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Cost-effectiveness analysis of recombinant human follicle-stimulating hormone alfa (r-hFSH) and urinary highly purified menopausal gonadotropin (hMG) based on data from a large German registry

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ABSTRACT

This was a retrospective real-world evidence analysis of the costs per live birth for reference recombinant human follicle-stimulating hormone alfa (r-hFSH-alfa) versus highly purified urinary human menopausal gonadotropin (hMG-HP), based on data from a

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German *in vitro* fertilization registry (RecDate). Pregnancy and live birth rates from the RecDate real-world evidence study over three complete assisted reproductive technology (ART) cycles using the same gonadotropin drug were used as clinical inputs. Costs related to ART treatment and to drugs were obtained from public sources. Treatment with r-hFSH-alfa resulted in higher adjusted cumulative live birth rates versus hMG-HP after one (25.3% vs. 22.3%), two (30.9% vs. 27.5%), and three (31.9% vs. 28.6%) ART cycles. Costs per live birth were lower with r-hFSH-alfa versus hMG-HP after one (€17,938 vs. €20,054), two (€18,251 vs. €20,437), and three (€18,473 vs. €20,680) ART cycles. r-hFSH-alfa was found to be a cost-effective strategy compared with hMG-HP over three cycles.

Introduction

The appropriate selection of gonadotropin preparations for ovarian stimulation (OS) during assisted reproductive technology (ART) treatment is based on several factors, including the overall benefit–risk evaluation, cost-effectiveness, and patient preference. Currently available gonadotropins for OS include recombinant human gonadotropins, such as recombinant human follicle-stimulating hormone (r-hFSH), and urinary human menopausal gonadotropins (hMG), including urinary hMG highly purified (hMG-HP) [1]. Different gonadotropin preparations display different biological properties, metabolic clearances, and half-lives [1,2]. r-hFSH contains only follicle-stimulating hormone (FSH) activity [1–3], whereas hMG-HP, which is extracted from the urine of postmenopausal women, contains both FSH and luteinizing hormone (LH) activity, as well as other proteins and metabolites [1,2,4].

To date, randomized controlled trials (RCTs) comparing different gonadotropin treatments have reported conflicting results. A number of RCTs and meta-analyses found no statistical difference in ART treatment outcomes between r-hFSH and urinary preparations (hMG, purified FSH [P-FSH], and highly purified FSH [HP-FSH]) [5–8], whereas others reported a difference in the live birth rate (LBR) and clinical pregnancy rate (CPR) between r-hFSH and hMG [9–14]. As a result, the European Society for Human Reproduction and Endocrinology (ESHRE) 2019 guidelines equally recommend both r-hFSH and hMG for OS [15]. It is known that RCTs include highly selected populations of expected normal responders that may not reflect women treated in every day clinical practice [16]. Therefore, supplementing data obtained from RCTs with real-world data may provide a more realistic picture of outcomes between r-hFSH and urinary preparations [16–20].

Historically, few real-world studies have reported on the differences between r-hFSH and urinary preparations [19,21,22], and only one of these studies [19] reported a comparison among specific recombinant and urinary preparations. A recent real-world analysis compared the effectiveness of reference follitropin alfa (r-hFSH-alfa, GONAL-f®, Merck Healthcare KGaA, Darmstadt, Germany), hereafter referred to as r-hFSH-alfa throughout, with hMG-HP (Menogon® HP, Ferring Pharmaceuticals Ltd, Saint-Prex, Switzerland [also known as Menopur® in some markets]) in a large (>28,000 patients) German population. This analysis showed that cycles stimulated with r-hFSH-alfa versus hMG-HP had increased cumulative LBRs and clinical and ongoing pregnancy rates, alongside decreased cancellation rates and gonadotropin usage per oocyte retrieval in the overall population [23]. The population investigated in the study by Bühler et al. represented a real-world patient group without the stringent inclusion and exclusion criteria usually applied for women with normal ovarian reserve (expected normal responders) typically included in gonadotropin registration RCTs [16]. Differences between each treatment group were also adjusted based on propensity score weighting for baseline covariates that reportedly influence cumulative live birth [24,25], such as age, body mass index, infertility type,

gonadotropin used, gonadotropin-releasing hormone (GnRH) analog protocol, year of first stimulation cycle, and *in vitro* fertilization (IVF) centre [23]. Furthermore, Bühler et al. identified several other factors that may explain the conflicting results reported by previous RCTs, including the inclusion of different types of r-hFSH and urinary preparations, and the absence of analysis of cumulative data for pregnancy and live birth owing to the inclusion of only fresh embryo transfers [23].

Cost-effectiveness analyses can help decision-makers make informed assessments on the optimal gonadotropin to be used for OS based on a comparison of all costs associated with ART cycles (including fresh and freeze–thaw embryo transfers). Analyses published to date were based on either clinical trial data [26–28], follow-up data from an RCT [29,30], clinical trial data and routine practice [31], data from a meta-analysis [32], or an observational study [19].

