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Nationwide survey of urological specialists regarding male infertility: results from a 2015 questionnaire in Japan

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Abstract

Purpose: To investigate the incidence, etiology, treatment indications, and outcomes regarding infertile male patients in Japan.

Methods: Between April, 2014 and March, 2015, the authors contacted 47 clinical specialists in male infertility who had been certified by the Japan Society for Reproductive Medicine. The participating clinicians were sent a questionnaire regarding information on their infertile patients, according to etiology and the number and success rates of male infertility operations that had been performed in their practice.

Results: Thirty-nine specialists returned the questionnaire and provided information regarding 7268 patients. The etiology of infertility included testicular factors, sexual disorders, and seminal tract obstruction. During the study year, the clinicians performed varicocelectomies, testicular sperm extractions (TESEs), and re-anastomoses of the seminal tract. The rate of successful varicocelectomies was >70%. The sperm retrieval rates with conventional TESE and microdissection TESE were 98.3% and 34.0%, respectively, while the patency rates with vasovasostomy and epididymovasostomy were 81.8% and 61.0%, respectively.

Conclusion: Surgical outcomes for infertile male patients are favorable and can be of great clinical benefit for infertile couples. To achieve this, urologists should work in collaboration with gynecological specialists in order to optimize the treatment of both partners.

KEYWORDS

epidemiology, etiology, male infertility, nationwide survey, postsurgical outcome

1 | INTRODUCTION

Infertility is defined as a failure to conceive after 12 months of regular, unprotected sexual intercourse.[1] Worldwide, it is estimated that one-in-six couples experience some form of infertility during their reproductive lifetime. In 1993, the World Health Organization (WHO) categorized the causes of infertility into male factors (24%), female factors (41%), dual partner (24%), and indeterminate (11%).[2] The

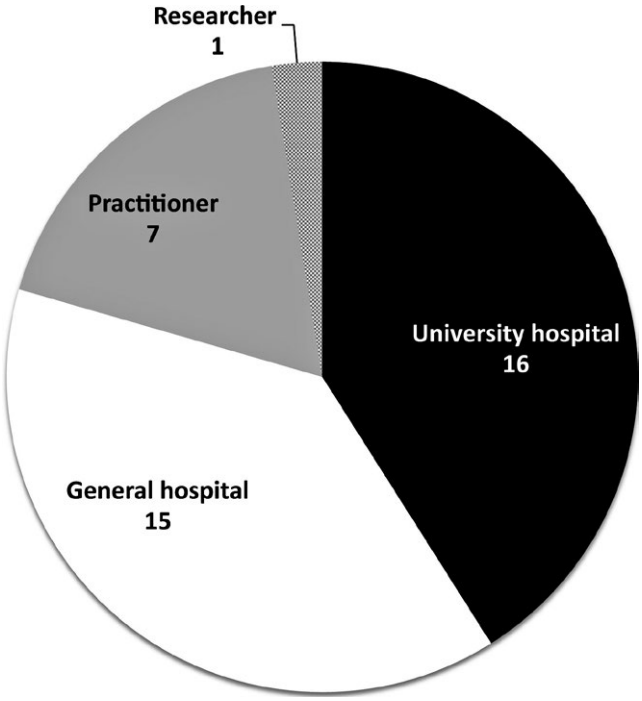


FIGURE 1 Responder characteristics: Affiliations of the responding urologists (n = 39)

above data are consistent with those of recent epidemiological studies from other countries, which reported that half of infertile couples have an underlying male component.[3] In Japan, the focus on female infertility is much greater than that on male infertility, with only 47 Japan Society for Reproductive Medicine (JSRM)-certified male infertility specialists practicing, as of April, 2016. Furthermore, much less is known about male fertility than about female infertility by both qualified medical professionals and the public. In order to improve the treatment outcomes among infertile male patients, one must begin by understanding the etiology of male infertility and the treatment options that are currently available. One researcher correctly stated that one of the main barriers to understanding the epidemiology and etiology of male infertility is a lack of consensus regarding the diagnosis of male reproductive dysfunction.[4]

The last Japanese nationwide survey on male infertility was conducted in 1997.[5] The purpose of the present study was to update the results of the previous survey. To this end, a survey was distributed to JSRM-certified specialists in male infertility that investigated the etiology, diagnosis, treatment protocols, and outcomes of infertile male patients.

