



An Infertile Couple's Long and Expensive Path to Varicocele Repair

Adithya Balasubramanian, Nannan Thirumavalavan, Jason M. Scovell, Jonathan Lo, Byung Ji, Elizabeth L. Godfrey, Alexander W. Pastuszak, and Larry I. Lipshultz

OBJECTIVE	To characterize the pathways to care that infertile couples requiring varicocele repair (VR) pursue prior to presenting to a male fertility clinic.
METHODS	An IRB-approved single center retrospective review of patients undergoing VR after presentation to an academic male fertility clinic was performed. Patients whose charts included partner histories were assessed for duration of attempting conception, prior workup, and assisted reproductive technology (ART) use.
RESULTS	A total of 405 couples were included. At presentation, mean age was 34.4 (SD ± 6.5) years for men and 31.1 (SD ± 4.3) years for women ($P < .0001$). A couple's first visit to a physician was a gynecologist in 59% (198/334) of couples, a reproductive endocrinologist (REI) in 25% (83/334) of cases, with 14% (47/334) presenting without a previous female workup and were self-referred, and 2% (6/334) seeing both a gynecologist and REI prior to presentation. On average, couples attempted pregnancy for 22.3 (SD ± 21.1, range 0-120) months prior to presentation. Eighteen percent of couples underwent ART prior to presentation. Couples who had undergone ART had lower pre-VR total motile sperm counts compared to couples not pursuing ART prior to presentation ($P = 0.031$). The majority (70.4%) of females had no abnormality in their workup, making varicocele the only correctable factor for infertility in the couple.
CONCLUSIONS	Our findings show a significant delay in referral of infertile men requiring VR. Eighteen percent of couples underwent costly ART prior to an inexpensive male workup. In an era of medical cost containment, early referral to a male infertility specialist is imperative. UROLOGY 124: 131–135, 2019. © 2018 Elsevier Inc.

As per American Society of Reproductive Medicine guidelines, infertility is defined as the inability of a couple to conceive after 1 year of regular, unprotected intercourse, or less than 6 months if the female is older than 35 years of age.¹ Unlike most medical conditions, infertility affects both partners in a couple. Approximately 15.5% of couples struggle with infertility and nearly 7 million annually seek infertility care in the United States.^{1,2} In approximately 50% of cases, a male factor is either partially or wholly responsible

for the infertility – in 20%, a male factor is the only identifiable cause, while in 27%, both partners have an identifiable defect.² However, women traditionally drive the workup for an infertile couple, either because they are usually already established patients of a gynecology practice, or because women may face more societal pressure. This phenomenon is evidenced simply by the fact that there are 49 REI fellowship programs, and only 13 male infertility programs. In addition to the number of fellowships, the number of practitioners is significantly different between the 2 specialties. There are 33,624 obstetrician-gynecologists (as of 2010) and only 12,517 practicing urologists (as of 2017) in the US.^{3,4} This may be a reflection on how a larger percentage of women than men maintain regular visits with their respective specialists. This familiarity with their obstetrician-gynecologists likely leads to women pursuing care for infertility first. Another large contributor to this discrepancy is that with recent advancements like in vitro fertilization (IVF) and intracytoplasmic sperm injection, severe male factor defects can be bypassed without a thorough evaluation of the male. Though this can sometimes be successful and result in a child for the couple, pursuing ART without a thorough evaluation of both partners neglects to search for and identify correctable causes in the male.

Conflict of Interest: AWP- Endo Pharmaceuticals - advisor, consultant, speaker. LIL-Boston Scientific - advisor Dr. Lipshultz American Medical Systems (Speaker) AbbVie (Consultant) Lipocine (Consultant) Aytu Bioscience (Consultant) Endo Pharmaceuticals (Speaker/Consultant). AB, NT, JMS, JLB, & ELG- none.

