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## NEW CORONAVIRUS INFECTION COVID-19 AND WOMEN'S REPRODUCTIVE HEALTH. FACTS AND ASSUMPTIONS

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The review presents data on the possible ways in which the SARS-CoV-2 and COVID-19 virus affects the female reproductive system and the already recorded negative consequences. Recommendations on pregnancy planning and the specifics of using hormonal contraceptive methods, as well as approaches to specific prevention of a new coronavirus infection from the standpoint of safety and preserving the reproductive health of women during the COVID-19 pandemic are outlined.

**Keywords:** new coronavirus infection, SARS-CoV-2, COVID-19, women's reproductive health.

The pandemic of new coronavirus infection (NCI) COVID-19 caused by the SARS-CoV-2 virus continues to inflict damage of medical and demographic nature irrespective of geographic position, financial status and the development level of the health care systems in involved countries. Over a 2-year period of NCI pandemic four main waves of infectious process have been registered against the background of multiple mutations of SARS-CoV-2. According to the official data of the interactive web-based dash-

boards of the World Health Organization, hosted by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, on COVID-19 (accessed on 04.02.2022) the total number of infected people around the world reached more than 380 mln. people, the number of deaths from NCI is 5.7 mln.; more than 10 billion doses of anti-covid vaccines manufactured by different companies have been administered. In the Russian Federation the number of confirmed cases of NCI exceeds 12 mln., the mortality rate is about 320 thousand people, more than 150 mln. doses of anti-covid vaccines have been administered [11].

According to the data of the Federal State Statistics Service the size of the standard population of the Russian Federation as of 1st August 2021 is 145.8 mln. people. The natural population decline (difference between the birth and death rate) is 421.9 thousand people, which is 59% more than for the same period in 2020. Thus, in 2021 the decrease in the population size of Russia was 2 times faster [10]. Of course, taking into account the dynamics of the demographic situation, and the NCI COVID-19 contributes to this, everyone's attention is focused on the clarification of potential influence of COVID-19 on the reproductive health (RH) of people, since the successful reproduction is required for any species to continue its existence. The status of the RH of the population is an important component of the social and demographic development. It influences to a great extent the level of the development of the society as a whole. RH care is defined as a set of methods, techniques, approaches and services that contribute to the RH and welfare by preventing and solving the problems of the reproductive sphere [10].

The question of the potential influence of the COVID-19 infectious agent on the human reproductive system currently remains open and is in the focus of the scientific interests. The understanding of the fact whether SARS-CoV-2 could damage the tissues of ovaries, endometrium, embryo at the early stage of its development is critical in the context of the safety of any type of human reproduction in the period of pandemic.

**NCI and its potential influence on the female reproductive system.** It is considered that potentially SARS-CoV-2 could negatively affect human reproductive system through its immediate influence on gonads, through damaging effect of the hyperthermia and systemic oxidative stress on the cells and tissues of the reproductive system, potential toxic effect of the medications, their high doses and long-term administration in the course of the NCI therapy [7, 31].

Nowadays the negative effect of the long-term fever as well as of the oxidative stress on the main parameters of the ejaculate, disturbance of the function and morphology of the sperm, damage of the membranes and DNA, induction of male sex-cells apoptosis is proved [29, 35]. However, the studies of the influence of hyperthermia and oxidative stress including the one associated with NCI COVID-19, on tissues and cells of the testes could not be found in the available publications.

The probability of immediate susceptibility of tissues and cells of the reproductive system to SARS-CoV-2 presents great interest. At present we know that this virus enters the target-cells with the help of the cellular receptor, angiotensin converting enzyme-2 (ACE-2), and transmembrane serine protease TM-PRSS2 that promotes the virus binding with the receptor ACE2 activating the virus S-protein. The necessary condition

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for the access of the virus to the cell is the presence of both ACE2 and TMPRSS2 receptors on the cell [12]. The role of other receptors in entrance of SARS-CoV-2 into the cells are being discussed. For example, the role of the transmembrane glycoprotein basigin (CD147), that is part of immunoglobulin gene super family and has high expression on the surface of many cells. It is assumed that cells, tissues and organs with high expression of the above-named receptors are more susceptible to SARS-CoV-2 [15].

In the study by F.M. Reis et al. (2011), the expression of ACE2 was registered in primordial, primary, secondary and antral follicles, stroma and corpus luteum of the ovaries of women of the reproductive age [34].

