



Testicular volume in non-obstructive azoospermia with a history of bilateral cryptorchidism may predict successful sperm retrieval by testicular sperm extraction

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Funding information

Japan Agency for Medical Research and Development, Grant/Award Number: 19gk0110027h0003

Abstract

Purpose: Cryptorchidism is one of the most common causes of non-obstructive azoospermia (NOA) in adulthood. Even if early orchidopexy is performed to preserve fertility potential, some patients still suffer from azoospermia. Fertility potential is significantly lower in bilateral than unilateral cryptorchidism. The aims of this study were to identify clinical parameters that predict the likely success of sperm recovery by microscopic testicular sperm extraction (micro-TESE) and also the likely outcome of intracytoplasmic sperm injection using sperm from NOA patients who submitted to bilateral orchidopexy.

Methods: Fifty-two NOA patients with a history of bilateral cryptorchidism underwent micro-TESE. The following clinical parameters were evaluated as predictive factors for successful sperm recovery: age at micro-TESE; age at orchidopexy; period from orchidopexy to micro-TESE; luteinizing hormone (LH); follicle-stimulating hormone (FSH); testosterone; average testicular volume; and body mass index.

Results: In the successful sperm retrieval group, average testicular volume was significantly greater, while serum LH and FSH, and body mass index were significantly lower. In a multivariate analysis, average testicular volume was positively correlated with successful sperm recovery.

Conclusion: Our results indicate that testicular volume in NOA patients with bilateral cryptorchidism is a predictor for successful sperm recovery.

KEYWORDS

cryptorchidism, microdissection testicular sperm extraction, non-obstructive azoospermia, orchidopexy, testicular volume

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1 | INTRODUCTION

Cryptorchidism is a common condition in childhood and is a major factor in adult male infertility. The mechanism by which cryptorchidism causes infertility has not yet been elucidated.¹ Pathological analyses of gonadal tissue obtained at orchidopexy in childhood showed that the number of adult dark (Ad) spermatogonia decreased with age.^{2,3} Cryptorchidism causes the testes to be exposed to a higher temperature than normal due to its position close to the trunk; this increased temperature impairs spermatogenic function.⁴ Orchidopexy at a young age is recommended for fertility preservation, as untreated cryptorchidism may lead to testicular dysfunction with age. If orchidopexy is not performed, azoospermia occurs in 43%-85.5% of ipsilateral cases⁵⁻⁷ and 88.6%-100% of bilateral cases.⁸ The recommended age for orchidopexy has been reduced from 10-15 years in 1950⁹ to 0.5-1.5 years currently.¹⁰

However, even patients who undergo orchidopexy at an ideal age may suffer from azoospermia; these patients account for 20% of non-obstructive azoospermia (NOA) cases.¹¹ The only treatment for azoospermia that offers a patient the possibility of fathering a child is intracytoplasmic sperm injection (ICSI) after testicular sperm extraction (TESE). As this treatment imposes considerable mental and physical burdens on a couple, investigation of factors that determine testicular function is important for NOA.

There are several reports on sperm retrieval from NOA patients who submitted to orchidopexy for TESE and ICSI.¹²⁻¹⁴ However, these studies reported data from small or heterogeneous populations that included ipsilateral cases; moreover, no data have been reported from a Japanese population. The aims of this study were to analyze and evaluate prognostic factors for successful TESE in NOA patients who have undergone bilateral orchidopexy.

2 | MATERIALS AND METHODS

2.1 | Patients

A retrospective study of 616 patients who submitted to micro-TESE at Dokkyo Medical University Saitama Medical Center from March 2010 to June 2018 was carried out. The details of the patients are as follows: 429 with NOA; 124 with obstructive azoospermia, including eight with cryptorchidism; six with cryptospermia, a condition in which sperm was only discovered after specimen centrifugation; seven with severe oligospermia, a condition defined as 0-5 million sperm/mL; seven with an ejaculation disorder; and 43 patients who were undefined because they had not undergone necessary or sufficient tests. The details of the 429 patients with NOA were 235 with idiopathic NOA; 24 with varicocele; 20 who had undergone chemoradiotherapy; eight with a chromosomal abnormality; 45 with Klinefelter syndrome; seven with an AZFc deletion; and 90 with cryptorchidism (bilateral 52, ipsilateral 38). Comorbidities with bilateral cryptorchidism were six patients with a history of varicocele;