In Germany, a reported 17,690 IVF and 45,381 intracytoplasmic sperm injection (ICSI) cycles were performed in 2019 [33]. The aim of this study was to evaluate the cost-effectiveness of the two most commonly prescribed gonadotropins in real-world clinical practice in Germany at the time of the study, r-hFSH-alfa and hMG-HP, in up to three complete ART cycles (including all fresh and freeze–thaw embryo transfers after a stimulation cycle) using cost per cumulative live birth. To the best of our knowledge, this is the first cost-effectiveness analysis comparing cumulative live birth (including fresh and freeze–thaw embryo transfers) for r-hFSH-alfa with hMG-HP in Germany using real-world data and, therefore, is a more accurate reflection of clinical practice.

Methods

Model structure

A decision-tree model was developed in Microsoft Excel (Fig. 1). The model structure comprised pregnancy and LBR states for one, two, and up to three complete ART cycles, where a complete ART cycle was defined as all embryos transferred (fresh or frozen) after a single stimulation cycle [23]. Each complete ART cycle included one fresh and up to three freeze–thaw embryo transfers after a stimulation cycle. This was validated on the basis that a maximum of three stimulations are funded by the German healthcare system and, from a European perspective, three complete ART cycles would usually represent the maximum number undertaken before dropout because of failure [34].

Each of the model states was associated with a separate cost: the proportion of patients at the end of each treatment pathway multiplied by the relevant source cost. The total sum of all pathways was used to generate overall costs for each intervention. Model outputs included LBR, total costs, cost per live birth, and incremental cost-effectiveness ratio (ICER), estimated as the difference in costs divided by the difference in LBR for r-hFSH-alfa versus hMG-HP.

Clinical inputs

Data from a real-world setting collected between 2007 and 2012 (RecDate database [23]) were used to inform clinical inputs for the comparison of the economic implications (cost per cumulative live birth) of r-hFSH-alfa versus hMG-HP from a German healthcare perspective. Full details regarding study methodology taking into account co-variates such as baseline characteristics and treatment variables can be found in the clinical paper [23]. Briefly, women were included in the study if they were undergoing a first cycle of ART treatment (IVF, ICSI, or both) during the study period, where OS was performed with r-hFSH-alfa or hMG-HP, and GnRH analogs (either agonist or antagonist) were used to prevent premature ovulation. Data for these women were only included in the analysis reported here until delivery, treatment discontinuation, or treatment switching [23]. It was assumed that the occurrence of ovarian hyperstimulation syndrome (OHSS) adverse events was inherently captured in the RecDate database and hence was not considered separately, and additional published data on OHSS rates were not considered.

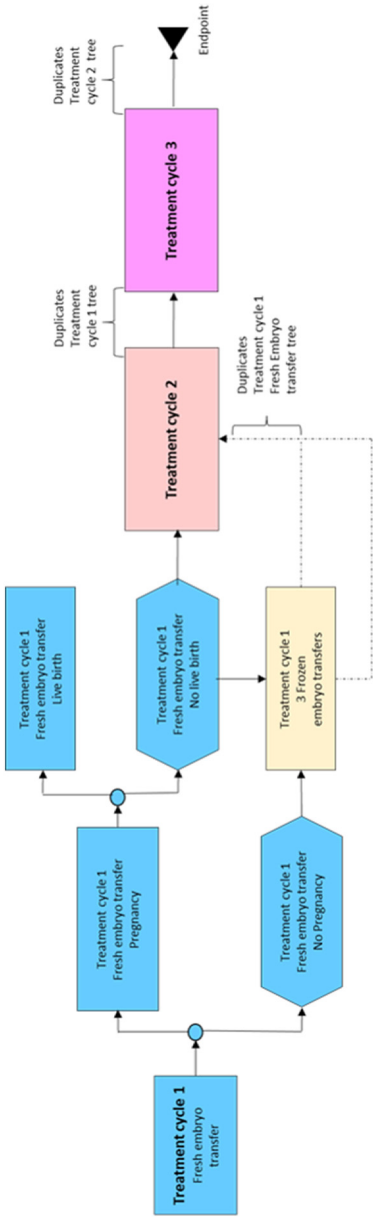

Fig. 1. Model structure. The model structure is the same for each treatment cycle, although only the full structure for the first cycle has been included in the figure for clarity.

Patients transitioning to the next ART cycle

The probability of moving from one model state to another was based on the outcomes obtained from the RecDate database (Table 1). The proportion of patients moving from pregnancy to live birth was conditional on the success of the previous stage.

Cost inputs

Cost inputs were categorized into those for assisted reproduction and birth and those for drugs. In order to take into account all expenses associated with live birth, all costs were included, regardless of whether they are paid by insurance or the patient. Treatment costs and drug costs are outlined in Table 2, Table 3, and Supplementary Table 1. Overall costs for ART cycles, including gonadotropin preparations, oocyte retrieval, embryo transfer, pregnancy, and live birth, were obtained from publicly available German sources. The costs for IVF/ICSI were the weighted proportions of IVF (27%) and ICSI (73%) procedures based on the yearbook of the German IVF register (covering 131 centres) from 2019 [33]. The cost of a live birth was assumed to be composed of the weighted average of vaginal and caesarean section births from the Fallpauschalen-Katalog [35], based on a reported proportion of 30.5% caesarean section births in Germany in 2020. Drug costs were obtained from the Lauer-Fischer GmbH WEBAPO® T InfoSystem [36]. The pharmacy selling price (including value added tax) was used for all gonadotropins.

