Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 4

hMG versus recFSH for ovulation induction in developing countries: a cost-effectiveness analysis based on the results of a recent meta-analysis

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Abstract

Objective: to conduct a cost-effectiveness analysis for estimation of the cost of an ongoing pregnancy in IVF/ICSI cycles comparing recombinant FSH vs human menopausal gonadotrophins

Methods: based on results of a recent published meta-analysis by our group, a Markov model was developed to conduct a cost-effectiveness analysis for estimation of the cost of an ongoing pregnancy in IVF/ICSI cycles. In addition, Monte Carlo micro-simulation was used to examine the potential impact of assumptions and other uncertainties represented in the model.

Results: the estimated average cost of an ongoing pregnancy is as: 13,946 EGP and 18,721 EGP for an hMG and recFSH cycle, respectively. On performing a sensitivity analysis on cycle costs, it was demonstrated that the recFSH price should be 0.61 EGP/IU to be as cost-effective as hMG at the price of 0.64 EGP/IU (i.e around 60% reductions in its current price). The difference in cost between hMG & recFSH in over 100,000 cycles would result in an additional 4,565 ongoing pregnancy if hMG was used.

Conclusion: hMG was clearly more cost-effective than recFSH. The decision to adopt a more expensive, cost-ineffective treatment could result in a lower number of cycles of IVF/ICSI treatment undertaken, especially in the case in most developing countries.
Introduction

The numbers of couples requiring advanced fertility treatment is increasing and hence, economic evaluation of different therapeutic interventions is important as the demand for services increases (1). This is especially important if we put into consideration that despite, remarkable advances in infertility understanding and its management, success is limited and multiple treatment cycles may be needed to achieve a successful pregnancy.

Ovarian stimulation represents an excellent example. Multifollicular development via gonadotrophin administration is still an integral component for ovarian stimulation in IVF/ICSI cycles. In the market, there are two major players: recombinant follicle stimulating hormone (recFSH) and human menopausal gonadotropin (hMG). Both effectiveness and costs should be considered together to aid the judgment about whether one drug should be preferred to a comparator (2).

Despite of its proven efficacy, the relatively high cost of recFSH as compared to hMG has its impact on consumption (3) especially in developing countries (4) where its price (150 Egyptian pounds for 75 IU recFSH) is almost 3 times that of hMG (50 Egyptian pounds for 75 IU). In developing countries, although the cost of one trial of IVF is much lower than that in Europe, yet the majority of people cannot afford this treatment because of the low per capita income (5). Even if they can afford one IVF cycle, it is documented that women in who do not pursue a second IVF cycle after the first fails, the major reason was financial (6)In a recently published meta-analysis by our group, it was demonstrated that there is no significant difference between hMG & recFSH regarding different IVF outcomes (7) with special concern to the most important outcome: Live Birth/ Ongoing Pregnancy rate (O.R.: 1.21, 95% CI 0.95-1.54). Based on results of this meta-analysis, we wished to conduct a cost effectiveness analysis for estimation of the cost of an ongoing pregnancy in an IVF/ICSI cycle from a perspective of a developing country: Egypt. Furthermore, this model is both representative of other developing countries in which the medical insurance and/or government support for infertility treatment is markedly limited.
Methods

The recurring nature of IVF/ICSI cycles dictated the building of a state transition model, also called a Markov model (Figure 1) (Tree Age Pro 2005 Software Inc., Williamstown, MA) to simulate the IVF treatment cycle with its key steps to examine the costs and effectiveness of recFSH versus hMG. Monte Carlo micro-simulation was also used to examine the potential impact of assumptions and other uncertainties represented in the model. The transition probabilities for different health states used in the present analysis (Figure 1) were based on pooled outcome data that were collected from our recently published meta-analysis (7) (Table 1).

The meta-analysis included eight truly RCTs (8-15) showing no significant difference between recombinant FSH and hMG regarding different outcomes (ongoing pregnancy/live birth rate (O.R 1.18; 95% C.I 0.93 - 1.50), clinical pregnancy rate (O.R 1.2; 95% C.I 0.99 - 1.47), miscarriage rate (O.R 1.2; 95% C.I 0.70 - 2.16), multiple pregnancy rate (O.R 1.35; 95% C.I 0.96 - 1.90) and incidence of moderate/severe OHSS (O.R 1.79; 95% C.I 0.74 - 4.33). There was a significant reduction in the amount of gonadotrophins utilized in favor of hMG over recombinant FSH (O.R -317.8; 95% CI -346.6 - -289.0) (7).

