

## Article

# Multicenter Post-Marketing Surveillance of Follitropin Alfa and Lutropin Alfa in Korean Patients with Severe Luteinizing Hormone Deficiency: Safety and Descriptive Real-World Outcomes

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## Abstract

**Purpose:** This post-marketing surveillance study evaluated the real-world safety and descriptive outcomes of a fixed 2:1 recombinant human follicle-stimulating hormone (r-hFSH) and recombinant human luteinizing hormone (r-hLH) combination among Korean women undergoing assisted reproductive technology with severe LH and FSH deficiency (baseline endogenous serum LH < 1.2 IU/L). **Methods:** A prospective, multicenter, observational study was conducted across 24 Korean fertility centers between August 2011 and May 2018. Safety outcomes included adverse events (AEs), adverse drug reactions (ADRs), and ovarian hyperstimulation syndrome (OHSS). Descriptive outcomes included endpoint-specific evaluable sets for follicular response and ultrasound-confirmed clinical pregnancy. Analyses were performed in safety ( $n = 600$ ), follicular-response evaluable ( $n = 537$ ), and pregnancy-evaluable ( $n = 486$ ) sets. **Results:** Among patients in the safety set (mean age, 34.6 years), AEs occurred in 2.7% (16/600; 95% confidence interval [CI], 1.6–4.3), ADRs in 2.2% (13/600; 95% CI, 1.3–3.7), and OHSS in 1.3% (8/600; 95% CI, 0.7–2.6), including one severe case. In the follicular-response evaluable set, follicular response ( $\geq 1$  follicle  $\geq 17$  mm) occurred in 99.3% (533/537; 95% CI, 98.1–99.7). In the pregnancy-evaluable set, clinical pregnancy occurred in 42.0% (204/486; 95% CI, 37.7–46.4), biochemical-only pregnancies in 3.1% (15/486; 95% CI, 1.9–5.0), and total pregnancies (clinical + biochemical-only, reported descriptively) in 45.1% (219/486; 95% CI, 40.7–49.5). **Conclusions:** In this historically constrained post-marketing surveillance cohort, the fixed 2:1 r-hFSH and r-hLH combination showed a favorable post-marketing safety profile and provided descriptive outcome information within endpoint-specific evaluable sets in women meeting the severe LH-deficiency criterion.



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**Keywords:** follitropin alfa; luteinizing hormone deficiency; lutropin alfa; postmarketing surveillance; real-world evidence

## 1. Introduction

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are crucial for regulating the menstrual cycle and follicular development. FSH stimulates follicular development, whereas LH is essential for steroidogenesis [1]. Women with low LH and FSH levels due to severely impaired hypothalamic or pituitary function are classified as having World Health Organization Group I anovulatory infertility or hypogonadotropic hypogonadism (HH) [2,3]. The International Committee for Monitoring Assisted Reproductive Technologies defines HH as gonadal failure characterized by reduced gametogenesis and decreased gonadal steroid production resulting from downregulated gonadotropin production or action [4].

Severe LH and FSH deficiencies can be acquired, functional, or congenital. Exogenous gonadotropins such as recombinant human FSH (r-hFSH), recombinant human LH (r-hLH), or human menopausal gonadotropin (hMG) have been used to treat women with HH during ovarian stimulation. In IVF protocols, a gonadotropin-releasing hormone (GnRH) analog is used to prevent premature ovulation and to induce final oocyte maturation before retrieval. However, GnRH analog protocols can cause transient deficiencies in FSH and LH levels, which may negatively affect pregnancy outcomes. Therefore, the coadministration of exogenous gonadotropins and GnRH analogs is necessary to stimulate follicular development, promote oocyte maturation, and support embryo implantation [5,6].

In assisted reproductive technologies (ARTs) performed in the Republic of Korea, r-hFSH is recommended for follicular development. In contrast, the addition of r-hLH has historically been limited to patients with LH levels < 1.2 IU/L. The fixed-dose r-hFSH/r-hLH formulation (Pergoveris<sup>®</sup>, Merck KGaA, Darmstadt, Germany) provides follitropin alfa and lutropin alfa in a 2:1 IU ratio, reflecting the approved co-administration strategy for women with severe LH deficiency. In clinical practice, LH activity may also be provided through separate r-hFSH and r-hLH injections or through urinary gonadotropin formulations such as hMG, which differ in source, composition, and relative LH/hCG activity. The fixed 2:1 formulation offers standardized concomitant FSH and LH support and reduces the need to adjust two separate recombinant products. Still, it should not be interpreted as evidence of superiority over alternative gonadotropin strategies in the absence of a comparator. Several studies have reported potential roles for LH supplementation in patients with poor ovarian function or hypo-response and in those receiving GnRH analogs [6–8].