2 | MATERIALS AND METHODS

This study's protocol was approved by the Yokohama City University Review Board. A national survey was conducted on male infertility with the assistance of the Ministry of Health, Labour and Welfare and with the support of Japan Urological Association, Japan Society of Andrology, Japan Society of Obstetrics and Gynecology, and JSRM. In Japan, clinicians who specialize in the treatment of male and female infertility must be certified by JSRM and include gynecologists and urologists. In April, 2015, there were 47 board-certified urologists who were practicing in Japan. These clinicians were mailed questionnaires and asked to report the number of new patients who they had evaluated between April, 2014 and March, 2015 and to provide information regarding: baseline semen analyses and diagnoses; the number, type, and outcome of surgical operations; and their working systems. The survey questionnaire was mailed in December, 2015 and the deadline for the survey responses was January, 2016.

The surgical procedures of interest included varicocelectomy, testicular semen extraction (TESE), and seminal tract re-anastomosis. The success rate of a varicocelectomy was based on whether or not there was an improvement in the semen analysis parameters after surgery, as determined by the responding urologist. The TESE was considered to be successful if intratesticular sperm were retrieved. The effectiveness of the seminal tract re-anastomosis, either a vasovasostomy (VVS) or a epididymovasostomy (EVS), was based on the number of patients who produced ejaculated sperm after surgery. As information was not obtained regarding the treatment of the infertile female partner and did not follow all the participants through to a successful pregnancy, only the data regarding pregnancy outcomes in a proportion of the cohort has been produced. There was no minimum follow-up period for the study cohort. Furthermore, which treatment methods that resulted in a successful pregnancy were not specifically evaluated.

3 | RESULTS

3.1 | Background of the responding urological specialists

Thirty-nine urological specialists returned a completed questionnaire and the response rate was 83.0%. Figures 1 and 2 illustrate the background characteristics of the responding urologists. Sixteen of the 39 responding urologists worked in a university hospital, 15 worked in a general hospital, and seven were urological practitioners. Only one responder was a researcher and did not treat infertile male patients in his institute (Fig. 1). During the year of the survey's completion, a total of 7268 patients visited the hospitals or clinics where the responding urologists practiced. Furthermore, 33 of the 39 responding urologists worked in more than one institute, including at female infertility treatment institutes and/or at the infertility departments of university hospitals or general hospitals, among other locations. They treated an additional 1446 infertile male patients monthly at these other institutions. The details of those patients were not investigated in this study (Table 1).

3.2 | Number of patients and their classification according to a semen analysis and diagnosis

Information was obtained regarding 7268 infertile male patients. Semen analysis data were available for 6551 patients and revealed

