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Use of a recombinant human follicle-stimulating hormone:recombinant human luteinizing hormone (r-hFSH:r-hLH) 2:1 combination for controlled ovarian stimulation during assisted reproductive technology treatment: A real-world study of routine practice in the Russian Federation

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A B S T R A C T

Two observational studies in the Russian Federation described patient demographics/clinical decision for treatment with recombinant human follicle-stimulating hormone:recombinant human luteinizing hormone (r-hFSH:r-hLH) 2:1 combination for ovarian stimulation (OS) during assisted reproductive technology (ART) and outcomes, respectively. The first (prospective) study enrolled 500 patients. After *post-hoc* regrouping to assign patients to discrete groups, 378 (75.6%) met the local Russian label for an r-hFSH:r-hLH 2:1 combination, 105 (21%) were treated according to other physician preference, and 17 (3.4%) met only the ESHRE Bologna criteria for a poor ovarian response. The clinical pregnancy rate per cycle was 30.4%. A total of 158/175 (90.3%) women achieving clinical pregnancy in the prospective study participated in the second (retrospective) study. The live birth rate per cycle was 25.8%. No new safety concerns were reported. These results support the use of the r-hFSH:r-hLH 2:1 combination in patients with a poor/suboptimal response to OS for ART treatment in the Russian Federation.

Introduction

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have complementary roles in folliculogenesis and oocyte maturation. Both are secreted from the anterior pituitary gland under gonadotropin-releasing hormone (GnRH) control. In assisted reproductive technology (ART), ovarian stimulation (OS) is performed using exogenous gonadotropins, with the objective to obtain a supra-physiological number of oocytes. Generally, GnRH agonist or antagonist down-regulation is needed to prevent premature ovulation. Usually, residual circulating LH is sufficient to support steroidogenesis in the follicle, and FSH is considered sufficient for OS. Nevertheless, in some cases, residual circulating LH is not sufficient to support steroidogenesis, and exogenous LH in addition to exogenous FSH is required for OS [1].

The 2:1 fixed-ratio combination of recombinant human FSH plus recombinant human LH (r-hFSH:r-hLH 2:1 combination; Pergoveris®; Merck KGaA, Darmstadt, Germany) has been developed to improve patient convenience and ease of use. This currently has marketing authorisation in 92 countries [2]. In most of these countries, the r-hFSH:r-hLH 2:1 combination is indicated for the stimulation of the follicular development in women with severe LH and FSH deficiency (hypogonadotropic hypogonadism) [2]; defined by The International Committee Monitoring Assisted Reproductive Technologies (ICMART) as a gonadal failure associated with reduced gametogenesis and reduced gonadal steroid production because of reduced gonadotropin production or action [3]. In the Russian Federation, the r-hFSH:r-hLH 2:1 treatment combination obtained regulatory approval in 2011 for patients with severe FSH and LH deficiency as well as those with a history of, or at risk of having, a poor or suboptimal response to OS, defined as <7 follicles/oocytes retrieved or FSH dose ≥3000 IU/cycle during the previous OS cycle, or who are of advanced maternal age (≥35 years) [4].

Patients with poor ovarian response (POR) represent an important subgroup of infertile patients. The estimated prevalence of POR in the population seeking infertility treatment ranges from 5.6% to 35.1%, depending on the POR definition used [5]; and live birth rates after IVF treatment in this group range between 5% and 11% [6–9].

POR cannot be attributed to a single cause, and patients with POR comprise several subpopulations [6,10–13]. The European Society of Human Reproduction and Embryology (ESHRE) Bologna criteria were developed to provide a definition of POR for use in clinical research [14]. The ESHRE Bologna criteria state that a patient should be considered a poor ovarian responder if they meet at least two of the following: advanced maternal age (≥40 years) or any other risk factor for POR; a previous POR (≤3 oocytes with a conventional stimulation protocol); or an abnormal ovarian reserve test (i.e., antral follicle count [AFC] <5–7 follicles or anti-Müllerian hormone [AMH] <0.5–1.1 ng/mL). In addition, two episodes of POR after maximal stimulation are sufficient to identify a patient as having predicted POR in the absence of advanced maternal age or an abnormal ovarian reserve test [14]. However, there remains a high degree of heterogeneity among patients classified as POR according to the ESHRE Bologna criteria, which may contribute to the lack of an effective treatment modality for these patients since the publication of the criteria and the reluctance of fertility experts to use these criteria in studies of patients with POR [15]. Consequently, efforts are ongoing to define specific subpopulations of poor ovarian responders and suboptimal responders (4–9 oocytes retrieved) [13,16].

The Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group proposed criteria for segmenting suboptimal and poor ovarian responders to assist individualizing treatment in clinical practice [11,17]. The POSEIDON group also proposed the number of oocytes needed to obtain at least one euploid embryo for transfer as an intermediate marker for the ART treatment success [18].

Treatment with the combination of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) during OS may have a beneficial effect on outcomes for some populations of poor ovarian responders and suboptimal responders compared with the FSH alone [19–22]. In standard clinical practice, clinicians use either an LH or human chorionic gonadotropin (hCG) as an LH-like activity source because they both bind to the LH/choriogonadotropin (LHCGR) receptor [23]. However, it has been demonstrated that LH and hCG initiate different cellular responses in the LHCGR receptor [23–25].

We conducted two studies on the patient population treated with an r-hFSH:r-hLH 2:1 combination in the Russian Federation. The first was a prospective, non-interventional study to describe the profiles of the patients receiving OS with the r-hFSH:r-hLH 2:1 combination in real-world clinical practice in the context of ART and to identify the real-world criteria used for OS with the r-hFSH:r-hLH 2:1 combination. The second was a retrospective study to assess the pregnancy outcomes of the women who achieved clinical pregnancy in the previous study.

