM (75.0% *vs.* 86.7%, P=0.002; 50.4% *vs.* 77.4%, P=0.028, respectively).

Conclusions: Like TESA, PESA is an appropriate and convenient way to obtain sperm for ICSI for patients with orgasmic dysfunction and anejaculation. Performing ICSI with sperm from the cauda epididymis can achieve favorable clinical pregnancy and live birth rates in patients with orgasmic dysfunction and anejaculation.

Keywords: Ejaculatory disorders; orgasmic dysfunction; anejaculation; percutaneous epididymal sperm aspiration (PESA); intracytoplasmic sperm injection (ICSI)

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Introduction

Ejaculation is a complex process accomplished by a synergy of sensory receptors, afferent pathways, cerebral sensory/motor areas, and efferent pathways. Ejaculatory disorders include orgasmic dysfunction, anejaculation, retrograde ejaculation, premature ejaculation, and delayed ejaculation (1). The etiology of ejaculatory disorders is complex and not completely understood. Orgasmic dysfunction refers to the difficult or absent orgasm after sufficient sexual stimulation, while anejaculation is the failure of antegrade or retrograde ejaculation during orgasm (1).

Orgasmic dysfunction and anejaculation can be treated with prostate massage, penile vibratory stimulation (PVS), rectal electrical stimulation, and surgical sperm retrieval to obtain sperm for assisted reproduction (2). Prostate massage and PVS are only effective in achieving ejaculation in a minority of patients (3-5). Electroejaculation (EEJ) can realize successful sperm retrieval in 90% of patients, but the quality of semen gathered from this method is often poor (6-9). Through surgical sperm retrieval, a relatively large quantity and high quality of sperm can be easily retrieved from the epididymis and used for intracytoplasmic sperm injection (ICSI) (10).

However, few studies have reported the outcomes of ICSI in patients undergoing percutaneous epididymal sperm aspiration (PESA) for severe orgasmic dysfunction or anejaculation. Our study aimed to analyze ICSI outcomes using sperm collected via PESA. To compare the ICSI outcomes of epididymal sperm, we established a control group containing patients with congenital bilateral absence of the vas deferens (CBAVD) who underwent PESA. For these patients, spermatozoa can only be obtained from the epididymis or testis. Sub-group analyses of patients with severe ejaculatory disorders (orgasmic dysfunction and anejaculation, frozen and fresh epididymal sperm, diabetic, and non-diabetic) were also conducted. We present the following article following the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/atm-20-1121a).

Methods

Patients

We retrospectively analyzed patients with orgasmic dysfunction and anejaculation who had received surgical sperm retrieval for ICSI between January 2013 and December 2018 in the Reproductive Medicine Center, the First Affiliated Hospital of Nanjing Medical University. Variables included in our analysis were male age, female age, metaphase II (MII) oocytes, fertilization rate (2PN), good embryos rate, clinical pregnancy rate, early pregnancy loss, and live birth rate. The clinical pregnancy rate, early pregnancy loss, and live birth rate of only the first fresh embryo transfer were included for statistics. The ICSI outcomes of CBAVD were set as control. The study was conducted following the tenets of the Declaration of Helsinki (as revised in 2013). The ethics committee of the First Affiliated Hospital of Nanjing Medical University approved this study (No. 2019-SR-128) and informed consent was taken from all the patients.

Exclusion criteria included the inability to reach orgasm via vaginal intercourse with ability via masturbation, and drug-related ejaculatory disorders (e.g., antipsychotics and antidepressants). An experienced male urologist evaluated all patients with a detailed case history, physical examination, and laboratory testing (e.g., post-ejaculatory urinalysis, hormone evaluation, fasting blood glucose, and transrectal ultrasonography). Only patients with a normal range of sex hormone levels, especially testosterone, prolactin, and follicle-stimulating hormone, were included. All participants and their partners were informed of the potential risks (pain, bleeding, and infection) of PESA, testicular sperm aspiration (TESA), and ICSI.

