Peer Review File

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Reviewer A

The manuscript entitled “Effects of the body mass index of males on hormone levels, sperm and embryo parameters, and clinical outcomes in non-obstructive azoospermia: a systematic review and meta-analysis”, examined the relationships between BMI and hormone levels, sperm and embryo parameters, and clinical outcomes in NOA. Below are my comments to improve the quality of the manuscript.

Abstract

- The background part did not mention the research status and research gap.

Reply: Thanks a lot for your comments. We have mentioned the research status and research gap in the background part as follows: Research has shown that the body mass index (BMI) is not correlated with sperm retrieval outcomes, while serum testosterone and gonadotropins are related to the BMI in NOA. Previously, no comprehensive assessment had been conducted on the effect of the BMI of males in NOA.

Changes in the text: We have modified our text as advised (see Page 1, line 24-27).

- The methods need to describe the sensitivity analysis and publication bias.

Reply: Thanks a lot for your comments. We have described the sensitivity analysis in the methods part: A sensitivity analysis was conducted for all the outcomes. As for publication bias, meta-analyses should include at least 10 studies for each outcome (18,19). This meta-analysis did not meet the above requirements for publication bias assessment, and thus publication bias was not assessed in this study.

Changes in the text: We have modified our text as advised (see Page 2, line 36-37).

18. Kicinski M, Springate DA, Kontopantelis E. Publication bias in meta-analyses from the Cochrane Database of Systematic Reviews. Stat Med 2015;34:2781-93.

19. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

Introduction

- Page 3 Line 99-100, the sentence “The number of cases in the former 2 studies …..” is unclear. I guess what the authors mean is "The results of the published studies were inconsistent, and the sample size in each study was relatively small, based on which a systematic review and meta-analysis should be done".

Reply: Thanks a lot for your comments. We have modified the sentence into “The results of the published studies were inconsistent, and the sample size in each study was relatively small, based on which a systematic review and meta-analysis should be done”.

Changes in the text: We have modified our text as advised (see Page 3, line 94-96).

Methods

- The methods need to describe the publication bias.

Reply: Thanks a lot for your comments. As for publication bias, meta-analyses should include at least 10 studies for each outcome (18,19). This meta-analysis did not meet the above requirements for publication bias assessment, and thus publication bias was not assessed in this study. We have made the above explanation in the methods.

Changes in the text: We have modified our text as advised (see Page 5-6, line 169-172).

18. Kicinski M, Springate DA, Kontopantelis E. Publication bias in meta-analyses from the Cochrane Database of Systematic Reviews. Stat Med 2015;34:2781-93.

19. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

Results

- It is significant to show specific levels of these indicators between the two groups, such as LH, FSH, TT, FT, cBAT, SHBG and PRL.

Reply: Thanks a lot for your comments. We have showed specific levels of these indicators between the two groups, such as LH, FSH, TT, FT, cBAT, SHBG and PRL, in Supplementary Table 1.

Changes in the text: We have modified our text as advised (see Page 6, line 201; Page 7, line 210, 221, 227, and 234).

Discussion

- The discussion section is not only to demonstrate the findings, but also to explain the clinical significance of the research.

Reply: Thanks a lot for your comments. We have explained the clinical significance of the research in the discussion section: Thus, clinicians may advise NOA patients with a BMI ≥25 kg/m2 to lose weight (e.g., by doing more exercise, controlling their diet, having healthy eating behaviors, keeping balanced and adequate nutrition). Lifestyle modification and weight management could exhibit a positive impact on reproductive outcomes for these obese patients. Patients with a BMI ≥25 kg/m^2 who wish to have children should fully understand these risks and be motivated to adopt a healthy lifestyle. Targeting these patients who consult fertility clinics and stimulating them to make lifestyle changes prior to pregnancy could assisting in lowering the cost of fertility treatment and failure of treatment. Healthcare providers and national healthcare systems should pay attention to obesity (e.g., via BMI monitoring) and help to mitigate obesity-associated infertility in NOA patients. Through developed intervention strategies and programs to realize normal weight, male patients could improve their overall health, especially reproductive health.

Changes in the text: We have modified our text as advised (see Page 12, line 390-402).

Tables
- The results of table 2 should be consistent with the Figures. Provide RRs, WMDs and their CIs to exactly two decimal places (only).
Reply: Thanks a lot for your comments. We have provided RRs, WMDs and their CIs to exactly two decimal places (only) in Table 2.
Changes in the text: We have modified relevant data as advised (see Table 2).

Reviewer B

The authors conducted a systematic review and meta-analysis to comprehensively evaluate the effects of the body mass index (BMI) of males on hormone levels, sperm and embryo parameters, and clinical outcomes in non-obstructive azoospermia (NOA). The BMI of males was an important factor affecting the follicle-stimulating hormone and total testosterone levels, testicular volume, sperm retrieval success, and live-birth rate in NOA. The topic of the manuscript is interesting, and the results and conclusions are clearly presented. However, there are several issues the authors should address by making modifications to the manuscript or by clarifying in their response.
1. Although the manuscript was formally reported according to MOOSE, the authors should mention that the systematic review was conducted in accordance with the PRISMA 2020 statement or MOOSE in the main text.
Reply: Thanks a lot for your comments. We have mentioned that the systematic review was conducted in accordance with the MOOSE in the Methods part.
Changes in the text: We have modified our text as advised (see Page 3, line 100-102).

