Reviewer’s report

**Title:** Assisted reproductive techniques with congenital hypogonadotropic hypogonadism patients: A systematic review and meta-analysis

**Version:** 4  **Date:** 10 Oct 2018

**Reviewer:** Andrew DWYER

Reviewer's report:

Gao and colleagues present a revised manuscript reporting results from a systematic review and meta-analysis of assisted reproductive techniques in patients with congenital hypogonadotropic hypogonadism (CHH). The authors have responded to many of the points raised in the initial manuscript review. However, there are still some elements that have not been fully addressed. I do not feel that the manuscript is suitable for publication until these concerns have been corrected. Detailed comments are provided for the authors below and have put comments and suggestions in the pdf related to grammar and clarity issues.

Title

The title of a systematic review and meta-analysis should be as descriptive as reasonably possible and should be presented in an unbiased manner. I recommend changing the title to more accurately reflect the work (without leading the reader). Perhaps instead of "…techniques improved fertility of…” use "…techniques for patients with …". This would be less leading.

Abstract

There are typos and grammar issues. Words are capitalized that should not be (e.g. Androgen, Pulsatile) please correct. The statement "about 30% lacks precision (see Rastrelli et al who report 75% (69-81) and 75% (60-85) for gonadotropin and GnRH therapy respectively). As this is the introduction, I suggest changing to "… is not sufficient to produce sufficient gametes in some patients". Please use active voice (i.e. "ART can effectively treat different causes of infertility". Similarly, begin the sentence with "A Systematic review and meta-analysis was performed to determine…". The phrase "wether it is" is unclear; I suggest replace with "whether outcomes are similar". Before reporting 388 pregnancies please indicate how many studies were included. It would be clearer to simply state "Pregnancy rate decreased with increasing age", similarly change to "live birth rates were not different from infertility due to other causes". The sentence "Despite CHH patients usually being azoospermic…” is not accurate as females are analyzed as well as males. I suggest adding males to clarify this point.
Comment 1: The authors have still not adequately responded to the comment #1 regarding retrospective single study reports. The potential bias of such an analysis must be clearly stated in the manuscript. The heterogeneity of results ($I^2=0.76$) underscores this key point.

Comment 3: The Authors have not adequately responded to the comment on incidence - please go to the original sources suggested in the initial review. The citation is a review citing another review!

Comment 7: The Authors respond "Although there were implications for heterogeneity and variability the expanded sample size was still representative". How can the authors determine this? Simply including more biased studies does not automatically make it more representative. Please respond and revise the manuscript accordingly to this important point.

Comment 17: The Authors have not fully responded to this point. Please explicitly make the point that this was the first report in the literature in the revised text.

Comment 18: It is not clear form the response how the Authors are responding to the remark from the initial review. Please clarify.

Comment 20: The use of the term dormant is not precise or clear. If the ovaries are dormant any gonadotrophic would stimulate them. Do you intend to mean that higher doses were required in some cases to achieve the desired response? Please be more precise here.

Background

Problems with precision and clarity - The ratio 3.6:1 does not vary by race- these data were not reported in this publication. Line 80: Please specify that HRT is different from fertility-inducing treatments. Line 81: please change fertility to chances for conception for precision. Line 83: please use obstructive fertility rather than "sperm transit obstacle" which is unclear.

I find it notable that 475 women were analyzed yet only 234 men. This is striking given the sex discordance. Please comment and clarify this point.

Please use fertility-inducing treatment instead of HRT throughout, as these are different treatments for different objectives.

Discussion

Lines 215-216: I respectfully and strongly disagree. The topic of safety was not assessed systematically and thus should be interpreted with caution
Lines 220-221: The reported rates are roughly 50/50 - please elaborate on this in your interpretation i.e.

Line 224: Patient preference was not assessed; please use "viable" instead of "preferable"

Lines 226-227: the I2 was 76, please elaborate on this (see point above)

Lines 236-237: I feel that it warrants mentioning that rates are similar to those observed in other forms of infertility.

Line 238: Please note that intrafollopian transfer cannot be used in male patients. Please clarify in the partner of a male patient.

Line 254-255: This is unclear; please place this in a clinical context to reflect that waiting is a clinical decision that must be based on the female's age and the specific fertility-inducing treatment regimen

Lines 257-259: "Therefore, early ART for unresponsive CHH patients who receive HRT for some time may be more beneficial" Are you suggesting that the data from this meta-analysis indicate that women should proceed more rapidly to ART? I think this statement is highly speculative and is not based on the analyses reported in the manuscript. Unless this can be justified, it should be removed.

Line 262-263: the reports are American studies from 2003 and 2005 - are there no more recent data available? Given the technologic advances in ART, it could be plausible that these are dated and do not necessarily reflect current rates. Moreover, the statement "These rates did not increase in CHH patients who receive ART therapy." It would be more accurate to simply state that Rates in patients with CHH undergoing ART are not different from other infertility populations.

Line 264: please specify the reporting of OHSS (see comment in uploaded pdf)

Line 270: please specify - retrospective and heterogeneous (I2=0.76)

Line 272: please add that ART have evolved considerably in recent decades

Line 275: please note that predictors include both testicular volume and cryptorchidism (maldescended testes)

Tables & Figures

Table 1: It would be easier if you ordered the publication by year, currently they are listed in a rather haphazard manner. What about SD for BMI?
Table 2: Please add year or reference number for publications, also please depict studies according to sex (male & female).

Figure 2: clarify that ES is effect size, please add year/reference number to each study.

Figure 4: a figure legend is needed.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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