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Observational Cohort Study of Perinatal Outcomes of Women with COVID-19

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Abstract

Background: Understanding the impact of SARS-CoV-2 infection on pregnancy outcomes and of pregnancy on COVID-19 outcomes is critical for ensuring proper prenatal and antenatal care. No similar studies have been published in Saudi Arabia.

Methods: We performed a prospective cohort study of pregnant women with confirmed SARS-CoV-2 infection who presented at King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh, Kingdom of Saudi Arabia. COVID-19 staging was performed, pregnancy-related complications were assessed, and neonatal infection was evaluated.

Results: We enrolled 81 patients (mean age 31.75 years, SD 5.25) of which there were 17 cases in the first trimester, 20 in the second trimester, and 34 in the third trimester. The distribution of COVID-19 severity was 40 patients with Stage A, 36 with Stage B, 4 with Stage C, and 1 with Stage D. Complications were pregnancy loss in 2 patients (one in each first and second trimester) and 1 fetal death after 20 weeks of pregnancy, 7 patients with fetal growth restriction, and 8 with pre-term delivery.

Conclusions: We did not observe an unusual frequency of pregnancy-related complications due to SARS-CoV-2 infection in this high-risk obstetric population and there was no evidence of vertical transmission in newborns from women who delivered while positive for the virus.

Keywords: Coronavirus, pregnancy, COVID-19, neonatal
Abbreviations: FGR, COVID-19, IUFD

Introduction

In March 2020, the World Health Organization (WHO) classified the outbreak of a novel coronavirus disease, COVID-19, as a pandemic. SARS-CoV-2 is a novel virus that was identified as the cause of an outbreak of pneumonia in the city of Wuhan, Hubei Province, China, in December 2019 [1]. This disease was named COVID-19, for "coronavirus disease 2019."

Genetically, SARS-CoV-2 and SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) are similar [2], yet these beta coronaviruses cause a different disease spectrum and have different transmission properties [3]. Data to assess fetal outcomes and risks

resulting from infection during the prenatal period are emerging [4,5]. Various reviews find little evidence supporting increased risk of miscarriage, preterm birth, pre-eclampsia, cesarean delivery, and perinatal death; others report evidence supporting increased risk of these outcomes in pregnant women with COVID-19 [6–10].

Some societies have published statements that pregnant women do not appear to be more susceptible than the general population to becoming infected with SARS-CoV-2 [11] and various studies support these statements [12]. However, other sources indicate that pregnant women are at higher risk of worse sequalae from the infection [13–17]. Indeed, this is an active area of research [18].

The currently available data on pregnant women with COVID-19 indicates that transmission from infected mother to infant is rare but possible. Whether transmission occurs through perinatal transmission [16,17,20–23] or during breast feeding [20,23,24] is unclear. There are case reports for neonates positive for COVID-19, including one in the United Kingdom [25] and 2 cases in China [23,26]. It is unknown whether this transmission to the newborns was in-utero, during delivery, or due to contact with infected subjects [4].

Dong et al. reported a case of a newborn with elevated IgM antibodies to SARS-CoV-2 born to a mother diagnosed with COVID-19 [27]. The antibodies were detected two hours after birth. Zeng et al. evaluated virus-specific antibodies in 6 pregnancy cases and found that two infants had elevated IgM concentrations [28]. Due to their large macromolecular structure, IgM antibodies do not cross the placenta, suggesting that these neonates produced IgM antibodies in response to intrauterine infection with SAR-CoV-2. However, Kimberlin and Stagno argued that more data are needed due to the high rate of false positives associated with IgM assays [29].

Here, we report the results of a prospective cohort study of pregnant women with documented COVID-19 infection. We evaluated pregnancy-related complications and the possibility of vertical transmission.

Methods

This study is a prospective cohort study, conducted at King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh, Kingdom of Saudi Arabia. The study population included all pregnant women infected with SARS-CoV-2, based on a positive polymerase chain reaction (PCR) test of a nasopharyngeal swab sample, presenting at KFSHRC between May 2020 to February 2021. COVID-19 disease severity was classified, and pregnancy-associated complications were assessed. Pregnancy-related complications included gestational diabetes, thrombophilia, connective tissue autoimmune diseases, thyroid diseases, and hematological diseases. COVID-19 disease in the patients was staged as A, B, C, or D:

- Stage A patients were asymptomatic.
- Stage B patients had mild to moderate disease, had O_2 saturation >94%, and did not require O_2 supplementation.
- Stage C patients had severe disease, had O_2 saturation <94%, required supplemental O_2, had a respiratory rate >30 breaths per minute (BPM), and exhibited infiltrates in >50% of the lung.
- Stage D patients were critical, exhibiting respiratory failure and multi-organ failure.

