

January 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7787-edited).

Title: Varicocele: How This Condition and Its Management Affect Men's Health

Author: Abdulaziz Baazeem

Name of Journal: *World Journal of Meta-Analysis*

ESPS Manuscript NO: 7787

1 Introduction: The introduction starts citing reference number 16. References need to be cited and numbered according to their presentation in the manuscript text.

Citations have been modified to comply with the requirements of the World Journal of Meta-Analysis

2 Diagnosis and classification: The term subclinical varicocele is repeated multiple times throughout the manuscript. Please present a clear definition of what the author means. Is it a nonpalpable varicocele?

Subclinical varicoceles are defined in the text as “varicoceles that are not palpable, but rather are detected using ancillary diagnostic measures”

3 I suggest changing: “no clear cut-off measures” to measurements.

The suggested change has been made

4 Varicocele in the male factor infertility: “there was a wide range of detecting varicocele among different centers”- A wide range of what? Of medical specialties involved? Of diagnostic exams or imaging?

The range is that of actually detecting a varicocele clinically among the involved subjects. The wording has been changed to “there was a wide range of varicocele detection among different centers” in order to help reduce confusion

5 This manuscript seems to be biased toward a surgical approach to treat varicocele over endovascular embolization approaches. There are many studies (not cited), that demonstrate equivalent safety, efficacy and success

rates after embolization. Therefore, embolization should be presented as a good alternative to surgery. This author can do a great service for the readers by comparing side-by-side pros and cons of surgery and embolization (e.g., using a table). Specific risks of each procedure and their incidence should be presented (e.g., arterial injury, hydrocele, etc.).

The intention was never to be biased toward surgery. If anything, this author believes that embolization is a better option than some forms of surgery. However, personal opinion aside, the text reflects the findings of meta-analyses and extensive reviews such as those by Diegido and by Cayan. Nevertheless, the paragraph has been expanded to elaborate more on the risks and benefits of embolization, as well as clarification that the failure rates are high with bilateral varicocele and that embolization remains a good option for unilateral varicocele.

6 Varicocele and Non-obstructive azoospermia: Please fix typo: improve semen quality index to upgrade"

The text has been modified to "in order to upgrade". Apologies for the typo.

7 Prophylactic varicocelectomy: I'm not sure if this is a correct use of the term prophylactic. Prophylaxis usually means prevention of disease from occurring. These patients here are not being treated before the development of varicocele. Is this term "prophylactic varicocelectomy" used routinely in the urologic literature?

The patients would be treated to prevent potential negative effects of varicocele rather than to prevent its occurrence. As the reviewer might have, I routinely meet young single asymptomatic men who were found to have a varicocele and were advised to have it repaired to prevent it from "causing problems". Unfortunately, as mentioned in the text, there is little evidence to support that hypothesis.

The term has been used in the literature, including the following articles:

- Pinto KJ, Kroovand RL, Jarow JP. Varicocele related testicular atrophy and its predictive effect upon fertility. J Urol. 1994 Aug;152(2 Pt 2):788-90.
- Glassberg KI, Korets R. Update on the management of adolescent varicocele. F1000 Med Rep. 2010 Apr 12;2.

8 Varicocele and scrotal pain: limiting physical activity, ~~that~~ which are impractical and of limited benefit. In a study ~~where~~ of 140 patients who were treated conservatively

Suggested changes have been made

9 Micronized purified flavonoid fraction: please explain to readers what is this. Is it a nutritional (oral) supplement?

It is the semi synthetic medication Dacron®. The text has been changed to “There is some evidence, based on the experience with a small number of patients, to suggest a possible benefit from the venotonic drug micronized purified flavonoid fraction in reducing varicocele-associated pain in men with normal sperm concentration.”

10 “To date, there are no studies that assess the effect of subclinical varicocele repair on scrotal pain.” -- I would rephrase this. If there is pain, then the varicocele is clinical (i.e., symptomatic), not subclinical. I believe the author means the effect of nonpalpable varicocele repair on scrotal pain?

The term subclinical varicocele is well recognized for the description of a varicocele that is not clinically detectable, but can be found with the use of ancillary techniques, such as ultrasonography, as outlined in the text under “Diagnosis and Classification”. This is the same regardless of the presence or absence of pain. I suggest using it to avoid confusion.

11 “Further support for the notion that ~~an etiology~~ a cause other than varicocele might be the reason behind treatment failure is noticed in the finding that failure rates...”

The suggested changes were made

12 “But this association with symptom duration ~~too~~ was not supported by findings and other studies.

