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EVALUATION OF THE IMPACT OF VACCINATION FROM COVID 19 ON THE COURSE AND THE OUTCOMES OF THE IVF PROGRAM

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Relevance: Regarding the COVID-19 pandemic that began in 2020, the issue of the impact of the disease on a woman's fertility continues to be debatable in the reproductive medicine community. Since the development of vaccines, misinformation has arisen regarding the negative impact of vaccination on female reproductive function. Several scientific papers proved the hypothesis wrong. However, further study of the effect of the Sputnik V vaccine on a woman's reproductive potential is essential.

The study aimed to evaluate the impact of vaccination of female patients with the Sputnik V vaccine on the course and outcomes of IVF/ICSI programs.

Methods: 1350 records of patients who underwent ART cycles from 2020 to 2021 were reviewed. The selected patients were divided into two groups: those vaccinated before the IVF/ICSI program and those who did not receive the vaccine. The groups were further divided into two age categories: ≤ 35 and > 35 .

Results: The study showed no difference in the number of received and mature oocytes between the two groups in both age categories. No significant difference was found in the average number of received blastocysts between the control group and the study group (≤ 35 : group I - 4.3, group II - 3.9; > 35 : group III - 2.2, group IV - 2.0). Similarly, the analysis of clinical pregnancy rate (CPR) did not demonstrate a statistically significant difference ($p > 0.05$).

Conclusion: The use of the Sputnik V vaccine against SARS-CoV-2 by female patients did not significantly impact the clinical and embryological indicators of the effectiveness of ART programs.

Keywords: *assisted reproductive technologies, covid-19, intracytoplasmic injection, in-vitro fertilization, vaccination*

Background: The SARS-CoV-2 RNA virus that causes the acute respiratory syndrome disease COVID-19 has affected more than 160 million people and sparked more than 6 million deaths. The outbreak of COVID-19 infection proved to be a test of strength for the entire global medical community, demonstrating different levels of the healthcare system's alert around the world for such challenges [1].

As of April 2022, there were 497,057,239 confirmed cases of COVID-19, including 6,179,104 deaths, according to the World Health Organization. The worldwide mortality rate from COVID-19 was 1.2% [2].

According to statistics, about 64.8% of the world's population has received at least one dose of the COVID-19 vaccine. In total, 11.41 billion doses of COVID-19 vaccine have been injected and 12.6 million doses are currently being vaccinated daily. In low-income countries, only 14.8% of the population has received at least one dose of the COVID-19 vaccine, as set forth in statistical data [3].

It should be pointed out that pregnant women represent one of the numerous high-risk groups for morbidity, mortality

and complications from COVID-19. A 2021 review of 10,000 pregnant women reported an increased mortality among pregnant women compared with controls -11.3% vs. 6.4%, respectively [4].

Despite the fact that the percentage of morbidity among pregnant women differed insignificantly from those in the general population, the percentage of complications, including possible extragenital pathologies, rose with increasing gestational age.

The highest risks of developing complications against COVID-19 are observed in pregnant women with somatic pathologies: chronic lung diseases, diabetes mellitus, diseases of the cardiovascular system, arterial hypertension, oncology, obesity (BMI > 30 kg/m²), chronic kidney and liver diseases [5]. Although there is increasing evidence on the safety of vaccines in pregnancy, vaccination rates among pregnant women remain low.

Hesitancy to vaccinate women of reproductive age has been exacerbated by misinformation on social media that COVID-19 vaccination causes infertility in women and increases perinatal losses.

Recent data on pregnancy outcomes among vaccinated women are encouraging, but these studies have small sample sizes or data that do not fully reflect fertilization rates, implantation rates, and early pregnancy losses [6, 7].

The purpose of the study is to evaluate the impact of the Sputnik V vaccine on the course and outcomes of IVF/ICSI programs in patients who received vaccination against COVID-19.