two with previous treatment for malignant lymphoma; two with chromosomal abnormalities [46XYinv(9)(p12q13), 45X/46XY]; and 12 with 47 XXY Klinefelter syndrome. Thirty-six patients with a history of bilateral cryptorchidism, but with no record of chemotherapy, chromosomal abnormality, or 47 XXY Klinefelter syndrome, were included in this study. Definition of NOA was serum FSH >10 mIU/mL or testicular volume <16 mL without any sign of obstruction.¹⁵⁻¹⁷ Thirty-six patients had a history of bilateral cryptorchidism before orchidopexy: testes in 22 of these patients were located in the inguinal canal; they were intra-abdominal in four patients; and were in a pre-scrotal position in two patients. The location of the testes of eight patients was not known prior to surgery. All patients with a history of bilateral cryptorchidism had undergone orchidopexy; none of the patients required varicocelectomy.

2.2 | Data collection

Two or more semen analyses were performed at an interval of 1-2 months, in accordance with World Health Organization guidelines (2010). Clinical history was recorded: age; history of cryptorchidism; radiotherapy; chemotherapy; previous genito-urinary infections; and surgical procedures. All patients underwent a physical examination: testicular size was measured using an orchidometer; epididymal distension was assessed; and the presence of the vasa was determined by palpation. Varicoceles were checked by palpation and ultrasonography. Endocrine examination, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, G-banding karyotype analysis, and Y chromosome microdeletion analysis were performed using standard clinical protocols.

G-banding karyotype analysis was performed at a clinical laboratory (SRL, Inc). Y chromosome microdeletion analysis was carried out at a clinical laboratory (SRL, Inc) using the GENOSEARCH™ AZF Deletion kit (MBL).

2.3 | Operative procedures

Surgical procedures were performed under local anesthesia. After scrotal disinfection, the scrotal skin and spermatic cord were injected with 10 mL of ridocalin and anapain. The procedure was started in the larger testicle. A complete longitudinal incision in the tunica albuginea was performed to enable visualization of testicular parenchyma. Multiple tiny pieces of testicular parenchyma were harvested from dilated and opaque areas. The specimens were immediately analyzed by an embryologist for the presence of sperm. If no sperm was found on one side, the same surgical procedure was immediately performed on the opposite side. At the same time, multiple testicular tissues were obtained and fixed in Bouin's solution and sent for histopathological examination.

All procedures were performed by the same surgeon (HO). The surgeon's experience included over 2000 micro-TESE procedures. Informed consent was obtained from all patients, and the procedure

was approved by Dokkyo Medical University Saitama Medical Center ethics committee (Number: 1734).

2.4 | Histopathological examination

Testicular tissues were cut into pathological sections and stained using hematoxylin-eosin (HE). Sections were then diagnosed on the Johnsen score by experienced pathologists: (a) normal spermatogenesis; (b) hypospermatogenesis; (c) late maturation arrest; (d) early maturation arrest; (e) Sertoli cell-only syndrome; and (f) tubular sclerosis. The sections were also assessed for the presence or absence of sperm.

2.5 | Statistical analysis

Comparisons of clinical parameters, age at micro-TESE, age at orchidopexy, period from orchidopexy to micro-TESE, serum hormone levels (LH, FSH, and testosterone), average testicular volume, and body mass index were conducted between successful and unsuccessful sperm extraction cases. A univariate analysis using the Mann-Whitney U test was performed for every factor, and a multivariate analysis was carried out for factors that showed a significant difference. SPSS v25.0 software (IBM) was used for all statistical analyses. *P*-value <.05 was defined as statistical significance.

