Real-World Effectiveness and Safety of Recombinant Human Follicle-Stimulating Hormone (rhFSH) in Infertile Women undergoing Assisted Reproductive Technology (ART): A Korean Nationwide Cohort Study

Joong Yeup Lee[1,†], Eun-Young Choi[2,3,†], Jung Ryeol Lee[4,5], Young Sik Choi[6,7], Ji Hyang Kim[8], Chang-Woo Choo[9], Yunju Choe[10], Hee-Jin Seo[10], Hyesung Lee[11], Yujeong Shin[12], Yejin Jeon[12], Ju-Young Shin[2,10,13,*] and Hoon Kim[5,14,*]

Despite widespread rhFSH use in infertile women undergoing ART, real-world comparative data on its effectiveness and safety across different rhFSH types remain limited. Using the HIRA claims database, we included 10,684 women aged 20–39 with infertility (2016–2021) who used only rhFSH in their first in vitro fertilization–embryo transfer (IVF-ET). Outcome variables comprised effectiveness (≥11 oocytes retrieved, pregnancy rates and live birth rate) and safety (ectopic pregnancy, miscarriage, preterm birth and ovarian hyperstimulation syndrome [OHSS]) in the whole cohort, further categorized into follitropin and other rhFSH. Baseline characteristics were described, and relative risks (RR) with 95% confidence intervals (CI) were estimated using a generalized linear model, adjusting for age and imbalanced variables. Of 10,684 patients prescribed rhFSH, 7.1% were aged 20–29, 41.6% were 30–34, and 51.3% were 35–39. ICSI was utilized in 57.7% of cycles, and 76.8% used the GnRH antagonist protocol. The live birth rate was 38.8%, and the OHSS rate was 5.9%. Comparing baseline characteristics of the follitropin (n = 2,594) and other rhFSH group (n = 8,090), ICSI (62.2% vs. 56.3%) and GnRH antagonist protocol (81.3% vs. 75.3%) were more common in the follitropin group. Women who received follitropin were more likely to have ≥11 oocytes retrieved (adjusted RR, 1.09; 95% CI: 1.02–1.16) and less likely to have OHSS (adjusted RR, 0.73; 95% CI: 0.60–0.90). These findings provide real-world evidence supporting rhFSH effectiveness and safety in fresh IVF cycles, with follitropin potentially offering advantages in oocyte retrieval and reduced OHSS rates.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Given the increasing global use of ART and the need to optimize treatment strategies, real-world studies on the effectiveness and safety of rhFSH preparations remain limited, particularly for follitropin, in assessing their impact on key clinical outcomes such as the live birth rate (LBR).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What are the clinical outcomes of rhFSH including live birth rate in infertile women undergoing ART with a fresh cycle, and are there differences between follitropin and other rhFSH?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This nationwide cohort study included 10,684 infertile women undergoing ART with rhFSH, with an overall live birth rate of 38.8%. Compared with the other rhFSH group (n = 8,090), the follitropin group (n = 2,594) had a significantly higher proportion of ≥11 oocytes retrieved (adjusted RR, 1.09; 95% CI: 1.02–1.16) and a lower rate of OHSS (0.73, 0.60–0.90). Other pregnancy outcomes, including clinical pregnancy rate and miscarriage rate, were comparable between the two groups.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These findings provide real-world evidence on the comprehensive effectiveness and safety of rhFSH, aiding clinical decision making in the initial fresh cycle of IVF-ET. Further, follitropin may offer advantages in oocyte retrieval and a reduced rate of OHSS, making it a favorable option for controlled ovarian stimulation.

Received March 28, 2025; accepted October 13, 2025. doi:10.1002/cpt.70136

[1]Hamchoon Women's Clinic, Seoul, South Korea; [2]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea; [3]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [4]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, South Korea; [5]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea; [6]Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, South Korea; [7]Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; [8]Fertility Center, CHA Bundang Women's Medical Center, CHA University Bundang Medical Center, Seongnam, South Korea; [9]Department of Gynecologic Endocrinology, Female Infertility, Fertility Preservation, Seoul Maria Fertility Hospital, Seoul, South Korea; [10]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea; [11]Department of Medical Informatics, Kangwon National University College of Medicine, Chuncheon, South Korea; [12]Clinical & Regulatory Affairs Group, Life Sciences, LG Chem, Ltd., Seoul, South Korea; [13]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, South Korea; [14]Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, South Korea. *Correspondence: Ju-Young Shin (shin.jy@skku.edu) and Hoon Kim (obgyhoon@gmail.com)

[†]These authors contributed equally to this work.

Infertility is a medical condition marked by the inability to achieve a clinical pregnancy after a year of regular, unprotected intercourse, or as a result of diminished reproductive capacity.[1] According to a World Health Organization report, the global prevalence of infertility is approximately 17.5%.[2] And decreased birth rates, increased prevalence of infertility and increased use of assisted reproductive technology (ART) were reported from various countries.[3] Amidst this trend, South Korea's total fertility rate is the lowest in the world.[4] In response, in South Korea, a national support system for ART was implemented in 2006, and the Korean government introduced insurance coverage for infertility-related medical services on October 1, 2017.[5] At the same time, under the National Health Insurance Act, all citizens of South Korea are required to enroll in the national health insurance system, and all medical institutions are designated to provide treatment within this system. Consequently, most ART procedures performed in Korea are now conducted under the national insurance system.

Controlled ovarian stimulation (COS) is important for successful ART treatment. During the COS, the exogenous gonadotropins are mostly used with gonadotropin-releasing hormone (GnRH) agonists or antagonists.[6] Among the exogenous gonadotropins, recombinant human follicle-stimulating hormone (rhFSH) is a key agent, which induces follicular development and growth, and is used in infertility treatments to retrieve multiple oocytes in a single cycle.[7] The four types of rhFSH preparations such as follitropin, follitropin alfa, follitropin beta, and follitropin delta have since been widely used for infertility treatment and included on the list of reimbursed drugs in Korea.[8] Despite the widespread use of rhFSH in infertility treatments, comprehensive research on its effectiveness and safety leveraging real-world data, including various types of rhFSH, remains scarce. Furthermore, while follitropin may demonstrate comparable effectiveness and therapeutic advantages, there is currently no real-world evidence to confirm these benefits. Although some studies have assessed the safety and efficacy of rhFSH in IVF and ICSI, they are often constrained by insufficient sample sizes or a lack of comprehensive comparisons between different rhFSH preparations.[9–11]

Hence, this study aimed to evaluate the effectiveness and safety of rhFSH as the primary objective by analyzing 12 clinical outcomes. Using Korea's real-world national data, we investigated a broad range of clinical outcomes, including the live birth rate, associated with rhFSH use in the initial fresh cycle among women aged 20–39 diagnosed with infertility, to address gaps in current evidence. As a secondary objective, we explored potential differences in effectiveness and safety between follitropin and other available rhFSH preparations.

