Peer Review File

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Reviewer A

1. **Comment:** Clarify what is meant by "idiopathic infertility."
   Reply: An excellent suggestion by the reviewer. We have clarified this definition throughout the manuscript.
   Changes in text: Included the words "diagnosed with" in the abstract and conclusion sections of the Abstract as well as in the Conclusion section of the manuscript

2. **Comment:** Typo.
   Reply: We apologize for this typo. It is corrected as suggested. We also spell checked the manuscript several times.
   Changes in text: p.3 Abstract, line 7 (removed "have")
   p.8 Results, line 9 (semen analyses)

3. **Comment:** Where there no blood tests ordered?
   Reply: If reproductive hormones were ordered on study subjects before referral to our center, then these tests were reviewed. However, we follow AUA and ASRM Best Practice Policies for evaluating male factor infertility and only order reproductive hormones if sperm concentrations are <10 mill/mL or if there is sexual dysfunction or if there are findings suggestive of an endocrinopathy (Ref 1).
   Changes in text: None

4. **Comment:** How can we be certain that vitamins/diets taken/changed?
   Reply: As noted by the reviewer, we are entirely uncertain which lifestyle recommendations given to patients to help them to conceive were actually carried out. We included this as a limitation of the study.
   Changes in text. P. 12 Line 2-4. We added this issue as a limitation of the study findings.

5. **Comment:** What is known about patients' comorbid conditions?
   Reply: The comorbid medical conditions of patients were considered in the male factor evaluation but not specifically recorded for the study.
   Changes in text: None.

6. **Comment: No table showing "what the outcomes are of the actual study."**
   Reply: Although there is no table regarding pregnancy outcomes, Figure 1 illustrates the pregnancy outcomes and the text reinforces this information. Also, there are tables that report the demographic, clinical and semen analyses findings for study patients. We believe that there is value in including Table 5 as it allows for a comparison of the study findings to published pregnancy rates among established (or classic) male factor

treatments.
Changes in text: None.

7. **Comment:** Were patients excluded from further study prior or after medical treatments?
   Reply: The reviewer's point is well taken. Patients who received medications or surgery *after* their male factor evaluations were excluded from the study.
   Changes in text: None

Reviewer B

1. **Comment:** Exclude or separately analyze those patients with <1 yr and >1 yr of infertility.
   Reply: The reviewer presents an excellent point that the range of infertility was 0.4 mos to 4 years in the study cohort, and that conception within 1 year is still consistent with fertility. In this study, only 1 couple tried < 1 year (0.4 yrs) and in fact this couple did not conceive in the subsequent 1 year of followup. Thus, a subset analysis of those trying <1 yr vs those trying > 1 yr as suggested by the reviewer would lack significance.
   Changes in text: None

2. **Comment:** Spontaneous pregnancy rates are known the second year of infertility.
   Reply: The reviewer presents an excellent point that there are measurable pregnancy rates the SECOND year after the diagnosis of infertility. They also present the generally accepted 10-15% rate of conception after 2 years of trying and include a reference for this. We have incorporated this reference information into the Conclusion and Reference sections of the manuscript. Regarding "causes" of the pregnancy rates, we list possible reasons in the Conclusion section but have no proof positive of any of them.
   Changes in text: p.10, Conclusion, lines 6-8; comparative statement explaining natural pregnancy rates in untreated infertile couples
   p.19, References. Suggested reference added and references renumbered.

3. **Comment:** Change in terminology and analyzing female factors
   Reply: This comment was very thought-provoking. In response to it, we researched the definitions of "idiopathic infertility" and "unexplained infertility" and realized that they are often used interchangeably, but that they are actually different (Ref 2). Idiopathic male infertility is when there are abnormal semen parameters without a defined cause. Unexplained infertility is when there are no semen analysis or other abnormalities identified. So, technically, the patients in our study are not idiopathic (as they have normal semen parameters) but have unexplained infertility. Because of this, we have changed the wording throughout the manuscript from "idiopathic" to "unexplained" infertility. Unfortunately, we did not collect detailed information about female factor evaluations and are unable to analyze the female factor contribution to this study. However, extrapolating on this idea, if we assume that female factors were to be

identified in say 20% of the couples in this study, and these couples were excluded from the study, then our natural conception pregnancy rates would likely have been even higher than we reported (as the denominator would be smaller).