Expression of basigin in the granulosa cells of the follicles of all the development stages, in the germinal epithelium, corpus luteum, female endometrium was confirmed in the studies of Anna M. Smedts et al. (2006), K.Li, R.A. Nowak (2020) [28].

Analysis of the manuscript by K. E. Stanley et al. (2020) testifies to the fact that SARS-CoV with little probability has a long-term effect on the human reproductive function due to the co-expression of ACE2 and TMPRSS2, as well as basigin in the cells of the antral follicles of the non-human primates and human cumulus [19]. European Society of Human Reproduction and Embryology (ESHRE) (2020) presented the information about the absence of receptors for SARS-CoV-2 in oocytes and embryos, therefore they are not susceptible to the influence of this virus. The shell of the oocyte provides high level of protection of the oocytes and embryos from the influence of SARS-CoV-2 [16]. Thus, the question whether SARS-CoV-2 virus affects the folliculogenesis, as well as the potential decrease in the quality of human oocytes remains debatable.

The expression of the ACE-2 and basigin (CD147) was observed in the human endometrium in epithelial and stromal cells throughout the menstrual cycle with predominant contraception in epithelial cells for ACE2 and in stromal ones – for CD147. It was noted that the expression of ACE-2 and basigin (CD147) in the endometrium changes in the course of the menstrual cycle – higher expression is observed in the secretory phase. Apparently, the expression level affects local homeostasis of the angiotensin-II and proliferative activity of the endometrium, could regulate its regeneration process. Thus, SARS-CoV-2 could potentially damage epithelial cells of the endometri-

um, influence the process of its cyclic remodeling, and consequently the embryo implantation [36].

**NCI and menstrual disorders.** NCI COVID-19 influences the parameters of female menstrual cycle. Findings of the study by K. Li et al. (2020) demonstrate that menstrual disorders (MD) are observed in 28% of women of the reproductive age after the NCI COVID-19. They are manifested in 25% changes in the volume of the menstrual blood loss and prolongation of the cycle - in 19% of cases [14]. According to the data of the study by Ya.A. Parphyonofy et al. (2020) an increase in the frequency of MD (oligomenorrhea/amenorrhea, abnormal uterine bleeding) are observed in 3-6 months after the NCI. It has direct dependence on the severity of NCI COVID-19 ( $p=0.002$ ) [9]. Based on the results of the survey of 1,031 women aged 15-45 a statistically significant increase in the variability of the menstrual cycle is observed since the beginning of pandemic ( $p=0.010$ ): changes in the regular pattern of the menstruation is noted in 46% of the surveyed women, deterioration of the pre-menstrual symptoms is observed in 53% of women; considerable increase in the volume of the blood loss during menstruation was revealed in 18%; 30% showed newly occurring dysmenorrhea; 9% had menoschesis up to 60-120 days (they had regular cycle before), 45% of the surveyed women said that they had decrease in libido [30]. In another study based on the results of the survey of 263 women aged  $26.3 \pm 6.9$  years an increase in the parameters of anxiety during the COVID-19 pandemic accompanied by decrease in duration ( $p=0.003$ ) and intensity of menstruation ( $p=0.002$ ) as compared to the values before the breakout of NCI [22] was established. In the study by Melekhova M.A., Boglakova Yu.V. (2021) no statistically significant differences in the evaluation of duration, intensity of menstruation and intensity of menstrual pain were observed between 583 women who had and who did not suffer from COVID-19, interviewed with the help of the survey created by the authors and located in social media. Statistically significant shortening of the last menstruation was noted in women vaccinated from COVID-19 relative to those who were not vaccinated (5 (4-6) and 5 (5-6) days, respectively,  $p=0.043$ ). But the values were still within the normal range of the duration of the menstruation [6].