METHODS

Data source

We analyzed data from the nationwide Health Insurance Review and Assessment (HIRA) database of South Korea, covering the period from January 1, 2010, to August 31, 2022. This database provides extensive records of healthcare utilization for all residents of South Korea, with patient identifiers securely anonymized. ART procedures can only be legally performed at designated "embryo-generating medical institutions," and reimbursement is restricted to these certified clinics through the national health insurance system administered by HIRA. Therefore, the HIRA database effectively captures all reimbursed ART cycles performed in certified institutions nationwide. The database also includes detailed information on demographic characteristics, diagnoses (based on International Classification of Disease, 10th revision [ICD-10] codes), diagnostic settings, dates, and other related details, and prescribed medications (national drug chemical codes, prescription dates, and others) until individuals either emigrate or die.[12]

Study cohort

The study cohort included female patients diagnosed with infertility between October 1, 2016, and September 30, 2021, aged 20–39 years and received single component rhFSH monotherapy for their first in vitro fertilization-embryo transfer (IVF-ET) initiating from October 1, 2018 to September 30, 2021. The cohort entry date (CED) was defined as the first date of rhFSH monotherapy prescribed for IVF, and gestational age was calculated from 2 weeks prior to oocyte retrieval. The study period for each cycle was defined from the initiation of rhFSH monotherapy for IVF-ET to the completion of fresh embryo transfer. Patients who have undergone oocyte retrieval within 4 weeks from CED, and before September 30, 2021, completed fresh embryo transfer after performing IVF or ICSI during the relevant cycle, were included. Details of the overall design for cohort selection are presented in **Figure S1**.

Exposure

Exposure was defined as prescription of single component rhFSH monotherapy including follitropin, follitropin alfa, follitropin beta for IVF-ET on the CED. Follitropin (by domestic company A, B) is approved in South Korea but is neither authorized by the EMA nor the FDA nor marketed in the EU or the United States. Among four types of rhFSH preparations, follitropin delta was excluded from the exposure variables in this study due to its shorter availability period from September 1, 2020. To exclude confounding effects from other medications such as hMG, the study focused on cases of rhFSH monotherapy for ovarian stimulation during each cycle. To address the primary objective of the study, all fresh cycles receiving rhFSH monotherapy (follitropin [company A, B], follitropin alfa, follitropin beta) were included. For the secondary objective, among all fresh cycles included for the primary objective, cycles were stratified into follitropin monotherapy (company A) and other rhFSH monotherapy to enable a comparative analysis. Details of the exposure are presented in **Table S1**. Additionally, ovarian stimulation protocols were identified through

prescription records. Protocols that included only GnRH agonists were categorized as agonist protocols, while those using solely GnRH antagonists were classified as antagonist protocols.

Clinical outcomes

The outcomes of interest included both effectiveness and safety measures in patients treated with all types of rhFSH. The evaluation variables consisted of those that can be confirmed by ICD-10 codes or procedure codes or the Anatomical Therapeutic Chemical (ATC) classification system codes, utilizing related diagnoses, procedures, or prescriptions. Effectiveness was assessed by the proportion of patients with 11 or more oocytes retrieved, the clinical pregnancy rate (CPR), the ongoing pregnancy rate (OPR), and the live birth rate (LBR) including single or multiple birth rates. Safety outcomes were evaluated by including the ectopic pregnancy rate, miscarriage rate, preterm birth (PTB) rate, ovarian hyperstimulation syndrome (OHSS), and severe OHSS cases accompanying paracentesis or hospitalization.

Demographic and clinical characteristics

We assessed baseline characteristics of patients using rhFSH to adequately account for potential confounding factors and biases between the follitropin group and other rhFSH groups. These were demographic characteristics, clinical characteristics such as cardiovascular comorbidities, endocrine disorders, autoimmune diseases, neuropsychiatric disorders, and female reproductive system disorders (e.g., polyp of genital tract, pelvic inflammatory diseases) and proxies of overall health status (e.g., Obstetric Comorbidity Index [OCI],[13] history of hospitalization). The characteristic assessment window was defined as a 1-year period before CED (**Figure S1**, demographic characteristics on the CED; comorbidities, proxies of health status during a year [CED-365 to CED-1]).

The details and codes used for definitions of exclusion criteria, exposures, outcomes, and covariates are presented in **Table S1**.

Statistical analyses

The demographic characteristics of the study subjects were assessed at the time of CED, along with comorbidities and overall health status during the year prior to CED. Baseline characteristics were presented as frequency and percentage for categorical variables, and as mean (standard deviation [SD]) for continuous variables. Differences in baseline characteristics were evaluated using the *P*-value, with a *P*-value < 0.05 considered statistically significant. The 12 pre-specified outcome variables for the study population were assessed and presented as frequency and percentage. For the secondary objective, the incidence rates of 12 clinical effectiveness and safety outcomes were estimated for both follitropin and other rhFSH groups. These rates were compared between the two groups using a generalized linear model (GLM) with a Poisson distribution, from which relative risk (RR) and 95% confidence intervals (CIs) were calculated. Crude RR, age-adjusted RR (Model 1), and RR further adjusted for imbalanced variables (Model 2, age, fertilization procedure, type of protocol utilized for COS, polyp of genital tract, pelvic inflammatory disease, and history of hospitalization) were estimated for each outcome, comparing the follitropin group with the other rhFSH group. In Model 2, imbalanced covariates were additionally adjusted as part of a sensitivity analysis to address potential confounding.

The potential heterogeneity of rhFSH effects in clinically selected subgroups, both of the total cohort and follitropin vs. the other rhFSH group, was examined for the 12 clinical outcomes according to age,[14] fertilization procedure,[15] type of COS protocol,[16] and number of oocytes retrieved.[17] We also did multiple sensitivity analyses to test the robustness of our main findings. Detailed information on sensitivity analyses and supplementary analyses is provided in **Appendices 1 and 2**. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC), provided by HIRA through a virtual access machine.

Ethics statement

This study was approved by the institutional review board of Sungkyunkwan University (No. SKKU 2023-04-045) and HIRA (M20230424005), which waived the informed consent, as only de-identified data were used in this study. This study follows the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

RESULTS

This study included 10,684 patients, consisting of 2,594 (24.3%) in the follitropin group and 8,090 (75.7%) in the other rhFSH group (**Figure 1**).

