Cost-saving treatment strategies in in vitro fertilization: a combined economic evaluation of two large randomized clinical trials comparing highly purified human menopausal gonadotropin and recombinant follicle-stimulating hormone alpha

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Objective: To assess the cost-effectiveness of two gonadotropin treatments that are available in the United Kingdom in light of limited public funding and the fundamental role of costs in IVF treatment decisions.
Design: An economic evaluation based on two large randomized clinical trials in IVF patients using a simulation model.
Setting: Fifty-three fertility clinics in 13 European countries and Israel.
Patient(s): Women indicated for treatment with IVF (N = 986), aged 18–38, participating in double-blind, randomized controlled trials.
Intervention(s): Highly purified menotropin (HP-hMG, Menopur) or recombinant follitropin alpha (rFSH, Gonal-F).
Main Outcome Measure(s): Cost per IVF cycle and cost per live birth for HP-hMG and rFSH alpha.
Result(s): HP-hMG was more effective and less costly versus rFSH for both IVF cost per live birth and for IVF cost per baby (incremental cost-effectiveness ratio was negative). The mean costs per IVF treatment for HP-hMG and rFSH were £2408 (95% confidence interval [CI], £2392, £2421) and £2660 (95% CI £2644, £2678), respectively. The mean cost saving of £253 per cycle using HP-hMG allows one additional cycle to be delivered for every 9.5 cycles.
Conclusion(s): Treatment with HP-hMG was dominant compared with rFSH in the United Kingdom. Gonadotropin costs should be considered alongside live-birth rates to optimize outcomes using scarce health-care resources. (Fertil Steril® 2009;91:1067–76. ©2009 by American Society for Reproductive Medicine.)

Key Words: Economic evaluation, cost-effectiveness, modeling, gonadotropins, in vitro fertilization, menotropin, recombinant FSH

In industrialized countries, an estimated 17% of couples seek medical advice for infertility (1). The lifetime prevalence of infertility in the United Kingdom (UK), defined as at least 1 year of unsuccessful attempts to conceive, has been reported to range between 17.3% and 26.4% (2, 3). Treatment for infertility has a very good prognosis, with 80%–90% of couples being successful after 1 year and 95% after 2 years (4).

In addition to proven effectiveness, in many markets, to qualify for reimbursement, treatments must meet rigorous economic criteria of cost-effectiveness. In light of the increasing demand for health care across all areas, health-care providers often resort to rationing as a means of controlling costs; such rationing often disregards evidence on relative cost-effectiveness of treatment options. In many markets, including the UK, treatment of infertility is an easy target for budget cutting because it is often viewed as a low health priority (5). Based on best available efficacy and cost-effectiveness evidence, the National Institute for Health and Clinical Excellence (NICE) recommends that up to three cycles should be reimbursed (6). Despite NICE's recommendation, in practice approximately only 25% of cycles are funded by the National Health Service (NHS) (7).

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The results of this study were presented in an abbreviated format at the European Society for Human Reproduction and Embryology meeting, which was held in Lyon, France, in July 2007.
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As a consequence of rationing within the NHS, the UK ranks among the lowest in Europe for provision of IVF when compared with countries such as Belgium and Denmark, which have more generous state funding (8). Furthermore, because of the relationship between a couple's ability to pay and access to infertility treatment, it is likely that many infertile couples do not seek or discontinue treatment because of limited financial resources (9, 10). When the macro aspects of infertility and assisted reproductive technologies (ART) treatment are considered, as in two recent studies, it is conceivable that access barriers, financial or legislative, which prohibit couples from seeking treatment can have a small but meaningful long-term demographic impact (11, 12).