Retrieval techniques

Either PESA or TESA was performed under local anesthesia by the same surgeon (Yang XY). All patients received a spermatic cord block with 1% lidocaine hydrochloride injection, typically 5 mL was injected into

the spermatic cord. After fixing the caput or cauda of the epididymis with the fingers, a 5.5 mm angiocatheter needle was directed through the skin into the caput or cauda of the epididymis. The needle was withdrawn, and the angiocatheter was retained in place. Next, a 10 mL syringe containing 1 mL of sperm buffer was attached to the angiocatheter. Negative pressure was created, and the angiocatheter was gently withdrawn and then pushed back into the caput or cauda epididymis until epididymal fluid appeared in the angiocatheter needle. The specimen was immediately examined under the microscope to confirm the presence of spermatozoa. If no spermatozoa were found, the same procedure was performed on the contralateral side. If no spermatozoa were retrieved from the second side, TESA was performed (11). Under a 400× phase-contrast microscope, 10 μL of epididymal fluid containing culture (0.5–1 mL) was dropped onto slides for analysis. If more than one progressively motile sperm could be observed in 10 visual fields, freezing was applicable; if one progressively motile sperm could be seen on the whole slide, the sperm would meet the ICSI standard.

Stimulation, ICSI, embryo culture, and pregnancy

Routine stimulation was adopted according to the patients' partners' case requirements. Transvaginal ultrasound was used to monitor the follicles continuously. Oocyte maturation was triggered by human chorionic gonadotropin (hCG) 5,000–7,500 IU or gonadotropin-releasing hormone agonist (GnRHa) 0.2 mg. Oocytes were retrieved 34–36 h later by vaginal ultrasound-guided follicular puncture. The conduction of ICSI, embryo culture, embryo transfer, embryo cryopreservation, and assessment were as previously described (12). Fresh embryo freezing or transfer was performed 3 or 5 days after fertilization. Whole embryo cryopreservation was carried out when the risk of ovarian hyperstimulation was high, and when the endometrium (thickness <7 mm) was not suitable for transplantation (13). Routine progesterone was given, and β-hCG was tested 2 weeks later to assess the pregnancy outcome. Clinical pregnancy was defined as a gestational sac with or without a fetal heartbeat, early pregnancy loss as spontaneous abortion within 12 weeks of gestation, and live birth as the number of live birth events (>24 weeks gestation).

Statistical analysis

Data were analyzed and expressed as mean ± SD using SPSS version 18.0 (IBM Corp., USA). The independent t-test or nonparametric test was used for comparisons between groups. To compare proportions between two groups (fertilization, transferable embryo rate, high-quality embryo rate, early pregnancy loss, clinical pregnancy, and live birth rates), the chi-square (χ^2) test or Fisher's exact test was used. Statistical significance was considered as $P<0.05$.

Results

Among the 96 participants with severe ejaculatory disorders, the majority were idiopathic, and 41 had orgasmic dysfunction, including 36 cases of primary and 5 cases of secondary dysfunction. There was 1 case of orgasmic disorder secondary to severe brain injury. Right cryptorchidism orchiopexy had been performed during preadolescence on 2 of the participants with adult orgasmic dysfunction, but the causal relationship could not be confirmed.

Among the 55 patients with anejaculation, 11 presented idiopathically and 44 with clear etiology, including diabetes mellitus (DM) (n=28), paraplegia (n=4), pelvic surgery (n=6), postoperative pituitary adenoma (n=2), congenital bilateral absence of the vas deferens (n=2), multiple sclerosis (n=1), and genitourinary tuberculosis (n=1). The sexual hormone levels of the 2 cases with postoperative pituitary adenoma had been normal for more than six months.

Of the 96 participants with severe ejaculatory disorders, 91 (94.8%) underwent PESA and ICSI. Of these 91 patients, sperm could be obtained from the cauda of the epididymis by PESA in 90 patients, and the caput of the epididymis in 1 patient. Compared to the CBAVD control group, no statistical difference was observed in MII oocytes (10.2±5.1 *vs.* 9.8±5.2, P=0.38), fertilization rate (78.6% *vs.* 80.2%, P=0.29), transferable embryo rate (89.1% *vs.* 87.2%, P=0.192), or high-quality embryo rate (72.1% *vs.* 69.0%, P=0.38). Age comparison with the control group showed statistical significance (male 30.7±5.4 *vs.* 29.4±5.2, P=0.016, female 29.1±4.9 *vs.* 28.0±4.6, P=0.048). We then compared the pregnancy rate of fresh embryo transfer between the two groups. No statistical difference was observed in the clinical pregnancy rate (54.7% *vs.* 63.4%, P=0.483), early pregnancy loss (6.9% *vs.* 8.6%, P=0.811), or live birth rate (47.2 *vs.* 53.5, P=0.393) (*Table 1*).