3 | RESULTS

The clinical characteristics of the patients with a history of cryptorchidism included in the present study are shown in Table 1. The median age at micro-TESE was 38.63 years, the median infertility period was 2.57 years, the median age at orchidopexy was 11.39 years, the period from orchidopexy to micro-TESE averaged 27.25 years, the median body mass index was 24.3 kg/m², and the median testicular volume was 9.65 mL. In endocrine examinations, median serum LH,

TABLE 1 Clinical data in NOA patients with a history of bilateral cryptorchidism

Patient (n)	36
Partner age (y)	34.1 (30-39)
Age at micro-TESE (y)	38.63 (24.5-53)
Infertility period (y)	2.57 (0.5-10)
Age at orchidopexy (y)	11.39 (0.5-46)
Period from orchidopexy to micro-TESE (y)	27.25 (2.9-38.8)
LH (IU/mL)	9.9 (0.1-20.1)
FSH (IU/mL)	25.97 (5-70.7)
Testosterone (ng/mL)	4.76 (1.29-13.18)
Average testicular volume (mL)	9.65 (5-16)
BMI (kg/m ²)	24.3 (19.1-31.42)

Note: Data represent mean (range).

FSH, and testosterone levels were 9.9 mIU/mL (0.1-20.1), 25.97 mIU/mL (5-70.7), and 4.76 mIU/mL (1.29-13.18), respectively. (Table 1) In histopathological examination, two patients had tubular sclerosis, 22 had Sertoli cell-only syndrome, eight had maturation arrest, and four had hypospermatogenesis.

To evaluate factors influencing sperm extraction by micro-TESE, age at micro-TESE, age at orchidopexy, period from orchidopexy to TESE, serum LH and FSH, testosterone, average testicular volume, and body mass index were compared between the group with successful retrieval and the unsuccessful group. The results of a univariate analysis revealed that average testicular volume was significantly greater (11.7 mL vs 7.13 mL) in the successful vs unsuccessful group; body mass index (23.37 ng/mL vs 25.46 ng/mL), and serum LH (6.98 mIU/mL vs 13.55 mIU/mL) and FSH (18.28 mIU/mL vs 35.58 mIU/mL) were significantly lower in the successful vs the unsuccessful group. There were no significant differences between the two groups with regard to age at micro-TESE, age at orchidopexy, period from orchidopexy to TESE, and serum testosterone. To further analyze the factors contributing to successful sperm extraction, a multivariate analysis was performed on average testicular volume, serum LH and FSH, and body mass index, all of which had shown significant differences between the successful and unsuccessful groups in the univariate analysis. Average testicular volume appeared to be independently associated with successful sperm retrieval by micro-TESE in patients with a history of bilateral cryptorchidism (Table 2).

Testicular spermatozoa were retrieved from 20 of 36 patients (55.6%) with a history of cryptorchidism and used for ICSI. Pregnancy was achieved in 12 of the 20 couples (rate of pregnancy per couple and per ICSI cycle were 60.0% and 37.5%, respectively). Eight of the pregnancies resulted in a live birth (40%).

The histology of small (0-10 mL) and large (>10 mL) testes was compared. A significantly higher rate of early maturation arrest occurred in the small testes group; moreover, the small testes group gave a Johnsen score of 1-2 compared to 3-10 for the large testes group. No significant differences were found for tubular sclerosis, Sertoli cell-only syndrome, late maturation arrest, and hypospermatogenesis (Table 3).

4 | DISCUSSION

The probability of future reproductive dysfunction is greater in patients who have been treated for bilateral cryptorchidism compared to those with unilateral cryptorchidism. Lee et al reported that paternity rates (65.3%) in patients with a history of bilateral cryptorchidism were significantly lower than in patients with unilateral cryptorchidism (89.7%) and in controls (93.2%).¹¹ Their study also showed that the bilateral cryptorchidism group had a significantly lower sperm density and higher FSH and LH levels than the unilateral cryptorchidism and control groups.¹⁸

There have been few long-term follow-up studies of cases of bilateral cryptorchidism in relation to testicular histology, serum

TABLE 2 Correlation between successful testicular sperm extraction and clinical and non-invasive variables, evaluated by uni- and multivariate logistic analysis

