

Evolving role of varicocele repair in the era of assisted reproduction



As the most common etiology of male factor infertility present in approximately one-half of infertile men, the varicocele represents one of the simplest, most cost-effective, and most effective avenues of treatment for an infertile couple and therefore should be actively sought out by reproductive medicine providers. The varicocele has been recognized as a cause of infertility since the late 19th century, with the first report of varicocele repair leading to natural pregnancy being published in 1929 (1). Numerous publications have since followed describing benefits of repair that include improved semen parameters and natural fertility. More recent data have suggested additional benefits in sperm DNA fragmentation, testosterone production, and even assisted reproductive technology (ART) outcomes. Now almost a century later, and after ART has been developed beyond our wildest dreams, the varicocele remains as an often forgotten pillar of simple, effective, and treatable infertility.

There are currently two primary challenges facing the varicocele in an infertile couple: 1) identifying it; and 2) defining the role of repair in the era of ART. Identifying the varicocele should be straightforward. An initial screening evaluation with a semen analysis of the male partner should be a routine component of the infertility evaluation, and if it is abnormal, referral to a male reproductive specialist is recommended (2). Despite this widely recognized recommendation by the American Society for Reproductive Medicine and others, approximately one-fourth of male partners are never even evaluated (3). Because the diagnosis of a clinical varicocele is made only by physical examination, it is readily identified by a male reproductive specialist who can then counsel the couple on the relative merits of repair versus observation for their given situation. The only thing standing between the couple with infertility secondary to a varicocele and effective treatment is the appropriate referral for an abnormal semen analysis result.

After the diagnosis is made, treatment of the varicocele must then find a new context within the framework of the current paradigm of ART. Serving to define and characterize this context, Samplaski et al. should be commended for their important contribution to the varicocele literature published in this issue of *Fertility and Sterility* (4). The authors retrospectively analyzed almost 400 men who underwent varicocele repair with the use of either embolization or a microsurgical approach, measuring the total motile sperm count (TMC) before and after repair and categorizing the results by the proportion of couples considered to be candidates for in vitro fertilization (IVF), intrauterine insemination (IUI), or natural conception. Not surprisingly, the mean TMC for the entire cohort increased >2.5-fold after repair. Interestingly, the most significant gains were observed in men with the lowest baseline TMC, with an almost sevenfold improvement among the men with baseline severe oligospermia. The most unique aspect of the study provides clinicians and

patients alike the framework necessary to fit varicocele repair into the ART algorithm: the categorization of the patients by the theoretic ART method required versus natural conception before and after varicocele repair. Almost two-thirds of couples that were candidates for IVF at baseline improved to IUI or natural conception counts after repair, and similarly, approximately two-thirds of couples that were candidates for IUI at baseline improved to natural conception counts. These results provide a resounding call to action for reproductive medicine providers to reconsider the importance of the male-factor evaluation as well as varicocele repair within the framework of ART.

The theoretic categorizations provided in Samplaski et al.'s study, though helpful for the purposes of counseling couples, unfortunately did not provide real-world ART decisions made by the particular patients or their physicians. Moreover, the authors calculated the TMC of 9 million required for natural conception by taking the lower limit of normal fertility cutoffs from the World Health Organization's (WHO) 2010 manual definition for each individual parameter of volume, concentration, and motility. Although TMC is the most clinically useful parameter of a semen analysis, the WHO 2010 manual did not identify a lower limit of normal for TMC, and it could possibly be higher than the 9 million calculated by simply combining all of the lower limits of its component parameters which were initially calculated independently. Samplaski et al.'s results, particularly the proportions of men achieving the "natural pregnancy >9 million" TMC after varicocele repair, should be interpreted with this consideration in mind. In addition, although not entirely feasible for a study like this, the lack of a comparison group limits the findings. Finally, and perhaps most importantly, the study is limited by a lack of the most important outcomes in reproductive medicine: pregnancy and live birth. Despite these noted limitations, the study represents a very large multicenter cohort of infertile men who underwent varicocele repair and is well designed to provide a counseling framework for couples trying to decide the value of having a varicocele repaired versus pursuing immediate ART.

Our group recently published a large meta-analysis of >1,000 patients, evaluating the impact of varicocele repair on pregnancy and live birth rates for both oligospermic and azoospermic men undergoing repair before ART (5). When comparing couples that underwent ART in which the male partner had a known varicocele never repaired with couples that underwent ART in which the male partner had a repaired varicocele, we showed that varicocele repair before ART resulted in a cycle ~1.7 times more likely to result in pregnancy and live birth (5).

Our meta-analysis findings underscore both the importance of the evaluation of the male partner as well as the treatment of a varicocele, if present, for improved outcomes of pregnancy and live birth in the era of ART (5), and the publication from Samplaski et al. provides additional perspective for how varicocele treatment can be contextualized within the complex framework of ART (4). It has long been understood that treatment of a varicocele may result in improved semen quality and natural conception, but we now know

that after varicocele repair, a majority of couples can actually “upgrade” from the broad category of semen quality requiring IVF or IUI to one that is less invasive. In other words, the simple identification and treatment of a varicocele can drastically alter the course of a couple’s fertility treatment toward a safer, less invasive, less expensive, and more natural pregnancy.

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