ABSTRACT

the dissertation by Yerkenova Sandugash Yerkenkyzy

on the topic: «IMPROVEMENT OF PREGRAVID PREPARATION IN WOMEN WHO HAVE RECOVERED FROM COVID-19», submitted for the degree of Doctor of Philosophy (PhD) in the educational program: 8D10141 «Medicine»

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Relevance of the research topic:

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has been recognized by the World Health Organization as a public health emergency of international concern and continues to have a significant impact on all areas of life, including women's reproductive health. According to WHO, pregnant women infected with COVID-19 are at increased risk of developing severe forms of the disease, pregnancy complications, and adverse perinatal outcomes [1].

Previous epidemics caused by other coronaviruses — SARS-CoV and MERS-CoV — demonstrated a significant increase in the incidence of pregnancy complications, including preterm birth, intrauterine growth restriction, and perinatal mortality. For instance, one study reported that among women who had recovered from SARS, the rate of spontaneous miscarriage reached 57%, while perinatal mortality was as high as 25% [2]. Similarly, MERS-CoV infection during pregnancy was associated with preterm delivery in 50% of cases and intrauterine fetal death in 27% of cases [3].

In the context of the new pandemic, research findings indicate that pregnant women with COVID-19 frequently develop pneumonia, hypoxia, and require oxygen support, as well as have a higher rate of cesarean section compared to the general population [4]. Other observations have shown that even asymptomatic pregnant patients can be a source of nosocomial infection transmission, necessitating strict adherence to isolation measures and careful monitoring of both maternal and fetal conditions [5].

Particular concern arises regarding the impact of COVID-19 on women's reproductive health. Numerous studies confirm that the SARS-CoV-2 virus enters cells via angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in the ovaries, endometrium, vagina, and placenta [6,7]. A meta-analysis by Li R. (2021) demonstrated that 28% of women experienced menstrual cycle disturbances following COVID-19 infection [8], while a study by Khan S.M. (2022) reported a decline in ovarian reserve, as indicated by decreased AMH levels, in recovered patients [9].

Clinical observations indicate the development of a specific "post-COVID reproductive syndrome," which includes:

- menstrual dysfunction (34–46% of cases) [10]
- decreased ovarian reserve (in 19% of patients) [11]
- endocrine infertility (2.3 times more frequent compared to the control group) [12]

According to the ISUOG recommendations [13], COVID-19 during pregnancy requires a specific management protocol, which includes regular assessment of fetoplacental blood flow, monitoring of maternal respiratory function, and timely delivery in the presence of life-threatening complications. Moreover, as noted by Belokrinitskaya T.E. and Shapovalov K.G. [14], even in the context of influenza epidemics, it has been demonstrated that viral infections during pregnancy significantly increase the risk of gestational complications and necessitate targeted pregravid preparation in high-risk groups.

Thus, the accumulated data indicate that women who have recovered from COVID-19 may face increased risks of reproductive health disorders and complications in subsequent pregnancies. These risks are attributed both to the potential direct damaging effects of the virus on reproductive system tissues and to indirect influences mediated by systemic inflammatory response, hypoxia, and coagulopathy.

The scientific problem lies in the absence of comprehensive clinical and laboratory criteria and evidence-based approaches for pregravid preparation of women after recovering from COVID-19. Despite the growing number of studies on the impact of the infection on reproductive health, there are no validated algorithms in the literature for prevention and preparation for pregnancy in the post-COVID period, which underscores the necessity of conducting the present study.

Aim of the dissertation research:

To develop and substantiate principles of pregravid preparation for women who have recovered from moderate and severe COVID-19, based on the analysis of clinical, laboratory, hormonal, and functional indicators, taking into account the identified post-COVID reproductive health disorders.

Research objectives:

1. To evaluate pregnancy and childbirth outcomes in women who have recovered from moderate and severe COVID-19 and to determine the incidence of major obstetric and perinatal complications.

2. To investigate the characteristics of reproductive function in women after COVID-19, including changes in the menstrual cycle, ovarian reserve, and hormonal status.

3. To analyze hemostatic parameters, levels of inflammatory markers, and hormonal shifts in non-pregnant women of reproductive age at 3 and 6 months post-COVID-19 recovery.

4. To develop and validate an algorithm for pregravid preparation in post-COVID women that takes into account key predictors of adverse reproductive prognosis and to assess its effectiveness.

