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ORIGINAL RESEARCH

Recombinant Human Follicle-Stimulating Hormone in Controlled Ovarian Hyperstimulation with Assisted Reproductive Technology in China: A Cost-Effectiveness Analysis

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Background: To compare the cost-effectiveness of originator (reference) recombinant human follicle stimulating hormone alfa (rhFSH-α) (follitropin alfa, GONAL-f) and its biosimilar (rhFSH, JinSaiHeng) in assisted reproductive technology (ART) from a Chinese patient perspective.

Methods: A decision tree model was developed to simulate the treatment pathway of infertile women undergoing ART using GONAL-f or JinSaiHeng. Published clinical and cost data were used to evaluate the cost-effectiveness of the rhFSH-α. The cumulative live birth rate (CLBR), direct medical costs and costs per cumulative live birth were estimated via an analytic decision-tree model.

Results: CLBR of GONAL-f was higher than JinSaiHeng preparation (88.3% vs 84.4%), while the cost per cumulative live birth was lower (51,475 vs 52,095 CNY).

Conclusion: The originator rhFSH-α was associated with higher CLBR and lower cost per cumulative live birth, with incremental cost per additional live birth of 38,096 CNY (Chinese Yuan).

Keywords: recombinant human follicle stimulating hormone, controlled ovarian stimulation, assisted reproductive technology, cost-effectiveness analysis

Introduction

In China, the notable elevation of women's reproductive autonomy, coupled with factors such as marital dynamics and career considerations has precipitated a delay in childbirth. Consequently, there has been a surge in women seeking fertility preservation options and assisted reproductive technology (ART).[1] However, infertility is a heavy burden on individuals and families. In China, the infertility rate has increased from 6.7% in 1988 to 15% in the early 2010s.[2,3] In 2018, the number of infertile women was estimated to exceed 40 million.[3] ART is a commonly used treatment option for women encountering fertility issues. In ART, gonadotropins are critical to follicle development and have a crucial role in optimizing clinical outcomes, such as being directly associated with pregnancy and live birth rate.[4] With a high financial burden,[4] patients and healthcare providers need to understand the cost-effectiveness of gonadotropins to maximize the live birth rate within limited resources. The cumulative live birth rate (CLBR) is proposed to assess IVF program effectiveness, incorporating fresh and thawed frozen embryo transfers.[5] In contrast to the usual "per cycle" or "per embryo transfer" pregnancy reporting, CLBR encompasses total live births. When initial fresh cycles fail, couples inquire about the chance of live birth with further ART. Patients prioritize CLBR as it comprehensively reflects live birth probability throughout treatment, influencing decisions on continuing IVF.[6]

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In the past decades, commercially available gonadotropin products were generated from human chorionic gonadotropin (hCG) extract, followed by human menopausal gonadotropins (hMG), urinary follicle-stimulating hormone (u-FSH), highly purified hMG, highly purified u-FSH, and recombinant FSH.[4,7] GONAL-f (follitropin α) was the first recombinant human FSH (r-hFSH) authorized in China in 2006. It has the advantages of constant supply, free from urinary protein contaminants, with higher biopotency and overall purity, guaranteed batch-to-batch consistency, high safety, and tolerability.[8–10] JinSaiHeng (recombinant human follitropin for injection) is another gonadotropin that is widely used in China. It is a biosimilar of GONAL-f, entered the market in 2014. By definition, a biosimilar medicine should be biologically similar to its originator. A multi-center, double-blind, randomized clinical trial based on a Chinese population shows that JinSaiHeng is comparable to GONAL-f in terms of the total number of oocytes and follicle growth obtained in a controlled ovarian hyperstimulation (COH) cycle with no statistical difference.[11] For patients and clinicians, however, a higher CLBR is the goal of therapy.[12]

Among infertile couples, treatment cost and cost-effectiveness are prominent considerations, alongside emotional factors. Additionally, biosimilar medications are increasingly utilized in clinical practice, highlighting the importance of testing their effectiveness to optimize their future applications. Therefore, in this study, we aimed to evaluate the cost-effectiveness of the originator rhFSH (GONAL-f) and its biosimilar (JinSaiHeng) in ART by building a cost-effectiveness analysis model to help Chinese patients choose FSH reasonably and maximize the CLBR while ensuring patient affordability.