Costs per live birth were calculated from the total costs and the LBR for the first cycle, cumulatively for the first and second cycles, and cumulatively for the first, second, and third treatment cycles, respectively.

Validation and sensitivity analysis

Clinical and cost inputs, model structure, and methodology were validated by the lead author who has extensive experience in assisted reproduction in Germany. The model outputs for LBR were validated by comparing calculated LBR from the decision tree with the live birth data directly derived from the RecDate database analysis. The robustness of the results to parameter input variation was assessed using deterministic (one-way sensitivity analysis [OWSA]) and probabilistic sensitivity analyses (PSA).

The OWSA was conducted to identify key drivers of the model outcomes. In this type of sensitivity analysis, the impact of each factor on the results was analysed by varying the parameters one at a time. The analysis was conducted on all clinical and cost inputs to assess the robustness of the study outcomes and hypotheses, by investigating the plausible upper and lower values from the reported

Table 1
Probabilities (numbers of patients) of moving between model states.

		r-hFSH-alfa (N = 17,725)	hMG-HP (N = 10,916)
First ART cycle	Stimulation 1 (fresh)	100% (17,725)	100% (10,916)
	Stimulation 1 to FET1	22.28% (3950)	14.73% (1608)
	FET1 to FET2	7.85% (1391)	3.91% (427)
	FET2 to FET3	2.20% (390)	0.77% (84)
Second ART cycle	Stimulation 2 (fresh)	24.96% (4424)	26.31% (2872)
	Stimulation 2 to FET1	5.09% (903)	3.55% (388)
	FET1 to FET2	1.40% (248)	0.90% (98)
	FET2 to FET3	0.28% (49)	0.14% (15)
Third ART cycle	Stimulation 3 (fresh)	5.91% (1047)	6.74% (736)
	Stimulation 3 to FET1	1.15% (203)	0.83% (91)
	FET1 to FET2	0.33% (59)	0.83%[a]
	FET2 to FET3	0.33%[a]	0.83%[a]

Data are reported as proportions (number).
ART, assisted reproductive technology. FET, frozen embryo transfer. hMG-HP, highly purified human menopausal gonadotropin. r-hFSH, recombinant human follicle-stimulating hormone.
[a] Assumptions were made in the absence of data from the database: Numbers are equal to previous cycle.

Table 2
Treatment costs included in the model.

	Cost (€) (2021)	Reference
Preparation of IVF treatment	€94	KBV codes: 08211, 08510, 32,575, 32,614, 32,618, 32,781, 08520, and 08521 (accessed Jan. 2021)
Ovarian stimulation, oocyte pick-up, and insemination	€1709[a]	KBV codes: 08542, 01510, 08539, 08537, 05230, 05330, 05211, 05350, 08540, 08555, 08550, Lauer-Fischer GmbH WEBAPO® InfoSystem (accessed Jan. 2021). Interview with key opinion leader
Embryo transfer, fresh	€188	KBV code: 08558
Embryo transfer, frozen (incl. storage)	€1319	Interview with key opinion leader
Pregnancy follow up	€521	KBV codes: 32,352 and 01770
No pregnancy	€6	KBV code: 32,352
Live birth[a]	€2557[b]	Fallpauschalen-Katalog 2020: Weighted average of vaginal and caesarean births (30.5% C-section births in 2020)
No live birth	€331	KBV codes: 31,301, 31,696, 31,823, and 31,502

ICSI, intracytoplasmic sperm injection. IVF, *in vitro* fertilization. KBV, *Kassenärztliche Bundesvereinigung*.
[a] The costs for IVF/ICSI were the weighted proportions of IVF (27%) and ICSI (73%) procedures based on the yearbook of the German IVF register (covering 131 centres) from 2019.
[b] The cost of a live birth was based on the weighted average of vaginal and caesarean births from the Fallpauschalen-Katalog (30.5% caesarean births in Germany in 2020).

Table 3
Drug costs included in the model.