Scientific novelty of the study:

For the first time in the Republic of Kazakhstan, a comprehensive analysis of obstetric and reproductive outcomes in women who have recovered from moderate and severe COVID-19 has been conducted. A significant correlation was established between the past infection and disruptions in hormonal balance, hemostatic system,

vitamin D levels, and inflammatory markers. New data were obtained on the dynamics of reproductive and psycho-emotional health recovery in women at 3 and 6 months post-illness. Based on the identified post-COVID changes, a scientifically substantiated algorithm for pregravid preparation was developed, taking into account individual clinical and laboratory characteristics and risk factors for adverse reproductive outcomes.

Practical significance of the dissertation:

An algorithm for pregravid preparation of women who have recovered from moderate and severe COVID-19, based on individual clinical and laboratory characteristics, has been developed and validated. Its implementation in the practice of women's consultation centers, reproductive health clinics, and outpatient facilities allows for improved pregnancy planning effectiveness, reduced frequency of complications, and enhanced reproductive outcomes. The obtained results can be utilized in the development of clinical protocols, preparation of educational programs, and training of specialists in obstetrics and gynecology.

Main points submitted for defense:

1. Moderate and severe COVID-19 in women of reproductive age significantly increases the risk of gestational and perinatal complications, including anemia, preterm birth, fetal hypoxia, atonic hemorrhage, and postpartum infections.

2. Persistent reproductive dysfunction has been identified in women after COVID-19, characterized by decreased ovarian reserve, hormonal imbalance (elevated FSH, LH, TSH with reduced estradiol), and vitamin D deficiency.

3. Signs of systemic inflammation and coagulopathy (elevated levels of D-dimer, C-reactive protein, interleukin-6, ferritin) persist 3 to 6 months after COVID-19 infection, accompanied by changes in hormonal profile and ovarian reserve.

4. The developed and validated algorithm for pregravid preparation of women after moderate and severe COVID-19, which includes correction of hormonal, inflammatory, and metabolic disorders, promotes restoration of reproductive system function and increases the likelihood of achieving physiological pregnancy.

5. Incorporating post-COVID monitoring into clinical practice is a promising direction for improving obstetric and gynecological care and preventing complicated pregnancies.

Conclusions:

1. Women who have recovered from moderate and severe COVID-19 are significantly more likely to develop pregnancy complications, including anemia (25.0%, OR=3.00, p=0.015), preeclampsia (18.3%, OR=4.27, p=0.022), preterm birth (15.0%, OR=3.35, p=0.049), and fetal hypoxia (16.7%, OR=5.88, p=0.021), which necessitates enhanced monitoring of this patient group.

2. Three months after COVID-19 recovery, women of reproductive age exhibit significant menstrual dysfunction (18.0%, OR=3.74, p=0.034), decreased ovarian reserve (AMH <1.0 ng/ml in 50.0%), and hormonal imbalances (TSH >2.5 μIU/ml in 60.0%), which persist in some patients up to six months.

3. Laboratory tests confirm persistent post-COVID alterations: vitamin D deficiency (52.0%, OR=5.9, p<0.005), hypercoagulation (D-dimer >0.5 μg/ml in

45.3%, OR=10.4, p<0.001), and systemic inflammation (CRP >5 mg/L in 30.0%), justifying the need for their correction during pregravid preparation.

4. The developed pregravid preparation algorithm demonstrated high clinical efficacy: it reduced the prevalence of vitamin D deficiency by 8.9 times (from 80.0% to 9.0%, p<0.001), decreased the prevalence of subclinical hypothyroidism sixfold (from 60.0% to 10.0%, p<0.001), completely eliminated systemic inflammation (CRP >5 mg/L from 100% to 0%, p<0.001), improved ovarian reserve 3.8 times (reduction of AMH <1 ng/ml from 50.0% to 13.0%, p=0.004), and decreased the incidence of menstrual cycle disorders 3.3 times (from 66.7% to 20.0%, p<0.001), which ensured the occurrence of physiological pregnancy in 63.3% of women with reduced AMH without ART.

Dissertation results validation:

The main findings and results of the study have been repeatedly presented and discussed at international and national scientific forums, ensuring their wide professional recognition and expert evaluation. In particular, reports on the dissertation topic were delivered at the 5th International Scientific and Educational Forum «Ana men Bala» (Almaty, 2022), *the International Conference on Gynecology and Obstetrics* (Dubai, 2024), as well as at the international congress «Global Health», organized jointly by the S. Kairbekova National Scientific Center, the Association of Management and Public Health, and the KMU «KSPH» (Almaty, 2022).

