Reviewer’s report

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

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Reviewer: Andrew DWYER

Reviewer's report:

Gao and colleagues present a meta-analysis of outcomes for assisted fertility treatment (ART) among patients with congenital hypogonadotropic hypogonadism (CHH) compared to individuals with other forms of infertility. This topic is of interest particularly in light of the meta-analysis by Rastrelli and colleagues. As such, this study could fill a gap in the field if placed in the proper clinical context. However, there are some issues with the manuscript in its current form that do not make it suitable for publication in BMC Endocrine Disorders. CHH is a rare condition, and as such, data are limited and often are reported in only retrospective single study reports. I do not feel that the manuscript appropriately emphasizes this crucial point. This does not mean that such a meta-analysis is not worthwhile. Rather, the appropriate analysis and disclaimers must be clearly stated. If not, the reader who may not be well-versed in this analytic approach may be led to inaccurate or spurious conclusions.

Major concerns:

1. Background - the description of CHH and incidence lacks precision and is inaccurate in some aspects. For instance, "secondary sexual immaturity and infertility" seems vague, why not simply state lack of puberty and infertility? GnRH is released "from" the hypothalamus not "in" the hypothalamus. The sexual discordance is not 5:1 (See Dzemaili et al Endocr Connect 2017). Incidence should be based on population studies - see original studies by Fromantin (French conscripts) and the Finnish population study by Raivio and colleagues. I question the 2/3 with anosmia (stated without reference). This is classically been about 50% in the literature. There is no discussion of the variety of treatments for fertility inducing regimens. Moreover, it can take 12-18 months to reach maximal testicular development and sperm count in males with CHH - should this not be noted and taken into consideration?

2. Methods - please clarify how you determined patients CHH and not another form of hypogonadism and infertility. Presumably, patients with combined pituitary hormone deficiency could be included - as the treatment is the same (i.e. hypogonadotrophic hypogonadism) Was this literature considered? Please note that ALL studies were
retrospective single centers - this is important as it has implications for heterogeneity and variability when interpreting the findings.

3. Results - The description of "pregnancy outcomes" lacks precision i.e. "duration was around 2 weeks in females and 6-12 months in males". This does not provide a rigorous description or interpretation of the data. Similarly the description of ART approaches lacks precision and clarity (lines 176-177). I do not believe that "ES" was defined (line 180). The I-square is reported as 73.06% yet no interpretation is offered. Please explain the significance of this in terms of heterogeneity and variability of studies. Please report confidence intervals rather than simple percentages - this would add to transparency and rigor. What about description of weighted differences and subgroup analyses? If a qualitative interpretation was done this should be explicitly stated for transparency and clarity. It seem that not all studies reported adverse events, please note that this introduces a reporting bias and should be noted - similarly the discussion and conclusions should be softened to this end. The observation that there was no statistical difference (lines 199-200) is hindered by the fact that analysis is limited to the few studies that reported on this. This should be noted as a limitation.

4. Discussion - It is never noted in the discussion that ART is the ONLY option for those who fail to conceive following fertility inducing hormone regimens. This may seem obvious, but it warrants mention. The discussion lacks precision i.e. please specify forms of infertility (lines 208-209) rather than stating broadly "other etiological infertility". Please report confidence intervals (see above). There are numerous statements that are not backed up by the data - this may be acceptable in certain cases when summarizing publications in a review article, but given that a meta-analysis was performed, it seems logical that these data should be the basis for supporting conclusions. The methods exclude case studies yet the discussion includes reference 6 - why is this included? This appears haphazard. Please be precise, - i.e. pregnancy rates were 50-60% (line 228) please refer to your analysis not those form the literature. I disagree with the conclusion in lines 236-237. Waiting may be advisable as maximal sperm counts are not attained until 12-18 months of treatment (and even longer in cases of cryptorchidism). Line 238 seems overly descriptive i.e. "higher doses of gonadotropins are needed to induce ovulation" please base statements on your analysis rather than the literature. I am not sure the authors can definitively declare that ectopic pregnancy and OHSS are "common adverse events" given that not all reported these events. Please clearly state (in the limitations) that there are no prospective studies thus additional sources of potential bias. Discussion should comment on the variable responses (see Figure 4)
Minor concerns

1. The manuscript could benefit from copy editing form a native English speaker. This would help clarity and precision.

2. Abstract - please note that hormone replacement therapy to induce fertility is specialized i.e. combined or sequential gonadotropin therapy or pulsatile GnRH - this is an important point and should be made explicitly clear. Also the comparison is not between treatments but rather outcomes to treatment. This point is important for precision.

3. Abstract - "efficiently" or effectively? please be clear in these terms

4. Tables and figures should be revised. Table 1 is hard to read and lacks precision. For instance how is hCG, HMG, recFSh different from "gonadotropins"? "Control option" could simply be "control group", please use n=89 instead of 89 cases for clarity. Many open cells make it difficult to read, perhaps use n/a. I suggest using "outcomes" rather than "pregnancy outcomes" as this include implantation rate - I suggest reordering with live birth as the final outcome.Consider adding check columns for the adverse events reported (and include n/a is not reported for clarity and transparency). Table 2 - I suggest adding the maximum score (e.g. 24) to aid the reader in interpreting the quality score. Figure 4 - what about the high variability? Please address this. Figure 5 is not readable due to resolution. Figure 6 is not readable.

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
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