Data from the National Health Insurance Sharing Service in Korea have shown that the number of women diagnosed with infertility was 150,000 in 2019 and 90,000 in 2020 (calculated through June 2020), with approximately 70,000 and 45,000 women receiving infertility treatment in those years, respectively [9]. As Korea faces the challenges posed by low birth rates and an aging population, the government recognizes the impending decline in the labor force as a significant social issue. To alleviate the financial burden on couples facing infertility and enhance birth rates, the government has been systematically increasing funding for fertility treatments each year [10]. The r-hFSH/r-hLH combination could be a viable option for achieving a successful pregnancy in women with infertility, especially in those predicted to have a poor ovarian response due to LH and FSH deficiency.

This post-marketing surveillance (PMS) study was conducted to assess the safety and descriptive real-world outcomes of r-hFSH/r-hLH in women with severe LH and FSH

deficiency, operationally defined by an endogenous serum LH level of  $<1.2$  IU/L, under routine clinical practice in Korea.

## 2. Materials and Methods

### 2.1. Study Design and Participants

This was a prospective, multicenter PMS study (EMR200061-507; ClinicalTrials.gov identifier: NCT01416987) conducted at 24 fertility centers in Korea between August 2011 and May 2018. A total of 620 Korean women with severe LH and FSH deficiency who underwent ART were treated with a fixed combination of follitropin alfa and lutropin alfa (recombinant human FSH/LH). All the patients who received at least one dose of r-hFSH/r-hLH were enrolled in the PMS cohort.

The study adhered to the Korean Ministry of Food and Drug Safety (MFDS) regulatory requirements for PMS, without protocol-driven intervention or randomization. All treatment decisions, including controlled ovarian stimulation (COS) regimens, dosing, and dose adjustments, were made at the treating physician's discretion in the context of routine clinical care. Demographic characteristics, baseline reproductive parameters, COS details (when available), safety data, follicular development, and pregnancy outcomes were prospectively recorded in case report forms (CRFs).