The outcomes of PESA and ICSI were further compared between participants with orgasmic dysfunction and anejaculation. No between-group difference was observed neither in age, nor in MII oocytes (10.0±5.7 *vs.* 10.4±4.7,

Table 1 Comparison of the ICSI outcomes with severe ejaculatory disorders and CBAVD

	Severe ejaculatory disorders	CBAVD	P
Male age (yr)	30.7±5.4	29.4±5.2	0.016*
Female age (yr)	29.1±4.9	28.0±4.6	0.048*
MII oocytes per cycle (n)	10.2±5.1	9.8±5.2	0.38
Fertilization rate (%)	78.6	80.2	0.29
Transferable embryo rate (%)	89.1	87.2	0.192
High-quality embryo rate (%)	72.1	69.0	0.323
Fresh embryo transfer cycle (n)	53	331	–
Clinical pregnancy (%)	54.7	63.4	0.483
Early pregnancy loss (%)	6.9	8.6	0.811
Live birth rate (%)	47.2	53.5	0.393

*, P<0.05. ICSI, intracytoplasmic sperm injection; CBAVD, congenital bilateral absence of the vas deferens.

Table 2 Comparison of the ICSI outcomes with orgasmic dysfunction and anejaculation

	Orgasmic dysfunction	Anejaculation	P
Male age (yr)	30.6±5.2	30.9±5.6	0.81
Female age (yr)	29.3±4.8	29.0±5.1	0.76
MII oocytes per cycle (n)	10.0±5.7	10.4±4.7	0.79
Fertilization rate (%)	76.5	80.1	0.23
Transferable embryo rate (%)	87.9	90.0	0.43
High-quality embryo rate (%)	70.4	73.2	0.45
Fresh embryo transfer cycle (n)	21	32	–
Clinical pregnancy (%)	52.4	56.3	0.54
Early pregnancy loss (%)	18.2	0	0.15
Live birth rate (%)	38.1	53.1	0.45

ICSI, intracytoplasmic sperm injection.

P=0.43), fertilization rate (76.5% *vs.* 80.1%, P=0.23), transferable embryo rate (87.9% *vs.* 90.0%, P=0.43), high-quality embryo rate (70.4% *vs.* 73.2%, P=0.45), clinical pregnancy rate (52.4% *vs.* 56.3%, P=0.54), and live birth rate (38.1% *vs.* 53.1%, P=0.45) (P>0.05) (*Table 2*).

The outcomes of PESA and ICSI using fresh and thawed sperm were compared. Similar to what was observed above, no statistical differences were observed in MII oocytes per cycle (10.8±5.6 *vs.* 9.7±4.8, P=0.31), fertilization rate (79.7% *vs.* 77.6%, P=0.46), transferable embryo rate (89.2% *vs.* 89.0%, P=0.95), high-quality embryo rate (72.5% *vs.* 71.7%, P=0.82), clinical pregnancy rate (57.7% *vs.* 51.9%, P=0.79), the spontaneous abortion rate (6.7% *vs.* 7.8%, P=1.0), and live birth rate (53.9% *vs.* 44.4%, P=0.49) (*Table 3*).

Of the patients receiving PESA and ICSI for anejaculation, 28 cases showed DM (diabetic group), and the other 25 cases were non-diabetic (non-diabetic group); we also compared the ICSI outcomes between these two groups. No statistical difference was observed in the couple ages, nor in MII oocytes (10.3±3.6 *vs.* 9.6±5.7, P=0.699), transferrable embryo rate (64.7% *vs.* 79.6%, P=0.085), high-quality embryo rate (50.4% *vs.* 77.4%, P=0.028), clinical pregnancy rate (52.9% *vs.* 75.0%, P=0.688), or live birth rate (52.9% *vs.* 75.0%, P=0.688). However, the fertilization

