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A direct healthcare cost analysis of recombinant LH versus hMG supplementation on FSH during controlled ovarian hyperstimulation in the GnRH-antagonist protocol

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Abstract

Purpose We have previously published a retrospective matched-case control study comparing the effect of recombinant LH (r-hLH) versus highly purified human menopausal gonadotropin (hMG) supplementation on the follicle-stimulating hormone (FSH) during controlled ovarian hyperstimulation (COH) in the GnRH-antagonist protocol. The result from that study showed that the cumulative live birth rate (CLBR) was significantly higher in the r-hLH group (53% vs. 64%, $p=0.02$). In this study, we aim to do a cost analysis between these two groups based on our previous study.

Methods The analysis consisted of 425 IVF and ICSI cycles in our previous study. There were 259 cycles in the r-hFSH + hMG group and 166 cycles in the r-hFSH + r-hLH group. The total cost related to the treatment of each patient was recorded. Probabilistic sensitivity analysis (PSA) and a cost-effectiveness acceptability curve (CEAC) were performed and created.

Results The total treatment cost per patient was significantly higher in the r-hFSH + r-hLH group than in the r-hFSH + hMG group ($4550 ± 798.86 vs. $4290 ± 734.6, $p=0.003$). However, the mean cost per live birth in the r-hFSH + hMG group was higher at $8052, vs. $7059 in the r-hFSH + r-hLH group. The CEAC showed that treatment with hFSH + r-hLH proved to be more cost-effective than treatment with r-hFSH + hMG. Willingness-to-pay was evident when considering a hypothetical threshold of $18,513, with the r-hFSH + r-hLH group exhibiting a 99% probability of being considered cost-effective.

Conclusion The cost analysis showed that recombinant LH is more cost-effective than hMG supplementation on r-hFSH during COH in the GnRH-antagonist protocol.

Keywords Recombinant FSH · Recombinant LH · Human menopausal gonadotrophin · Cost-effectiveness · Cumulative live birth

What does this study add to the clinical work

The cost analysis showed that recombinant LH is more cost effective than hMG supplementation on r-hFSH during COH in the GnRH-antagonist protocol in Taiwan.

Introduction

Urinary and recombinant gonadotropin products are routinely used for ovarian stimulation (OS) in assisted reproductive technologies (ART). Among the gonadotropins, a follicle-stimulating hormone (FSH) is necessary to stimulate

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follicular growth in the ovaries, while the role of the luteinizing hormone (LH) appears to be beneficial in certain subgroups of women [1, 2]. Our previous study comparing the treatment outcomes of LH versus highly purified human menopausal gonadotropin (HP-hMG) supplementation on FSH in the GnRH-antagonist protocol revealed that the recombinant human follicle-stimulating hormone (r-hFSH) + recombinant human luteinizing hormone (r-hLH) group performed better in terms of numbers of oocytes retrieved, mature oocytes, fertilized oocytes and cumulative live birth rate (CLBR) (53.28% vs. 64.46%, $p = 0.023$) [3].

Choosing the optimal gonadotropin preparations for ovarian stimulation (OS) relies on various considerations, such as assessing the overall balance between benefits and risks, considering patient preferences, and evaluating cost-effectiveness. Decision-makers can utilize cost-effectiveness analyses to make informed assessments regarding the most suitable gonadotropin for OS. These analyses involve comparing all expenses associated with assisted reproductive technology (ART) cycles, which encompass both fresh and frozen-thawed embryo transfers, thus enabling a comprehensive evaluation to be performed. Previous studies involving analysis of the cost-effectiveness of gonadotropin in ART have included comparing r-hFSH-alfa with HP-hMG [4–6], r-hFSH-alfa with r-hFSH-alfa biosimilars [7], and r-hFSH plus r-hLH in comparison with (HP-hMG) [8]. There has not yet been a study performed comparing the cost-effectiveness of hFSH + r-hLH versus r-hFSH + hMG. This study aimed to compare the pharmaco-economics of OS with r-hFSH + r-hLH versus r-hFSH + hMG in the antagonist cycle by evaluating both the cost per live birth and cost-effectiveness through the use of patient files taken from a recently published study.