Materials and methods: This retrospective cohort study was undertaken in the clinic of the Institute of Reproductive Medicine, the city of Almaty, Kazakhstan, involving the patients who underwent ART programs followed by embryo transfer (ET) from January 2020 to December 2021.

As the primary data source for the study, 1350 outpatient records of patients treated with ART were analysed.

The inclusion criteria were: the age of the patient between 18 years and 40 years, the transfer of one or two embryos in a fresh cycle. Exclusion criteria were: the presence of a severe male factor in the history, the transfer of thawed embryos.

Taking into account the negative impact of the age factor of women on the effectiveness of ART cycles, the subjects were additionally divided into two categories by age: ≤ 35 and > 35 . The number of selected embryos for transfer was regulated by individual indications for the transfer of one or two embryos into the uterine cavity of a woman.

The selected cohort of patients was divided into the study group, in which 486 patients were selected, vaccinated with two components of the vector vaccine "Gam-COVID-Vac" "Sputnik V" 1.5-3 months before the start of the in vitro fertilization/intracytoplasmic injection (IVF/ICSI) program. All patients were vaccinated in full, i.e., two components of the Sputnik V vaccine with an interval of 21 days. The control group consisted of 864 patients who did not receive vaccination against COVID-19 and completed the IVF/ICSI

program with a fresh cycle embryo transfer.

In the study group and control group, two age categories were separated out: ≤ 35 and >35 . Thus, the study cohort was divided into 4 groups:

Group I - the study group of patients under 35 years of age who received the Sputnik V vaccine;

Group II - the study group of patients over 35 years of age who received the Sputnik V vaccine;

Group III - the control group of patients under 35 who did not receive the vaccine;

Group IV - the control group of patients over 35 years of age who did not receive the vaccine.

The study groups were analysed with the key performance indicators of ART programs; the average number of received oocytes, the number of mature oocytes per transvaginal puncture (TVP), information on the cleavage of embryos and their blastulation on days 5 and 6, the number of good-quality blastocysts, as well as the number of transferred embryos into the uterine cavity were calculated. Based on the results of ART programs, the clinical pregnancy rate (CPR) and early losses up to 12 weeks were assessed.

In patients enrolled in the study, two main protocols of controlled superovulation stimulation were used: a long protocol with gonadotropin releasing hormone agonists (Diphereline®, France) and protocol with gonadotropin releasing hormone antagonists (Cetrotide®, Germany). After receiving the woman's oocytes on the day of the follicle TVP, the fertilization was carried out with the husband's sperm by IVF or ICSI. The choice of the fertilization method was determined by the individual parameters of the patients. The indications for the use of the ICSI method were a mild form of oligoasthenoteratozoospermia of a man, or female factors of infertility requiring the use of ICSI. So, with long-term primary infertility of a married couple, with infertility of unknown origin, genital endometriosis in a patient, the ICSI method is prioritized in fertilization, because when using the mentioned method, the chance for normal fertilization of more oocytes increases. The maturity and quality of oocytes

during the IVF/ICSI program was determined on the day of TVP by an embryologist and entered into the border database. Embryo transfers into the uterine cavity of the patients were carried out on the fifth day of embryo cultivation. For transfer, 1 or 2 embryos of good or moderate quality were selected according to the blastocyst assessment method of Gardner et al. [8]. The reproductive scientist determined the number of embryos for transfer as required by the indications and contraindications for the transfer of 1 or 2 embryos.

After embryo transfer, post-transfer hormonal support was prescribed to all patients: micronized progesterone (vaginal form) in a dose of 600 mg per day. Also, the folic acid in a dose of 400 mg per day and acetylsalicylic acid in a dose of 100 mg per day were prescribed.