Patients were subdivided into 3 groups based on trimester. Pregnancy-related complications evaluated were fetal growth restriction (FGR), preterm labor (defined as delivery prior to 37 weeks), and miscarriage (defined as occurring before 20 weeks of gestation) or intrauterine fetal demise (IUFD, defined as spontaneous fetal death after 20 weeks of gestation). We also evaluated type of delivery, either Cesarean or vaginal delivery.

To investigate the possibility of vertical transmission, neonates who were born to women positive at the time of delivery were evaluated by the neonatal intensive care unit (NICU) service for neonatal infection by PCR testing of the amniotic fluid, placenta, and cord blood. The newborns were tested for SARS-CoV-2 by nasopharyngeal swab PCR testing shortly after birth and again after 48 hours. Newborns of these mothers were also monitored for respiratory complications.

The inclusion criteria for the study were (i) pregnant women with confirmed infection with SARS-CoV-2 and who were admitted to KFSHRC at any gestational age; (ii) pregnant women with confirmed infection with SARS-CoV-2 at the time of delivery (intrapartum infection) and who delivered at KFSHRC; (iii) pregnant women previously infected with SARS-CoV-2 during the current pregnancy and who delivered in KFSHRC. The exclusion criteria were (i) any patient that declined to participate in the study or (ii) pregnant patients without clinically confirmed SARS-CoV-2 based on a positive PCR test.

Data were collected in an Excel workbook. Analyses were conducted using SAS/JMP version 15.0 software. The analyses were descriptive with continuous data summarized with means and standard deviations and categorical data summarized with frequency counts and percentages.

The study protocol was approved by the institutional review board at KFSHRC and conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. All participants provided informed consent. All cases are kept anonymous with patients assigned case numbers to safeguard their identities. Only the primary investigator and co-investigator collected and entered the patient data. Data are kept in an encrypted Microsoft Office file and then transferred into PI Laptop Database program supported by the Biostatistics Department. Patients had the right to decline enrollment into this study and were informed that this choice will not alter their care at KFSHRC.

Results

We enrolled 81 pregnant women who tested positive for SARS-CoV-2 during the period from May 2020 to February 2021. Most patients were enrolled in the months of June and July 2020 (**Figure 1**). Only two infected subjects were enrolled in early 2021.

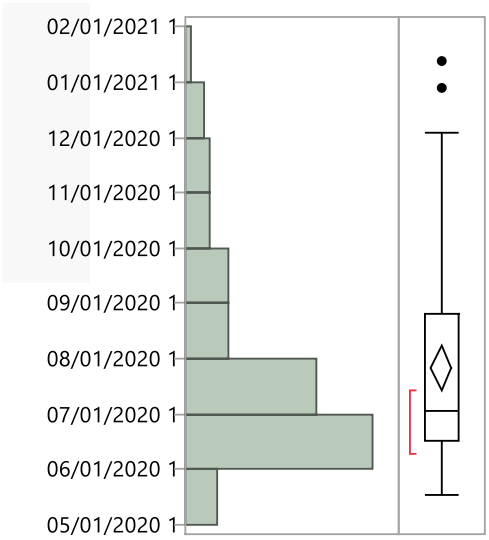

Figure 1. Enrollment of pregnant women who tested positive for SARS-CoV-2 between May 2020 and February 2021. Left shows the raw data, right shows a box and whisker plot with the majority of infected subjects indicated with a red bracket.

The mean age of the 81 patients was 31.75 years. A similar proportion of second and third trimester patients were enrolled: 30 during the second trimester (37%) and 34 during the third trimester (41%) (Table 1). Only 20% (17) of the patients were in the first trimester. Most of the patients were asymptomatic (49%) or had mild COVID-19 symptoms (44%). Four patients (4.9%) had stage C severe COVID-19 and only 1 patient was stage D in critical condition.

Table 1. Clinical variables in the 81 pregnant patients positive for SARS-CoV-2.

