

## ANNOTATION

Dissertation work Shaimerdenova Gulbanu Ganikyzy on the topic: "**Clinical manifestations, complications, outcomes and effectiveness of etiotropic therapy of coronavirus infection COVID-19 in pregnant women**", submitted for the degree of Doctor of Philosophy (PhD) on speciality 8D10141 - "Medicine"

### **Relevance of the research topic.**

At the end of 2019, the global community was unexpectedly shaken by the emergence of a new virus - coronavirus (COVID-19). This virus, which originated in animals, was previously unknown in medical practice and has become a serious challenge for global health. Coronaviruses belong to the family of RNA-containing viruses and were previously known to cause simple respiratory infections in humans. However, in late 2019, an unusual spread of respiratory illnesses was reported in the city of Wuhan, Hubei Province in China, which has caused serious alarm.

The first cases of COVID-19 coronavirus infection were associated with seafood and animal markets, indicating a probable zoonotic origin of coronavirus infection. Further investigations led to the identification of a virus in the initial samples that was named SARS-CoV-2 because of its structural similarity to the SARS virus that caused the 2002-2003 outbreak.

Since early 2020, COVID-19 coronavirus infection has become a global pandemic, affecting millions of people and causing significant economic and social damage. Within a short time, the disease has spread to almost every country in the world, forcing governments and health organisations to take urgent action to protect the population and reduce the development of the disease. This was the first time that mankind had encountered this strain, which was previously unknown. Consequently, control measures were unknown.

By the end of January 2020, there are 9,826 confirmed cases in 27 countries (as well as 15,238 probable cases in China), with 213 deaths. Between December 2019 and November 2023, there are 6,934,072 fatal cases worldwide.

Risk groups for treatment of COVID-19 coronavirus infection are: age over 60 years (risk increases with age), pregnant women, concomitant BSC (arterial hypertension, CHD, CHF), cerebrovascular disease, concomitant chronic diseases of the respiratory system (COPD, AD, fibrotic changes in the lungs) endocrinopathies (diabetes mellitus, metabolic syndrome, obesity), immunodeficiency states; other severe chronic diseases (CKD, etc.) and smoking.) and smoking.

The total population of Kazakhstan as of 1 January 2023 is 19,932,169. The population of Shymkent city is 1,538,152. In Kazakhstan in 2022 RAGS bodies registered 42,310 births. Shymkent city has a high birth rate - 27.89 per 100 thousand population. According to statistical data Shymkent city has the following statistics on the spread of coronavirus infection COVID-19 during the pandemic period: 38

thousand 149 cases, of which 1646 pregnant women: 2020-537,2021-892,2022-217 women.

During pregnancy, physiological changes occur in the immune, cardiovascular and respiratory systems. An important issue is the specific course of SARS-CoV-2 coronavirus infection during pregnancy. A systematic review including 18 studies (114 pregnant women) showed that the most characteristic symptoms in pregnant women are: fever (87.5%) and cough (53.8%). In addition, fatigue (22.5%), diarrhea (8.8%), dyspnea (11.3%), sore throat (7.5%) and myalgia (16.3%) were common. The following pregnancy complications have been recorded: miscarriage (2%), fetal growth retardation (10%), fetal distress (10.7%) and preterm labor (21.3-39.0%). According to the latest WHO data, there are also fatalities.

Maternal mortality remains a major public health problem worldwide. During the pandemic in Kazakhstan, the maternal mortality ratio per 100,000 live births was 53.3 in 2020 and 44.9. The main cause of maternal mortality in Kazakhstan is extra genital diseases (77 per cent). At the same time, 80 per cent of extra genital diseases presented as a cause of maternal mortality was due to COVID-19 coronavirus infection during the pandemic in Kazakhstan.

The importance of COVID-19 coronavirus infection in pregnant women during the pandemic prompted this study.

**Purpose of the study:** To investigate the course, risk of complications, and outcomes of COVID-19 coronavirus infection in pregnant women and the efficacy of etiotropic treatment with remdesivir.

**Objectives of the study:**

1. Conduct a comparative analysis of clinical and laboratory features, frequency and nature of complications, outcomes in pregnant women with coronavirus infection COVID-19 from the Kazakh population.
2. Determine perinatal outcomes in women with coronavirus infection COVID-19.
3. Assess the effectiveness of the antiviral drug Remdesivir in pregnant women infected with coronavirus infection COVID-19.
4. Develop and implement recommendations reflecting the principles of early diagnosis, routing, prevention of coronavirus infection COVID-19 in pregnant women.

**Research Methods.**

Clinical studies were conducted according to the clinical protocol of diagnosis and treatment "Coronavirus infection COVID-19 in pregnant women, women in labour and delivery" dated 5 August 2021. Clinical diagnosis was based on the data of subjective and objective methods of examination of patients: anamnesis, complaints, analysis of medical records of patients under inpatient treatment according to the form 003/u, 003-2/u.