Materials and Methods

Development of a Decision Tree Model

A decision tree model was developed in Microsoft Excel to simulate the treatment pathway of infertile women undergoing ART using GONAL-f or JinSaiHeng, as well as to estimate CLBR, direct medical costs, the cost per cumulative live birth, and the incremental cost per live birth. Since ART is currently not covered by medical insurance reimbursement in China, the research perspective of this study is from the patient's point of view.

The model hypothetically comprised of 1 fresh embryo transfer, and up to 3 frozen embryo transfers until first delivery. Figure 1 illustrates the structure of the fresh and frozen cycles of the same model, respectively. The number of fresh and frozen cycles was validated by clinical experts as an appropriate setting in China.

Clinical Inputs

Transition probabilities represent the likelihood of moving between different states during infertility treatment. Within this model, transition probabilities for key states in the model are based on a multicenter, double-blind, randomized controlled, non-inferior trial that included 267 infertile women with normal ovarian reserve from 6 reproductive

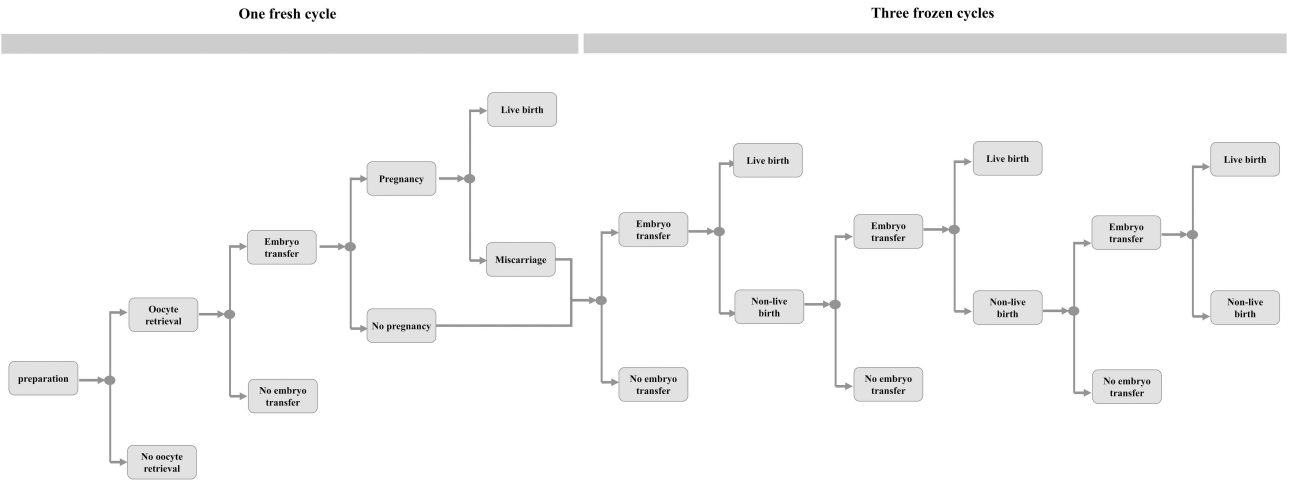

Figure 1 Cost-effectiveness model decision-tree structure of rhFSH for ART.

Table 1 Transition Probabilities for Key States in the Model

	GONAL-f					
	n	Total number of patients[#]	Transition probability	Lower limit	Upper limit	Distribution
Oocyte retrieval	132	133	99.2%	97%	100%	Beta
Embryo transfer-fresh cycle	132	132	100%	100%	100%	Beta
Clinical pregnancy-fresh cycle	61	132	46.21%	38%	55%	Beta
Live birth-fresh cycle*	56	61	91.8%	84%	97%	Beta
Embryo transfer-frozen cycle**	76	76	100%	90%	100%	Beta
OHSS-mild to moderate	3	133	2.26%	0	5%	Beta
OHSS-severe	1	133	0.75%	0	3%	Beta
	JinSaiHeng					
	n	Total number of patients[#]	Transition probability	Lower limit	Upper limit	Distribution
Oocyte retrieval	127	134	94.8%	90%	98%	Beta
Embryo transfer-fresh cycle	127	127	100%	100%	100%	Beta
Clinical pregnancy-fresh cycle	54	127	42.52%	34%	51%	Beta
Live birth-fresh cycle*	54	54	100%	100%	100%	Beta
Embryo transfer-frozen cycle**	73	73	100%	90%	100%	Beta
OHSS- mild to moderate	6	134	4.48%	0	5%	Beta
OHSS- severe	1	134	0.75%	0	3%	Beta

