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Experience in using biosimilars in IVF programs with donor oocytes in protocols with micronized progesterone

*A.T. Abshekenova^{1,2}, A.N. Rybina^{1,2}, E. Askar^{1,2},
Sh.K. Karibaeva^{1,2}, R.K. Valiev¹, V.N. Lokshin¹*

¹«International Clinical Center for Reproductology «PERSONA»» LLP, Almaty, the Republic of Kazakhstan;

²«Asfendiyarov Kazakh National Medical University» NPJSC, Almaty, the Republic of Kazakhstan

ABSTRACT

Relevance: Stimulation of oocyte donors' superovulation occupies a key place in the development of assisted reproduction technology (ART) in general. Oocyte donation programs involve young and healthy women undergoing severe ovarian stimulation protocols to obtain good-quality oocytes. Advances in recombinant DNA technology led to the development of recombinant follitropin alfa.

The study aimed to evaluate the effectiveness of the biosimilar follitropin alfa in the superovulation stimulation cycles of oocyte donors in comparison with the original medication in Progesterin primed ovarian stimulation (PPOS) protocols.

Materials and Methods: A prospective cohort study included 25 oocyte donors who underwent superovulation induction. The first group consisted of 25 oocyte donors in whose superovulation was stimulated with a bio-analogue of follitropin alfa. The second group (control) included the same 25 donors stimulated with the original rFSH drug. The resulting donor oocytes were fertilized using Intra-Cytoplasmic Sperm Injection (ICSI) or frozen. The program's result was determined by taking a blood test for b-hCG 14 days after embryo transfer.

Results: The number of mature oocytes in the study groups did not differ significantly, amounting to 20.6 ± 1.1 in group 1 and 21.2 ± 1.3 in group 2. The average number of fertilized oocytes in group 1 was 5.6 ± 0.8 , and in group 2 – 6.1 ± 1.1 ; thus, the fertilization rate in the two groups did not differ (67.5% in group 1 vs 79.2% in group 2, $p > 0,05$). The blastulation rate (49.1% in group 1 and 52.2% in group 2) did not differ significantly in both the biosimilar group and the original medication. The Top Quality Blastocysts in Group 1 were 1.5 ± 0.7 (55%) vs 1.8 ± 0.5 (48%) in Group 2. At that, the cumulative pregnancy rate in both groups did not differ statistically significantly.

Conclusion: Biosimilars were not inferior to the original medication in terms of the proportion of mature oocytes in oocyte donors. The study's results confirm that biosimilars demonstrate favorable and comparable efficacy to the original medication in oocyte maturation in IVF/ICSI cycles.

Keywords: progesterin-primed ovarian stimulation, biosimilars, PPOS, micronized progesterone, IVF, Intra-Cytoplasmic Sperm Injection (ICSI).

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Опыт применения биосимиляров в программах ЭКО с донорскими ооцитами в протоколах с микронизированным прогестероном

*А.Т. Абшекенова^{1,2}, А.Н. Рыбина^{1,2}, Е. Аскар^{1,2},
Ш.К. Каробаева^{1,2}, Р.К. Валиев¹, В.Н. Локишин¹*

¹ТОО «Международный Клинический Центр Репродуктологии «PERSONA»», Алматы, Республика Казахстан;

²НАО «Казахский Национальный Медицинский Университет им. С.Д. Асфендиярова», Алматы, Республика Казахстан;

АННОТАЦИЯ

Актуальность: Стимуляция суперовуляции доноров ооцитов занимает ключевое место в развитии ВРТ в целом. В программах донорства ооцитов участвуют молодые и здоровые женщины, проходящие протоколы тяжелой стимуляции яичников, чтобы получить ооциты хорошего качества. Достижения в технологии рекомбинантных ДНК привели к разработке рекомбинантного фоллитропина альфа.

Цель исследования – оценить эффективность биоаналога фоллитропина альфа в циклах стимуляции суперовуляции доноров ооцитов по сравнению с оригинальным препаратом в протоколах PPOS.

Материалы и методы: В проспективное когортное исследование вошли 25 доноров ооцитов, прошедших индукцию суперовуляции. Первую группу представляли 25 доноров ооцитов, у которых суперовуляцию стимулировали биоаналогом фоллитропина альфа. Вторую группу составили те же 25 доноров ооцитов, которых стимулировали оригинальным препаратом. Полученные донорские ооциты оплодотворяли с использованием внутрицитоплазматической инъекции спермы (ИКСИ) или замораживали. Результат программы определялся путем взятия анализа крови на б-ХГЧ через 14 дней после переноса эмбрионов.

