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OPINION ARTICLE

Pharmacoeconomy in ART: The importance of the gonadotrophin choice

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Abstract Assisted Reproductive Technologies (ART) have created a number of relevant economic implications. Results deriving from cost-effectiveness studies have had some important medical and social consequences. The costs of ART are specific to the healthcare system in each of the countries were the procedure is performed, reflecting the varying degrees of public and private responsibility for purchasing healthcare and total healthcare expenditure. The analysis of different cost components per treatment cycle demonstrates that the hormonal stimulation stage is the most expensive part of IVF/ICSI cycles. The use of a more costly preparation could be justified only in case of a significantly higher live birth rate. Currently, human gonadotrophins seem to be more cost-effective than recombinant preparations.

1. Introduction

Assisted Reproductive Technologies (ART) are now widely accepted as clinically effective in the treatment of many forms of infertility and over the last decade the annual increase in ART services as been approximately 5–10% in developed countries (1). Increasing demand for ART is related to increased infertility in modern populations, which may be attributed to couples delaying efforts to get pregnant until they are older and less fertile, sexually transmitted diseases, low sperm counts and the stress of modern daily life.

Despite increasing demand for ART treatments, financial constraints are causing many national healthcare providers and private insurers to limit access in countries where such procedures are provided. Couples are therefore somehow unable to afford ART and, consequently, many patients withdraw from treatment or choose not to pursue treatment because of the costs.

It is therefore of growing importance to limit the cost of each treatment, mainly by reducing the cost of drugs which are widely utilized during the procedure.

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1.1. The economic impact of ART

In most developing countries ART, when available, is restricted for patients who can economically afford them, as government healthcare services are generally inadequate to provide them or are not interested in providing them because infertility is not considered as a priority. Unfortunately, in many of these countries, where the family and the presence of children are of the utmost importance, childlessness often creates social problems for women who are isolated and scarcely considered in their communities (2).

The costs of ART is specific to the healthcare system in each of the countries were the procedure is performed, reflecting the varying degrees of public and private responsibility for purchasing healthcare and total healthcare expenditure. The cost of treatment in the United States, for example, is higher than any other of the major developed countries. This is the result of the high cost of healthcare in the United States in general, with a standard fresh cycle costing $12,513 and a live birth costing $41,132 (3). Although in developing countries the cost per cycle and the cost per live birth are significantly lower than in more developed countries, such treatment is still an out-of-the-pocket expense for the majority of these people. With such a high expenditure in order to achieve results, it appears obvious to focus on whether ART represents a valuable social investment, particularly in cases of limited public health care resources, in other words, if such services are cost-effective.

1.2. Drug effectiveness……

The costs of treatment cycle include ovarian stimulation, ultrasound scanning, sperm preparation, follicular aspiration, embryo transfer, embryology staff and an operating room with an anaesthesiologist. In some cases, the additional cost of cryopreservation of oocytes and embryos counts needs to be added. Additionally, in order to achieve a more precise calculation of costs perinatal care and the impact of multiple births should be accounted for as well.

Based on the available evidence, the cost-effectiveness of IVF depends on four primary factors: experienced or estimated treatment success rates, the age of the woman, multiple pregnancy and the costs of treatment (4).

A detailed analysis of different cost components per treatment cycle demonstrates that the hormonal stimulation stage is the most expensive part of IVF/ICSI cycles (about 60% of the total cost) (5). This percentage could be even higher if we consider older women who have increased costs per cycle than younger women, because of the higher mean dosages of FSH needed during hormonal stimulation. The available evidence suggests a declining effectiveness and increasing cost in older patients which sustains the argument that IVF is cost-ineffective in women aged 40 and older. Therefore, in certain patient populations funding is often restricted by decision-makers.

Recombinant follicle-stimulating hormone (rFSH) was introduced on the market in the beginning of the 1990s as a significant technological improvement in regard to specific activity and purity. Clinical trials suggested that recombinant gonadotrophins were the gold standard for infertility treatment because of their superiority in safety, purity and effectiveness as compared with urinary gonadotrophins (6). However, the more advanced technology used for the preparation of recombinant products was inevitably related to a significantly higher cost of the drug. In the beginning no studies were directed toward a cost-analysis, but emphasized only whether the new preparation was more efficient or effective than the old one. Nevertheless human preparations, such as human follicle-stimulating hormone (hFSH) and human menopausal gonadotrophins (hMG), were and still are widely utilized, particularly in developing countries, where financial support for infertility treatment is markedly limited. The relatively high cost of rFSH, compared with human-derived gonadotrophins, represents a major problem in countries where the patient has to partially or totally pay for the expense of the drugs. However, even in countries where the cost is fully reimbursed by national health services, the high social economic request for infertility drugs is an increasing problem.

