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ORIGINAL RESEARCH

# Economic evaluation of highly purified human menopausal gonadotropin versus recombinant human follicle-stimulating hormone in fresh and frozen in vitro fertilization/intracytoplasmic sperm-injection cycles in Sweden



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Jaro Wex
Ahmed M Abou-Setta

PharmArchitecture, London, UK

**Abstract:** Gonadotropin-releasing hormone-analog type, fertilization method, and number of embryos available for cryopreservation should be incorporated into economic evaluations of highly purified human menopausal gonadotropin (HP-hMG) and recombinant human follicle-stimulating hormone (r-hFSH), as they may affect treatment costs. We searched for randomized trials and meta-analyses comparing HP-hMG and r-hFSH. Meta-analysis showed no significant difference in live births (odds ratio 0.82, 95% confidence interval [CI] 0.66–1.01), but a greater number of oocytes with r-hFSH (mean difference [MD] 1.96, 95% CI 1.02–2.90). Using a cost-minimization model for Sweden, accounting for embryo availability, survival following thawing, and patient dropout, we simulated patients individually for up to three cycles. R-hFSH was found to be cost-saving, at 2,767 kr (95% CI 1,580–4,057) per patient (€315 or $411); baseline savings were 6.43% of the total HP-hMG cost. In fresh cycles only, the savings for r-hFSH were 1,752 kr (95% CI 48–3,658) per patient (€200 or $260). In univariate sensitivity analyses, savings were obtained until the price of r-hFSH increased by 30% or the dosage of HP-hMG decreased by 38%–62% of baseline value. In probabilistic sensitivity analysis, r-hFSH was cost-saving in 100% of the simulated cohort per patient and in 85% per live birth; the respective percentages for fresh cycles only were 97.3% and 73.1%. In conclusion, a greater number of oocytes with r-hFSH allows for more frozen embryo transfers, thereby reducing overall treatment cost.

**Keywords:** recombinant human FSH, highly purified menopausal gonadotropin, meta-analysis, economic analysis, in vitro fertilization, cryopreservation

## Introduction

Gonadotropins, commonly used in modern assisted reproduction, differ according to their source and amount of luteinizing hormone (LH) activity.[1] Highly-purified human menopausal gonadotropin (HP-hMG) uses human chorionic gonadotropin to provide the LH activity. Recombinant human follicle-stimulating hormone (r-hFSH), on the other hand, has no intrinsic LH activity.

Numerous clinical trials and systematic reviews have shown comparative live-birth rates for HP-hMG and r-hFSH in women undergoing standard in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), also reporting higher numbers of oocytes retrieved with r-hFSH.[2–4] Even so, cumulative live-birth rates per started fresh cycle are rarely reported, due to short patient follow-up periods and high attrition rates

Correspondence: Jaro Wex
PharmArchitecture, 145-157 St John Street, London EC1V 4PY, UK
Tel +44 2030 511 424
Fax +44 2030 511 435
Email jaro.wex@pharmarchitecture.com

after the completion of the fresh IVF/ICSI cycle. This is troubling, because live-birth rates per started fresh cycle are strongly associated with the number of embryos available for transfer, and hence the number of oocytes retrieved,[5] implying that outcome of stimulation in a fresh cycle could affect cumulative success rates of the treatment. Additionally, it has been demonstrated that success rates may differ according to the fertilization method (IVF versus ICSI)[3,6] and type of gonadotropin-releasing hormone analog (GnRH) used.[7]

Evidence on the effectiveness of treatments consisting of both fresh and frozen embryo transfer (FET) cycles is scarce and incomplete. It has been established that frozen cycles are associated with lower success rates,[8,9] although this difference may be attributed to confounding factors: frozen cycles are typically not the first cycles women undertake, and effectiveness declines with successive failed attempts. A recent review found no significant differences between r-hFSH and urinary gonadotropins in frozen cycles,[10] although it included only two trials comparing r-hFSH and HP-hMG: one reporting live-birth rates after fresh transfer[11] and one reporting cumulative live-birth rates.[12] Even so, the routine use of FET in general has been demonstrated to increase overall live-birth rates. In the UK, FET was found to increase the cumulative live-birth rate by nearly 16%.[13]

In addition, the trend towards single-embryo transfers (SETs) rather than double-embryo transfers (DETs) has a bearing on the cumulative success rates. Even though SET has been demonstrated to be less effective than DET on a per-cycle basis, there seems to be no significant difference between one cycle with DET and two cycles with SET.[14] Also, based on individual patient data from eight trials (n = 1,367), the live-birth rate in additional frozen SETs contributed to a cumulative live-birth rate not significantly lower than the rate after one fresh DET (38% vs 42%), with a minimal risk of multiple gestations and a higher chance of delivering a term singleton live birth compared with DET.[15,16] Simulation studies also suggest that if all good-quality embryos are replaced over multiple FETs, repeated SET has the potential to produce more live births than repeated DET.[17]

In IVF-treatment programs with embryo cryopreservation, up to 42% of all implantations were able to be derived by FET,[18] and FET procedures contribute an additional 25%–50% chance of pregnancy for those couples who have embryos cryopreserved.[19,20] With advances in embryo cryopreservation, live-birth rates associated with FETs have nearly doubled over the past decade,[21] thus making combinations of fresh and frozen cycles even more dependent on the availability of supernumerary embryos. From an economic standpoint, as the use of FET can markedly contribute to the overall success of IVF/ICSI cycles,[22] it can decrease the overall cost of treatment per live birth.

In light of the evidence on the importance of the number of oocytes retrieved, the method of oocyte fertilization, and GnRH analog used, economic comparisons of different gonadotropin preparations should incorporate not only evidence on standard IVF and ICSI separately but also according to the stimulation protocol (GnRH long agonist vs GnRH antagonist). Moreover, they should model the effect of FET and dropout rates on the cumulative live-birth rate rather than limiting the analyses to fresh cycles only.

## Methods

In order to assess the efficacy of HP-hMG and r-hFSH, we designed a rapid literature review of evidence on women undergoing IVF/ICSI.[23,24] Numerous reviews have been conducted to provide evidence for this comparison, including a recent Cochrane systematic review comparing urinary and recombinant gonadotrophins.[25] The Cochrane review was not deemed to be specifically suitable for the purpose of this study's analyses, as it combined studies using hMG or HP-hMG, did not report separately on GnRH agonist/antagonist protocols in IVF and ICSI, and used a composite-outcome measure of ongoing pregnancy or live births. Even so, we did use it to identify previously known trials and reran the search to include evidence from randomized trials not available at the time of the Cochrane review.

In brief, trials with patient populations consisting of women undergoing IVF or ICSI and randomized to HP-hMG or r-hFSH were eligible for inclusion. We conducted updated electronic searches for trials in Medline, Embase, and Central using the following keywords, and a modified version of the Cochrane highly sensitive search strategy: FSH, follicle-stimulating hormone, recombinant, hMG, and human menopausal gonadotropin/gonadotropin. Trials including women undergoing transfer from donor oocytes or embryos were excluded. All dosages and durations of gonadotropins were included, in order to truly represent the variability of clinical protocols. We extracted and meta-analyzed data on live births according to the protocol used (GnRH long agonist/IVF, GnRH long agonist/ICSI, GnRH antagonist/IVF, and GnRH antagonist/ICSI). We meta-analyzed the number of oocytes retrieved separately for GnRH-agonist and GnRH-antagonist protocols. For the meta-analyses, odds ratios less than one and mean difference less than zero favored HP-hMG and vice versa.

The intention of this study was to combine fresh and frozen cycles based on the availability of frozen embryos,

hence comparative data on numbers of embryos available for freezing were also sought. However, even though studies reported numbers of embryos transferred, available information on additional embryos was inadequate. Therefore, in order to model treatment pathways, the number of oocytes retrieved was used as a proxy for the number of embryos available for transfer. To account for embryo-quality criteria required for transfer or cryopreservation, a literature review was conducted to identify source data on the number of good-quality embryos as a percentage of the number of oocytes retrieved. Only one such study involving HP-hMG and r-hFSH was identified.[26]

Each patient was simulated individually through up to three cycles, accounting for the availability of good-quality embryos for transfer. The number and quality of available embryos determined whether frozen transfer would take place and whether there would be supernumerary embryos available for cryopreservation. We assumed that if good-quality frozen embryos were available after thawing, frozen transfer would be performed; if not, then a new fresh cycle would begin. The percentage of patients with embryos surviving freezing/thawing was calculated as 90%, from the most recent Swedish registry data.[27] The number of embryos transferred (SET vs DET) was also sampled based on the Swedish registry data. Dropout rates following each cycle were also factored into the model. In addition, we assumed that following a live birth, women would not undergo additional treatments.

To model success rates in women starting IVF/ICSI treatment and control for possible selection bias, we sought to identify clinical evidence from studies on women who had not been treated previously, and separately for the first, second, and third cycles. Among the reports included in the review, only one relatively small study (n = 127) provided live-birth data on patients who had not undergone IVF/ICSI prior to randomization,[28] in women undergoing an IVF GnRH-agonist cycle. Therefore, we used data from a prospective cohort study conducted in Norway (n = 1,136)[29] as the source for the base-case economic evaluation.

As neither the data from the Norwegian cohort study nor meta-analyses of any of the four stimulation protocols reported significant differences for live-birth rates, equal effectiveness was assumed and cost-minimization analysis was conducted. To allow Swedish-specific calculation of cost per live birth and utilize crucial data on success rates after SET and DET, the evaluation was based on the most recent success-rate data from the 2010 Swedish IVF registry (Table 1).[27]

**Table 1** Numbers of cycles and success rates per embryo transfer in IVF and ICSI used as evidence base

| | IVF | ICSI | IVF+ICSI | % IVF |
|---|---|---|---|---|
| SET | 3,634 | 3,392 | 7,026 | 51.72% |
| DET | 1,088 | 1,476 | 2,564 | 42.43% |
| SET+DET | 4,722 | 4,868 | 9,590 | 49.24% |
| % SET | 76.96% | 69.68% | | |
| % DET | 23.04% | 30.32% | | |
| | 100.00% | 100.00% | | |
| | **Fresh IVF** | **Fresh ICSI** | **Frozen IVF+ICSI** | |
| Live births per SET | 28.06% | 27.81% | 21.10% | |
| Live births per DET | 25.62% | 25.82% | 22.10% | |

**Abbreviations:** IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SET, single-embryo transfer; DET, double-embryo transfer.

To account for the entire population of patients, we chose the registry success rates. Since the registry combines outcomes from all cycles in a sequence, we also analyzed an additional scenario with success rates adjusted for decreasing effectiveness in subsequent cycles. In this scenario, success rates in individual cycles 2 and 3, relative to cycle 1, were modeled as 88% (23%/26%) and 72% (19%/26%), respectively.[30] We attributed mean success rates to cycle 2 and multiplied those for cycle 1 by 1.13 (26%/23%) and for cycle 3 by 0.82 (19%/20%), to reflect relative effectiveness with cycle 1 the most and cycle 3 the least effective. In the base-case scenario, all three cycles were assumed to have the mean success rates from the registry.

The mean number of oocytes retrieved was obtained from the Norwegian cohort study comparing HP-hMG versus r-hFSH,[29] where the advantage of r-hFSH was found to be smaller than in the meta-analysis. For this reason, and also to model only patients with no prior treatments, the cohort study data rather than the meta-analysis results were used for the number of oocytes retrieved. Individual variation in the number of oocytes retrieved was modeled as a Poisson distribution based on the reported mean numbers of oocytes and validated by expert opinion based on distributions of oocyte numbers from a clinical trial[2] and Human Fertilisation and Embryology Authority (HFEA) data from the UK.[31]

The number of embryos available for transfer or freezing was obtained indirectly based on the percentage of oocytes retrieved. This link between oocytes retrieved and embryos was reported by Ziebe et al,[11] accounting for embryo-quality criteria: minimum quality and top quality. The authors defined the minimum embryo quality as four or more blastomeres on day 3, while top-quality embryos had seven or more blastomeres, both with ≤20% fragmentation. Based on local expert opinion, in Swedish practice

six cells are required to meet minimum quality standards, while good-quality embryos are required to have eight cells, also with the same fragmentation criterion. It has also been reported that only embryos with at least seven blastomeres on day 3 and ≤20% fragmentation were used for cryopreservation,[32] meeting the top quality criteria from Ziebe et al. As according to expert opinion, in 90% of SET procedures only good- or top-quality embryos are used, the figures corresponding to top-quality embryos from Ziebe et al were used for SET: 11.3% and 9.0% for HP-hMG and r-hFSH, respectively. In DET, however, good- and top-quality embryos are used in only 10% of cycles, hence the numbers of embryos of minimum quality from Ziebe et al were used: 36.4% and 33.9%, respectively.

It was assumed that if a patient is treated with IVF in the first cycle, IVF would also be offered in subsequent cycles, with no option for switching. Also, if a patient was treated with SET in cycle 1, SET would also be modeled in cycles 2 and 3. Dropout rates after the first and second cycles were taken from an analysis of 4,102 cycles from the German IVF registry,[33] as Swedish dropout data were not available.

Drug market prices were provided by Merck Serono Sweden.[34] Cost of Gonal-F (Merck Serono, Darmstadt, Germany) formulation accounting for at least 90% of the market share (900 IU) was used along with the corresponding formulation of Menopur (1,200 IU; Ferring Pharmaceuticals, Copenhagen, Denmark) (Table 2). Cost per IU was the basis for costing. As this was a cost-minimization analysis, only costs of gonadotropins were considered, assuming the cost of other resources to be identical or captured by treatment tariffs that do not differentiate between stimulation protocols.

**Table 2** Costs and formulations of gonadotropins used in the study. Menopur was HP-hMG and Gonal-F was r-hFSH used in the analyses

| Gonadotropins | Menopur syringe | Gonal-F pen |
|---|---|---|
| Drug price per package | 3,534.00 kr | 3,599.50 kr |
| Drug amp per package | 1 | 1 |
| Drug IU per amp | 1,200.00 kr | 900.00 kr |
| Gonal-F/Menopur cost per 1 IU | 2.95 kr | 4.00 kr |
| Used price per 1 IU | 2.95 kr | 4.00 kr |
| Dose IVF | 2,197 IU | 1,959 IU |
| Drug cost per IVF cycle | 6,470.17 kr | 7,834.91 kr |
| Dose ICSI | 2,319 IU | 1,845 IU |
| Drug cost per ICSI cycle | 6,829.46 kr | 7,378.98 kr |

**Notes:** Gonal-F is a registered trademark of Merck Serono, Darmstadt, Germany; Menopur is a registered trademark of Ferring Pharmaceuticals, Copenhagen, Denmark.

**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotropin; r-hFSH, recombinant human follicle-stimulating hormone; IU, international unit; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

As no first-cycle-specific data were available from the literature review, gonadotropin use for both IVF and ICSI was obtained from the observational study by Bjercke et al.[29] A recent meta-analysis[35] reported the same difference for drug use as found in the registry study for IVF (235 IU vs 238 IU, respectively, $P = 0.03$), but the former did not report data for IVF and ICSI separately, hence the observational data were used instead. Treatment length in days was also obtained from this study[29]: 11.4 days for HP-hMG and 10.8 days ($P = 0.008$) for r-hFSH in IVF; 12.3 and 10.9 days for ICSI ($P = 0.0001$), respectively. No convenience/utility advantage or reduction in drug wastage with the Gonal-F pen device compared to syringe injections was considered in the analysis.

Cost calculations were based on costs of drugs and costs of procedures. Costs of procedures were derived as the difference between total costs of treatment and costs of drugs. Costs of treatment were based on tariffs from two public and two private infertility treatment centers (Table 3). Costs were calculated both for public and private centers, and averages from four fertility centers were used.

Costs of procedures were used to calculate the cost differential associated with longer duration of treatment for HP-hMG. It was assumed that longer treatment increases the average costs of treatment minus costs of gonadotropins proportionately, rather than costs of any specific procedures; disaggregated cost-of-treatment data were not available. The input variables are shown in Table 4. The perspective was that of the payer, public or private. Only direct medical costs encompassed by the tariff price were considered. Even though difference in treatment length was accounted for in the calculation, it was conservatively assumed that difference in nonmedical, indirect costs and societal costs would be negligible. Incremental cumulative values were calculated

**Table 3** Costs of IVF and ICSI procedures for two public and two private centers used in the analyses

| | |
|---|---|
| Private treatment cost | |
| IVF 1 | 32,000.00 kr |
| IVF 2 | 24,000.00 kr |
| ICSI 1 | 35,000.00 kr |
| ICSI 2 | 24,000.00 kr |
| FET 1 | 8,000.00 kr |
| FET 2 | 10,000.00 kr |
| Public treatment cost | |
| IVF/ICSI 1 | 33,808.00 kr |
| IVF/ICSI 2 | 26,816.00 kr |
| FET 1 | 8,006.00 kr |
| FET 2 | 8,543.00 kr |

**Abbreviations:** IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; FET, frozen embryo transfer.

**Table 4** Other input variables and assumptions incorporated in the model

| Variable | Value | Study | Comments |
|---|---|---|---|
| Oocytes retrieved, IVF HP-hMG | 8.7 | Bjercke et al[29] | Ziebe et al[11] reported greater difference in IVF, but did not report on ICSI (10.0) |
| Oocytes retrieved, IVF r-hFSH | 10.3 | Bjercke et al[29] | Ziebe et al[11]: 11.8 |
| Oocytes retrieved, ICSI HP-hMG | 8.92 | Bjercke et al[29] | |
| Oocytes retrieved, ICSI r-hFSH | 11.21 | Bjercke et al[29] | |
| Min quality embryos (% oocytes) IVF HP-hMG | 36.4% (DET), 11.3% (SET) | Ziebe et al[11] | Four or more blastomeres on day 3, ≤20% fragmentation. In Swedish practice, six cells are required and also ≤20% fragmentation |
| Min quality embryos (% oocytes), IVF r-hFSH | 33.9% (DET), 9.0% (SET) | Ziebe et al[11] | As above |
| Success-rate decrement in the 2nd fresh cycle | 0% | Croucher et al[30] | Only used in alternative scenarios |
| Success-rate decrement in the 3rd fresh cycle | 0% | Croucher et al[30] | Only used in alternative scenarios |
| Success-rate decrement in the 2nd frozen cycle | 0% | Assumed, based on Croucher et al[30] | Only used in alternative scenarios |
| Success-rate decrement in the 3rd frozen cycle | 0% | Assumed, based on Croucher et al[30] | Only used in alternative scenarios |
| % embryos of min (good) quality available for transfer after thawing | 89.79% | IVF registry | Compared to 92.98% surviving vitrification and 75.86% surviving slow freeze (Bernal et al[73]) |
| Dropout rate before the 2nd fresh cycle | 39.30% | Schröder et al[33] | |
| Dropout rate before the 2nd frozen cycle | 19.65% | Verberg et al[74] | Based on mild vs conventional stimulation (half the dropout before fresh cycles) |
| Dropout rate before the 3rd fresh cycle | 44.10% | Schröder et al[33] | |
| Dropout rate before the 3rd frozen cycle | 22.05% | Verberg et al[74] | As above |
| Drug dosage increase in the 2nd cycle (not used in baseline scenario) | 20.51% | Croucher et al[30] | Used only in alternative scenarios. Based on hMG, assumed the same would apply for other drugs |
| Drug-dosage increase in the 3rd cycle (not used in baseline scenario) | 33.33% | Croucher et al[30] | As above |

**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotropin; r-hFSH, recombinant human follicle-stimulating hormone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SET, single-embryo transfer; DET, double-embryo transfer.

per patient starting treatment and per live birth for combinations of one, two, and three fresh and frozen cycles. As IVF and ICSI cycles are approximately 30 days in duration and up to three fresh treatment cycles can be completed within the course of a single year,[13] no discounting was applied in the analyses.

In the model, each patient was simulated individually, accounting for distribution of oocytes retrieved. The cohort of 10,000 patients was deemed sufficient for results to remain robust after the model was tested for convergence. Variation in individual simulations of public and private centers was comparable to variation between public and private centers. For this reason, even though only results from public centers are reported in detail, the findings are applicable to both settings. The results were reported as live-birth rates, costs per patient starting treatment program, and cost per live birth.

Due to the relative simplicity of the modeling approach, dictated by the paucity of direct evidence, we addressed uncertainty in a series of scenario analyses, univariate sensitivity analyses, and probabilistic sensitivity analyses (PSAs). To address combined uncertainty associated with input variables, we varied all uncertain values by 20%. The following variables were included in the PSAs: number of oocytes retrieved, number of minimum-/good-quality embryos, percentage of embryos surviving cryopreservation, success rates, dropout rates, drug dosage, and treatment length. Uniform distributions were used for sampling to account for maximum uncertainty, and all variables were treated as independent, assuming no correlation. PSA was run separately for treatments with fresh and frozen cycles, depending on availability of frozen embryos and for treatment with fresh cycles only.

# Results

## Effectiveness

Meta-analyses of data derived from the included randomized trials demonstrated no significant difference between r-hFSH and HP-hMG regarding live-birth rate for the different stimulation protocols and choice of fertilization with standard IVF or ICSI: GnRH-agonist IVF (odds ratio [OR] 0.74, 95% confidence interval [CI] 0.54–1.01), GnRH-agonist ICSI (OR 0.85, 95% CI 0.39–1.87), and GnRH-antagonist ICSI (OR 0.91, 95% CI 0.66–1.25) (Figure 1). Similarly, when the data were combined, the difference was not significant (OR 0.82, 95% CI 0.66–1.01). The number of oocytes retrieved was significantly greater in patients receiving r-hFSH compared to HP-hMG, both for GnRH-agonist (mean difference [MD] 1.89, 95% CI 0.76–3.02) and GnRH-antagonist (MD 2.16, 95% CI 0.74 to 3.59) protocols, and for combined data (MD 1.96, 95% CI 1.02–2.90) (Figure 2).

For the cohort of 1,000 patients undergoing up to three fresh or frozen cycles depending on frozen availability, the simulations produced no difference in live-birth rates: 44.62% (95% CI 43.64%–45.60%) vs 44.64% (43.66%–45.62%) for HP-hMG and r-hFSH, respectively. No differences were found between the comparators in individual treatment cycles when fresh and frozen transfers were combined. When fresh and frozen transfers in cycles 2 and 3 were analyzed separately, r-hFSH was associated with more frozen transfers and HP-hMG with more fresh transfers; the difference was significant in cycle 2 for both fresh and frozen and in cycle 3 for frozen transfers only (Figure 3).

In simulation with only fresh transfers available, no difference in effectiveness of treatments consisting of up to three cycles was found: 43.28% (95% CI 42.32%–44.26%) for HP-hMG and 42.58% (95% CI 41.61%–43.56%) for r-hFSH. Similarly, there was no difference in individual cycles 1–3 (Figure 4).

## Costs

Economic simulations showed that using r-hFSH is cost-saving compared to HP-hMG in a combination of fresh and frozen IVF and ICSI cycles in Sweden, with 43,030 kr for HP-hMG and 40,263 kr for r-hFSH, saving 2,767 kr (95% CI 1,580–4,057) per patient starting treatment. The savings were

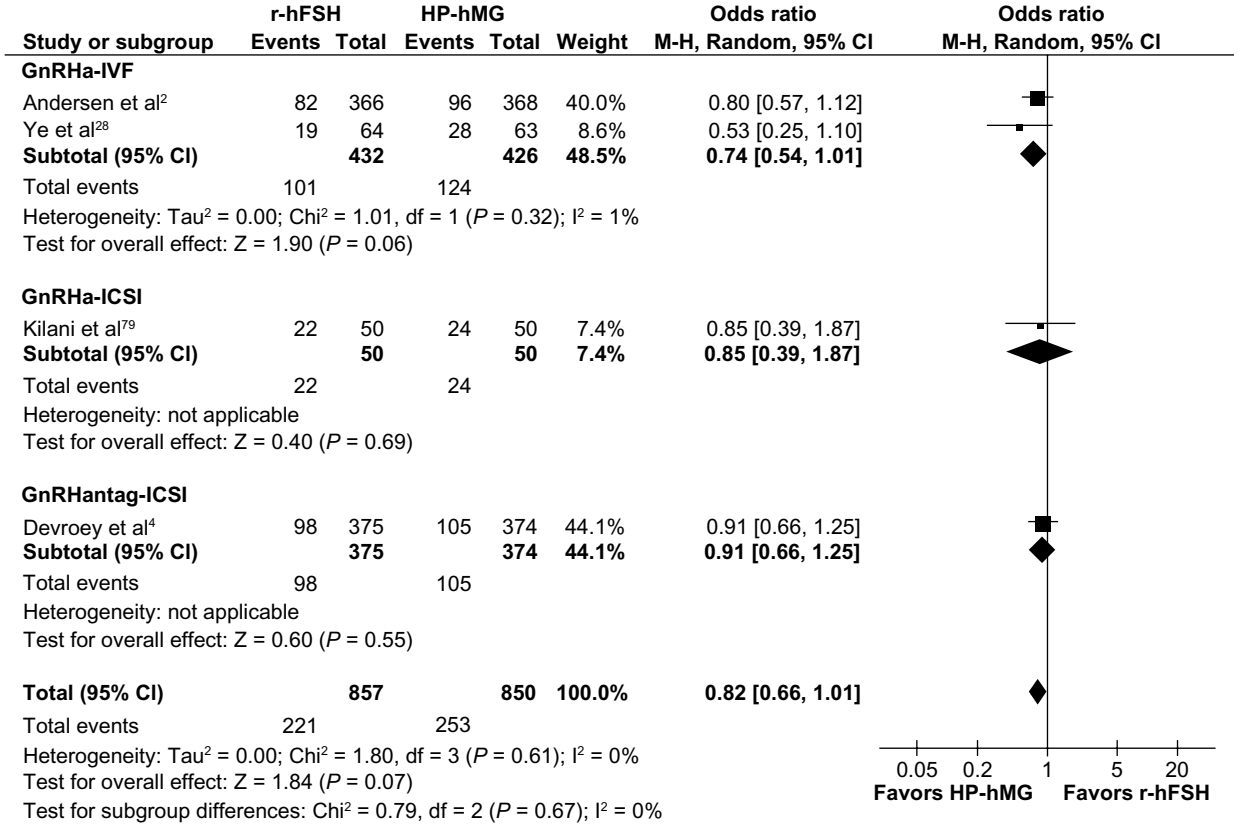


**Figure 1** Live-births for HP-hMG versus r-hFSH by stimulation protocol and IVF/ICSI procedure.
**Note:** Odds ratios are derived by a random-effects model using Mantel–Haenszel (M-H) tests.
**Abbreviations:** CI, confidence intervals; df, degrees of freedom; HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone; GnRHa-IVF, gonadotrophin releasing hormone agonists in IVF; GnRHa-ICSI, gonadotrophin releasing hormone agonists in ICSI; GnRHantag-ICSI, gonadotrophin releasing hormone antagonists in ICSI; Z, Z-test of the null hypothesis.

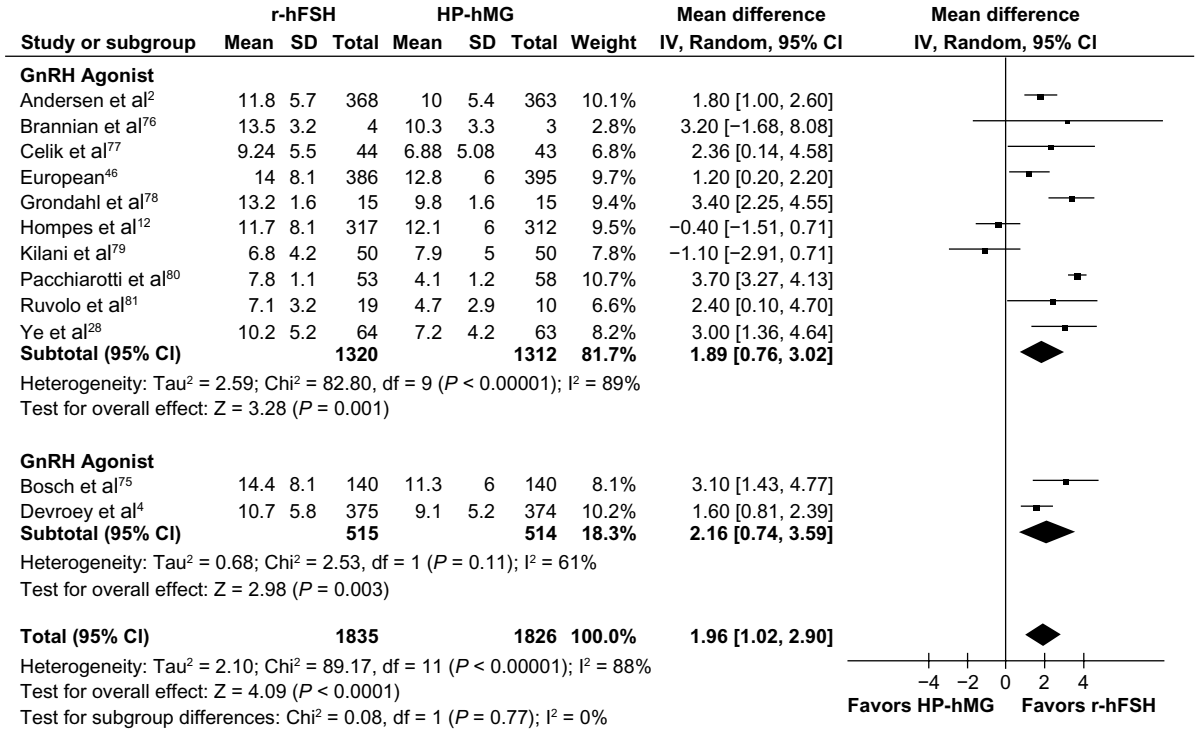


**Figure 2** Number of oocytes retrieved for HP-hMG versus r-hFSH by stimulation protocol.
**Note:** Mean differences are derived by a random-effects model using Inverse Variance (IV) tests.
**Abbreviations:** CI, confidence intervals; df, degrees of freedom; HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone; SD, standard deviation; IV, inverse variance; GnRH, gonadotrophin releasing hormone; Z, Z-test of the null hypothesis.

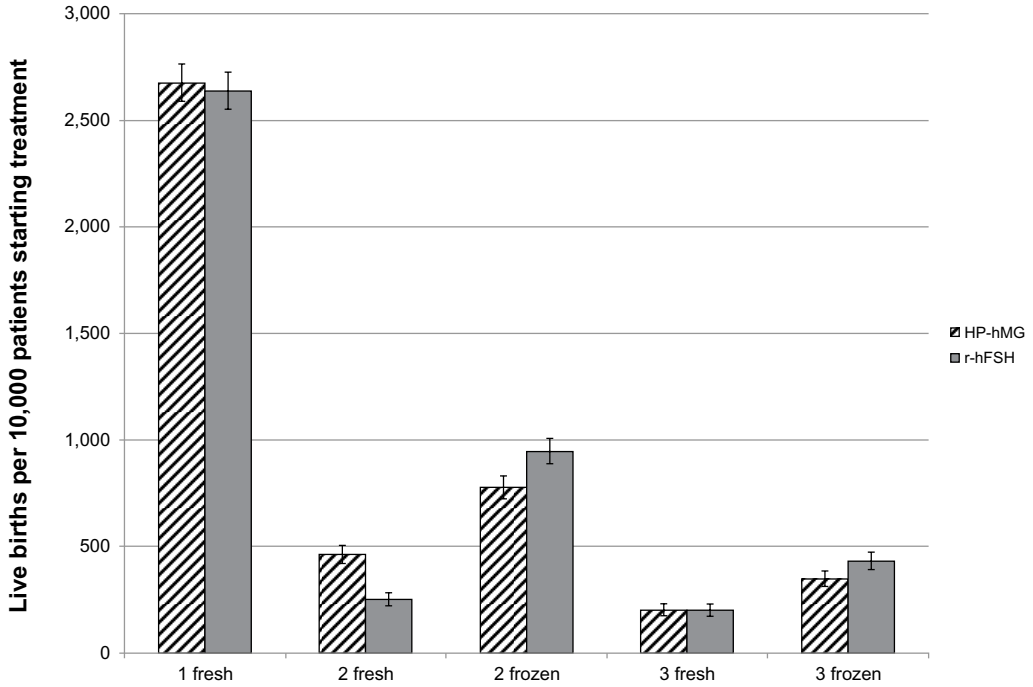


**Figure 3** Live deliveries per 10,000 patients starting treatment in combinations of fresh and frozen cycles based on embryo availability. Results disaggregated by fresh and frozen transfers.
**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone.

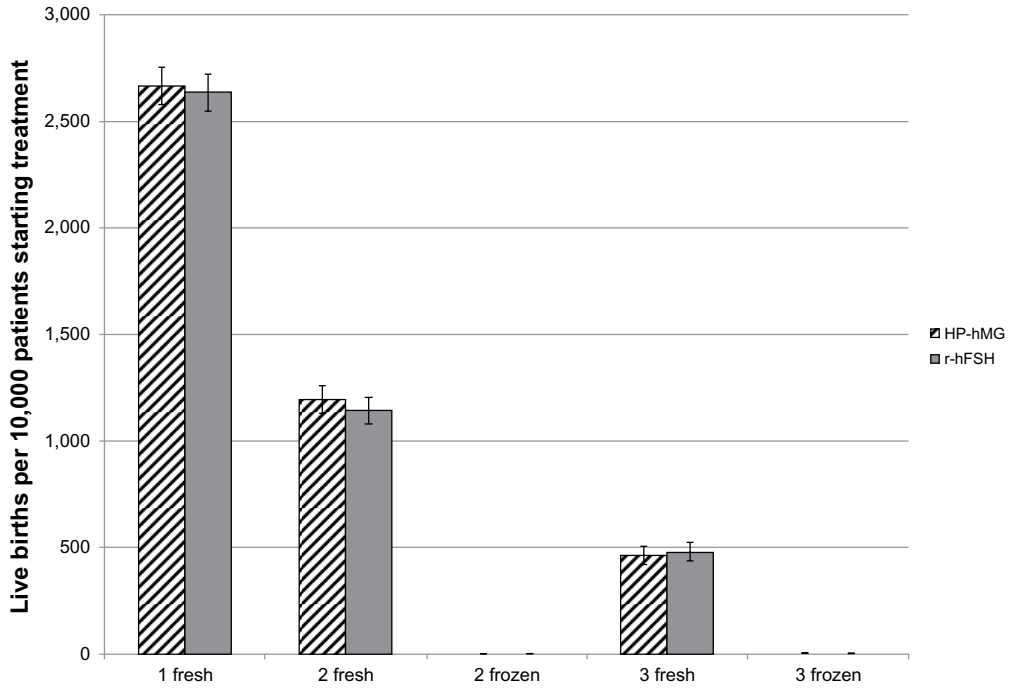


**Figure 4** Live births per 10,000 patients starting treatment in fresh cycles only based on embryo availability. Results disaggregated by cycle.
**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone.

equivalent to €315 or $411. Cost savings from using r-hFSH instead of HP-hMG were 6.43%, expressed as percentage of the total cost of treatment with HP-hMG. The difference in treatment cost resulted primarily from the higher cost of treatment with HP-hMG in cycle 2 (1,628 kr), owing to a greater number of higher-cost fresh transfers with HP-hMG; r-hFSH was associated with a greater number of less costly frozen transfers (Figure 5). Costs of HP-hMG and r-hFSH

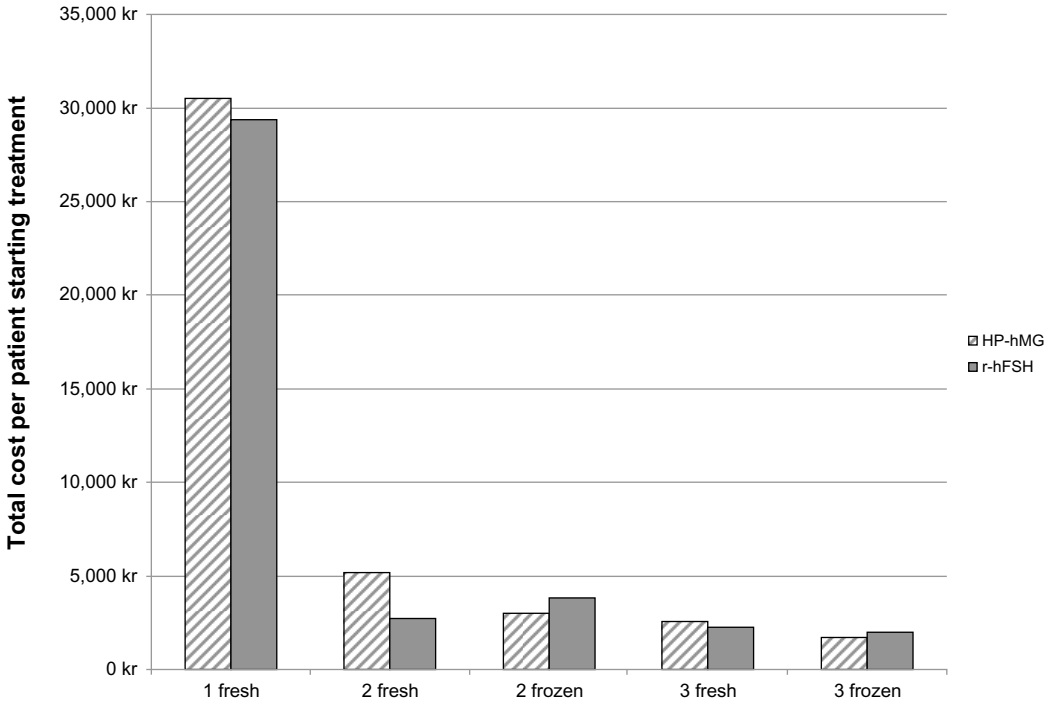


**Figure 5** Total cost per patient starting treatment in combinations of fresh and frozen cycles based on embryo availability. Results disaggregated by fresh and frozen transfers.
**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone.

were 7,917 kr and 8,468 kr, respectively, while the respective costs of procedures were 35,112 kr and 31,795 kr.

When only fresh cycles were considered, the total treatment costs were 49,561 kr for HP-hMG and 47,809 kr for r-hFSH, saving 1,752 kr (95% CI 48–3,658) per patient starting treatment. The savings were equivalent to €200 or $260. The savings from using r-hFSH instead of HP-hMG were 3.54%, expressed as percentage of the total cost of treatment with HP-hMG. The difference in treatment cost was attributed primarily to the slightly higher cost of treatment with HP-hMG in cycle 1 (1,140 kr) and 2 (588 kr), owing to the higher procedure cost associated with greater treatment length with HP-hMG. Costs of HP-hMG and r-hFSH were 10,273 kr and 11,746 kr, respectively, while the respective costs of procedures were 39,288 kr and 36,063 kr.

On a per-live-birth basis, r-hFSH was less costly, at 90,195 kr (€10,282 or $13,394) compared to 96,436 kr (€10,994 or $14,321) with HP-hMG per treatment consisting of up to three fresh or frozen cycles (Figure 6). In simulations restricted to fresh cycles only, the costs per delivery were 114,512 kr (€13,054 or $17,005) with HP-hMG and 112,280 kr (€12,800 or $16,674) with r-hFSH.

## Sensitivity analysis

Table 5 shows the modeled scenarios with alternative input assumptions. In treatments combining fresh and frozen cycles, cost savings from using r-hFSH instead of HP-hMG varied across scenarios from 5.53% to 8.12%, expressed as the percentage of the total cost of treatment with HP-hMG. Expressed in currency, the savings per patient starting treatment varied from 2,653 kr to 3,345 kr.

In the univariate sensitivity analyses, the results were found to depend on price and dosage of gonadotropin, treatment length, success rates, and number of oocytes retrieved. When unit price of r-hFSH was varied, cost savings from using r-hFSH versus HP-hMG obtained up until the price of r-hFSH increased by 30% based on cost per patient starting treatment and 31.5% based on cost per live birth. For gonadotropin dosage, the break-even point (no savings) was reached when dosage of HP-hMG was decreased by 38% to 62% of baseline value. When treatment length was varied, the savings were achieved even with no difference between HP-hMG and r-hFSH up until treatment with r-hFSH was set to be 20% longer than the baseline difference of 0.6 days for IVF and 1.4 days for ICSI. Variation in success rates did not affect cost per patient starting treatment, but for difference in average cost per live delivery, HP-hMG became more cost-effective when its effectiveness was increased by 11% relative to baseline. Cost savings from using r-hFSH decreased with decreasing difference in the number of oocytes retrieved, but the break-even point was only reached with more oocytes retrieved with HP-hMG (50% and 70% relative to the baseline

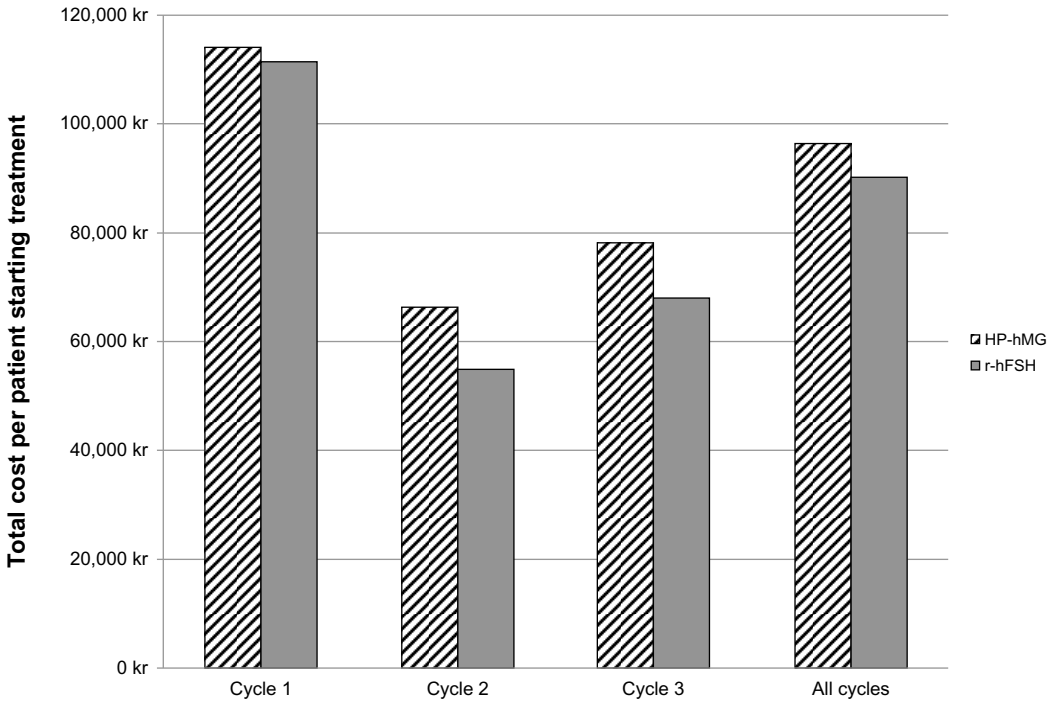


**Figure 6** Total cost per live birth in combinations of fresh and frozen cycles based on embryo availability.
**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotrophins; r-hFSH, recombinant human follicle stimulating hormone.

**Table 5** Alternative scenarios with varied input assumptions modeled in the analysis

| Scenario | Dropout reduction[a] applied | Drug dosage increment[b] applied | Success decrement[b] applied | Difference in live births | Live births per 10,000 patients, HP-hMG | Live births per 10,000 patients, r-hFSH | Total cost per patient, HP-hMG | Total cost per patient, r-hFSH | Difference in total cost |
|---|---|---|---|---|---|---|---|---|---|
| 1 Base case, public centers | 50% | No | No | 2 | 4,462 | 4,464 | 43,030 kr | 40,263 kr | −2,767 kr |
| 2 | 0% | No | No | −20 | 4,117 | 4,097 | 41,219 kr | 37,874 kr | −3,345 kr |
| 3 | 0% | No | Yes | −65 | 4,315 | 4,250 | 40,661 kr | 37,495 kr | −3,166 kr |
| 4 | 0% | Yes | Yes | 41 | 4,355 | 4,396 | 40,966 kr | 37,705 kr | −3,261 kr |
| 5 | 50% | Yes | Yes | −4 | 4,671 | 4,667 | 42,726 kr | 39,860 kr | −2,866 kr |
| 6[c] | 50% | No | No | 61 | 4,279 | 4,340 | 47,938 kr | 45,286 kr | −2,653 kr |
| 7[d] | 50% | No | No | −70 | 4,328 | 4,258 | 49,561 kr | 47,809 kr | −1,752 kr |
| 7 Base case, IVF only | 50% | No | No | 35 | 4,497 | 4,532 | 41,951 kr | 39,012 kr | −2,939 kr |
| 8 Base case, ICSI only | 50% | No | No | 66 | 4,472 | 4,538 | 43,305 kr | 40,353 kr | −2,951 kr |
| 9 Base case, private centers | 50% | No | No | 2 | 4,462 | 4,464 | 43,030 kr | 40,263 kr | −2,767 kr |

**Notes:** [a]Dropout reduction before frozen cycles relative to before fresh cycles; [b]increment or decrement relative to preceding cycles; [c]scenarios involving fresh cycles only, assuming unavailability of frozen embryos; [d]scenarios involving fresh cycles only, assuming unavailability of frozen embryos.

**Abbreviations:** HP-hMG, highly-purified human menopausal gonadotropin; r-hFSH, recombinant human follicle-stimulating hormone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

difference). Dropout rates had no impact on difference in cost outcomes.

The probabilistic sensitivity analyses demonstrated that within the varied input range, r-hFSH remains cost-saving in 100% of the simulated cohort per patient starting treatment (Figure 7) and 85% per live delivery (Figure 8). The respective figures for fresh cycles only were 97.3% and 73.1%.

## Discussion

The results of the review and simulation modeling demonstrated the comparative efficacy of r-hFSH and HP-hMG in terms of live-birth rates. The economic model in the Swedish setting additionally demonstrated cost saving per live birth as a result of the increased number of oocytes retrieved with r-hFSH allowing for more cryopreserved embryos and more frozen cycles. Since differences in the costs associated with each stimulation therapy exist, a cost analysis performed according to regional prices is important for clinicians, patients, and policy-makers.

Several previous meta-analyses have compared the efficacy of r-hFSH to that of hMG and HP-hMG.[3,7,25,35–37] A recent review found no evidence of a difference between HP-hMG versus r-hFSH in ongoing pregnancy rate per started cycle (26.7% vs 24.3%), embryo transfer (33.0% vs 29.4%), or live-birth rates per embryo transfer (35.1% vs 30.8%).[7]

Most reviews include only trials using GnRH agonists long downregulation and include both standard IVF and ICSI patients in the analyses. In addition, they include trials that used hMG or HP-hMG, assuming a similar class effect of individual human gonadotropins. Subgroup analyses done to include only women downregulated with a GnRH-agonist long protocol or whose embryos were fertilized using standard IVF have shown a higher probability of success with hMG and HP-hMG.[3,37] Since across Europe the proportion of ICSI constitutes 66.5% of fresh assisted reproductive technology cycles, this does not completely represent reality.[38,39] Additionally, most trials comparing gonadotropins do not report on cumulative live-birth rates per treatment program, embryo quality, or dropout rates in subsequent frozen cycles. This gap in the literature is therefore filled with data from observational studies and IVF registries. Furthermore, it should be noted that some reviews limited inclusion of trials based on stimulation characteristics, eg, excluding fixed-dose studies[35] or including only published trials.[25]

In previous economic studies involving sequences of fresh and frozen cycles, probability of oocyte retrieval was typically either not considered or based on incomplete evidence. In a study comparing recombinant and urinary FSH, the number

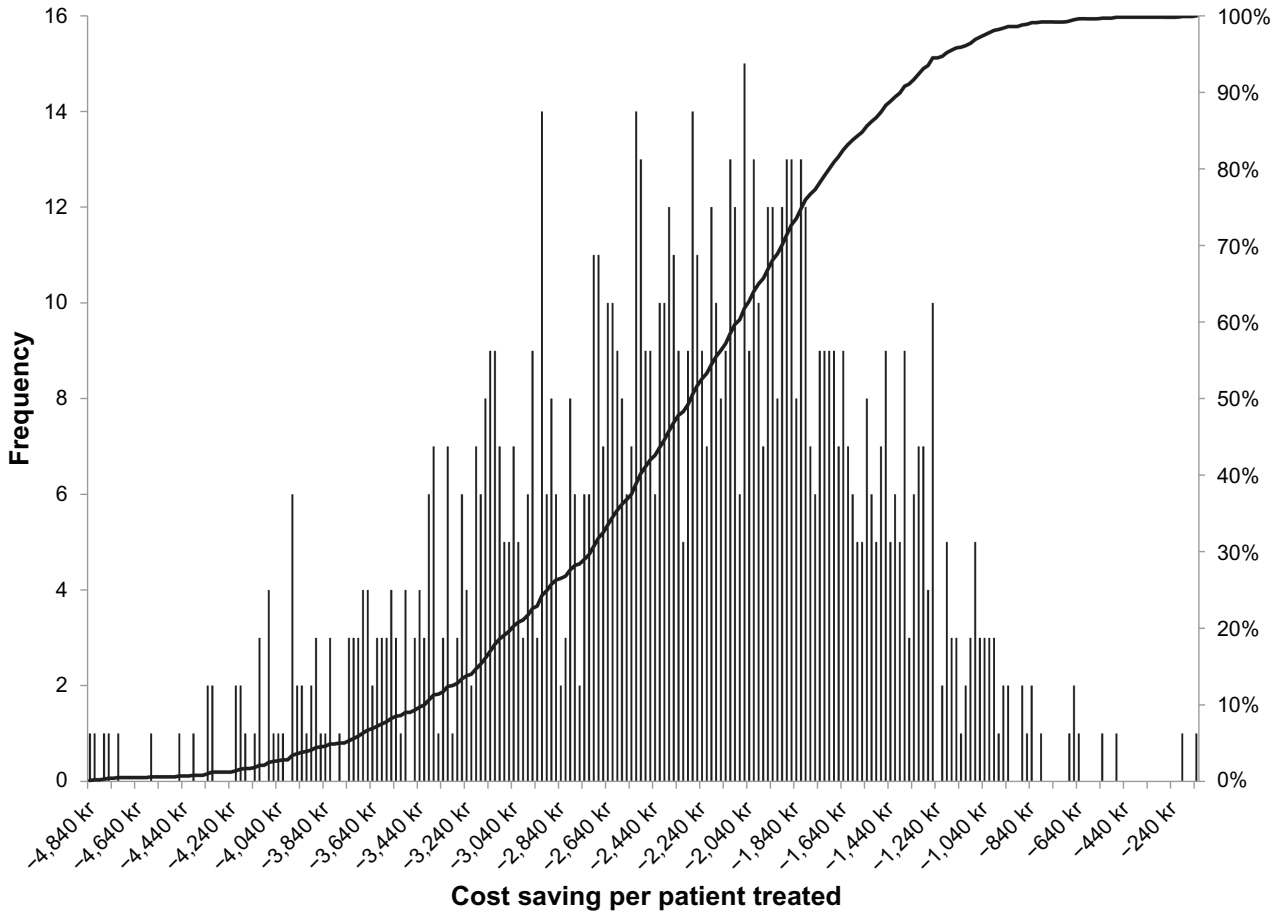


**Figure 7** Probabilistic sensitivity analysis for cost per patient starting treatment in combinations of fresh and frozen cycles showing distribution and cumulative distribution for a cohort of 1,000 patients.

of supernumerary embryos available for cryopreservation was not accounted for.[40] The number of frozen embryos available and successfully transferred was modeled using Australian and New Zealand data in an economic study of impact of maternal age.[41] The results depended on availability of embryos for frozen transfer, which were different for different age-groups, leading to a threefold difference in the probability of frozen cycles ranging from 0.27 to 0.77, depending on maternal age. This study, however, did not aim to compare different stimulation options. In a German model, even though the probability for cryopreservation survival was used, no data on the actual number of oocytes or embryos available for freezing were reported.[42] The same effectiveness-data source and simplified architecture of the decision model were adopted in a recent economic evaluation in Greece.[43] In one study comparing two gonadotropins, probabilities of subsequent frozen cycle, based on expert opinion, were different for the two comparators, but availability of embryos for cryopreservation was not considered.[44]

The availability of cryopreserved embryos as directly related to the number of oocytes retrieved was modeled previously in the UK.[45] In that study, at least three supernumerary oocytes had to be available for a cryopreserved embryo to be offered. This parameter was varied in the sensitivity analysis from 3 to 7, assuring robustness of the model, but evidence on the number of oocytes in HP-hMG and r-hFSH was obtained from two clinical trials: European and Israeli Study Group (EISG) study[46] and the Menotrophin Versus Recombinant FSH in vitro Fertilization Trial (MERIT),[2] while in this model registry data validated by a meta-analysis were used instead, accounting for different embryo-quality criteria for SET and DET and efficiency of cryopreservation. The number of oocytes retrieved, success rates, drug dosage, and treatment length were different in the two studies; importantly, the current analyses were based on a model built on mean values rather than individual data. Furthermore, in the UK study, the number of embryos transferred was not modeled to be associated with success rates, whereas in the present study, success rates for SET and DET were obtained from the Swedish registry. The percentage of SET modeled on Swedish practice was considerably higher than in the two randomized controlled trials. Most notably,

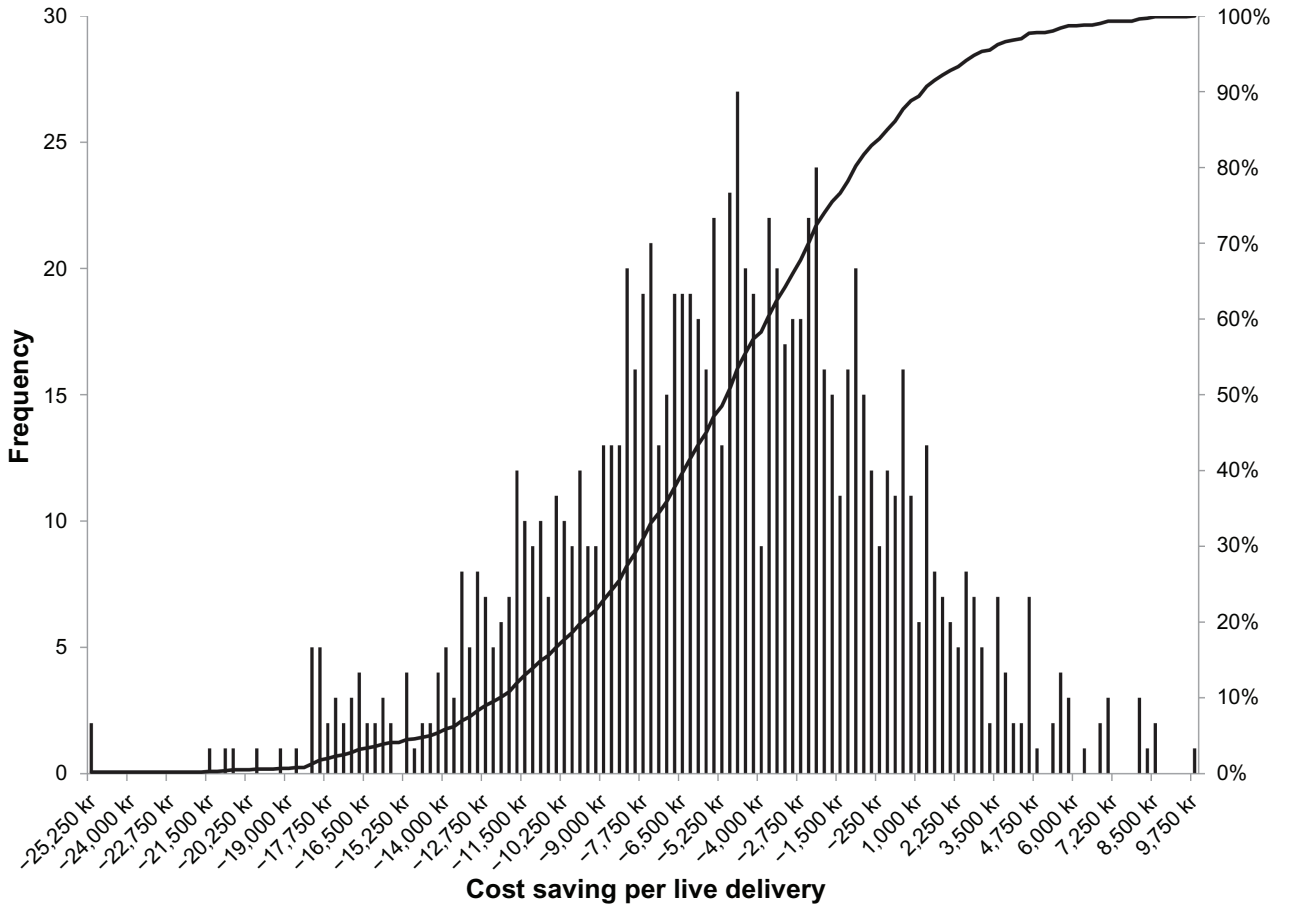


**Figure 8** Probabilistic sensitivity analysis for difference in cost per live delivery in combinations of fresh and frozen cycles showing distribution and cumulative distribution for a cohort of 1,000 patients.

however, the UK study showed higher cumulative live-birth rates of HP-hMG (53.7%, 95% CI 49.3%–58.1%) vs r-hFSH (44.6%, 95% CI 40.2%–49.0%), the advantage resulting from trial data, and model assumptions of success in frozen cycles depending on success in fresh cycles with a decrement applied. Since the combined EISG and MERIT data produced statistically significantly greater success rates in fresh cycles, the advantage of HP-hMG also carried to frozen cycles. That approach, justified as pregnancy in fresh IVF/ICSI cycle from which the frozen embryos originated had been shown to be a predictive factor for pregnancy in frozen–thawed cycles,[47,48] was not used in this cost-minimization analysis; instead it was based on equal success rates for the two compared options.

Finally, the UK study did not compare numbers of fresh and frozen cycles per treatment in the two treatment arms, making it impossible to draw conclusions about contribution of the number of oocytes and embryos to the total cost of treatment.

Another economic evaluation, conducted in the Swedish setting, did not address the choice of gonadotropins, focusing on SET vs DET, but it can be used to compare and cross-validate cost data used in our model.[49] This study was based on detailed costing with diagnosis-related groups tariff for individual procedures, unlike in our model, where tariffs covering the entire treatment cycle had been obtained from the centers as 26,873 kr for IVF, 31,023 kr for ICSI, and 9,107 kr for FET, and comparable to tariffs used in our study. In our study, however, costs of ovarian hyperstimulation syndrome, miscarriage, maternity, and pediatric care were not considered, following the evidence of no difference in these outcomes between the two compared options. This led to underestimation of total cost per live birth, while the cost differential between treatments was not affected. The cost calculated per live-born child was 197,647 kr in the DET group and 218,042 kr in the SET group, excluding costs for loss of productivity but including maternal and neonatal costs for up to 6 months postdelivery. In contrast, in our study, cost per live birth was 96,436 kr for HP-hMG and 90,195 kr for r-hFSH.

Results of an economic evaluation typically depend on drug dosage, which we obtained from the Norwegian registry study.[29] The discrepancy in dosage between experimental

and pragmatic studies could be attributed to the fact that in some trials the starting and daily dosage of r-hFSH was higher than the one commonly used in routine practice,[2,46] even though lower dosage of r-hFSH has been found to produce success rates as high as those with the higher dose. In one study, starting doses for r-hFSH varied between 150 and 300 IU.[3] In other reviews, gonadotropin dosage was highly heterogeneous and often not meta-analyzed, due to the marked heterogeneity between the data from individual trials. This interindividual variation combined with differences in treatment practice suggests that good-quality large single studies, whether randomized controlled trials or prospective cohorts, can provide more reliable evidence on drug dosage. In a recent observational study restricted to consecutive ICSI patients with first cycle only, the mean dosage of r-hFSH was significantly lower than that of HP-hMG (1,639.2 vs 2,356.4 IU, $P < 0.001$).[50] This is in line with the Norwegian study used in our analysis, also at the same time producing more oocytes and more mature oocytes. Gonadotropin-dosage data are available from large registries and have been used in other economic analyses,[51] with results favoring r-hFSH (2,073 vs 2,540 IU), but we used the more recent Scandinavian study including only patients who had not been treated previously. Had we used the drug dosage from those other registries, our results would be even more in favor of r-hFSH. Even so, a recent meta-analysis of 16 randomized studies reported greater mean gonadotropin dose for HP-hMG than r-hFSH (235.46 IU, 95% CI 16.62–454.30; $P = 0.03$).[35] It should be noted that the use of a pen device is likely to have contributed to the efficiency of gonadotropin administration. In a study comparing r-hFSH administered via pen and via syringe, the difference in total drug dosage was 1,909.38 vs 2,100.65 IU ($P < 0.001$)[52]; also, duration of stimulation was greater in the syringe group: 9.70 vs 10.47 days ($P < 0.05$). Interestingly, in this study, the number of embryos available for freezing was also greater in the pen group: 4.56 vs 1.30 ($P < 0.05$).

