

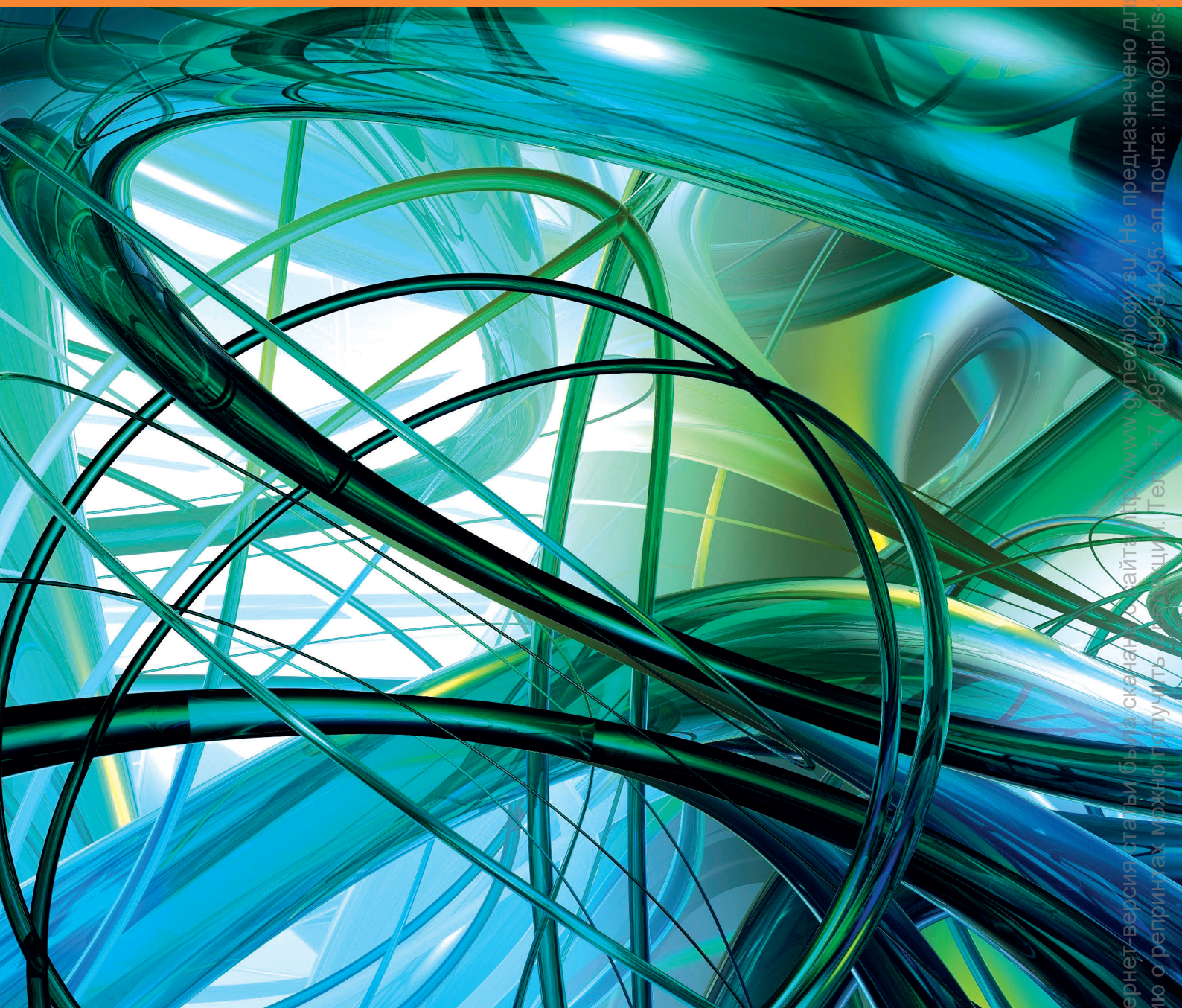
ISSN 2313-7347 (print)

ISSN 2500-3194 (online)

# АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих  
рецензируемых журналов и изданий ВАК

2022 • том 16 • № 2



OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2022 Vol. 16 No 2

[www.gynecology.ru](http://www.gynecology.ru)

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<https://doi.org/10.17749/2313-7347/ob.gyn.rep.2022.277>

# An impact of the novel coronavirus infection (COVID-19) on human reproductive function

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## Abstract

The latest data on the impact of the novel coronavirus infection (COVID-19) on female and male reproductive health are reviewed. Pathological changes in organs and tissues of human reproduction system after COVID-19 as well as recommendations for rehabilitation of couples planning pregnancy after COVID-19 are discussed. Moreover, issues of the reproductive health resulting from altered psychologic status in women after COVID-19 were highlighted as well.

**Keywords:** COVID-19, coronavirus infection, infertility, assisted reproductive technologies, reproductive health

**For citation:** Garibidi E.V., Shatunova E.P., Fedorina T.A., Garibidi D.E. An impact of the novel coronavirus infection (COVID-19) on human reproductive function. *Akusherstvo, Ginekologiya i Reprodukcya = Obstetrics, Gynecology and Reproduction*. 2022;16(2):176–181. <https://doi.org/10.17749/2313-7347/ob.gyn.rep.2022.277>.

## Влияние новой коронавирусной инфекции (COVID-19) на репродуктивную функцию человека

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## Резюме

В данном обзоре литературы представлена актуальная информация о влиянии новой коронавирусной инфекции (COVID-19) на репродуктивное здоровье женщин и мужчин. Рассмотрены такие вопросы, как патологические изменения в органах и тканях репродуктивной системы после перенесенного COVID-19, рекомендации по реабилитации пар, планирующих беременность после перенесенного COVID-19. Освещены вопросы репродуктивного здоровья в результате изменения психологического состояния у женщин после COVID-19.

**Ключевые слова:** COVID-19, коронавирусная инфекция, бесплодие, вспомогательные репродуктивные технологии, репродуктивное здоровье

**Для цитирования:** Гарибиди Е.В., Шатунова Е.П., Федорина Т.А., Гарибиди Д.Е. Влияние новой коронавирусной инфекции (COVID-19) на репродуктивную функцию человека. *Акушерство, Гинекология и Репродукция*. 2022;16(2):176–181. <https://doi.org/10.17749/2313-7347/ob.gyn.rep.2022.277>.

**Highlights****What is already known about this subject?**

- ▶ There were investigated effects of SARS-CoV-2 on various organs and systems during COVID-19 pandemic as well as its impact on female and male reproductive function.
- ▶ The study was conducted to assess changes in organs and tissues in COVID-19 survivors as well as diseased patients due to subsequent complications.
- ▶ The effect of COVID-19-infection on the centers of the brain responsible for the menstrual function was studied.

**What are the new findings?**

- ▶ Analyzing observations and conducted studies allows to understand what consequences related to COVID-19-infection it may lead to as well as assess the scale of the catastrophe occurring throughout human body due to subsequent complications.
- ▶ Summarizing information on the impact of COVID-19 on human reproductive function will allow to conduct proper preparation for further pregnancy.
- ▶ An opportunity to evaluate long-term results after COVID-19 in men emerged.

**How might it impact on clinical practice in the foreseeable future?**

- ▶ A clinical protocol involving consultation with andrologist and reproductive physician should be introduced for couples having problems with conception before COVID-19-infection.
- ▶ Women with low follicular reserve who have not suffered from COVID-19 are recommended to undergo oocyte cryopreservation followed by vaccination.
- ▶ Men with low levels of sperm concentration, motility and morphology in semen analysis are recommended to undergo sperm cryopreservation.

**Основные моменты****Что уже известно об этой теме?**

- ▶ Проведено изучение влияния SARS-CoV-2 на различные органы и системы в период пандемии COVID-19 и особенности влияния на репродуктивную функцию женщины и мужчины.
- ▶ Изучены изменения в органах и тканях у выживших пациентов, перенесших новый вид вирусной инфекции, а также у пациентов, погибших в результате осложнений после заражения COVID-19.
- ▶ Изучено влияние коронавирусной инфекции на центры головного мозга, отвечающие за менструальную функцию женщин.