The use of more expensive products, however, does not necessarily determine increased total treatment costs and cost-ineffectiveness for healthcare expenditure. There is a possibility that more expensive medications lead to such an improvement of efficacy, or live birth rate, that the total cost per established pregnancy may be significantly reduced.

Currently, there is no a clear evidence of the superiority of rFSH over human gonadotrophins in effectiveness. In terms of clinical efficacy there are a number of meta-analyses demonstrating no significant difference in clinical/ongoing pregnancy/live birth rate, miscarriage rate, multiple pregnancy rate and incidence of ovarian hyperstimulation syndrome between rFSH and hMG (7,8) and between rFSH and hFSH (9). A previously published meta-analysis of recombinant versus human FSH concluded that the pregnancy rate per started cycle was better with rFSH (10). However, in the same study the use of follitrophin alfa did not have an advantage in patients with intracytoplasmic sperm injection (ICSI) compared with urinary products.

Many contradicting results have been reported during the last fifteen years, either considering randomised controlled trials (RCTs), or highly recognised meta-analyses. Problems arise from different outcomes (clinical, ongoing pregnancy rate or live birth rate) in RCTs and from the studies included or excluded from the meta-analysis, possibly altering the results.

1.3. ……and drug cost-effectiveness

It is of extreme importance to develop a system of robust analysis of cost-effectiveness, modelled for each country taking into consideration varying drug costs, but with a similar efficacy in ART results.

To conduct a precise analysis efficacy should be expressed as number of live births per initiated cycle or patient, depending on the randomisation. Average cost per treatment should be based on each of the gonadotrophin treatment options. Cost per live birth for each treatment option is obviously related to the cost of treatment and the efficacy.

Recently Baker et al. compared the efficacy of highly purified hFSH (HP-hFSH) versus rFSH in volunteers undergoing controlled ovarian stimulation for IVF (11). In this report the authors concluded that there were no statistically significant differences in live birth rate between HP-hFSH and rFSH treatment groups (38.2% in each group). If we build a decision tree model of a complete cycle for this study, in which all the probabilities of the procedure are considered (cancelled cycles, pregnancies, deliveries and miscarriages), we could create a

cost-effectiveness analysis calculating the cost for each live birth. Firstly, we need to calculate the cost of the cycle in reference to the Italian Formulary (as HP-hFSH is not yet available in the US market) and we need to multiply the cost of each ampoule of hFSH (€ 18.0) or rFSH (€ 40.5) by the mean number of vials used in the cycle in hFSH and rFSH group, respectively (35.2 and 36.2). The cost of the cycle obtained is significantly lower for the hFSH group (€ 633.8 vs. € 1466.1). The ratio between this cost and the efficacy (live birth rate) is the cost of a single pregnancy, which is significantly lower for the human preparation (€ 1803 in hFSH group and € 4117 in rFSH group).

A further essential parameter to be considered in cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER) expressed as the difference in cost of the two treatment options divided by the difference in number of deliveries per cycle or patient. It represents the cost required to achieve one additional unit of clinical effectiveness (one more live birth) between two different treatment options. In the model we adopted for the Baker trial ICER is € 183,779. In conclusion, depending on cost per live birth and ICER, although hFSH is not more effective than rFSH, it is clearly more cost-effective than the recombinant preparation.

Probabilistic sensitivity analysis should be performed to address uncertainty in the parameters used in the model of the study. To avoid interpretation problems, the so-called cost-effectiveness acceptability curve (CEAC) is used. The CEAC provides the policy-maker with the probability that a certain treatment is cost-effective at different values of the outcome of interest (or levels of willingness to pay). Furthermore, the one-way sensitivity analysis, is adopted to calculate the cost-effectiveness using a range of estimates of pregnancy rate along the confidence intervals and for a range of cost of a preparation.

Referring to the Baker trial we could provide different results of cost-effectiveness either along the variation of pregnancy rate (Fig. 1), or for different costs of cycle with the recombinant preparation (Fig. 2). In the first case there is no pregnancy rate at which rFSH becomes more cost-effective than hFSH, while only for a cost of cycle lower than € 633 with a decrease of more than 55%, the recombinant preparation could be recommended as more cost-effective.