For total of 10,684 patients, the majority of patients were in their 30s (ages 30–34: 41.6%, ages 35–39: 51.3%), and the average number of outpatient visits per patient was 19.4 (SD = 12.5) during 1 year prior to CED. More patients underwent ICSI (57.7%) than IVF (42.3%). The GnRH antagonist protocol was used in 76.8% of patients for COS, more than three times the usage of the GnRH agonist protocol (21.7%). For 1.6% of these patients, ovarian stimulation protocols could not be identified in the claims data. Among comorbidities, more than 10% of patients had thyroid disorders (15.5%), autoimmune disorders (12.5%), polyps of the genital tract (13.0%), and leiomyoma (10.7%). The average OCI score, which comprehensively assessed gynecological conditions and health status of patient, was 1.3 (SD = 1.2). Within 1 year prior to CED, 11.9% of patients were hospitalized or visited the emergency room (**Table 1**).

Follitropin vs. other rhFSH

The proportion of patients undergoing ICSI was significantly higher in the follitropin group (62.2% vs. 56.3%). The use of the GnRH antagonist protocol was significantly higher in the follitropin group compared to the other rhFSH group (81.3% vs. 75.3%). No differences were observed in the prevalence of comorbidities between the two groups, except for a lower rate of polyps of the genital tract (11.8% vs. 13.3%) and a higher rate of pelvic inflammatory disease (9.2% vs. 5.8%) in the follitropin group compared to the other rhFSH group (**Table 1**). In terms of proxies for overall health status, including OCI, emergency room visits, and outpatient visits, there was no difference between the two groups. However, hospitalization during 1 year prior to CED was significantly higher in the follitropin group compared to the other rhFSH group (13.0% vs. 11.5%; **Table 1**).

Clinical outcomes

Among the 10,684 patients, 11 or more oocytes were retrieved after rhFSH prescription in 44.1% of women (**Table 2**). A total of 5,049 patients (47.3%) achieved clinical pregnancy, and ongoing pregnancy was confirmed in 4,231 patients (39.6%). Additionally, 4,140 patients (38.8%) proceeded to delivery, resulting in live births, of which 3,222 (30.2%) were singletons and 918 (8.6%) were multiples. Among all participants, 1,549 (14.5%) showed pregnancy-related adverse outcomes, including 73 (0.7%) ectopic

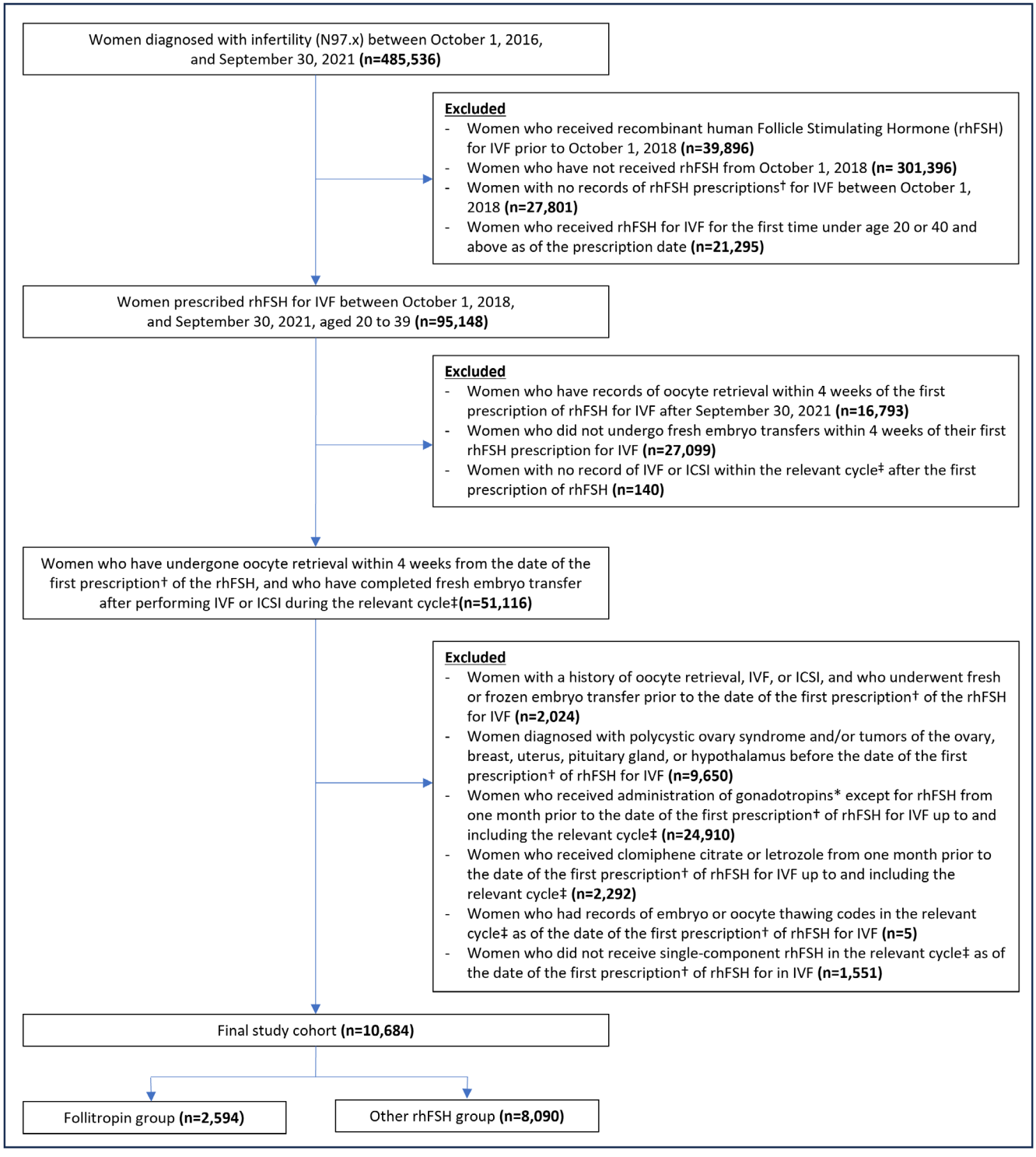

Figure 1 Study flowchart for cohort construction. †The prescription of the drug of interest (rhFSH) for in vitro fertilization refers to cases with records of oocyte retrieval within 4 weeks from the CED. ‡This cycle refers to the period from the CED to the date of fresh embryo transfer. *Gonadotropins other than the drug of interest (rhFSH) include follitropin delta, lutropin alone, combined formulations, and menotrophin formulations.

pregnancies, 1,042 (9.8%) miscarriages, and 434 (4.1%) preterm births. A total of 630 patients (5.9%) were diagnosed with OHSS. Of these, 164 patients (1.5%) underwent paracentesis, and 136 patients (1.3%) were hospitalized with OHSS diagnosis.