	Dosage regimen per stimulation cycle	Cost per cycle (€)
r-hFSH-alfa (FSH dose)[a]	FSH 1546 IU	€972
hMG-HP (FSH dose)[a]	FSH 2147 IU	€1072
GnRH agonists: Triptorelin (77.06%[b])	0.1 mg/day (1 package = 15)	€213.32/15 pens
GnRH antagonists: Cetrorelix (22.94%[b])	6–7 days 0.25 mg/day (one package of 6 or 7 syringes)	€377.43/package
hCG (Ovitrelle® pen)	1 pen (250 μg)	€55.04/pen
Progesterone	3 × 200 mg vaginally/day, over 15 days	€44.14/package

Drug costs obtained from Lauer-Fischer GmbH WEBAPO® InfoSystem. Pharmacy selling price (including value added tax) was used for all gonadotropins.
FSH, follicle-stimulating hormone. GnRH, gonadotropin-releasing hormone. hCG, human chorionic gonadotropin. hMG-HP, highly purified human menopausal gonadotropin. IU, international units. r-hFSH, recombinant human follicle-stimulating hormone.
[a] Treatment dose based on RecDate.
[b] Based on % use in RecDate.

outcomes and by investigating outcomes around the upper and lower 20% variance of the cost inputs. The results of the OWSA are presented as a Tornado diagram.

The PSA was conducted for incremental costs and live births, and the results are presented as a cost-effectiveness plane and acceptability curves (CEAC). In the PSA, each input was assigned a specific sampling distribution. A value from the distribution was then randomly drawn, and an ICER was calculated for the combinations of values. This procedure was repeated 1000 times. The resulting distribution of the ICERs of these repeated samples reflects an empirical distribution of the results of the analysis and are presented as the cost-effectiveness plane.

Willingness-to-pay (WTP) thresholds for fertility treatments are not well-established in health economics. Based on definitions from the Commission on Macroeconomics and Health, the World Health Organization (WHO) determined that interventions that have a cost-effectiveness ratio of less than three times the gross domestic product (GDP) per capita are cost-effective [37]. In addition, as reported in McDougall et al., 2020, the WHO consider an intervention that costs less than the national annual GDP per capita as highly cost-effective [38]. Data from the World Bank [39] identifies that the latest GDP per capita from Germany is €33,927. Consequently, the authors established €30,000 per incremental live birth as a conservative WTP threshold. Any intervention that is below this threshold would be determined as cost-effective.

Results

Live birth rate

After the first complete ART cycle the LBR was 25.3% for r-hFSH-alfa and 22.3% for hMG-HP. The LBR increased to 30.9% for r-hFSH and 27.5% for hMG-HP after two complete cycles. After three complete ART cycles, the LBR was 31.9% in the r-hFSH group compared with 28.6% in the hMG-HP group (Table 4).

Total costs (product of source costs and probability)

Fig. 2 shows the breakdown of the total costs after three cumulative ART cycles, calculated based on the individual cost components (Tables 2 and 3) multiplied by the relevant probability rates (for pregnancy and live birth) from the RecDate database.

Medication costs were lower for r-hFSH-alfa because a lower dose was used in the RecDate database compared with hMG-HP. Pregnancy- and birth-related costs were higher for r-hFSH-alfa because OS with r-hFSH-alfa resulted in more pregnancies and live births (resulting in more pregnancy- and delivery-related costs) when compared with OS with hMG-HP. In a scenario where the costs attributed to ongoing pregnancies and deliveries were not included in the evaluation, total costs were lower for r-hFSH-alfa versus hMG-HP: first cycle €3658 versus €3692; first and second cycles €4565 versus €4660; first, second, and third cycles €4779 versus €4907.

Costs per live birth

The costs per live birth in the model were lower with r-hFSH-alfa compared with hMG-HP after one, two, and three completed cumulative ART cycles (Table 4).

Incremental cost-effectiveness ratio

ICERs were calculated as €2430 after the first, €836 after the second, and below zero after the third complete ART cycle, showing that, even after the first complete ART cycle, r-hFSH-alfa is cost-effective compared with hMG-HP. With additional cycles, the ICER of r-hFSH-alfa improves further, and r-hFSH-alfa becomes the dominant economic strategy in the third cycle. In all cycles, the ICER is lower than the WTP threshold of €30,000 per incremental live birth, and therefore, r-hFSH-alfa was deemed cost-effective.

Sensitivity analyses

One-way sensitivity analysis

The Tornado diagram for the OWSA for incremental live births with r-hFSH-alfa versus hMG-HP indicates that the model results were most sensitive to the probability of live birth and pregnancy,

Table 4
Key clinical and cost-effectiveness results (cumulative).

	r-hFSH-alfa	hMG-HP	Difference
First complete ART cycle			
Live birth rate	25.3%	22.3%	3.0%
Cost per live birth	€17,938	€20,054	
Two complete ART cycles (cumulative)			
Live birth rate	30.9%	27.5%	3.5%
Cost per live birth	€18,251	€20,437	
Three complete ART cycles (cumulative)			
Live birth rate	31.9%	28.6%	3.4%
Cost per live birth	€18,473	€20,680	

ART, assisted reproductive technology. hMG-HP, highly purified human menopausal gonadotropin. r-hFSH-alfa, recombinant human follicle-stimulating hormone alfa.

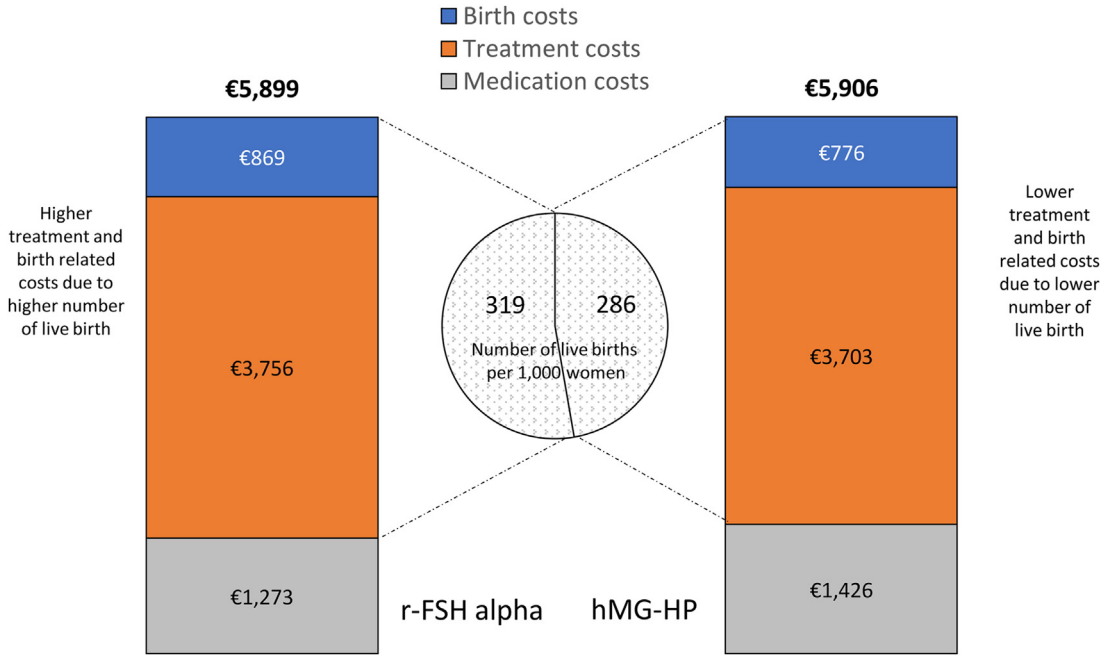

Fig. 2. Total cumulative costs after three cycles including cost breakdown. Source costs were multiplied with the probability in the decision tree. Medication costs included costs for r-hFSH-alfa and hMG-HP, respectively. Treatment costs include all costs related to preparation and execution of IVF/ICSI including fresh and frozen embryo transfers, as well as pregnancy-related follow-up costs. Birth costs include costs for live birth and miscarriage. The live birth costs and treatment costs for r-hFSH-alfa are higher than for hMG-HP as r-hFSH-alfa results in a higher number of pregnancies and births (319/1000 patients vs. 286/1000 patients). hMG-HP, highly purified human menopausal gonadotropin. ICSI, intracytoplasmic sperm injection. IVF, *in vitro* fertilization. r-hFSH-alfa, recombinant human follicle-stimulating hormone alfa.

compared with all clinical and cost inputs (Fig. 3). In other scenario analyses, variation in different inputs had a much smaller impact on the overall results, which underlines the robustness of the model outcomes.

Probabilistic sensitivity analysis

The PSA for the third complete cumulative ART cycle shows that the majority of ICER data points were in the upper-right and lower-right quadrants of the cost-effectiveness plane (Fig. 4A). This suggests the results obtained from the analysis are robust and that treatment with r-hFSH-alfa can be considered cost-effective. The cost-effectiveness planes for the first and second complete ART cycles are shown in the Supplementary figure.

Fig. 4B shows the CEACs based on 1000 Monte-Carlo simulations for cycle 1, cycles 1 and 2, and cycles 1, 2, and 3, individually. The CEAC summarizes the probability that the ICER is cost-effective in relation to possible values of a WTP threshold. As observed here, even after the first cycle, there is a high probability that r-hFSH-alfa is cost-effective at a very low WTP threshold of €6000. This probability increases further with the addition of the second and third cycles.

Discussion

This cost-effectiveness study compared two commonly prescribed ART treatments, r-hFSH-alfa and hMG-HP, and was based on data obtained from a German fertility registry (RecDate database), which included data from 28,641 women who initiated their first ART cycle (17,725 received r-hFSH-alfa and 10,916 received hMG-HP) [23]. Compared with hMG-HP, r-hFSH-alfa was associated with higher cumulative LBR (CLBR) and lower costs per live birth for up to three complete ART cycles (following a stimulation cycle and related fresh and freeze–thaw embryo transfers).

The lower cost per live birth and calculated ICERs clearly show that OS before ART treatment with r-hFSH-alfa can be interpreted as being cost-effective versus ovarian stimulation with hMG-HP. This finding becomes even more apparent when costs attributed to ongoing pregnancies and deliveries were excluded from the calculation. In this scenario, the product leading to more pregnancies and live births (r-hFSH-alfa) does not accrue costs related to the higher number of pregnancies and deliveries. This results in lower total costs for all three cycles for r-hFSH-alfa.

