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## INVITED COMMENTARY

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### Controversies in varicocele repair – much ado about nothing?

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Varicoceles have long been implicated in the pathogenesis of male factor infertility and recently, hypogonadism. Despite this, over the past half-century there has been widespread debate and disagreement among clinicians regarding the benefit of varicocele repair. In this commentary, we discuss recent data that has begun supporting the role of varicocele repair in treating male infertility and hypogonadism.

In 2003, Evers and Collins published a seminal meta-analysis addressing the topic of varicocele repair for male factor infertility.<sup>1</sup> They concluded that “varicocele repair does not seem to be an effective treatment for male or unexplained subfertility.” However, the authors noted concerns with the overall quality of the studies examined in the meta-analysis, including the lack of control groups and appropriate blinding, and high attrition rates during the follow-up period. Patients with subclinical or nonpalpable varicoceles and normal preoperative semen parameters were included in the meta-analysis, possibly masking the beneficial effect of repair of clinically apparent varicoceles in men with abnormal semen parameters. Analysis restricted to trials involving subfertile men with clinically apparent varicoceles showed there was a higher relative benefit to varicocele repair, but this was not statistically significant, possibly due to insufficient power.<sup>1</sup> Of note, neither the European Association of Urology nor American Society of Reproductive Medicine guidelines recommend repair of subclinical varicoceles.<sup>2,3</sup>

As the treatment of varicoceles evolves, so does the need for high-quality evidence regarding its proper role in the treatment of male factor infertility. Most studies, including those examined in the early versions of the Evers and Collins meta-analysis, involved the use of nonmicrosurgical techniques of varicocele repair. However, microsurgical techniques have become increasingly popular and may be superior with regard to postoperative improvement in semen analysis parameters, complication rates, and recurrence rates.<sup>4</sup> One of the few randomized controlled trials to compare microsurgical subinguinal varicocelectomy to a control group with pregnancy rate as a primary outcome demonstrated a higher pregnancy rate within a follow-up period of 1 year as well as improved semen parameters in the treatment group.<sup>5</sup>

The 2012 update of Evers and Collins’ meta-analysis, including this trial, calculated an odds ratio of 1.47 in favor of varicocele repair in terms of natural pregnancy rate.<sup>6</sup> The authors were reluctant to conclude that varicocele repair was beneficial for infertility treatment, again citing concerns due to the methodologies of the studies examined.<sup>6</sup> A nonrelated 2007 meta-analysis reported natural pregnancy odds ratio of 2.87 in favor of surgical varicocelectomy. The number needed to treat was 5.7.<sup>7</sup>

Previous studies using natural pregnancy rate as the outcome measure may have overlooked men with nonobstructive azoospermia

and couples requiring assisted reproductive techniques (ARTs) as potential beneficiaries of varicocele repair. Esteves and Glina demonstrated the presence of sperm in the ejaculate of 8 out of 17 formerly azoospermic men after subinguinal microsurgical varicocele repair.<sup>8</sup> Men who remain azoospermic after varicocele repair may have a higher rate of successful sperm retrieval during subsequent testicular microdissection sperm extraction.<sup>9</sup> In a comparison of 80 men with clinically palpable varicoceles who underwent subinguinal microsurgical varicocelectomy versus 162 untreated men, the former group demonstrated higher pregnancy and live birth rates with lower miscarriage rates with the subsequent use of intracytoplasmic sperm injection.<sup>10</sup> This evidence demonstrates a possible role for varicocelectomy to “downgrade” the type of ART required by an infertile couple or increase its success rate in a cost-effective manner.

The role of varicocele repair may not necessarily be limited to the treatment of male factor infertility, as there is emerging evidence that varicocele repair can be of benefit in hypogonadal men. A series of 272 men with clinically palpable varicoceles undergoing subinguinal microsurgical varicocelectomy demonstrated a statistically significant increase in serum testosterone level for the subset of men with preoperative baseline testosterone  $\leq 400$  ng dl<sup>-1</sup>.<sup>11</sup> One prospective study demonstrated an improvement in serum testosterone level for patients with preoperative baseline serum testosterone  $< 300$  ng dl<sup>-1</sup> who underwent microsurgical varicocelectomy. In this study, the group undergoing microsurgical varicocelectomy also experienced improved erectile function as measured by International Index of Erectile Function-5 questionnaire.<sup>12</sup>

There remains the need for well-conducted prospective randomized controlled trials in order to provide higher-level evidence to support varicocele repair for the above-mentioned indications. The ideal trial would involve patients with palpable varicoceles and abnormal conventional semen parameters by World Health Organization criteria, well-documented pre- and post-treatment semen analyses, and pre- and post-treatment serum hormone profiles. There should be a robust mechanism for patient randomization into treatment and observation arms. Follow-up should occur for an appropriate timeframe with minimal patient attrition. Accruing patients for such studies may be difficult because of the fact that patients may not be willing to be randomized to an observation arm because of the potential delay in treatment. Assisted reproductive technologies as well as crossover to the treatment arm may aid in convincing patients to enroll.

Contemporary studies with improved methodology and incorporating microsurgical techniques of varicocele repair have been increasingly optimistic regarding the benefits of varicocele repair in treating male factor infertility and hypogonadism. As prospective studies with improved methodology continue to be published and the body of literature accumulates, it is our opinion that varicocele repair will no longer remain “much ado about nothing.”

#### COMPETING INTERESTS

All authors declare no competing interests.

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