The National Institute for Health and Clinical Excellence (NICE) suggests the use of probabilistic sensitivity analyses,

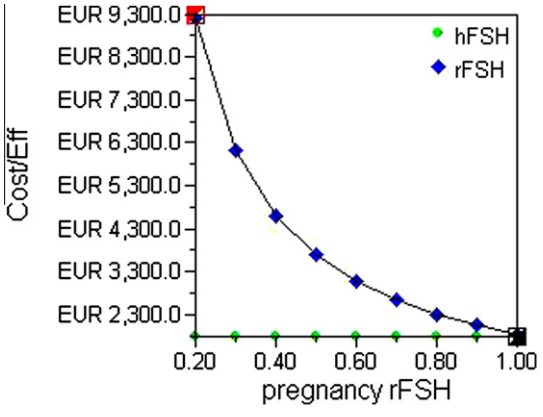

Figure 1 One-way sensitivity analysis of cost-effectiveness ratio on rFSH pregnancy rate referred to Baker et al. (11).

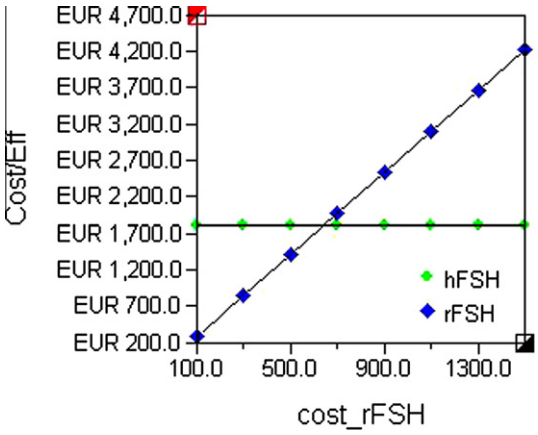

Figure 2 One-way sensitivity analysis of cost-effectiveness ratio on rFSH cost per cycle referred to Baker et al. (11).

with simultaneous variation of all input parameters, because the results obtained using this method are most robust (12).

For IVF/ICSI cycles, the higher cost of one medication over another could be justified if a larger number of mature oocytes are retrieved, a higher fertilization rate is obtained, more numerous high quality embryos are available for transfer or cryopreservation and, more importantly, higher implantation and live birth rates are achieved. In IUI cycles the more expensive product could be justified only if a higher live birth rate is obtained. Furthermore, it is extremely important to quantify the expense of a single protocol including costs of multiple pregnancies and ovarian hyperstimulation syndrome.

There are various reports comparing cost-effectiveness of rFSH and human-derived gonadotrophin (hMG and hFSH), demonstrating the prevalence of one protocol over another, but conflicting results have been obtained.

It is notable that studies of the late 1990s and the beginning of this century tend to demonstrate the prevalence of rFSH (13–15), while the latest studies affirm that human compounds, with similar efficiency and effectiveness, but with a lower price, tend to be more cost-effective (16–19). It cannot be excluded that the first enthusiastic clinical results in favour of rFSH have been now carefully reviewed in the new light of considering a reasonable healthcare expenditure. Recently, more importance has been given to the cost of the preparation with more in-depth and precise studies having been conducted on ART during the last few years.

If we consider intrauterine insemination (IUI) only few reports have been published with such strict criteria and the analyses demonstrate that human compounds, namely hFSH, are more cost-effective than rFSH (20), independently on the type of patients considered (21). To comply with NICE guidelines and to best inform medical decision-makers, uncertainty was addressed by performing a sensitivity analysis: rFSH would represent a more cost-effective alternative only with a higher effectiveness (70% increase), or with a hypothetical reduction of price of 26.5% (20).

Data are accumulating suggesting equivalent or non inferior clinical efficacy and efficiency of human gonadotrophins compared with rFSH in IVF; therefore, costs may influence the number of cycles that patients can afford to achieve the success. This is particularly true if the patient has to support

the total expenditure of the treatment or, even if the cost is covered by the national health care system, if the financial availability is limited. Similarly to IUI, a sensitivity analysis along the variation of rFSH cost, led to the conclusion that an equivalent total IVF cost between human (hMG) and recombinant preparation would be achieved only with a rFSH price reduction of 11.9% (17).

This would suggest that, within a fixed and limited budget, the use of human gonadotrophins could allow additional cycles with an increasing live birth rate per patient, which is in the end the major goal of our treatment.

2. Conclusions

In conclusion we believe that the use of ART has had relevant economic implications in general. Results deriving from cost-effectiveness studies have had some important medical and social consequences, either when the patient has to pay out of her own pocket the cost, or when the expenditure is partially or totally covered by the national healthcare system. Application of such results to ART may assist policy-makers, managers, clinicians and patients to adopt certain decisions on treatment or protocols, instead of another. With the final aim of achieving a high live birth rate, with a safe treatment, with less complications, in a minimum time, with the least amount of cost expenditure. Currently, human gonadotrophins seem to respect these characteristics more than recombinant preparations, but further cost-analysis are strongly encouraged to support this statement.

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