Notes: *Live birth rate in the model was defined as the proportion of patients with successful pregnancies; [#]Total number of patients with successful pregnancies. **It was assumed that 100% of women who do not achieve a successful delivery of a live neonate, would have a successful embryo transfer with a frozen embryo.
Abbreviations: rhFSH, Recombinant human follicle stimulating hormone; OHSS, Ovarian hyper-stimulation syndrome.

facilities.[11] GONAL-f and its biosimilar were evaluated in terms of oocyte fertilization rate, clinical pregnancy rate, live birth rate, and adverse events.[11] We also assumed that the frozen cycle pregnancy rate equal to the fresh cycle one and the live birth rate for each successive frozen cycle has no difference[13,14] between intervention arms (Table 1).

Cost Inputs

Cost inputs were categorized into medication costs, IVF/ICSI costs, birth-related costs, and adverse event (OHSS, mild to moderate, and severe) costs. The information on OHSS was obtained from the electronic medical records of patients.[11] The definition, classification, and severity of OHSS were adopted according to the accepted criteria in China.[15] Drug prices were extracted from a publicly available China province tendering database and were the average of the most recent provincial tendering prices. The unit price of GONAL-f is 232 CNY (Chinese Yuan)/75 IU, and unit price of JinSaiHeng is 226 CNY/75 IU. Medication costs are calculated by the dosages utilized in clinical trials as well as drug unit cost (Table 2).[9–11]

Costs were applied to each step of ART modelled including controlled ovarian stimulation, oocyte retrieval, no oocyte retrieval, embryo transfer, etc. The above information was obtained from many hospitals and IVF/ICSI centers in Beijing, Guangzhou, Shenzhen, Jiangsu and Chongqing, China. The birth-related costs consisted of vaginal, and C-section birth

Table 2 Daily Dosing of GONAL-f and JinSaiHeng

	Total dose (IU)	Mean Daily dose (IU)	Treatment Duration (day)
Originator rhFSH-α	2215.4	199.6	11.1
Biosimilar rhFSH	2302.2	203.7	11.3

Abbreviation: rhFSH, Recombinant human follicle stimulating hormone.

Table 3 ART, Birth, OHSS Related Cost Inputs

	Model Inputs value	Lower Limit	Upper Limit	Distribution
ICSI & IVF (%)				
IVF follicle punctuations	73	70	78	Dirichlet
ICSI follicle punctuations	27	22	31	Dirichlet
IVF/ICS related cost (CNY)				
General treatment, treatment plan	82	20	145	Gamma
Serological tests	3192	2000	4500	Gamma
Oocyte retrieval	2540	1500	4500	Gamma
Discontinuation before ovum pick-up	2075	1600	2500	Gamma
Anesthesia, including monitoring	783	250	1200	Gamma
IVF and embryo transfer	7133	1500	13,400	Gamma
ICSI and embryo transfer	10,200	6500	15,400	Gamma
IVF, no embryo transfer	5900	3000	11,000	Gamma
ICSI, no embryo transfer	8580	5000	13,000	Gamma
Blood test for β-HCG, pregnancy test	44	30	50	Gamma
Birth-related cost (CNY)				
Live birth	10,021	7000	12,750	Gamma
Miscarriage	1548	500	2690	Gamma
OHSS costs (CNY)				
Blood test (×1)	19	18	20	Gamma
Liver function test (×1)	220	189	250	Gamma
Hospitalization	8750	75,000	27,500	Gamma
B-mode ultrasonography	125	70	180	Gamma

Abbreviations: IVF, In vitro fertilization; ICSI, Intracytoplasmic sperm injection; OHSS, Ovarian hyper-stimulation syndrome.

costs in case of successful live birth, and dilation and curettage cost in case of miscarriage. The mild to moderate OHSS would incur various tests and monitor costs, while the severe OHSS would incur the cost of hospitalization (Table 3).

Sensitivity Analysis

One-way sensitivity analysis (OWSA) was conducted for all clinical parameters by investigating outcomes around the upper and lower values of the reported outcomes. OWSA for cost input and clinical effectiveness were conducted by investigating outcomes around the upper and lower 25% and 10% variance of input parameters, respectively. Probabilistic sensitivity analysis (PSA) was conducted for incremental live births using 1,000 Monte-Carlo iterations.

