Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: a systematic review and meta-analysis

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Objective: To evaluate how varicocele repair (VR) impacts pregnancy (PRs) and live birth rates in infertile couples undergoing assisted reproduction wherein the male partner has oligospermia or azoospermia and a history of varicocele.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Azoospermic and oligospermic males with varicoceles and in couples undergoing assisted reproductive technology (ART) with IUI, IVF, or testicular sperm extraction (TESE) with IVF and intracytoplasmic sperm injection (ICSI).
Intervention(s): Measurement of PRs, live birth, and sperm extraction rates.
Main Outcome Measure(s): Odds ratios for the impact of VR on PRs, live birth, and sperm extraction rates for couples undergoing ART.
Result(s): Seven articles involving a total of 1,241 patients were included. Meta-analysis showed that VR improved live birth rates for the oligospermic (odds ratio [OR] = 1.699) and combined oligospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after VR (OR = 8.360). Sperm retrieval rates were higher in persistently azoospermic men after VR (OR = 2.509).
Conclusion(s): Oligospermic and azoospermic patients with clinical varicocele who undergo VR experience improved live birth rates and PRs with IVF or IVF/ICSI. For persistently azoospermic men after VR requiring TESE for IVF/ICSI, VR improves sperm retrieval rates. Therefore, VR should be considered to have substantial benefits for couples with a clinical varicocele even if oligospermia or azoospermia persists after repair and ART is required. (Fertil Steril® 2016;106:1338–43. ©2016 by American Society for Reproductive Medicine.)
Key Words: Varicocele, varicocele repair, varicocelectomy, assisted reproductive technology, male factor infertility

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Infertility affects approximately 15% of couples and is defined as the inability of a sexually active couple to achieve pregnancy within 1 year (1, 2). A male factor is present within an estimated 50% of infertile couples, and a varicocele can be detected in >35% of the men in these relationships (2). Although a prior meta-analysis has shown improvement in pregnancy (PRs) and live birth rates in natural cycles after varicocele repair (VR), there is not a consensus regarding additional benefit to fertility beyond natural conception (3–6).

Advancements in assisted reproductive technology (ART) have brought the additional value of VR into question. With the advent of IVF and then intracytoplasmic sperm injection

Received April 13, 2016; revised July 17, 2016; accepted July 18, 2016; published online August 12, 2016.
E.W.K. has nothing to disclose. L.E.W. has nothing to disclose. S.R. has nothing to disclose. K.C. has nothing to disclose. R.M.C. has nothing to disclose.
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Fertility and Sterility® Vol. 106, No. 6, November 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.07.1093

(ICSI) came the ability to achieve pregnancy with far fewer sperm than are necessary with IUI. Because VR improves semen parameters, it offers the ability to help couples with severe oligospermia and even azoospermia avoid costly ART strategies (7, 8). For those who still require ART despite VR, there may also be the benefit of improved semen quality through reduction of deleterious effects such as reactive oxygen species and DNA fragmentation (9, 10).

At present, few studies have addressed the question of how VR versus having a persistent untreated varicocele impacts the live birth and pregnancy outcomes of patients with oligospermia and azoospermia who pursue ART. The goal of this systematic review and meta-analysis is to provide a comprehensive analysis of the current data and a context for how to counsel infertile couples and fellow practitioners trying to determine the value of VR in the era of ART.

MATERIALS AND METHODS

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used in the design and execution of this study. Institutional Review Board approval was not required for this study.

Literature Search and Inclusion Criteria

A literature search was performed through PubMed using the primary search terms "varicocele," "varicocelectomy," "male infertility," and "assisted reproductive technology." Our inclusion criteria were that the articles represent original research evaluating couples with men who have semen parameter abnormalities and a clinical varicocele who did or did not undergo a VR. Furthermore, the studies were required to report on fertilization rates, PRs, or live birth rates and whether or not ART of any type was used. Articles not available in English were excluded. Each of the selected studies was further evaluated for quality and risk of bias. Specifically, the study design and data collection method for each article was systematically screened. Verification bias and selection bias were additionally considered for each study to confirm the results were applicable for the specific outcomes in this meta-analysis.

Data Analysis

Six of the seven articles reported on IVF outcomes and were included in the meta-analysis (11–16). One of the articles included data only for IUI and was excluded from the meta-analysis (17). The results from this study were included as part of the systematic review. To assess the possible associations between the outcome variables (pregnancy, live birth, and sperm retrieval) and status of varicocele (repaired vs. persistent), counts of success and failure of each outcome for the varicocele treatment groups were obtained from the existing literature. Odds ratios (OR) for the success of the respective outcome variable for VR versus untreated varicocele were computed for the individual studies. Due to small and zero counts in some of the studies and for the sake of consistency across analyses, each OR for the individual studies has an associated 95% exact confidence interval (CI) for purposes of inference.

For the meta-analyses combining multiple studies, conditional logistic regression was used for each outcome variable with study as a stratification variable. When goodness-of-fit statistics indicated heterogeneity among the studies (residual score test, $P<.20$), a rescaling factor was used to modify the standard errors to prevent underestimation of the variation and account for overdispersion. The rescaling factors are based on an unstratified generalized estimating equation approach to an overdispersed logistic model with both study and treatment as covariates. Ninety-five percent CIs and P values based on Wald test statistics incorporating the rescaled standard errors were computed for the meta-analysis OR. All analyses were done in SAS v9.3.

RESULTS

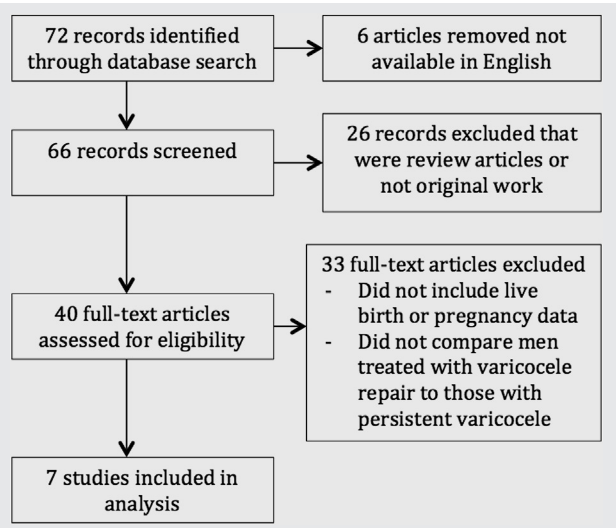
Literature Search

The literature search resulted in 72 articles for review. Six articles were not available in English and were excluded. Twenty-six articles were either review articles or did not represent original work. Of the remaining 40 articles, 7 reported on fertilization rates, PRs, or live birth rates among men with a clinical varicocele and abnormal semen parameters who subsequently underwent VR (11–17). Supplemental material provides a list of the 33 excluded articles. Two of the articles included only men with grade III varicocele, whereas the other five articles included all grades of clinical varicocele (13, 15). Each of these seven studies was retrospective and met our requirements for study quality. These results are summarized in Figure 1 and pertinent characteristics of each study are reviewed in Table 1.

Pregnancy Rate

All seven articles included data on PR. Of the four articles reporting on men with oligospermia undergoing IVF or IVF/ICSI, three studies (11, 12, 14) showed a statistically

FIGURE 1



Literature search results.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

TABLE 1

Study characteristics.

Author/year	Varicocele grade	Semen analysis characteristics	ART method	Cohort size
Gokce/2013	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IVF/ICSI	306
Esteves/2010	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IVF/ICSI	242
Pasqualotto/2012	Only grade III	"Poor semen parameters"	IVF/ICSI	248
Ashkenazi/1989	All grades	"Subfertile Semen"	IVF	22
Haydardedeoglu/2010	Only grade III	Nonobstructive azoospermia	IVF/ICSI with TESE	269
Inci/2009	All grades	Nonobstructive azoospermia	IVF/ICSI with TESE	96
Daitch/2001	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IUI	58

Note: ART = assisted reproductive technology; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

significant increase in PR among those who had undergone VR. The remaining article (13) did not show a statistically significant difference in PR associated with VR. As a group, the meta-analysis did not show a statistically significant difference in PR for men with oligospermia; however, there was a trend toward higher PRs associated with VR (OR = 1.695, P=.073).