**Что нового дает статья?**

- ▶ Анализ проведенных наблюдений и исследований позволяет понять, к каким последствиям может привести новая коронавирусная инфекция, оценить масштаб катастрофы в организме человека в результате полученных осложнений.
- ▶ Обобщение информации по влиянию COVID-19 на репродуктивную функцию человека позволит правильно провести подготовку к беременности.
- ▶ Появилась возможность оценить отдаленные результаты после перенесенного заболевания у мужчин.

**Как это может повлиять на клиническую практику в обозримом будущем?**

- ▶ Для пар, которые уже имели проблемы с зачатием до перенесенной COVID-19-инфекции, при подготовке к беременности следует ввести в клинический протокол консультации врача-андролога и врача-репродуктолога.
- ▶ Женщинам с низким фолликулярным резервом, не переболевшим COVID-19, следует рекомендовать криоконсервацию ооцитов и после криоконсервации ооцитов рекомендовать вакцинацию.
- ▶ Мужчинам, имеющим в спермограмме низкие концентрации сперматозоидов, сниженные показатели их подвижности и морфологии, следует рекомендовать криоконсервацию спермы.

**Introduction / Введение**

The World Health Organization announced the novel coronavirus infection COVID-19 as dangerous virus infection coupled to multiple organ damage. In addition to the effect on the respiratory system, COVID-19 may affect extrapulmonary sites by altering hemostasis, cardiovascular, hepatic, renal, neurological, intestinal systems, and endocrine system. Ophthalmological and dermatological symptoms were described as well. No doubt, the human reproductive system is not an exception to this list.

### COVID-19 pathomorphological pathway in organs and tissues / Патоморфологический путь вируса COVID-19 в органах и тканях

The endothelial dysfunction is manifested as increased barrier permeability, enhanced production of prothrombotic factors, and activated immune cells. All such processes are systematic and may damage entire vascular bed that may account for multiple organ changes in COVID-19 [3]. SARS-CoV-2 mainly enters human body via angiotensin-converting enzyme 2 (ACE2) receptor due

to exerting higher affinity for ACE2 receptor. Given that SARS-CoV-2 is transmitted via airborne particles and droplets, COVID-19 was initially considered as a highly contagious disease targeting the respiratory system. Moreover, it was noted that it resulted in a more aggressive course in males than in females [4, 5]. Because males less care about own health than females, the former visit doctors for preventive treatment less frequently, therefore suffering from more chronic diseases, which is coupled to higher percentage of severe diseases and lethal outcomes in males. It was proved that ACE2 levels are higher in males than in females as well as in patients with diabetes mellitus and cardiovascular diseases. Overlapping of COVID-19-related effects with pre-existing prothrombotic status substantially elevates the risk of thromboembolic complications [6]. Based on the up-to-date data, death is caused by thrombosis resulted from damage to the vascular endothelium in COVID-19 [7].

Long-term observations allowed to find out any human organs and systems may be targeted by SARS-CoV-2. Moreover, some studies allow to suspect that certain cerebral structures may be also affected. Also cytokine storm syndrome and vasculitis causing acidosis, impaired blood clotting problems such as thromboses and haemorrhage result in prolonged brain hypoxia [8]. SARS-CoV-2 enters via blood brain barrier and damage brain centres responsible for diverse body functions. M.T. Heneka et al. showed that more than 1/3 of the diseased patients developed neurological symptoms in acute COVID-19 [9]; 25 % of subjects suffered from damage to the central nervous system [10]. Hypoxia resulting from pulmonary damage along with drug toxic effects used during therapy exert adverse impact on the subcortical structures. ACE2 receptors are expressed not only in alveolar type II cells but also in other organs: intestine, spleen, liver, lymph nodes, and reproductive system resulting in multiple organ lesions. In case of entering systemic circulation, it results in virus dissemination and subsequent damage to the vascular endothelium causing organ-related complications [11].