The suggested change was made

13 Surgery for varicocele is not a single type of operation. There are many different surgical approaches in the literature, which should be presented in a comparative way, with relative advantages and disadvantages of each surgical technique.

The text mentions that “Various techniques have been reported when treating varicocele for pain, including high ligation, subinguinal and inguinal microsurgery, conventional inguinal (Ivanissevich), scrotal and laparoscopic approaches, as well as percutaneous interventional radiological procedures such as sclerotherapy or embolization with reasonable results.” Furthermore, Diegidimo’s review of these various techniques is cited.

14 Varicocele and hypogonadism: ART – please write the full name in the text before using the abbreviation.

It is written on page 10 of the document: “They might require sperm retrieval procedures which, if successful, would be followed by assisted reproductive techniques (ARTs), such as in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).”

Reviewer #2:

15 Author has written interesting minireview on varicocele, with the aim to reflect potential influence of varicocele and varicocelectomy on mens health. I would suggest several changes in the manuscript: -In order for this paper to qualify to this journal I would suggest to add description of the kind of article this is in the title. I personally would add here “minireview” since this article lacks a lot to be misconfused with systematic review or meta analyses.

There should be no confusion of this article being a systematic review or meta-analysis as there were no claims of it being so in the text or title. The article has been submitted simply as a review article. Following the reviewer’s suggestion, I searched for the difference between a review article and a mini review. All I could find was that a mini review is less than 3 journal pages long. This review is longer than that. I would like to keep the title as it is unless the editor sees a benefit from adding the phrase “mini review” to it.

16 -As instructions to the authors state “There are unstructured abstracts (no less than 200 words)” this abstract should be longer and more informative what would aid its chances to being cited. Also authors should more clearly state their aim in the abstract and also should add more conclusions in the abstract and not just state we give overview so please read our paper.

In order to avoid redundancy, the summary section has been removed from the main manuscript and edited to present a more informative abstract.

17 -As stated in the instruction to the author: The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author’s name. - Also change the references according to the instructions to the authors i.e. year;volume:pages.

Citations have been modified to comply with the requirements of the World Journal of Meta-Analysis

18 -Author nicely states that varicocele is prevalent condition, but to support this as this in one of the driving points to write this paper I would suggest in the introduction section to add some more discussion on various papers which researched varicocele prevalence.

The classic data from the 60's and 70' was used in the introduction. I saw it more fitting to use the WHO data in the "Varicocele and Male Factor Infertility" section and dedicated a full paragraph to present its figures. The line "However, in a more recent study, it was found to be present in 24.2% of healthy young men" was added to the introduction as well.

The line "Varicocele repair is currently considered to be the most commonly performed procedure to treat male infertility" has also been added to the introduction. The statement has been made by Binsaleh and Lo (Can Urol Assoc J. 2007 Sep;1(3):277-8) and Mehta and Goldstein (Asian J Androl. 2013 Jan;15(1):56-60). And although it is very plausible, no actual numbers were provided in either article. I do not object if the editor wishes to remove it due to this concern.

19 -In etiology section I would suggest to add: Anatomical differences between left and right vein, on the left side testicular vein has right angle insertion in renal vein while on the right side it is sharpangled into the vena cava inferior.

The fact that the left spermatic vein drains into the relatively high-pressure left renal vein as compared to the low-pressure inferior vena cava for the right spermatic vein has been mentioned. I am unaware of any studies that specify the angle of entry as a possible cause of higher varicocele rate on the left. I would gladly cite any suggested studies.

20 -Please define what is advanced age. in one sentence in the etiology section

The text has been modified to "Its prevalence appears to increase with advancing age, increasing by about 10% with each decade. The prevalence in the elderly was described to reach 42% in a study that involved men with a mean age of 60.7 years."

-21 in diagnosis section: It would add to the value of this paper if the author could give its comment on other diagnostic method namely thermography, scintigraphy, venography.

The lines "Scintigraphy and thermography have been suggested as methods that are comparable or even superior to ultrasonography in detecting varicocele. With the exception of venography, these techniques are considered simple and non-invasive." Were added to the text. Two new references were cited.

22 - in indication section: One of the indications is also ipsilateral testicular atrophy also add cosmetic indication also define pain as scrotal pain.

The listed indications were for varicocele repair in adults, as mentioned in the manuscript. Ipsilateral testicular hypotrophy alone is generally accepted as an indication for repair in adolescents.

23 in male factor infertility section: next to the each proposed mechanism add corresponding references instead of adding them all before listing mechanisms. This would be much more valuable for the readers.

The suggested changes have been made.

Sincerely yours,

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