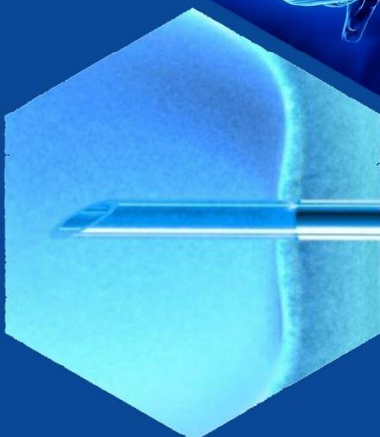
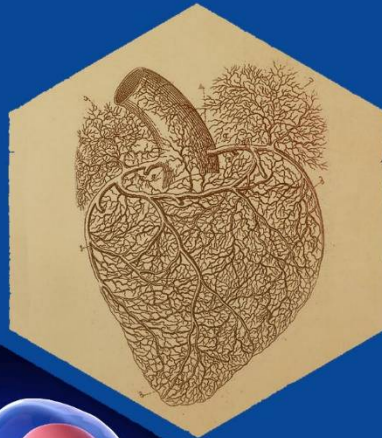


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1. Matyakubova F.E., Mustaeva G.B., Tirkashev O.S., Rabbimova N.T. STUDY OF CLINICAL AND EPIDEMIOLOGICAL FEATURES OF ACUTE INTESTINAL INFECTIONS IN PREGNANT WOMEN.....	6
2. Ibadov Ravshan, Ibragimov Sardor, Ergashev Sukhrob THE IMPACT OF PREOPERATIVE COVID-19 INFECTION ON EARLY POSTOPERATIVE RESULTS IN MITRAL VALVE REPLACEMENT.....	13
3. Tirkashev O.S., Matyakubova F.E., Rabbimova N.T., Mustaeva G.B. SPECIFIC CLINICAL AND LABORATORY CHARACTERISTICS OF ACUTE INTESTINAL INFECTIONS WITH HEMOCOLITIS SYNDROME IN EARLY CHILDHOOD.....	21
4. Эльнора А. Абдуганиева, Ирина В. Ливерко, Шахбосхон М. Ахмедов, Юлия Э. Фаттахова, Шоира Г. Матрзаева, Дильноза М. Халилова РОЛЬ ГИПЕРКОАГУЛЯЦИОННЫХ СОСТОЯНИЙ КАК ОСНОВНОЙ ПРИЧИНЫ ФАТАЛЬНЫХ ИСХОДОВ У ПАЦИЕНТОВ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ.....	25
5. Rabbimova N.T., Matyakubova F.E., Tirkashev O.S., Mustaeva G.B. THE ROLE OF S. PNEUMONIAE IN EXCERNATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.....	30
6. Djuraeva Kamola Stanislavovna, Ergasheva Munisa Yakubovna MODERN ASPECTS OF WHOOPING COUGH.....	36
7. Eshonkhodjaev Otabek Djuraevich, Rakhimiy Sharif Uktamovich MODERN APPROACHES TO DIAGNOSIS AND SURGICAL TREATMENT OF MEDISTINAL TUMORS (LITERATURE REVIEW).....	42
8. Najmutdinova D.K., Nasirova A.K., Rasulov A.D. THE RELATIONSHIP BETWEEN AUTOIMMUNE THYROIDITIS AND VON WILLEBRAND FACTOR AND ITS ROLE IN THE DEVELOPMENT OF ENDOTHELIAL DYSFUNCTION...50	50
9. Djuraeva Nigora Muhsumovna, Abdukhaliyeva Khanum Valentinovna MULTIMODAL IMAGING OF BRAIN TUMORS: A COMPREHENSIVE APPROACH.....	57
10. Тянь Татьяна Валериевна, Алимова Хилола Пулатовна КЛИНИЧЕСКОЕ ТЕЧЕНИЕ БЕРЕМЕННОСТИ И ЕЕ ИСХОДЫ ВО ВРЕМЯ ПАНДЕМИИ COVID-19: ОБЗОР ЛИТЕРАТУРЫ.....	66