Certain research findings were presented at the *Science and Youth – Conference on the Quality of Medical Care and Health Literacy (2024)* and at the 3rd International Scientific and Practical Conference "Reproductive Health of Adolescents and Youth" (Almaty, 2024).

Thus, the validation encompassed both international and national scientific platforms, confirming the relevance and significance of the conducted research.

Publications related to the dissertation topic:

Based on the dissertation materials, 6 scientific papers have been published, which meets the requirements of the Committee for Quality Assurance in Science and Higher Education.

Among them:

3 articles in journals recommended by the Committee:

1. Долгосрочное воздействие LONG COVID на репродуктивную систему женщин: обзор литературы // Репродуктивная медицина. – 2023. – №3(56). – С. 35–39.
2. Влияние инфекции SARS-COV-2 на репродуктивную систему // Вестник КазНМУ. – 2022. – №1. – С. 28–36.
3. Влияние коронавирусной инфекции на женскую репродуктивную систему: обзор литературы // Репродуктивная медицина. – 2023. – №2(55). – С. 46–52.

3 articles published in international journals indexed in the Scopus database, including Q1 journals:

4. Preconception care to improve pregnancy outcomes in COVID-19 survival Women: A systematic review // Research J. Pharm. and Tech. – 2023. – Vol. 16, Issue 11. – P. 5485–5491 (Q3, процентиль 27%).
5. Interrupted time series analysis of the impact of the COVID-19 pandemic and compulsory social health insurance system on fertility rates: a study of live births in Kazakhstan // Frontiersin Public Health. – 2024. – Vol. 22. – P. 1250–1262 (Q1, процентиль 86%).
6. Structural and Hormonal Changes in Reproductive-Age Women Post-COVID-19: A Cross-Sectional Ultrasound and Biochemical Study // Diagnostics (Basel). – 2025. – Vol. 15(12):1536. doi:10.3390/diagnostics 15121536 (Q1, процентиль 72%).

Information on Implementations:

Implementation acts of the results of scientific research work were developed at the bases of SKE on REM «City Polyclinic №24», SKE on REM «City Polyclinic № 16», SKE on REM «City Polyclinic № 20», Talgar District Central Regional Hospital, SKE on REM «City Clinical Hospital № 4».

Based on the results of the dissertation work, developed:

Certificate of registration in the State Register of Rights to Objects Protected by Copyright. Name of the object: "Algorithm of pregravid preparation after COVID-19." Date of registration: 10.02.2025 Certificate number: №54390. Algorithm of medical procedures for the implementation of the pregravid preparation program for women who have recovered from moderate and severe COVID-19, aimed at optimizing reproductive health.

Personal contribution of the doctoral candidate:

The author independently conducted an analysis of domestic and foreign literature on the issue of reproductive health in women who have recovered from COVID-19 and on pregravid preparation. The research objectives and tasks were formulated, and the study design and inclusion/exclusion criteria were determined. Data collection and initial processing were carried out, including retrospective and prospective analysis of pregnancy, childbirth, and the postpartum period in women who had COVID-19, as well as preparation for pregnancy.

The doctoral candidate independently developed and implemented a set of measures to improve pregravid preparation, which included health assessment, correction of identified disorders, and individualized support for women. An analysis of the dynamics of laboratory test results and pelvic ultrasound findings was conducted during the preparation for pregnancy and throughout the pregnancy period.

The doctoral candidate conducted statistical processing and interpretation of the obtained data, compared the research results with literature data, and assessed the effectiveness of the proposed measures. Scientific statements presented for defense were formulated, and practical recommendations were substantiated for implementation in the activities of women’s health clinics and primary healthcare institutions.

Publications on the dissertation topic were prepared, reports were presented at scientific conferences, and the dissertation manuscript and abstract were finalized.

Volume and structure of the dissertation:

The dissertation has been prepared in accordance with established guidelines and consists of an introduction, literature review, materials and methods, results of original research, conclusion, and a reference list comprising 128 sources. The dissertation is presented in 116 pages of computer-typed text, formatted according to required standards, and includes 34 tables and 6 figures.

The work was carried out from 2021 to 2023 in Almaty, based at the I.S. Zhekenova City Infectious Diseases Hospital, Municipal State Enterprise on the Right of Economic Management (SKE on REM) City Hospital № 4, SKE on REM City Maternity Hospital № 4, and SKE on REM City Maternity Hospital № 1, with financial support from the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan under the project "Impact of COVID-19 on women's reproductive health and protection of women's health" (grant № AR14872263).