Letters to the Editor

We wish to comment on two observations. The first concerns the authors’ assessment of methodical validity of each included trial. The authors stated that this was done independently by two reviewers using a pre-determined scoring system consisting of eight criteria. It was also described that for each trial included, any disagreement not resolved by consensus was referred to a third reviewer for resolution. There are only two authors with no additional reviewer acknowledged in the paper. One can assume therefore that the authors constituted the panel of reviewers. For two to reach independent agreement on 26 scores spread over eight criteria, for each of 17 studies is a daunting task. How did the authors measure consensus on their disagreement? Did they assess each trial based on Kappa’s inter-rater measurement of agreement (Landis and Koch, 1977), or was this based on a minimum cut-off point of total score or percentage of maximum score?

Our second observation is that the authors did not sufficiently emphasize the clinical bottom line, which is of interest to clinicians and their patients. The authors used two statistical parameters to compare the clinical pregnancy rates; the odds ratio (OR), a useful statistical tool in systematic reviews for data combination and construction of meta-analysis trees; and the risk difference (or absolute risk reduction – ARR) which on inversion can be converted to the number needed to treat (NNT). The clinical bottom line therefore, from overall meta-analysis in Daya and Gunby’s review is that 27 (NNT = 27; 95% confidence intervals, –261 to –14) (Ola and Hammadieh, 1999) patients need to be treated with rFSH to produce one additional pregnancy over that from use of uFSH.

Highly purified urinary FSH (e.g. Metrodin HP; Serono, Welwyn, UK) also lacks LH activity and protein contaminants and is considerably cheaper than recombinant FSH (e.g. Gonal F; Serono). The average costs respectively are £614 versus £866 for a typical treatment cycle (comprising 225 IU of FSH daily for 11 days). A simple cost-effectiveness analysis therefore approximates to an additional cost of £6789 to achieve one extra pregnancy. However, a cost-benefit equation (i.e. total cost per absolute, rather than incremental number of pregnancies) would confer an apparent advantage to recombinant FSH.

References

Recombinant versus urinary FSH for ovarian stimulation in assisted reproduction
Dear Sir,
We find the systematic review by Daya and Gunby (1999) very interesting. Apart from dealing with an issue of current interest in assisted reproduction, this paper is an example of a rigorously conducted meta-analysis of a homogeneous selection of randomized controlled trials.

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Dear Sir,

We would like to thank Ola et al. for their interest in our work and for highlighting the rigour of our meta-analysis. In response to their first concern about agreement analysis, we would like to confirm that there were only a few instances in which our assessments disagreed; the kappa values (which were not indicated in our paper) ranged from 0.9 to 1.0. In those instances in which we disagreed, resolution was easily achieved by reviewing the relevant papers and discussing the respective issues to reach a consensus. Consequently, there was no need to seek arbitration from a third reviewer. The total validity score for each trial was calculated, as indicated in our paper, as the sum of the scores of each validity criterion.

Regarding the second concern about the ‘clinical bottom line’, we are somewhat surprised with the authors’ method of reporting the estimates of treatment effect and their cost-effectiveness analysis. We calculated the risk difference as a weighted (for sample size) mean difference in pregnancy rates between recombinant follicle stimulating hormone (rFSH), representing the experimental group, and urinary FSH (uFSH), representing the control group. The risk difference was in favour of rFSH, with an increase in the clinical pregnancy rate of 5.2% when follitropin alpha (Gonal F; Ares Serono, Geneva, Switzerland) was compared with uFSH in cycles of IVF, and 3.7% when follitropin beta (Puregon or Follistin; Organon, Oss, The Netherlands) was compared with uFSH (the latter was not statistically significant). The authors’ use of the term absolute risk reduction (ARR) (and the related term relative risk reduction) obtained from the computer programme they used to develop a critically appraised topic on this subject (Ola and Hammadieh, 1999) is unfortunate because it conveys the impression that rFSH reduces the ‘risk’ (or event rate i.e. pregnancy rate) compared with uFSH [and the corresponding number needed to treat (NNT) has a negative value]. Clearly, a reduction in risk was not the finding in our study. The more appropriate term is the absolute treatment effect (ATE) (Daya, 1999) or absolute benefit increase. Although, numerically in this instance, ATE and ARR are the same, it is important to use the term that conveys the correct message about the effect of treatment.

The NNT (of 27), to which the authors refer, was not provided in our paper but was calculated by them using the whole data set we published. We wish to point out that the NNT varies depending on which subgroup is analysed. Also, when the difference between two treatments is not statistically significant, the confidence interval for the NNT is difficult to describe. Our subgroup analyses indicated that, although the overall result was statistically significant, it was in large part because of the difference between follitropin alpha and uFSH in IVF. In this group, the risk difference was 5.2%, giving an NNT of 19 (95% confidence interval 10 to 50). The other subgroup analyses produced risk differences that were smaller and not statistically significant. Consequently, the conclusion should be that for every 19 women treated with follitropin alpha, one additional pregnancy will be achieved compared to (treating the same 19 women with) uFSH.

The cost-effectiveness analysis presented by Ola et al. is incomplete because it addresses only the cost of the drugs and not the savings that would be accrued from the cost of cycles avoided owing to the higher pregnancy rate with rFSH. If one were to assume that a ‘typical treatment cycle required 225 IU of FSH daily for 11 days’ then, using the authors’ figures, the cost difference between rFSH (i.e. follitropin alpha) and uFSH is £866.00 – 614.00 = £252, which is the cost incurred by each patient to obtain an improvement in pregnancy of 5.2%. In actual fact, the cost difference would be much smaller because we have observed, in a meta-analysis of the secondary outcomes, a significant reduction in the total amount of rFSH used compared with uFSH. Assuming that the non-drug-related cost for one cycle of IVF is £2000, then the cost per pregnancy can be calculated as shown in Table I.

It is clear from this analysis that the cost per pregnancy is higher when uFSH is used compared with rFSH (follitropin alpha). Furthermore, using the event rates and drug costs as shown in the table, the cost per pregnancy would become identical only if the non-drug-related costs per cycle were as low as £600. Based on the cost of IVF treatment in Canadian centres, this scenario is highly unlikely. Therefore, we submit that the clinical bottom line is that rFSH is more efficacious than uFSH and, in IVF, the use of follitropin alpha is more cost-effective than uFSH.

### References
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### Table I. Cost-effective analysis of recombinant FSH in IVF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total cost of cycle (£)</th>
<th>Clinical pregnancy rate (%)</th>
<th>Cost per pregnancy (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFSH (follitropin alpha)</td>
<td>866.00</td>
<td>2000.00</td>
<td>2866.00</td>
</tr>
<tr>
<td>uFSH</td>
<td>614.00</td>
<td>2000.00</td>
<td>2614.00</td>
</tr>
<tr>
<td>Difference</td>
<td>252.00</td>
<td>5.2</td>
<td>252.00</td>
</tr>
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