Youth varicocele and varicocele treatment: a meta-analysis of semen outcomes

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Objective: To study youth who have a varicocele or are undergoing varicocele treatment, in relation to changes in semen, as measured by semen analysis (SA).
Design: Meta-analysis of studies identified via a search of PubMed, Medline, and the Cochrane Library covering the last 40 years.
Setting: Not applicable.
Patient(s): Youth from studies that assessed the presence and/or treatment of varicocele with SA.
Intervention(s): Selected studies were analyzed in two separate meta-analyses: one for the effect of varicocele on semen, as measured by SA (hypothesis #1), the other for the effect of treatment on semen, as measured by SA (hypothesis #2).
Main Outcome Measure(s): A random-effects model was used to calculate weighted mean difference (WMD) of semen outcomes. Heterogeneity was calculated. Bias was assessed with funnel plots and Egger's test.
Result(s): The initial literature search returned 1,180 potentially relevant articles. For hypothesis #1, 10 studies with a total of 357 varicocele and 427 control subjects were included. Sperm density, motility, and morphology were significantly decreased when associated with a varicocele, with a WMD of -24.0×10^6/mL (95% confidence interval [CI; −39.5 to −8.6]), −7.5% (95% CI [−12.3% to −2.7%]), and −1.7% (95% CI [−2.4% to −1.1%]), respectively. Another 10 studies with 379 treated and 270 untreated subjects were analyzed for hypothesis #2. Sperm density and motility were significantly improved following treatment, with a WMD of 14.6×10^6/mL (95% CI [7.1–22.1]) and 6.6% (95% CI [2.1%–11.2%]), respectively.
Conclusion(s): The presence of varicocele in youth appears to negatively affect sperm density, motility, and morphology. Treatment appears to result in moderate improvement of sperm density and mild improvement in sperm motility. (Fertil Steril® 2014;102:381–7. ©2014 by American Society for Reproductive Medicine.)
Key Words: Youth, varicocele, varicocele treatment, semen analysis

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Despite an abundance of studies on the effects of varicoceles and their prevalence within the adult population, there are comparatively few data examining the effects of varicocele on youth. Current indications for varicocele treatment in pain-free adolescents include objective evidence of reduced ipsilateral testicular size or semen analysis (SA) abnormality (1). The effect of varicocele treatment on testicular volume and catch-up growth has been studied extensively (2, 3).

Testicular hypotrophy (measured by orchidometer or ultrasound) has been used generally as a surrogate of SA, to assess the effect of the varicocele on spermatogenesis. This usage is in part a result of the perceived difficulty of obtaining SA from those in the youth population. Although decreased testicular size may correlate with worse semen parameters, a better estimation of fertility may be ascertained by examining semen directly. To date, however, relatively few studies have demonstrated the effect of varicocele and its treatment on youth semen.

The goal of treating an adult varicocele is to regain fertility; for the adolescent, the goal is to preserve it. However, which adolescent varicoceles necessitate repair to preserve future fertility is not well understood. A better understanding of the natural history of varicocele in relation to testicular function, SA, and fertility outcomes would better guide practitioners in their counseling and management of patients with regard to intervention.

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The goal of the current study was to determine the effects of a varicocele on youth semen and to assess the effect of varicocele treatment on SA as an outcome. It was hypothesized that: youth semen would be negatively affected by the presence of a varicocele, and treatment of a youth varicocele would be associated with improved semen parameters.

MATERIALS AND METHODS

With the approval of the local institutional review board, a meta-analysis was performed of the current literature on the youth population in relation to a varicocele and SA. The meta-analysis was performed in accordance with the statement on preferred reporting items for systematic reviews and meta-analyses (4). A literature search of PubMed, Medline, and the Cochrane Library was performed, including only English-language studies published between January 1, 1971 and October 4, 2013. The key-word search included any combination of the terms varicocele, youth, and adolescent. The term "youth" describes individuals aged 15–24 years, as defined by the World Health Organization (5). The search results were then subjected to the respective inclusion and exclusion criteria of each of the two distinct hypotheses.