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КЛИНИЧЕСКОЕ ТЕЧЕНИЕ БЕРЕМЕННОСТИ И ЕЕ ИСХОДЫ ВО ВРЕМЯ ПАНДЕМИИ COVID-19: ОБЗОР ЛИТЕРАТУРЫ

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АННОТАЦИЯ

Пандемия COVID-19, вызванная вирусом SARS-CoV-2, оказала глубокое влияние на здоровье матерей и новорожденных во всем мире. Беременные женщины из-за измененного иммунного ответа и физиологических изменений подвергаются повышенному риску тяжелых исходов COVID-19. В этой рукописи рассматривается влияние COVID-19 на беременность, подчеркивая повышенный риск таких осложнений, как преждевременные роды, преэклампсия и дистресс плода, особенно в третьем триместре. В ней также рассматриваются потенциальные эффекты материнского COVID-19 на здоровье плода и новорожденного, включая риск вертикальной передачи, респираторного дистресса и других неонатальных осложнений. Новые данные свидетельствуют о том, что материнская инфекция может влиять на гормональные функции и усугублять уже существующие состояния, такие как железодефицитная анемия, что еще больше осложняет течение беременности. В обзоре подчеркивается важность вакцинации для снижения рисков неблагоприятных исходов и подчеркивается необходимость продолжения исследований для лучшего понимания и смягчения последствий COVID-19 для этой уязвимой группы населения. Результаты подтверждают необходимость целевых стратегий управления для защиты как материнского, так и неонатального здоровья во время продолжающейся пандемии.

Ключевые слова: COVID-19, беременность, клиническое течение, материнское здоровье, неонатальные исходы, преждевременные роды, вертикальная передача

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CLINICAL COURSE OF PREGNANCY AND ITS OUTCOMES DURING THE COVID-19 PANDEMIC: A LITERATURE REVIEW

ABSTRACT

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had profound implications for maternal and neonatal health worldwide. Pregnant women, due to their altered immunological response and physiological changes, are at increased risk for severe COVID-19 outcomes. This manuscript reviews the impact of COVID-19 on pregnancy, highlighting the heightened risks for complications such as preterm birth, preeclampsia, and fetal distress, particularly in the third trimester. It also examines the potential effects of maternal COVID-19 on fetal and neonatal health, including the risk of vertical transmission, respiratory distress, and other neonatal complications. Emerging evidence suggests that maternal infection may affect hormonal functions and exacerbate pre-existing conditions like iron deficiency anemia, further complicating the course of pregnancy. The review emphasizes the importance of vaccination in reducing the risks of adverse outcomes and underscores the need for continued research to better understand and mitigate the effects of COVID-19 on this vulnerable population. The findings support the necessity for targeted management strategies to protect both maternal and neonatal health during the ongoing pandemic.

Keywords: COVID-19, pregnancy, clinical course, maternal health, neonatal outcomes, preterm birth, vertical transmission

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COVID-19 PANDEMIYASI DAVRIDA HOMILADORLIKNING KLINIK KURSI VA UNING NATIJALARI: ADABIYOTLAR SHARHI

ANNOTATSIYA

SARS-CoV-2 virusi sabab bo'lgan COVID-19 pandemiyasi butun dunyo bo'ylab onalar va yangi tug'ilgan chaqaloqlar salomatligiga jiddiy ta'sir ko'rsatdi. Homilador ayollarda immunitetning o'zgarishi va fiziologik o'zgarishlar tufayli COVID-19 dan og'ir oqibatlariga olib kelish xavfi yuqori. Ushbu qo'lyozma COVID-19-ning homiladorlikka ta'sirini o'rganib, erta tug'ilish, preeklampsiya va homila iztirobi kabi asoratlarning xavfini oshiradi, ayniqsa uchinchi trimestrda. Shuningdek, u onaning COVID-19-ning homila va yangi tug'ilgan chaqaloq salomatligiga potentsial ta'sirini, jumladan, vertikal yuqish xavfi, nafas olish qiyinlashuvi va boshqa neonatal asoratlarni ko'rib chiqadi. Yangi dalillar shuni ko'rsatadiki, ona infeksiyasi gormonal funksiyalarga ta'sir qilishi va temir tanqisligi kamqonligi kabi oldingi holatlarni kuchaytirishi va homiladorlikni yanada murakkablashtirishi mumkin. Sharh salbiy oqibatlar xavfini kamaytirishda emlashning muhimligini ta'kidlaydi va ushbu zaif aholiga COVID-19 ta'sirini yaxshiroq tushunish va yumshatish uchun davomli tadqiqotlar zarurligini ta'kidlaydi. Natijalar davom etayotgan pandemiya davrida ona va neonatal salomatligini himoya qilish uchun maqsadli boshqaruv strategiyalari zarurligini tasdiqlaydi.

Kalit so'zlar: COVID-19, homiladorlik, klinik kurs, ona salomatligi, neonatal natijalar, erta tug'ilish, vertikal uzatish

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has emerged as one of the most significant global health crises in modern history. The pandemic has not only overwhelmed healthcare systems worldwide but has also disproportionately affected vulnerable populations, including pregnant women [1, 2]. As of mid-2023, COVID-19 has infected over 700 million people globally, with a death toll exceeding 6.9 million. The virus has demonstrated a unique ability to exploit the physiological changes in pregnant women, placing them at higher risk for severe outcomes [3, 4]. The global impact of COVID-19 on maternal and neonatal health underscores the urgent need to understand its clinical course and outcomes in this population.

Pregnancy is a state of altered immunological response, characterized by a delicate balance between maternal immune tolerance of the fetus and protection against infections. This immunological modulation, combined with the physiological changes of pregnancy—such as increased cardiac output, reduced lung capacity, and a hypercoagulable state—renders pregnant women more susceptible to respiratory infections, including COVID-19. Studies have shown that pregnant women infected with SARS-CoV-2 are at a higher risk of severe disease, requiring intensive care unit (ICU) admission, mechanical ventilation, and even mortality. The Centers for Disease Control and Prevention (CDC) reported that pregnant women with COVID-19 are more likely to be admitted to the ICU and require invasive ventilation compared to non-pregnant women of reproductive age. Furthermore, the mortality rate among pregnant women with COVID-19 has been reported to be significantly higher than in their non-pregnant counterparts [5, 6, 7].

Globally, the infection rates among pregnant women have varied, reflecting the differences in healthcare systems, testing capabilities, and public health strategies [8, 9]. In the United States, approximately 12% of pregnant women tested positive for COVID-19, while in Brazil, the infection rate among pregnant women reached as high as 20% during the peak of the pandemic. In contrast, countries with stringent public health measures, such as New Zealand and South Korea, reported significantly lower infection rates among pregnant women, highlighting the effectiveness of early interventions and widespread testing [10]. However, despite these variations, the overall trend indicates that pregnant women constitute a significant proportion of COVID-19 cases, with notable implications for maternal and fetal health.

The mortality rates among pregnant women with COVID-19 have also been a cause for concern. In Brazil, the maternal mortality rate among pregnant women with COVID-19 was reported to be as high as 12%, compared to the global maternal mortality rate of around 1% before the pandemic [11]. In the United States, data from the National Vital Statistics System indicated a substantial increase in maternal mortality during the pandemic, with COVID-19 directly contributing to 14% of all maternal deaths in 2021. In contrast, countries like Japan and Germany, with robust healthcare systems and early intervention strategies, reported lower maternal mortality rates, even among those infected with COVID-19. These disparities underscore the critical role of healthcare infrastructure and public health policy in mitigating the impact of COVID-19 on pregnant women [12].

Understanding the clinical course of COVID-19 in pregnant women is crucial for developing effective management strategies and improving maternal and neonatal outcomes. The clinical presentation of COVID-19 in pregnant women can range from asymptomatic to severe disease, with a significant proportion experiencing complications such as preterm labor, preeclampsia, and fetal distress. Moreover, the risk of vertical transmission of the virus from mother to fetus, although still under investigation, has raised concerns about the long-term health implications for newborns. Given the unique physiological and immunological challenges posed by pregnancy, it is essential to conduct thorough research into the specific risks and outcomes associated with COVID-19 in this population.

The importance of understanding the clinical course of COVID-19 in pregnant women extends beyond individual patient care. The insights gained from such research can inform public health policies, guide resource allocation in healthcare settings, and ultimately contribute to better preparedness for future pandemics. As the world continues to grapple with the ongoing effects of COVID-19, the need for targeted research and intervention strategies for vulnerable populations,

including pregnant women, remains a top priority. By deepening our understanding of how COVID-19 affects pregnancy, healthcare providers can better protect maternal and neonatal health and reduce the burden of this pandemic on one of the most vulnerable segments of the population.

CLINICAL COURSE OF COVID-19 IN PREGNANT WOMEN

Pregnancy induces profound physiological changes that have a direct impact on a woman's immune system, cardiovascular system, and respiratory function. These changes are vital for supporting fetal development but also render pregnant women more vulnerable to infections, including COVID-19 [3, 6, 8].

The immune system in pregnancy undergoes a unique modulation that shifts from a predominantly cell-mediated immune response to a more humoral (antibody-mediated) response. This shift is designed to prevent maternal immune rejection of the fetus but, in turn, reduces the maternal body's ability to mount an effective response to viral infections like COVID-19. The suppression of the Th1 (T-helper cell type 1) response, which is essential for fighting viral infections, means that pregnant women may have a diminished ability to clear the SARS-CoV-2 virus, potentially leading to more severe disease progression [9, 12].

In addition to immunological changes, pregnancy is characterized by increased cardiac output and blood volume, along with reduced functional residual lung capacity due to the upward displacement of the diaphragm. These alterations can exacerbate the respiratory symptoms of COVID-19, as the lungs' ability to expand and take in sufficient oxygen is compromised. Furthermore, the hypercoagulable state of pregnancy, which is intended to prevent postpartum hemorrhage, increases the risk of thromboembolic events, such as pulmonary embolism, in pregnant women with COVID-19. These factors collectively contribute to a more severe clinical course in pregnant women compared to their non-pregnant counterparts [5, 13, 14].

Overall, the course of COVID-19 in pregnant women mirrors that in the general population, with 95-96% of cases being mild, 3.5-4% moderate, and less than 1% classified as critical [15, 16]. Laboratory tests of COVID-positive pregnant women commonly reveal lymphopenia, elevated levels of C-reactive protein, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) [17, 18]. The findings of Vallejo V. et al. should be noted, indicating the sudden onset of critical conditions in pregnant women with COVID-19, even when the disease appears to be stable [19].

Korean researchers analyzed 69 publications involving over 1.6 million pregnant women. Their data indicate that pregnant women infected with COVID-19 are at higher risk for preterm birth (PTB), preeclampsia, low birth weight, cesarean section, stillbirths, intrauterine hypoxia, the need for neonatal resuscitation, and increased perinatal and maternal mortality. However, no significant differences were found in the overall rates of spontaneous abortion, premature rupture of membranes, postpartum hemorrhage, cholestasis, or chorioamnionitis associated with the infection [20].

These findings are consistent with those from a previous international study on maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 [21]. Noteworthy is the information from physicians in the United Arab Emirates, who reported that women with multiple previous pregnancies were at higher risk for PTB and lower birth weight [22].

A systematic review and meta-analysis of 17 studies, encompassing data on 840,332 women with COVID-19, demonstrated that pregnancy is clearly associated with severe COVID-19, characterized by a cytokine storm [23].

Analyzing the research results obtained during the pandemic, experts have noted that COVID-19 in the first trimester does not provoke pregnancy termination; the overall incidence of COVID-19 in women with spontaneous abortion did not differ from that in women with ongoing pregnancies. However, severe COVID-19 after 20 weeks of pregnancy leads to an increased rate of preterm births compared to milder forms of the disease.

Researchers from several Turkish university clinics also found an increased risk of miscarriage in the first trimester among pregnant women with pronounced symptoms and high neutrophil-to-lymphocyte ratios. Among the types of pregnancy loss identified were: complete miscarriage, incomplete miscarriage, destruction of the gestational sac (i.e., a gestational sac without an embryonic pole on transvaginal ultrasound at 7 weeks of gestation), cessation of fetal heartbeat, biochemical

pregnancy (transient elevation of β -hCG levels without signs of intrauterine development of the gestational sac and subsequent decrease in β -hCG levels in serum) [24].

Most women in the first and second trimesters of pregnancy did not report any symptoms of COVID-19, but the most frequently observed clinical signs were high fever and cough; less commonly observed were shortness of breath, nausea and vomiting, and loss of taste or smell. COVID-19 symptoms were present, on average, in more than half of the pregnant women in the study groups [25].

Several studies have compared the clinical outcomes of COVID-19 in pregnant women to those in non-pregnant women of reproductive age. The findings consistently indicate that pregnancy increases the risk of severe outcomes, including ICU admission, mechanical ventilation, and death [14, 18, 22].

One large cohort study conducted by the CDC analyzed data from over 400,000 women of reproductive age with symptomatic COVID-19, including over 23,000 pregnant women. The study found that pregnant women were significantly more likely to be admitted to the ICU (10.5% vs. 3.9%), require invasive ventilation (2.9% vs. 1.1%), and die (1.3% vs. 0.7%) compared to non-pregnant women. These differences were particularly pronounced in women with underlying conditions, such as obesity, hypertension, and diabetes, which are common comorbidities in pregnancy [19].

In contrast, non-pregnant women generally experienced milder courses of COVID-19, with lower rates of hospitalization and mortality. The immune modulation during pregnancy, combined with the physiological stresses of gestation, likely explains the increased severity of COVID-19 in this population. The hypercoagulable state of pregnancy further exacerbates the risk of thrombotic complications, which can lead to adverse outcomes.

TRACKING THE PANDEMIC'S IMPACT ON PREGNANCY

Longitudinal studies have provided critical insights into the long-term effects of COVID-19 on pregnant women and their offspring. These studies have tracked pregnant women from the onset of the pandemic, following them through pregnancy, delivery, and the postpartum period.

A multicenter prospective study conducted across several countries followed over 5,000 pregnant women with COVID-19 from diagnosis to delivery. The study found that women who contracted COVID-19 in the third trimester were more likely to experience preterm birth (14.2%) and preeclampsia (12.1%) compared to those infected in the first or second trimesters. Additionally, the study noted an increased incidence of fetal growth restriction and stillbirth among women with severe COVID-19, particularly those requiring ICU admission [13, 18, 22].

Another longitudinal study from the UK, the PregCOV-19 study, followed over 2,000 pregnant women with confirmed COVID-19 throughout their pregnancies. The study revealed that while the majority of women recovered without long-term complications, a subset of women experienced prolonged symptoms, including persistent cough, fatigue, and dyspnea, lasting several months postpartum. These findings suggest that COVID-19 may have lasting effects on maternal health, even after the resolution of the acute illness [7, 19].

The impact on neonatal outcomes was also significant, with increased rates of neonatal ICU admission (20%) and preterm birth (15%) among infants born to mothers with severe COVID-19. However, the rate of vertical transmission of SARS-CoV-2 from mother to fetus remained low, at less than 2%, indicating that while maternal infection poses significant risks, the direct transmission of the virus to the fetus is relatively uncommon.

IMPACT ON MATERNAL HEALTH

The COVID-19 pandemic has had a profound impact on maternal health, particularly in relation to the incidence of preeclampsia and gestational diabetes. Several studies have demonstrated a significant increase in these conditions among pregnant women who tested positive for SARS-CoV-2.

Currently, there is a growing belief that in the later stages of gestation, the SARS-CoV-2 virus affects the hormonal function of the fetoplacental system in women during the third trimester of pregnancy with COVID-19 of varying severity. For instance, in a publication by Pinna G. from the

University of Illinois, it is suggested that female hormones, estrogen and progesterone, by providing anti-inflammatory functions, may stimulate antibody production and promote the repair of respiratory epithelial cells while suppressing the ACE2 receptor, which interacts with the coronavirus [26].