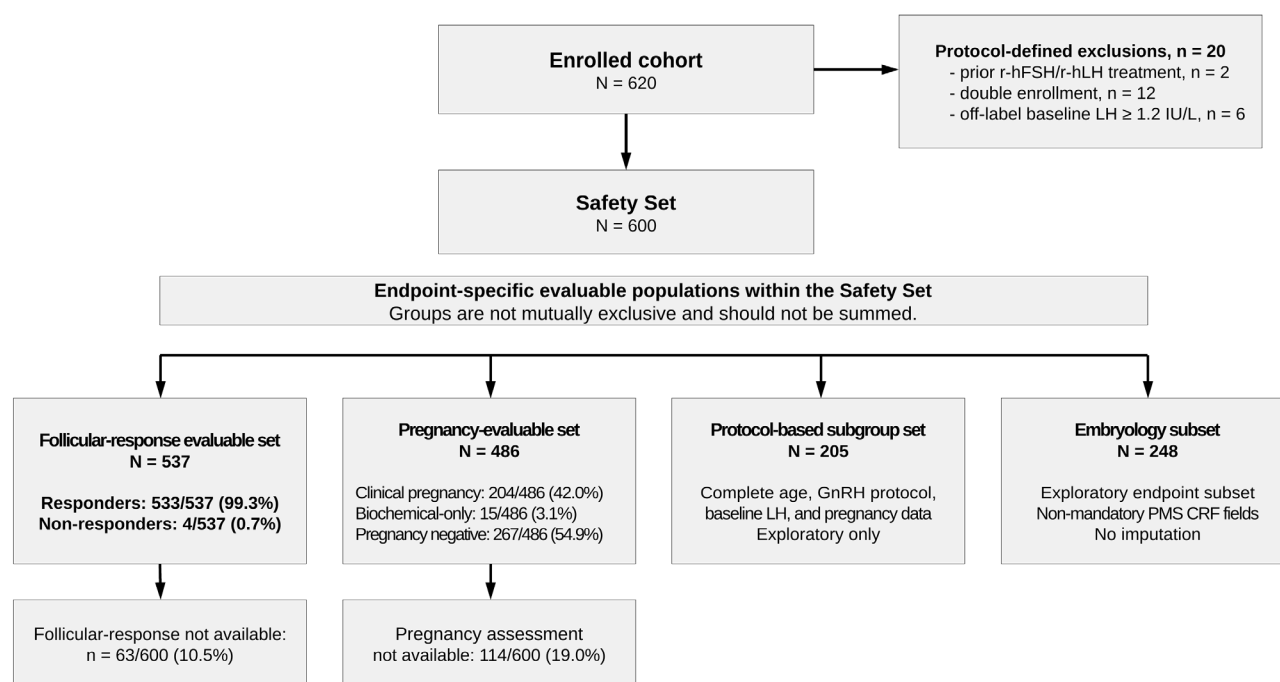
### 2.2. COS Protocols

COS was performed using either GnRH antagonist or agonist protocols according to routine clinical practice. The starting dose of r-hFSH/r-hLH generally followed local clinical standards, and subsequent dose adjustments were made at the physician's discretion based on ovarian response. Because this was a PMS study without protocol-driven stimulation algorithms, protocol selection may have influenced observed outcomes; therefore, protocol-related analyses were prespecified as descriptive and exploratory.

Human chorionic gonadotropin (hCG) was administered when at least one follicle reached a mean diameter of  $\geq 17$  mm on transvaginal ultrasonography, in line with standard ART practice. Oocyte retrieval, laboratory procedures, embryo transfer, and luteal support were performed in accordance with institutional protocols.

### 2.3. Population Analysis

In the enrolled cohort ( $n = 620$ ), the safety set comprised 600 patients with valid safety documentation after applying protocol-defined exclusions. Within the safety set, the follicular-response evaluable set included 537 patients with documented follicular response assessment; of these, 533 (99.3%) had at least one follicle  $\geq 17$  mm, and 4 (0.7%) were coded as non-responders. The pregnancy-evaluable set included 486 patients with documented pregnancy outcomes (204 clinical pregnancies [42.0%], 15 biochemical-only pregnancies [3.1%], and 267 negative pregnancies [54.9%]). Pregnancy assessment data were not available for 114/600 patients (19.0%). The protocol-based subgroup set ( $n = 205$ ) required complete data for age, GnRH protocol, baseline LH level, and pregnancy outcomes. The embryology subset ( $n = 248$ ) included cycles with available embryology variables. The non-responder set ( $n = 4$ ) was a subset of the follicular-response evaluable set (Figure 1).



**Note:** Evaluable populations were endpoint-specific and should not be interpreted as a single hierarchical efficacy population. Outcomes are descriptive, and no imputation was performed.

Abbreviations: CRF, case report form; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PMS, post-marketing surveillance; r-hFSH/r-hLH, recombinant human follicle-stimulating hormone/recombinant human luteinizing hormone.

**Figure 1.** Patient disposition and endpoint-specific evaluable populations. Evaluable populations were endpoint-specific within the safety set and were not mutually exclusive; therefore, they should not be summed or interpreted as a single hierarchical efficacy population. Outcomes were descriptive, and no imputation was performed. Abbreviations: CRF, case report form; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PMS, post-marketing surveillance; r-hFSH/r-hLH, recombinant human follicle-stimulating hormone/recombinant human luteinizing hormone.

## 2.4. End Points

The primary descriptive clinical outcome was clinical pregnancy, defined as an ultrasound-confirmed intrauterine pregnancy (presence of a gestational sac with or without a yolk sac). Follicular response was summarized as a descriptive ovarian response endpoint and was defined as the presence of at least one follicle with a mean diameter of  $\geq 17$  mm on the day of trigger (hCG) administration.

The total pregnancy rate was defined as the sum of biochemical-only and clinical pregnancies and was summarized descriptively. Total pregnancy and biochemical-only pregnancy were not used to support comparative or causal conclusions regarding effectiveness.

Biochemical pregnancy was defined as a positive serum or urine hCG test without ultrasound confirmation and is reported separately as a descriptive outcome.

Exploratory embryology outcomes (available-case subsets) included the number of retrieved oocytes, the number of metaphase II (MII) oocytes, fertilization rate, and blastocyst formation rate. Because these variables were available only in a subset, they were interpreted as exploratory indicators of ovarian response and laboratory progression, not as confirmatory effectiveness endpoints.

## 2.5. Safety Endpoints

Safety endpoints included the incidence and profile of AEs and adverse drug reactions (ADRs), and the occurrence and severity of ovarian hyperstimulation syndrome (OHSS).

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0; ADRs were defined as AEs for which the investigator could not exclude a causal relationship with r-hFSH/r-hLH.

OHSS severity was graded using the protocol-defined criteria recorded in the PMS case report form (CRF), aligned with standard OHSS classifications. Serious AEs (SAEs) were assessed for their association with r-hFSH/r-hLH.