The cost-effectiveness model presented in the current study may be of particular value to decision-makers for a multitude of reasons due to the following strengths. First, it is based entirely on real-world data from 71 German IVF centres, which represented 58% of all IVF centres in Germany at the time of the study [23]. Using real-world data ensures the inclusion of a heterogeneous patient population, which provides a more realistic treatment landscape than RCTs; the population typically included in gonadotropin clinical trials reportedly reflects only 38% of patients actually treated in a real-world setting [16]. Furthermore, the real-world setting is more relevant for cost-effectiveness analyses than RCTs, which have specific objectives and do not consider the cost implications faced in clinical practice. The strength of the underlying clinical data from using propensity score weighting to adjust for known confounders at baseline [23] provides confidence in the interpretation of the data. This method of analysis is considered to be one of the most important tools in health economic evaluations [40].

A second strength of this study is that the results are based on the real-world use of only two brands of gonadotropins. Other studies included data that combined recombinant and all urinary preparations, which may potentially mask any treatment differences. For example, a meta-analysis conducted by Bordewijk et al., in 2019 identified 28 randomized clinical trials that compared r-hFSH with urinary gonadotropins in 7553 women; however, only seven of these trials (n = 3397) compared r-hFSH with hMG-HP [8]. Owing to differences in the FSH content and glycosylation patterns caused by the different manufacturing methods used for the preparations, direct comparisons between specific gonadotropins were not possible [8].

Furthermore, our analysis provides information on the relative cost of r-hFSH-alfa versus hMG-HP in terms of cumulative live births, including up to three complete ART cycles (i.e., up to three fresh ART cycles and related FET cycles). Cumulative live birth is considered the preferred primary outcome in the

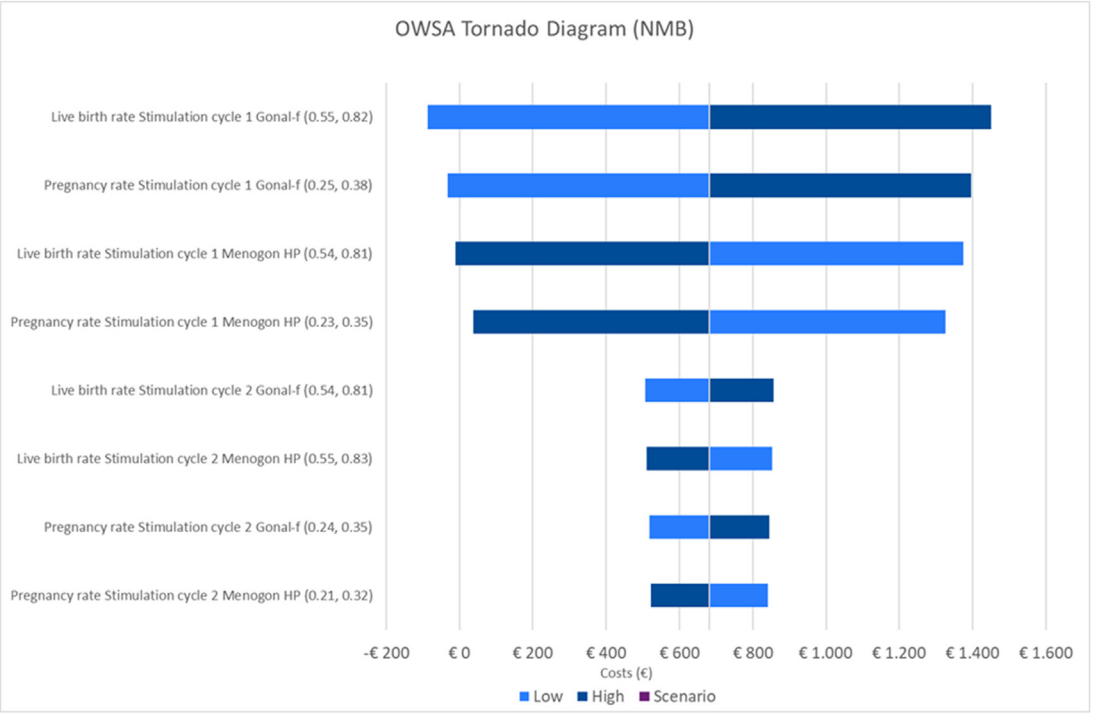

Fig. 3. Tornado diagram for the one-way sensitivity analysis for live birth. A OWSA was run considering NMB rather than ICER, to avoid implausible results. NMB is calculated as increment efficacy multiplied by 30,000 increment costs, where 30,000 is the threshold for assumed willingness to pay. hMG-HP, highly purified human menopausal gonadotropin. ICER, incremental cost-effectiveness ratio. NMB, net monetary benefit. OWSA, one-way sensitivity analysis. r-hFSH-alfa, recombinant human follicle-stimulating hormone alfa.