Based on such data, it may be considered that any human body system may be affected by SARS-CoV-2 regardless of transmission route, viral effect, and magnitude of tissue damage.

### **An impact of SARS-CoV-2 on female reproductive system / Влияние коронавируса на женскую репродуктивную систему**

R. Li et al. found that SARS-CoV-2 affects the female reproductive system [12] via ovarian granulosa cells

that impairs oocyte quality providing all reasons to believe that it causes recurrent pregnancy loss. In turn, multiple pregnancy loss results in damaged endometrial endothelial cells affecting embryo implantation [13]. At early gestation age, higher rate of pregnancy loss is observed both in natural and in vitro fertilization cycles. Taking into consideration lack of evidence base about direct impact of SARS-CoV-2 on ovarian and endometrial tissues, studies investigating a role of this virus in the field are under way.

New living conditions faced by general population due to the COVID-19 pandemic as well as profound prolonged stress may definitely severely affect the reproductive system given that structures in the hypothalamus-pituitary-adrenal axis exert reciprocal effects. In turn, it results in establishing chronic stress followed by suppressed estrogens and norepinephrine release eventually resulting in diverse menstrual disorders. Enforced isolation, hypodynamia, malnutrition, family conflicts, and unemployment may aggravate menstrual disorders in the form of amenorrhea, inter-menstrual uterine bleeding, and form anovulatory cycles [14]. Similar stressful situations in men resulted in impaired semen parameters manifested as lowered sperm quality and motility.

Stress-dependent disorders arise due to psychogenic factors so that adolescents and young women are succumb to them more often because of unstable hypothalamus-pituitary-adrenal axis [15].

### **Male infertility / Бесплодие у мужчин**

Based on the data published by the Chinese scientists, the human testis may be potentially targeted SARS-CoV-2 because the ACE2 receptor is highly expressed in testicular stem cells resulting in spermatozoa. It is a mere reason of why the latter is affected at the earliest stages of development [16]. Moreover, ACE2 is found in Leydig cells producing testosterone, the most prominent hormone for sexual vigor and male health. It is also believed that SARS-CoV-2 may infect Sertoli cells, the so-called "nurse cells".

Numerous publications showed that SARS-CoV-2 may exert multimodal effects on male reproductive system: i) due to the binding to testicular ACE2 receptors directly affecting testes; ii) indirectly targeting testes by inducing testicular inflammatory and immune response [17]. In this regard, the study with 81 male patients with COVID-19 [18] found low and high level for testosterone and luteinizing hormone (LH), respectively, with low testosterone/LH ratio [19]. This finding indicates that the virus may potentially target testes to reduce Leydig cell function. Other researchers observed that post-COVID-19 spermogram

had lowered concentration of sperm cells with low motility present within the three months post-infection [20]. Thus, it was found out that the coronavirus negatively impacted on the male reproductive system within the mean 60 to 120 day-follow-up after recovery [21, 22].

The study conducted in the South India confirmed the arguments about damaging effect of SARS-CoV-2 on male fertility and quality of embryos while using assisted reproductive technologies. Moreover, it also confirmed the hypothesis of the previous study that COVID-19 may have a long-term detrimental effect on sperm cells, particularly on DNA and cell morphology. A rehabilitation period of men may last long enough exceeding 4 months. In addition, irreversible sequelae causing persistent changes such as oligospermia, asthenozoospermia, and teratozoospermia may finally result in male infertility [13]. Furthermore, inflammatory process is also found in the testis, whereas autopsy of COVID-19 non-survivors provided clear evidence of finding the virus presence in testicular tissue [16].

## Outlooks / Перспективы

Taking into consideration that SARS-CoV-2 was found in the sperm cells, it may not rule out that it could be transmitted from male to female as well as to fetus at conception [16].

During ovum fertilization, SARS-CoV-2-infected chromosomes or viral fragments (via transcriptome) are transmitted to offspring to be further incorporated into RNA-ribosome complex immediately involved in production of nascent proteins. Such an insight is novel that emerged recently and requires long-term follow-up. Currently, it is difficult to predict an outcome of female infection would it result in potential fetal pathology or other consequences. Making an analogy with herpesvirus-triggered effects on host cell, it is evident that herpes simplex virus can live intracellularly as it was confirmed using electron microscopy by the renowned reproductive biologist, professor Elizaveta Bragina [23].