Methods

Study design

The results reported in this manuscript relate to two non-interventional, observational, multicentre studies conducted in the Russian Federation. The aim of the first study (EMR200061_509, hereafter referred to as the prospective study) was to report on the profiles of patients who were treated with the r-hFSH:r-hLH 2:1 combination in real-life daily clinical practice in an ART setting. The aim of the second study (MS200061_0016, hereafter referred to as the retrospective study) was to report the pregnancy outcomes for the women who achieved clinical pregnancy in the prospective study. Data for the prospective study were collected between April 2016 and January 2017, and data for pregnancy outcomes in the retrospective study were collected between September 2019 and January 2020. The studies were conducted in compliance with the respective protocols, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization–Good Clinical Practice guidelines, and the applicable regulatory requirements. The study protocols were approved by central and local ethics committees before initiation. All patients provided written informed consent before entry in the prospective and retrospective studies. All patient data were collected anonymously.

Study participants

Women of reproductive age requiring *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) at 20 centres in the Russian Federation were enrolled in the first study (Supplementary Table 1). Patients prescribed the r-hFSH:r-hLH 2:1 combination were included in the study sequentially in a routine manner. There were no special recruitment strategies (e.g., advertisements or specific clinics for trial enrolment). This was to ensure that, as far as possible, the study population was representative of the general population of women of reproductive age seeking ART. The inclusion criteria for the prospective study were an established diagnosis of infertility requiring ART (IVF or ICSI); decision of the investigator to assign OS with the r-hFSH:r-hLH 2:1 combination; negative pregnancy test at inclusion in the study; and informed consent to participate. The exclusion criteria were concomitant treatment with clomiphene or any gonadotropins other than r-hFSH (GONAL-f®, r-hFSH-alfa. Merck KGaA, Darmstadt, Germany); any contraindications for the r-hFSH:r-hLH 2:1 combination according to the local label; and previous participation in the study (a patient could participate in the study only once; only one cycle per patient was evaluated). Women with a positive pregnancy status, confirmed as the presence of at least one transvaginal ultrasound confirmed gestational sac in the uterus with or without foetal heart activity 35–42 days after a recombinant hCG (r-hCG) injection, were eligible for inclusion in the second (retrospective) study. Women who did not provide written informed consent were excluded.

Endpoints

The primary objective of the first (prospective) study was to describe the demographic, medical history, baseline clinical characteristics, and the criteria used for the administration of the r-hFSH:r-hLH 2:1 combination. The patient profiles included, but were not limited to, age, number of oocytes in the previous cycle, ovarian reserve tests, dose of gonadotropins in the previous cycle, and other factors.

Secondary endpoints were the characteristics of previous ART treatment, the current protocol used for ART treatment, and outcomes of IVF/ICSI cycles (number and sizes of follicles, number of oocytes retrieved/fertilized/frozen, number of embryos transferred/frozen, biochemical pregnancy rate, clinical pregnancy rate, and cycle discontinuation rate). The fertilization rate was calculated as the number of patients with oocytes fertilized divided by the total number of patients (per patient) and the number of oocytes fertilized divided by the number of oocytes retrieved (per oocyte). Biochemical pregnancy, clinical pregnancy, and cycle discontinuation were defined according to the ICMART and WHO consensus glossary [3]. If the answer to either of the questions 'Did the patient receive a trigger' or 'Was oocyte retrieval performed' was 'No' (according to the case report form), then the patient was considered to have cycle discontinuation.

Serious adverse events (SAEs), regardless of a causal relationship to the medications under observation (r-hFSH:r-hLH 2:1 combination and/or r-hFSH), and suspected non-serious adverse reactions (i.e. adverse events [AEs] considered at least possibly related to the medications under observation) were recorded and monitored. AEs of special interest (e.g. ovarian hyperstimulation syndrome [OHSS]) were also recorded and monitored. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 19.1). The period for AE recording started from the date when informed consent was signed by the patient and continued until the last visit. Each AE occurring during the study was recorded on a case report form, including a description of the AE, an assessment of the seriousness, severity and duration of the AE (onset and resolution dates and times), causal relationship and any potential causal factors, actions taken regarding the medicinal product (e.g., dose reduction or withdrawal), treatment required, and outcome.

The primary objective of the second (retrospective) study was to describe the live birth outcomes of pregnancies (referred to the individual new born; for example, a twin delivery represents two live births) achieved in the first (prospective) study. The abnormal pregnancy outcomes missed spontaneous abortion/missed miscarriage, stillbirth, or termination of pregnancy were described as a secondary objective. Live birth, missed spontaneous abortion/missed miscarriage, and stillbirth were defined according to the ICMART and World Health Organisation (WHO) consensus glossary [3]. The termination of pregnancy (induced abortion or elective abortion) was defined as an artificial interruption of pregnancy.

Treatments and follow-up

Each patient was followed up for a single treatment cycle. Women started an OS protocol with the r-hFSH:r-hLH 2:1 combination as assigned by the investigator according to his/her routine practice. Pituitary down-regulation was achieved with either a GnRH agonist or antagonist. Patients received either the r-hFSH:r-hLH 2:1 combination throughout the duration of OS or r-hFSH-alfa (GONAL-f) alone for 5–7 days followed by the r-hFSH:r-hLH 2:1 combination beginning on Days 6–8 of OS. The gonadotropin dose could be adjusted according to the patient response; the total daily dose of r-hFSH-alfa should, usually, not exceed 450 IU. Treatment with the r-hFSH:r-hLH 2:1 combination was continued until adequate follicular development was observed, as assessed by ultrasound and/or serum oestradiol levels. Ovulation was triggered by the administration of hCG and/or a GnRH agonist. Oocyte retrieval was performed approximately 35–36 hours after ovulation was triggered.