Follitropin vs. other rhFSH

The proportion of patients retrieving more than 11 oocytes was significantly higher in the follitropin group than in the other rhFSH group (47.3% vs. 43.1%; Model 1 adjusted RR = 1.09, 95%

Table 1 Demographic and clinical characteristics of study population

Characteristics	Total (*n* = 10,684)	Follitropin (*n* = 2,594)	Other rhFSH (*n* = 8,090)	*P*-value
Age group (years), *n* (%)				
20–24	43 (0.4)	11 (0.4)	32 (0.4)	0.060
25–29	717 (6.7)	185 (7.1)	532 (6.6)	
30–34	4,446 (41.6)	1,128 (43.5)	3,318 (41.0)	
35–39	5,478 (51.3)	1,270 (49.0)	4,208 (52.0)	
Medical aid[a] recipients, *n* (%)	19 (0.2)	5 (0.2)	14 (0.2)	0.792
Fertilization procedure, *n* (%)				
IVF	4,518 (42.3)	981 (37.8)	3,537 (43.7)	<0.01
ICSI	6,166 (57.7)	1,613 (62.2)	4,553 (56.3)	
Type of protocol utilized for COS, *n* (%)				
GnRH agonist protocol[b]	2,315 (21.7)	444 (17.1)	1,871 (23.1)	<0.01
GnRH antagonist protocol	8,201 (76.8)	2,108 (81.3)	6,093 (75.3)	
Unknown	168 (1.6)	42 (1.6)	126 (1.6)	
Comorbidities[c], *n* (%)				
Hypertension	118 (1.1)	29 (1.1)	89 (1.1)	0.940
Heart failure	15 (0.1)	4 (0.2)	11 (0.1)	0.769
Type 2 diabetes mellitus	140 (1.3)	29 (1.1)	111 (1.4)	0.322
Thyroid disorder	1,657 (15.5)	371 (14.3)	1,286 (15.9)	0.051
Autoimmune disorders	1,332 (12.5)	327 (12.6)	1,005 (12.4)	0.806
Anxiety	242 (2.3)	47 (1.8)	195 (2.4)	0.075
Depression	175 (1.6)	39 (1.5)	136 (1.7)	0.535
Polyp of genital tract	1,384 (13.0)	305 (11.8)	1,079 (13.3)	0.037
Endometriosis	780 (7.3)	193 (7.4)	587 (7.3)	0.753
Pelvic inflammatory diseases	705 (6.6)	239 (9.2)	466 (5.8)	<0.001
Leiomyoma	1,139 (10.7)	293 (11.3)	846 (10.5)	0.229
OCI, mean (SD)[d]	1.3 (1.2)	1.2 (1.2)	1.3 (1.2)	0.280
Patients hospitalized[c], *n* (%)	1,267 (11.9)	337 (13.0)	930 (11.5)	0.040
Emergency room visits[c], *n* (%)	1,272 (11.9)	313 (12.1)	959 (11.9)	0.772
No. of outpatient visits[c], mean (SD)	19.4 (12.5)	19.6 (12.1)	19.3 (12.6)	0.365

COS, controlled ovarian stimulation; GnRH, gonadotropin hormone-releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OCI, obstetric comorbidity index; rhFSH, recombinant human follicle-stimulating hormone; SD, standard deviation. [a]Medical aid recipients refer to Medicaid beneficiaries in South Korea. [b]GnRH agonist protocol includes all protocols utilizing GnRH agonists for COS, including the long, short, and ultrashort protocols. [c]Comorbidities, patients hospitalized, emergency room visits, and No. of outpatient visits were examined during CED−365 days to CED, for the proxies of healthcare utilization and maternal conditions. [d]OCI is a maternal comorbidity index to estimate the risk of severe maternal morbidity, characterized by acute maternal end-organ damage or death.

CI: 1.02–1.16). However, the proportion of OHSS was significantly lower in the follitropin group (Model 1 adjusted RR = 0.73, 95% CI: 0.60–0.90). There were no significant differences in pregnancy outcomes such as CPR, OPR, and LBR between the two groups. Additionally, point estimates suggested a slightly lower incidence of preterm labor and severe OHSS (defined as cases accompanied by paracentesis) in the follitropin group compared with the other rhFSH group, whereas the point estimate for ectopic pregnancy was slightly higher in the follitropin group. However, none of these differences were statistically significant (**Table 3**).

Also, for the exploratory analysis, there were no differences between the two groups in terms of other abnormal pregnancy outcomes (Gestational diabetes mellitus, gestational hypertension, placenta previa, and placenta abruption; **Table S2**).

Subgroup and sensitivity analyses

Subgroup analyses of clinical outcomes, stratified by age group, showed that patients aged 20–29 had the highest proportion of more than 11 oocytes retrieved, CPR, OPR, LBR, PTB, OHSS, and OHSS with paracentesis, followed by those aged 30–34, and 35–39 (**Table 4**). The miscarriage rate was highest in the 35–39 age group (11.1%), followed by the 20–29 age group (8.7%), and no significant differences were observed between IVF and ICSI groups. The GnRH antagonist protocol showed a higher proportion of patients retrieving more than 11 oocytes, as well as higher CPR, OPR, and LBR compared to the GnRH agonist protocol, while showing a lower incidence of OHSS. Notably, the proportion of OHSS requiring paracentesis was significantly lower in patients receiving the GnRH antagonist protocol with rhFSH (**Table 4**). Patients with 11 or more oocytes retrieved had significantly higher

CPR, OPR, and LBR compared to those with < 11 oocytes but also experienced higher rates of OHSS and OHSS with paracentesis (Table 4).

Subgroup analyses for the secondary objective showed generally consistent trends across subgroups, with a significantly lower proportion of OHSS in the 35–39 age group in the follitropin group (crude RR = 0.65, 95% CI: 0.47–0.89). Additionally, the follitropin group had a significantly higher proportion of patients retrieving 11 or more oocytes in the IVF subgroup (adjusted RR = 1.28, 95% CI: 1.16–1.42) and a lower proportion of OHSS in the ICSI group (adjusted RR = 0.72, 95% CI: 0.55–0.94). In the GnRH agonist protocol group, the follitropin group demonstrated a higher CPR (adjusted RR = 1.20, 95% CI: 1.03–1.40) and a lower incidence of OHSS (adjusted RR = 0.47, 95% CI: 0.29–0.77) compared to the other rhFSH (Tables S3–S6). Sensitivity analyses confirmed the robustness of these findings, with consistent results across various analyses (Tables S7 and S8). As follitropin alfa accounted for 82% of the other rhFSH group, we conducted separate comparisons between follitropin and follitropin alfa. The results were consistent with our comparison between follitropin and other rhFSH, and patients receiving follitropin had lower estimated doses (IU) per cycle compared to those treated with follitropin alfa (Appendix 2, Tables S9 and S10).