Of the two articles evaluating men with azoospermia who underwent testicular sperm extraction (TESE) with IVF/ICSI, neither illustrated a statistically significant difference in PRs between the VR and untreated varicocele groups (15, 16). However, when combining these two studies, the meta-analysis showed a statistically significant improvement in PR favoring VR (OR = 2.336, P=.044). The summary meta-analysis of all six of these studies including men with oligospermia and azoospermia showed an overall increase in PR among those undergoing VR compared with those with untreated varicocele (OR = 1.760, P=.011). Table 2 provides the ORs and CIs in tabular format and Figure 2 illustrates these results as a forest plot.

The only study reporting IUI outcomes did not illustrate a statistically significant improvement in PR associated with VR (OR = 1.989, 95% CI 0.565–8.834). This was not included in the group IVF analysis.

Live Birth Rate

Six of the seven articles included data on live birth rate (11–13, 15, 16). Of the three articles reporting on men with oligospermia undergoing IVF/ICSI, two (11, 12) showed a statistically significant increase in live birth rate among those who had undergone VR. The remaining article (13) did not show a statistically significant difference in live birth rates when comparing the VR and untreated varicocele groups. Meta-analysis showed a statistically significant difference in live birth rate favoring VR for men with oligospermia (OR = 1.699, P=.042).

Of the two articles (15, 16) evaluating men with azoospermia and with varicocele who underwent TESE with IVF/ICSI, neither alone illustrated a statistically significant improvement in live birth rate among men who underwent VR. Combining the data from these two studies in meta-analysis, there appears to be a strong trend toward improvement in live birth rate favoring VR, as this finding narrowly missed statistical significance (OR = 2.208, P=.052). The meta-analysis of all five IVF studies also shows an increase in live birth rate among those undergoing VR compared with those with untreated varicocele (OR = 1.761, P=.002). Table 2 provides the ORs and CIs in tabular format and Figure 2 illustrates these results as a forest plot.

The Daitch et al. (17) study, which was the only study reporting IUI outcomes, illustrated a statistically significant

TABLE 2

Odds ratios comparing varicocele repair with persistent varicocele.

A. Pregnancy rate

Patient group	Odds ratio	95% confidence interval	P value
Oligospermia			
Ashkenazi	Infinity	(3.526, Infinity)	
Esteves	1.829	(1.026, 3.275)	
Gokce	1.872	(1.155, 3.035)	
Pasqualotto	0.96	(0.522, 1.792)	
Oligospermic group	1.695	(0.951, 3.020)	.0733
Azoospermia			
Haydardedeoglu	2.621	(0.947, 7.743)	
Inci	1.604	(0.244, 18.108)	
Azoospermic group	2.336	(1.022, 5.342)	.0444
Combined oligospermia and azoospermia	1.760	(1.139, 2.720)	.0109

B. Live birth rate

Patient group	Odds ratio	95% confidence interval	P value
Oligospermia			
Esteves	1.873	(1.038, 3.365)	
Gokce	2.227	(1.348, 3.697)	
Pasqualotto	0.915	(0.475, 1.802)	
Oligospermic group	1.699	(1.020, 2.831)	.0417
Azoospermia			
Haydardedeoglu	2.559	(0.971, 6.903)	
Inci	1.212	(0.179, 13.993)	
Azoospermic group	2.208	(0.994, 4.904)	.0518
Combined oligospermia and azoospermia	1.761	(1.223, 2.537)	.0024