Drug costs for recFSH and hMG were based on the most recent wholesale acquisition costs for the two agents in Egypt obtained from the Egyptian Ministry of Health (i.e. retail cost). Although these are the official prices, it should be noted that there is a variation in these prices between centers (i.e. actual price). All other costs corresponding to the relevant health states were taken (Table 2) and included costs incurred for ovarian stimulation, monitoring, oocyte retrieval, laboratory procedures, and luteal phase support and pregnancy determination. The costs considered were for the year 2005, and were obtained from the Egyptian IVF-ET Center, Maadi, Cairo, Egypt.

Figure 1 represents the first complete cycle with all probabilities commencing with ovarian stimulation to ovum retrieval (i.e. yes or no); oocytes recovered (i.e. yes or no); IVF or intracytoplasmic sperm injection (ICSI); the subsequent health states are identical for each of IVF and ICSI); fertilization (i.e. yes or no); embryo transfer (i.e. yes or no); and ending with either clinical pregnancy or negative β-hCG. If the patient became pregnant, then either ongoing pregnancy or miscarriage was obtained. If no pregnancy occurred, then either the patient restarted the cycle or discontinued for non-medical reasons; the probability of which varied by cycle number. Probability of discontinuation at the end of the cycle (failed clinical
pregnancy) was obtained from another recent study as it was not possible to obtain it from meta-analysis (16). The probability of discontinuation after the 1st cycle is 0.489, after the second cycle would reach 0.524 and after the 3rd cycle is 0.571 (16). Patients ending with miscarriage were re-entered into the cycle. Probabilities were, again, drawn from the meta-analysis (7).

The OHSS complication is independent of IVF outcome. Hence, the cost incurred for OHSS management was placed early in the cycle to accumulate them regardless of where the cycle may end (i.e. ongoing pregnancy, re-start, or stopping IVF). Patients, who cancelled early in the cycle for failed stimulation, were re-entered into the “start cycle” state, re-incurring the costs of ovarian stimulation.

It was decided to run a Markov model for three cycles as many patients pursue a live birth through infertility treatment over a long treatment course, sometimes up to 10 or more cycles of treatment, however, financial and other personal costs often limit most patients to only 3 cycles of treatment. Then, to perform the analysis, a virtual population of 100,000 patients (the 'Markov cohort') was 'treated' in the computer simulation of ART treatment in Monte Carlo simulations. These large numbers of patients and simulations provided a high degree of statistical accuracy and allowed confidence limits around the outcome estimates to be generated with precision.
Results

Running the Markov model through three treatment cycles for recFSH resulted in the individual’s probability of ending at re-starting the cycle is 6.6%, an ongoing pregnancy is 35.9%, and in discontinuing IVF is 57.5% (Figure 2). While for hMG, by the end of the 3rd cycle, the individual’s probability of ending at re-starting the cycle is 6%, in ongoing pregnancy is 40.8%, and in discontinuing IVF is 53.2% (Figure 3). The hMG cycle costs on average EGP 13,946 per ongoing pregnancy, versus an average of EGP 18,721 per pregnancy, and a final 36% chance for recFSH (Table 4). On performing sensitivity analysis on cost of hMG versus recFSH, it was found that the recFSH price should be 0.61 EGP/IU to be as cost effective as hMG at the price of 0.64 EGP/IU (i.e. around 60% reduction in its current price).

The total cost of 100,000 cycles in the hMG arm equals 1,392,633,925.40 (one billion and three hundred and ninety two million and six hundred and thirty three thousands). Total cost of 100,000 cycles in the recFSH arm equals 1,870,117,337.40 with the difference estimated (i.e. recFSH – hMG) equaling 477,483,412. The number of hMG cycles that can be done using this difference (i.e. 477,483,412/ 13,946) is 34,238 cycles with 4,565 ongoing more pregnancies if hMG was used.
Discussion

The construction of economic models in an IVF/ICSI setting involves multiple decision points and many necessary assumptions in building realistic models of a quite complex care process (17). The uncertainty plays an important role in dealing with assumptions and it is important in terms of validity and acceptability. For this reason, the best available evidence from practice should always support decision models. The current Markov model was based on results of the most recently published systematic review and meta-analysis, which is considered the top of hierarchy of Evidence-Based Medicine. In addition, the results of a meta-analysis usually reflect a wide range of clinical settings and patient characteristics; thus, the results can be broadly generalized among typical patients.