Methods

Model

A model structure was developed using Microsoft Excel (Fig. 1). The model structure was comprised of the live birth rate (LBR) state for one complete ART cycle, which is defined as all embryos transferred (fresh and/or frozen) after a single stimulation cycle or live birth [3]. The proportion of patients at the end of each treatment pathway was multiplied by the relevant cost (i.e., the cost of stimulation, embryo transfer, pregnancy or missed abortion), with the total sum of all pathway costs then used to generate the total 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 + hMG versus r-hFSH + r-hLH.

Clinical inputs

Data from a retrospective analysis collected between 2013 and 2018 [3] were used for comparison of the economic implications (cost per CLBR of r-hFSH + hMG versus

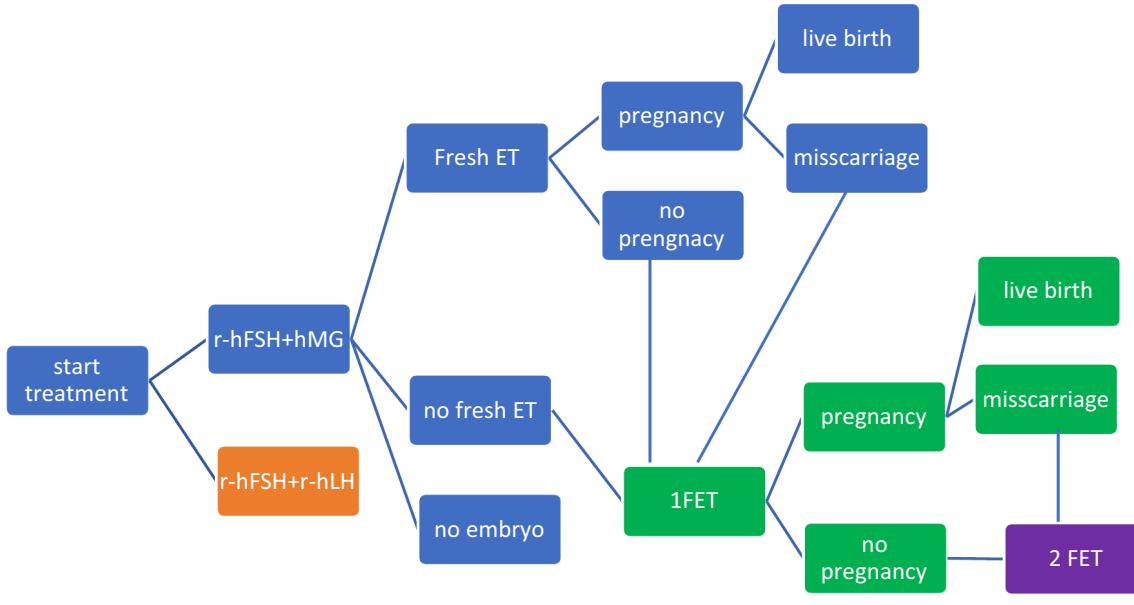

Fig. 1 Module structure. There were up to 4 times of FET in the r-hFSH + hMG group and 3 times in the r-hFSH + r-hLH group

r-hFSH + r-hLH). Details regarding study methodology, such as baseline characteristics and treatment variables, can be found in a previous paper [3]. Briefly, the study compared the effect on women who had received the GnRH antagonist protocol and r-hFSH + hMG or r-hFSH + r-hLH regimen over a five-day period for COH during an in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycle in Taichung Veterans General Hospital (TCVGH, Taiwan). Propensity score matching was applied to select matched subjects with balanced age, anti-mullerian hormone (AMH) level, and oocyte retrieval date across the two groups with a ratio of 2:1. The probability of moving from one model state to another was based on the outcome of the previous study. All subjects enrolled in this study involved patients who had either completed a simulation cycle with live birth or had transferred all embryos from one stimulation cycle. There were up to 4 times of frozen embryo transfer (FET) in the r-hFSH + hMG group and up to 3 times of FET in the r-hFSH + r-hLH group (Tables 1 and 2). The mean number of embryo transfer was 2.2 and 2 in fresh cycle; 2.1 and 1.9 in the first FET; 1.7 and 1.6 in the second FET; 1.8 and 1.75 in the third FET, 2 and 0 in the fourth FET in r-hFSH + hMG and r-hFSH + r-hLH group, respectively.