### 2.6. Handling of Incomplete Data

Incomplete documentation is an inherent feature of this real-world PMS design, in which several variables, such as detailed GnRH protocol information, hormonal assays, and embryology parameters, were non-mandatory CRF fields. Accordingly, the unavailability of protocol and embryology details was expected by design rather than reflecting selective loss to follow-up. The potential for information bias was acknowledged, particularly for subgroup, protocol, and embryology analyses.

No imputation procedures were performed. Complete-case analyses were applied to subgroup evaluations, and available-case analyses were used for embryology endpoints. All denominators were reported explicitly for each endpoint to avoid interpreting unavailable assessments as treatment failures. Pregnancy outcomes were summarized only in the pregnancy-evaluable set, while the 114/600 cases without available pregnancy assessments were reported as non-evaluable for pregnancy outcome interpretation.

### 2.7. Statistical Analyses

Safety and descriptive outcome analyses were performed on the safety set and endpoint-specific evaluable sets, respectively. Continuous variables were summarized as means  $\pm$  standard deviations, medians, and ranges (minimum–maximum), whereas categorical variables are presented as counts and percentages. Two-sided 95% confidence intervals (CIs) for key binary outcomes were calculated using the Wilson score method. Descriptive summaries and table generation were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and Wilson 95% CIs were calculated using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical outputs were independently checked according to prespecified quality-control procedures. No imputation was performed, and no formal hypothesis testing was conducted.

## 3. Results

### 3.1. Patient Disposition and Analysis Sets

The CRFs were prospectively collected from 620 patients enrolled across 24 sites in Korea between August 2011 and May 2018. Of these, 600 patients comprised the safety set after application of protocol-defined exclusions. Within the safety set, 537 patients had evaluable follicular response assessments, and 486 patients had evaluable pregnancy outcomes. Pregnancy assessment was not available for 114/600 patients (19.0%). A total of 205 patients qualified for the protocol-based subgroup set (complete age, GnRH protocol, baseline LH, and pregnancy data), and four patients were coded as follicular non-responders.

### 3.2. Baseline Characteristics

Baseline characteristics of the safety set ( $n = 600$ ) were summarized in Table 1. The mean age was  $34.6 \pm 3.8$  years, and the mean infertility duration was  $4.10 \pm 2.73$  years. Prior ART experience was reported in 511 (85.2%) patients. Baseline serum LH levels were consistently low by eligibility definition (mean,  $0.70 \pm 0.31$  IU/L; maximum, 1.19 IU/L), and the median baseline LH value (0.74 IU/L) was used for exploratory subgroup description. Baseline FSH levels were available in a subset ( $n = 130$ ; mean,  $3.25 \pm 2.26$  IU/L);

because of limited availability, baseline FSH levels were summarized descriptively and were not used for comparative inference.

**Table 1.** Baseline characteristics.

| Characteristic                           | Category/Statistic               | Safety Set, <i>n</i> = 600 |
|------------------------------------------|----------------------------------|----------------------------|
| <b>Age, years</b>                        | <i>n</i>                         | 600                        |
|                                          | Mean $\pm$ SD                    | 34.58 $\pm$ 3.83           |
|                                          | Median                           | 34.00                      |
|                                          | Min, Max                         | 22.00, 47.00               |
|                                          | 20–29                            | 47 (7.83)                  |
|                                          | 30–39                            | 486 (81.00)                |
|                                          | 40–49                            | 67 (11.17)                 |
| <b>Concurrent disease</b>                | <i>n</i>                         | 600                        |
|                                          | Yes                              | 66 (11.00)                 |
|                                          | No                               | 534 (89.00)                |
|                                          | Hepatic impairment               | 3 (0.50)                   |
|                                          | Renal impairment                 | 1 (0.17)                   |
|                                          | Other                            | 63 (10.50)                 |
| <b>Allergic history</b>                  | <i>n</i>                         | 600                        |
|                                          | Yes                              | 10 (1.67)                  |
|                                          | No                               | 590 (98.33)                |
| <b>Infertility duration, years</b>       | <i>n</i>                         | 600                        |
|                                          | Mean $\pm$ SD                    | 4.10 $\pm$ 2.73            |
|                                          | Median                           | 3.50                       |
|                                          | Min, Max                         | 0.00, 20.42                |
|                                          | <3.50                            | 298 (49.67)                |
|                                          | $\geq$ 3.50                      | 302 (50.33)                |
| <b>Cause of infertility <sup>a</sup></b> | <i>n</i>                         | 600                        |
|                                          | Ovary factor: ovulatory disorder | 82 (13.67)                 |
|                                          | Cervical factor                  | 3 (0.50)                   |
|                                          | Uterine factor                   | 84 (14.00)                 |
|                                          | Oviduct factor                   | 88 (14.67)                 |
|                                          | Intra-abdominal abnormality      | 80 (13.33)                 |
|                                          | Male factor                      | 120 (20.00)                |
|                                          | Immunological factor             | 15 (2.50)                  |
|                                          | Unknown cause                    | 223 (37.17)                |