Use of "real-life" registry data is likely to produce effectiveness results different from use of controlled trials. In Trew et al,[51] r-hFSH was associated with better outcomes than HP-hMG in respect of number of oocytes retrieved (11 vs 10), number of mature oocytes retrieved (9 vs 8), number of oocytes/embryos frozen per cycle (2.1 vs 1.7), and number of embryos thawed and used in FET (0.74 vs 0.67); *P*-values for all differences were less than 0.01. In addition, in a German registry study, live-birth rate following frozen transfers was higher with r-hFSH compared to hMG (9% vs 7%).[42] Efficacy trials are experimental in design, and are used to detect significant differences between competing interventions in a specific control scenario.[53] Effectiveness studies on the other hand tend to be more pragmatic in nature, allowing natural variability of patient populations, intervention administration, and follow-up durations to factor into the analyses. These studies often show lower success rates, but are closer to real-life conditions.

Interestingly, there was a discrepancy between the Swedish registry data used in our analysis and findings from clinical trials of greater live-birth rates in SET than in DET.[54] This could have resulted from preferential use of DET in patients with greater risk factors, such as age, as percentage of SET decreased from 98.5% for age <25 years to 40.3% for age ≥42 for IVF, and from 85.5% to 31.3% for ICSI. Another possible explanation is the use of more restrictive embryo-quality criteria in SET compared to DET. While this discrepancy would be a limitation if the model were used to compare SET vs DET protocols, it would not affect the conclusions drawn on the use of gonadotropins.

One of the highly debated issues is whether embryo cryopreservation offers the same success rates as fresh cycles. It should be noted that the method of cryopreservation has been demonstrated to affect the success rates by both influencing the number of available embryos after thawing and by affecting embryo quality.[55] Vitrification is becoming accepted as the most preferred method of oocyte and embryo cryopreservation. At present, postthaw survival rates vary between 30% and 78% between centers, depending on prethaw criteria and the stage at which embryos are frozen,[56] with vitrification cryosurvival reaching 96.02% and 75.3% embryos having 100% blastomere survival.[57] The combination of elective SET with an optimized cryopreservation program has been predicted to become the standard of care for routine IVF/ICSI treatment.[56] Meanwhile, in Sweden, slow freezing is still the standard practice for embryo cryopreservation. The cost saving in countries using vitrification may be greater than in countries still primarily using slow-freezing techniques.

Even if embryos are available following thawing, clinicians have questioned the success of these embryos compared with ones produced from a fresh cycle. It has been suggested that controlled ovarian hyperstimulation adversely affects implantation following IVF-ET.[26] A recent systematic review[58] provided limited proof that cryoembryo transfers may in fact be more successful than transfers from fresh cycles. The argument is that when transferring cryothawed embryos, the uterine endometrial lining has returned to normal and is more favorable for implantation. This same theory

explains why blastocyst transfers have been demonstrated to have a higher success rate than cleavage-stage transfers.[59] Indeed, it has been proposed that success rates would increase if all, not only supernumerary, embryos were cryopreserved.[57] In this study, which included only patients of age <38 years, a 27.8% ongoing pregnancy rate was achieved in fresh ET contrasted with 39% in frozen ET, with a comparable number of embryos transferred. Furthermore, the success rates in the first, second, and third or more frozen–thawed cycles, when all earlier frozen–thawed cycles from the same egg retrieval had failed, were compared, and there was no significant difference in pregnancy or live-birth rate.[60] If such a scenario were adopted, success rates following FET would be modeled as higher than in standard fresh cycles, thus further increasing the advantage of r-hFSH in our model. This is further complicated by the assumption in our model of the same success rates for all frozen cycles; it must however be noted that natural FETs are associated with lower success rates compared to estrogen-plus-progesterone cycles.[61]

The use of cumulative rates per treatment instead of rates following fresh cycles is becoming an important benchmark in reproductive trials and meta-analyses. It has become recognized that by only investigating differences in fresh cycles, the true comparative effectiveness of interventions is often distorted. Commonly used interventions including SET,[14] blastocyst transfers,[59] and in this case r-hFSH have different effectiveness portfolios depending on whether evidence is only taken from fresh cycles or from the cumulative success across all fresh and frozen cycles generated from a single stimulation. In most cases, the availability of additional embryos for cryopreservation reduces any comparative advantage of success from fresh cycles only. In the current study, we used the cumulative live-birth rates in the economic model, as this related to true effectiveness of the interventions.

One of the key assumptions in our model was the association between the number of oocytes retrieved and the number of embryos available for transfer or cryopreservation. The average number of embryos available for freezing had been found to be strongly dependent on the number of oocytes retrieved, with the cumulative pregnancy rate after stimulated and frozen cycles following a single-stimulation cycle being significantly higher in those with a higher number of oocytes obtained. Despite the small reduction in fertilization rate, the retrieval of many preovulatory oocytes produced ongoing pregnancy rates per stimulation (fresh- plus frozen-cycle embryo transfers) of 28.3% when six to ten preovulatory oocytes were retrieved and 41.5% when more than ten were retrieved.[19] The number of embryos actually frozen can depend on the number of embryos available for freezing, in that some centers require a minimum number of embryos, ie, a single supernumerary embryo may not qualify for cryopreservation. When two embryos are transferred (DET) and the total number of top-quality embryos is 3.5,[62] the remaining single embryo may be lost. This would further disadvantage treatment, producing even marginally fewer good-quality embryos with stringent quality criteria applied.

In Sunkara et al's study,[31] based on the UK HFEA data, there was a strong association between the number of oocytes and the live-birth rate that rose with increasing number of eggs up to 15, plateaued between 15 and 20 eggs, and declined beyond 20 eggs. While this finding and the nomogram constructed by the authors can have practical use at an individual level, it is unlikely that it could be used to predict live-birth rates for different gonadotropins in fresh cycles. A mean difference of one supernumerary oocyte can be of paramount importance in making a subsequent cryocycle possible, with all the economic implications, but a mean difference of one embryo in a fresh cycle between nine and ten embryos can only lead to predicted advantage in live-birth rate of 1%, most likely with no statistical significance, as corroborated by the results of our analysis.

Embryo quality and selection of embryos for transfer based on quality criteria have been engraved in the minds of embryologists and clinicians since the start of assisted reproduction. It is natural to assume that higher-quality embryos, including on a genetic level,[63] have a higher probability of implanting and developing into a normal fetus, eventually leading to a live birth. The specific criteria, however, are difficult to establish, as evidence is limited due to multiple-embryo transfers either confounding the analysis or lacking in the case of SET, when additional embryos are not used.[64] More rigorous approaches revealed that neither number of cells nor blastomere fragmentation were good predictors of implantation outcome.[65] Recently, new evidence has disproved these assumptions, and on the contrary has shown that selection based on quality criteria may in fact be decreasing success rates,[48,66] highlighting the clinical importance of the number of embryos available for transfer, with its economic implications. Furthermore, not only the embryo-quality criteria but also the timing of cryopreservation affects pregnancy and delivery rates.[67] With extended postthaw culture time and combined with the greater number of available embryos, success rates would be predictably greater.[68]

Economic evaluations in reproductive medicine are common, especially for treatment interventions, but are often either underreported or lack high-quality methods.[69] Omission of incremental cost analyses, sensitivity analyses to confirm robustness of the models used, and discounting are the common methodological weaknesses as gauged by international standards. These criteria[70] were conformed to during the course of this study with the exception of discounting, noted not to have been undertaken due to the short time horizon. Economic studies conducted by a health economist or in a health economics department are often more methodologically sound and relate to the complexities of studies of this nature.[69] At the same time, less than half of economic evaluations use live birth as the primary outcome measure, with a fifth using a clinical pregnancy as the desired outcome. We agree with the conclusions of Moolenaar and colleagues that long-term effectiveness outcomes are of more importance than surrogate outcomes, and further believe that cumulative live birth is the most appropriate outcome measure in studies of reproductive medicine.[69]

Even though in medical decision-making clinical and cost considerations are important, patient preferences should also be taken into account. A recent study revealed that in terms of stimulation, patients preferred low dose variability, FSH derived from DNA technology over highly purified extract from urine from postmenopausal women, and injection pens over conventional syringe and short administration times.[71] It can be speculated that patients would also prefer frozen cycles compared to fresh ones, although an unexpectedly large group of Swedish patients choose not to use their cryopreserved embryos. In a recent study, 30.6% in the SET group and 34.7% in the DET group had all their embryos destroyed, and some couples chose to continue with stimulated fresh cycles instead of frozen–thawed cycles.[72] Greater emphasis on more rational choices of treatment options would increase success rates while also reducing the number of multiple pregnancies, lowering treatment cost, and helping patients to meet their preferences.

## Disclosure

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