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From the Center for Reproductive Medicine, Scott Department of Urology, Baylor College of Medicine, Houston, TX

Address correspondence to: Nannan Thirumavalavan, M.D., Department of Urology, Baylor College of Medicine, 1 Baylor Plaza, ALKT-N730, Houston, TX 77030. E-mails: nannan@bu.edu; thirumav@bcm.edu

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The most common correctable cause of male infertility is the varicocele, an abnormal dilation of the pampiniform plexus of veins in the spermatic cord.⁵ The overall prevalence of varicoceles is approximately 15% in the general population, but 40% in infertile men.⁶ Varicoceles can affect spermatogenesis due to a combination of testicular temperature elevation, oxygen deprivation, and retrograde reflux of gonadal toxins from incompetent veins.⁷ These phenomena may result in cellular level changes such as increased germinal cell apoptosis, Sertoli cell dysfunction and reduced testosterone production by Leydig cells. Together these phenomena may result in testicular atrophy, discomfort, infertility, and hypogonadism. Varicocele repair (VR) is beneficial in infertile men with abnormal semen parameters and improves pregnancy rates in couples attempting natural pregnancy as well as those pursuing ART.^{7,8} In some patients, it can eliminate the need for ART altogether or reduce the need for more intense ARTS such as IVF or intracytoplasmic sperm injection.⁸ As such, evaluation of the male is critical in the workup of an infertile couple.

Though guidelines exist regarding the workup of male and female infertility, the adherence to these guidelines and real-world workup of patients has not been extensively studied.^{9,10} The literature on this subject is primarily limited to studies investigating correctable forms of infertility in women. Consequently, much of the literature on this topic is produced by gynecologists, reproductive endocrinologists (REI) and endocrinologists. Practice pattern studies focused on male infertility and procedures for correctable pathologies including VR are limited.^{11,12} Only one practice pattern paper has been published on VR.¹³ This work focused on identifying an optimal surgical approach for varicocele repair among adolescents, not adults. There is therefore a need to understand practice patterns and guideline adherence specifically among adult male patients encountering infertility. Understanding these facets of VR can assist in minimizing a couple's overtreatment and thereby reduce costs to both couples and the healthcare system. We aimed to characterize infertile

couples requiring VR and their journey prior to arrival in a male infertility clinic.

METHODS

Patients who underwent microsurgical VR by one of two surgeons (LIL and AWP) between 2009 and 2017 at an academic andrology clinic were identified using billing data. As described previously, men presenting for infertility at our center are examined in the standing position.¹⁴ A varicocele is diagnosed if a venous diameter is greater than 3mm, and retrograde flow is confirmed, when the patient is standing. If the patient presenting with infertility has a varicocele, either palpable or subclinical, and one abnormality on semen analysis, a VR is offered. Our surgical techniques have also been previously described.¹⁴

An IRB approved retrospective chart review was performed on all patients who underwent VR primarily for infertility, excluding those who had VR performed primarily for pain. Baseline characteristics recorded included patient age, primary vs secondary infertility, and duration of attempting pregnancy. Total motile sperm counts (TMC) on presentation were also recorded. Data regarding female partner age, workup prior to seeing a male fertility specialist, the couple's prior use of assisted reproductive technologies and any comorbidities and findings noted on prior reproductive workups were also obtained from direct chart review. Available previous pregnancy data recorded in the chart were documented. Descriptive statistics, including means and standard deviations (SD) were used to report continuous variables. Student's *t*-test was utilized to compare continuous variables. Chi-squared analyses were performed to compare categorical variables.