Pregnancy was registered by performing a urine test and/or taking HCG blood test 2 weeks after the transfer of the embryo(s) into the woman's uterine cavity. After 10-14 days from a positive pregnancy test, an ultrasound of the pelvic organs was performed in order to detect a uterine pregnancy. When assessing early pregnancy losses, terminations up to 12 weeks of pregnancy were evaluated: spontaneous abortions and non-developing pregnancies. The data were recorded using transvaginal ultrasound of the pelvic organs on the onset of complaints that characteristic of spontaneous abortion (bleeding), or spontaneously during the next control ultrasound in a non-developing pregnancy.

The subjects provided informed consent to be enrolled in the study.

Results:

The control group was sampled in such a way that the quantitative ratio in the age categories was similar (Figure 1). The largest number of patients belonged to the age category up to 35 years: group I - 68.8% (vaccinated) and group III - 64% (unvaccinated), respectively. The age category over 35 years was 31.2% among vaccinated women (group II) and 36% among unvaccinated women (group IV).

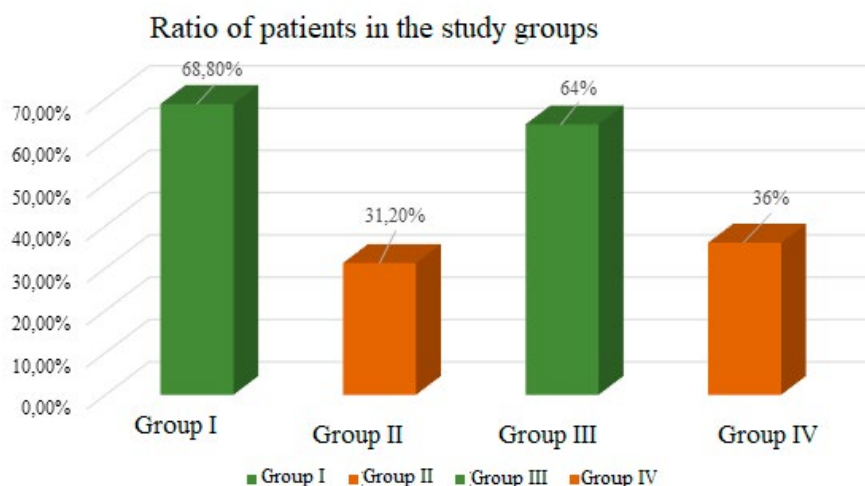


Figure 1 - The ratio of patients in the study groups.

The choice of a hormonal stimulation protocol that has a direct impact on the number and quality of the obtained oocytes is a critical and of utmost importance in ongoing IVF programs. The ratio of stimulation protocols using GnRH agonists and antagonists in groups of vaccinated and unvaccinated women was 30%:70%.

Table 1 - Comparison of performance indicators of ART programs in vaccinated and unvaccinated women in different age categories

Items	Study group(n=486)		Control group (n=864)		p-value
	Group I	Group II	Group III	Group IV	
Number of patients, n	334	152	552	312	
Average number of received oocytes, n	11,3	9,5	11,4	8,1	
Average number of mature oocytes, n	7,9	6,1	8	5,9	
Average number of received blastocysts, n	4,3	2,2	3,9	2,0	
Average number of good quality blastocysts, n	3,9	2	2,6	1,5	
Percentage of clinical pregnancy, %	48,4 (n=162)	36,3 (n=263)	47,6 (n=55)	34,4 (n=107)	>0.05
Percentage of early pregnancy losses, %	8,6 (n=14)	15 (n=39)	7,5 (n=4)	16,4 (n=18)	>0.05

Following the assessment in groups I and III (table 1), no differences were found - the average number of oocytes received was 11.3 and 11.4, respectively. In the age group of women over 35 years old (groups II and IV), the average number of received oocytes was 9.5 and 8.1, respectively. No significant difference was found between the control and study groups.

According to the study, the average number of mature oocytes did not differ significantly and amounted to 7.9-8.0 in women under 35 years of age and 5.9-6.1 in women over 35 years of age (Figure 2).