Table 1. Cont.

| Characteristic                        | Category/Statistic       | Safety Set, <i>n</i> = 600 |
|---------------------------------------|--------------------------|----------------------------|
| Previous ART experience <sup>a</sup>  | <i>n</i>                 | 600                        |
|                                       | Yes                      | 511 (85.17)                |
|                                       | No                       | 89 (14.83)                 |
| Previous ART cycle count <sup>*</sup> | <i>n</i>                 | 379 †                      |
|                                       | Mean ± SD                | 2.45 ± 1.79                |
|                                       | Median                   | 2.00                       |
|                                       | Min, Max                 | 1.00, 14.00                |
| Previous ART procedure <sup>a</sup>   | <i>n</i>                 | 511 <sup>b</sup>           |
|                                       | OI                       | 12 (2.35)                  |
|                                       | IUI                      | 142 (27.79)                |
|                                       | IVF-ET                   | 356 (69.67)                |
|                                       | GIFT                     | 0 (0.00)                   |
|                                       | ZIFT                     | 0 (0.00)                   |
|                                       | ICSI                     | 85 (16.63)                 |
|                                       | Other                    | 13 (2.54)                  |
| Serum LH, IU/L <sup>c</sup>           | <i>n</i>                 | 600                        |
|                                       | Mean ± SD                | 0.70 ± 0.31                |
|                                       | Median                   | 0.74                       |
|                                       | Min, Max                 | 0.01, 1.19                 |
|                                       | <0.74                    | 296 (49.33)                |
|                                       | ≥0.74                    | 304 (50.67)                |
| Serum FSH, IU/L <sup>c</sup>          | <i>n</i>                 | 130                        |
|                                       | Mean ± SD                | 3.25 ± 2.26                |
|                                       | Median                   | 2.84                       |
|                                       | Min, Max                 | 0.10, 14.38                |
|                                       | <2.84                    | 65 (50.00)                 |
|                                       | ≥2.84                    | 65 (50.00)                 |
| Previous treatments for infertility   | <i>n</i>                 | 600                        |
|                                       | Yes                      | 370 (61.67)                |
|                                       | No                       | 230 (38.33)                |
| r-hFSH/r-hLH dosing <sup>d</sup>      | Treatment duration, days | 5.36 ± 3.62                |
|                                       | Total dose, IU           | 918.21 ± 806.32            |
|                                       | Daily dose, IU/day       | 170.64 ± 51.58             |

Note: Data are presented as *n* (%) unless otherwise indicated. PMS CRF fields were not mandatory for all variables; therefore, denominators vary. <sup>a</sup> Multiple responses were allowed. <sup>b</sup> Patients with prior ART experience (*n* = 511). <sup>c</sup> Serum hormone levels were assessed within 1 year prior to treatment with r-hFSH/r-hLH. <sup>\*</sup> ART was performed at any time before r-hFSH/r-hLH initiation. † Data not available for prior ART cycle count: 132 patients. <sup>d</sup> Dosing summaries were calculated using cycles with complete dosing data. ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; IVF-ET, IVF-embryo transfer; OI, ovulation induction; IUI, intrauterine insemination; GIFT/ZIFT, gamete/zygote intrafallopian transfer; PMS, post-marketing surveillance; CRF, case report form.

Dose summaries were calculated using cycles with available start/stop dates and total dose values; denominators varied by parameter owing to non-mandatory CRF fields. Daily dose was calculated as the cumulative dose divided by the treatment duration (in days).

### 3.3. Safety Outcomes

Safety outcomes for the safety set ( $n = 600$ ) were summarized in Table 2. Seventeen AEs were reported in 16 patients (2.7%; 95% CI, 1.6–4.3), including 13 ADRs in 13 patients (2.2%; 95% CI, 1.3–3.7). OHSS was the most frequently reported event (8/600, 1.3%; 95% CI, 0.7–2.6) and was graded as mild ( $n = 4$ ), moderate ( $n = 3$ ), or severe ( $n = 1$ ) using protocol-defined criteria consistent with the Golan classification and subsequent refinements; seven OHSS cases were considered ADRs based on investigator assessment. SAEs were reported in two patients (0.33%; OHSS and ectopic pregnancy). Causality for both SAEs was assessed as “likely,” and both patients recovered without discontinuation of the study drug.