Infertility management is not, and probably will not be covered anytime in the near future, by the health authorities in developing countries (5). Even in developed countries, where the government partly or completely covers infertility treatment, cost-effectiveness is of utmost importance. The contribution of the cost of medications to the overall cost of assisted reproduction is significant. In the medical literature, there is a number of cost effectiveness analyses comparing recFSH versus hMG (3,18–21) with number of similarities: direct involvement of pharmaceutical companies, model gonadotrophin drug therapies over three cycles of IVF, using expert clinical panels to provide estimates of outcomes (except Hatoum et al., 2005), all compared recombinant versus urinary FSH (except Lloyd et al., 2003). Differences in their approach include the choice of evidence and information on which they based their modeling. The present analysis is distinguished from other mentioned above being based on a recently published meta-analysis (7) (assumptions are best evidence & bias is minimized) with no involvement of pharmaceutical companies.

As it can be seen, the hMG arm exerts “absolute dominance” over the recFSH arm (figure 2 – 3). Further analyses, such as Incremental Cost Effectiveness, Threshold Analysis, etc., were therefore not possible.

One may argue that if there is no significant difference between both drugs and one is cheaper than the other, then it would be logic that hMG is more cost effective and no need for such a complex analysis. However, IVF/ICSI cycles involve numerous steps. Each has its outcome probabilities and associated uncertainties. Therefore, it cannot simply be judged that the least costly treatment is the most effective or vice versa. Uncertainty plays a major
role here. Moreover, it is important to know precisely how big the difference between the two drugs is.

Some may also argue that the meta-analysis from which the transition probabilities were drawn, found no statistically significant difference between hMG versus recFSH. We opted to repeat the calculations assuming identical effectiveness of both treatments of 25% of ongoing life birth rate, and re-examine their cost-effectiveness (Table 3). The results were in the same direction, although the difference was less. From the calculation shown in Figure 4, price of recombinant FSH should be reduced more than 50% to be equivalent to hMG in its cost effectiveness.

In Egypt, only around 50% of the Egyptian infertile couples could afford to pay for IVF (22). We doubt that Egypt as a developing country, which has some private health care structures in place to offer tertiary level infertility care, stands alone in this matter. It was shown that in many developing countries around 10 per cent of all women’s visits to doctors (all categories of medical doctors) are related to problems of childlessness. (23)

Whereas the real cost for each live test-tube birth in the US is estimated at about $50,000, in a developing country setting, that cost could reach as high as $100,000 (24). If IVF services are provided entirely by the private sector, then new reproductive technologies will benefit only a small proportion of infertile women, primarily elites, who can afford the costs associated with this technology (Inhorn et al., 1991)

In conclusion, from an economic evaluation point of view, hMG was more cost-effective than recFSH. The decision to adopt a more expensive treatment could result in a lower number of cycles of IVF/ICSI treatment especially if patients are paying for it.
### Table 1: IVF Transition Probabilities

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_cancel_hMG</td>
<td>Probability of failed stimulation or fertilization in the Lab hMG</td>
<td>0.038</td>
</tr>
<tr>
<td>P_cancel_recFSH</td>
<td>Probability of failed stimulation or fertilization in the Lab recFSH</td>
<td>0.041</td>
</tr>
<tr>
<td>P_clin_preg_hMG</td>
<td>Probability of clinical pregnancy hMG</td>
<td>0.310</td>
</tr>
<tr>
<td>p_clin_preg_recFSH</td>
<td>Probability of clinical pregnancy recFSH</td>
<td>0.265</td>
</tr>
<tr>
<td>p_miscar_hMG</td>
<td>Probability of miscarriage hMG</td>
<td>0.136</td>
</tr>
<tr>
<td>p_miscar_recFSH</td>
<td>Probability of miscarriage recFSH</td>
<td>0.122</td>
</tr>
<tr>
<td>p_OHSS_hMG</td>
<td>Probability of OHSS hMG</td>
<td>0.019</td>
</tr>
<tr>
<td>p_OHSS_recFSH</td>
<td>Probability of OHSS recFSH</td>
<td>0.010</td>
</tr>
</tbody>
</table>