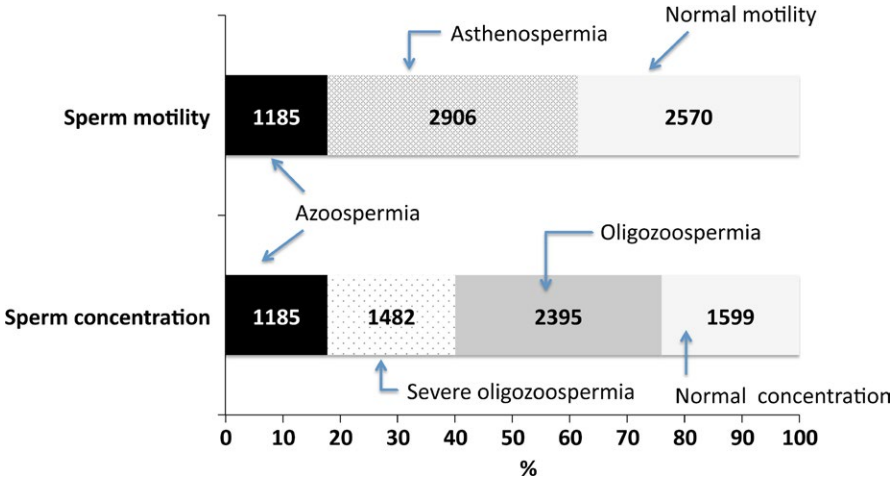


FIGURE 2 Distribution of the patients according to a semen analysis. Asthenospermia: sperm motility <40%; severe oligospermia, sperm concentration: $<5 \times 10^6$/mL; oligospermia, sperm concentration: $<15 \times 10^6$/mL

that 1185 (17.8%) patients had azoospermia, 3877 (58.3%) had oligospermia (sperm concentration: $<15 \times 10^6$/mL), including 1482 with severe oligozoospermia (sperm concentration: $<5 \times 10^6$/mL), and 2906 (43.7%) had asthenospermia (motility: <40%) (Fig. 2).

The etiology of infertility included testicular factors (n = 5991, 82.6%), sexual disorders (n = 980, 13.5%), and seminal tract obstruction (n = 286, 3.9%). A more detailed classification is shown in Table 2. The most common causes of testicular factor infertility were idiopathic (42.1%) and varicoceles (30.2%), followed by chromosomal abnormalities and azoospermia factor microdeletion, drug-induced testicular damage, an undescended testis, and hypogonadotropic hypogonadism.

Compared to the study that was conducted in 1997, the number of patients with sexual dysfunction had increased from 50 to 980. The number of patients with erectile dysfunction (ED) and ejaculatory disorders was 442 and 538, respectively. The number of patients with obstruction of the seminal tract was 286 (3.9%). Furthermore, there was a reversal in the distribution of patients with a sexual disorder and seminal tract obstruction, compared to that in the previous nationwide study (Fig. 3).

TABLE 1 Details regarding the patients who had been treated by the responding urologists at facilities other than their own affiliations

Variable	Number of responders	Number of patients treated per month
University hospital (urology)	3	19
General hospital (urology)	2	36
ART-certified institute (gynecology)	23	1173
Non-ART-certified institute (gynecology)	2	88
Urological clinic	3	130
Do not examine male infertility patients other than at their own affiliations	6	0
Total	39	1446

ART, assisted reproductive technology.

3.3 | Number and effect of surgical treatments

In total, 2394 operations were performed in the year of the survey's completion. A varicocelectomy was the most frequently performed operation (1388 per year) and included microscopic low ligation of the seminal vein (n = 1202, 86.6%), open high ligation (n = 108, 7.8%), and laparoscopic high ligation (n = 77, 5.9%). The most common indication for a varicocelectomy was a varicocele that was greater than Grade 2 (low ligation: 88.0%; high ligation: 100%; laparoscopic surgery: 85.7%) (Fig. 4). The effects of the varicocelectomy over time were assessed by using surveys that were conducted at 3 months and 6 months after the procedure. Nineteen responding urologists completed the survey at 3 months and 18 of the latter completed the survey at 6 months. Most of the cases (n = 1026, 74.0%) were considered to be successful, based on the results of postoperative semen analyses, and the number of confirmed pregnancies was 316. The overall success rate of varicocelectomies was >70% (Fig. 5).

Conventional TESE (C-TESE) was performed on 231 patients. The number of patients whose sperm were retrieved and who had a confirmed pregnancy was 227 (98.3%) and 130 (56.2%), respectively. Microdissection TESE (micro-TESE) was performed on 695 patients (Fig. 6) and the number of patients whose sperm were retrieved and who had a confirmed pregnancy was 236 (34.0%) and 82 (11.8%), respectively.