It is well-known that psycho-emotional distress is an important reason of the development of functional MD, since the

chronic activation of hypothalamo-pituitary-adrenal axis leads to suppression of the hypothalamus- hypophysis-ovaries axis. Nonovulation, oligomenorrhea and amenorrhea, hyperplastic processes of endometrium, abnormal uterine bleedings, formation of the ovarian masses are those very gynecologic pathologies that are associated with MD, and in their turn may result in fertility disorders. In different countries on different continents statistically significantly similar data are obtained about high level of psycho-emotional tension in the period of NCI COVID-19 pandemic. For example, in Germany based on the results of the cross-section study that involved 15,704 residents of Germany aged  $\geq 18$  high prevalence of generalized anxiety (44.9%), depression (14.3%), psychological distress (65.2%) and fear connected with COVID-19 (59%) was revealed [25]. Online survey of 1,653 people from 63 countries showed that in more than 70% of respondents stress level exceeded the average level. Notably, 59% corresponded to the criteria of clinically significant anxiety, 39% informed about moderate depression symptoms [39].

Large-scale meta-analysis (2021) shows the following prevalence rate of psycho-emotional disorders among the population amid the COVID-19 pandemic ( $n=189159$ ): depression – 15.97% (95% CI 13.24-19.13), anxiety – 15% (95% CI 12.29-18.54), insomnia – 23.87% (95% CI 15.74-34.48), posttraumatic stress disorder – 21.94% (95% CI 9.37-43.31), psychological distress – 13.29% (95% CI 8.80-19.57) [32]. A connection between the anxiety induced by COVID-19, stress, depressive symptoms and increased prevalence of MD is revealed [37]. T. Ding et al. (2020), based on the registered decrease in the level of Anti-Müllerian hormone (AMH), increase in the level of testosterone and lactotropin in 78 women of older reproductive age (median is 43.5) against the background of COVID-19 of various degree of severity relative to the healthy women of the similar age group, drew a conclusion about the probable negative effect of NCI on ovarian reserve and endocrine function of ovaries in patients with COVID-19 [13].

**NCI and pregnancy.** A lot of reports of different kind have been published about the specific features of the NCI COVID-19 course in pregnant women, obstetric and perinatal outcomes in this category of patients. The data mainly refers to the manifestations of the NCI in the 2nd and 3rd trimesters of the pregnancy. Part of the studies are indicative

of the absence of the severe course of COVID-19 in pregnant women as compared to non-pregnant ones [27, 33]. Others point to an increased risk of hospitalization to the intensive care units, necessary use of artificial pulmonary ventilation and lethal outcome in pregnant women. The presence of bronchial asthma, arterial hypertension, diabetes mellitus, excess body weight and obesity, kidney and liver diseases could be associated with the increased risk of severe course of COVID-19 in pregnant women [5, 18].

Pregnant women with manifested NCI COVID-19 of various degree of severity demonstrate high frequency of pre-term labor (14.3-25%), C-section (42%-72%) [1, 5, 18, 23], that undoubtedly subsequently bring about the risks of the disturbance of the reproductive health of a women. Active discussion of the possibility to use vertical transmission of SARS-CoV-2 is going on. In a number of studies the vertical transmission of virus has not been proved in the case of the negative SARS-CoV-2 RNA samples from the newborns analyzed with PCR (nasopharyngeal swab, amniotic fluid, umbilical cord blood and human milk) [21]. Other manuscripts speak for the probable vertical transmission of COVID-19 [5, 18]. Perinatal outcomes in pregnant women with COVID-19 are characterized by the development of the fetus distress (26.5-39%), infantile asphyxia (1.4%). Perinatal mortality rate is 0.35 – 2.2% [5,23].

The amount of papers devoted to the obstetric and perinatal outcomes or risk of early pregnancy loss in the case of NCI manifestation in the 1st trimester is limited, the evaluation periods during pandemic differ, the data are controversial. Besides, unfavorable outcomes of gestation in the 1st trimester are subsequently associated with the development of various diseases of female reproductive system, in particular with infertility and recurrent miscarriage [4]. S. Cosma et al. (2021) conducted the research during the first wave of COVID-10 pandemic. They stated that NCI CIVUD-19 if manifested in the 1st trimester of pregnancy proceeds in asymptotic or mild form. No cases of covid-associated pneumonia were registered. The conclusion has been drawn about the absence of the high risk of spontaneous miscarriage in the 1st trimester of gestation against the background of NCI COVID-19 and probable favorable disease progression at the beginning of the pregnancy [20]. In the study by Yu.V. Khaydukova et al. (2021) the pregnancy outcomes in 50 women with manifestation of NCI COVID-19

(1st and 2nd wave) in the 1st trimester of gestation have been analyzed retrospectively. Moderate to mild form of the NCI prevailed. There were no patients with extremely severe course of the disease. 16% of women underwent artificial abortion. In half of the cases it happened due to the diagnosed NCI and it was necessary to take medications that were counter-indicative in case of pregnancy. In 42% of cases inevitable miscarriage occurred. Moreover, according to the data of ultra-sound examination non-developing pregnancy was revealed in 81% of cases. The pregnancy prolonged and finished in delivery at term in 42% of cases. It was established that the severity of NCI/presence of pneumonia do not have statistically significant effect on the pregnancy outcome in the form of its prolongation or inevitable miscarriage. Even mild form of NCI in the 1st trimester of gestation is associated with high risk of unfavorable outcome [2].

