Author's response to reviews

Title: Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility

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Authors’ response to comments received from Reviewers

Manuscript Title

Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility

The authors are grateful to the expert Reviewers for their constructive comments and the time spent in reviewing the article in detail.

Reviewer 1 (Marinus J Eijkemans)

1. "The manuscript addresses an important issue in Fertility Medicine. The modelling approach is interesting, but given that there are RCT’s on the subject that reach opposite conclusions, the modelling exercise should be better founded and, particularly, the results of the promised sensitivity analysis should be shown and should be extensive to convince readers"

A mathematical modelling study was undertaken because of lack of RCTs addressing the study question. We accept that there are RCTs and cost-effectiveness analyses of IUI vs. IVF (i.e. head to head comparison). However, no RCTs exist comparing the overall cost and outcome of IUI followed by IVF for IUI failures vs. primary offer of IVF, taking into account frozen embryo transfer and where funding for all procedures comes from the same budget. Moreover, we explain in discussion that as policy makers have to develop service now (and not in the future), mathematical modelling studies like ours de facto provide the only rational alternative to the current gap in evidence.

Major compulsory revision

2. "Show results of extensive sensitivity analysis"
We welcome this important point. Sensitivity analysis was performed by using alternative estimates of the Live Birth Rate (LBR) for all the three different modalities of IUI. This is now described in the methods, and results presented in the results section (Table 4, and Table 5), and suitably discussed.

3. "Effectiveness of IUI: How can C-IUI have lower effectiveness than U-IUI?"

As (unlike is the case for IVF) there are no population-based data about the LBR of C-IUI, we have used an LBR value for C-IUI based on the Cochrane review which has showed that LBR of C-IUI is 60% lower than that of S-IUI (Athaullah et al, 2002), - we have now made this more clear in the text. Additionally, in the sensitivity analysis, we also used C-IUI LBR estimates that are higher than that of U-IUI, to address the Reviewer's point. It is important to emphasise that using these higher estimates makes no difference to the overall results of the analysis, ie IUI of any modality followed by IVF for IUI failures remains less cost effective than a primary offer of IVF.

4. "Effectiveness of FET: your estimates seems rather high to me"

LBR values for FET are based on population-based national data collated by HFEA (Human Fertilisation and Embryology authority) reported in NICE guidance on subfertility management (http://www.nice.org.uk/page.aspx?o=106334). This is the best source of evidence about "real world" effectiveness of FET in the UK, in an unselected population setting.

5. "Can you mimic Goverde analysis, with their assumptions about effectiveness per cycle, and show how results would be in your model?"

We are familiar with this publication and we have used an LBR value of 8.7 per cycle for S-IUI in our sensitivity analysis, as reported by Goverde et al (2000). However, we have not used Goverde et al estimate of IVF effectiveness per cycle as it is widely recognised that the result of IVF in Goverde et al (2000) was exceptionally poor (LBR=12.2%). Such poor results from IVF would not be acceptable in most clinics, and indeed the population-based HFEA database which includes data on all IVF treatments administered in the UK confirms that significantly better results are obtained in the UK (LBR=19.6%).

Minor essential revisions

6. "The abstract needs to be made more specific "

a. "Mention the effectiveness parameter (LB)"
We have added the phrase 'live birth-producing pregnancy' in the background as such: 'In practice, it is therefore important to examine the comparative outcomes (live birth-producing pregnancy), costs, and cost-effectiveness of primary offer of IVF, compared with primary offer of IUI followed by IVF for couples failing IUI.'

b. "(Results) Cost-effectiveness ratios for IVF (?) compared to what ?"

The cost-effectiveness ratio refers to the total cost per unit of outcome of interest, in this context, live birth-producing pregnancies. As such cost effectiveness ratios (for the same unit of outcome) relating to each treatment strategy can be compared to each other. On the other hand, the incremental cost-effectiveness ratio (i.e. the additional cost for one additional unit of outcome) compares cost and effectiveness of "IUI+IVF" to primary offer of IVF, (as explained in the 'Results' section of the abstract) which was used as the reference category.

7. "Introduction: last sentence of first paragraph: How do you avoid transition to IVF if you do IVF in all couples? Doesn't make sense to me"

We have edited the text to make this clearer. In our model we have used a hypothetical cohort of 100 couples whose treatment experience was simulated sequentially with different treatment strategies. When IVF is considered as the treatment strategy, the hypothetical couples are treated with only one cycle of IVF (fresh and frozen). When primary offer of IUI is considered, the couples are treated with 1 to 6 cycles of IUI. Those who fail IUI and would like to continue subfertility treatment were given one full cycle of IVF.

8. "The 'subtitles' in the Results section seem a bit odd to me"

We have modified by adding the phrase 'cost-effectiveness of'. Now the subtitles read: "Cost-effectiveness of 'head to head' comparison of primary IUI vs. primary IVF" and "Cost-effectiveness of "IUI+IVF" vs. primary IVF".

Discretionary revision

9. Correction: The Netherlands and not Netherlands

Addressed.
We are grateful for the Reviewer's constructive comments and suggestions.

Major compulsory revisions

1. "The authors must refer to a checklist on economic analysis, for example a list as produced by Drummond et al"

We are thankful for this comment. We have now incorporated an additional file (Additional File 1) including the EVEREST statement/checklist for economic evaluation studies, along with a detailed description about how each EVEREST criterion is addressed in our study (see Additional File 1).

2. "Spontaneous pregnancies that occur without treatment would be the reference strategy, and the other strategies must be compared to this baseline strategy (Fertil Steril 2000 Apr; 73(4): 748-54)"

Although in principle this is an important point when comparing a treatment modality vs. no treatment, in our study we have assumed a hypothetical cohort of couples who could be sequentially be treated with one of two treatment strategies, with exactly the same patient and disease characteristics. Although some spontaneous pregnancies in these couples would have occurred independently of the treatment strategy, this would not have in any way affected the differential comparisons of the two compared strategies, which is the purpose of our study. For this reason we were unable to improve the manuscript in this respect.

3. "The authors must do a systematic search in their sources of evidence"

We have used the excellent systematic review conducted by NICE to underpin their 2004 guidance on subfertility treatments. In addition, we have searched MEDLINE for any more recent studies on LBR of S-IUI, U-IUI, and C-IUI. Relevant studies are referenced in relevant parts of the manuscript. We now make this clear in the methods section.

4. "There is no systematic description of the strategies under study"

The strategies are described in the methods section and schematic diagram of the model is presented in Figure 1.
Potential differences in the prognosis by patient characteristics (e.g. age) or disease type (e.g. underlying aetiology of subfertility) are not taken account as our study assumed an identical hypothetical cohort of couples that are expected to have identical prognostic factors and indications, as also explained above (see point 2 response to Reviewer 2).

Similarly, we are not aware of any prognostic factors that would differentially influence the effectiveness of IUI and IVF. For example, although clearly a younger age favourably influences the outcome of IUI, it similarly does influence the outcome of IVF, and so on. We allude to the above in the discussion section. We were therefore unable to improve the article further.

Summary of the response

In conclusion, we have addressed all the points raised by the reviewers, in a way that also adds considerable value to the original manuscript. We once more are thankful to the Reviewers for their very helpful feedback.

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