RESULTS

In total, 405 couples were included in the analyses. At presentation, the mean age was 34.4 (SD ± 6.5, range 16- 63) years for men and 31.1 (SD ± 4.3, range 19-43) years for women. Men were significantly older than their female counterparts ($P < 0001$). Of the 405 couples, 59% (198/334) were first seen by a gynecologist only, 25% (83/334) a REI only, 14% (47/334) presented without an initial female workup, and 2% (6/334) saw both a gynecologist and REI prior to presenting to a male infertility clinic (Fig. 1). When comparing couples presenting with primary vs secondary infertility, there were no differences in pre-

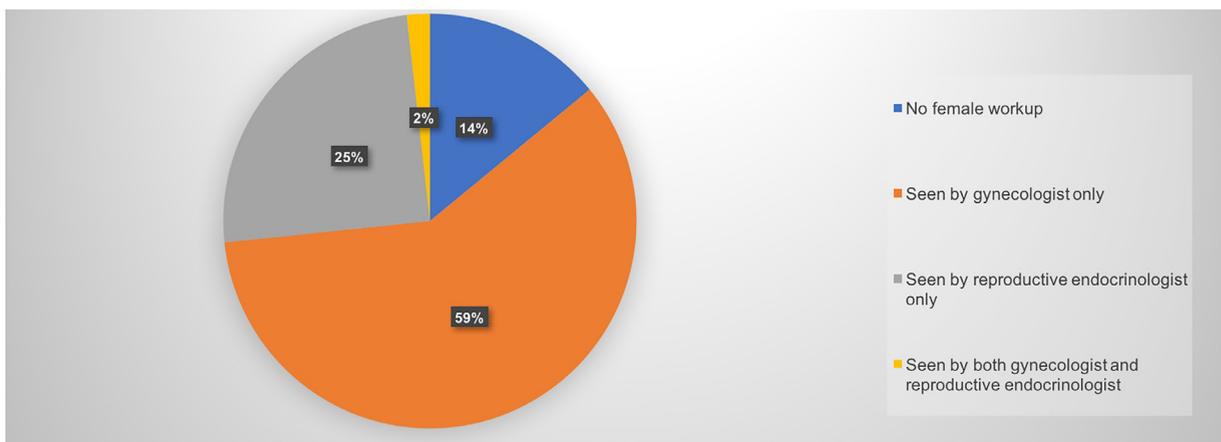


Figure 1. Female workup prior to presenting for male factor evaluation.

vious workup or type of provider seen ($X^2, P > .05$). On average, couples were attempting to initiate pregnancy for 22.3 (SD \pm 21.1, range 0-120) months prior to presenting for male evaluation. Couples with primary infertility were trying for pregnancy for an average of 21.4 (SD \pm 19.9, range 0-120) months, while couples with secondary infertility were trying for pregnancy for an average of 28.8 (SD \pm 27.8, range 7-108) months prior to presentation for male workup. However, this difference did not reach statistical significance ($P = .114$).

Couples in whom only the female partner had exclusively seen a physician (gynecologist) prior to presentation attempted pregnancy for an average of 20.7 months (SD \pm 20.6 months, range 0-108). Couples who had exclusively seen REIs prior to male evaluation attempted pregnancy for an average of 25.8 months (SD \pm 23.3, range 3-120), and couples who had seen both gynecologists and REIs prior to presenting for male factor evaluation had attempted pregnancy for an average of 19.5 months (SD \pm 12.6, range 7-42). However, none of these differences were statistically different. Couples in whom the female partner had not had a workup prior to presenting for male factor evaluation had attempted pregnancy for an average of 23.8 (SD \pm 22.5, range 2-84) months. In total, 18% of couples utilized some form of ART prior to presentation; 38 of 344 couples had undergone IUI cycles (range 1-10), 29 of 344 couples had undergone IVF cycles (1-4), and 5/344 underwent both IUI and IVF cycles (Fig. 2). Couples undergoing IUI or IVF had an average pre-VR total motile sperm count (TMC) of 8.9 (SD \pm 10.5, range 0-50.8) million sperm, while couples who did not pursue ART had an average pre-VR TMC of 13.2 (SD \pm 16.9, range 0-88.4) million sperm. Couples who had undergone IUI or IVF had lower pre-VR TMC compared to couples not pursuing ART prior to male factor evaluation ($P = .031$). The majority (70.4%) of females had no abnormality in their workup, making varicocele the only correctable factor for infertility in the couple. The female factor infertility conditions that couples presented with are listed in Table 1. The presence or absence of female factors contributing to infertility were not statistically different between couples pursuing ART vs those who did not ($X^2, P = .794$).