In the prospective study, patients were followed up until one of the following events occurred: the IVF/ICSI cycle was completed, and a positive biochemical pregnancy test was recorded; the cycle was completed, and a negative biochemical pregnancy test was recorded; the cycle was cancelled because of the risk of OHSS or other AEs, according to the judgement of the principal investigator; or no oocytes/embryos were available for insemination/transfer. The observation period for patients who did not achieve clinical pregnancy was estimated to be 1 month. Patients with a positive biochemical pregnancy at Visit 2 were followed up until the clinical pregnancy status was established (estimated as 2 months). In the second study, to document the pregnancy outcome, a retrospective follow-up of patients with an established clinical pregnancy was performed through a single face-to-face interview with the investigator or by three phone contacts.

Statistical analysis

The sample size was not calculated based on statistical considerations, but rather on feasibility based on clinical assumptions and the knowledge of patients in the participating study centres. Patient characteristics were summarized descriptively. Patients were initially grouped as follows (Supplementary Table 2): whole study sample group, patients meeting the Russian label for the r-hFSH:r-hLH 2:1 combination (detailed in Introduction), patients meeting the ESHRE Bologna criteria for POR (detailed in Introduction), patients meeting both the Russian label for the r-hFSH:r-hLH 2:1 combination and the ESHRE Bologna criteria for POR, and patients receiving the r-hFSH:r-hLH 2:1 combination according to other physician preference according to real-world clinical practice in the Russian Federation. In view of the diverse patient demographics, medical history, baseline clinical characteristics, and the diverse clinical decisions used for the administration of r-hFSH:r-hLH 2:1 combination treatment, patients were regrouped *post hoc* according to those meeting the r-hFSH:r-hLH 2:1 combination criteria for treatment according to the Russian label and those treated according to other clinical decisions to classify patients based on their clinical profile and the product indications used to assign them to treatment (other physician preference or ESHRE Bologna only criteria), to avoid having the same patients in more than one group.

Results

First (prospective) study

Five hundred patients were enrolled in the first (prospective) study. According to baseline clinical characteristics and the criteria used for the administration, 378 patients met the Russian label, 176 patients met the ESHRE Bologna POR criteria, 159 patients met both the Russian label and the ESHRE Bologna POR criteria, and 105 patients were treated according to other physician preference. The baseline characteristics of these subgroups are shown in Supplementary Table 2. To avoid having patients in overlapping groups, the patients were regrouped *post hoc* in subgroups as follows: those meeting exclusively the Russian label (n = 378 [75.6%]) (Fig. 1), those meeting only the ESHRE Bologna POR criteria (n = 17 [3.4%]), and those meeting other physician preference (n = 105 [21.0%]). According to the baseline characteristics of the patients treated according to other physician preference, the

reasons listed for administering the r-hFSH:r-hLH 2:1 combination could be grouped as follows: a reduction of the ovarian reserve (49/105 [46.7%]); to maximize the number of mature oocytes (24/105 [22.9%]); previous endometriosis/ovarian surgery/tubal damage (21/105 [20.0%]); hyper-responders (4/105 [3.8%]); LH deficiency (3/105 [2.9%]); or normal ovarian reserve (4/105 [3.8%]). Owing to the small number of patients (n = 17 [3.4%]) only meeting the ESHRE Bologna criteria, the results for these patients are not evaluated as a separate cohort in this manuscript but were included as part of the overall group.

The demographics, medical history, and baseline characteristics of all enrolled patients according to the regrouping are presented in Table 1. Overall, the median age was 37.0 (range 20–51) years. The median age of patients in the Russian-label cohort was 38.0 (range 23–51) years; most were aged ≥35 years at baseline (n = 330 [87.3%]; 110 [29.1%] of whom were aged ≥40 years) (Table 1). The median AFC was 6.0 (range 1–30) in both the overall cohort and in the Russian-label cohort. The median AMH was 1.3 (range 0.1–22.0) ng/mL in the overall cohort and 1.2 (range 0.1–22.0) ng/mL in the Russian-label cohort. The most common conditions impacting fertility were tubal damage (overall n = 201 [40.2%]; Russian label n = 164 [43.4%]), surgery for ovarian cysts (overall n = 111 [22.0%]; Russian label n = 74 [19.6%]), chlamydia infection (overall n = 55 [11.0%]; Russian label n = 48 [12.7%]), and ovarian endometrioma (overall n = 53 [10.6%]; Russian label n = 33 [8.7]). Two-hundred and thirty-one [46.2%] women overall and 209 [55.3%] women in the Russian-label cohort had undergone a previous IVF/ICSI cycle. The characteristics of the OS protocols are presented in Table 2. The median duration of OS was 9 (range 1–41) days in both the overall cohort and in the Russian-label cohort. Similar proportions of patients received dose adjustments in the overall (21.8%) and Russian-label (22.5%) cohorts. The median number of oocytes retrieved was 6 (range 0–29) in the overall cohort and 6 (range 0–27) in the Russian-label cohort. Similar numbers of embryos were transferred in each cohort. Sixty-one (12.2%) women in the overall cohort and 53 (14.0%) women in the Russian-label cohort had a cycle discontinuation before embryo transfer (the reasons for discontinuation are shown in Table 3). The clinical pregnancy rate per initiated cycle was 30.4% in the overall cohort and 27.2% in the Russian-label cohort (Table 3).