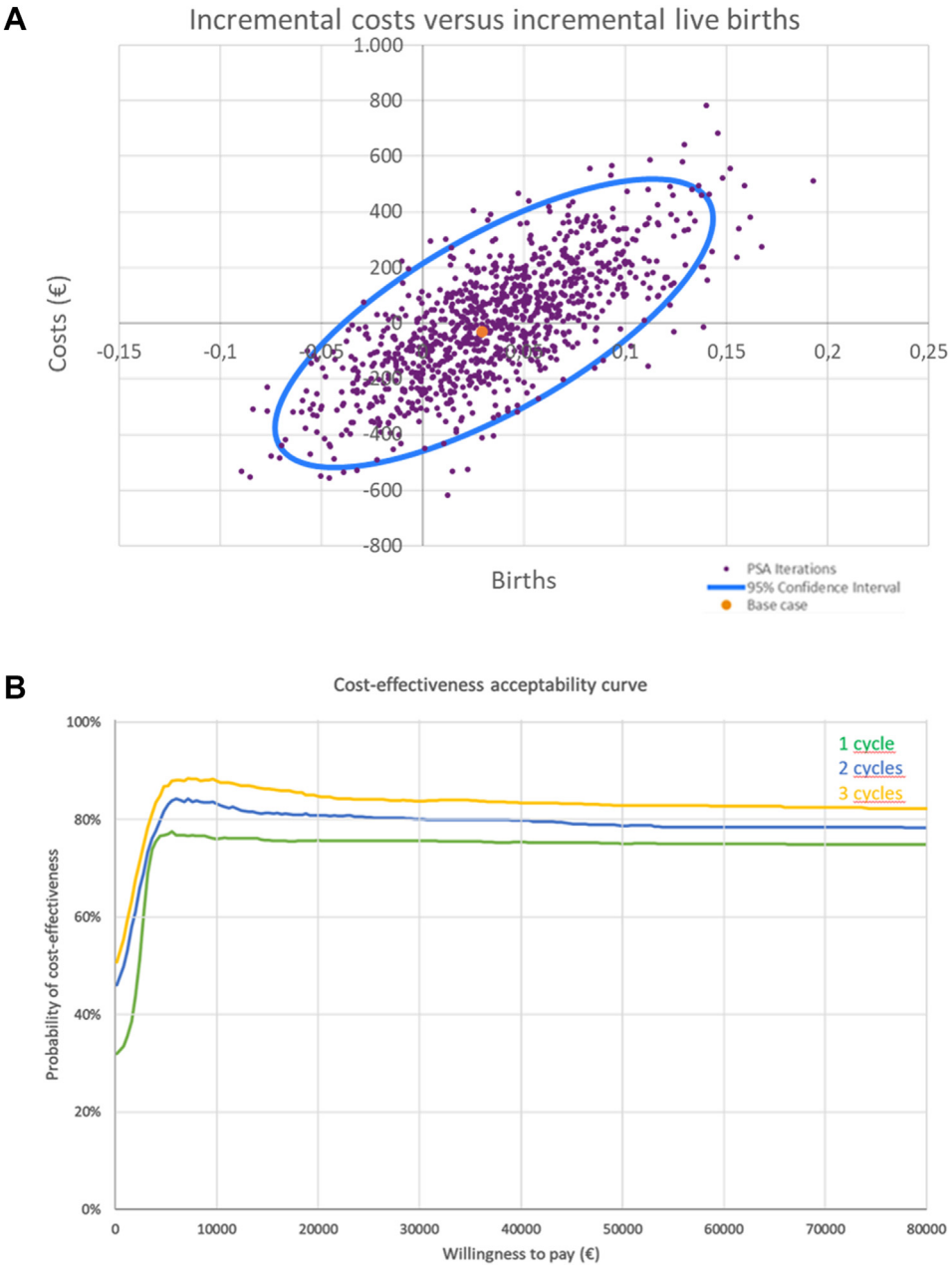

Fig. 4. Probabilistic sensitivity analysis: A) Cost-effectiveness plane for the third complete ART cycle. B) Cost-effectiveness acceptability curves for the first, second, and third complete ART cycle. ART, assisted reproductive technology. PSA, probabilistic sensitivity analysis.

Consolidated Standards of Reporting Trials (CONSORT) statement in 2014 to improve the quality of clinical trial reporting for infertility treatments [41–44] and is an increasingly recognised outcome to measure the success of an ART treatment program [15].

Another strength of our study is that selection bias was limited by censoring of stimulation cycles (if treatment was discontinued or was switched to another treatment than the one given for the first cycle), rather than deleting cases, which helped improve the meticulousness of the data analysis.

Finally, the robustness of the model was assessed using OWSA as well as PSA, which is the mandated method used by Health Technology Assessment agencies globally and is the predominant way in which the impact of uncertainty within a health economic evaluation is quantified [45].

Our findings are aligned with two other studies showing that OS prior to ART with r-hFSH is considered cost-effective versus OS with other gonadotropin preparations (hMG-HP and/or u-hFSH) [19,32], using real-world data from about 25,000 ART cycles performed in Germany in 2002 [19] or using data from a published meta-analysis [32].