Cost

Cost inputs were categorized into treatment phases, including all treatment-related direct healthcare costs beginning from initiation of ART treatment up until gestational age at 12 weeks of pregnancy. The costs were based on the real cost for each patient, as recorded in their clinical records, as well as in the database of our Clinical Information Research & Development Center at TCVGH. The cost of oocyte pick-up (OPU) included charges for procedures regarding oocyte retrieval, the pre-op test, anesthesia, insemination and embryo culture costs. The costs for the hormonal test and sonography included the test on the FSH, estradiol, progesterone, LH and sonography during the COH cycle. Costs for COH medication included drugs for COH and the triggering of ovulation. Costs for fresh embryo transfer (ET), including cost of ET and luteal phase support (LPS) medication, all of which had accumulated until the day of the hCG test for an unsuccessful pregnancy, a gestational period of 12 weeks or a confirmed missed abortion if pregnancy failed later.

Table 1 The pregnancy rate and live birth rate of each embryo transfer procedure

	r-hFSH + hMG ($n = 259$)	r-hFSH + r-hLH ($n = 166$)
Pregnancy rate of fresh ET	35.9% (46/128)	42.3% (30/71)
LBR for Fresh ET	27.34% (35/128)	35.21% (25/71)
Pregnancy rate of FET 1	67.1% (96/143)	71.3% (72/101)
LBR of FET 1	56.66% (81/143)	65.34% (65/101)
Pregnancy rate of FET 2	75% (21/28)	73.9% (17/23)
LBR of FET 2	64.29% (18/28)	65.22% (15/23)
Pregnancy rate of FET 3	60% (3/5)	75% (3/4)
LBR of FET 3	60% (3/5)	50% (2/4)
Pregnancy rate of FET 4	100% (1/1)	0
LBR of FET 4	100% (1/1)	0

Table 2 Cumulative live birth rate (per start cycle)

Cumulative LBR	r-hFSH + hMG ($n = 259$)	r-hFSH + r-hLH ($n = 166$)
Fresh ET	13.51% (35/259)	15.06% (25/166)
Fresh + 1st FET	45.94% (119/259)	54.21% (90/166)
Fresh + 1st FET + 2nd FET	51.73% (134/259)	63.25% (105/166)
Fresh + 1st FET + 2nd FET + 3rd FET	52.89% (137/259)	64.46% (107/166)
Fresh + 1st FET + 2nd FET + 3rd FET + 4th FET	53.28% 1(138/259)	64.46% (107/166)

Costs of FET, including medication for endometrium priming, monitoring using sonography, hormonal tests, embryo thawing, and ET and LPS after FET, all of which had accumulated up until the day of the hCG test for unsuccessful pregnancy, a gestational period of 12 weeks or a confirmed missed abortion if pregnancy failed later. Costs of miscarriage management included ultrasound monitoring, OPD follow-up, medication and surgery for missed abortions. Costs of OHSS were applied to only those patients who had visited an ER or had been admitted for abdominal tapping, iv hydration and close observations. The cost for embryo cryopreservation was calculated separately. All charges, originally paid in Taiwanese Dollars (NTD), were converted to their equivalent in US Dollars (USD) at the exchange rate of 30 NTD to 1 USD, when the study was performed.

Statistical analyses and cost-effectiveness analysis

Data were presented as the mean ± Standard Deviation (SD), or as the percentage. Group comparison was performed with either the Chi-square test or Student t-test, using SPSS (Version 18). Significance of differences was set at $p < 0.05$ for all the above tests.

The ICER was calculated by comparing the incremental costs of each patient undergoing treatment with r-hFSH + r-hLH versus r-hFSH + hMG, along with the corresponding incremental effectiveness in terms of live birth rate. The incremental costs represent the additional expenses incurred by a patient when opting for r-hFSH + r-hLH treatment rather than r-hFSH + hMG treatment. With regards to incremental effectiveness, it signifies the additional percentage increase in the live birth rate observed when r-hFSH + r-hLH treatment is utilized when compared to r-hFSH + hMG treatment.