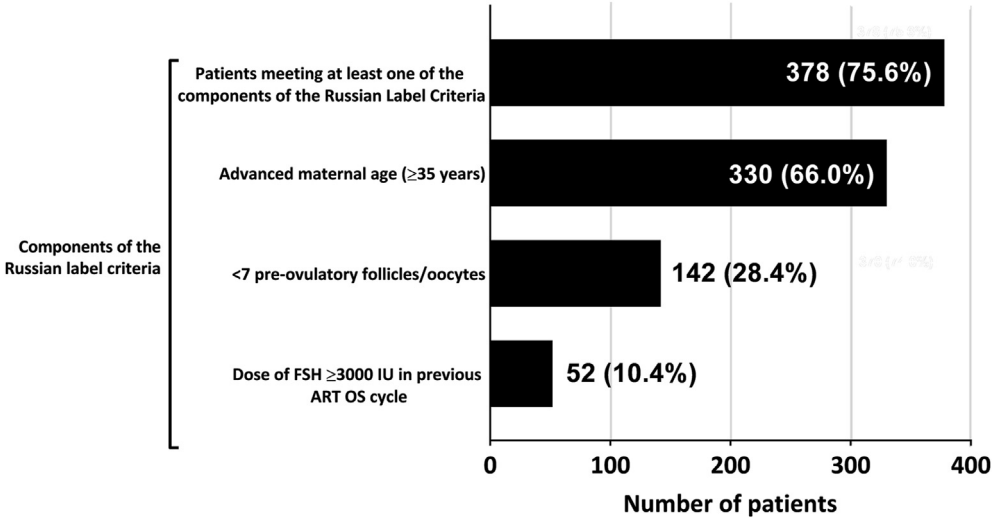

Fig. 1. Number (proportion) of patients meeting at least one of the components for the r-hFSH:r-hLH 2:1 combination indication in the Russian-label cohort. ART, assisted reproductive technology; FSH, follicle-stimulating hormone; IU, international units; OS, ovarian stimulation.

Table 1
Patient demographics, medical history, and baseline characteristics.

	Russian label (n = 378)	Physician preference (n = 105)	Total (n = 500)
Age, years	37.7 ± 3.4 (38, 23–51)	30.9 ± 2.8 (31, 20–34)	36.0 ± 4.4 (37, 20–51)
≥40, n (%)	110 (29.1)	0	110 (22.0)
≥35, n (%)	330 (87.3)	0	330 (66.0)
BMI, kg/m^2	24.0 ± 4.2 (23.1, 16.7–41.1)	22.4 ± 3.7 (21.6, 16.8–37.5)	23.6 ± 4.1 (22.9, 16.7–41.1)
Basal FSH on day 3, IU/L	8.3 ± 3.9 (7.5, 0.1–29.9)	7.7 ± 4.4 (7.0, 1.9–38.7)	8.2 ± 4.0 (7.4, 0.1–38.7)
AFC	6.8 ± 3.8 (6, 1–30)	8.9 ± 5.5 (7, 2–30)	7.2 ± 4.3 (6, 1–30)
AMH, ng/mL	1.8 ± 2.1 (1.2, 0.1–21.0)	3.0 ± 3.6 (1.7, 0.1–22.0)	2.0 ± 2.5 (1.3, 0.1–22.0)
Previous IVF/ICSI cycles			
Number of patients with previous IVF attempts, n (%)	209 (55.3)	22 (21.0)	231 (46.2)
Number of previous IVF cycles	2.0 ± 1.4 (1, 1–8)	1.5 ± 0.7 (1, 1–3)	2.0 ± 1.4 (1, 1–8)
Dose of FSH in the previous cycle, IU	2260.1 ± 883.8 (2250, 75–4925)	1786.8 ± 451.4 (1800, 825–2700)	2216.0 ± 863.2 (2175, 75–4925)
Number of oocytes in the last previous conventional OS	5.1 ± 4.1 (5, 0–27)	10.7 ± 3.6 (10, 7–20)	5.6 ± 4.3 (5, 0–27)
Past or present conditions			
Tubal damage, n (%)	164 (43.4)	30 (28.6)	201 (40.2)
Chlamydia infection in anamnesis, n (%)	48 (12.7)	5 (4.8)	55 (11.0)
Ovarian endometriomas, n (%)	33 (8.7)	12 (11.4)	53 (10.6)
Ovarian surgery for ovarian cysts, n (%)	74 (19.6)	25 (23.8)	111 (22.2)
Shortening of the menstrual cycle, n (%)	35 (9.3)	4 (3.8)	41 (8.2)
Chemotherapy, n (%)	1 (0.3)	0 (0)	1.0 (0.2)
Other[a], n (%)	115 (30.4)	33 (31.4)	150 (30.0)

Data are presented as mean ± SD (median, range) unless otherwise stated. Data for seventeen patients who met only the ESHRE Bologna criteria are not presented as a separate subgroup but are included in the total group.
AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; IU, international unit; OS, ovarian stimulation; SD, standard deviation.
[a] Other past or present conditions: adenomyosis, adhesiotomy, amenorrhea, Asherman's syndrome, autoimmune thyroiditis, azoospermia, bilateral tubectomy, cervical polyps, endometriosis, diminished ovarian reserve, endometrial polyp or surgery, euthyroid goitre, fallopian tube removal, Hashimoto's thyroidosis, hyperprolactinaemia, hypogondal hypogonadism, hypothyroidism, hysterectomy, previous IVF, abdominal laparoscopy/laparotomy, ureaplasma infection, unknown infertility, leyomyoma, male infertility, metabolic syndrome, miscarriage, myoma, myomectomy, nodular euthyroid goitre, obesity, oligoastenoteratospermia, ovarian drilling, ovarian surgery, PCOS, chromosomal abnormalities, primary hypothyroidism, recurrent pregnancy loss, relative marriage, salpingolysis, spontaneous miscarriage, foetal loss syndrome, thyrotoxicosis with diffuse goitre, tubal pregnancy, and uterus bicornis.