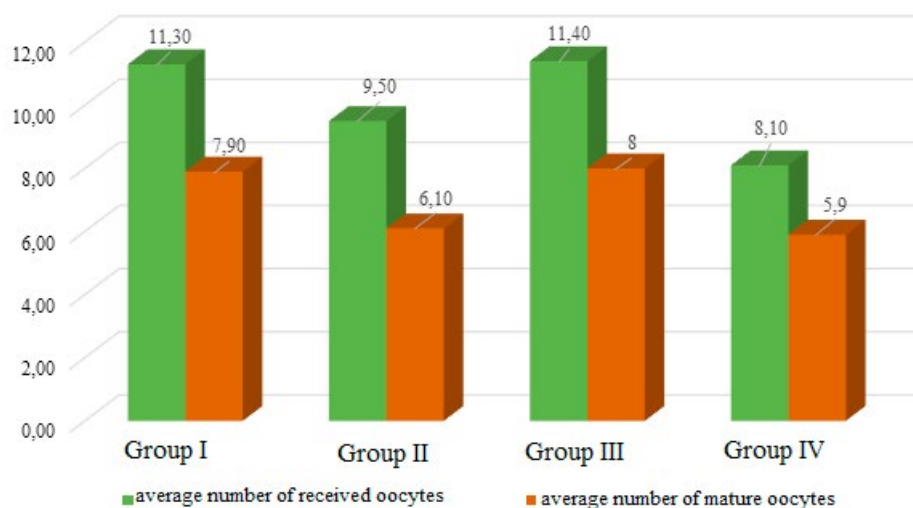


Figure 2 - The average number of received oocytes in the study groups.

Following the analysis, the percentage of growth to the blastocyst stage did not differ significantly in comparison groups I and III - 50%, this rate was lower and amounted to 35% in the older age category of women in groups II and IV.

Consequently, the study enables to determine the clinical pregnancy rate (CPR) after embryo transfer in recent IVF programs (Figure 3). In women under 35 years of age, CPR was 48.4% and 47.6% in groups I and III, respectively ($p > 0.05$); in women over 35 years of age (II and IV), this rate was insignificantly lower and amounted to 36.3% and 34.4% in groups II and IV, respectively ($p > 0.05$).

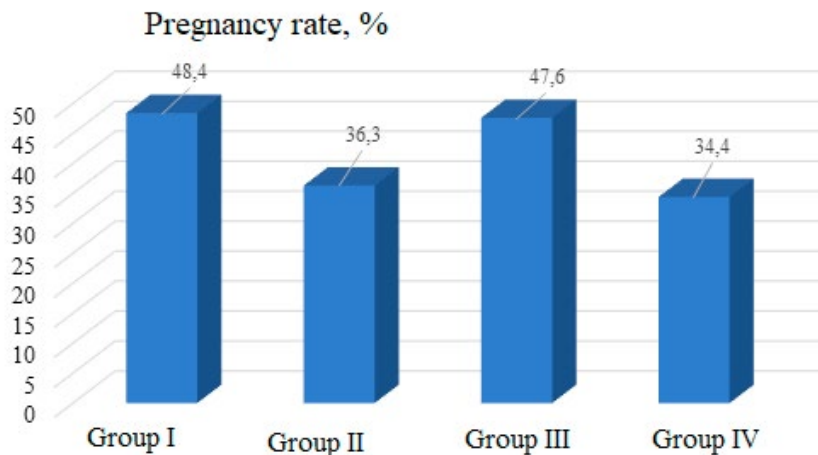


Figure 3 - The percentage of clinical pregnancies in the comparison groups

The frequency of early pregnancy losses in the group of women under 35 did not differ significantly and amounted to 4.6% and 7.5% in comparison groups I and III, respectively. Early pregnancy losses in older age groups II and IV were significantly higher compared to the group of women younger than 35 years, but there was no significant difference between vaccinated and unvaccinated patients – 15% and 16.4%, respectively.