Table 2 Effectiveness and safety of total study population treated with rhFSH

	Patients (*N* = 10,684)
Oocytes retrieved (≥ 11 oocytes)	4,716 (44.1)
Pregnancy	
Clinical pregnancy rate	5,049 (47.3)
Ongoing pregnancy rate	4,231 (39.6)
Live birth	
Live birth rate	4,140 (38.8)
Single birth rate	3,222 (30.2)
Multiple birth rate	918 (8.6)
Pregnancy-related adverse outcomes	
Ectopic pregnancy rate	73 (0.7)
Miscarriage rate	1,042 (9.8)
Preterm birth rate	434 (4.1)
OHSS	630 (5.9)
OHSS+Paracentesis	164 (1.5)
OHSS+Hospitalization[a]	136 (1.3)

Values are *n* (%) unless stated otherwise. OHSS, ovarian hyperstimulation syndrome; rhFSH, recombinant human follicle-stimulating hormone.
[a]OHSS+Hospitalization refers to patients who have a hospitalization record with a diagnosis of OHSS.

DISCUSSION

Main findings

This study represents the first to conduct a comparative analysis using nationwide real-world data, comparing follitropin vs. other rhFSH. In this retrospective cohort analysis of national data, we evaluated the effectiveness and safety of rhFSH in infertile women undergoing ART with a fresh cycle, within a real-world clinical setting. Our analyses revealed CPR of 47.3%, OPR of 39.6%, and LBR of 38.8% in women aged 20–39 undergoing their first IVF cycle with rhFSH. Compared to other

Table 3 Effectiveness and safety of patients treated with follitropin vs. other rhFSH

	Follitropin (*n* = 2,594)	Other rhFSH (*n* = 8,090)	Crude RR (95% CI)	Adjusted RR (95% CI)	
				Model 1[a]	Model 2[b]
Oocytes retrieved (≥ 11 oocytes)	1,226 (47.3)	3,490 (43.1)	1.10 (1.03, 1.17)	1.09 (1.02, 1.16)	1.08 (1.01, 1.15)
Pregnancy					
Clinical pregnancy rate	1,216 (46.9)	3,833 (47.4)	0.99 (0.93, 1.06)	0.98 (0.92, 1.05)	0.98 (0.92, 1.05)
Ongoing pregnancy rate	1,022 (39.4)	3,209 (39.7)	0.99 (0.93, 1.07)	0.99 (0.92, 1.06)	0.98 (0.91, 1.05)
Live birth					
Live birth rate	1,002 (38.6)	3,138 (38.8)	1.00 (0.93, 1.07)	0.99 (0.92, 1.06)	0.98 (0.92, 1.06)
Single birth rate	784 (30.2)	2,438 (30.1)	1.00 (0.93, 1.09)	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)
Multiple birth rate	218 (8.4)	700 (8.7)	0.97 (0.83, 1.13)	0.96 (0.83, 1.12)	0.94 (0.81, 1.10)
Pregnancy-related adverse outcome					
Ectopic pregnancy rate	21 (0.8)	52 (0.6)	1.26 (0.76, 2.09)	1.27 (0.77, 2.11)	1.27 (0.76, 2.11)
Miscarriage rate	249 (9.6)	793 (9.8)	0.98 (0.85, 1.13)	0.99 (0.86, 1.14)	0.98 (0.85, 1.13)
Preterm birth rate	95 (3.7)	339 (4.2)	0.87 (0.70,1.10)	0.87 (0.69, 1.09)	0.85 (0.67, 1.07)
OHSS	121 (4.7)	509 (6.3)	0.74 (0.61, 0.90)	0.73 (0.60, 0.90)	0.75 (0.61, 0.92)
OHSS+Paracentesis	33 (1.3)	131 (1.6)	0.79 (0.54, 1.15)	0.78 (0.53, 1.14)	0.86 (0.59, 1.27)
OHSS+Hospitalization[c]	32 (1.2)	104 (1.3)	0.96 (0.65, 1.43)	0.94 (0.63, 1.40)	0.95 (0.64, 1.42)

Values are *n* (%) unless stated otherwise. CI, confidence interval; COS, controlled ovarian stimulation; OHSS, ovarian hyperstimulation syndrome; rhFSH, recombinant human Follicle-Stimulating Hormone; RR, relative risk. [a]Model 1: adjusted for age. [b]Model 2: further adjusted for variables (age, fertilization procedure, type of protocol utilized for COS, polyp of genital tract, pelvic inflammatory disease and history of hospitalization), which indicates a significant imbalance between the two groups, in addition to the variables adjusted in model 1. [c]OHSS+Hospitalization refers to patients who have a hospitalization record with a diagnosis of OHSS.

Table 4 Effectiveness and safety outcomes of total study population treated with rhFSH: Subgroup analysis stratified by age, fertilization procedure, type of protocol utilized for COS[a], number (≥11 or <11) of oocytes retrieved