COMMENT

Our results show a significant delay in referral of infertile men requiring VR during couple evaluation of

Table 1. Female Factors Identified Within the Cohort

Comorbidity/Finding on Workup	Incidence (Total n = 321)
No abnormality found	226 (70%)
Ovulatory factor (PCOS)	49 (15.3%)
Tubal factor	15 (4.7%)
Uterine factor	14 (4.4%)
Endometriosis	13 (4%)
Cervical factor	3 (0.9%)
Other/unexplained	1 (0.3%)

fertility. The importance of pursuing VR is rooted in evidence that suggests that varicoceles contribute towards a progressive disease process.^{15,16} Lessons from the adolescent population provide further evidence of this underlying pathophysiology. Okuyama et al. compared treated vs untreated varicocele in 40 pubertal boys and demonstrated that varicoceles may result in substantial worsening of semen parameters compared to the patients who underwent VR.¹⁷ Work by Mori et al. further supported this association by demonstrating that sperm progressive motility and concentration were lower in adolescent patients with varicoceles.¹⁸ Evidence suggesting that varicoceles are not static lesions that have an initial impact with no further effects should be combined with studies demonstrating the efficacy of VR. Multiple studies have demonstrated that VR is effective in reducing the need for ART procedures.^{8,14,19,20} In addition, even if ART is required, success rates are higher after VR, as semen quality, and sperm DNA quality are improved.²¹⁻²⁵

Couples in the present study were primarily screened by gynecologists with no evaluation by urologists prior to presentation at our clinic. Given that the average female age of our population was below 35 years old, American Society for Reproductive Medicine guidelines recommend that both a male and female evaluation be undertaken following 12 months of trying to conceive. In contrast, couples in this study took 22 months on average to present for male factor evaluation. In addition, 50% (158/316) of couples waited longer than 1

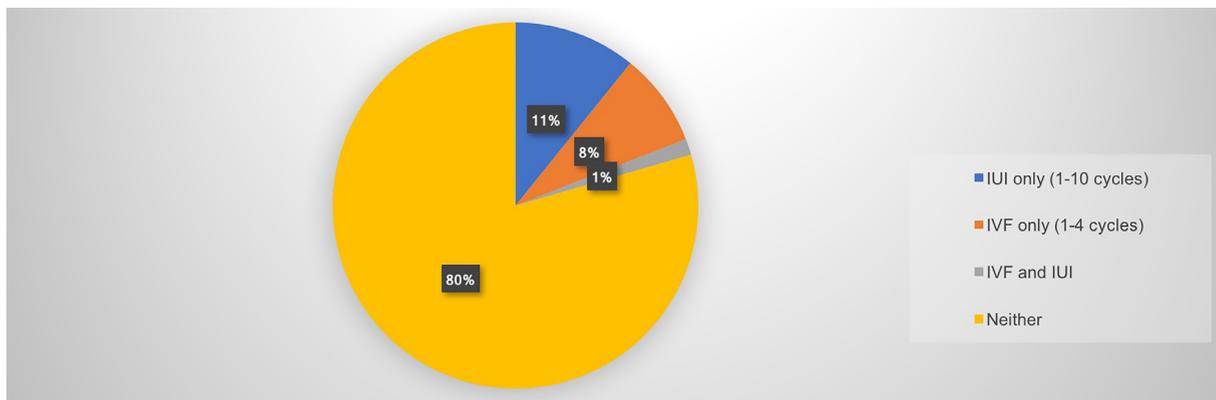


Figure 2. Use of assisted reproductive technologies prior to presenting for male factor evaluation.

year to have an evaluation for male factor. This strongly supports the need for a more proactive approach to ensure that both partners get appropriate, parallel evaluation when infertility is a concern.