Sensitivity analysis

To conduct probabilistic sensitivity analysis (PSA), we employed a Monte Carlo simulation involving 10,000 bootstrap trials using the R package (R 4.2.2). Within this analysis, a cost-effectiveness plane was utilized to calculate both the incremental cost per patient and the incremental effectiveness, based on the results obtained from the PSA. Subsequently, we generated a cost-effectiveness acceptability curve (CEAC) to depict the probability that treatment involving r-hFSH + r-hLH proved to be cost-effective at various specific willingness-to-pay (WTP) thresholds. This curve would allow us to understand the likelihood of whether treatment with r-hFSH + r-hLH would be considered cost-effective across different levels of willingness to pay.

Results

A total of 259 patients and 166 patients were included in the r-hFSH + hMG and r-hFSH + r-hLH groups, respectively. The basic characteristics of the patients have been reported in our previous study [3], with the fertility outcomes shown in Tables 1 and 2. The CLBR was significantly higher in the r-hFSH + r-hLH group than that seen in the r-hFSH + hMG group (64.46% vs. 53.28%, $p < 0.05$). There were 5 and 3 patients who had experienced moderate OHSS in the r-hFSH + hMG and r-hFSH + r-hLH groups, respectively. There were no ectopic pregnancies in either group.

The average cost per patient in each categorization is shown in Fig. 2 and Table 3. There are no significant

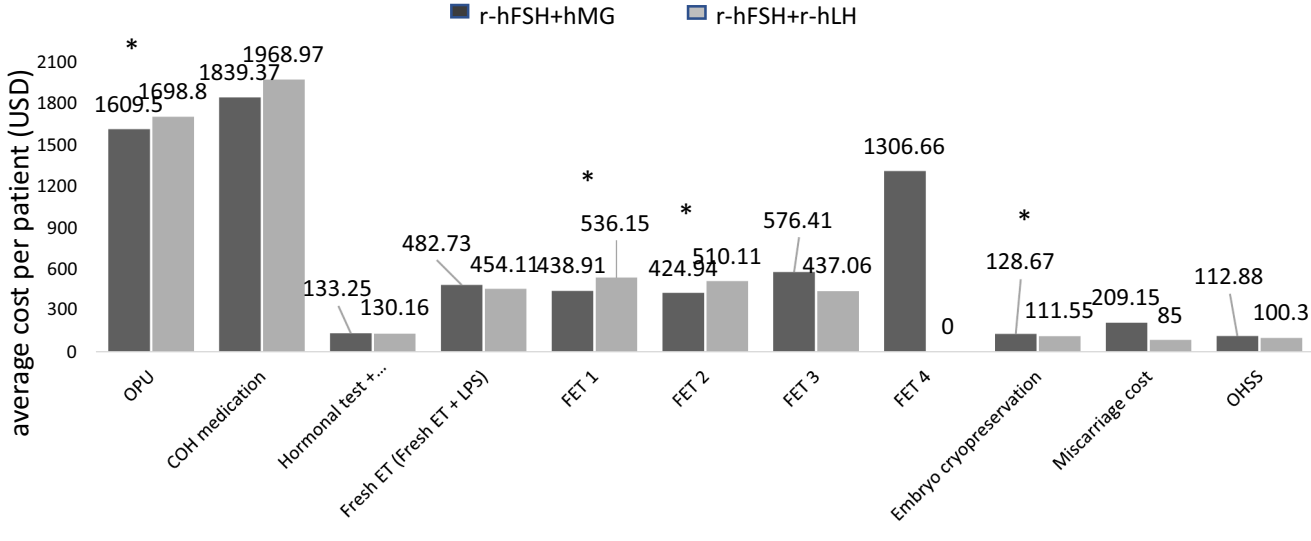

Fig. 2 The details regarding treatment costs in the two groups. * With significant differences

Table 3 Key clinical and cost-effectiveness results (cumulative)