A VVS or EVS was performed on 44 patients (from 11 institutes) and 36 patients (from 10 institutes), respectively. No patient was treated by using transurethral resection of the ejaculatory duct. The success rate of the VVS and EVS was 81.8% (36/44) and 61.1% (22/36), respectively. A back-up C-TESE procedure was performed by seven of the 11 institutes for the VVS and nine of the 10 institutes for the EVS concurrent with re-anastomosis. Pregnancy was confirmed in 22 women whose partner had received both the VVS and EVS (Fig. 7).

TABLE 2 Distribution of the patients according to the etiology of male infertility

Etiology of male infertility	Number of patients	%
Testicular factors		
Total	5991	82.6
Idiopathic	3053	42.1
Varicocele	2193	30.2
Chromosomal or genetic anomaly		
Klinefelter's syndrome	129	1.8
Other chromosomal anomaly	85	1.2
Azoospermia factor microdeletion	98	1.4
Drug-induced male infertility		
Anticancer drugs	94	1.3
Other drugs	38	0.5
Undescended testis		
Postoperative	98	1.4
Untreated	15	0.2
Hypogonadotropic hypogonadism		
Congenital	42	0.6
Acquired	28	.4
Others	118	1.6
Sexual dysfunction		
Total	980	13.5
Erectile dysfunction	442	6.1
Ejaculatory disorder	538	7.4
Seminal tract obstruction		
Total	286	3.9
Unknown obstructive lesion	86	1.2
Postepididymitis	52	0.7
Postvasectomy	48	0.7
Postinguinal herniorrhaphy	42	0.6
Congenital absence of the vas deferens	39	0.5
Disorder of the ejaculatory duct or seminal vesicle		
Mullerian duct cyst	3	0.04
Ejaculatory duct obstruction	5	0.07
Cystic dilation of the seminal vesicle	4	0.06
Other disorder	4	0.06
Young's syndrome	3	0.04
Others (eg Kartagener's syndrome)		
Total	11	0.2

4 | DISCUSSION

The present study aimed to elucidate the epidemiology, etiology, and management options for infertility in a cohort of Japanese men. The data were obtained through a questionnaire that was distributed to

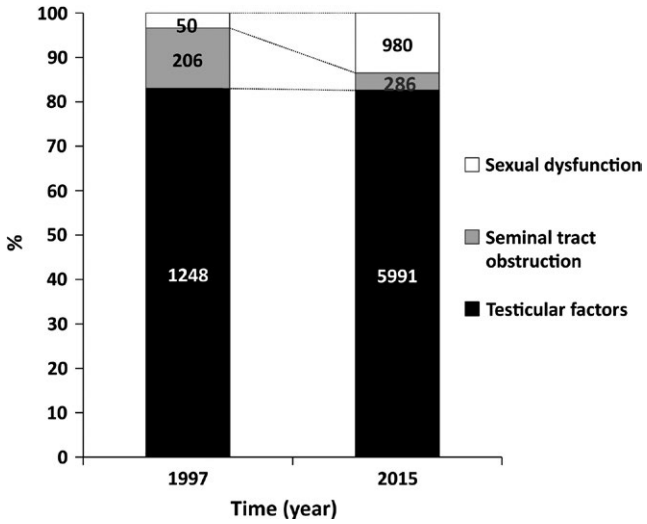


FIGURE 3 Comparison of this study (2015) to that of another study in 1997;[5] the distribution of patients according to the etiology of infertility. Compared to the previous study in 1997, the number of patients with sexual dysfunction increased from 50 to 980. There was a reversal in the distribution of patients with a sexual disorder and seminal tract obstruction