A critical component in economic evaluations is the clinical outcomes data on which cost-effectiveness claims are made. Accumulating data now show that treatment outcome differs significantly depending on the gonadotropin chosen. As previously reported by the European and Israeli Study Group (EISG), patients treated with either highly purified (HP) hMG or recombinant FSH (rFSH) achieved similar ongoing pregnancy rates (13). A subsequent analysis of the EISG IVF cohort demonstrated that patients receiving HP-hMG achieved a statistically significant (P=.037) higher ongoing pregnancy rate (31%) than patients receiving rFSH (20%) (14). An integrated analysis of the EISG and menotrophin versus recombinant FSH in vitro fertilization trial (MERiT) studies that was reported in an article by Sørensen et al. and in an earlier article by Platteau et al. demonstrated significantly higher live-birth rates of 27% with HP-hMG compared with 21% with rFSH (odds ratio [OR] = 1.36; 95% confidence interval [CI], 1.01–1.83; P=.04) (15). Additionally, a recent meta-analysis by Al-Inany et al. (16) has shown that there is a statistically significant increase in live-birth rate with patients treated with hMG compared with rFSH (P<.05). In clinical terms, this translates into a number needed to treat (NNT) to get an additional live birth with hMG versus rFSH of 23 (95% CI, 11–200) for a 25% baseline chance of live birth with IVF.

Because of the need to optimize outcomes with limited financial resources, it is important to consider the costs of all elements of the treatment options. One possible variation in IVF costs can be attributed to different gonadotropin regimes. Previous studies have explored the cost-effectiveness of ART using a variety of different clinical parameters and assumptions (17). Cost-effectiveness of recombinant and urinary FSH has been compared (18–24), and one study included urinary hMG as an additional comparator (21). Urinary hMG and its highly purified preparation were analyzed jointly in comparison with rFSH for ovulation induction (25). HP-hMG alone was compared with rFSH, but the analysis combined IVF and intracytoplasmic sperm injection (ICSI) patients (26). Of all identified economic studies involving HP-hMG, only one was based on patient-level data from a randomized trial (27), and in one, efficacy data were extracted from a meta-analysis (24). While many studies reported cost per clinical or ongoing pregnancy (18, 19, 22–26, 28), cost per live birth or per baby was addressed less frequently (29) and mainly in studies not involving comparison of gonadotropins (27). No report of cost per live birth after stimulation with HP-hMG has been identified in published sources. Only one study involving HP-hMG and rFSH was conducted in the UK setting, although it was not specific to IVF patients (26). Our previous study comparing HP-hMG and rFSH in IVF patients in the UK setting was a cost-minimization analysis (27) based on one clinical trial only (30). Pooling of two large randomized controlled trials (RCTs) allowed us to conduct the first analysis of live-birth rates after stimulation with the two gonadotropins and of the related costs in IVF patients in the UK.

Existing economic evidence suggests that cost savings could be achieved by using HP-hMG. Based on a randomized clinical trial, menotropin was found to be less expensive per cycle in the UK when compared with rFSH, allowing 13% more cycles to be offered (13, 26). A recent study based on a simulation model using outcomes from an RCT demonstrated cost-savings resulting from using HP-hMG instead of rFSH (27, 30). Menotropin was also found to be cost saving compared with rFSH in a model based on a meta-analysis of clinical trials (25).

As new clinical data become available, it is common practice to update economic evaluations to incorporate new efficacy results, while adjusting resource use and changes in costs. Therefore, our study is based on the two RCTs involving IVF patients treated with HP-hMG or rFSH with cost per live birth as the primary outcome in the analysis. Since new adequately powered trials of gonadotropins in subfertile patients are unlikely to be conducted, pooling of results from existing trials remains a valuable and informative technique (31).

Decision analytic models are commonly used to evaluate treatments for which sufficient cost data have not been collected alongside clinical trials (32). Ideally, prospective clinical trials should be conducted to determine both efficacy and costs, but the value and feasibility of such approach is limited in multiple multistep interventions, such as assisted reproduction (28); therefore modeling enables representation of each stage and cycle of the treatment process and unbiased assessment of health outcomes and resource use. We employed state-of-the-art simulation modeling to combine best available costs and efficacy evidence.

MATERIALS AND METHODS

Overview

An economic evaluation comparing HP-hMG (Menopur; Ferring Pharmaceuticals, St. Prex, Switzerland) and rFSH (follitropin alpha; Gonal-F, Merck Serono, Geneva, Switzerland) was conducted based on a discrete event simulation (DES) model. The objective of the study was to determine the following: