



ORIGINAL

Coronavirus impact on female reproductive system of fertile age: short-term and delayed consequences

Repercusiones de los coronavirus en el aparato reproductor femenino en edad fértil: consecuencias a corto plazo y diferidas

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ABSTRACT

Introduction: even though the COVID-19 pandemic has come to an end, several short-term and delayed consequences of coronavirus infection remain insufficiently studied, which determines the relevance of this study. The study aims to analyse the impact of coronavirus infection on the course of pregnancy and reproductive health of females of fertile age in different periods according to the data of medical institutions of Turkestan city.

Methods: the following research methods were used in the study: bibliographic, discrete statistics, cluster, and frequency analysis.

Results: in this study, 301 cases of pregnancy of females diagnosed with coronavirus infection of different severity were statistically analysed. The study examined several aspects related to the study group including duration of hospitalisation, number of previous pregnancies and deliveries, complications of pregnancy and delivery occurring on COVID-19, haematological parameters, and oxygen saturation levels of pregnant females. The main clinical features of pregnancies with COVID-19 were identified. Thus, the result of the study was an analysis of the presented statistical sample and a comprehensive review of the current literature on the short-term and delayed effects of coronavirus infection on the female reproductive system.

Conclusions: the results obtained are of significant practical importance for specialists in obstetrics, gynaecology, reproductology and public health because they can serve as a basis for the development of effective clinical recommendations and strategies for managing the reproductive health of females who have undergone coronavirus infection.

Keywords: Pregnancy Planning; Obstetric Care; COVID-19; Labour Complications; Infertility; Menstrual Disorders.

RESUMEN

Introducción: aunque la pandemia de COVID-19 ha llegado a su fin, siguen sin estudiarse suficientemente varias consecuencias a corto y largo plazo de la infección por coronavirus, lo que determina la pertinencia de este estudio. El objetivo del estudio es analizar el impacto de la infección por coronavirus en el curso del embarazo y la salud reproductiva de las mujeres en edad fértil en diferentes periodos según los datos de las instituciones médicas de la ciudad de Turquestán.

Métodos: en el estudio se utilizaron los siguientes métodos de investigación: bibliográfico, estadística discreta, análisis de conglomerados y de frecuencias.

Resultados: en este estudio se analizaron estadísticamente 301 casos de embarazo de mujeres diagnosticadas de infección por coronavirus de distinta gravedad. En el estudio se examinaron varios aspectos relacionados con el grupo de estudio, como la duración de la hospitalización, el número de embarazos y partos anteriores, las complicaciones del embarazo y el parto que se produjeron con COVID-19, los parámetros hematológicos y los niveles de saturación de oxígeno de las hembras embarazadas. Se identificaron las principales características clínicas de los embarazos con COVID-19. Así pues, el resultado del estudio fue un análisis de la muestra estadística presentada y una revisión exhaustiva de la bibliografía actual sobre los efectos a corto y a largo plazo de la infección por coronavirus en el sistema reproductor femenino.

Conclusiones: los resultados obtenidos revisten una gran importancia práctica para los especialistas en obstetricia, ginecología, reproductología y salud pública, ya que pueden servir de base para la elaboración de recomendaciones y estrategias clínicas eficaces para la gestión de la salud reproductiva de las mujeres que han sufrido una infección por coronavirus.

Palabras clave: Planificación del Embarazo; Atención Obstétrica; COVID-19; Complicaciones del Parto; Infertilidad; Trastornos Menstruales.

INTRODUCTION

In the context of Kazakhstan's national health programme, high priority is given to maternal and child health, as it directly affects fertility, demographic growth, and social well-being.⁽¹⁾ The COVID-19 pandemic has had a significant impact on all areas of health care, including obstetrics and gynaecology, which highlights the need for research on the impact of coronavirus infection on the reproductive system of females of fertile age. The global crisis caused by COVID-19 has triggered the emergence of several new risks and threats, requiring adaptation of the healthcare system to ensure the safety and health of both expectant mothers and new-borns.

Kazakh scientists studied the reproductive health of females of childbearing age during the coronavirus pandemic and in isolation. Zhaganova et al.⁽²⁾ analyzed the reproductive health of females in Kazakhstan, highlighting that female and child health is a key indicator of biosocial and economic well-being and reflects the effectiveness of the healthcare system. Researchers expressed concern about rising maternal mortality rates from 2018 to 2020, primarily due to complications from extragenital pathology.

The direct impact of coronavirus infection on the health of females of reproductive age was investigated by Dzhusupova et al.⁽³⁾ and Jainakbayev et al.⁽⁴⁾ They conducted a questionnaire survey among 204 COVID-19-exposed females aged 17-35 years, 54,4 % of whom had a history of completed pregnancies and 15,7 % of whom had undergone abortion. The researchers found that the most common complaints were hair loss, apathy, irritability, and cognitive impairment. The researchers' study focused on the general medical consequences of infection in females of reproductive age, while this study is focused on reproductive health.

Mereke et al.⁽⁵⁾ explored theoretical aspects of coronavirus infection in pregnant females, focusing on biochemical markers and their correlation with disease severity and childbirth outcomes. They concluded that more severe infections increased the risk of pregnancy and labor complications, a perspective not addressed in the current study. On the other hand, Dzhusupova and Seiduanova⁽⁶⁾ highlighted potential impacts of coronavirus on the female reproductive system, including prolonged forms of infection like post-COVID-19, ICU stays, medication side effects, and related conditions. They did not definitively determine how COVID-19 affects the reproductive system in females, an area this study aims to clarify. The study aims to analyse data on the impact of coronavirus infection on pregnancy based on information obtained from health facilities in Turkestan. The study will analyse both short-term and long-term consequences of the impact of coronavirus infection on the female reproductive system.

METHOD

Statistical data for the study were obtained by analysing medical records, including data from case histories, newborn medical records, diagnostic reports, and results of medical examinations. Baseline information related to the severity of coronavirus infection, multiplicity of pregnancy and delivery, general somatic condition of pregnant females and new-borns, as well as the results and methods of delivery. The information was extracted from the records of medical institutions and health authorities in Turkestan city. Thus, a statistical sample including 301 cases of pregnancy in 2020 was formed. Considering the size of the sample, and its polymorphism by age and nosological parameters, it is a representative data set for analysing broad population groups both in the Republic of Kazakhstan and in other countries.

The present sample was divided into several groups. The main purpose of dividing pregnant females into

groups (mild, moderate, and severe forms of COVID-19) was to carefully analyse the impact of coronavirus infection of different severity on the course of pregnancy and female reproductive health. This allowed a better understanding of the variation in clinical scenarios and their impact on pregnancy outcomes.

In this study, part of the diagnoses was billed according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code as U07,1, indicating a laboratory-confirmed case of COVID-19. In the other part, COVID-19 was classified as U07,2, indicating a clinically confirmed case based on characteristic symptoms and clinical examination without laboratory confirmation.⁽⁷⁾ This separation provided an opportunity to study the impact of different clinical variants of COVID-19 more accurately on pregnancy and reproductive health of females. Important physiological parameters including blood oxygen saturation, haematocrit and platelet count were also systematically measured and monitored on admission and discharge from the obstetric hospital. The study sample structure is shown in figures 1 and 2.

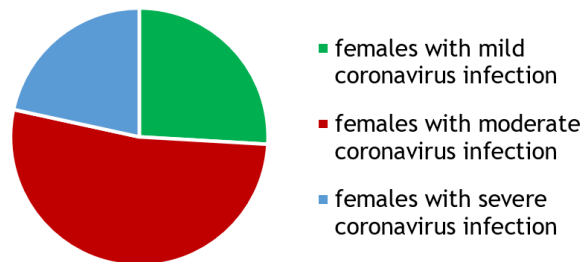


Figure 1. The nosological structure of the study group depends on the severity of the course of the coronavirus infection

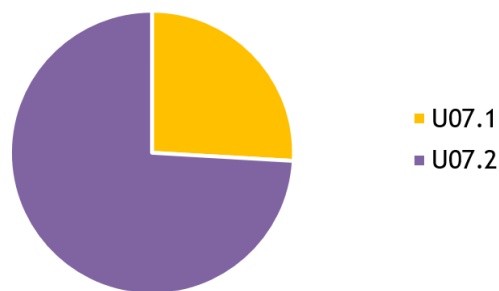


Figure 2. The nosological structure of the study group depends on the ICD-10 diagnostic code used for the diagnosis of coronavirus infection

To analyse the statistical sample in detail, a variety of scientific methods were used. In this study, the method of discrete statistics was used to analyse and interpret categorical data such as multiplicity of pregnancy and delivery, and numerical indicators of analyses of somatic condition of pregnant females and new-borns. The application of discrete statistics allowed for the description and identifying relationships between categories and determining the statistical significance of differences between them. The method of frequency analysis was applied to study in more detail the distribution of parameters in the group. This method was used to determine the frequency of different categories such as severity of infection and pregnancy outcomes. The method of cluster analysis was used to examine the structure in more detail, the use of this method made it possible to identify subgroups based on the similarities between the different variables. The use of this method was used to identify groups of pregnant females with similar characteristics and to determine which factors have a similar impact on the reproductive system.

A search and analysis of the current scientific literature was conducted to gain a deeper understanding of the main global trends in the field under review and to optimise the substantiation of conclusions and recommendations. The search was performed using a bibliographic method and covered authoritative scientometric databases including CINAHL, Web of Science, Cochrane Library, Science Direct, PubMed and EMBASE. The search covered literature published between 2019 and 2023, allowing the selection of the 20 best-performing sources.

RESULTS

Pregnant females in the study sample were subject to both planned and emergency hospitalisation in an obstetric hospital, the mean duration of hospitalisation was 27,3 weeks (5 to 40 weeks, mean standard deviation (σ) was 10,7), the mode was 37 weeks, and the median (Me) was 30. The distribution of these parameters between the groups is presented in Table 1. The study revealed a trend towards earlier hospitalisation in

females with severe coronavirus infection, indicating that this variant of the disease course may lead to early complications requiring medical intervention. Statistical indicators confirm that pregnant females with severe COVID-19 were more likely to be hospitalised earlier in pregnancy. There was also a significant variation in the timing of hospitalisation, which may be related to individual characteristics of the course of pregnancy and infection. These data emphasise the need for closer monitoring and early intervention in pregnant females with severe COVID-19.

Table 1. Gestational age (in weeks), at the time of admission to an obstetric hospital, in females with coronavirus infection, depending on the severity of the disease

Group	Amount of females	Average value (μ)	Mode	Me	σ
Females with mild coronavirus infection (weeks)	78	27,96	36	31	10,2
Females with moderate coronavirus infection (weeks)	158	28,3	35	31	11,14
Females with severe coronavirus infection (weeks)	65	24,24	31	27	9,77

A clear correlation between the severity of coronavirus infection and oxygen saturation levels was found: the more severe the course of COVID-19, the lower both initial and follow-up values, indicating a significant impact of the infection on the quality of gas exchange in pregnant females. All subgroups showed an overall improvement in mean oxygen saturation values by the time of discharge. The standard deviation was significantly higher in the severe subgroup, indicating a greater variation in values and potentially a more unpredictable course of the disease. Information regarding oxygen saturation levels in the study sample is presented in table 2.

Table 2. Saturation values at the time of hospitalization and discharge from the obstetric hospital, in females with coronavirus infection, depending on the severity of the disease

Group	At hospitalisation				At discharge			
	μ	Mode	Me	σ	μ	Mode	Me	σ
Among the full sample (%)	95,58	95	94	2,3	97,39	98	96	1,11
Females with mild coronavirus infection (%)	96,36	95	96,5	1,39	97,58	97	98	1,02
Females with moderate coronavirus infection (%)	95,7	94	96	1,98	97,4	96	98	1,27
Females with severe coronavirus infection (%)	94,8	95	91	3,3	97,1	96	98	1,12

The haematocrit study was aimed at identifying possible risks associated with the aggravation of the general condition of females against the background of physiological haemodilution in pregnancy, as well as potential complications due to impaired placental circulation. The haematocrit level correlated only partially with the severity of COVID-19 and did not reach the values characteristic of oxygen saturation in this context. There was an overall slight increase in mean values by the time of discharge. However, the subgroups showed different patterns of haematocrit change, which may reflect differences in COVID-19 exposure and response. There was a higher variation (standard deviation) at the time of hospitalisation, especially in the subgroups with moderate and severe disease severity. Data regarding the haematocrit parameter are shown in table 3.

Table 3. Haematocrit values at the time of admission and discharge from the obstetric hospital, in females with coronavirus infection, depending on the severity of the disease

Group	At hospitalisation				At discharge			
	μ	Mode	Me	σ	μ	Mode	Me	σ
Among the full sample (%)	30,77	27	30	4,6	31,76	30	33,2	2,45
Females with mild coronavirus infection (%)	30,01	29	32,42	3,94	32,42	31,2	33,2	1,32
Females with moderate coronavirus infection (%)	30,47	28,1	30,2	5,02	31,68	30,3	2,23	32,2
Females with severe coronavirus infection (%)	31,89	27,4	32,2	3,91	31,69	29,1	32,8	3,38

Source: Own elaboration.

Platelet counts were analysed to identify probable episodes of increased coagulation that could cause thromboembolic complications in the early postpartum period, as well as cases of decreased platelet counts associated with the development of obstetric haemorrhage during and after delivery.

The study also identified a variety of complications. The most common extragenital complications identified during the study were those related to the respiratory system. There were 206 pregnant females (68,6 %) with such complications. The most common complication was community-acquired pneumonia diagnosed in 148 patients (47 % of all pregnant females and 72 % of females with respiratory system pathology). Of these, 106

cases (71 %) had bilateral lung involvement and 34 (23,65 %) had unilateral lung involvement. In addition, in 68 cases (45 %) pneumonia had a lower lobe localisation. There were also 6 (4 %) cases of subtotal and 2 (1,35 %) cases of total lung involvement. Furthermore, 30 patients had mixed bacterial-viral pneumonia. Bronchitis was detected in 28 pregnant females (9,2 % of all and 13,5 % among respiratory diseases). Bronchopneumonia was diagnosed in 30 (9,7 % and 14,5 %, respectively). Two cases of bilateral pneumonia developed acute respiratory distress syndrome. Anaemia was noted in 20 % of all examined patients (62), and two cases were assessed as severe. In 77,6 % (48 patients) anaemia was associated with respiratory diseases. There were also isolated cases of subclinical hypothyroidism, pyelonephritis, cystitis, tubulointerstitial nephritis, conjunctivitis, and liver cysts, which did not affect the pregnancy.

Table 4. Platelet counts at the time of hospitalisation and discharge from obstetric hospital, in females with coronavirus infection, depending on the severity of the disease

Group	At hospitalisation			At discharge		
	μ	Me	σ	μ	Me	σ
Among the full sample (thousand/ μ L)	257,7	244	82,69	294,26	303	82,14
Females with mild coronavirus infection (thousand/ μ L)	245,1	236	67,45	286,28	303	38,27
Females with moderate coronavirus infection (thousand/ μ L)	257,64	244	75,85	291,62	303	88,1
Females with severe coronavirus infection (thousand/ μ L)	261,63	246	104,51	302,77	303	81,47

In the study, 42 cases of obstetric complications (13,5 %) and 20 cases of complications during labor and postpartum (6,3 %) were observed. Labor complications included umbilical cord issues, premature rupture of membranes, and abnormal fetal presentation. Caesarean sections were performed in 36 cases, 22 of which were elective, primarily due to severe maternal respiratory conditions or fetal heartbeat changes. Severe pre-eclampsia was found in 8 cases (2,5 %), all linked to severe respiratory issues. Two postpartum cases required relaparotomy due to atonic uterine bleeding, leading to severe posthemorrhagic anemia associated with severe pneumonia. Thromboembolic complications occurred in 2 cases, related to pulmonary artery thromboembolism and varicose veins. There were 6 stillbirths, with no neonatal deaths reported, indicating high-quality care. Apgar scores at 1 minute were: 0 points (1,9 %), 6 points (4,17 %), 7 points (50,83 %), and 8 or more points (43,1 %). At 5 minutes, scores improved to 0 points (1,9 %), 7 points (3,98 %), and 8 or more points (94,12 %). Mechanical asphyxia occurred in 18 neonates (5,9 %), and 52 newborns were hospitalized for respiratory failure, often correlated with maternal COVID-19 severity. Three neonates required ventilators, and 8 were treated with the Bobrov apparatus, with an average ICU stay of 7 days. Notably, 77,9 % of neonates did not require oxygen support.

New-borns in the study were frequently underweight, as indicated in Table 5. The analysis revealed a significant link between maternal COVID-19 infection and the risk of low birth weight. However, on average, there was no substantial correlation between newborn birth weight and the severity of maternal COVID-19. Notably, severe COVID-19 cases showed increased standard deviations in neonatal weight, indicating greater variability in this measure among affected infants. This variability may stem from individual responses to severe COVID-19, potentially impacting fetal growth due to conditions like hypoxia. These findings underscore the importance of closely monitoring such patients and providing timely medical interventions to mitigate risks associated with neonatal weight abnormalities.

Group	μ (mg)	Me	σ
Among the full sample (g)	3365,31	3500	801,8
Children born to females with mild coronavirus infection (d)	3379,6	3540	602,29
Children born to females with moderate coronavirus infection (d)	3376,92	3500	766,53
Children born to females with severe coronavirus infection (d)	3337,551	3470	981,36

In the study, 301 pregnancies in females with COVID-19 were analyzed statistically. Factors such as duration of hospital admission and results from tests including oxygen saturation, hematocrit, and platelet count at admission and discharge were considered. COVID-19 was associated with increased risks for various complications in both mothers and neonates. Common complications included pneumonia of varying severity, bronchopneumonia, respiratory distress syndrome, threatened pregnancy termination, premature rupture of membranes, and thromboembolic and hemorrhagic complications during the postpartum period. The study documented 6 cases of stillbirth and hospitalization of 52 newborns in the anaesthesiology and intensive care unit.

DISCUSSION

A similar correlation between the severity of the course of the disease and the dynamics of the treatment background was revealed for the platelet count. There is a clear relationship between severity and starting values: severe cases show lower starting values and greater variability. Improvement of values by the time of discharge indicates the effectiveness of treatment and recovery of body functions, while the greater variation in values in severe cases emphasises the need for an individual approach to treatment and monitoring. The data concerning platelet counts in the study sample are summarised in Table 4. This formalised approach to the measurement and analysis of these parameters provides a more accurate assessment of the general health of pregnant females in the context of coronavirus infection and provides a basis for adequate medical intervention.

Thus, the severity of COVID-19 in the mother correlates with the frequency of complications of pregnancy and labour, as well as with the condition of the newborn. It is indicative that with the increasing severity of COVID-19 in mothers, there was no significant decrease in the average weight of new-borns, but an increase in the mean standard deviation of this parameter was registered. ^(8,9,10) This observation indicates an increased risk of extremely low birth weight in several individual cases, which requires close attention of medical personnel for early detection of such situations and prompt medical care. The data obtained in the study should be correlated with the results of studies conducted by foreign colleagues. It is also important to supplement the material regarding the effect of COVID-19 on the female reproductive system, pathogenetic mechanisms and delayed effects. ⁽¹¹⁾⁻⁽¹³⁾

Magalhães and Sampaio-Rocha-Filho⁽¹⁴⁾ examined the impact of coronavirus infection on birth outcomes and the nervous system, assessing the risk of neurological disorders in pregnant females with COVID-19. They found that although pregnant females with COVID-19 have a higher risk of preterm labor and surgical delivery, birth outcomes and mortality rates are similar to those of healthy pregnant females. Additionally, COVID-19 patients have a higher risk of developing neurological symptoms compared to the general population, which is particularly true for pregnant females over 50. ⁽¹⁵⁾⁻⁽¹⁷⁾ This study supports these findings, emphasizing the neurological impact of COVID-19 on pregnant females while omitting factors such as neonatal status, clinical and laboratory conditions, and delayed reproductive outcomes. ⁽¹²⁾