Second (retrospective) study

A total of 175 women with established clinical pregnancy were considered eligible for inclusion in the retrospective study, of whom, 158 (90.3%) were enrolled in the retrospective study. The other 17 (9.8%) either declined to participate (n = 13), did not provide informed consent (n = 2), or were lost to follow-up (n = 2).

One-hundred and twenty-nine (81.6%) of the 158 women in the overall cohort and 88 (80.7%) of the 109 women in the Russian-label cohort had at least one live birth (Table 4) (25.8% and 23.3%, respectively, per initiated cycle).

Safety

At least one AE was reported by 22 (4.4%) of 500 patients: nine (1.8%) had reproductive system disorders (hydrosalpinx or uterine polyp), four (0.8%) had mild OHSS (all cases of which resolved),

Table 2
Characteristics of OS for the whole study population and according to the subgroup.

	Russian label (n = 378)	Other physician preference (n = 105)	Total (N = 500)
Duration of OS, days	8.6 ± 4.0 (9, 1–41)	8.9 ± 2.0 (9, 3–15)	8.6 ± 3.7 (9, 1–41)
Daily dose of r-hFSH, IU	336.8 ± 225.6 (300.0, 131.3–2250.0)	262.8 ± 172.2 (225.0, 150.0–1556.3)	326.1 ± 221.1 (300.0, 131.3–2250.0)
Daily dose of r-hLH, IU	122.2 ± 35.6 (150.0, 75.0–204.5)	97.2 ± 34.2 (75.0, 75.0–196.9)	117.5 ± 36.6 (135.0, 75.0–204.5)
Total dose of r-hFSH, IU	2529.9 ± 1219.1 (2400, 300–12,300)	2244.6 ± 1137.4 (1950, 900–7500)	2487.8 ± 1197.5 (2400, 300–12,300)
Total dose of r-hLH, IU	1053.9 ± 642.9 (1050, 150–6150)	872.1 ± 382.3 (750, 225–1950)	1014.5 ± 594.4 (900, 150–6150)
Number of subjects with r-hFSH:r-hLH 2:1 combination dose adjustment, n (%)	85 (22.5)	24 (22.9)	109 (21.8)
LH level, IU[a]			
Before treatment	5.6 ± 2.7 (n = 288) (5.2, 0.1–16.6)	5.7 ± 4.2 (n = 87) (4.6, 0.7–35.6)	5.6 ± 3.1 (n = 389) (5.0, 0.1–35.6)
At initiation of OS	4.2 ± 2.4 (n = 21) (3.9, 0.9–9.0)	2.5 ± 1.1 (n = 5) (2.2, 1.5–4.2)	3.9 ± 2.3 (n = 26) (3.6, 0.9–9.0)

Data are presented as mean ± SD (median, range) unless otherwise stated. Data for seventeen patients who met only the ESHRE Bologna criteria are not presented as a separate subgroup but are included in the total group.
IU, international unit; OS, ovarian stimulation; r-hFSH, recombinant human follicle-stimulating hormone; r-hLH, recombinant human luteinizing hormone; SD, standard deviation.
[a] Before treatment: reported in 288 women in the Russian-label cohort, 87 women in the cohort treated according to other physician preference and 389 women in the total group. At the initiation of OS: reported in 21 women in the Russian-label cohort, five women in the cohort treated according to other physician preference and 26 women in the total group.

three (0.6%) reported infections (nasopharyngitis or respiratory tract), three (0.6%) underwent hysteroscopic investigation or experienced progesterone increase, and three (0.6%) had an ectopic pregnancy. No deaths were reported during the study. At least one SAE that required hospitalization was reported by five (1.0%) of 500 patients (ectopic pregnancy [n = 3 (0.6%)] and hydrosalpinx [n = 2 (0.4%)]); all SAEs resolved. Five AEs were judged by the investigator to be related to the medication(s) under investigation (the r-hFSH:r-hLH 2:1 combination and/or r-hFSH): three (0.6%) cases of OHSS, one (0.2%) case of premature progesterone rise, and one (0.2%) ectopic pregnancy (this patient had a history of salpingo-oophoritis and fallopian tube disorder, which are risk factors for ectopic pregnancy). Five patients (1%) discontinued a cycle because of an AE, including OHSS (n = 1 [0.2%]).

The rate of abnormal pregnancy outcomes for the women who achieved clinical pregnancy in the prospective study was 19.6% (31 of 158 women) in the overall cohort and 20.2% (22 of 109 women) in the Russian-label cohort (Table 4). Of the 158 women in the overall cohort, there were 31 cases of spontaneous abortion, three cases of still birth, and two cases of induced abortion. Of the 109 women in the Russian-label cohort, there were 21 cases of spontaneous abortion, two cases of still birth, and two cases of induced abortion (multiple outcomes per subject were reported) (Table 4). In all cases (overall cohort), the events were considered by the investigator as serious, but unrelated to the study treatment. The majority of cases reported were mild or moderate in severity; 10 cases were reported as severe; for six cases, the severity was not indicated by the investigator.

Discussion

This was the first study conducted to analyse the use of the r-hFSH:r-hLH 2:1 combination for OS during ART in the Russian Federation. The patient demographics at baseline were indicative of a population at risk of a poor or suboptimal response (advanced maternal age, POR in a previous treatment cycle, or abnormal ovarian reserve): 75.6% of patients met the Russian label, and 21.0% were treated according to other physician preference, according to the judgement of the treating physician (3.4% met only the ESHRE Bologna criteria). The clinical pregnancy rate per initiated cycle was 27.2% in

Table 3
ART outcomes for the whole study population and according to the subgroup per initiated cycle.

