Author's response to reviews

Title: Cryo-thawed embryo transfer: natural versus artificial cycle. A non-inferiority trial. (ANTARCTICA trial)

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Version: 2 Date: 1 May 2012

Author's response to reviews: see over
Dear Mr. Nazareno,

First of all we would like to thank you, as well as the reviewers for their comments on our manuscript “Cryo-thawed embryo transfer: natural versus artificial cycle. A non-inferiority trial. (ANTARCTICA trial)” (MS: 1659382457625028). All comments were taken into account and we hope you consider our manuscript improved and suitable for publication.

We answered all questions below and we hope you’ll find our response sufficient.

Sincerely Yours

on behalf of all authors,

Eva Groenewoud

Reviewer 1:

“I am confused about the authors' objectives: are they planning to have patient preferences study, economic analysis study, observing adverse events or all these will be included in the randomised trial. Please explain”

Our primary outcome is life birth rate per started cryo-cycle (line 117). Since this is a non-inferiority trial we expect no difference regarding this primary outcome. The choice in future daily practice for one protocol over the other might be based also on other secondary endpoints such as cost-efficiency or patients preferences. Therefore this study contains several secondary outcomes as well as mentioned by the reviewer (patient’s preference, costs etc). This is outlined in lines 86 – 89 and lines 117-120.

“Please explain why to adopt the non inferiority design. There is no meaning of “natural cycle is difficult to plan” as mentioned. We should look to which is more superior”

We agree with the reviewer that most RCTs investigate superiority of one of the 2 treatment options. However, based on the current literature we decided to opt for the non-inferiority design. Currently there are no RCTs on this subject. The information available is based on retrospective studies. The results of these studies are heterogeneous but suggest no difference in pregnancy
rates. Preliminary results of a systematic review we’re currently working on show no difference in pregnancy rates either between both options, justifying our methodological choice.

Reviewer 2:

“in the NC-FET arm, patients might ovulate before or without administration of hCG. According to the study protocol, these will be drop out. But this is not necessarily the case. If ovulation is well timed retrospectively, through serial blood tests and ultrasound scans, NC-FET can be carried out successfully (Weissman et al., Reprod Biomed Online. 2011 Oct;23(4):484-9). Furthermore, the use of hCG for triggering ovulation prior to NC-FET is controversial and this point should be discussed (Fatemi et al., Fertil Steril. 2010 Nov;94(6):2054-8).”

When we designed and started this study in 2009 little information regarding endometrium preparation in natural cycle FET was available. The described protocol for NC-FET is the one we successfully used in our clinic at that time. We discussed the option of combing ultrasound with LH determinations in either blood or urine. There are several issues when using LH determination for timing FET. (Groenewoud et al, Reprod Biomed Online. 2012 Feb;24 (2):191-6) Also there is no information on whether pregnancy rates could be improved if we would adjust planning of thawing and transfer according to the presence of LH surge. To the best of our knowledge, no such studies have been conducted in patients undergoing ultrasound monitored unstimulated cycle FET.

We included your comment and our answer in the discussion section.

Taking the above mentioned into consideration as well as the burden of daily LH determinations in blood, if ultrasound would be combined with regular LH determination, we decided to abstain from daily LH monitoring.

“Perhaps only regarding the remarks made above about spontaneous ovulation without hCG in NC-FET arm, as well as mentioning the debate on the use of hCG in this context.”

The use of HCG in natural cycle FET remains a matter of debate. The prospective studies you’d mentioned weren’t published in 2009 when we designed and started this trial. Since the outcome of these conflicting outcomes we’ve decided to proceed with natural cycle FET as written. More over there are several retrospective analysis suggesting no difference in pregnancy rates. (Chang et al J Assist Reprod Genet (2011) 28:369–374, Weissman et al, RBM online Vol 19. No 1. 2009 66-71) As mentioned before we’re working on a systemic review of the available RCTs and retrospective studies. Coarse reading of the review reveals no difference in pregnancy rates between both treatments. This review will hopefully be published this year.

When the trial will be finished this will be one of the focuses in the discussion. (line 199-206)