Author’s response to reviews

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

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Author’s response to reviews:

Dear Prof. Michael O'Reilly and Prof. Andrew A Dwyer:

Thank you for your letter and for the reviewer’s comments concerning our manuscript entitled “Assisted reproductive techniques improved fertility of congenital hypogonadotropic hypogonadism patients: A systematic review and meta-analysis” (ID: BEND-D-18-00229R4). Those reminders are valuable and very helpful for revising and correcting our paper. We have studied carefully and have made correction which we hope meet with approval. The main corrections in the paper and responds are as follows:

Title section:

①We have changed the title to “Assisted reproductive techniques for patients with congenital hypogonadotropic hypogonadism patients: A systematic review and meta-analysis” according to your advice.

Abstract section:

①Line 24-27: We have corrected the words such as “androgen” and “pulsatile”.

② Line 27-28: The statement about 30% lacks precision, we changed this sentence to "...is not sufficient to produce sufficient gametes in some patients with Congenital hypogonadotropic hypogonadism (CHH)."

③ Line 29-30: We have re-written this sentence to “A Systematic review and meta-analysis was performed to determine that assisted reproductive techniques (ART) can effectively treat different causes of infertility”.

④ Line 34: The phrase "whether it is" is unclear, we have corrected to “whether outcomes are similar”.

⑤ Line 45: For the advice “before reporting 388 pregnancies please indicate how many studies were included”, we have re-written the sentence to “A total of 388 pregnancies occurred among 709 CHH patients who received ART (effectiveness 46%, 95% confidence interval 0.39 to 0.53) in the 20 studies we included.”

⑥ Line 49-53: We have re-written this part clearly that “Pregnancy rate decreased with the increase in age which showed in the meta-regression. Fertilization, implantation and live birth rates (72%, 36% and 40%) showed no significant differences as compared to infertility due to other causes.”

⑦ The sentence "Despite CHH patients usually being azoospermic…” is not accurate as females are analyzed as well as males. We changed this sentence to “Despite CHH patients usually being difficult to generate gametes, their actual chances of fertility are similar to subjects with other non-obstructive infertility.”

Response to reviewer reports:

① Comment 1 and 7: “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.”

Response: There are some limitations in our study. Most importantly, there are significant statistical heterogeneities among included studies. Various levels of heterogeneity could be explained by differences in regions, sample size, criteria of CHH, testis volume in male patients and treatment periods. We have analyzed the influence of the age and sex factors, but got no difference. Moreover, the research types were not restricted in the process of literature search. Retrospective or prospective studies, multicenter or single center studies all made sense to the meta-analysis. Unfortunately, for rare disease just as CHH, we have found only 20 retrospective studies consistent with the aims of the study. But we believed that 20 studies and 709 CHH patients could illustrate the issue to a large extent. We have written the limitations in discussion section.
Comment 3: “Incidence should be based on population studies - see original studies in English, American and French.”

Response: We have consulted the references according to the reviewer’s suggestion and the following adjustments have been made: The incidence of CHH is approximately 1/86000–1/10000 (Fraietta R et al Clinics 2013), and the ratio of male versus female is about 3.6-1 which varies from race to race (Bry-Gauillard et al Annales d'endocrinologie 2010; Quinton et al Clinical endocrinology 2001; Seminara et al Endocrine reviews 1998).

Comment 17: “The methods exclude case studies yet the discussion includes reference 6, why is this included?”

Response: Reference 10 was not included in the 20 studies of this meta-analysis. It was the first report that ART treatment applied in the CHH patient in 1992. In this study, an ART method called Intra-Fallopian transfer was initially used for a male patient with Kallmann’s syndrome. And it was of great significance to our review.

Comment 18: “Please be precise, i.e. pregnancy rates were 50-60% (line 228) please refer to your analysis not those from the literature.”

Response: We have re-written this part in the manuscript and the results of our meta-analysis were showed in paragraph 1 of discussion section. “The fertilization rate, implantation rate and live birth rate are 72%, 36% and 51%, which showed no significant differences as compared to other cohorts as well.”