In the study by F. Halici-Ozturk et al. (2021) SARS-CoV-2 RNA analysis of tissues of the spontaneous abortus from 21 pregnant women with confirmed NCI COVID-19 using the method of real-time reverse transcription polymerase chain reaction (RT-PCR) revealed negative results [26].

Today medical community does not recommend postponing pregnancy planning and childbirth to a post-covid period [29, 30]. In this regard against the background of pandemic both at the stage of pregnancy planning and during pregnancy, it is necessary to observe all the measures of non-specific, pharmacological and specific prophylaxis to prevent SARS-CoV-2 infection or development of the severe NCI COVID-19 [29, 30]. The only means of specific prophylaxis is vaccination. Taking into account high probability of SARS-CoV-2 infection during pregnancy and absence of the data about the adverse effect of anti-COVID-19 vaccines on male and female fertility, vaccination is recommended to men and women of reproductive age at the stage of childbirth planning [7].

R. Orvieto et al. (2021) did not reveal negative effect of anti- SARS-CoV-2 vaccine mRNA on the ovarian reserve in the nearest cycle following vaccination in the programs of assisted reproductive technologies (Art) [3]. N.V. Dolgushina et al. (2021), published preliminary data about the absence of negative effect of the Russian vaccine Gam-COVID-Vac on the ovarian reserve and level of anti-phospholipid antibodies in women based on the assessment of the number of antral follicles, determination of the level of

Anti-Mullerian, follicle-stimulating, thyroid-stimulating hormones, estradiol, antiphospholipid antibodies in blood serum before vaccination and 90 days after the administration of the 1st component of the vaccine [24]. Pregnancy planning is possible in 28 days after the administration of the 1st component of the vaccine, that is in the period when the protective immunity against SARS-CoV-2 is being developed [7].

In the study by A. Edelman et al. (2022), the connection between the anti-COVID-19 vaccine and changes in the cycle and duration of menstruations was evaluated in those who received vaccine (n=2403), relative to those who did not (n=1556). Anti-COVID-19 vaccine was associated with the less than 1 day changes in the duration of the cycle for both cycles of the vaccine administration relative to the cycles before vaccination (0.71 day fewer following the 1st dose, 98.75% (CI 0.47-0.94), 0.91 day fewer following the 2nd dose, 98.75% (CI 0.63-1.19). No notable changes relative to the three basic cycles were observed in non-vaccinated women [17].

It is recommended to start pregnancy planning in not less than three months after the COVID-19 and with necessary adequate preconception preparation. For patients who have had COVID-19 it is recommended to postpone the programs of ART until complete recovery. In this respect it is necessary to have individual approach in groups of infertile patients. All the patients of the ART programs who have had COVID-19 and have additional risk factors of thromboembolic complications (TEC), it is necessary to give preventive doses of low molecular heparin (LMH) prior to and throughout the ovarian stimulation [7].

**NCI and contraception.** During COVID-19 pandemic the issue of availability and safety of various methods of contraception, especially of hormone one, to prevent unwanted pregnancy and negative consequences of its interruption for RH of women remains topical. In 2020 at the beginning of the pandemic WHO supports the use of all the contraception methods without special limitations. Additional attention is paid to the absence of necessity to remove intra-uterine contraception systems including levonorgestrel releasing intrauterine system as well as implants in patients with NCI. If necessary it is possible to somewhat prolong the period of their usage in observance of a number of recommendations. For example, in addition to levonorgestrel releasing intrauterine system it is possible to use oral progestogen-containing con-



traceptives (PC) or barrier contraception. Considering NCI treatment patterns one should remember that the use of some antibiotics could decrease the efficiency of hormone contraceptives [38].

