Author's response to reviews

Title: A multi-centre randomised controlled study of pre-IVF outpatient hysteroscopy in women with recurrent IVF implantation failure: Trial of Outpatient Hysteroscopy - [TROPHY] in IVF

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Version: 2 Date: 22 October 2009

Author's response to reviews: see over
Date: 20/10/2002


Dear Editor-in-Chief,

We would be very grateful if you could consider the above mentioned manuscript for publication in Reproductive Health. We have addressed the reviewer’s comments point by point and have amended the revised manuscript accordingly and highlighted the changes.

We would therefore be very grateful if you could now consider it for publication in Reproductive Health.

Kind Regards

Yours sincerely

Dr. Tarek El-Toukhy, MD MRCOG
(On behalf of the authors)
Reviewer's report

Title: A multi-centre randomised controlled study of pre-IVF outpatient hysteroscopy in women with recurrent IVF implantation failure: Trial of Outpatient Hysteroscopy - [TROPHY] in IVF

Version: 1 Date: 3 August 2009

Reviewer: Sjors Coppus

Reviewer's report:

Major Compulsory Revisions
- none

*We thank the reviewer for his comment.*

Minor Essential Revisions
- Regarding the protocol, a few issues have to be clarified before publication in my opinion:
  a- In the protocol a statement about the expected incidence of intra-uterine pathology is missing. This is stated in the patient information though, where the authors mention that they expect to find polyps/fibroids or other pathology in 25% of women undergoing office hysteroscopy.

  *Answer: We thank the reviewer for his comment. This information has been added to the revised and highlighted manuscript (page 3).*

  b- This is an important point, as the difference in outcome between both groups can only be attributed to those 25% cases with cavitary pathology that is treated during OH. The other 75% of randomised women will not contribute to a difference between both arms. As a result, the number of women that have to be randomized to detect the minimally important difference of 10% increase in live birth in the OH group is quite large, with a total number of 758, as a result of which I question the feasibility of this study.

  *Answer: We thank the reviewer, but disagree with his comment. Four of the studies included in our systematic review (El-Toukhy et al., 2008 - reference No. 20 in the revised and highlighted manuscript) reported a*
significant improvement in the clinical pregnancy rate in women with no intrauterine pathology and normal hysteroscopic findings after Outpatient Hysteroscopy compared to women in the control group who did not undergo Outpatient Hysteroscopy before their IVF treatment cycle (OR=1.63, 95% CI 1.35-1.98, P<0.001) with an NNT of 7 (95% CI 5-11). Therefore, the anticipated improvement in pregnancy and live birth rates can be extended to include those with normal hysteroscopic findings as much as those with cavity abnormalities. Thus, we consider the power calculation for the study to be correct irrespective of the incidence of hysteroscopic abnormalities encountered during the trial. However, we intend to do subgroup analysis based on hysteroscopic findings (normal vs abnormal hysteroscopic findings). This has been highlighted in the revised and highlighted manuscript (page 11).

b- Do the authors have an assumption about the number of women that are eligible for inclusion annually in the participating centers?

**Answer:** We thank the reviewer for his comment. Based on good audit data, participating centres will have double the number of eligible women annually to ensure completion of the study on time. The study period was based on only 50% participation rate amongst eligible women. This has been added to the manuscript for clarification (page 10 of the revised and highlighted manuscript).

c- Regarding the design of the trial, did the authors consider a design in which all women with recurrent IVF implantation failure undergo a saline infusion contrast sonography, and to randomize between OH or non-OH in only those women with an abnormality on SIS? This would most likely reduce the sample size considerably.

**Answer:** We thank the reviewer for his comment. However, based on current evidence, Outpatient hysteroscopy is expected to significantly improve the IVF outcome in both women with a normal uterine cavity and those with abnormalities. Therefore, we feel that an added
intervention such as a saline hysterosonography is unlikely to offer an added benefit with regard to patient selection.

Discretionary Revisions
- None

Level of interest: An article whose findings are important to those with closely related research interests
We thank the reviewer for his comment.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
We thank the reviewer for his comment.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: A multi-centre randomised controlled study of pre-IVF outpatient hysteroscopy in women with recurrent IVF implantation failure: Trial of Outpatient Hysteroscopy - [TROPHY] in IVF

Version: 1 Date: 1 September 2009
Reviewer: Ilza Monteiro

Reviewer's report:

“Multicenter randomized controlled study to evaluate if performing pre-IVF outpatient hysteroscopy improves the likelihood of achieving a live birth rate in women who had failed in two or four cycles.I RECOMEND the approval of this paper because it is a trial with a great methodological value about an issue without a solution (recurrent IVF implantation failure). This issue requires more studies to determine better treatment protocols. In my opinion it is import to publish the protocols of this kind of studies.

1. Actually there are a few randomized controlled studies about IVF.
2. There is an indiscriminate trend to perform several procedures, including the diagnosis hysteroscopy during the diagnosis of the infertility and treatment of the infertile couple, especially when the IVF is performed.
3. The authors performed a good randomization because they propose an important stratification variable such as body mass index, age, basal FSH level and the number of cycles that had fail. These variables are very important to the outcome of the treatment because they minimized the risk of error in the interpretation of the results. The other important point of these study was that the authors had an special attention for the “analysis by intention-to-treat” valuing the methodology of this study.

We thank the reviewer for his/her comments and encouraging remarks.

Level of interest: An article of importance in its field

We thank the reviewer for his/her comments and encouraging remarks.

Quality of written English: Acceptable

Declaration of competing interests:
I declare that I have no competing interests