Cumulative LBR	r-hFSH + hMG	r-hFSH + r-hLH	Difference
Fresh ET + 1st FET			
Live birth rate	45.9%	54.2%	8.3%
Cost per live birth (USD)	9199	8237	
Fresh ET + 1st FET + 2nd FET			
Live birth rate	51.7%	63.3%	11.6%
Cost per live birth (USD)	8261	7175	
Fresh ET + 1st FET + 2nd FET + 3rd FET			
Live birth rate	52.9%	64.5%	11.6%
Cost per live birth (USD)	8101	7059	
Fresh ET + 1st FET + 2nd FET + 3rd FET + 4th FET			
Live birth rate	53.28%	64.46%	11.2%
Cost per live birth (USD)	8052	7059	

differences seen in the cost of COH medication, hormonal tests, sonography, fresh ET, missed abortion, or OHSS, between both groups. The cost of OPU is shown to be higher in the r-hFSH + r-hLH group ($1,698.8 ± 502.91 vs. $1,609.5 + 459.89, $p = 0.04$). The details show that the costs for insemination and embryo culture are higher in the r-hFSH + r-hLH group, with the cost for FET1 and FET 2 also higher in the r-hFSH + r-hLH group. The details show that this is due to the cost of LPS medication being higher. Total treatment costs per patient were significantly higher in the r-hFSH + r-hLH group than the r-hFSH + hMG group ($4,550 ± 798.86 vs. $4,290 ± 734.6, $p = 0.003$). However, the costs per live birth were lower with r-hFSH + r-hLH compared with r-hFSH + hMG after fresh ET and following FETs (Table 3). Total treatment cost per live birth was more cost-effective in the r-hFSH + r-hLH group ($7,059) than the r-hFSH + hMG group ($8,052). The ICER was calculated as $2,325 for the r-hFSH + r-hLH group versus the r-hFSH + hMG group (Table 4).

Moreover, we also divided our patients according to total treatment cost and found that except for the patients whose treatment cost was more than $5,100, live birth rates all seemed to be higher in the r-hFSH + r-hLH group than the r-hFSH + hMG group when total treatment cost was < $3600, or in the ranges of $3600-$3,899, $3900-$4,199, $4200-$4499, $4500-$4799 and $4800-$5099. It was discovered that when total treatment cost was between $4200and 4499, the CLBR was significantly higher in the r-hFSH + r-hLH group (82.1% vs. 54.9%, $p = 0.022$). (Fig. 3).

Sensitivity analysis

The results of PSA are presented on a cost-effectiveness plane (Fig. 4a), allowing for assessment of the level of confidence in the analysis outputs considering the uncertainties in the model inputs. The ICER between the r-hFSH + r-hLH and r-hFSH + hMG groups was determined to be $2,325 with a 95% confidence interval for ICER ranging from $745 to $9,665.

Figure 4b illustrates a CEAC generated from multivariate probabilistic sensitivity analysis (PSA) consisting of 10,000 Monte Carlo iterations. This curve represents the likelihood of the r-hFSH + r-hLH group being deemed more cost-effective when compared to the r-hFSH + hMG group across various willingness-to-pay (WTP) thresholds. Through this analysis, it was determined that when considering a hypothetical threshold of $18,513, the r-hFSH + r-hLH group exhibited a 99% probability of being considered cost-effective.

Discussion

This cost-effectiveness study compared r-hFSH + hMG with r-hFSH + r-hLH in an antagonist protocol using a previous propensity score matching case–control retrospective study

Table 4 Model clinical input, cost outputs and costs per live birth

	r-hFSH + hMG	r-hFSH + r-hLH	Incremental	*p*-value
Live birth rate	53.3%	64.5%	11.2%	0.030
Mean total cost ($)	4290	4450	260	0.003*
Cost per live birth	8052	7059	2325	