Cryptorchidism	Success of sperm retrieval n = 20	Failure of sperm retrieval n = 16	Univariate analysis			Multivariate analysis	
			Odds ratio	95% confidence interval	P	Odds ratio	P
Age at TESE (y)	40.02 (33.1-53)	36.91 (24.5-48.9)	1.087	0.967-1.222	.158	—	—
Age at orchidopexy (y)	10.1 (3-45)	13 (0.5-46)	0.983	0.935-1.034	.525	—	—
Period from orchidopexy to TESE (y)	29.92 (8-36.9)	23.91 (2.9-38.4)	1.062	0.99-1.141	.085		
LH (IU/mL)	6.98 (0.1-17.9)	13.55 (8.1-20.1)	0.785	0.659-0.934	.001 [*]	0.943	.74
FSH (IU/mL)	18.28 (5-33.9)	35.58 (19.2-70.7)	0.904	0.838-0.976	.001 [*]	0.921	.362
Testosterone (ng/mL)	5.5 (2.76-13.18)	3.85 (1.29-8.66)	1.343	0.948-1.901	.073	—	—
Average testicular volume (mL)	11.7 (5-16)	7.13 (3-12)	1.328	1.089-1.619	.001 [*]	1.313	.045 [*]
BMI (kg/m ²)	23.37 (19.1-31.42)	25.46 (23.43-29.27)	0.728	0.534-0.993	.026 [*]	0.716	.59

Note: Data represent mean (range).

*Statistically significant ($P < .05$).

TABLE 3 Comparison of histopathological findings between small (0-10 mL) and large testis (>10 mL)

	Average testicular volume		
	0-10 mL n = 22	>10 mL n = 14	
Tubular sclerosis (%)	2 (9.1)	0 (0)	0.246
Sertoli cell-only syndrome (%)	16 (72.7)	6 (42.9)	0.073
Early maturation arrest (%)	2 (9.1)	4 (28.5)	0.018 [*]
Late maturation arrest (%)	0 (0)	2 (14.3)	0.068
Hypospermatogenesis (%)	2 (9.1)	2 (14.3)	0.629
Johnsen score 1-2	18 (81.8)	6 (42.9)	0.016 [*]
Johnsen score 3-10	4 (18.2)	8 (57.1)	0.016 [*]

*Statistically significant ($P < .05$).

FSH, and testicular volume. Cortes and Thorup reported that the histology of testicular tissues at orchidopexy is a useful prognostic factor of fertility potential and is correlated with serum FSH level and testicular volume in childhood.¹⁹ It has also been shown that patients with a history of bilateral cryptorchidism and high FSH levels do not have complete spermatogenesis in the testis.²⁰ Rusnack et al reported that severely affected testes in patients with a history of bilateral cryptorchidism have higher FSH levels and lower testicular volumes than in moderately affected testes and in patients with a history of unilateral cryptorchidism.²¹ Our observation here of a positive correlation between large testicular volume and histopathological findings is similar to previously reported studies.

Serum FSH level and testicular volume have been suggested as prognostic factors of future fertility potential. These studies recruited infertile patients with a history of cryptorchidism and who had undergone orchidopexy. For patients with sperm in a semen sample, assisted reproductive technology offers the possibility of

fathering a child providing the fertility of the partner is not compromised. The present study provides an assessment of fertility potential and prognostic factors in azoospermic patients with a history of cryptorchidism who had undergone orchidopexy. In the successful sperm retrieval group, testicular volume was significantly greater, serum LH and FSH levels and body mass index were significantly lower. In the multivariate analysis, testicular volume correlated positively with successful sperm recovery. This finding contradicts a previous review article that suggested there were no reliable positive prognostic factors for sperm recovery from NOA patients, including those with Klinefelter syndrome or varicocele.²² Testicular volume is thought to be a specific factor in patients with a history of bilateral cryptorchidism.