Changes in text: p.2, Abstract, unexplained infertility used in 4 places.
p.3, Background, unexplained infertility used in 3 places
p.10, Conclusion, unexplained infertility used in 3 places.

4. **Comment:** Recording and assessing impact of antioxidants and lifestyle changes.
Reply: Assessing the details of lifestyle and diet modifications that occurred in this study would have made this a much more powerful study! Unfortunately, our followup survey for patients needed to be brief to assure good compliance and response rates, and exact details regarding lifestyle changes were not evaluated for individual patients. This is certainly a limitation of the study and we note this in the Conclusion section.
Changes in text: p.11, Conclusion, line 2. Introduced this study limitation

Reviewer C

Comment: Inconsistency: with infertility of 0.4 yrs, this would be not technically be considered infertility

Reply: Similar to the observation made by Reviewer B, we note that men were evaluated whenever they presented to us with infertility. Among study subjects, 1 couple had tried for < 1 yr (0.4 yrs) but the remainder had tried > 1yr. In addition, this couple failed to conceive in followup. By excluding this couple, our pregnancy rate data would be even higher.
Changes in text: None

Comment: Inconsistency: Table 4, one abnormal semen analysis.
Reply: The reviewer notes correctly that 1 semen analysis was actually abnormal (sperm concentration) on a patient whose second semen analysis was entirely normal. Because of this, he was included in the study. To clarify this matter, we have added more specific semen analysis inclusion criteria in the Methods section of the manuscript.
Changes in text: p.6, Methods, Line 10. Added qualification to semen analysis criteria.

Comment: Study weakness: little information on the female partner.
Reply: Similar to the comment from Reviewer B, we did not collect detailed information about female factor evaluations and are unable to analyze the female factor contribution to this study. This has been noted as a limitation of the study. However, extrapolating on this idea, if we assume that female factors were to be identified in say 20% of the couples in this study, and these couples were excluded from the study, then our natural conception pregnancy rates would likely have been even higher than we reported (as the denominator would be smaller).
Changes in text: p.12, Conclusion, Lines 5-8. Include lack of female factor information as a study limitation.

Comment: Add additional data on BMI

Reply: Height and weight data was not recorded on every patient in the study and BMI was not used to "clear" men of male factor infertility, so these data were not included in the study.

Changes in text: None.

Comment: Study conclusion not supported.

Reply: The reviewer is correct in that we did not quantify lifestyle or diet changes that occurred in study followup. As such, we do not actually "conclude" that such changes made by patients are responsible for the pregnancies observed. The main conclusions of our study are that (1) pregnancy rates among evaluated and cleared male factor patients is high and (2) the male factor evaluation is more robust that we may have thought. In the rest of the Conclusion section, we speculate (as one does in manuscripts) regarding the findings and we use the word "provocative" when speculating about lifestyle changes. In addition, our statement that "Medical care in the form of *counseling* at-risk patients regarding lifestyle issues…*may have* value in improving the fertility potential" is not a conclusion but an alternative interpretation. Our suggestion that further research that drills down on lifestyle changes is needed is also very reasonable.

Changes in text: None

Comment: Typo in Abstract

Reply: Noted and corrected.

Changes in text: p3. Abstract, line 7. Removed the word "have."

Comment: Acknowledge the probabilistic nature of pregnancy. Provide interquartile ranges for semen analysis parameters.

Reply: We agree with idea of emphasizing the "probabilistic" nature of pregnancy and have altered the manuscript as per the comments from Reviewer B to include a comparison the pregnancy rates in this study with published spontaneous pregnancy rates of couples occurring after their infertility diagnosis (Snick et al. Hum Reprod Upd, 1997). We did not feel that an interquartile range analysis of semen quality would be valuable in this study because of selection bias, since all study subjects were selected because they had normal semen quality and not because (as in the latest WHO 2010 guidelines) they were fertile.

Changes in text: p. 10, Conclusion, lines 6-8; comparative statement explaining natural pregnancy rates in untreated infertile couples and p.19, References. Suggested reference added and references renumbered.

References:

1. Gangel EK. AUA and ASRM Produce Recommendations for Male Infertility. Am Fam Physician. 2002 Jun 15;65(12):2589-2590.
2. Arafa M, Agarwal A, Majzoub A et al. Efficacy of antioxidant supplementation on conventional and advanced sperm function tests in patients with idiopathic male infertility. Antioxidants. 2020 9: 219. doi:10.3390/antiox9030219