Discussion: Following the study, the increase in the proportion of women under 35 years of age in both groups can be substantiated by the general age trend in relation to patients undergoing ART programs. According to the information database of the IRM, 70% of the patients of the clinic are under 35 years old, and scientific evidence indicates that distrust of vaccines is most pronounced among the younger part of the female population, which also suggests the possible impact of negative information that refers to the relationship of infertility with vaccination [9].

Due to the formation of syncytiotrophoblast in the developing embryo, it is assumed that cross-immune reactivity can lead to damage to the developing trophoblast, which may adversely affect embryo implantation [10, 11]. So, this cross-immune reactivity can cause lifelong infertility not only after vaccination, but also with COVID-19 disease. Laboratory studies of the mechanism of interaction with the viral protein did not evidence the presence of immune cross-reactivity [12].

To date studies have not established an association of the COVID-19 mRNA vaccine with fertility markers or clinical and embryological parameters [8], however, the number of clinical cases is currently insufficient to provide an extensive study and further work is required to take up the question. Analysis of our data also indicates that vaccination to reduce the risk of COVID-19 incidence does not have a significant impact on the primary clinical and embryological parameters and the effectiveness of ART programs.

According to the literature, 10–14 oocytes is the optimal number for obtaining follicles in women under 35 years of age, which is consistent with the data from our study [13].

Meanwhile, the decrease in the number and quality of oocytes in the group of patients older than 35 years is substantiated by the increase in the woman's age, when a decrease in the ovarian reserve and a deterioration in the quality of the received oocytes occur.

Moreover, Orvieto et al. reported insignificant difference between the groups before and after vaccination in a number of parameters, such as the quantity of obtained and mature oocytes, the frequency of fertilization, and others during the IVF/ICSI program. The older women over 35 years of age can be divided into a separate group, where a decrease in the quality of oocytes obtained by TVP and the percentage of growth to the blastocyst stage occurs, which is consistent with previously published data that evidences the effect of age on key performance indicators of ART programs [14].

Conclusion: The outcomes of this study did not show a negative effect of vaccination with Sputnik V on the number and quality of oocytes obtained, blastulation rate, good/excellent quality blastocyst yield, CPR and early pregnancy loss.