Результаты: Число зрелых ооцитов в исследуемых группах достоверно не различалось, составив $20,6 \pm 1,1$ в 1-й группе и $21,2 \pm 1,3$ во 2-й группе. Среднее число оплодотворенных ооцитов в 1-й группе составило $5,6 \pm 0,8$, а во 2-й группе – $6,1 \pm 1,1$, при этом частота оплодотворения в двух группах не различалась ($67,5\%$ в 1-й группе против $79,2\%$ во 2-й группе, $p > 0,05$). Частота бластуляции ($49,1\%$ в 1-й группе и $52,2\%$ во 2-й группе, $p > 0,05$) достоверно не отличалась как в группе биосимиляра, так и в группе оригинального препарата. Количество ТҚВ в 1-й группе составило $1,5 \pm 0,7$ (55%) против $1,8 \pm 0,5$ (48%) в группе 2. При этом уровень частоты наступления беременности (ЧНБ) в обеих группах также не имел статистически значимых различий.

Заключение: Биосимилары оказались не уступающими оригинальному препарату в отношении доли зрелых ооцитов у доноров ооцитов. Результаты исследования подтверждают, что биосимилары демонстрируют благоприятную и сопоставимую эффективность с оригинальным препаратом в процессе созревания ооцитов в циклах ЭКО/ИКСИ.

Ключевые слова: прогестинная стимуляция яичников, биосимилары, PPOS, микронизированный прогестерон, ЭКО, внутрицитоплазматическая инъекция спермы (ИКСИ).

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Микронизацияланған прогестерон протоколында донорлық ооциттермен ЭҚҰ бағдарламаларында биосимиларларды қолдану тәжірибесі

А.Т. Абшекенова^{1,2}, А.Н. Рыбина^{1,2}, Е. Аскар^{1,2},
Ш.К. Каробаева^{1,2}, Р.К. Валиев¹, В.Н. Локишин¹

¹«PERSONA» халықаралық репродуктология клиникалық орталығы» ЖШС, Алматы, Қазақстан Республикасы;
²«С.Д.Асфендияров атындағы Қазақ Ұлттық Медицина Университеті, Алматы, Қазақстан Республикасы

АНДАТПА

Өзектілігі: Жалпы ҚРТ дамуында негізгі орынды ооцит донорларының супреовуляциясын ынталандыру алады. Ооциттерді донорлық бағдарламаларға сапалы аналық жасушаларды алу үшін аналық безді ынталандырудың күрделі протоколдарынан өтетін жас, дені сау әйелдер қатысады. Рекомбинантты ДНҚ технологиясының жетістіктері рекомбинантты фоллитропин альфаның дамуына әкелді.

Зерттеудің мақсаты – Ооцит донорларының супреовуляция стимуляция циклдеріндегі PPOS протоколында фоллитропин альфа биосимиларлы препаратпен түпнұсқалық препаратты салыстырғанда тиімділігін бағалау.

Материалдар мен әдістері: Проспективті когорттық зерттеуге супреовуляция индукциясы жүргізген 25 ооцит донорлары кірді. Бірінші топ 25 ооцит донорынан тұрды, олардың супреовуляциясы фоллитропин альфа биоаналогымен ынталандырылды. Екінші топ түпнұсқалық препаратпен ынталандырылған сол 25 донорларынан тұрды. Алынған донорлық ооциттер интрацитоплазмалық сперматозоидты енгізу (ИКСИ) көмегімен ұрықтандырылды немесе мұздатылды. Бағдарламаның нәтижесі эмбрионды тасымалданғаннан кейін 14 күннен кейін в-ХГЧ анализін алу арқылы анықталды.