	Russian label (N = 378)	Other physician preference (N = 105)	Total (N = 500)
Number of follicles[a]	8.1 ± 6.2 (7, 1–55)	10.4 ± 6.1 (9, 1–33)	8.5 ± 6.2 (7, 1–55)
Number of follicles with size ≥16 mm[b]	6.1 ± 4.3 (5, 1–24)	7.9 ± 5.2 (6, 1–24)	6.4 ± 4.5 (5, 1–24)
Number of oocytes retrieved[c]	6.5 ± 4.4 (6, 0–27)	9.6 ± 6.2 (8, 1–29)	7.2 ± 4.9 (6, 0–29)
Number of fertilized oocytes[c]	4.8 ± 3.5 (4, 0–20)	7.1 ± 4.7 (6, 1–26)	5.3 ± 3.8 (4, 0–26)
Number of embryos transferred[d]	1.5 ± 0.6 (2, 1–4)	1.5 ± 0.5 (2, 1–3)	1.5 ± 0.6 (2, 1–4)
No embryo transfer performed, n (%)	53 (14.0)	8 (7.6)	61 (12.2)
Lack of available oocytes/ embryos	38 (10.1)	4 (3.8)	42 (8.4)
Adverse event (including OHSS)	4 (1.1)	1 (1.0)	5 (1.0)
Other reason (e.g. poor quality of the endometrium or patient decision)	11 (2.9)	3 (2.9)	14 (2.8)
Number of embryos frozen[e]	0.9 ± 1.4 (0, 0–7)	1.9 ± 2.6 (1, 0–13)	1.2 ± 1.8 (0, 0–13)
Cycle discontinuation rate[f], %	14.0	7.6	12.2
Cycle discontinuation according to Internationally Harmonized Consensus[f], %	1.1	0.0	0.8
Patient fertilization rate[g], %	98.9	100.0	99.2
Oocyte fertilization rate[h], %	73.7	74.8	74.3
Embryo implantation rate[i], %	22.6	30.6	25.5
Biochemical pregnancy rate per cycle[j], %	35.2	43.8	38.6
Clinical pregnancy rate per cycle[k], %	27.2	35.2	30.4
At least one live birth delivery, n (%)	88 (23.3)	29 (27.6)	129 (25.8)
Single	80 (21.4)	24 (22.9)	115 (23.0)
Twins	8 (2.1)	5 (4.7)	14 (2.8)

Data are presented as mean ± SD (median, range) unless otherwise stated. Data for seventeen patients who met only the ESHRE Bologna criteria are not presented as a separate subgroup but are included in the total group.
ART, assisted reproductive technology; β-hCG, beta-human chorionic gonadotropin; OHSS, ovarian hyperstimulation syndrome.
[a] Total number of follicles reported for 376 women in the Russian-label cohort and 498 women in the total group.
[b] Number of follicles with size ≥16 mm reported for 369 women in the Russian-label cohort, 103 women in the cohort treated according to other physician preference and 489 women in the total group.
[c] Number of oocytes retrieved and number of fertilized oocytes reported for 374 women in the Russian-label cohort and 496 women in the total group.
[d] Number of embryos transferred reported for 325 women in the Russian-label cohort, 97 women in the cohort treated according to other physician preference and 439 women in the total group.
[e] Number of embryos frozen reported for 344 women in the Russian-label cohort, 101 women in the cohort treated according to other physician preference and 462 women in the total group.
[f] Cycle discontinuation rate = number of women with cycle discontinuation/total number of women) x 100. Defined according to [3]. i.e. if the answer to either of the questions 'Did the patient receive a trigger' or 'Was oocyte retrieval performed' were 'No' (as per the case report form data), then the person was considered as a patient with cycle discontinuation (i.e. cycle was cancelled before oocyte retrieval).
[g] (Number of patients with oocytes fertilized/total number of patients) x 100.
[h] (Number of oocytes fertilized/number of oocytes retrieved) x 100.
[i] (Number of gestational sacs observed/number of embryos transferred) x 100.
[j] (Number of initiated cycles with a positive serum β-hCG biochemical pregnancy test/total number of initiated cycles) x 100.
[k] (Number of initiated cycles with gestational sac[s] with heartbeat [intra-uterine or extra-uterine] or extra-uterine pregnancies or miscarriages confirmed by histological evidence/total number of initiated cycles) x 100.

the Russian-label cohort, which is higher than the rates reported in previous studies in similar populations (range 8.6%–14.1% [6–9,26,27]. In the Russian-label cohort, the live birth rate per cycle was 23.3%, which is higher than previously reported in this patient population (range 5%–11% [6–9,26].

Table 4
Pregnancy outcomes for patients included in the retrospective study.

	Russian label (n = 109)	Other physician preference (n = 37)	Total (n = 158)
At least one live birth delivery, n (%)	88 (80.7)	29 (78.4)	129 (81.6)
Single	80 (73.4)	24 (64.9)	115 (72.8)
Twins	8 (7.3)	5 (13.5)	14 (8.9)
Abnormal pregnancy outcomes in women included in the retrospective analysis, n (%)	22 (20.2)	9 (24.3)	31 (19.6)
Spontaneous abortion	21 (19.3)	9 (24.3)	31 (19.6)
Still birth	2 (1.8)	1 (2.7)	3 (1.9)
Induced abortion	2 (1.8)	0 (0.0)	2 (1.3)

Data are presented as n (%). Data for twelve patients who met only the ESHRE Bologna criteria are not presented as a separate subgroup but are included in the total group.
Abnormal pregnancy outcomes were defined according to the ICMART terminology [3]. The termination of pregnancy (induced abortion or elective abortion) was defined as artificial interruption of pregnancy.

