Letters to the Editor

Models of cost-effectiveness of recombinant FSH versus urinary FSH

Dear Sir,

We read with great interest the two articles comparing the cost-effectiveness of recombinant (r)FSH versus urinary (u)FSH (Daya et al., 2001; Sykes et al., 2001). We appreciate the efforts
undertaken by the authors of both papers to build up cost-effectiveness models in IVF/ICSI programmes. In both articles, the cornerstone of building up the model was the assumption that rFSH is associated with a better pregnancy rates per started cycle than uFSH. This assumption is based on evidence provided by a meta-analysis (Daya and Gunby, 1999).

The National Institute of Clinical Excellence (NICE) has recently announced that it will be analysing the cost effectiveness of treatment for fertility in UK (Barlow, 2001). It is expected that this analysis will be based on the best available evidence. We do not think these two articles (Daya et al., 2001; Sykes et al., 2001) will be considered to help the decision-makers for the reasons discussed below.

The Cochrane Library is the best single source for evidence-based medicine and its systematic reviews are well designed and well conducted. However, when registering a review with the Cochrane Collaboration, reviewers agree to keep it up to date. This entails repeating, at periodic intervals, the steps involved in the original review. The most logistically demanding aspect in the original review. The most logistically demanding aspect of keeping a review up to date is the identifi cation of new studies (Cochrane Library Handbook, 2001). Unfortunately, this was not the case on this topic. Although this systematic review was updated in 2000 (Daya and Gunby, 2000), no further update has been undertaken since then, thus there is a possibility of missing some important studies that may affect the results.

On conducting a Medline search and searching the abstract of the ESHRE and ASRM meetings for 2001, we identifi ed fi ve additional randomized controlled trials testing the exact question upon which cost-effectiveness was based (Gordon et al., 2001; Ng et al., 2001; Strehler et al., 2001; Westergaard et al., 2001; Diedrich et al., 2002).

Based on the updated meta-analysis of Daya and Gunby (Daya and Gunby, 2000) we added the fi ve trials and there was no signifi cant difference between rFSH and uFSH in pregnancy rate/stated cycle (Figure 1). Estimated odds ratio (OR) is 1.06 [95% confi dence interval (CI) 0.94–1.19]. If we exclude the Gordon et al. trial because it used varying doses of LH (Gordon et al., 2001), OR is 1.06 (0.93–1.19). If we compare trials between rFSH versus HMG alone, OR is 0.9 (0.7–1.09). If we compare rFSH versus uFSH–HP (highly purified) alone, OR is 1.12 (0.93–1.25). If we compare rFSH versus purifi ed uFSH, the OR is 1.2 (0.9–1.5). Thus there was no signifi cant difference in the subgroup analysis. In our data analysis we used only studies that performed down-regulation using long protocol.

Given the cost of medications presented in both articles, it does not need modelling to assume with confi dence that uFSH is more cost-effective than the costly rFSH. There is no reason to suggest that the cost-effectiveness modelling presented by the authors is restricted to the UK. Extracting data from selected studies (sponsored by the same pharmaceutical company) as done in the Sykes et al. article and ignoring all other studies because they were done in UK does not seem to be appropriate. As far as we know there is no national variation in response to either rFSH or uFSH. Publishing these two articles in a journal like Human Reproduction will defi nitely have great impact of wider application in other countries. Implementing the principles of evidence-based medicine, whether in the UK, The Netherlands, Egypt, etc. (even if they are different health care systems) will ultimately result in providing our patients with the best care in a cost-effective way.

In conclusion, the assumption on which both papers built their own models is now outdated and the conclusions reached by the authors in both articles are therefore not valid.

References


Diedrich, K. (2002) Results of multicountry multi-center, randomized clinical trial comparing the efficacy and safety of highly purified menotrophin and

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**Figure 1.** Update comparison between recombinant versus urinary FSH.
follitropin alpha in 727 patients undergoing IVF/ICSI. *Fertil. Steril.*, in press.