REFERENCES

1. Гриднев О. В., Муравьев С. М. Участие Минздрава России в мероприятиях по профилактике и борьбе с новой коронавирусной инфекцией, организуемых в зарубежных государствах // Вестник Рос. Здрав. надзора. – 2020. – №.4. – С. 15-22. [Gridnev O.V., Muravyev S.M. Uchastie Minzdrava Rossii v meropriyatiyah po profilaktike i borbe s novoy koronavirusnoy infektsiyey, organizuemyh v zarubezhnyh gosudarstvah // Vestnik Ros. Zdrav. Nadzora – 2020. – №.4. – S. 15-22. (in Russ).]. <https://doi.org/10.35576/2070-7940-2020-4-15-22>.
2. WHO COVID-19 Dashboard. Geneva: World Health Organization. –2020. . <https://covid19.who.int/>
3. Hannah R., Mathieu E., Rodés-Guirao L., Appel C., Giattino Ch., Ortiz-Ospina E., Hasell J., Macdonald B., Beltekian D., Roser M. Coronavirus pandemic (COVID-19) // Our world in data. – 2020. <https://ourworldindata.org/covid-vaccinations?country=JPN~USA>.
4. Mostaufred Ali K., Khan N., Mustagir G., Rana J., Haque R., Rahman M. COVID-19 infection during pregnancy: a systematic review to summarize possible symptoms, treatments, and pregnancy outcomes // medRxiv. – 2020. <https://doi.org/10.1101/2020.03.31.20049304>.
5. Ortiz E. I., Herrera E., De La Torre A. Coronavirus (COVID 19) infection in pregnancy // Colombia Médica. – 2020. – T. 51. – №. 2. <https://doi.org/10.25100/cm.v51i2.4271>.
6. Wei S.Q., Bilodeau-Bertrand M., Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis // CMAJ. – 2021. – Vol. 193 (16). – P. E540-E548. <https://doi.org/10.1503/cmaj.202604>.
7. Lu-Culligan A., Iwasaki A. The false rumours about vaccines that are scaring women // New York Times. – 2021. – Vol. 26. <https://www.nytimes.com/2021/01/26/opinion/covid-vaccine-rumors.html>.
8. Fei Ch., Zhu Sh., Dai Zh., Hao L., Luan Ch., Guo Q., Mengand Ch., Zhang Y. Effects of COVID-19 and mRNA vaccines on human fertility // Hum. Reprod. – 2022. – Vol. 37(1). – P. 5-13. <https://doi.org/10.1093/humrep/deab238>.
9. Schaler L., Wingfield M. COVID-19 vaccine—can it affect fertility? // Irish Journal of Medical Science (1971). – 2021. – P. 1-3. <https://doi.org/10.1007/s11845-021-02807-9>
10. Morris R. S. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility // Reports. – 2021. – Vol. 2(3). – P. 253-255. <https://doi.org/10.1016/j.xfre.2021.05.010>
11. Frendo J., Olivier D., Cheynet V., Blond J., Bouton O., Vidaud M., Rabreau M., Evain-Brion D., Mallet F. Direct involvement of HERV-W Env glycoprotein in human trophoblast cell fusion and differentiation // Mol. Cell. Biol. –2003. – Vol. 23(10). – P. 3566-3574. <https://doi.org/10.1128/MCB.23.10.3566-3574.2003>.
12. Aharon D., Lederman M., Ghofranian A., Hernandez-Nieto C., Canon Ch., Hanley W., Goukko D., Lee J.A., Stein D., Buyuk E., Copperman A.B. In vitro fertilization and early pregnancy outcomes after coronavirus disease 2019 (COVID-19) vaccination // Obstet. Gynecol. – 2022. – Vol. 139(4). – P. 490-497. <https://doi.org/10.1097/AOG.0000000000004713>
13. Magnusson Å., Källén K., Thurin-Kjellberg A., Bergh C. The number of oocytes retrieved during IVF: a balance between efficacy and safety // Human reproduction. – 2018. – Vol. 1(33). – P. 58-64. <https://doi.org/10.1093/humrep/dex334>.
14. Orvieto R., Noach-Hirsh M., Segev-Zahav A., Haas J., Nahum R., Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? // Reproductive Biology and Endocrinology. – 2021. – Vol. 1(19). – P. 1-4. <https://doi.org/10.1186/s12958-021-00757-6>.

ОЦЕНКА ВЛИЯНИЯ ВАКЦИНАЦИИ ОТ COVID-19 НА ТЕЧЕНИЕ И ИСХОДЫ ПРОГРАММ ЭКО

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Аннотация

Актуальность: В связи с пандемией COVID-19, начавшейся в 2020 году, актуальность вопроса о влиянии болезни на фертильность женщины продолжает оставаться дискуссионной в медицинском репродуктивном сообществе. С началом разработки вакцин появилась недостоверная информация касательно негативного влияния вакцинации на репродуктивную функцию женщины. В ряде научных работ данная гипотеза опровергается, однако необходимы дальнейшие исследования, позволяющие оценить влияние вакцины «Спутник V» на репродуктивный потенциал женщины.

Цель исследования – оценить влияние вакцины «Спутник V» на течение и исходы программ ЭКО/ИКСИ у пациенток, получивших вакцинацию от COVID-19.

