# 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, thereare9,826 confirmed cases in27countries (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%), dyspnoea (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 labour (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, andoutcomes of COVID-19 coronavirus infection in pregnant women and the efficacy ofetiotropic treatment with remdesivir.

# Objectives of the study:

1.To study the features of clinical manifestations, frequency and nature ofcomplications, outcomes of the disease in pregnant women with COVID-19coronavirus infection in I,II,III trimesters.

2 To determine perinatal outcomes in women with COVID -19 coronavirus infection and the long-term follow-up of pregnant women with COVID -19.

 3. To evaluate the efficacy of the antiviral drug Remdesivir in pregnant women infected with COVID -19 coronavirus infection.

 4. To develop and implement recommendations reflecting the principles of early diagnosis, routing, and prevention of COVID-19 coronavirus infection 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-reactiveprotein, 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 centre of Shymkent, and the perinatal centre of Shymkent. We analyzed case histories of 410 women from December 2020 to February 2021

The inclusion criteria for the study were:

1. Pregnant women with a confirmed and probable case of COVID -19 coronavirus infection;
2. Receivingtreatmentinhospitalsandperinatalcentresin2020-2021. 3.Independence from race, nationality.

Exclusion Criteria:

1. PregnancywithoutcoronavirusinfectionCOVID-19;
2. Inabilitytofulfiltherequirementsofthestudy(difficulttocontactbirth mothers to collect catamnestic data, lack of understanding, rudeness);
3. Absence of pregnancy.

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,protocolNo.1of16.03.2021. All pftientss 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:

 1. For the first time in the Republic of Kazakhstan clinical manifestations, frequency of complications of coronovirus COVID-19 infection in pregnant women depending on trimesters were determined.

 2. Peculiarities of perinatal outcomes of pregnancy inwomenwithCOVID

19coronavirus infection and distant catamnesis were determined.

3. The efficacy of the etiotropic antiviral drug Remdesivir in pregnant womenwith COVID-19 coronavirus infection was studied.

# Practical relevance.

 1.An algorithm for assessing the severity of COVID-19 in pregnant women using the WHO ABCDE approach has been developed to facilitate early recognition oflife-threateningconditions,therebyimprovingtheprognosisofpregnantwomen

With COVID-19.

 2. We have created an algorithm of tactics for the management of pregnant women with coronavirus infection. This development facilitates the identification of this nosology and timely treatment measures proving the prognosis of this category of patients.

# The main points put forward for defence.

 1.The severityofCOVID-19 disease increases with increasing gestational age. Common complications in pregnant women with COVID-19 are: preterm labour, antenatal fetal death.

 2.Women with COVID-19 coronavirus infection are at risk of giving birth to babies with short stature, prematurity, and low Apgar scores.

 3.The use of etiotropic drug Remdesivir in pregnant women with COVID-19coronavirus infection statistically significantly does not lead to positive dynamics of temperature normalisation, respiratory rate, subjective reduction of dyspnoea, cough.

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

1. VIII nternational 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. Republicaninterdisciplinaryscientificconference"PandemicCOVID-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. Republicanscientific-practicalconferencewithinternationalparticipation "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 Gynaecologists 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)

# Publicationsonthesubjectofthethesis.

On the materials of the study published in periodicals 19 printed works, including: 4 publications in periodicals of Kazakhstan 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; 1 article in English in the indexed in the information base Thomson Reuters web of science and Scopus Cytosource with percentile 2022=61 (Iran); 14 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); 3certificates 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. Disease severity of COVID-19 coronavirus infection increased with increasing gestational age (209-50.9%) (p=0.000).Pregnant women with COVID-19had higher risk of preterm labour, antenatal fetal death compared to women with out the disease (p>0.05).

2 The analysis of perinatal outcomes of newborns revealed that women withCOVID-19 coronavirus infection are significantly more likely to give birth to babieswith low growth (p=0.002), premature (p=0.001), lower Apgar score (p=0.001), who subsequently stay in the neonatal pathology department more often (p=0.001) than those born to women without COVID-19 coronavirus infection.

3. Women at risk of severe disease were in the age group of 33 to 42 years(55%-35) and with gestational age of 22-36 weeks (70%-42), in whom the etiotropic drug remdesivir was used. According to the clinical criteria considered, statistically significant efficacy of the drug was not confirmed in our study (p>0.05).

4. Application of the WHO ABCDE severity assessment algorithm in pregnant women with coronavirus infection COVID-19 will reduce mortality, shorten the duration of treatment of coronavirus infection.