According to Avtandil Chogovadze, head of the Reproductive Cell and Tissue Bank: "Today, when the whole world fights against coronavirus infection and saves patients' lives, few people think of such potential complications as infertility. I believe that full-fledged studies aimed at exploring virus-related impact on the human reproductive system will be conducted later. However, it is proven, that the virus causes infertility, this might not of any aid to the recovered patients. It will come down solely to state such a sad fact"<sup>1</sup>. While considering

the treatment of cancer patients, it is worth noting that around 100 % of patients who underwent chemotherapy and radiological treatment become infertile. Taking into consideration high mortality rate due to cancer, few years oncologists ranked number one patient's survival. However, over time they came to conclusion that it is necessary to inform patients about methods for preserving reproductive material mortality rate in cancer declines, quality of medical assistance becomes improved so that recovered patients begin to think of opportunity for planning birth of new pregnancies. Currently, clinical recommendations on infertility management have been extended. Taking into consideration harmful effects from COVID-19 on reproductive system, it has been concluded to obligatorily inform patients about potential development of infertility due to severe COVID-19. Hence, many patients may be able to conserve semen and oocytes, thereby securing reproductive function.

To date, there have been confirmed the pediatric cases of COVID-19. However, an impact of the novel coronavirus infection on a child's body has not been fully explored. Likewise, no data on virus-related effect on reproductive capacity in children suffered from COVID-19 before sexual maturation are available.

## Conclusion / Заключение

Taking into consideration the seriousness of the current situation developed during the COVID-19 pandemic, it should clearly recognized that long-term outcomes will not be obtained in the near future and multiple factors require detailed investigation.

Couples preparing for pregnancy after COVID-19 take a crucial step to result in healthy offspring, who, therefore, must adhered to the following steps:

1) conducting laboratory and instrumental assays according to the clinical recommendations (Assisted Reproductive Technology and COVID-19. Russian Association of Human Reproduction Recommendations on preventing SARS-CoV-2-associated novel coronavirus infection in conducting assisted reproductive technology. Approved by the Council of All Russia Public Organization "Russian Association of Human Reproduction". Dated of: May 20, 2020);

2) before planned pregnancy, undergo examination by specialist doctors due to complications emerged after COVID-19;

3) undergo post-COVID-19 patient rehabilitation;

4) a personalized approach to pregnancy planning is necessary during ongoing COVID-19 pandemic.

<sup>1</sup> Coronavirus can lead to infertility. *Institute of Human Stem Cells*, 2021. (In Russ.). Available at: <https://hsci.ru/news/koronavirus-mozhet-privesti-k-besplodiyu>.



ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 22.11.2021. Revision received: 07.04.2022.	Поступила: 22.11.2021. В доработанном виде: 07.04.2022.
Accepted: 21.04.2022. Published: 30.04.2022.	Принята к печати: 21.04.2022. Опубликовано: 30.04.2022.
Author's contribution	Вклад авторов
Garibidi E.V. – concept and design, review of publications, text writing; Shatunova E.P., Fedorina T.A. – concept and design, text editing; Garibidi D.E. – review of publications.	Гарибиди Е.В. – концепция и дизайн, обзор публикаций, написание текста; Шатунова Е.П., Федорина Т.А. – концепция и дизайн, редактирование текста; Гарибиди Д.Е. – обзор публикаций.
All authors have read and approved the final version of the manuscript.	Все авторы прочитали и утвердили окончательный вариант рукописи.
Conflict of interests	Конфликт интересов
The authors declare no conflict of interest.	Авторы заявляют об отсутствии конфликта интересов.
Funding	Финансирование
The authors declare no funding.	Авторы заявляют об отсутствии финансирования.
Provenance and peer review	Происхождение статьи и рецензирование
Not commissioned; externally peer reviewed.	Журнал не заказывал статью; внешнее рецензирование.

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