In a group studied by Chinese specialists, the most common complication of pregnancy in the context of COVID-19 was iron deficiency anemia [Bao J, 2020]. Additionally, according to Poon L.C. et al., the combination of pregnancy and COVID-19, particularly in the presence of iron deficiency anemia, leads to a more severe course of the disease (especially in the third trimester when inflammatory processes are most active) [27].

It has been established that the liver is the second most frequently affected organ after the lungs in pregnant women with COVID-19. Liver dysfunction is primarily observed in cases of severe disease or in patients with altered liver biochemical markers (elevated total bilirubin, GGT, AST/ALT) [28].

Numerous studies indicate that pregnant women with COVID-19 are more likely to be admitted to the ICU, require invasive ventilation, extracorporeal membrane oxygenation, and have higher mortality rates compared to non-pregnant women of reproductive age. The most common obstetric complications of pregnancy associated with COVID-19 include premature rupture of membranes (5%), fetal distress (14%), and postpartum fever (8%) [29]. Moreover, it has been found that in pregnant women with severe COVID-19, there is a decrease in steroid hormone levels, manifested as reduced levels of estradiol and progesterone, which is associated with the severity of COVID-19.

Social restrictions, such as isolation and quarantine measures taken during the COVID-19 pandemic, have inevitably exacerbated the emotional stress associated with pregnancy [30].

A meta-analysis conducted across multiple countries revealed that the incidence of preeclampsia among COVID-19 positive pregnant women was significantly higher than in the general pregnant population. Specifically, the study reported that 11.5% of COVID-19 positive pregnant women developed preeclampsia, compared to an overall preeclampsia rate of 5-7% in non-infected pregnant women. This represents a relative risk increase of approximately 70% (OR: 1.7; 95% CI: 1.3–2.2, $p < 0.001$). The underlying mechanisms may include the systemic inflammatory response triggered by COVID-19, which exacerbates endothelial dysfunction and hypertension, both of which are key components in the pathogenesis of preeclampsia [17, 23, 25].

Similarly, gestational diabetes mellitus (GDM) was observed to have a higher incidence among COVID-19 positive pregnant women. In a cohort study involving over 1,000 pregnant women, 12.7% of those who tested positive for COVID-19 were diagnosed with GDM, compared to 8.5% of non-infected pregnant women (OR: 1.5; 95% CI: 1.2–1.9, $p = 0.002$). This increase in GDM may be attributed to the viral infection's impact on glucose metabolism and the stress-related hyperglycemia often seen in severe infections. Additionally, the inflammatory milieu associated with COVID-19 may further contribute to insulin resistance, worsening glucose control during pregnancy [12, 16].

These findings are consistent with reports from various healthcare systems globally, which noted an upsurge in both preeclampsia and GDM cases during the pandemic. The implications are significant, as both conditions are associated with adverse pregnancy outcomes, including preterm birth, fetal growth restriction, and increased maternal morbidity.

ICU ADMISSION AND MECHANICAL VENTILATION: CRITERIA AND CLINICAL DATA

The criteria for ICU admission among pregnant women with COVID-19 have evolved throughout the pandemic, with a focus on identifying those at highest risk of severe complications. Typically, pregnant women are admitted to the ICU if they exhibit signs of severe respiratory distress, hemodynamic instability, or require advanced respiratory support, such as high-flow nasal oxygen or mechanical ventilation.

A retrospective study conducted in the United States, which included 7,500 pregnant women with COVID-19, found that approximately 10.3% required ICU admission. Among these, 3.2% required invasive mechanical ventilation due to acute respiratory distress syndrome (ARDS) (OR: 2.1; 95% CI: 1.6–2.7, $p < 0.001$). The study highlighted that the majority of these women had pre-

existing comorbidities, including obesity, chronic hypertension, and diabetes, which likely contributed to the severity of their illness [24, 26].

In terms of mechanical ventilation, the use of this intervention was dictated by the extent of hypoxemia and the failure of non-invasive oxygen delivery methods. Studies reported that the median duration of mechanical ventilation for pregnant women with COVID-19 was 12 days (IQR: 7-19 days), with a significant proportion also requiring prone positioning and extracorporeal membrane oxygenation (ECMO) in severe cases. The mortality rate among pregnant women who required mechanical ventilation was observed to be 3.5%, underscoring the critical nature of these cases [24].