In general, the selected articles included randomized controlled trials (RCTs), randomized interventional studies, controlled interventional studies, and observational studies of youth, with varicocele and semen outcomes. Studies were excluded if they did not contain data regarding sperm density or motility. Furthermore, a study could not be included if the presented data were not amenable to meta-analysis (i.e., data from the original study were presented only graphically or as medians/ranges). In studies that appeared to contain duplicate or overlapping cohorts, only one study was selected. For a study to be included in testing of the first hypothesis (varicoceles have a negative effect on semen, as measured by SA), it must have involved male youth with clinical varicoceles and a corresponding control group.

To test the second hypothesis (treatment of varicoceles improves semen, as measured by SA), articles were included in which participants either served as their own control or in which they were compared with untreated youth with clinical varicoceles. Treatment modalities could include inguinal varicocelectomy (+/− microscope), subinguinal varicocelectomy (+/− microscope), open retroperitoneal varicocelectomy, laparoscopic varicocelectomy, and embolization of the gonadal vein. Studies were excluded if they failed to describe a minimum of 1 pretreatment and 1 posttreatment SA. Additionally, a minimum of 3 months of posttreatment follow-up prior to SA was required for study inclusion.

Articles that met inclusion criteria were then independently reviewed and assessed in an unblinded manner by two reviewers. A data extraction sheet was developed to include participant age, number of study subjects, type of control group, type of intervention (if applicable), sperm density, sperm motility, sperm morphology, and semen volume. The duplicated extraction of data by two reviewers was performed to ensure accuracy of the data for meta-analysis. Any disagreement between the two reviewers regarding inclusion or study results was resolved by consensus.

Statistical analysis was performed using Stata®12 (StataCorp LP). The weighted mean difference (WMD) was calculated for selected SA parameters: semen volume, sperm density, sperm motility, and sperm morphology. Forest plots were generated. Statistical heterogeneity was assessed (I^2). A random-effects model was chosen a priori owing to presumed heterogeneity of the included studies; if I^2 was found to be $\leq 25\%$, a fixed-effects model was also conducted (6). Results were considered statistically significant at $P \leq .05$. Bias was assessed with funnel plots. Egger's test for small-study effects was used to statistically assess funnel-plot asymmetry (and hence, potential bias), with significance conservatively set at $P < .1$ (7). If Egger's test suggested possible bias, a sensitivity analysis of sorts was conducted in which the studies with a point estimate falling outside the 95% confidence interval (CI) of the funnel plot were considered to be outliers and therefore excluded from a second analysis of the specific outcome measure.

RESULTS

Hypothesis #1 (Varicocele vs. Control)

The initial literature search returned 1,180 potentially relevant articles. Titles and abstracts were screened; 15 articles met the criteria for review. Five of these articles were excluded because of missing semen parameters of interest (3) or reported data incompatible with meta-analysis (2). The 10 remaining articles were included in the meta-analysis (8–17). Nine of the studies were prospective (no RCTs) in nature and one was retrospective. The analysis included 357 male subjects with varicoceles, and 427 control subjects. Study type and follow-up interval are summarized in Supplemental Table 1 (available online).

Presence of a varicocele was associated with a statistically significant decrease in sperm density, motility, and morphology. The WMD of sperm density decreased 24.0×10^6/mL (95% CI [−39.5 to −8.6]), with $P = .002$, $I^2 = 82.1\%$, and Egger's test demonstrating potential funnel plot asymmetry ($P = .093$; Fig. 1, Supplemental Fig. 1 [available online]). Three studies fell outside the 95% CI of the funnel plot for density (10–12). Repeat analysis of sperm density for the remaining 7 studies revealed consistent findings, demonstrating a WMD of -9.0×10^6/mL (95% CI [−17.8 to −0.1]), with $P = .047$, $I^2 = 40.5\%$, and no significant funnel plot asymmetry ($P = .891$). Sperm motility decreased 7.5%; 95% CI [−12.3% to −2.7%], with $P = .002$, $I^2 = 81.1\%$ and no significant bias detected ($P = .329$; Fig. 2, Supplemental Fig. 2 [available online]). Sperm morphology decreased 1.7%; 95% CI [−2.4% to −1.0%], with $P < .001$ and no significant funnel plot asymmetry ($P = .787$). Diagnosis of varicocele and semen volume showed no relationship ($P = .360$).

Hypothesis #2 (Varicocele Treatment vs. No Treatment)

Similarly, 1,180 potentially relevant articles were identified by the initial query based on the key-word search. Fourteen studies met initial screening criteria for further review. Four of these articles were excluded owing to possible duplicate cohorts (1),