The importance of involving urologists in the evaluation of couple infertility early in the process is evident when considering that, in the present study, 70% of females did not have a correctable form of infertility upon evaluation by gynecologists, with only the male varicoceles remaining as the only correctable factor for most couples. More importantly, varicocele was only discovered following evaluation by a urologist. This delay and subsequent discovery of a correctable etiology of male infertility underscores why primary care physicians, reproductive endocrinologists, and gynecologists should proactively refer couples facing infertility to reproductive urologists. Conversely, urologists should seek to be actively involved in caring for infertile couples.

For many men in our study, the exclusive form of evaluation prior to clinic presentation was a semen analysis (SA). Without visiting a urologist, the diagnoses, and infertility treatments for many couples were dictated based solely on semen parameters. However, a SA alone is not a substitute for a male factor evaluation which includes a clinical examination, comprehensive history, and other pertinent investigations. While a SA can definitively identify several etiologies of infertility including azoospermia, severe asthenospermia, or globozoospermia, it is not a test of male fertility, and rather is merely a guide in evaluation and treatment.²⁶ SA in combination with additional screening exams is required to accurately diagnose male factor infertility, including varicocele. Exclusively relying upon the SA is further limited by the fact that the test is susceptible to intraindividual variability stemming from diurnal and seasonal variations.²⁶

The reference values employed in SA are dictated by World Health Organization (WHO) standards are routinely revised and were changed in 2009 based upon new semen parameters aggregated from several reference studies.²⁷ This change in SA threshold values has been shown in work by Esteves et al. to have led to the reclassification of many males with borderline SA parameters.²⁸ Men deemed "fertile" based on prior values were reclassified as infertile and vice versa. These nuances in analysis and interpretation underscore why an experienced urologist must play an active role in analyzing and managing couples facing infertility.

Novel biomarkers for assessing the efficacy of varicocele repair continue to be discovered. Agarwal et al. demonstrated that sperm DNA fragmentation testing, an emerging metric for assessing varicocele repair, may prove useful for assessing treatment efficacy for patients with normal semen parameters.²⁹ Similarly work by Camargo et al. indicates that proteomic signatures can further broaden the molecular parameters for assessing sperm quality.³⁰ Since men with normal standard semen analyses may have abnormalities detected on physical exam or with more advanced testing, early referral for male workup is prudent.

There are several limitations in our study that should be discussed. First, this is a retrospective review and suffers from the limitations inherent with this type of study design. Our study was performed in an academic health care system, with fellowship-trained urologists specializing in male reproductive dysfunction. Thus, our results may not be generalizable to other healthcare systems, including community practices, and additional data are needed to determine whether these patterns are comparable to those in other practice settings. However, we suspect that the delay in presentation for male factor evaluation that is identified in our study likely underestimates the phenomenon in community practices, where a large, well-advertised male fertility clinic may not be present or readily accessible. Insurance coverage and other measures of socioeconomic status, including income level or occupational status, were not analyzed in the present study, and could influence care sought by couples. Another limitation of this study is the group of patients that are not captured by our methodology. It is unclear how many men with varicoceles, imperfect semen analyses, or both undergo IVF successfully, and thus never see a male infertility specialist for evaluation. In these patients, an opportunity to improve reproductive potential and even avoid IVF is missed. In addition, a significant cost savings could be missed as varicocele repair is traditionally covered by insurance. Despite these limitations, the assessment of referral patterns surrounding infertility and VR remain a critical topic for urologists.

CONCLUSIONS

The present study is amongst the first to provide information on referral patterns and characteristics of infertile couples with an emphasis on varicocele and VR. Our work demonstrates the delay in presentation of infertile couples to a male infertility clinic, and should emphasize the need for a thorough male workup for all couples facing infertility.

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