Comment 20: “The use of the term dormant is not precise or clear. If the ovaries are, dormant any gonadotropin 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.”

Response: Due to the weak ovarian function in older women, higher doses of gonadotropins are needed to induce ovulation to match the desired response (Kumbak Acta obstetricia et gynecologica Scandinavica 2006; Yavangi Iranian Journal of Reproductive Medicine 2012). Therefore, early ART for unresponsive CHH patients who received HRT for some time may be more beneficial. We supplemented this part to discussion section.

Background section:

Line 80: We supplemented this part to background section to explain that HRT is different from fertility-inducing treatments. “Alternate methods have been described for patients with no response to hormone replacement therapy (HRT) which aimed to supplement its lacking hormone, rather than inducing ovulation by sequential treatment of estrogen and progestogen in women.”
② Line 81: We changed the fertility to chances to conception rate for precision.

③ Line 83: We use obstructive fertility rather than "sperm transit obstacle" according to your advice.

④ Response for “I find it notable that 475 women were analyzed yet only 234 men. This is striking given the sex discordance”: There were more female CHH patients accepted ART when failed to fertility, though the ratio of male versus female is about 3.6-1. The 709 patients we included in this meta-analysis comprised by a large part of male patients.

Discussion section:

① Line 215-216: We added the limitation in discussion section to compare the safety of ART in CHH patients or others. “Last, it seems that not all studies reported adverse events, and some like OHSS is not considered to be an adverse event, so more studies should be included to avoid the reporting bias.”

② Line 220-221: For this specific population, the overall pregnancy rate per ET cycle was about 46% (95% confidence interval 0.39 to 0.53), which was comparable to the patients with other etiological infertility including tubal factor infertility (TI), male factor infertility (MI) and unexplained infertility (UI) which showed 50/50 roughly.

③ Line 224: We have corrected it to “Hence, ART is a viable option for CHH patients with unsuccessful long-term HRT.”

④ Line 236-237: We supplemented the section that “ICSI combined with TESE may improve their fertility and the pregnancy rates could be similar to those observed in other forms of infertility.”

⑤ Line 238: We corrected this sentence to “Intra-Fallopian transfer was initially applied for the spouse of a male patient with Kallmann’s syndrome.”

⑥ Line 254-255: We have re-written this part that “Waiting may be advisable as maximal sperm counts are not attained until 12-18 months of treatment, and even longer in cases of cryptorchidism. However, like in normal population, chances of fertility in CHH patients after ART reduced with the increase in age. Quality and quantity of follicles both decreased. And due to the weak ovarian function in older women, higher doses of gonadotropins are needed to match the desired response. Therefore, early ART for unresponsive CHH patients who received HRT for some time may be more beneficial.”
We supplemented this part to discussion that “With the advancement of technology, various ART treatments were applied on CHH patients in different situations such as age, gender, region, duration and extent of illness. The success rate increased to 55%.”

We adjusted the content in the adverse events of results section. “Six trials mentioned ovarian hyperstimulation syndrome (OHSS) but there was no OHSS occurrence in the included studies.”

In the limitation section, we added the accurate I2 to this part. “Hence, the significant statistical heterogeneities (I2=73.06% in pregnancy rate) of the materials influenced the analysis of the outcomes and caused the deficiency of representation.”

We add this sentence to limitation that “Great progress in ART treatment also made sense to patients in different decades.”

We adjusted this part that “For example, testis volume and cryptorchidism (maldescended testes) is an important indicator for sperm production, but adequate data was not available for analysis.”

Tables & Figures

Table 1: We ordered the publication by year, and added the SD for BMI into the table.

Table 2: We added year for publications and gender (male & female) to the table.

Figure 2 and 4: We have supplemented the legends and notes in the manuscript. And years to each studies were added into the figures.

Once again, thank you very much for your comments and suggestions.

Best wishes,

Yinjie, Gao