Results

Decision Tree Analysis

The results of the base case analysis are outlined in Table 4. Results indicated that GONAL-f was associated with a higher CLBR, with an increase of 3.9% (88.3% vs 84.4%). Individually, the total cost of GONAL-f is slightly higher than that of JinSaiHeng (45,474 vs 43,983 CNY), but when the cost per live birth (total cost/CLBR) was calculated, the total cost of GONAL-f (51,475 vs 52,095 CNY) was lower than that of JinSaiHeng. From the perspective of pharmacoeconomics, this translated into an incremental cost-effective ratio (ICER) of 38,096 CNY (approximately 6,000$).

Sensitivity Analysis Results

The OWSA for the base-case comparisons indicated that the results were sensitive to the probability of live birth, the probability of pregnancy and OHSS costs (Figure 2). Probabilistic sensitivity analysis confirmed the robustness of the model outcomes. Sensitivity analyses supported that GONAL-f was a cost-effective strategy (Figure 3).

Table 4 Incremental Cost-Effectiveness Analysis of GONAL-f and JinSaiHeng

	GONAL-f	JinSaiHeng	Difference
Clinical outcome			
Cumulative live birth rate (%)	88.3	84.4%	3.9%
Cost outcome			
Medication cost (CNY)	6945	6998	−53
OHSS management costs (CNY)	75	85	−11
IVF/ICSI costs (CNY)	23,207	22,415	792
Birth-related costs (CNY)	15,247	14,485	762
Total costs (CNY)	45,474	43,983	1,490
Cost-effectiveness outcome			
Cost per cumulative live birth* (CNY)	51,475	52,095	−620
Incremental cost per additional live birth (CNY)	38,096		

Notes: *Cost per cumulative live birth=total cost/cumulative live birth rate; ICER= total cost difference/cumulative live birth rate difference.

Abbreviations: OHSS, Ovarian hyper-stimulation syndrome; rhFSH, Recombinant human follicle stimulating hormone; IVF, In vitro fertilization; ICSI, Intracytoplasmic sperm injection.

Discussion

In this study, the cost-effectiveness analysis of the originator (GONAL-f) and its biosimilar (JinSaiHeng) was simulated and estimated using a pharmacoeconomic decision tree model, which reflected the current clinical practice in China.

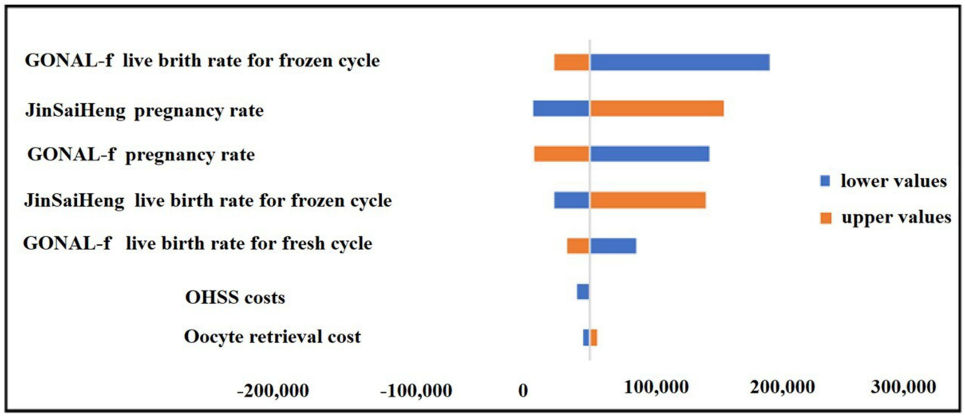

Figure 2 Tornado graph of OWSA. OWSA for cost input was estimated using a 25% variation of parameters, while OWSA for clinical efficacy by 10% variance.

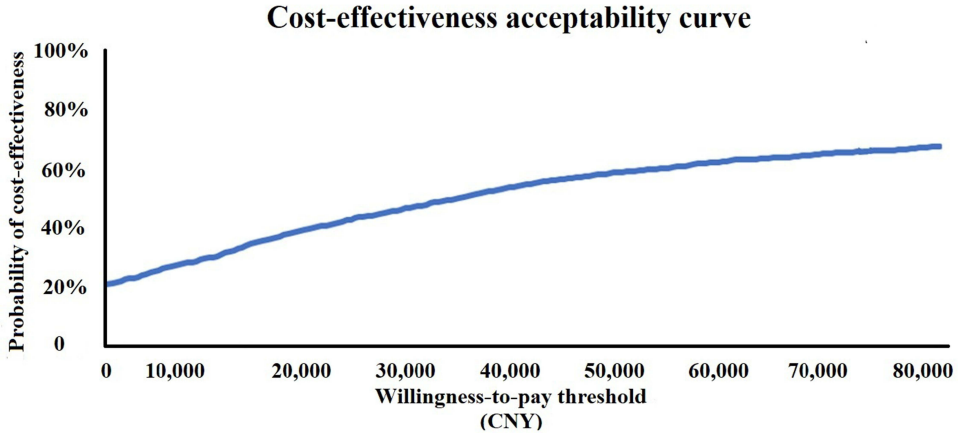

Figure 3 Cost-effectiveness acceptability curve based on probabilistic sensitivity analysis.