**Table 2.** Safety outcomes by MedDRA system organ class (safety set,  $n = 600$ ).

| Adverse Event Category<br>(MedDRA v21.0)             | Patients [ $n$ (%)] | Events | ADR [ $n$ (%)] | ADR<br>Events |
|------------------------------------------------------|---------------------|--------|----------------|---------------|
| Reproductive system and breast disorders             | 8 (1.33)            | 8      | 7 (1.17)       | 7             |
| – Ovarian hyperstimulation syndrome                  | 8 (1.33)            | 8      | 7 (1.17)       | 7             |
| Gastrointestinal disorders                           | 3 (0.50)            | 3      | 2 (0.33)       | 2             |
| – Abdominal pain (lower)                             | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| – Nausea                                             | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| – Abdominal distension                               | 1 (0.17)            | 1      | 0 (0.00)       | 0             |
| General disorders and administration site conditions | 3 (0.50)            | 3      | 3 (0.50)       | 3             |
| – Injection site erythema                            | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| – Injection site pain                                | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| – Injection site pruritus                            | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| Infections and infestations                          | 1 (0.17)            | 1      | 0 (0.00)       | 0             |
| – Nasopharyngitis                                    | 1 (0.17)            | 1      | 0 (0.00)       | 0             |
| Pregnancy, puerperium, and perinatal conditions      | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| – Ectopic pregnancy                                  | 1 (0.17)            | 1      | 1 (0.17)       | 1             |
| Respiratory, thoracic, and mediastinal disorders     | 1 (0.17)            | 1      | 0 (0.00)       | 0             |
| – Nasal obstruction                                  | 1 (0.17)            | 1      | 0 (0.00)       | 0             |
| TOTAL                                                | 16 (2.67)           | 17     | 13 (2.17)      | 13            |

Note: Adverse events were collected according to routine post-marketing surveillance procedures and coded using MedDRA terminology; percentages were based on the safety set ( $n = 600$ ). Overall AE incidence was 2.7% (16/600; 95% CI, 1.6–4.3), overall ADR incidence was 2.2% (13/600; 95% CI, 1.3–3.7), and OHSS incidence was 1.3% (8/600; 95% CI, 0.7–2.6). OHSS severity was graded according to protocol-defined criteria: mild (abdominal distension/discomfort), moderate (nausea/vomiting/diarrhea + mild ultrasonographic evidence), and severe (ascites/hydrothorax, coagulation abnormalities, or hospitalization). ADR, adverse drug reaction.

### 3.4. Descriptive Follicular Response and Pregnancy Outcomes

Follicular response ( $\geq 1$  follicle measuring  $\geq 17$  mm) occurred in 533/537 cycles (99.3%; 95% CI, 98.1–99.7) in the follicular-response evaluable set ( $n = 537$ ) (Table 3). Clinical pregnancy (ultrasound-confirmed intrauterine gestational sac  $\pm$  yolk sac) occurred in 204/486 cycles (42.0%;

95% CI, 37.7–46.4) in the pregnancy-evaluable set (Table 3). These outcomes are descriptive and should be interpreted within their endpoint-specific evaluable populations.

**Table 3.** Follicular response and pregnancy outcomes (follicular-response evaluable set,  $n = 537$ ; pregnancy-evaluable set,  $n = 486$ ).

| Parameter                                      | Value                             |
|------------------------------------------------|-----------------------------------|
| Follicular-response evaluable set              | $n = 537$                         |
| – Patients with $\geq 1$ follicle $\geq 17$ mm | 533 (99.26%; 95% CI, 98.10–99.71) |
| – Non-responders ( $<17$ mm follicles)         | 4 (0.74%; 95% CI, 0.29–1.90)      |
| Pregnancy-evaluable set                        | $n = 486$                         |
| – Clinical pregnancy (ultrasound-confirmed)    | 204 (41.98%; 95% CI, 37.67–46.41) |
| – Biochemical-only pregnancy                   | 15 (3.09%; 95% CI, 1.88–5.03)     |
| – Pregnancy negative                           | 267 (54.94%)                      |

Note: Pregnancy outcomes are reported in the pregnancy-evaluable set ( $n = 486$ ) based on documented pregnancy assessments; pregnancy assessment was not available for 114/600 patients (19.0%) in the safety set. Confidence intervals were calculated using the Wilson score method.