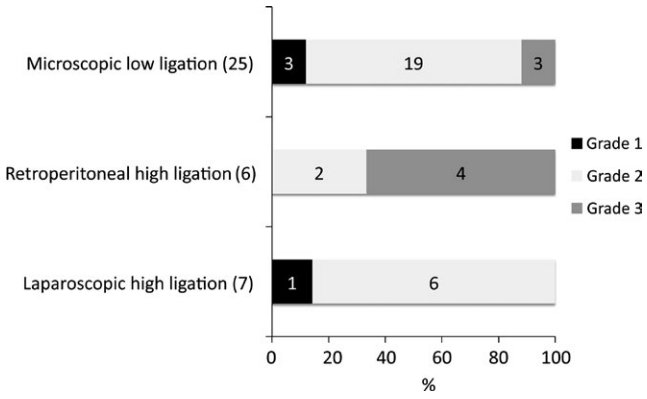
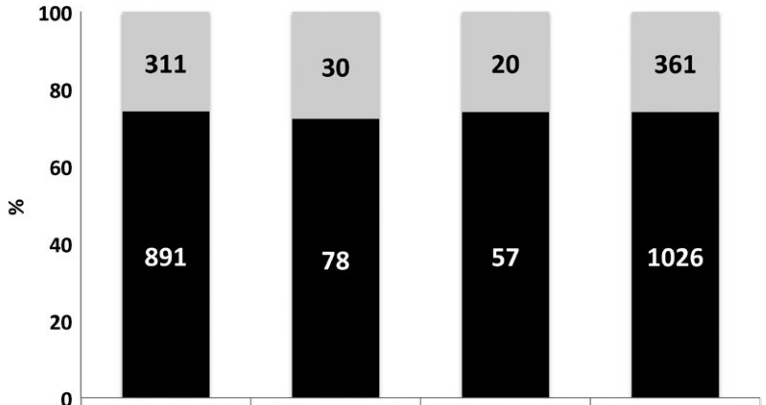


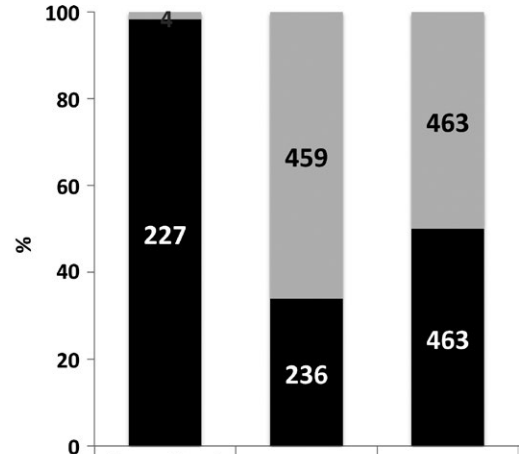
FIGURE 4 Indications for a varicocelectomy, according to the clinical grade and surgical technique. The numbers in parentheses indicate the number of responding urologists. The most common indication for a varicocelectomy (regardless of the surgical technique) was a varicocele greater than Grade 2

47 JSRM-certified specialists in male infertility. The survey response rate was 83.0% and 7253 infertile male patients were identified. In the previous study that had been conducted in 1997, data for only 5369 patients who had been treated at 308 institutes were obtained and a cause of infertility was identified in only 1504 of the latter.[6] These data show that the number of patients being evaluated and treated for male infertility has increased in the past 17 years. The true extent of this increase is difficult to gauge because many of the responding urologists also saw patients in assisted reproductive technology (ART)-certified facilities and it is reasonable to suppose that some infertile patients might have been under the care of non-urology or gynecology specialists. The incidence of male infertility is much larger than previously expected because of two reasons. First, there has been a