Нәтижелері: Зерттелетін топтардағы жетілген ооциттер саны айтарлықтай ерекшеленбеді, 1-топта 20,6±1,1 және 2-топта 21,2±1,3 құрады (тіісінше 81,1% қарсы 82%). 1-топтағы ұрықтанған ооциттердің орташа саны 5,6±0,8, ал 2-топта – 6,1±1,1 болды, ал екі топтағы ұрықтандыру деңгейі бір-бірінен айырмашылығы жоқ (1-топта – 67,5%, 2-топта – 79,2%, p> 0,05). Бластуляция жылдамдығы (1 топта 49,1% және 2 топта 52,2%, p>0,05) биосимиларлық топта да, бастапқы дәрілік топта да айтарлықтай ерекшеленбеді. 1-топтағы TQB саны 1,5±0,7 (55%), 2-топтағы 1,8±0,5 (48%) болды. Сонымен қатар, екі топтағы NNB деңгейінде де статистикалық маңызды айырмашылықтар болған жоқ (42,8%). 46,5%-ға қарсы, p>0,05.

Қорытынды: Биосимиларлар ооцит донорларындағы жетілген ооциттердің үлесі бойынша бастапқы препараттан кем түспейтін болып шықты. Зерттеу нәтижелері биосимилар ЭҚҰ/ИКСИ циклдерінде ооциттердің жетілу процесінде түпнұсқалық препарат секілді қолайлы және салыстырмалы тиімділігі растайды.

Түйінді сөздер: прогестин аналық безді ынталандыру, биосимиларлар, PPOS, микронизацияланған прогестерон, IVF, цитоплазмаға сперматозоидты енгізу (ИКСИ).

Introduction: Oocyte donation (OD) is increasingly used worldwide as a method to overcome infertility resulting from a variety of factors, including the age-related decline in fertility. Oocyte donors are, by definition, healthy, potentially (or proven) fertile women who undergo voluntary ovarian stimulation (OS) treatment. Since the appearance of this technique in the 1980s, the number of cases in which OD has been indicated has steadily increased [1].

According to ESHRE registries, more than 178 027 OD cycles had been performed only in Europe by 2011, accounting for 5% of all ART cycles [2]. More than 22% of the OD cycles were performed in Spain and 9.7% in the Czech Republic [3]. More recently, the 18th ESHRE report on ART showed a continuing expansion of OD treatment numbers in Europe, with a 40.4% increase since 2013 [4].

OS protocols involve administering exogenous gonadotrophins to maintain FSH and LH concentrations above a critical threshold required to stimulate the simultaneous growth of multiple follicles in a single cycle [5].

Gonadotrophin treatment contributes a significant proportion of the cost of ART; thus, the introduction of biosimilars of recombinant follicle-stimulating hormone (rFSH) alpha may alleviate the costs of ART, improving affordability [6]. The first rFSH biosimilar launched in Europe was Bemfola® in 2014 [7, 8], which has proven popular in Spain [9]. A second rFSH biosimilar, Ovaleap®, was approved in Europe in 2013 and launched in 2016 [7].

The basis of the demonstration of equivalence between a biosimilar and the reference product primarily relies on exhaustive, highly sensitive physicochemical and biological

activity comparability assessments later supported by clinical studies, leading to a total development time of typically 6 to 12 years [7, 10]. For biosimilar rFSH development, the European Medicines Agency (EMA) recommends the «number of oocytes retrieved» as the primary endpoint to demonstrate comparability of clinical efficacy against the reference product, as pregnancy rates are influenced by multiple factors unrelated to ovarian stimulation [11-13].

Due to the elaborate manufacturing process of recombinant biological products, they are often high-priced. This fact may limit individuals' access to high-quality infertility treatments. By verifying similar physicochemical and biochemical properties in non-clinical studies and demonstrating comparable efficacy and safety as the reference product, biosimilars can enhance access to high-quality biological products. Cinnal-f (CinnaGen, Iran) was developed in genetically modified Chinese hamster ovary cells as a biosimilar to the innovative original drug and received the approval of the Food and Drug Administration of Iran in June 2013 (IRC: 3125387962296341) [11, 14, 15].

The study aimed to evaluate the effectiveness of the biosimilar follitropin alfa in the superovulation stimulation cycles of oocyte donors in comparison with the original drug in PPOS protocols.

Materials and Methods: The prospective cohort study included 25 oocyte donors from February 2023 until September 2023 at the International Clinical Center for Reproductology «PERSONA».

All donors were divided into 2 groups with an interval of 3 months. The first group (main) included 25 oocyte donors stimulated with the biosimilar rFSH (Cinnal-f by CinnaGen, Iran). The second group (control) included the same 25 donors stimulated the original rFSH drug.