Therefore, this study supports the use of the r-hFSH:r-hLH 2:1 combination in patients who had, or are at risk of having, a poor or suboptimal response to OS for ART treatments.

The indication for the r-hFSH:r-hLH 2:1 combination according to the Russian label or the ESHRE Bologna criteria includes patients with POR in a previous treatment cycle. Patients with POR comprise several broad subpopulations [6,10–13]: the term POR can encompass patients who are poor ovarian responders or suboptimal responders (4–9 oocytes retrieved) [11,13,16–18]. Treatment with the combination of FSH and LH during OS may have a beneficial effect on reproductive outcomes for some populations of poor ovarian responders and suboptimal responders compared with use of FSH alone [6,19–21,28]. However, despite the recognition of the different POR patient populations, the outcomes of previous studies and meta-analyses may reflect how the patient groups have been classified [20,28] or the problems inherent with using a binary classification of POR, such as that defined in the ESHRE Bologna criteria [6]. This lack of the recognition of the range and heterogeneity of POR may contribute to inconsistencies in the reported outcomes among the different analyses.

As previously stated, the r-hFSH:r-hLH 2:1 combination is indicated for women who have severe LH and FSH deficiency. In the Russian Federation (and in Mexico and Belarus), the r-hFSH:r-hLH 2:1 combination is also indicated in women who have a history of, or are at risk of having, a poor or suboptimal response to OS for ART. LH and FSH deficiency is caused by reduced gonadotropin production or action because of internal or external factors, such as congenital (genetic or idiopathic) or acquired (functional, organic or iatrogenic-transient) causes [1]; and is characterized by low or normal gonadotropin levels and low oestradiol levels [29,30]. The indication for the r-hFSH:r-hLH 2:1 combination does not define the medical condition or aetiology causing severe LH and FSH deficiency; furthermore, there are no national or international guidelines on specific serum thresholds that define severe LH and FSH deficiency [29,30]. Therefore, as the criteria for (severe) LH and FSH deficiency are broad and subject to the individual assessment of the treating physician, different diagnoses of LH and FSH deficiency are treated with the r-hFSH:r-hLH 2:1 combination. This may be particularly important when considering that, although the causes and effects of LH and FSH deficiency are well characterized, the concept of the reduced action is less understood, and it is not clear if and how decreased action may be related to the risk of a suboptimal response to OS. For example, this may have important clinical implications, particularly as diminished action combined with GnRH down-regulation may result in an unexpected hyporesponse to gonadotropins [1].

Two-thirds of patients enrolled in this study were of advanced maternal age (≥35 years old), and 22% were aged ≥40 years. Age is an important factor associated with fertility outcomes and a risk factor for suboptimal or POR to OS during ART. In a meta-analysis of seven trials (902 ART cycles) evaluating the impact of r-hFSH and r-hLH during OS for ART in women aged ≥35 years, the addition of LH was

observed to improve implantation rates (seven trials; 1810 embryos; OR 1.36 [95% CI 1.05, 1.78]) and clinical pregnancy rates (seven trials; 902 patients; OR 1.37 [95% CI 1.03, 1.83]) [31] compared with r-hFSH alone. A beneficial effect on implantation rates was also observed in women aged 36–39 years in a systematic review that evaluated six randomized controlled trials in women of advanced reproductive age treated with r-hFSH and r-hLH compared with r-hFSH alone, regardless of the down-regulation protocol [32]; however, this systematic review observed no beneficial effect of r-hFSH and r-hLH for women aged ≥40 years compared with r-hFSH alone. A recent systematic review and meta-analysis of 12 studies by Conforti et al. reported that, in a subgroup of women aged between 35 and 40 years, treatment with r-hFSH and r-hLH resulted in higher clinical pregnancy rates (OR 1.45 [95% CI 1.05, 2.00]; $I^2 = 0\%$; $p = 0.03$) and implantation rates (OR 1.49 [95% CI 1.10, 2.01]; $I^2 = 13\%$; $p = 0.01$) compared with women treated with r-hFSH monotherapy, despite fewer oocytes being recovered in the patients treated with r-hFSH and r-hLH versus r-hFSH monotherapy (weighted mean difference −1.03 [95% CI −1.89, −0.17]; $I^2 = 0\%$; $p = 0.02$) [22].

Low ovarian reserve is another important determinant of a suboptimal or poor response to OS that is usually assessed using AFC and/or AMH levels. AFC, measured by ultrasound, takes into account the number of follicles with a diameter of 2–10 mm present in both ovaries [33]. AMH is a protein secreted by granulosa cells in the ovary, and its serum levels act as a biomarker of an antral and pre-antral follicle size [34]. The mean (standard deviation [SD]) AFC in the Russian-label cohort was 6.80 (3.79), with a median (Q1:Q3) of 6.0 (3.0:8.0), and the mean (SD) AMH level was 1.80 (2.06), with a median (Q1:Q3) of 1.20 (0.70:2.11), indicative of a population at risk of POR. Based on age and baseline ovarian reserve markers, the cohort treated according to other physician preference comprised patients with a better prognosis than those in the Russian-label cohort, and the majority were undergoing their first ART cycle. As the Russian label includes patients with a normal ovarian reserve, the treating physician took into account other factors when prescribing the r-hFSH:r-hLH 2:1 combination in the patients treated according to other physician preference (see Results). These were mostly related to a reduction of ovarian reserve (47%), physician effort to maximize the number of mature oocytes (23%), and a possible risk of a low ovarian response because of previous endometriosis/ovarian surgery/tubal damage (20%). For example, a woman who is aged <35 years, with no unexpected poor or suboptimal response to a previous stimulation, and no evidence of severe LH and FSH deficiency, but who has only between 7–9 oocytes recovered in a previous ART cycle, would not meet the Russian label but would be defined as low prognosis according to the POSEIDON criteria (subgroup 1b). Furthermore, as pre-stimulation ovarian reserve parameters are not included in the Russian label, women in POSEIDON Group 3 (aged <35 years with AFC <5; AMH <1.2 mg/mL) would not meet the Russian label but could be considered as low prognosis because of reduced ovarian reserve biomarkers [11].