By contrast, our results are in disagreement with two other published cost-effectiveness analyses in which hMG-HP was compared with r-hFSH-alfa. One study, using discrete event simulation modelling [29], was based on pooled data from two RCTs (the MERIT trial [13] and the EISG trial [46]). The authors reported on CLBR, but only included one fresh cycle and up to two related freeze–thaw embryo transfers, based on only 1-year follow-up data from the MERIT trial [30] and assuming equal success rates between fresh and frozen embryo transfers. The other study [31] only considered the cost-effectiveness for one fresh ART cycle based on efficiency data from only two RCTs (the MERIT trial ([13,30] and the MEGASET trial [47]). Compared with these two studies [29,31], the results reported here may be more relevant from a payer/stakeholder perspective, as they are based on patients treated in real-life practice (instead of typically good prognosis patients included in RCTs) and used a longer-term perspective of up to three completed ART cycles to assess CLBR (instead of only one completed ART cycle). Furthermore, in contrast with other studies, our study compared two specific FSH brands (instead of combining different recombinant or urinary FSH products in pooled groups). In addition, realizing that there is no widely accepted WTP for fertility, our study assumes an explicit WTP threshold based on GDP using WHO recommendations (as outlined in the "Methods" section), whereas in other studies, no WTP was considered.

Although the model data in our study are robust, more recent real-world data would reflect the current situation of clinical practice in terms of LBR achieved during ART treatment. We hypothesize that this will not have much impact on the findings reported here, as treatment protocols and clinical practice in Germany have not changed considerably over the past 10 years. However, more studies are planned to confirm that the results of this analysis may be generalizable to other European populations, since our results are based on data from a German database, and the pricing structure in Germany is different to that of other European countries. We also acknowledge the limitation that, in our study, assumptions had to be made where data were missing/incomplete (i.e., for some probabilities for moving between treatment stages [Table 1]) and for OHSS, which was assumed to be reflected in the dropout rates.

Summary

This is the first cost-effectiveness study comparing CLBR for r-hFSH-alfa versus hMG-HP in a large German registry, using real-world data from 28,641 women. r-hFSH-alfa was associated with higher CLBR and lower cost per live birth compared with hMG-HP for up to three complete ART cycles. Treatment with r-hFSH-alfa led to lower overall medication costs, as a lower dose was needed per live birth. The robustness of the results was confirmed in one-way and probabilistic sensitivity analyses. Overall, the data and objective evaluation indicate that r-hFSH-alfa is cost-effective versus hMG-HP for OS before ART treatment. Cost-effectiveness using more recent data and versus other FSH comparators should be considered in future analysis, when additional data become available.

Role of the funding source

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Availability of data and materials

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

Authors' contributions

Conception and design of the analysis, interpretation of data, and critical review of the manuscript: KB, CR, JES, ML, AA, TDH, EF, VL, and RF.

Practice points

- Currently available gonadotropins for ovarian stimulation (OS) during assisted reproductive technology (ART) treatment include recombinant human follicle-stimulating hormone (r-hFSH) and urinary highly purified human menopausal gonadotropins (hMG-HP)
- r-hFSH contains only follicle-stimulating hormone (FSH) activity, whereas hMG-HP, which is extracted from the urine of postmenopausal women, contains both FSH and luteinizing hormone activity, as well as other proteins and metabolites
- Randomized controlled trials (RCTs) comparing different gonadotropin treatments have reported conflicting results, with a number of RCTs and meta-analyses finding no statistical difference in ART treatment outcomes and others reporting a difference in live birth and clinical pregnancy rates between r-hFSH and hMG
- A recent real-world analysis comparing the effectiveness of reference r-hFSH-alfa with hMG-HP in >28,000 patients in Germany showed that cycles stimulated with reference r-hFSH-alfa versus hMG-HP had increased cumulative live birth rates and clinical/ongoing pregnancy rates, alongside decreased cancellation rates and gonadotropin usage per oocyte retrieval
- In our analysis, the costs per live birth were found to be lower for originator r-hFSH-alfa versus hMG-HP in the German setting because of higher live birth rates in up to three complete ART cycles

Research agenda

- Cost-effectiveness studies of reference r-hFSH-alfa versus hMG-HP based on more recent real-world data.
- Cost-effectiveness studies of reference r-hFSH-alfa versus hMG-HP in other countries.

Declaration of competing interest

KFB has received honoraria or consultation fees from Merck Healthcare KGaA, Darmstadt, Germany, Ferring, Bayer, Stiftung Endometriose Forschung, and Takeda and is a member of an advisory board for Merck.

CR is an employee of Pharma Value Consulting, Switzerland.
JES, ML, and TDH are employees of Merck Healthcare KGaA, Darmstadt, Germany.
AA was an employee of Merck Healthcare KGaA, Darmstadt, Germany, at the time of the analysis.
EF is an employee of IQVIA, Real World Solutions, London, UK.
VL is an employee of IQVIA, Real World Solutions, Amsterdam, NL.
RF has received honoraria for lectures from Merck Healthcare KGaA, Darmstadt, Germany, and affiliates.

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Appendix A. Supplementary data

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