Micronized progesterone—Utrogestan 200 mg (Besins Healthcare (UK) Ltd) – was used to block the endogenous luteinizing hormone (LH) peak in both groups. The resulting oocytes were distributed to recipients. Fertilized by Intra-Cytoplasmic Sperm Injection (ICSI) and cultured, embryos with good morphology on days 5 and 6 were transferred into the recipients' uterine cavities.

Exclusion criteria for recipients:

- 1) Married couples in which the woman's age is >52 years,
- 2) The man is over 50 years old,
- 3) Severe forms of pathospermia in the spouse (azoospermia, cryptozoospermia, globulospermia).

Ovarian stimulation and embryo culture

Stimulation scheme with biosimilar rFSH.

The primary group patients were prescribed hMG (Menotropin-Menopur, Ferring International Center SA, Germany) at a dose of 150 IU/day and biosimilar recombinant FSH at a dose of 150 IU from the 2nd—3rd day of menstruation after ultrasound and blood tests to confirm the initial hormone profile.

Protocol with the original rFSH drug. In the protocol with the original rFSH preparation, superovulation was stimulated with hMG (Menopur, Ferring International Center SA, Germany) at a dose of 150 IU/day and original recombinant FSH - 150 IU/day from days 2-3 of menstruation, after ultrasound and blood tests to confirm the initial hormone profile.

Micronized progesterone (Utrozhestan, Besins Healthcare, Belgium) at 200 mg/day was used as progesterone priming orally until the day of trigger administration. Follicular monitoring began on days 7-8 of the menstrual cycle (MC) and was carried out every 2-3 days using transvaginal ultrasound to record the number and size of growing follicles. The dosage of gonadotropins was adjusted depending on the response to stimulation. Thus, when three or more dominant follicles with a diameter of 18 mm were reached, a trigger was prescribed with GnRH agonists (Diferelin 0.2 mg, Ipsen Pharma Biotech, France). When follicles grew to 12, a double trigger was used: a GnRH agonist (Diferelin 0.2 mg) combined with hCG 5000 IU (Moscow Endocrine Plant, Russia). Transvaginal puncture of the follicles was performed 34-36 hours after the trigger under ultrasound guidance. All follicles with a diameter of more than 14 mm were punctured.

The process of egg fertilization was carried out in vitro by classical IVF or ICSI, depending on the quality of the sperm. Cultivation was carried out until the blastocyst stage, and then embryos with good morphology were transferred into the uterine cavity of the recipients.

Luteal phase support was provided to recipients with vaginal progesterone preparations in a dosage of 600-800 mg/day at the discretion of the reproductologist. 14 days after embryo transfer, the onset of pregnancy was detected by determining the level of b-hCG in the blood.

Evaluation criteria. The primary outcome of this study was the number of oocytes retrieved and the degree of maturity. Secondary outcomes included fertilization rate, blastulation percentage, and number of embryos on day 5 or 6 with the highest quality (Top Quality Blastocysts) and pregnancy rate.

Statistical analysis. The data obtained during the study were subjected to statistical processing using the variation statistics method using the free version of the Jamovi™ program. When comparing mean values, the Mann-Whitney U test was used. Qualitative variables are described by absolute (n) and relative (%) values. The χ^2 test was used to compare frequencies and qualitative variables. A probability value (P-value) of less than 0.05 was considered statistically significant.

Results: A total of 50 stimulation programs for oocyte donors were included in the study.

Table 1 presents the main characteristics of the oocyte donors in the study. Donor age, body mass index, and duration of stimulation were similar in both groups ($p>0.05$).

Table 1 – Main characteristics of oocyte donors and duration of stimulation

Characteristics	1st group (biosimilars; n=25)	2nd group (original drug; n=25)
Age (years)	27.4 ± 2.4	
BMI (kg/m ²),	22.7 ± 2.1	
Duration of OS (day)	10±1	10±2

Note. Values presented ± standard deviation – SD; BMI – body mass index;

If we look at the figures in Table 2, the average cost of one donor stimulation program in group 1 was 929,88 US dollars, significantly lower than the cost of stimulation programs in IVF/ICSI cycles with other original drugs.



Table 2 – Pharmacoeconomics of stimulating donors with biosimilars compared with other original drugs presented on the market in the Republic of Kazakhstan.