Commonly accepted clinical and laboratory methods of investigation (complaints, history taking, objective examination of the patient's status, determination of peripheral blood parameters, the state of the blood coagulation system and basic biochemical tests (LDH, ALT, AST)) were accepted for the diagnosis of COVID-19.

### **Object and subject of the study.**

The object of the study is pregnant women with a clinical diagnosis of COVID-19 coronavirus infection. Patients included in the study were recruited in infectious diseases hospitals and prenatal centers of the Republic of Kazakhstan. The subjects of the study are the course of pregnancy with COVID -19, clinical manifestations of COVID -19; laboratory studies: general blood analysis (haemoglobin, leukocytes, platelets, neutrophils, erythrocyte sedimentation rate (ESR)), biochemical blood analysis (lymphocytes, C-reactive protein, blood for procalcitonin, coagulogram, LDH, troponin), instrumental methods of research: ROGC, CT, ultrasound of pelvic organs. In accordance with the aim and objectives of the study, the impact of COVID- 19 coronavirus infection on the course of pregnancy in the conditions of Shymkent city was studied. The study was conducted on the basis of the city infectious disease hospital, the city infectious disease center of Shymkent, and the perinatal center of Shymkent. We analyzed case histories of 410 women from December 2020 to February 2021.

The research work was approved by the Ethical Committee of JSC "South Kazakhstan Medical Academy" from 21.11.2020, according to the established protocols of the Helsinki Declaration of 1964. Conclusion of the ethical committee, protocol No.1 of 16.03.2021. All patients were included in the study after signing informed consent.

The study was conducted in accordance with the international rules of "Good clinical practice" (National Institute on Drug, Abuse, 2017), and also complied with the principles of the Declaration of Helsinki.

### **Scientific novelty of the results of the study:**

For the first time in pregnant women of the Kazakh population, the following were determined:

1. Clinical manifestations, frequency and nature of complications of coronavirus infection COVID-19 in pregnant women in the Kazakh population were determined.
2. The mutual influence of COVID-19 and pregnancy on each other was determined.
3. The features of perinatal pregnancy outcomes in women who have had coronavirus infection COVID-19 were established.
4. An assessment of the effectiveness of the etiotropic antiviral drug Remdesivir in pregnant women with coronavirus infection COVID-19 was performed.

### **Practical relevance.**

1. Pregnant women with COVID-19 upon admission to hospital must undergo an assessment of the severity of COVID-19 using the WHO ABCDE approach, which can reduce the time for identifying life-threatening conditions (ARDS, ARF, PE, sepsis, shock, MODS, AHF) by 1.5 bed days.
2. When monitoring pregnant women with COVID-19, we should adhere to the "Algorithm for the tactics of managing pregnant women with coronavirus infection" developed by us, based on the assessment of respiratory rate, SpO<sub>2</sub>, heart rate and the choice of adequate treatment tactics depending on the severity.

### **The main points put forward for defense.**

1. The severity of COVID-19 increases with increasing gestational age. Common complications in pregnant women with COVID-19 include premature birth and antenatal death of the fetus.
2. A comparative analysis of clinical and laboratory data showed significant changes (decreased saturation, respiratory rate, degree of respiratory failure, increased levels of

C-reactive protein, ferritin, D-dimer) in the group of pregnant women compared to non-pregnant patients.

3. Women with COVID-19 coronavirus infection are at risk of giving birth to children with short stature, premature births, and low Apgar scores.

4. The use of the etiotropic drug Remdesivir in pregnant women with COVID-19 coronavirus infection does not statistically significantly lead to positive dynamics in normalizing temperature, respiratory rate, subjective reduction in shortness of breath, cough.