### Table 2: IVF Model Costs and Units

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Value EGP</th>
<th>Name</th>
<th>Description</th>
<th>Value EGP</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.ovum_pickup</td>
<td>Ovum pickup</td>
<td>4,000</td>
<td>c_recFSH *</td>
<td>Cost of recFSH Unit</td>
<td>1.93</td>
</tr>
<tr>
<td>c_Fertilization</td>
<td>Lab procedure</td>
<td>500</td>
<td>u_recFSH †</td>
<td>Units recFSH required</td>
<td>2192 ±463.5</td>
</tr>
<tr>
<td>c_Trans</td>
<td>Embryo transfer</td>
<td>1,000</td>
<td>c_hMG *</td>
<td>Cost of hMG Unit</td>
<td>0.64</td>
</tr>
<tr>
<td>c_OHSS</td>
<td>OHSS Management</td>
<td>4,000</td>
<td>u_hMG †</td>
<td>Units hMG required</td>
<td>2077 ±463.9</td>
</tr>
<tr>
<td>c_MISC</td>
<td>Miscarriage</td>
<td>1,000 ±500</td>
<td>c_GnRHa *</td>
<td>GnRHa unit cost</td>
<td>35</td>
</tr>
<tr>
<td>c_bHCG</td>
<td>One βHCG test</td>
<td>50</td>
<td>u_GnRHa †</td>
<td>units GnRHa required</td>
<td>11</td>
</tr>
<tr>
<td>c_antenatal care</td>
<td>Antenatal care</td>
<td>500</td>
<td>c_LP_support*</td>
<td>Leuteal phase support</td>
<td>1400</td>
</tr>
</tbody>
</table>

* MOHP list price

Table 3: Monte Carlo Simulation hMG versus recFSH stats per ongoing pregnancy and assuming identical effectiveness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>hMG</th>
<th>recFSH</th>
<th>Parameter</th>
<th>hMG</th>
<th>recFSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Using transitional probabilities</td>
<td>Assuming identical effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13,926</td>
<td>18,701</td>
<td>Mean</td>
<td>9,297</td>
<td>13,118</td>
</tr>
<tr>
<td>SD</td>
<td>± 6,512</td>
<td>± 8,749</td>
<td>SD</td>
<td>± 1,058</td>
<td>± 2,541</td>
</tr>
<tr>
<td>Minimum</td>
<td>8,664</td>
<td>11,566</td>
<td>Minimum</td>
<td>5,143</td>
<td>11,566</td>
</tr>
<tr>
<td>Maximum</td>
<td>3,6093</td>
<td>43,247</td>
<td>Maximum</td>
<td>12,593</td>
<td>21,297</td>
</tr>
<tr>
<td>25th percentile</td>
<td>8,664</td>
<td>11,566</td>
<td>2.5 percentile</td>
<td>8,664</td>
<td>11,566</td>
</tr>
<tr>
<td>Median</td>
<td>9,214</td>
<td>12,116</td>
<td>Median</td>
<td>8,664</td>
<td>12,066</td>
</tr>
<tr>
<td>75th percentile</td>
<td>27,043</td>
<td>35,747</td>
<td>97.5 percentile</td>
<td>12,093</td>
<td>20,797</td>
</tr>
</tbody>
</table>

100,000 runs, random allocation, Prices in EGP
Figure 1: The IVF Cycle State Transition (Markov) Model
Figure 2: recFSH: By the end of the 3rd cycle, the individual’s probability of ending at re-starting the cycle is 6.6%, an ongoing pregnancy is 35.9%, and in discontinuing IVF is 57.5%.
Figure 3: hMG: By the end of the 3rd cycle, the individual’s probability of ending at re-starting the cycle is 6%, in ongoing pregnancy is 40.8%, and in discontinuing IVF is 53.2%
Figure 4. Sensitivity analysis on cost of human menopausal gonadotrophin (HMG) versus recombinant FSH (rFSH)
References

5. Aboulghar MA. The importance of fertility treatment in the developing world. BJOG. 2005 Sep;112(9):1174-6