Table 3 Comparison of the ICSI outcomes using fresh and thawed epididymal sperm

	Fresh sperm	Thawed sperm	P
Male age (yr)	31.2±5.3	30.4±5.5	0.51
Female age (yr)	29.4±5.0	28.9±4.9	0.61
MII oocytes per cycle (n)	10.8±5.6	9.7±4.8	0.31
Fertilization rate (%)	79.7	77.6	0.46
Transferable embryo rate (%)	89.2	89.0	0.95
High-quality embryo rate (%)	72.5	71.7	0.82
Fresh embryo transfer cycle (n)	26	27	–
Clinical pregnancy (%)	57.7	51.9	0.79
Early pregnancy loss (%)	6.7	7.8	1.00
Live birth rate (%)	53.9	44.4	0.49

ICSI, intracytoplasmic sperm injection.

Table 4 Comparison of the ICSI outcomes in patients with and without diabetes mellitus

	Diabetes mellitus	Non-diabetic	P
Male age (yr)	30.2±4.8	31.6±6.3	0.488
Female age (yr)	28.5±4.3	29.5±5.9	0.352
MII oocytes per cycle (n)	10.3±3.6	9.6±5.7	0.699
Fertilization rate (%)	75.0	86.7	0.002*
Transferable embryo rate (%)	64.7	79.6	0.085
High-quality embryo rate (%)	67.2	77.4	0.028*
Fresh embryo transfer cycle (n)	17	15	–
Clinical pregnancy (%)	52.9	75.0	0.688
Early pregnancy loss (%)	0	0	–
Live birth rate (%)	52.9	75.0	0.688

*, P<0.05. ICSI, intracytoplasmic sperm injection.

rate and high-quality embryo rate in DM patients were lower than those in patients without DM (75.0% *vs.* 86.7%, P=0.002; 50.4% *vs.* 77.4%, P=0.028, respectively) (*Table 4*).

Discussion

Orgasmic dysfunction and anejaculation are two uncommon but powerful factors of male infertility. Ejaculatory disorders may be caused by congenital, endocrine, medicinal, and neurogenic or psychological factors. However, the exact cause of some ejaculatory disorders, especially orgasmic dysfunction, is not clear, which poses a great challenge to the treatment.

Orgasmic dysfunction and anejaculation can be treated through psychological counseling, pharmacotherapy (levodopa and ephedrine), PVS, and EEJ (14). In patients with ejaculatory disorders, PVS can be used for the retrieval of semen as it is less invasive than EEJ and surgical sperm retrieval, but it may not be effective for all patients (15). Patients with anejaculation caused by a spinal cord injury or orgasmic dysfunction can provide semen through EEJ, but spermatozoa with low motility are not optimal for assisted reproductive technology (16). Surgical sperm retrieval, by either PESA or TESA, can be used as an alternative in

patients with severe ejaculatory disorders, or when PVS and EEJ have previously been unsuccessful (17).

The invention of ICSI was first reported by Palermo *et al.* in 1992, and concurrently new treatment options for severe ejaculatory disorders emerged, namely PESA or TESA (18). The spermatozoa collected by PESA are more motile than those retrieved by TESA, and laboratory processing of epididymal sperm is easier than that of testicular sperm. Furthermore, Shih *et al.* reported that TESA and PESA yielded similar pregnancy and miscarriage rates (19). For these reasons, we believe that PESA, like TESA, is an appropriate and convenient way to obtain sperm for ICSI in cases of patients with orgasmic dysfunction and anejaculation.

In the present study, the clinical pregnancy rate of PESA-based ICSI was 54.7% (28/53) in the fresh embryo transfer cycle (53 of 91). There was one case of ectopic gestation and two cases of spontaneous abortion, which meant the live birth rate was 47.2% (25/53). These results are similar to those reported by Soeterik *et al.* (16). Compared to the CBAVD group, sperm from the epididymis achieved similar clinical pregnancy and live birth rates in ICSI using either fresh or frozen sperm (*Tables S1* and *S2*). In the subgroup analysis, no statistical difference was observed in fertilization rate, transferrable embryo rate, high-quality embryo rate, clinical pregnancy rate, and live birth rate (P>0.05). Frozen and fresh epididymal sperm achieved similar outcomes, which is consistent with the results reported previously (20,21).