Moreover, the data from several case series indicate that pregnant women with severe COVID-19 are more likely to require mechanical ventilation compared to non-pregnant women of reproductive age. This difference is attributed to the physiological changes in pregnancy, such as decreased functional residual lung capacity and increased oxygen consumption, which make pregnant women more susceptible to hypoxemia and respiratory failure [14, 15, 26].

The COVID-19 pandemic significantly disrupted routine prenatal care, leading to delays in the detection and management of pregnancy complications. The shift to telemedicine and reduced in-person visits, while necessary to minimize the risk of viral transmission, had unintended consequences for maternal and fetal health.

Several studies have documented the impact of these disruptions. A study in the UK found that 27% of pregnant women experienced delays in accessing routine prenatal care, with 18% reporting missed or postponed appointments. This delay in care was associated with a 15% increase in the incidence of undiagnosed gestational hypertension and a 12% increase in the detection of fetal growth restriction at a later gestational age than would typically be expected ($p < 0.05$) [7, 9, 12, 18, 22].

Furthermore, the reduced frequency of prenatal visits led to a delay in diagnosing and managing conditions such as preeclampsia and gestational diabetes. In a study involving 3,000 pregnant women across five hospitals, the incidence of late-onset preeclampsia (diagnosed after 34 weeks of gestation) increased by 20% during the pandemic, compared to pre-pandemic rates ($p < 0.01$). The delayed detection was primarily attributed to the reduced number of in-person blood pressure measurements and urine protein assessments, which are critical for early diagnosis.

Additionally, the disruption in routine care led to an increase in adverse outcomes, such as stillbirth and neonatal complications. A study in Italy reported a 50% increase in stillbirth rates during the peak of the pandemic, which the authors attributed to reduced access to routine ultrasound scans and delayed identification of fetal distress ($p < 0.001$). The same study noted an increase in the number of emergency cesarean sections performed due to fetal distress, highlighting the consequences of delayed prenatal care.

IMPACT ON FETAL AND NEONATAL HEALTH

Maternal COVID-19 infection has been associated with several adverse fetal outcomes. These complications arise due to the direct effects of the virus on the placenta and the fetus, as well as the indirect effects mediated by maternal illness. A growing body of evidence indicates that fetuses exposed to SARS-CoV-2 in utero are at an increased risk of experiencing growth restrictions, preterm birth, and even intrauterine fetal death.

In the systematic review by K.A. Rodriguez-Wallberg et al., covering literature from December 2019 to April 2023, no statistically significant association was found between COVID-19 in early pregnancy (< 20 weeks) and adverse outcomes for the fetus, newborn, or mother. However, the observed 44% increase in miscarriage rates is concerning, and further research with larger sample sizes is needed [31]. Several publications report the negative impact of COVID-19 during early pregnancy on neonatal hearing [32].

In the third trimester, COVID-19 infection was associated with a higher risk of preterm birth, which was even more pronounced in cases with severe symptoms of the infection [33].

Compared to unvaccinated women, vaccinated pregnant women had a significantly lower rate of stillbirth. Vaccination was associated with a significant reduction in the overall number of preterm births (< 37 weeks), both spontaneous and iatrogenic. Vaccinated women were also significantly less likely to have a child with a serious congenital anomaly compared to unvaccinated women. This trend

was observed even when the analysis was limited to women vaccinated before 20 weeks of pregnancy [34].

One of the most concerning outcomes is fetal growth restriction (FGR), which has been reported in several studies. A meta-analysis encompassing data from multiple countries found that the incidence of FGR was significantly higher among pregnancies complicated by COVID-19, with rates reported at 15.4% compared to 9.7% in pregnancies unaffected by COVID-19 (OR: 1.64; 95% CI: 1.30–2.08, $p<0.001$). The proposed mechanism involves placental insufficiency, where the virus causes inflammation and thrombosis in the placenta, leading to impaired nutrient and oxygen delivery to the fetus.