Методы: Были проанализированы 1350 амбулаторных карт пациенток, прошедших лечение методами ВРТ с 2020 по 2021 гг. В исследуемую когорту вошли пациентки, прошедшие вакцинацию перед программой ЭКО/ИКСИ и пациентки, не получившие вакцину, в 2-х возрастных категориях: моложе 35 лет и старше 35.

Результаты: Исследования продемонстрировали отсутствие различий в показателях количества полученных и зрелых ооцитов между группами в обеих возрастных категориях. Среднее количество эмбрионов, дошедших до стадии бластоцисты между контрольной и исследуемой группой составило 4,3 против 3,9 у пациенток до 35 лет и 2,2 против 2,0 у пациенток старше 35 лет (разница недостоверна). Анализ частоты клинической беременности (ЧКБ) не показал статистической разницы в обеих возрастных категориях женщин ($p > 0.05$).

Заключение: Проведение пациенткам вакцинации «Спутником V» от SARS-CoV-2 не оказало значимого влияния на клинико-эмбриологические показатели и эффективность программ ВРТ.

Ключевые слова: вспомогательные репродуктивные технологии, covid-19, интрацитоплазматическая инъекция, экстракорпоральное оплодотворение, вакцинация.

COVID-19 ВАКЦИНАЦИЯСЫНЫҢ ЭҚҰ БАҒДАРЛАМАСЫНЫҢ БАРЫСЫНА ЖӘНЕ ОНЫҢ НӘТИЖЕЛЕРІНЕ ӘСЕРІН БАҒАЛАУ

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Андатпа

Өзектілігі: 2020 жылы басталған COVID-19 пандемиясына байланысты аурудың әйелдің ұрпақты болу қабілеттілігіне әсері туралы мәселенің өзектілігі медициналық репродуктивтік қоғамдастықта пікірталас тудыруда. Вакциналарды әзірлеудің басталуымен бірге вакцинацияның әйелдің репродуктивтік функциясына теріс әсері туралы жалған ақпарат пайда болды. Бірқатар ғылыми еңбектерде бұл болжам жоққа шығарылады, бірақ «Спутник V» вакцинасының әйелдің репродуктивті әлеуетіне әсерін бағалау үшін қосымша зерттеулер қажет.

Зерттеу мақсаты – «Спутник V» вакцинасының COVID-19-ға қарсы вакцина алған пациенттерде ЭҚҰ/ИКСИ бағдарламаларының барысы мен нәтижелеріне әсерін бағалау.

Әдістер: 2020 жылдан бастап 2021 жылға дейін ҚРТ әдісімен емделген пациенттердің 1350 амбулаториялық картасы талданды. Зерттелетін шоғыр екі топқа бөлінді: ЭҚҰ/ИКСИ бағдарламасы алдында вакцинациядан өткен пациенттер және вакцина алмаған пациенттер, 2 жас санатында: 35 жастан кіші және 35 жастан жоғары.

Нәтижелер: Зерттеулер екі жас санаттарындағы топтар арасында алынған және жетілген ооциттердің саны бойынша айырмашылықтардың жоқтығын көрсетті. 35 жасқа дейінгі бақылау және зерттелетін топ арасындағы бластоцист сатысына жеткен эмбриондардың орташа саны 3,9-ға қарсы 4,3 және 35 жастан асқан 2,0-ге қарсы 2,2 құрады (мәліметтер әзірше анық емес). Жүктіліктің басталу жиілігін (ЖБЖ) талдау әйелдердің екі жас санатында статистикалық айырмашылықты ($p > 0.05$) көрсеткен жоқ.

Қорытынды: Пациенттердің SARS-CoV-2-ден «Спутник V» вакцинасын қолдануы ҚРТ бағдарламаларының клиникалық-эмбриологиялық көрсеткіштері мен тиімділігіне айтарлықтай әсер еткен жоқ.

Түйінді сөздер: қосалқы репродуктивтік технологиялар, COVID-19, интрацитоплазматикалық инъекция, экстракорпоралдық ұрықтандыру, вакцинация.

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