### 3.5. Subgroup and Embryology Outcomes

Exploratory subgroup analyses (protocol-based set,  $n = 205$ ) were summarized by age group, GnRH protocol, baseline LH level, and prior ART experience (Table 4). Numerically higher clinical pregnancy rates were observed among patients aged  $<35$  years, GnRH antagonist cycles, patients with baseline LH levels  $\geq 0.74$  IU/L, and patients without prior ART experience; however, these findings are descriptive only and should not be interpreted as treatment recommendations because of the complete-case subset design, protocol variability, and absence of formal modeling. Exploratory embryology outcomes were available for 248/537 cycles (46.2%) and included  $7.5 \pm 3.1$  retrieved oocytes,  $5.2 \pm 2.4$  MII oocytes, 68.3% fertilization, and 42.6% blastocyst formation (Table 5).

**Table 4.** Subgroup analyses based on protocol-defined and clinical characteristics (available-case subsets).

| Subgroup                     | $n$ | Clinical Pregnancy (%) | Site-Reported Pregnancy (%) |
|------------------------------|-----|------------------------|-----------------------------|
| Age $< 35$ years             | 76  | 27.6                   | 32.8                        |
| Age $\geq 35$ years          | 129 | 17.8                   | 22.5                        |
| GnRH agonist                 | 31  | 14.8                   | 18.5                        |
| GnRH antagonist              | 143 | 24.3                   | 28.0                        |
| Baseline LH $< 0.74$ IU/L    | 96  | 16.7                   | 20.8                        |
| Baseline LH $\geq 0.74$ IU/L | 109 | 25.9                   | 30.5                        |
| Prior ART–Yes                | 112 | 18.7                   | 23.0                        |
| Prior ART–No                 | 93  | 24.5                   | 29.1                        |

Note: Subgroup denominators reflect available-case documentation within PMS case report forms and are reported explicitly to avoid denominator misinterpretation. These subgroup findings are exploratory and descriptive; no formal hypothesis testing or adjusted modeling was performed. GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; ART, assisted reproduction technologies; PMS, post-marketing surveillance.

**Table 5.** Exploratory embryology outcomes (available-case subset; cycles with embryology data,  $n = 248/537$ ).

| Outcome                              | <i>n</i> | Value                      |
|--------------------------------------|----------|----------------------------|
| Cycles with embryology data          | 248      | 248/537 (46.2%)            |
| Retrieved oocytes                    | 248      | $7.5 \pm 3.1$ (range 2–18) |
| Mature (MII) oocytes                 | 248      | $5.2 \pm 2.4$              |
| MI rate (%)                          | 248      | 69.3%                      |
| Normally fertilized embryos (2PN, %) | 248      | 68.3%                      |
| Cleavage embryos (%)                 | 248      | 61.0%                      |
| Blastocyst formation rate (%)        | 248      | 42.6%                      |

Note: Embryology variables were captured as exploratory endpoints and were available for a subset of cycles: 248 of 537 cycles (46.2%). Percentages are based on cycles with documented embryology data. These data provide limited descriptive context for ovarian response and laboratory progression and were not used to support comparative or causal effectiveness conclusions.

### 3.6. Data Review of Follicular Non-Responder Records

Four patients were coded as follicular non-responders in the PMS CRF. During data review, individual records showed inconsistencies between the follicular-response coding and the site-reported pregnancy-status fields in some cases. These records were retained in the follicular-response denominator for transparency but were not used to support conclusions about effectiveness. Because the number of cases was small and the fields were not fully concordant, the finding is presented as a data-quality limitation rather than as a separate clinical subgroup.

## 4. Discussion

This multicenter Korean PMS study primarily characterizes the post-marketing safety profile of the fixed 2:1 r-hFSH/r-hLH formulation in women undergoing ART who met the severe LH-deficiency criterion [11,12]. In the 600-patient safety set, AEs occurred in 2.7% of patients, ADRs in 2.2%, and OHSS in 1.3%, including one severe OHSS case. No new safety signal was identified within the scope of this PMS dataset.

Follicular-response and pregnancy outcomes were summarized as descriptive outcomes within endpoint-specific evaluable populations. Follicular response was observed in 533/537 patients, and clinical pregnancy was observed in 204/486 patients with documented pregnancy assessment. These outcomes provide clinically interpretable descriptive information, but they should not be interpreted as comparative or causal evidence of effectiveness [13,14].