Consumption of drugs for 1 OS cycle (doses 150/150 UI for 10 days)	Biosimilars	Original drug #1	Original drug #2	Original drug #3
FSH cost (USD)	441,18	685,55	749,24	705,45
hMG	482,09			360,46
Progesterone cost (USD)	6,60			
Summary	929,88	1174,24	1237,93	1189,72

The average number of oocytes received and the percentage of their maturity in both groups of oocyte donors did not differ (80 vs. 81%, respectively, $p>0.05$), as indicated in Table 3.

Table 3 – Comparative characteristics of the maturity of the obtained oocytes in two groups of oocyte donors.

	1 st group (biosimilars; n=25)	2 nd group (original drug; n=25)	P Value
Average number of oocytes to fertilization	8.3 ± 1.2	7,7 ± 1.1	
Average number of fertilized oocytes	5.6 ± 0.9	6.1 ± 0.8	
Fertilization %	67,5%	79,2%	p=0,001
Average number of blastocysts	2.7 ± 0.5	3.75 ± 0.5	
Blastulation %	49,1%	53.5%	p>0,05
TQB	1.5 (55%)	1.8 (48%)	p>0,05

The study showed that 67.5% in the first group and 79.2% in the second group ($p=0.001$) had fertilized eggs. The frequency of blastulation in the study groups did not differ significantly (49.1% in group 1 and 53.5% in group 2, $p>0.05$), and the number of high-quality blastocysts did not differ in both groups (55% versus 48%) $p>0.05$, as indicated in Table 4.

Table 4 – Results of embryological and clinical protocols in patients of the study groups

	1 st group (biosimilars; n=25)	2 nd group (original drug; n=25)	P Value
Average number of received oocytes	25,4 ± 2.9	26,1 ± 3.1	
Average number of mature oocytes	20,6 ± 2.6	21,2 ± 2.9	p=0,001
Mature %	81,1%	81,2%	p=0,001

The resulting embryos were transferred into the recipients' uterine cavities on days 5-6 of cultivation or frozen using the vitrification method.

In 14 patients in the study group and 13 patients in the control group, embryos were transferred into the uterine cavity. In both groups, pregnancy occurred in 6 cases; the cumulative pregnancy rate was 42.8% and 46.5%, respectively, $p>0.05$ (Table 5).

Table 5 – Data on pregnancy rate in both groups of oocyte donors

	1 st group (Cinal - F; n=25)	2 nd group (Gonal - F; n=25)	P Value
Number of patients with ET in a fresh cycle	14	13	
Clinical pregnancy rate	6 (42,8%)	6 (46,5%)	p>0,05

Discussion: The results of this prospective cohort study indicated that biosimilars demonstrate comparable effectiveness and safety to the original product in stimulating oocyte donors for ovarian and infertility treatment through ICSI. The trial population met the expected eligibility criteria and was appropriately balanced. The primary outcome measure chosen was the percentage of MII oocytes, as it was argued to reflect better the stimulation quality rather than fertilization, which depends on various factors such as sperm quality, culture conditions, and ICSI technique. A previous study 2015 reported that 80.6% of oocytes retrieved from ovarian stimulation with r-hFSH were in the MII group.

The percentage of MII oocytes resulting from treatment with biosimilars was deemed non-inferior to that achieved with the original drug, based on a pre-specified non-inferiority margin. In 2013, the European Medicines Agency issued a guideline recommending the consideration of equivalent efficacy in the number of retrieved oocytes as a primary outcome to establish bio-similarity for r-hFSH products. A 2015 multicenter phase-three study comparing another biosimilar follitropin alfa with the original drug in ovarian stimulation for IVF reported an average of 10.4 ± 6.14 oocytes retrieved with the original drug.

Another study comparing r-hFSH with urinary FSH in IVF patients found a mean retrieved oocyte count of 9.3 ± 5.0. Similarly, a 2000 prospective and randomized study

comparing ovarian stimulation with r-hFSH versus highly purified urinary FSH in an ICSI program reported an average of 10.7 ± 6.8 collected oocytes for the r-hFSH group. The total number of retrieved oocytes in our study aligns with findings from these previous studies.