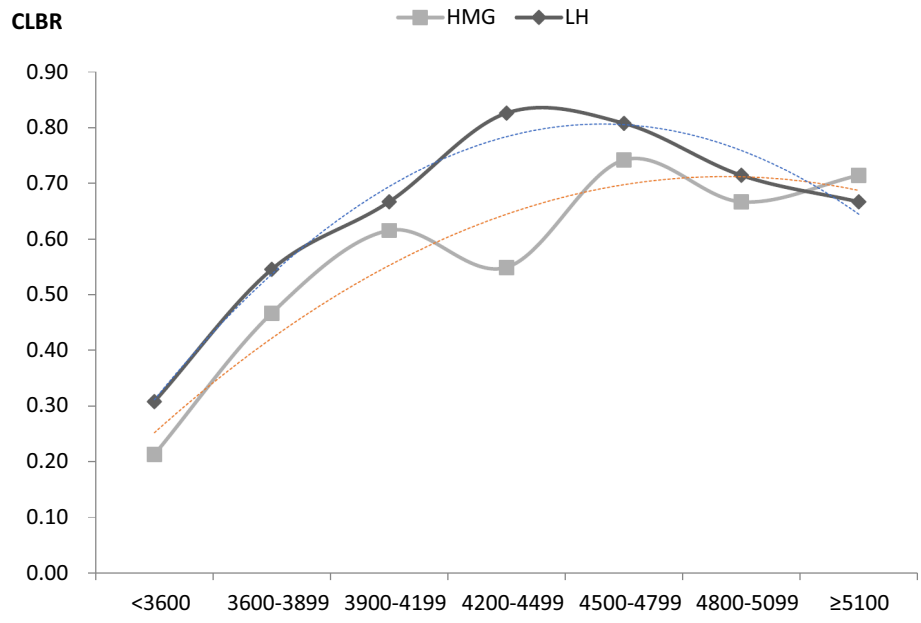

Fig. 3 The total treatment cost and CLBR for each treatment group

[3]. The results presented here indicate that r-hFSH + r-hLH is associated with a higher LBR and a lower cost per live birth when compared with r-hFSH + hMG for CLBR in ART cycles.

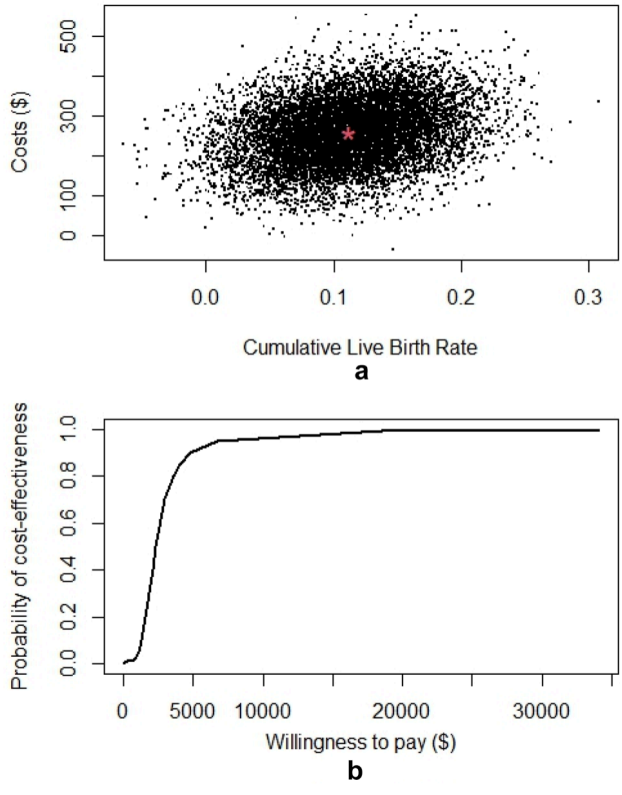

Fig. 4 Probabilistic sensitivity analysis: **a** Cost-effectiveness plane **b** Cost-effectiveness acceptability curve

Although the unit price of r-hLH is higher than hMG, there is no significant difference seen in the cost of COH medication in the two groups. This may be due to a lower total gonadotropin dose being given to the r-hFSH + r-hLH group [3]. The cost of OPU was higher in the r-hFSH + r-hLH group, which may be due to their oocyte retrieval number being higher, and therefore the costs of insemination and culture became higher. The mean cost for first and second FET was shown to be higher in the r-hFSH + r-hLH group, with the details revealing that there were more patients in this group using Crinone Vaginal Gel 8% (Merk Serono) rather than progesterone inj 25 mg/ml injection for luteal phase support. The unit price is more expensive for Crinone Vagina Gel than progesterone injection. Currently, using these two types of progesterone for luteal support provides for the same live birth rate in the FET cycle [9].