	Subgroup 1				Subgroup 2			Subgroup 3			Subgroup 4		
	Aged 20–29 (*n* = 760)	Aged 30–34 (*n* = 4,446)	Aged 35–39 (*n* = 5,478)	*P* value	IVF (*n* = 4,518)	ICSI (*n* = 6,166)	*P* value	GnRH agonist protocol[b] (*n* = 2,315)	GnRH antagonist protocol (*n* = 8,201)	*P* value	≥11 oocytes retrieved (*n* = 4,716)	<11 oocytes retrieved (*n* = 5,968)	*P* value
Oocytes retrieved (≥11 oocytes), *n* (%)	424 (55.8)	2,232 (50.2)	2,060 (37.6)	**<0.001**	1,950 (43.2)	2,766 (44.9)	0.081	900 (38.9)	3,763 (45.9)	**<0.001**			
Pregnancy, *n* (%)													
Clinical pregnancy rate	416 (54.7)	2,245 (50.5)	2,388 (43.6)	**<0.001**	2,170 (48.0)	2,879 (46.7)	0.171	985 (42.5)	3,993 (48.7)	**<0.001**	2,441 (51.8)	2,608 (43.7)	**<0.001**
Ongoing pregnancy rate	365 (48.0)	1,957 (44.0)	1,909 (34.9)	**<0.001**	1,838 (40.7)	2,393 (38.8)	0.051	807 (34.9)	3,369 (41.1)	**<0.001**	2,070 (43.9)	2,161 (36.2)	**<0.001**
Live birth, *n* (%)													
Live birth rate	356 (46.8)	1,919 (43.2)	1,865 (34.1)	**<0.001**	1,808 (40.0)	2,332 (37.8)	**0.021**	791 (34.2)	3,294 (40.2)	**<0.001**	2,031 (43.1)	2,109 (35.3)	**<0.001**
Single birth rate	263 (34.6)	1,502 (33.8)	1,457 (26.6)	**<0.001**	1,419 (31.4)	1,803 (29.2)	**0.016**	642 (27.7)	2,540 (31.0)	**0.003**	1,578 (33.5)	1,644 (27.5)	**<0.001**
Multiple birth rate	93 (12.2)	417 (9.4)	408 (7.5)	**<0.001**	389 (8.6)	529 (8.6)	0.955	149 (6.4)	754 (9.2)	**<0.001**	453 (9.6)	465 (7.8)	**<0.001**
Pregnancy-related adverse outcome, *n* (%)													
Ectopic pregnancy rate	6 (0.8)	24 (0.5)	43 (0.8)	0.315	32 (0.7)	41 (0.7)	0.788	14 (0.6)	55 (0.7)	0.729	37 (0.8)	36 (0.6)	0.259
Miscarriage rate	66 (8.7)	368 (8.3)	608 (11.1)	**<0.001**	441 (9.8)	601 (9.7)	0.981	198 (8.6)	824 (10.0)	**0.032**	486 (10.3)	556 (9.3)	0.087
Preterm birth rate	58 (7.6)	174 (3.9)	202 (3.7)	**<0.001**	176 (3.9)	258 (4.2)	0.455	81 (3.5)	347 (4.2)	0.115	199 (4.2)	235 (3.9)	0.463
OHSS	61 (8.0)	294 (6.6)	275 (5.0)	**<0.001**	305 (6.8)	325 (5.3)	**0.001**	178 (7.7)	451 (5.5)	**<0.001**	426 (9.0)	204 (3.4)	**<0.001**
OHSS+ Paracentesis	15 (2.0)	79 (1.8)	70 (1.3)	0.079	101 (2.2)	63 (1.0)	**<0.001**	64 (2.8)	100 (1.2)	**<0.001**	120 (2.5)	44 (0.7)	**<0.001**
OHSS+ Hospitalization[c]	10 (1.3)	76 (1.7)	50 (0.9)	**0.002**	62 (1.4)	74 (1.2)	0.433	44 (1.9)	91 (1.1)	**0.003**	89 (1.9)	47 (0.8)	**<0.001**

GnRH, gonadotropin hormone-releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; rhFSH, recombinant human follicle-stimulating hormone.Bold values are statistically significant ($P < 0.05$). [a]Patients who did not have a GnRH agonist or antagonist prescription during the evaluation period (Unknown group) were 168 (1.6%). [b]GnRH agonist protocol includes all protocols utilizing GnRH agonists for COS, including the long, short, and ultrashort protocols. [c]OHSS+Hospitalization refers to patients who have a hospitalization record with a diagnosis of OHSS.

rhFSH groups, the follitropin group showed a statistically significantly higher proportion of patients with 11 or more oocytes, as well as a lower proportion of OHSS. In subgroup analyses, the follitropin group had a higher oocyte retrieval rate in IVF, and in cases using the GnRH agonist protocol, the pregnancy rate was significantly higher in the follitropin group. Sensitivity analyses further confirmed the robustness of these findings, showing consistent results of higher oocyte retrieval and lower proportion of OHSS, also in comparison of follitropin vs. follitropin alfa.

Comparison with previous studies

The main results of CPR and LBR were generally consistent with a study among a similar patient population using the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART-CORS) from 2011 to 2012,[18] which reported CPR (33.8–64.8%) and LBR (29.9–56.5%) depending on age, compliance and stage of embryo transfer. However, the SART-CORS dataset lacked specific gonadotropin information, and the higher proportion of older patients in our cohort likely explains some of the observed differences. When comparing pregnancy outcomes between patients who received different types of rhFSH, no statistically significant differences were observed in CPR (46.9% vs. 47.4%), OPR (39.4% vs. 39.7%), or LBR (38.6% vs. 38.8%) which are in line with the established efficacy profile of rhFSH demonstrated in comparison between follitropin and follitropin alfa (CPR: 55.4% vs. 51.9%; OPR: 44.1% vs. 43.0%) in a phase 3 randomized controlled trial,[11] also comparison between follitropin alfa and follitropin beta (CPR: 46.2% vs. 47.9%; LBR: 37.9% vs. 40.7%) in a retrospective cohort study.[19] These consistent findings across studies suggest that different rhFSH preparations yield comparable effectiveness in promoting successful ART outcomes in similar patient populations.

The subgroup analyses largely aligned with findings from previous studies, though subtle divergences were observed in certain aspects. Despite recommendations against routine ICSI use in ART cycles without male factor infertility,[20,21] ICSI is increasingly used for non-male-factor indications, such as older reproductive age, poor ovarian responders, and repeated IVF failures. Additionally, data from the ESHRE European IVF Monitoring indicates that ICSI is now used in approximately three-fourths of all IVF cycles in Europe,[22] and a UK study also shows an increase from 48% (2005–2009) to 51% (2015–2018) in first cycles.[23] In our study, ICSI use was even higher at 57.7%, with a greater proportion in the follitropin group compared to the other rhFSH group (62.2% vs. 56.3%), possibly reflecting differences in the underlying infertility diagnoses or clinical characteristics between the two groups. Second, mild cases of OHSS are unlikely to be captured in claims data, as patients may not visit clinics, and symptoms would resolve spontaneously if pregnancy were not achieved. Therefore, the OHSS cases in our data likely represent moderate-to-severe cases. In our study, the overall incidence of OHSS was 5.9% (7.7% in agonist; 5.5% in antagonist protocols), which is lower than in Phase IV RCT (24.4% in agonist; 15.3% in antagonist protocols)[24] due to a higher proportion of older patients (35–39 years: 51.3% vs. 25.3%) and the potential underreporting of OHSS codes. While paracentesis rates were higher in our cohort (1.2% vs. 0% in antagonist; 2.8% vs. 2% in agonist protocols), hospitalization rates were lower (1.1% vs. 1.7% in antagonist; 1.9% vs. 3.6% in agonist protocols),[24] implying greater preference in Korea for outpatient OHSS management with paracentesis rather than hospitalization.

For the birth trend in supplementary analyses, according to the 2021 Assisted Reproductive Technology Fertility Clinic and National Summary Report,[25] singleton births from ART in the U.S. increased from 57.8% in 2012 to 89.3% in 2021, while twin births decreased from 40.2% to 10.4%. In South Korea, following the introduction of ART insurance coverage, guidelines on the recommended number of embryos transferred have also been emphasized to reduce multiple gestations. Consistent with this trend, a slight decline in the multiple birth rate was observed in our study cohort (**Figure S3**).