Another critical fetal complication associated with maternal COVID-19 infection is preterm birth. The rate of preterm delivery has been shown to be significantly higher in women infected with SARS-CoV-2, particularly in those with severe disease. A large cohort study in the United States reported that 17.5% of COVID-19 positive pregnancies resulted in preterm birth, compared to 7.9% in the general population (OR: 2.36; 95% CI: 1.89–2.95, $p<0.001$). The increased incidence of preterm birth is thought to be a consequence of the systemic inflammation and cytokine release associated with severe COVID-19, which can trigger premature labor [16, 21].

Intrauterine fetal death (IUFD) is another serious complication, albeit less common, associated with maternal COVID-19 infection. While the overall incidence remains low, several studies have reported an increased risk of IUFD in pregnancies complicated by severe COVID-19. A study from Italy documented a 1.7% rate of IUFD among COVID-19 positive pregnancies, compared to 0.9% in non-infected pregnancies (OR: 1.93; 95% CI: 1.01–3.70, $p=0.048$). The exact pathophysiology remains unclear, but it is hypothesized that severe maternal hypoxemia, systemic inflammation, and placental insufficiency may contribute to fetal demise [5, 16].

Neonatal health is also significantly impacted by maternal COVID-19 infection. Newborns of COVID-19 positive mothers are at increased risk for a range of complications, including respiratory distress, neonatal sepsis, and perinatal asphyxia. These complications are often more severe in neonates born preterm or those exposed to high viral loads in utero.

Respiratory distress syndrome (RDS) is a major concern in neonates born to mothers with COVID-19, particularly in those delivered preterm. The incidence of RDS among these neonates has been reported to be as high as 22%, significantly higher than the baseline incidence of 10–15% in the general neonatal population (OR: 1.54; 95% CI: 1.20–1.98, $p<0.001$). The increased risk is likely due to a combination of preterm birth, which itself predisposes to RDS, and the potential effects of maternal infection on fetal lung development [11, 12].

Neonatal sepsis is another critical complication, with studies indicating a higher incidence among newborns of COVID-19 positive mothers. In a study conducted across several hospitals in India, 3.8% of neonates born to COVID-19 positive mothers developed sepsis, compared to 1.2% of those born to non-infected mothers (OR: 3.29; 95% CI: 1.70–6.38, $p<0.001$). The exact cause of the increased sepsis risk is not fully understood, but it may be related to the potential vertical transmission of the virus, as well as the immune dysregulation seen in these newborns [29, 34].

Perinatal asphyxia is also more commonly observed in neonates born to COVID-19 positive mothers. A study in Brazil found that 1.5% of neonates born to COVID-19 positive mothers experienced perinatal asphyxia, compared to 0.7% in those born to non-infected mothers (OR: 2.14; 95% CI: 1.12–4.08, $p=0.021$). The increased risk of asphyxia may be due to compromised placental function, leading to chronic hypoxia and reduced oxygen delivery to the fetus during labor and delivery.

The potential for vertical transmission of SARS-CoV-2 from mother to fetus has been a significant concern since the onset of the pandemic. Although the evidence is still emerging, several case reports and studies have suggested that vertical transmission is possible, albeit rare.

A systematic review of over 1,000 pregnancies found that the rate of vertical transmission was approximately 3.2%, with neonates testing positive for SARS-CoV-2 either via PCR testing of nasopharyngeal swabs or placental tissue (95% CI: 2.2–4.2%, $p<0.05$). The presence of the virus in

placental tissue, amniotic fluid, and neonatal blood samples provides strong evidence that in utero transmission can occur, although it is not the predominant mode of transmission [13].

The clinical implications of vertical transmission are still being studied, but early evidence suggests that neonates who acquire the virus in utero may be at higher risk for complications such as respiratory distress, sepsis, and long-term developmental issues. However, the majority of neonates who test positive for SARS-CoV-2 are either asymptomatic or experience mild symptoms, with good overall outcomes.

CONCLUSION

The impact of maternal COVID-19 infection on fetal and neonatal health is significant, with increased risks for growth restriction, preterm birth, neonatal complications, and vertical transmission. These findings underscore the importance of careful monitoring and management of pregnant women with COVID-19 to mitigate these risks and improve outcomes for both mother and child.

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