Three previous studies have reported on the outcome of TESE in azoospermic men with a history of cryptorchidism.¹²⁻¹⁴ There are two notable points of difference in this study compared to these previous studies. Firstly, obstructive azoospermia was excluded as far as possible. It is well known that the risk of epididymal abnormalities is high in patients with a history of cryptorchidism.²³ Therefore, patients with a history of cryptorchidism are not automatically classified as NOA. The coexistence of spermatogenic dysfunction and congenital seminal duct anomalies is common and is found in up to 60% of azoospermic patients with a history of cryptorchidism.¹⁴ The exclusion criteria are essential in proving a relationship between spermatogenic dysfunction and cryptorchidism. The diagnosis of NOA was made on serum FSH level (>10 IU/mL) or mean testicular volume (<16 mL) without any sign of obstruction.¹⁵⁻¹⁷ Eight patients were excluded from this study on these criteria. Secondly, only bilateral cases were considered. Bilateral cryptorchidism is associated with a higher risk of infertility than unilateral cryptorchidism according to a previous study.¹¹ Unilateral cryptorchidism is a primary maldevelopment that impairs fertility potential in the normal contralateral testis.

If orchidopexy is not undertaken before patients are two years old, then histopathological deterioration in the descended scrotal testis is increasingly observed with time.²⁴ The mechanisms of this impairment of a normal testis by unilateral cryptorchidism have not yet been elucidated, but may be related to primary impairment of spermatogenesis in the descended scrotal testis²⁵ or to immunological mechanisms due to the presence of anti-sperm antibodies.^{26,27} The pathophysiology of impaired spermatogenesis associated with unilateral cryptorchidism may differ from that of bilateral cryptorchidism. Therefore, analysis of the association of cryptorchidism and fertility potential is improved by restricting the focus to bilateral cases. The incidence of unilateral cryptorchidism was reported to be 0% (0/30) in the study by Negri et al, but incidences of 21% (8/38) and 20% (16/79) were found by Raman and Shlegel and Vernaeve et al, respectively.¹²⁻¹⁴ The occurrence of unilateral cases is a major problem in assessing whether or not cryptorchidism affects spermatogenesis because the TESE outcome reflects the unaffected testis in unilateral cryptorchidism cases. Therefore, ipsilateral cryptorchidism and obstructive azoospermia were excluded as far as possible in the present study.

Although Raman and Shlegel found that testis volume was significantly correlated with sperm recovery, this finding was not corroborated by Negri et al and Vernaeve et al.¹²⁻¹⁴ Negri et al reported a higher proportion of obstructive azoospermia (14/30; 46.6%) than in the present study.¹⁴ Obstructive azoospermia patients generally have a large testicular volume and high sperm retrieval rate; therefore, the association with testicular volume and sperm recovery might be underestimated. Vernaeve et al included patients with a larger not average testicular volume and a relatively high rate of unilateral cryptorchidism (more than 25%).¹² Raman and Shlegel's study likewise contained unilateral cases (8/38; 21.05%).¹³ Previous studies also included the scrotal testis of patients with ipsilateral cryptorchidism in their TESE, which would have influenced the determination of an association between testicular volume and sperm recovery at TESE. The present study is the first to suggest that testicular volume is an effective factor in determining the probability of successful sperm recovery in NOA patients who have undergone bilateral orchidopexy.

The sperm retrieval rate, pregnancy rate, and live birth rate were similar to those in the series reported by Vernaeve et al, Raman and Shlegel, and Negri et al.¹²⁻¹⁴

The present study has several limitations. (a) The retrospective nature of the study affected the quality of the data. (b) Pre-operative testicular position and testicular volume at orchidopexy, which affect future fertility, were not completely followed.²⁸

In conclusion, we show here that testicular volume in azoospermic men with a history of bilateral cryptorchidism might be an effective prognostic factor for successful sperm recovery at micro-TESE.

ACKNOWLEDGMENTS

We would like to thank all the clinical embryologists, nurses, and medical doctors of Dokkyo Medical University Saitama Medical Center for their assistance with recruitment and sampling.

DISCLOSURES

Conflict of interest: The authors report no declarations of interest. **Human rights statements and informed consent:** This study was approved by the institutional review board of Dokkyo Medical University Saitama Medical Center. (Number: 1734) All patients signed an informed written consent form before entering the study, and they were informed that they could terminate their cooperation with us whenever they wanted without any consequences.

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How to cite this article: Osaka A, Iwahata T, Kobori Y, et al. Testicular volume in non-obstructive azoospermia with a history of bilateral cryptorchidism may predict successful sperm retrieval by testicular sperm extraction. *Reprod Med Biol*. 2020;19:372–377. <https://doi.org/10.1002/rmb2.12338>