In a 2015 clinical trial comparing r-hFSH and highly purified urinary FSH for ovarian stimulation in women, the reported treatment duration for the r-hFSH group was 9.9 days. A subsequent Phase III study in 2016, comparing the efficacy and safety of a biosimilar r-hFSH with the original drug, reported a treatment duration of 9.7 days for the original drug group. The duration of ovarian stimulation was similar between the treatment groups and aligned with findings from comparable studies. Additionally, there were no statistically significant differences in the mean number of vials used or in clinical and ongoing pregnancy rates [5, 6, 13].

A critical study proposed that the number of embryos in culture during embryo transfer could be a crucial predictor of pregnancy outcome. Our findings revealed no significant

differences in the number or quality of embryos between the biosimilars and original drug groups.

Biosimilars had a comparable safety profile with the original drug. There were no cases of ovarian hyperstimulation syndrome in any group. Diligent monitoring through ultrasonography and using a low FSH dose effectively minimized the risk of developing the ovarian hyperstimulation syndrome. This trial aimed to establish the non-inferiority of biosimilars compared to the innovative product. However, it may not have had sufficient power to detect significant differences in adverse effects between the two.

Conclusion: Biosimilars have proven to be non-inferior to the original drug in terms of the proportion of mature oocytes in oocyte donors. The study results affirm that biosimilars exhibit a favorable and comparable performance to the original drug in facilitating the oocyte maturation in IVF/ICSI cycles. Notably, the efficacy and safety profiles of the reference product and the biosimilar candidate were similar.

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Authors' data:

Abshekenova A.T. – MD, PhD doctoral student, «International Clinical Center for Reproductology «PERSONA»» LLP; «Asfendiyarov Kazakh National Medical University» NPJSC, Almaty, the Republic of Kazakhstan, tel. 87078305002, e-mail: abshekenova@gmail.com, ORCID ID: <https://orcid.org/0000-0002-3138-6650>;

Askar E. – MD, PhD doctoral student of «International Clinical Center for Reproductology «PERSONA»» LLP; «Asfendiyarov Kazakh National Medical University» NPJSC, Almaty, the Republic of Kazakhstan, tel. 87075670670, e-mail: edel_weiss2013@mail.ru, ORCID ID: <https://orcid.org/0000-0002-2538-3728>.

Rybina A.N. – MD, PhD doctoral student, «International Clinical Center for Reproductology «PERSONA»» LLP; «Asfendiyarov Kazakh National Medical University» NPJSC, Almaty, the Republic of Kazakhstan, tel. 87772636715, e-mail: oedema@mail.ru, ORCID ID: <https://orcid.org/0000-0002-9368-66837>.

Karibaeva Sh.K. – MD, Candidate of Medical Sciences, Director for Strategic Development of «International Clinical Center for Reproductology «PERSONA»» LLP; «Asfendiyarov Kazakh National Medical University» NPJSC, Almaty, the Republic of Kazakhstan, tel. 87017550675 E-mail: sh.karibaeva@gmail.com, ORCID ID: <https://orcid.org/0000-0001-5691-8652>,

Valiev R.K. – MD, Candidate of Medical Sciences, Associate Professor, Medical Director «International Clinical Center for Reproductology «PERSONA»» LLP, Almaty, the Republic of Kazakhstan, tel. 87772258189, e-mail: rvaliev75@mail.ru, ORCID ID: <https://orcid.org/0000-0003-2526-42917>.

Lokshin V.N. – Doctor of Medical Sciences, Professor, Academician of the National Academy of Sciences of the Republic of Kazakhstan, President of the Kazakhstan Association of Reproductive Medicine, President of the International Academy of Reproductology, General Director of the «International Clinical Center for Reproductology «PERSONA»» LLP, Almaty, the Republic of Kazakhstan, tel. 87017558209, e-mail: v_lokshin@persona-ivf.kz, ORCID ID: <https://orcid.org/0000-0002-4792-5380>.

Address for correspondence: Abshekenova A.T., «International Clinical Center for Reproductology «PERSONA»» LLP, Utegov St. 32A, Almaty 050060, the Republic of Kazakhstan.

Authors' input:

contribution to the study concept – Lokshin V.N., Karibaeva Sh.K.

study design – Abshekenova A.T., Lokshin V.N., Karibaeva Sh.K., Valiev R.K.

execution of the study – Abshekenova A.T., Askar E.

interpretation of the study – Abshekenova A.T., Rybina A.N.

preparation of the manuscript – Abshekenova A.T., Rybina A.N., Askar E.

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