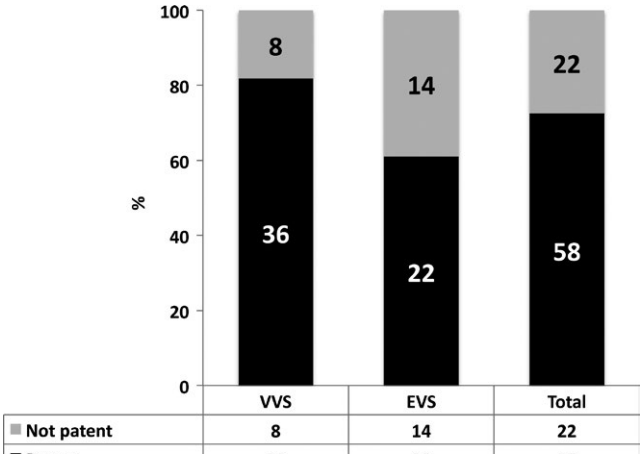
	Microscopic low ligation	Retroperitoneal high ligation	Laparoscopic high ligation	Total
Not improved	311	30	20	361
Improved	891	78	57	1026
Confirmed pregnancy	282	12	22	316

FIGURE 5 Outcomes of varicocelectomy. The overall success rate of the technique was >70% and 316 patients went on to father children



	Conventional TESE	Micro TESE	Total
Sperm Not retrieved	4	459	463
Sperm retrieved	227	236	463
Confirmed pregnancy	130	82	212

FIGURE 6 Outcomes of testicular semen extraction (TESE). The number of patients who were treated with conventional TESE and whose sperm were retrieved or who had a confirmed pregnancy was 227 (98.3%) and 130 (56.2%), respectively. The number of patients who were treated with microdissection TESE (micro-TESE) and whose sperm were retrieved or who had a confirmed pregnancy was 236 (34.0%) and 82 (11.8%), respectively



	VVS	EVS	Total
Not patent	8	14	22
Patent	36	22	58
Confirmed pregnancy	15	6	21

FIGURE 7 Outcome of re-anastomosis of the seminal tract. The success rates of vasovasostomy (VVS) and epididymovasostomy (EVS) were 81.8% (36/44) and 61.1% (22/36), respectively. Pregnancy was confirmed in 22 women whose partner received both of these procedures

change in the concept of the "infertile couple" and increasing recognition of male infertility through media and educational initiatives. The authors speculate that a general increase in awareness among infertile male patients over the preceding 17 years might have led to an increase in these patients seeking consultation for infertility issues.

Second, the authors also speculate that an increase in paternal age has contributed to a worsening of sperm quality. Recently, epidemiological data have confirmed that, in Japan, as well as in other developed countries, the age at marriage is rising. A consequence of this is an increase in the maternal and paternal age, the latter of which has increased by 15% over a period of 10 years in the UK.[6] Several reports have confirmed that increased paternal age adversely affects sperm motility[7] and leads to a prolongation of the time to pregnancy.[8] However, further large-scale epidemiological studies in Japanese patients are necessary in order to confirm the above findings.

The results of the semen analyses revealed that 18.7% of the patients had azoospermia, 58.3% had oligozoospermia (of which 22.2% had severe oligozoospermia, defined as a sperm concentration of $<5 \times 10^6$/mL), and 43.7% had asthenospermia. These results cannot be compared directly to those that were obtained by the 1997 survey[5] because, since then, both the semen analysis parameters and the age distribution of patients have changed. At the time of this previous survey, the reference range for semen analysis, as established by the WHO, was a sperm concentration of $>20 \times 10^6$/mL and motility of >50%.[9] This is in contrast to a sperm concentration of $>15 \times 10^6$/mL and motility of >40% at the time of the

present study.[10] The frequency of azoospermia among infertile men has been reported to range from 2% to 15% and these data are consistent with those of this study.[11,12] It is unclear whether there is sufficient public knowledge regarding the prevalence of men with abnormal semen parameters. The authors expect that by increasing public awareness about this important health issue, the number of male patients seeking medical advice about infertility issues will increase. In this study, more advanced analyses of sperm quality, such as DNA fragmentation, capacitation, and evaluation of the acrosomal reaction, were not performed.[13] These should be investigated in future studies in order to allow a more comprehensive assessment of the factors that contribute to male infertility in an effort to develop a national strategy for the declining birth rate.