Russian guidelines (5th version) give reference to joint recommendations of the Spanish colleagues – a group of experts from Spanish medical scientific communities (Spanish Menopause Society, SMS; Sociedad Española de Ginecología y Obstetricia, SEGO; Sociedad Española de Trombosis), that are made for women in the period of menopausal transition using CHC. In case of mild NCI it is recommended to stop using CHC for the period of isolation and limited mobility. If hormonal contraception is required then it is possible to continue the use of CHC if there are no risk factors of TEC. Otherwise, to start using PC together with preventive doses of LMH. In case of NCI of moderate severity, if it is impossible to stop using hormonal contraception, it is also recommended to start using PC together with preventive doses of LMH. If the disease course is severe then CHC should be discontinued, LMH should be prescribed in accordance with the treatment protocols. It is recommended to resume taking CHC only after recovery and full mobilization [7].

It is advised to provide an opportunity of long-distance medical consultations (using various means of on-line communication without personal contact) with regards to contraception, its beginning and termination, and the choice of contraception methods [26, 41, 61].

Thus, to clarify the consequences of NCI for the female reproductive health it is necessary to conduct further research. It is reasonable in the period of pandemic to take measures aimed at prevention of negative effect of distress on the reproductive system. The strategy of maintaining reproductive health in the conditions of NCI and psycho-social distress should include certain approaches and methods that have positive influence on a woman's body as a whole and reproductive system in particular: compliance with work and rest schedule, sleep hygiene, healthy balanced diet, physical activity, meditation and yoga, psychological assistance, balanced psycho-correction and psychotherapy (on indications), reasonable (safe and efficient) contraception and pregnancy planning. Women of reproductive age who have had NCI, especially in severe form, should be included into the group of high risk in terms of development of disorders of the menstrual and reproductive functions, and should undergo a more profound follow-up care.

It is necessary to ensure availability of medical consultation, including long-distance ones, on the use of various contraception methods during pandemic to prevent unwanted pregnancy. The usage of CHC is reasonable with due account of additional evaluation of risks with regard to manifestation of or previous NCI. It is not recommended to postpone the pregnancy planning and childbirth to a post-covid period. After the previous NCI the pregnancy should be planned in not less than three months against the background of adequate pre-conception preparation. Considering the absence of data on negative effect of anti-COVID-19 vaccines on female fertility, fetus at the early stage of gestation, pregnancy course and perinatal outcomes, vaccination is recommended including the stage of pregnancy planning (in compliance with the practice guidelines) as the low level of collective immunity (<70-80%) could be one of the reasons of high NCI incidence among the population.

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## THE GENETICS OF MUCOPOLYSACCHARIDOSES

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This review aims to summarize scientific data on the contribution to the study of hereditary lysosomal disease - mucopolysaccharidoses. The article presents a review of the literature on the clinical picture and diagnosis of mucopolysaccharidosis in patients, the frequency of these diseases in the world is given. The available medical literature on the study of MPS was analyzed using the PubMed database, eLIBRARY.RU, Google Academia

**Keywords:** mucopolysaccharidosis.

**Introduction.** The first information about disorders of lysosomal accumulation appeared at the end of the 19th

century, and Tay-Sachs disease was first described in 1881 and 1882. The disease was named after doctors Warren Thau and Bernard Sachs and French dermatologist Philippe Gauche. 50 years later, in 1932, Dutch physician John Pompei announced the type II glycogen disease that would later become his name. Pompe disease is the first hereditary disease to be identified as a lysosomal storage disorder. Lysosomes were discovered experimentally between 1949 and 1952, when the biochemist Christian de Dube and colleagues discovered that they were the organelles responsible for the intracellular degradation and reuse of macromolecules. This finding further elucidates the pathophysiological basis

of lysosomal storage disorders. After the first clinical phenotype was identified in the 19th century, lysosomes were recognized in 1955/56, and since 1963 the biochemical defects underlying LSD have been proven and knowledge of LSD has increased. In the 1970s and 1990s, research focused on the mannose phosphate 6 receptor pathway, the sorting mechanism of lysosomal enzymes, the identification of the molecular basis of LSD, and the development of tools and strategies to investigate lysosomal biology. Attempts to treat these diseases with enzyme replacement therapy were first made in the 1990s. Currently, research is focused on the role of lysosomes as signaling platforms for the control of cellular

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