The final results show that the total cost per patient was higher for those being treated with r-hFSH + r-hLH than r-hFSH + hMG, which was the result of the increase in costs associated with a successful pregnancy and the higher proportion of live birth seen with r-hFSH + r-hLH when compared with r-hFSH + hMG. To overcome issues of reporting and interpreting cost-effectiveness ratios we conducted an incremental analysis, which helps compare two products for establishing cost-effectiveness. We report an ICER of $2,325 for r-hFSH + r-hLH compared with r-hFSH + hMG. Through this analysis, it was determined that when considering a hypothetical threshold of $18,513, the r-hFSH + r-hLH group exhibited a 99% probability of being considered cost-effective.

Previous cost-effectiveness studies comparing COH medication, including originator r-hFSH-alfa with

r-hFSH-alfa biosimilars, have shown conflicting findings, with some studies favoring originator r-hFSH-alfa and others favoring r-hFSH-alfa biosimilars [7, 10–12]. A recent cost-effectiveness analysis study comparing r-hFSH and hMG based on data from a German registry revealed that r-hFSH-alfa was found to be a cost-effective strategy when compared with hMG-HP over three cycles [5]. There have also been pharmacy economic analysis studies performed which have compared rFSH plus rLH with hMG based on a retrospective study [13] showing that r-FSH + r-LH is a cost-effective option [8]. Currently there are no studies comparing the cost-effectiveness of r-hFSH + r-hLH with r-hFSH + hMG. Hence, our study provides more options and evidence which will assist both clinicians and patients in their decision making.

Another strength found in our study is that our analysis provides information on relative costs in terms of cumulative live births. Cumulative live birth is a better indicator of quality and success in IVF/ICSI treatment, as cryopreservation is an integral part of IVF [14]. Moreover, except for dividing patients according to their total treatment cost and clearly showing the r-hFSH + r-hLH group having a higher CLBR in the same range of treatment costs, we have conducted PSA using a 10,000 trial simulation, which is the mandated method used by Health Technology Assessment agencies globally, and is also the predominant way in which the impact of uncertainty within a health economic evaluation is quantified [15].

Our study does have some limitations. First, it was based on a retrospective study. However, the study utilized propensity score matching to reduce any bias caused by demographic factors or baseline characteristics. Second, we only analyzed medical costs up until the gestational period of 10 weeks, rather than the costs incurred during the entire prenatal course and/or any following pregnancy-related complications. This limitation is due to the fact that not every woman in the study received antenatal care in our hospital. A final limitation is that the study is from one single center in Taiwan. Although the costs surrounding every patient could be clearly recorded in detail, country-specific prices and assumptions need to be considered before generalizing our present results with other centers or countries.

Conclusion

To the best of our knowledge, this study is the first cost-effectiveness analysis comparing r-hFSH + r-hLH with r-hFSH + hMG in the antagonist cycle using CLBR as the primary outcome. Our study has shown that although the total treatment cost per patient was higher in the r-hFSH + r-hLH group than the r-hFSH + hMG group, the r-hFSH + r-hLH group remained more cost-effective. The CLBR was seen to be relatively higher for the r-hFSH + r-hLH group when total treatment cost was lower than $5,100. The sensitivity analysis showed that when considering a hypothetical threshold of $18,513, the r-hFSH + r-hLH group exhibited a 99% probability of being considered cost-effective. Further studies based on a larger dataset, perhaps a nationwide and multicenter collaboration analysis which would include the costs of a prenatal course and any possible pregnancy complications would provide a more holistic understanding of the implications of the different treatment regimens.

Author contributions J-CC: Protocol/project development, Data Collection, Manuscript writing. M-JC: Protocol/project development, manuscript revision. Y-MC: Data analysis, prepared the figures and manuscript revision. H-FK: prepared the figures and tables. Y-CY: prepared the figures and tables. H-FG: Data collection or management. L-YC: Data collection or management. Y-FC: Data analysis. S-TC: Data analysis. All authors reviewed the manuscript.

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Data availability All data generated and analyzed during this study are included in this published article and its supplementary information files.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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Consent to participate Not Applicable.

Consent to publish Authors are responsible for correctness of the statements provided in the manuscript.

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