**The main provisions of the work have been reported and discussed in the form of scientific reports.**

1. VIII international Scientific Conference of Young Scientists and Students "Prospects of Development of Biology, Medicine and Pharmacy" (Shymkent, 2020).
2. International Student Scientific Conference " V Interdisciplinary Scientific Forum» (Moscow, 2021).
3. Republican interdisciplinary scientific conference "Pandemic COVID-19: Actual problems and ways of solution" (Almaty, 2021).
4. Interdisciplinary Conference of Young Scientists "COVID-19. Clinic. Diagnosis. Treatment. prevention" (Nur-Sultan, 2021).
5. Republican scientific-practical conference with international participation "LIFE AFTER COVID-19". (Almaty, 2021).
6. 75th International Scientific and Practical Conference of Medical Students and Young Scientists "Modern Medicine and Pharmacy: New Approaches and Current Research (Samarkand, 2021).
7. 83rd International Medical Congress of Young Scientists "Actual problems of theoretical and clinical medicine" (Donetsk, 2021).
8. Scientific and practical conference of young scientists dedicated to the 30th anniversary of independence of the Republic of Uzbekistan "Immunology and genetics: modern achievements" (Tashkent, 2021).
9. International Scientific and Practical Conference "COVID-19 and other topical infections of Central Asia" (Shymkent, 2022).
10. IX International Scientific Conference of Young Scientists and Students "Prospects of Development of Biology, Medicine and Pharmacy" (Shymkent, 2022)
11. Interdisciplinary Conference of Young Scientists "COVID-19. Clinic. Diagnosis. Treatment. Prevention" (Astana, 2023)
12. XVIII International (XXVII All-Russian) Pirogov Scientific Medical Conference of Students and Young Scientists (Astana, 2023)
13. I International Congress of Obstetricians and Gynecologists of Kazakhstan "Family Health - the Future of Kazakhstan" (Almaty, 2023)
14. National School on Infectious Diseases(Ufa,2023)

15. International Student Scientific Conference "V Interdisciplinary Scientific Forum" (Moscow, 2023)
16. I Congress of the Association of Infectious Diseases and Hepatology of Kyrgyzstan (Bishkek, 2023)
17. 11th International Scientific and Practical Conference "Current Issues of Medicine" and "V Satellite Forum on Public Health and Health Policy" (Baku, 2024)

### **Publications on the subject of the thesis.**

Based on the research materials, 19 printed works were published in periodicals, including: 6 publications in periodicals of Kazakhstan recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; 2 articles in English indexed in the Web of Science and Scopus information database with a percentile of 2022=61 (Netherlands) and 2023=51 (Iran); 11 publications in conference proceedings (Kazakhstan, Russia, Ukraine, Uzbekistan, Kyrgyzstan).

### **Approbation and implementation of the results of the research work.**

The obtained results of research are implemented in practical health care: "Algorithm COVID-19 in pregnant women (doctor's tactics)", "Assessment of the severity of COVID-19 in pregnant women using the WHO ABCDE approach" on the basis of the City Infectious Diseases Hospital of Shymkent (Appendix A); 3 certificates of registration of rights to the object of copyright: on the subject of the thesis "Questionnaire for pregnant women who had COVID-19 as a tool to study perinatal outcomes" №36414 from 05.02.2023, "COVID-19 algorithm in pregnant women (physician's tactics)", №36535 dated 01.06.2023, "COVID-19 in pregnant women (database)" №23606 dated 29.04.2021 (Appendices B, C).

### **Author's contribution to the study.**

During the research work, the author developed the methodological structure of the thesis (study design, inclusion and exclusion criteria), conducted statistical processing of the obtained results, prepared and published the results of the study in journals recommended by the Committee for Control in the Sphere of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, as well as reported at scientific and practical conferences. The author independently carried out the screening and recruitment of patients, collection of material, analysis.

### **Conclusions.**

1. A comparative analysis of clinical and laboratory data of patients from the Kazakh population with COVID-19 showed more pronounced changes in the form of a decrease in the saturation level in 28.2%, an increase in respiratory failure in 72.0%, an increase in the levels of C-reactive protein in 55.1%, ferritin in 30.7%, D-dimer in 30.0% in the group of pregnant women compared to non-pregnant patients ( $p < 0.05$ ). Complete recovery in the main group occurred 2.1 times less often, and deaths 1.6 times more often. Frequent complications in pregnant women with COVID-19 are: premature birth (19.4%), antenatal fetal death (2.0%) ( $p < 0.05$ ).
2. Analysis of perinatal outcomes of newborns revealed that women with COVID-19 coronavirus infection significantly more often give birth to children with short stature ( $p=0.002$ ), premature births ( $p=0.001$ ), with a lower Apgar score ( $p=0.001$ ), who are subsequently more often admitted to the neonatal pathology department ( $p=0.001$ ) than those born to women without COVID-19 coronavirus infection.

3. Women in the age group from 33 to 42 years (55%-35) and with a pregnancy period of 22-36 weeks (70%-42), who were given the etiotropic drug remdesivir, were at risk of developing a severe form of the disease. According to the clinical criteria considered, statistically significant efficacy of the drug was not confirmed in our study ( $p < 0.05$ ).

4. The developed algorithm for patient management tactics and assessment of the severity of COVID-19 using the WHO ABCDE approach made it possible to significantly reduce the number of complications (7.8%), diagnostic errors and reduce the time for identifying life-threatening conditions by 1.5 bed days ( $p < 0.05$ ). The introduction of these recommendations and algorithms into the practice of medical institutions increased the level of training of specialists, which contributed to improving the treatment outcomes for pregnant women with COVID-19 and reducing mortality.