Clinical implications

Notably, the follitropin group in our study showed a significantly higher rate of retrieving 11 or more oocytes while demonstrating a lower incidence of OHSS compared to the other rhFSH group, consistent across stratified analyses by age and ART strategy. Although variables such as gonadotropin dosage, antral follicle count (AFC), and anti-Müllerian hormone (AMH) were not directly compared between groups, the higher oocyte yield in the follitropin group is clinically significant,[26] as it increases the selection pool of high-quality embryos, potentially improving OPR and LBR.[27–30] Also, patients retrieving fewer than 11 oocytes achieved comparable pregnancy outcomes with follitropin and other rhFSH, while those retrieving 11 or more oocytes had significantly lower OHSS rates with follitropin (**Table S6**). These findings suggest follitropin offers effective outcomes with a favorable safety profile compared to other rhFSH. Despite the potential for selection bias due to unmeasured confounders, sensitivity analyses supported the consistency of these results. This observation of a higher proportion of patients with ≥ 11 oocytes retrieved, accompanied by a lower incidence of OHSS in the follitropin group, is particularly noteworthy given the well-established positive correlation between oocyte yield and OHSS risk. This finding may suggest a pharmacological and structural property[31] unique to follitropin or reflect the higher representation of patients within the follitropin group who achieved an optimal oocyte yield (11–15 oocytes). Further investigation is warranted to elucidate the underlying mechanism.

While two primary approaches are used to prevent premature luteinization in ART: desensitizing the pituitary gland with a GnRH agonist or inhibiting luteinizing hormone (LH) secretion from the pituitary using a GnRH antagonist.[32] In our study, 76.8% of patients underwent COS with a GnRH antagonist protocol, which was more frequently used in the follitropin group compared to the other rhFSH group (81.3% vs. 75.3%). The GnRH antagonist protocol is often preferred for its simplicity and safety,[33,34] our findings suggest the GnRH agonist protocol with follitropin may offer better outcomes in certain subgroups.

Additionally, the follitropin group demonstrated a lower proportion of OHSS in patients aged 35–39, indicating potential benefits of follitropin for older patients.[11] Accordingly, stratifying patients by factors such as age, stimulation protocols and fertilization procedures can improve ART success rates and reduce complications like OHSS, rather than relying on standardized "one-size-fits-all" treatments.[35]

Strengths and limitations

This study has several strengths that enhance its credibility. First, the large sample size provides enhanced generalizability, minimizing confounding effects. Using the HIRA database, a comprehensive real-world data source covering nearly all first IVF cycles in South Korea ensures generalizability to diverse clinical settings. The nationwide claims data eliminate selection biases, reflecting IVF outcomes across the study period. Second, anonymized patient IDs in the HIRA database enable comprehensive tracking of medical histories, ART outcomes (pregnancy and delivery data), reducing recall bias. The database also facilitates analysis of the associations between medical conditions, ART outcomes, and maternal and infant health, while providing accurate medication usage data and addressing concerns about missing pregnancy outcomes or underreported ART cycles common in registry data.

This study also has several limitations that should be considered when interpreting the findings. First, as the HIRA database is not a dedicated ART registry, detailed clinical information (such as reasons for ART cycles, AMH, AFC, BMI, total rhFSH dose, endometrial thickness, number of embryos transferred, and number of frozen embryos) is not available. Additionally, the number of retrieved oocytes can only be obtained as categorized information (< 11 or ≥ 11 oocytes) rather than exact counts, and accurate infertility etiologies such as male factor infertility cannot be reliably determined from diagnostic codes alone, which may hinder comprehensive evaluation and accurate assessment of the safety and effectiveness of the treatments. However, patients with infertility undergoing their first fresh IVF-ET cycle and similar OCI scores ensure comparable baseline conditions, minimizing underlying differences and disease progression. Second, the use of claims data may introduce discrepancies between recorded and actual diagnoses and lacks certain clinical details such as pregnancy status and gestational age. This is particularly relevant for key outcomes such as CPR and OPR, which were challenging to assess based solely on ultrasound reimbursement data, given the possibility of natural pregnancies. To address this, outcomes were defined by restricting the timeframe to those unlikely to include natural pregnancies based on oocyte retrieval dates and menstrual cycle information. Third, the study period, starting with insurance coverage in October 2017, excluded earlier ART patients. Follitropin delta, reimbursed from September 2020, had limited data due to a short exposure period and was excluded from analysis, warranting further study as more data become available. Fourth, the HIRA database includes only reimbursed medications, limiting our ability to verify the use of non-reimbursed ovulation inducers, which may have influenced the selection and classification of the study population. However, the likelihood of non-reimbursed medication use in first IVF cycles is very low.

CONCLUSION

This landmark study is the first to comprehensively evaluate the effectiveness—including crucial outcome, LBR—and safety of rhFSH in a real-world ART setting among 10,684 women aged under 40 with their initial fresh cycles using nationwide data. The secondary comparative analysis showed the comparable clinical safety and effectiveness between follitropin and other rhFSH. Compared to other rhFSH, the follitropin group demonstrated a higher proportion of patients with 11 or more oocytes, along with a lower proportion of OHSS, suggesting it is a favorable option for controlled ovarian stimulation. The findings empower both healthcare providers and patients to make more informed decisions about incorporating rhFSH into ART strategies, ultimately aiming to enhance the success rates of fertility treatments.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank the Health Insurance Review and Assessment (HIRA) for providing the nationwide database (study number: M20230424005).

FUNDING

This work was supported by LG Chem. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICTS OF INTEREST

J.Y.L. has received honoraria for participation on the advisory board of LG Chem and Ferring Pharmaceuticals. J.-Y.S. received grants from the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, the National Research Foundation of Korea, and pharmaceutical companies, including Pfizer, UCB, Yuhan, Organon, Celltrion, and SK bioscience. H.K. has received honoraria for participation on the advisory board of Bayer, consulting for Merck and LG Chem, and lectures for Roche Diagnostics, Amgen and Organon. No other relationships or activities have influenced the submitted work. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

J.Y.L. and E.-Y.C. wrote the manuscript; J.Y.L., E.-Y.C., Y.S., Y.J., J.-Y.S., and H.K. designed the research; All authors performed the research; E.-Y.C., Y.C., H.-J.S., and H.L. analyzed the data; J.-Y.S. and H.K. contributed new reagents/analytical tools.

DATA AVAILABILITY STATEMENT

No additional data are available to the public.

1. Vander Borght, M. & Wyns, C. Fertility and infertility: definition and epidemiology. *Clin. Biochem.* **62**, 2–10 (2018).
2. World Health Organization. Infertility prevalence estimates, 1990-2021 (2023).