Among the 55 anejaculation patients, 28 patients (50.9%) showed DM, a progressive condition that requires close attention. There are an estimated 113.9 million adults with DM in China, and this number is expected to increase with time (22-24). Neuropathy is most commonly caused by DM (25), and diabetic neuropathy may impair reproductive function in males. Agbaje *et al.* reported that the rate of sperm apoptosis and the damage of spermatozoon ultrastructure were more obvious in diabetic patients than in healthy males (26). In this study, the fertilization rate and high-quality embryo rate of patients with DM were lower than those in non-diabetic patients.

Other causes of anejaculation include paraplegia, extirpative pelvic surgery, postoperative pituitary adenoma, multiple sclerosis, and genitourinary tuberculosis. In paraplegic patients, PVS could be used to induce ejaculation because of the integrity of the reflex arc in the spinal cord. In patients with spinal cord injury above T10, the stimulation may achieve a better result than in those with cord injury in the lower levels. In EEJ, rectal electrodes are used to stimulate the peripheral nerves of the prostate to induce ejaculation, but anesthesia is required, and rectal injury may occur as a consequence. The success rate of EEJ was more than 90%, but one-third of them required ICSI on account of poor sperm quality (16).

Compared with EEJ, PESA is more manipulatable. In the absence of ejaculation, spermatozoa accumulate in the epididymis, especially in the area of the cauda. Logically, the cauda epididymis is often chosen as the puncture site for patients with orgasmic dysfunction and anejaculation. Puncture of the vas deferens has previously been used for retrieving sperm (27); however, the vas deferens is relatively hard, and piercing it requires specialized needles.

Our study had some limitations that should be noted, with a small sample size being the first obvious constraint. The second is the lack of appropriate control groups involving electro-ejaculated sperm, testicular sperm, or penile vibratory stimulation sperm. Additionally, the retrospective nature of the study may have also restricted the quality and richness of the data.

In conclusion, PESA, like TESA, is an appropriate and convenient way to obtain sperm for ICSI for patients with orgasmic dysfunction and anejaculation. Using sperm from the cauda epididymis, ICSI can achieve favorable clinical pregnancy and live birth rates in patients with orgasmic dysfunction and anejaculation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of the First Affiliated Hospital of Nanjing Medical University has approved this study (No. 2019-SR-128) and informed consent was taken from all the patients.

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Supplementary

Table S1 Comparison of the ICSI outcomes between severe ejaculatory disorders and CBAVD by using fresh sperm

	Severe ejaculatory disorders	CBAVD	P
Male age (yr)	29.4±5.0	27.9±4.3	0.082
Female age (yr)	31.5±5.2	29.4±4.7	0.049
MII oocytes per cycle (n)	10.8±5.5	8.4±3.6	0.013
Fertilization rate (%)	79.7	79.1	0.796
Transferable embryo rate (%)	89.2	86.5	0.240
High-quality embryo rate (%)	81.4	76.7	0.110
Fresh embryo transfer cycle (n)	26	179	–
Clinical pregnancy (%)	57.7	65.9	0.411
Early pregnancy loss (%)	6.7	9.3	1.0
Live birth rate (%)	53.8	58.7	0.642

ICSI, intracytoplasmic sperm injection; CBAVD, congenital bilateral absence of the vas deferens.

Table S2 Comparison of the ICSI outcomes between severe ejaculatory disorders and CBAVD using frozen sperm

	Severe ejaculatory disorders	CBAVD	P
Male age (yr)	28.9±4.9	27.4±4.2	0.093
Female age (yr)	30.4±5.5	28.8±4.7	0.084
MII oocytes per cycle (n)	9.7±4.8	8.5±3.5	0.108
Fertilization rate (%)	77.6	81.0	0.158
Transferable embryo rate (%)	89	86.9	0.357
High-quality embryo rate (%)	71.7	70.9	0.802
Fresh embryo transfer cycle (n)	27	113	–
Clinical pregnancy (%)	51.9	70.8	0.06
Early pregnancy loss (%)	7.7	8.1	1
Live birth rate (%)	44.4	62.8	0.087

ICSI, intracytoplasmic sperm injection; CBAVD, congenital bilateral absence of the vas deferens.