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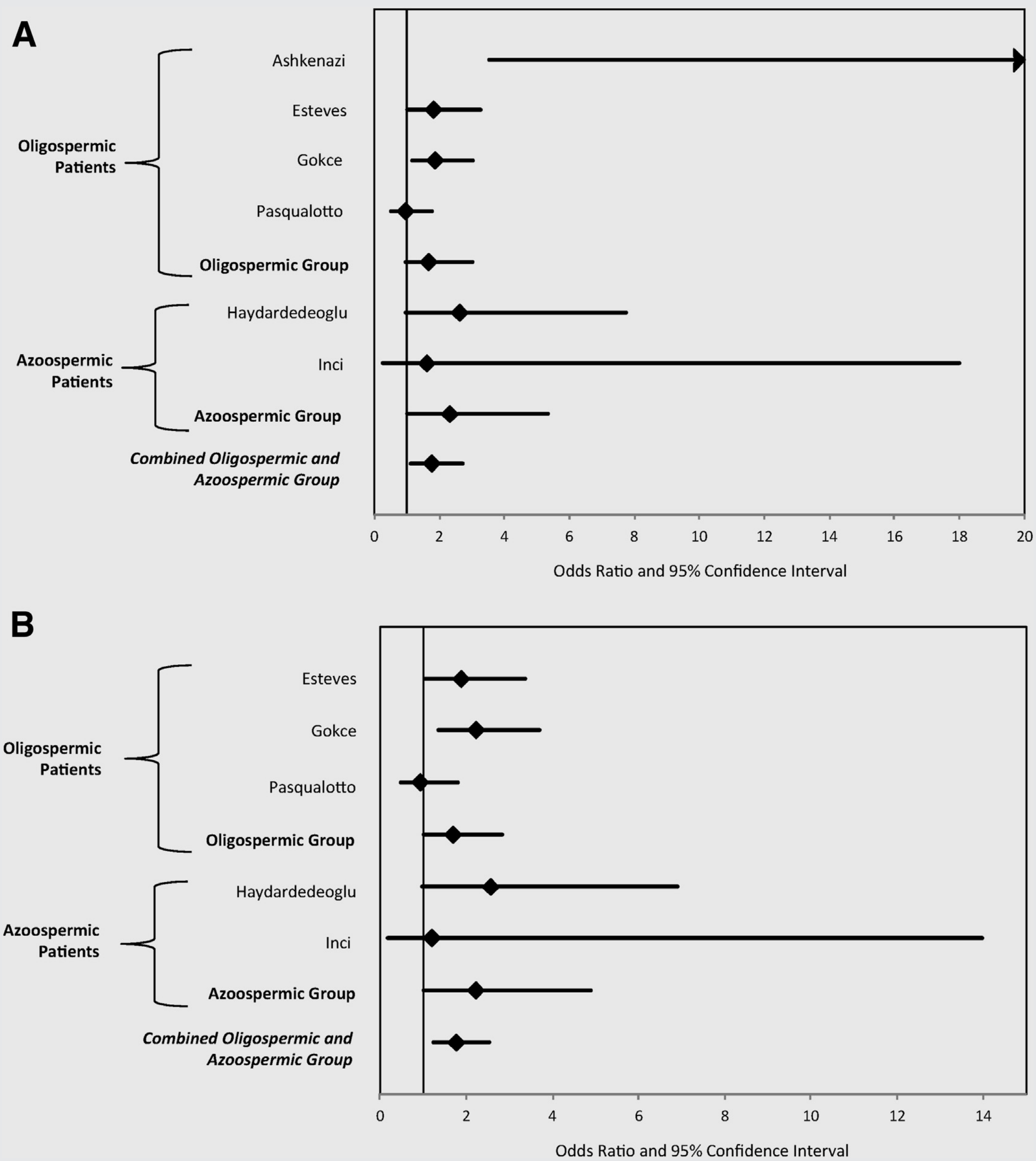
FIGURE 2



(**A**) Forest plot for pregnancy rates. (**B**) Forest plot for live birth rates.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

improvement in live birth rate associated with VR (OR = 8.360, 95% CI = 1.170–363.002). This study was not included in the group analysis.

Sperm Retrieval Rate

Of the two articles (15, 16) reporting on azoospermic men undergoing TESE with IVF/ICSI, one reported an improvement in sperm retrieval rates associated with VR. As a group, meta-analysis demonstrated that the sperm retrieval rate was improved among those having undergone VR (OR = 2.509, P=.0001).