When modelling the clinical route of assisted reproduction, 1 fresh cycle and 3 frozen cycles were considered. In terms of costs, since IVF/ICSI and medication costs are paid for by patients at their own expense in China, we calculated the costs from the patient's perspective, which is more in accordance with the true reality in China. Our analysis relied on clinical data from a Chinese population-based, multi-center, double-blind, non-inferiority, randomized controlled trial. To investigate the efficacy and safety of the biosimilar of GONAL-f (JinSaiHeng) in ART of COH, Yang et al conducted a randomized controlled trial in 267 infertile women with normal ovarian reserve who were administered with JinSaiHeng (n = 134) or GONAL-f (n = 133). The study was conducted from 2017 to 2019 in 6 reproductive medical centers in China. The six reproductive centers are located in diverse regions across China, indicating that the population mentioned in the article is fairly representative. The total number of oocytes, usage of FSH, fertilization rate of oocytes, clinical pregnancy rate, live birth rate, and the incidence of OHSS were compared between the two groups. There was no statistically significant difference in baseline data between the experimental and control groups. The data between the two groups were comparable, and the results were reliable.

The findings demonstrate that GONAL-f may increase CLBR in patients receiving COH with ART and is a cost-effective option, compared to the willingness-to-pay (WTP) threshold of 1 time GDP per capita in China in 2022 (85,698 CNY, equal to 12,741 USD). The incremental cost per additional live birth is 38,096 CNY, which suggests that GONAL-f is more cost-effective if the WTP for a live birth is more than 38,096 CNY. These findings are susceptible to some uncertainty, which is influenced by model parameters including pregnancy rate, live birth rate, and WTP per live birth.

In terms of total costs, GONAL-f is just 1,490 CNY more expensive than JinSaiHeng. This is because GONAL-f has a higher CLBR, which boosts IVF/ICSI and birth-related costs, thereby increasing the total cost of GONAL-f. However, the incidence of OHSS, especially mild to moderate OHSS, is lower in GONAL-f, which saves adverse event-related costs. The total dosage of GONAL-f is reduced (2,302 IU vs 2,215 IU). Therefore, although the peer unit price of GONAL-f is somewhat higher, the overall costs of medication are diminished.

The findings of our study may assist physicians and patients in making decisions about which rhFSH to use for ART. Savings of overall cost with comparable clinical efficacy offer several benefits for both patients and healthcare providers. Given that ART is self-paid/uninsured in China, the reduced treatment expenses make it more financially accessible, thereby enhancing the accessibility of ART treatments and enabling more patients to receive necessary care.

Our findings are similar to those of previous studies from other countries.[16–19] Previous cost-effectiveness studies showed that GONAL-f has a higher CLBR than JinSaiHeng.[16] This outcome is consistent with the results of a meta-analysis comparing rhFSH and its biosimilars. In terms of cost, the results of this study are congruent with the findings of another cost-effectiveness study,[17] which demonstrates that GONAL-f may save adverse event-related costs.

Of course, our study has some limitations. All clinical inputs in our model were from a single clinical trial in China and validated by clinical experts. Although hospitals from different regions of China are selected, they are not fully representative of the whole nation. We performed a univariate sensitivity analysis for this, which showed that the cost input data had little influence on the final conclusion.

This is the first health economics study on rhFSH, both the originator and its biosimilar in China. If further clinical data on ART become available in the future, they may be updated using the pharmacoeconomic model developed in this work, and additional real-world data can be used to assess the effectiveness, safety, and economics in diverse regions and populations.

Ethics Statement

This study was approved by the Ethics Committee of China Pharmaceutical University. We confirm that informed consent was obtained from the study participants. And we followed the guidelines outlined in the Declaration of Helsinki.

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Disclosure

Angying Du is an employee of Merck Serono Co. Ltd., China (an affiliate of Merck KGaA Darmstadt, Germany). All other authors have no conflicts of interest to declare.

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