Author’s response to reviews

Title: Sequential E2 Levels not Ovarian Maximal Diameter Estimates were Correlated with Outcome of Cetrotide Therapy for Management of Women at High-risk of Ovarian Hyperstimulation Syndrome: A randomised Controlled Study

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Author’s response to reviews:

Reviewer reports:

Elijah Onwudiwe (Reviewer 1):

1. Comment: There are some grammatical errors on the manuscript. The author should do the corrections as indicated on the tract changes.

Response: corrected

2. Comment: I don't know if the author used only GnRH agonist for the stimulation or FSH/HMG because am aware that the agonist is used for the purposes of down regulation and not stimulation as alluded by the author.

Response: only agonist was used as stated in aim of work and methodology; anywhere the applied GnRH agonist induction protocol meant GnRH plus FSH/HMG (background- line 71-74 - page 3)
3. Comment: The author should indicate in the methodology how the severity of nausea and vomiting was measured

Response: Scores for nausea & Vomiting were added( patients and methods-line 92-97 -page 4)

4. Comment: Did the author consider the renal function tests of the participants to this study since renal dysfunction is associated with OHSS and the Cetrotide is also excreted via the renals.

Response: revision of patients files and preliminary lab examinations assured normal liver and renal function and patients with liver or renal affection were excluded from the study.( patients and methods -line 86-89- page 4 )

5. Comment: The discussion flow is deficient as the author did more of the literature review of other authors without putting his own study in perspective

Response: adjusted

6. Comment: The author evaluated the efficacy but not safety of Cetrotide as stated in his aims.

Response: there was no need to evaluate safety of a drug with settled safety and the used dose and duration of therapy was less than the traditional antagonist protocol induction of ovulation, so it is meaningless to evaluate the safety (background -line 71-74 -page 3 )

7. Comment: The author should look at his aim again as it did not mention anything about the E2 and OMD but mentioned only the safety and efficacy of cetrotide

Response: corrected(background-line 71-74 -page 3 )
8. Comment: The author should include a flow chart on randomization
Response: added(Results-line 139-140- page 6 )

Mário Sousa (Reviewer 2): -

1. Comment: A better definition of the control group is necessary regarding the ovulation trigger
Response: added(patients and methods-line 113-115- page 5 )

2. Comment: Why AA did not use antagGnRH as ovulation induction and agGnRH for ovulation trigger, when necessary, as this scheme avoids OHSS?
Response: because the scope of the study to evaluate the agonist.

3. Comment: In AA Hospital, from how many patients these 48 OHSS cases derived? It was IVF or ICSI?
Response: clarified in the flowsheet(Results-line 139-140- page 6 )

4. For all, what was the CP rate, the IR and the LBDR? And the luteal support? It would be better if AA describe the stimulation, gamete and embryo handling procedures. Why AA did not use the other patients as controls additionally?
Response: the study targeted to include only patients at high risk for development of OHSS and as shown in methodology were divided into study group to evaluate the effect of adding Cetrotide as a therapeutic line or not and cases that did not receive Cetrotide were considered as positive control and for this target no need for negative control(patients and methods -line 112-118- page 5 )
5. Comment: Is it correct to have moderate and severe OHSS patients without treatment besides avoiding embryo transfer (control group)?

Response: patients of both groups received symptomatic treatment in the form of analgesics, antispasmodics and antemetics as written in methodology (patients and methods -line 112-118- page 5 )

6. Comment: Table 5: where is day 8?

Response: added( results -line 186- page 11 )

7. Comment: the 3 cases with hospitalization for antiemetic and crystalloid replacement fluid therapy had not paracentesis?

Response: these cases were admitted for management of vomiting and/or distension, but they did not have severe ascites to be invasively managed. Additionally, management of cases developed ascites was illustrated in the preceding paragraph where two cases with severe ascites were admitted to hospital for paracentesis.( results -line 214-217 -page 13 )

8. Comment: Of the hospitalized cases there were no other complications?: thrombosis, pleural effusion?

Response: not encountered as the majority of cases were in range of mild to moderate OHSS( results-line 214-217- page 13 )

9. Comment: What AA mean with "both therapeutic policies" in cases treated with antagGnRH as trigger?

Response: "both therapeutic policies" means cycle cancellation, i.e., embryo transfer and freezing with symptomatic treatment only (control group) or received Cetrotide injection (Study
group) in addition to cancellation and symptomatic treatment. (discussion-line 223- page 13) (patients and methods-line 112-118- page 5)

10. Comment: Do AA with "favorable outcome" mean "no dangerous complications"?
Response: as defined as study outcome and written in discussion favorable outcome was shown as change in E2 level and resolution of associated clinical manifestations. (patients and methods-line 125-129- page 5) (discussion-line 217- page 13)

11. Comment: Why AA did not discuss the antagGnRH protocol and the agGnRH as trigger?
Response: because it was out of scope of the study

12. Comment: Please verify if there are not any articles on the subject from 2017.
Response: the study duration ended and submitted at 2016, so there was no articles in 2017 were available. However, during this revision, two articles published in 2017 concerning the topic were added. (discussion -line 253-256- page 14)