3. Hanevik, H.I. & Hessen, D.O. IVF and human evolution. *Hum. Reprod. Update* **28**, 457–479 (2022).
4. GBD 2021 Fertility and Forecasting Collaborators. Global fertility in 204 countries and territories, 1950-2021, with forecasts to 2100: a comprehensive demographic analysis for the global burden of disease study 2021. *Lancet* **403**, 2057–2099 (2024).
5. Kim, M. National policies for infertility support and nursing strategies for patients affected by infertility in South Korea. *Korean J. Women Health Nurs.* **27**, 1–5 (2021).
6. Depalo, R. *et al*. GnRH agonist versus GnRH antagonist in in vitro fertilization and embryo transfer (IVF/ET). *Reprod. Biol. Endocrinol.* **10**, 26 (2012).
7. Fritz, M.A. & Speroff, L. *Clinical Gynecologic Endocrinology and Infertility* 8th edn. 1342–1351 (Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, PA, 2011).
8. Chua, S.J. *et al*. Biosimilar recombinant follitropin alfa preparations versus the reference product (Gonal-F®) in couples undergoing assisted reproductive technology treatment: a systematic review and meta-analysis. *Reprod. Biol. Endocrinol.* **19**, 51 (2021).
9. Choo, C.W. *et al*. Effectiveness and safety of recombinant human follicle-stimulating hormone (Follitrope™) in inducing controlled ovarian stimulation in infertile women in real-world practice: a prospective cohort study. *Reprod. Sci.* **30**, 2842–2852 (2023).
10. Choi, B.C. *et al*. A comparative, observational study evaluating dosing characteristics and ovarian response using the recombinant human follicle-stimulating hormone pen injector with small-dose dial in assisted reproductive technologies treatment in Asia: IMPROVE study. *Reprod. Biol. Endocrinol.* **20**, 15 (2022).
11. Hu, L. *et al*. Efficacy and safety of recombinant human follicle-stimulating hormone in patients undergoing in vitro fertilization-embryo transfer. *Aging (Albany NY)* **12**, 4918–4930 (2020).
12. von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C. & Vandenbroucke, J.P. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* **335**, 806–808 (2007).
13. Bateman, B.T. *et al*. Development of a comorbidity index for use in obstetric patients. *Obstet. Gynecol.* **122**, 957–965 (2013).
14. Howles, C.M., Saunders, H., Alam, V. & Engrand, P. Predictive factors and a corresponding treatment algorithm for controlled ovarian stimulation in patients treated with recombinant human follicle stimulating hormone (follitropin alfa) during assisted reproduction technology (ART) procedures. An analysis of 1378 patients. *Curr. Med. Res. Opin.* **22**, 907–918 (2006).
15. Lintsen, A.M. *et al*. Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. *Hum. Reprod.* **22**, 2455–2462 (2007).
16. Liu, C. *et al*. Live birth rate of gonadotropin-releasing hormone antagonist versus luteal phase gonadotropin-releasing hormone agonist protocol in IVF/ICSI: a systematic review and meta-analysis. *Expert Rev. Mol. Med.* **26**, e2 (2023).
17. Baker, V.L., Brown, M.B., Luke, B. & Conrad, K.P. Association of number of retrieved oocytes with live birth rate and birth weight: an analysis of 231,815 cycles of in vitro fertilization. *Fertil. Steril.* **103**, 931–938 (2015).
18. Keyhan, S. *et al*. How compliant are in vitro fertilization member clinics in following embryo transfer guidelines? An analysis of 59,689 fresh first in vitro fertilization autologous cycles from 2011 to 2012. *Fertil. Steril.* **106**, 645–652 (2016).
19. Cao, J.-X. & Song, J.-Y. Follitropin alpha versus Follitropin Beta in IVF/ICSI cycle: a retrospective cohort study. *Drug Des. Devel. Ther.* **18**, 4359–4369 (2024).
20. Intracytoplasmic sperm injection (ICSI) for non-male factor indications: a committee opinion. *Fertil. Steril.* **114**, 239–245 (2020).
21. ESHRE. Good clinical treatment in assisted reproduction. ESHRE position statements (2008).
22. Smeenk, J. *et al*. ART in Europe, 2019: results generated from European registries by ESHRE†. *Hum. Reprod.* **38**, 2321–2338 (2023).
23. Paffoni, A., Vitagliano, A., Corti, L., Somigliana, E. & Viganò, P. Intracytoplasmic sperm injection versus conventional in vitro insemination in couples with non-male infertility factor in the 'real-world' setting: analysis of the HFEA registry. *J. Transl. Med.* **22**, 687 (2024).
24. Toftager, M. *et al*. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. *Hum. Reprod.* **31**, 1253–1264 (2016).
25. Centers for Disease Control and Prevention. 2021 Assisted Reproductive Technology Fertility Clinic and National Summary Report. US Dept of Health and Human Services; 2023.
26. Fanton, M., Cho, J.H., Baker, V.L. & Loewke, K. A higher number of oocytes retrieved is associated with an increase in fertilized oocytes, blastocysts, and cumulative live birth rates. *Fertil. Steril.* **119**, 762–769 (2023).
27. European Medicines Agency. *Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Human Follicle Stimulating Hormone (r-hFSH)* (Committee for Medicinal Products for Human Use (CHMP), London, 2013).
28. Dickey, R.P, Sartor, B.M. & Pyrzak, R. What is the most relevant standard of success in assisted reproduction?: no single outcome measure is satisfactory when evaluating success in assisted reproduction; both twin births and singleton births should be counted as successes. *Hum. Reprod.* **19**, 783–787 (2004).
29. Buckett, W. & Tan, S.L. What is the most relevant standard of success in assisted reproduction? The importance of informed choice. *Hum. Reprod.* **19**, 1043–1045 (2004).
30. Braakhekke, M., Kamphuis, E.I., Dancet, E.A., Mol, F., van der Veen, F. & Mol, B.W. Ongoing pregnancy qualifies best as the primary outcome measure of choice in trials in reproductive medicine: an opinion paper. *Fertil. Steril.* **101**, 1203–1204 (2014).
31. Ulloa-Aguirre, A., Zariñán, T., Dias, J.A., Kumar, T.R. & Bousfield, G.R. Biased signaling by human follicle-stimulating hormone variants. *Pharmacol. Ther.* **268**, 108821 (2025).
32. Huirne, J.A. & Lambalk, C.B. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* **358**, 1793–1803 (2001).
33. Lambalk, C.B. *et al*. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. *Hum. Reprod. Update* **23**, 560–579 (2017).
34. Kadoura, S., Alhalabi, M. & Nattouf, A.H. Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/ICSI cycles of polycystic ovary syndrome women: a systematic review and meta-analysis. *Sci. Rep.* **12**, 4456 (2022).
35. Mol, B.W. *et al*. Personalized ovarian stimulation for assisted reproductive technology: study design considerations to move from hype to added value for patients. *Fertil. Steril.* **109**, 968–979 (2018).