The majority of the patients in this study (n = 5991, 82.4%) had testicular factor infertility, which was most commonly idiopathic (n = 3053, 42.1%) or due to varicoceles (n = 2193, 30.2%). These findings are consistent with those that were reported by a study that found that the cause of infertility is indeterminate in ~50% of cases[11] and also those of another study that reported that 40% of male infertility cases were of unclear etiology, while 32.3% were secondary to varicoceles.[12] Most cases of idiopathic male infertility are treated empirically with standard hormone regimens, which have limited proven benefit.[14] Additional studies are needed in order to further explore the etiology of idiopathic infertility and to develop more effective therapeutic modalities.

The number of patients with sexual dysfunction (n = 980, 13.5%) was significantly increased, compared to the previous 1997 survey.[5] Sexual dysfunction is broadly divided into ED and ejaculatory dysfunction. The causes of ED include vasculogenic, neurogenic, and psychogenic factors, while those of ejaculatory dysfunction include spinal cord injury, diabetes, psychogenic factors, and nerve injury secondary to pelvic and/or retroperitoneal surgery.[15] Recently, the number of patients with psychogenic erectile and ejaculatory disturbances has increased. One study reported that the stress of trying to conceive could adversely affect the couple's usual approach to sexual activity, in such a way that intercourse no longer focuses on sexual satisfaction, but rather induces feelings of urgency, pressure, and anxiety, especially for men.[16] This study also recommended that fertility experts should acknowledge this problem and identify the psychosocial problems that adversely affect a couple's sexual enjoyment. Furthermore, once such issues are identified, it is important that clinicians address these problems and provide appropriate support; for example, in the form of counseling.

Compared to the 1997 study, this study identified an ~10% decrease in the proportion of patients with obstruction of the seminal tract (n = 286). Obstructive azoospermia contributes to 6.1%[12] to 13.6%[17] of male infertility. One reason for this observation could include an increase in the number of patients who undergo TESE in gynecological clinics without consulting a urological specialist for examination of the obstruction.

Varicoceles affect 15%-20% of healthy men and ≤35% of infertile men.[18] These data are consistent with this study's results, which found that 30.2% of the men in this study's cohort had varicoceles. The exact mechanism whereby varicoceles cause infertility has not been elucidated, but it has been demonstrated that the semen parameters are adversely affected by the presence of a varicocele[19] and that a varicocelectomy can restore fertility. In the current study, the efficacy of all the surgical approaches for the treatment of varicoceles (inguinal, retroperitoneal, and laparoscopic) was >70%. The most commonly performed technique was microscopic low ligation of the seminal vein (n = 1202, 86.6%). Although previous studies have demonstrated that microscopic low ligation had higher rates of success, compared to those of high ligation, including laparoscopic ligation, this study found no difference in the efficacy rates among the three surgical techniques. The success of a varicocelectomy was determined based on whether there was an improvement or not in the semen analysis after surgery. Previous studies cited that the improvement rate of sperm motility and density after a varicocelectomy was ~70%[20] and this rate was similar to that observed in the present study. Many recent reports on treatment outcomes do not evaluate the effectiveness of interventions, but rather simply take into account the average value of semen examination results of all the patients who underwent a varicocelectomy. In a recent meta-analysis, it was concluded that varicocelectomies resulted in improved sperm concentration, motility, and pregnancy rates.[19,21,22] Furthermore, many studies have demonstrated that the varicocelectomy improves sperm function, DNA fragmentation, and ART outcomes.[23,24] Importantly, >30% of the patients in this study whose semen parameters improved after a varicocelectomy went on to father children. This statistic clearly highlights the effectiveness of this treatment option. As many male patients are investigated by gynecologists as part of the female partner's infertility workout, it is possible that a diagnosis of a varicocele could be missed, which could adversely affect the couple's fertility outcome. The current study demonstrates the importance of performing a thorough physical examination of the male partner in order to avoid missing this common and easily treatable diagnosis. To this end, the authors recommend that all fertility specialists, including gynecologists, communicate effectively with their patients and inform them of the success rate of the varicocelectomy. Furthermore, there should be more collaborative practice between gynecologists and urologists in the treatment of male infertility.