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Dear Sir,

Thank you for the opportunity to respond to the comments made by Drs Al-Inany and Afnan regarding our paper on cost-effectiveness modelling of recombinant (r)FSH versus urinary (u)FSH in assisted reproduction (Daya et al., 2001). The two main points in their letter pertain to having up-to-date evidence to make inferences and the use of modelling in cost-effectiveness research.

In addressing the first point, it should be emphasized that the control arm of the meta-analysis (Daya and Gunby, 1999) focused on uFSH and not urinary gonadotrophins (such as HMG). Consequently, the reference made by Drs Al-Inany and Afnan to comparisons with HMGs is not germane to the discussion of the meta-analysis. Their comment that the additional studies they identified evaluating the efficacy of recombinant rFSH were testing the ‘exact question upon which [our] cost effectiveness was based’ is incorrect because, in all five studies, the control group received HMGs. The sole study that included a rUFSH arm (Gordon et al., 2001) was included in the Cochrane meta-analysis (Daya and Gunby, 2001). From a methodological point of view, their approach of using the crude aggregate data from the meta-analysis (as if these results were observed from one study) and adding the data from each of their newly found studies is a simplification of the technique of meta-analysis and is statistically incorrect. In fact, the odds ratio (OR) they used for this purpose was 1.17 [95% confidence interval (CI) 1.01 −1.37], which is different from the OR of 1.21 (95% CI 1.04 −1.42) observed in the Cochrane meta-analysis (Daya and Gunby, 2001). Interestingly, Drs Al-Inany and Afnan missed five other new studies that did compare rFSH and uFSH; these studies will be included in the Cochrane meta-analysis when it is updated.

The meta-analysis (Daya and Gunby, 1999) to which we referred in our cost-effectiveness study provided clear evidence of an improvement in pregnancy rate with rFSH compared with uFSH (overall OR 1.20, 95% CI 1.02–1.42). The probabilities for the various outcomes used in the cost-effectiveness analysis were estimated from the best evidence available at the time, including data from the Cochrane meta-analysis, which had been submitted but not yet published at the time the manuscript was being prepared. The Cochrane meta-analysis included six more studies than the *Human Reproduction* publication, but the overall ORs for clinical pregnancy were virtually identical. Thus, empirical evidence and not assumption was used to provide the probability estimates for our model.

The second point pertains to the need for modelling in cost-effectiveness analysis. The view of Drs Al-Inany and Afnan that uFSH is more cost-effective than rFSH because the latter is more expensive is simplistic and one-sided because cost-effectiveness analysis involves a comparison of both costs and outcomes. Typically, treatment with assisted reproductive technologies is a multi-step, multi-cycle approach in which many different outcomes are possible (e.g. successful ovarian stimulation, successful oocyte retrieval, fertilization, cleavage, implantation and so on) and these outcomes may vary from cycle to cycle. Randomized trials designed to evaluate the cost-effectiveness of interventions of such complex treatments require considerable resources, a very large sample size and a lengthy follow-up period to provide any meaningful information from all the outcome scenarios that can be encountered. Although such trials are possible to conduct, they are unlikely to be undertaken largely because the costs involved are prohibitive.

An effective method of overcoming these limitations is to employ modelling techniques with computer simulation, an approach that is well established in cost-effectiveness research. This method also allows confidence intervals to be constructed around the estimates of the various outcomes so that the precision of the overall results can be ascertained. In our analysis, rFSH, despite its higher costs, was found to be more cost-effective than uFSH because the total amount of gonadotrophin required was lower and the clinical pregnancy rate was higher with rFSH. Further, results observed in the UK study have now been replicated in studies we have completed in USA, Spain and Germany. These studies all confirm that significantly fewer cycles are required to achieve a pregnancy when rFSH is used instead of uFSH.

In conclusion, the results from valid randomized trials confirm the clinical superiority of rFSH in treatment with assisted reproductive techniques and its greater cost-effectiveness confers benefit that will be appreciated by policy makers, health care providers, insurance companies and consumers.

References