Mark et al.⁽¹⁸⁾, Khan et al.⁽¹⁹⁾ conducted an extensive review of perinatal outcomes for females with coronavirus infection and their newborns. They identified common pregnancy complications, including preterm labor, caesarean sections, thromboembolic and hemorrhagic issues, and respiratory decompensation. The study highlighted a caesarean section rate of 57 %, significantly higher than the WHO recommended 21 %, and a preterm labor rate of 28 %, compared to the recommended 11 %. Additionally, there was a high incidence of respiratory failure and respiratory distress syndrome in newborns. ⁽²⁰⁾

Many researchers have examined the impact of COVID-19 on pregnancy, reproductive health, and obstetric services. Liu et al.⁽²¹⁾ and Li et al.⁽²²⁾ analyzed data from the Canadian Institute for Health Information, including 136,445 hospital deliveries, to study birth frequencies, preterm births, and stillbirths during the first wave of the pandemic. They found a decrease in early pregnancy obstetric interventions in 2020, while preterm birth rates remained stable. Stillbirth rates were generally stable but peaked in Ontario in April 2020. These changes were attributed to healthcare system modifications during the pandemic, such as quarantine measures and hospital distancing, rather than the direct impact of the virus.

Henarejos-Castillo et al.⁽²³⁾ and Taşkaldıran et al.⁽²⁴⁾ investigated the impact of coronavirus on the female reproductive system, particularly focusing on uterine tissue damage. They found that the virus's pathogenicity and tissue damage depend on its ability to penetrate and replicate in specific cells, aided by enzymes like cathepsins B and L, furin, and neutrophil elastase. While ACE2 levels are low in endometrial cells, the expression of basigin, furin, cathepsins, and TMPRSS4 can facilitate virus entry. The study noted that older females might be more susceptible due to higher ACE2 levels.

The impact of infection on new-borns was addressed by Wróblewska-Seniuk et al.⁽²⁵⁾ and Ghema et al.⁽²⁶⁾ After studying several perinatal outcomes in mothers with COVID-19 of varying severity, the researchers concluded that, despite the low probability, vertical transmission still occurred in the studied sample. The main risks for new-borns in this context were pathologies from the group of respiratory and digestive system disorders. ^(27,28) These results are consistent with available data on perinatal outcomes, but both vertical infection and episodes of gastrointestinal complications were absent in this study.

The study results were compared with similar studies of foreign colleagues, and additional material on the effects of coronavirus infection on the female reproductive system, their main manifestations and the pathogenetic basis of the process was reviewed.

CONCLUSIONS

The study results indicate that COVID-19 does not directly affect pregnancy and fetal development pathologically. However, it significantly worsens the overall health of pregnant women, indirectly impacting

pregnancy outcomes. Severe cases of COVID-19 increase the risk of complications during the antenatal, intrapartum, and postnatal periods, with pneumonia being the most common issue. This can lead to respiratory failure, acute respiratory distress syndrome, and the necessity for emergency cesarean sections. Other complications include premature placental detachment, fetal growth retardation due to placental insufficiency, anemia, and thrombocytopenia, which heighten the risk of bleeding during labor and postpartum. Newborns from mothers with COVID-19 are at a higher risk of respiratory failure and infectious complications due to prematurity and low birth weight.

The study also explored the impact of COVID-19 on the female reproductive system. It found that direct infection of ovarian cells by SARS-CoV-2 is unlikely due to the lack of necessary receptors and cofactors. Thus, COVID-19 does not directly disrupt folliculogenesis and oogenesis. However, over a third of reproductive-age women experience menstrual cycle disorders due to stress, systemic inflammation, and endometrial damage linked to ACE2 receptors. These factors indirectly affect reproductive function. Despite the absence of direct pathogenic effects, COVID-19 significantly complicates pregnancy and childbirth, increasing the incidence of maternal and fetal complications.

Future research on this topic entails a detailed analysis of existing scientific data and the generation of new knowledge regarding the impact of coronavirus infection on the reproductive systems of fertile-aged females. It is crucial to address gaps in understanding the virus's mechanisms affecting pregnancy, identify potential long-term consequences, and develop effective treatment and prevention methods.

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