The rate of sperm retrieval by using micro-TESE was 34%, which was slightly lower compared to that seen in other reports.[25,26] However, given that it was not known how many patients in this study's cohort had non-obstructive azoospermia, it is difficult to compare this study's results with those of previous studies. The rates of conception of the patients who underwent C-TESE were higher than those of the patients who underwent micro-TESE (>50% vs <25%, respectively). The most likely reason for this difference in pregnancy rate is the smaller number of retrieved sperm and ART cycles in the micro-TESE group, compared to the C-TESE group. Given that the quality of the spermatozoa that are retrieved from severely hypo-functional testes could be decreased, no matter which TESE procedure is performed, it is important to continue to improve sperm-retrieval techniques and to develop novel drug therapies that can improve sperm quality.[27,28]

In the current study, the success rate of re-anastomosis was very high (VVS: 81.8%; EVS: 61.1%). These results were similar to those

that were reported by others who conducted a nationwide Japanese survey on the outcomes following seminal tract re-anastomosis for obstructive azoospermia.[29] Importantly, patients with an obstruction of the seminal tract conceive naturally following seminal tract re-anastomosis. Given the success rate of re-anastomosis and the potential for conception, it is important that information regarding the efficacy of this procedure is clearly communicated to patients and reproductive specialists, including both urologists and gynecologists.

Many of the institutes that participated in this study also performed C-TESE at the time of re-anastomosis in order to have "back-up" sperm should the latter procedure not prove to be successful. It is possible that this complementary procedure contributed to the pregnancy outcomes that were observed in this study and therefore future work should focus on improving the success rate of isolated re-anastomosis. If the patency rate improves and sperm are identified in the ejaculate, then the number of pregnancies by TESE-intracytoplasmic sperm injection might decrease and the number of spontaneous pregnancies and those due to artificial insemination might increase. In turn, this might reduce the physical, mental, and economic burden of infertile couples.

There are several limitations of the present study. First, questions were simplified in order to increase the response rates. Second, only patients with ED and ejaculation disorders were included in the "sexual dysfunction" category. Third, rather than using a standardized assessment method, the individual responders decided whether or not there was an improvement in the semen analysis results. Nevertheless, despite these limitations, all the physicians who participated in this survey were male infertility experts and therefore the authors believe that their evaluations would not have differed significantly. Fourth, the period of data collection ranged from April, 2014 to March, 2015, while the response period of the questionnaire was between December, 2015 and January, 2016. Therefore, there was no standardized follow-up period for patients. Finally, detailed information regarding the treatment of the female partners was not collected.

In conclusion, the prevalence of infertile male patients under treatment by specialist clinicians has increased in Japan over the past 17 years. In this study, the etiology of male infertility was evaluated and the available treatment options were reviewed. It was found that the overall outcome of male infertility surgery is favorable and is recommended for the treatment of infertile couples, following a collaborative decision between the patients and clinical specialists, including gynecologists and urologists. There also should be an increased level of dedication to improving service delivery for male infertility in Japan and to reducing regional discrepancies in patients' access to infertility specialists. Such a change would be invaluable in improving the outcomes for infertile patients in Japan.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: The protocol for the research project was approved by the Yokohama City University Ethics Committee, Yokohama, Japan. All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. This article does not contain any study with animal participants that were performed by any of the authors.

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