2. The authors should clearly state the type of studies included in the inclusion criteria, and the PICOS framework for eligibility should be briefly described in the Abstract and main text.
Reply: Thanks a lot for your comments. We have clearly stated the type of studies included in the inclusion criteria, and briefly described the PICOS framework for eligibility in the Abstract and Methods parts.
Changes in the text: We have modified our text as advised (see Page 1-2, line 31-35; Page 4, line 120-134).

3. The authors included the studies with the BMI information of patients (BMI<25 kg/m2 or BMI ≥25 kg/m2). However, the data form Table 1 (characteristics of the included studies) indicated that some cohort studies did not have group information on BMI of study subjects.
Reply: Thanks a lot for your comments. The reason why some cohort studies did not have group information on BMI of study subjects is that patients in these cohort studies were grouped according to the outcomes (success of sperm retrieval, pregnancy), and then the associations between the BMI of males and the outcomes were explored.

4. The authors mentioned in the results section that the included studies were all cohort studies, so the authors should describe the follow-up time of each cohort study in the characteristics of the included studies.

Reply: Thanks a lot for your comments. We have added "Follow-up time" column in Table 1. It can be seen that the follow-up time was not available in all the cohort studies. All patients with non-obstructive azoospermia (NOA) underwent testicular sperm extraction (TESE). In the study of Li et al. (16), clinical pregnancy was established by gestational sacs under B-ultrasonography or specific clinical signs of pregnancy 35 days after embryo transplantation. In the study of Shrem et al. (27), pregnancy was determined by positive beta Human Chorionic Gonadotropin (bHCG) test 14 days after embryo transfer. We have made the above description in the characteristics of the included studies.

Changes in the text: We have modified our text as advised (see Page 6, line 181-186).

16. Li F, Yang Q, Shi H, et al. Effects of obesity on sperm retrieval, early embryo quality and clinical outcomes in men with nonobstructive azoospermia undergoing testicular sperm aspiration-intracytoplasmic sperm injection cycles. Andrologia 2019;51:e13265.

27. Shrem G, Brudner Y, Atzmon Y, et al. The influence of obesity, smoking, and serum follicular stimulating hormone in azoospermic patients on testicular sperm extraction-intra cytoplasmic sperm injection outcomes: A retrospective cohort study. Medicine (Baltimore) 2019;98:e14048.

5. The authors described the relationship between multiple clinical indicators and BMI, but did not clarify which indicators were baseline indicators and which were follow-up outcome indicators.

Reply: Thanks a lot for your comments. We have clarified in the Methods part that reproductive hormones [luteinizing hormone (LH, mIU/mL), follicle-stimulating hormone (FSH, mIU/mL), total testosterone (TT, ng/mL), free testosterone (FT, pg/mL), calculated bioavailable testosterone (cBAT, ng/mL), sex hormone-binding globulin (SHBG, nmol/mL), and prolactin (PRL, ng/mL)] were baseline indicators; sperm parameters [testicular volume, ejaculate volume, sperm motility degree (A+B), the sperm retrieval rate, and sperm retrieval success], embryo parameters (embryo transfer, the embryo implantation rate, the fertilization rate, and the good-quality embryo rate), and clinical outcomes (the clinical pregnancy rate, pregnancy, livebirth rate, and abortion rate) were follow-up outcome indicators.

Changes in the text: We have modified our text as advised (see Page 4, line 134-136).

6. Meta-analysis results suggested that high heterogeneity may exist for some indicators, and the authors should actively explore the source of heterogeneity.

Reply: Thanks a lot for your comments. Age, lifestyle and previous medical history may be the source of heterogeneity, but due to the limitations of the study design, our data did not support the exploration of the source of heterogeneity. We have acknowledged this limitation in the Discussion part.

Changes in the text: We have modified our text as advised (see Page 13, line 409-412).

Reviewer C

Dear authors,

The article entitled "Effects of the body mass index of males on hormone levels, sperm and embryo parameters, and clinical outcomes in non-obstructive azoospermia: a systematic review and meta-analysis" is an interesting, well written paper which needs only minor corrections:

Introduction

1. Page 3, line 86: I would suggest you replace the word "affect" with another word such as "is related".

Reply: Thank you very much for your comments. We have replaced the word "affect" with "be related to".

Changes in the text: We have modified our text as advised (see Page 3, line 81).

2. I suggest you make a comment about the methods that have been used for the estimation of testicular volume in included studies (clinical or imaging) and how the use of different methods could affect the translation of the results. I would, also, suggest you mention a possible explanation for the greater testicular volume in obese vs normal weight group and the role of the missing data about the cryptorchidism and orchiopexy in some of the included studies in the formulation of the results.

Reply: Thank you very much for your comments. We have added "Method for estimating testicular volume" column in Table 1, and made comments about the methods and how the use of different methods could affect the translation of the results as well as the role of the missing data about the cryptorchidism and orchiopexy in some of the included studies in the formulation of the results in the discussion section as a limitation: As for methods for estimating testicular volume, three included studies applied an orchidometer, two used ultrasound, and seven did not report specific methods, which may have affected the reliability of the results. Missing data about the cryptorchidism and orchiopexy in some of the included studies may also have affected the reliability of the results. However, we could not perform subgroup analysis based on methods for estimating testicular volume, cryptorchidism and orchiopexy due to limited data, which requires future studies. We have also mentioned a possible explanation for the greater testicular volume in obese vs normal weight group in the discussion section: Compared with normal weight patients, obese patients have lower testosterone levels, and the body may attempt to compensate for lower testosterone levels by secreting more pituitary hormones, which may relate to an increase in testicular volume; individual differences also exist in testicular volume.

Changes in the text: We have modified our text as advised (see Page 13, line 412-419; Page 11, line 365-369).