The most common reason why no embryo transfer was performed in our analysis was a lack of oocytes/embryos for transfer (42 [8.4%] overall). This was similar to that reported in the Efficacy and Safety of Pergoveris in Assisted Reproductive Technology (ESPART) study for cycles cancelled because of no ovarian response (7.6% [35/462 cycles]) [6]; however, it was much lower than the rates of cycles cancelled because of the lack of oocytes/embryos reported in retrospective single-centre cohort studies of women classified as POR according to the ESHRE Bologna criteria [9] or other criteria [35]; which were around 25%. Furthermore, previous real-world studies of treatment with the r-hFSH:r-hLH 2:1 combination have shown numerically higher rates of cycles where embryo transfer was not performed than are reported in this study. In a large, multi-centre post-marketing surveillance study of the r-hFSH:r-hLH 2:1 combination in routine clinical practice in Germany, embryo transfer was not performed in 388 of 2220 started cycles (17.5%) [36]; and in an analysis of the German IVF registry (DIR) 2010, embryo transfer was not performed in 11,580 of 75,928 plausible cycles (15%) [37].

Treatment with the r-hFSH:r-hLH 2:1 combination was well tolerated, and no new safety concerns were identified. The doses of gonadotropins used (starting dose of 300 IU r-hFSH and 150 IU r-hLH) are those recommended by the Russian label for OS in ART [4]; and only one patient who met the Russian label had a cycle discontinued because of OHSS. Mild OHSS was reported in four patients who received an embryo transfer, all of which resolved. There were no deaths reported in this study, and the safety

results are consistent with the known safety profile of the r-hFSH:r-hLH 2:1 combination [4,38]. Therefore, the higher pregnancy rates observed in the current study were not accompanied by an increased risk of OHSS, and the incidence of OHSS was similar to that observed in the ESPART trial (<1% of patients in both studies) [6]. Overall, 19.6% of women in the retrospective study had an abnormal pregnancy outcome, the majority of which were spontaneous abortion. Although the specific characteristics of the women who had an abnormal pregnancy outcome are not reported here, it should be noted that a high proportion of women in the prospective study were of advanced maternal age, which is associated with an increasing risk of foetal loss (13.7% in women aged 35–37 years, 19.8% in women aged 38–40 years, and 29.9% in women aged 41–42 years) [39]. Furthermore, as female age increases, the risk of other disorders that may contribute to abnormal pregnancy outcomes also increases [39]; including tubal disorders, which were reported in 40% of women in the prospective cohort.

As with all observational studies, there are limitations to the data presented here. A major limitation was the lack of a control cohort in the respective centres, which may differ in the patient populations they serve. Owing to the variability among centres, and because the potential for bias was not assessed, we cannot determine how representative the study population was of the general population undergoing OS for ART in the Russian Federation. Furthermore, any potential variability in clinical pregnancy rates among centres, or differences in the populations treated at each centre, could not be assessed. These factors need to be taken into account when considering the broader interpretation of the clinical outcomes.

Summary

This cohort of 500 patients from real-world clinical practice in the Russian Federation was prescribed the r-hFSH:r-hLH 2:1 combination for OS during ART treatment at the discretion of their treating physician. At least 75% of this cohort can be considered poor or suboptimal responders because they met the Russian label; however, a higher clinical pregnancy rate was observed than has been previously reported in suboptimal response/POR populations in the literature, without an increased risk of AEs. This study supports the use of the r-hFSH:r-hLH 2:1 combination in patients who have had, or are at risk of having, a poor or suboptimal response to OS for ART treatment in the Russian Federation.

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Authors' contributions

All authors contributed to the conception and design of the analysis, as well as interpretation of data and critical review of this manuscript. All authors approved the manuscript for submission to the journal.

Data availability

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

Declaration of competing interest

TDH and ML are employees of Merck Healthcare KGaA, Darmstadt, Germany.

AE and OR are employees of Biopharma, LCC Merck, Moscow, Russian Federation, an affiliate of Merck KGaA.

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Practice points

- Patients with a poor or suboptimal ovarian response to OS represent an important subgroup of patients seeking infertility treatment.
- Treatment with the combination of a follicle-stimulating hormone (FSH) and luteinizing hormone (LH) during OS may have a beneficial effect on outcomes for some populations of poor ovarian responders and suboptimal responders compared with FSH alone.
- In this real-world study of routine practice in the Russian Federation, >75% of patients met the local Russian label for the r-hFSH:r-hLH 2:1 combination, and 21.0% were treated according to other physician preference, according to the judgement of the treating physician.
- The clinical pregnancy rate per initiated cycle was 27.2% in the Russian-label cohort, and the live birth rate per cycle was 23.3%. Both rates are higher than the rates reported in previous studies in similar populations (8.6%–14.1% for the clinical pregnancy rate and 5%–11% for the live birth rate).
- This study supports the use of the r-hFSH:r-hLH 2:1 combination in patients who had, or are at risk of having, a poor or suboptimal response to OS for ART treatments.

Research agenda

- Heterogeneity among specific subgroups of patients classified as poor or suboptimal responders in current criteria needs to be addressed in new criteria, so that effective treatment modalities can be established for these patients.
- More evidence is needed to evaluate the value of the r-hFSH:r-hLH 2:1 combination in patients with a suboptimal or poor ovarian response according to the POSEIDON classification [11].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2022.01.009.

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