The fixed 2:1 IU ratio reflects the approved recombinant co-administration formulation designed to provide concomitant FSH and LH support in women with severe LH and FSH deficiency [15,16]. This differs from strategies using separate r-hFSH and r-hLH injections, in which each component may be adjusted independently, and from hMG-based regimens, which provide gonadotropin activity through urinary-derived preparations with different compositions and relative LH/hCG activity [15]. OHSS remains a known risk in ovarian stimulation, and the low OHSS incidence in this PMS cohort should be interpreted within the limits of routine safety reporting [17,18]. The approved indication and product-specific regulatory context are also relevant when interpreting this post-marketing experience [19]. Because this PMS study did not include a comparator arm, the findings characterize post-marketing experience with the fixed formulation [20] and do not establish superiority over other gonadotropin regimens or dosing strategies.

Baseline LH levels were uniformly low by study eligibility, with a maximum observed value of 1.19 IU/L. Exploratory subgroup summaries using the median baseline LH value

of 0.74 IU/L showed numerically higher pregnancy rates among patients with relatively higher baseline LH levels within this severely deficient range. This observation is biologically plausible because LH contributes to theca-cell androgen production, estrogen synthesis, and follicular maturation [21–23]; however, the subgroup set was limited to complete-case data and was not adjusted for potential confounders. The finding should therefore be interpreted as exploratory. Baseline FSH was available in a smaller subset and was not suitable for robust outcome-stratified interpretation.

Protocol variability is another important interpretive issue. GnRH agonist and antagonist protocols were both used in accordance with local routine practice, and protocol selection was not randomized. Numerically different outcomes across protocol categories may reflect differences in patient selection, center practice, stimulation strategy, and other unmeasured clinical factors rather than protocol effects [24]. For this reason, protocol subgroup results were presented descriptively and were not used to infer that one protocol was preferable in this population.

Incomplete documentation must also be considered when interpreting the results. Pregnancy outcomes were summarized in the pregnancy-evaluable set, and pregnancy assessment was not available for 114/600 patients in the safety set. Similarly, GnRH protocol information, hormonal variables, and embryology outcomes were non-mandatory PMS CRF fields. These unavailable data may introduce selection and information bias, particularly for subgroup and embryology analyses. To limit overinterpretation, no imputation was performed, denominators were reported for each endpoint, subgroup analyses were limited to complete cases, and embryology outcomes were treated as an exploratory subset.

Embryology outcomes provide limited descriptive context for ovarian response, including retrieved oocytes, MII oocytes, fertilization, and blastocyst formation among cycles with available laboratory data [25,26]. Because these data were available for only 248/537 cycles, they should be interpreted only as exploratory and cannot establish treatment benefit. The study is further limited by its observational PMS design, lack of randomization, absence of a comparator, incomplete cycle-specific and laboratory variables, and lack of live-birth or long-term pregnancy follow-up. Economic analyses of recombinant LH versus hMG supplementation have also been reported, but cost outcomes were outside the scope of this PMS analysis [27,28]. Future Korean ART research should include prospectively standardized protocol variables, complete embryology and pregnancy follow-up, comparator groups, and, where feasible, randomized or well-controlled real-world designs. In conclusion, this multicenter Korean PMS study supports a favorable post-marketing safety profile of the fixed 2:1 r-hFSH/r-hLH formulation in women meeting severe LH-deficiency criteria. The follicular-response and pregnancy outcomes provide clinically interpretable descriptive information within endpoint-specific evaluable populations, but should not be interpreted as evidence of superiority over alternative gonadotropin regimens.

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**Institutional Review Board Statement:** According to the Korean Bioethics and Safety Act (Article 15(2)) and its Enforcement Rule (Article 13, Paragraph 1, Subparagraph 3), the present analysis qualifies for exemption from Institutional Review Board (IRB) review. The applicable basis is that

the study constitutes research using pre-existing data or documents concerning research subjects, without the collection or recording of personally identifiable information, and therefore meets the minimal-risk threshold set out in Article 15(2). Specifically, this manuscript reports a descriptive analysis of post-marketing surveillance data that had been previously collected and de-identified, and did not involve new participant enrollment, additional patient contact, intervention, randomization, or any new collection of personally identifiable information.

**Informed Consent Statement:** The requirement for informed consent was waived in accordance with the applicable regulatory PMS framework and participating institutional policies.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## Abbreviations

The following abbreviations are used in this manuscript: ADR, adverse drug reaction; AE, adverse event; ART, assisted reproductive technology; CI, confidence interval; COS, controlled ovarian stimulation; CRF, case report form; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; hMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; LH, luteinizing hormone; MedDRA, Medical Dictionary for Regulatory Activities; MFDS, Ministry of Food and Drug Safety; MII, metaphase II; OHSS, ovarian hyperstimulation syndrome; PMS, post-marketing surveillance; r-hFSH, recombinant human follicle-stimulating hormone; r-hLH, recombinant human luteinizing hormone; SAE, serious adverse event.

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