DISCUSSION

To our knowledge, this article represents the first meta-analysis evaluating how VR impacts ART outcomes for patients with azoospermia and oligospermia. The impact of VR is an important reproductive medicine topic for every fertility specialist, particularly given the observation that treatment of the male factor is underused (18). In addition, considering the financial burden associated with ART, it is critical to know whether VR confers some additional benefit, even if natural conception is not achieved after the repair.

The present study is a unique meta-analysis because it evaluates the data regarding men with oligospermia and azoospermia. It is important to consider these two groups both individually and as a whole given the proposed pathophysiology of infertility in men with varicocele. Specifically, VR has been shown to decrease the high sperm DNA fragmentation rates and reactive oxygen species associated with varicoceles, and this type of DNA damage has been associated with worse outcomes in ART treatments (10, 19–21). Although patients with oligospermia and nonobstructive azoospermia may represent a similar population along a continuum versus entirely unique populations, oxidative stress likely plays a role in each.

It is not entirely clear why varicocele may impact pregnancy and live birth rates differently in the individual azoospermic and oligospermic patient populations. Although there was not sufficient data to incorporate the impact of VR on specific semen parameters into the analysis, a generalized improvement in semen quality is likely a contributing factor to these improvements. Perhaps there are events during the early phases of pregnancy that are impacted by sperm damage and oxidative stress that are unique to the process of transit through the epididymis and vas deferens. Evidence has suggested that the impact of DNA fragmentation may not be fully realized until later in pregnancy, thus leading to higher miscarriage rates (22). The present findings of improved live birth rates but unchanged PRs among patients with oligospermia do fit such a hypothesis. Although this meta-analysis cannot provide specific answers to these questions, it does illustrate that, although patients with oligospermia and azoospermiac requiring ART benefit from VR, the value may materialize through different mechanisms. The variability in outcomes across these two populations reinforces the need for further study into how VR impacts semen quality and ART outcomes.

Although analysis of the individual groups showed unique impacts on PRs and live birth rates, VR was uniformly associated with improved ART outcomes in the combined analysis of men with oligospermia and azoospermia. These improvements highlight the most important finding from this study from the perspective of counseling patients. The decision to pursue VR is often complex and requires the consideration of multiple factors that include patient age, desire for multiple children, baseline semen characteristics, cost, timing, and tolerability of ART. Many couples pursue VR with the hope of avoiding the need for ART. However, for couples requiring IVF despite VR, this meta-analysis demonstrates that these couples still benefit with respect to live birth and PRs with ART.

This study does have limitations to be considered. Each of the studies in this review was retrospective and thus represented lower quality evidence relative to prospective and randomized trials. In addition, the reviewed studies did not uniformly provide data on objective semen quality characteristics and therefore limited our ability to provide correlation between our findings and hypotheses of how VR impacts ART outcomes. Correlating VR with clinical outcomes and semen parameters including additional advanced semen studies such as DNA fragmentation may help to further characterize how VR impacts ART results. In addition, there was inconsistency and heterogeneity across the studies with respect to varicocele grade reporting. The possibility of a dose-response relationship between varicocele grade and ART outcomes may be missed in the absence of such data.

Whereas the findings suggest some difference in how VR impacts oligospermic and azoospermic patients, those differences may also represent inadequate sampling. The P values for live birth and pregnancy outcomes among the individual groups were each relatively close to our significance threshold of .05 (.073, .044, .042, .052). Greater sampling would likely provide clarity and significance to these trends.

In conclusion, this systematic review and meta-analysis provides evidence that in infertile couples undergoing ART, wherein the male partner has a diagnosis of oligospermia or nonobstructive azoospermia and a varicocele, that VR results in improved PRs and live birth rates. Sperm retrieval rates are higher in patients who have persistent nonobstructive azoospermia after VR requiring TESE for IVF/ICSI. Counseling couples with male factor infertility secondary to a varicocele should include these additional benefits of VR in the era of ART.

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