Variables	Mean (SD) or Frequency counts and percentages
Age (years)	31.75 (5.25)
Gestational age at positive test (days)	177.18 (71.42)
Trimester at positive test:	
First	17 of 81 (20%)
Second	30 of 81 (37%)
Third	34 of 81(41%)
COVID-19 Stage:	
A (asymptomatic Covid-19)	40 of 81 (49%)
B (mild to moderate disease)	36 of 81 (44%)
C (severe disease)	4 of 81 (4.9%)
D (critical)	1 of 81 (1.2%)
Risk factors:	
DM	18 of 81 (14.5 %)
Thrombophilia	7 of 81 (8.6%)
Connective tissue autoimmune disease	2 of 81 (1.6 %)
Thyroid diseases	12 of 81 (9.7 %)
Hematological disease	3 of 81 (2.4 %)

Among the 81 women, 80 were followed to delivery. One patient was diagnosed with a missed abortions and underwent medical termination of pregnancy. Among the 80 women followed to delivery, pre-term delivery (10%) and FGR (8.6%) were the most common complications (**Table 2**). The frequency of Cesarean section delivery or vaginal delivery were similar, 48% by Cesarean and 52% by vaginal delivery.

Table 2. Pregnancy or delivery-related complications in SARS-CoV-2–positive women followed to delivery or loss of pregnancy. N = 80.

Variables	Mean (SD) or Frequency counts and percentages
Miscarriage	
First trimester (up to week 12)	1 of 81 (1.2%)
Second trimester (13- 20 weeks)	1 of 81 (1.2%)
FGR	7 of 81 (8.6%)
IUFD or still birth	1 of 81 (1.2%)
Pre-term delivery	8 of 81 (10%)
Gestational age at delivery (days)	266 (16.51)
Mode of delivery:	
Cesarean section	38 of 80 (48%)
Spontaneous vaginal delivery	41 of 80 (52%)

IUFD, intrauterine fetal demise (fetal loss from 20-23 weeks), stillbirth (≥ 24 weeks gestation). FGR: Fetal growth restriction

We evaluated the frequency of any of the detected complications (miscarriage, FGR, IUFD, or pre-term delivery) in the 81 patients followed through to delivery or loss of pregnancy (**Table 3**). By Fisher's Exact test, we found a significant difference in the frequency of pregnancy-related complications in patients with different stages of COVID-19. Surprisingly, the complication frequency was higher for asymptomatic patients (22.5% of Stage A) than for those with mild symptoms (9.1% of Stage B).

Table 3. Association of COVID-19 disease stage with pregnancy-related complications.

Stage	Frequency counts and percentages	P value
A (asymptomatic Covid-19)	9 of 40 (22.5%)	
B (mild to moderate disease)	3 of 36 (9.1%)	0.017
C (severe disease)	2 of 4 (50%)	
D (critical)	1 of 1 (100%)*	

*Delivered preterm at 36 weeks due to complications of psychiatric illness
Significance was determined with Fisher's Exact test

Eight of the pregnant women were positive for SARS-CoV-2 intrapartum. Four patients were stage A and the remaining 4 patients were stage B. We tested all 8 of the babies delivered by these women for SARS-CoV-2. The newborns were immediately isolated from

the mother and tested after birth and 48 hours after delivery. These tests, as well as the tests of the amniotic fluid, placentas, and cord blood, were negative. It was noted that all 8 patients had a normal antenatal course and delivery apart from the infection. Six patients were delivered by Cesarean section for obstetric indications, and 2 delivered vaginally.

Discussion

In March 2020, SARS-CoV-2 had reached Saudi Arabia and COVID-19 has become a significant threat to the population's health and a burden to the healthcare system. As the pandemic hit Saudi Arabia, concern for pregnant women rose, and experts were concerned about the potential for vertical transmission from infected mothers to the newborns.

Based on reports from leading societies reported before the pandemic, the frequency for first- trimester miscarriage and FGR is 10% [30,31] and pre-term labor is 12% [32]. We noted a similar prevalence in our infected group of patients regardless of stage of disease. In a study with the largest series of patients with COVID-19 in the first trimester of pregnancy, showed no significant difference in the cumulative incidence of COVID-19 in women who experienced spontaneous abortion [33] In a systematic review with 2375 women with signs and symptoms of COVID-19, who were in the second and third trimester of pregnancy, neonates do not represent any additional risk for adverse outcomes neither during the prenatal period nor after birth. [34] However as the evidence on risk for adverse outcomes from coronavirus disease 2019 (COVID-19) among pregnant women is still emerging other systematic reviews concluded there were associations with adverse pregnancy outcomes, maternal complications, and indicators of severe illness. However, the absolute risks were low. [35] and in a comprehensive overview of 66 systematic reviews, supports that pregnant woman with COVID-19 may be at increased risk of adverse pregnancy and birth outcomes. [36]

The preterm births are a live birth that occurs before 37 completed weeks of pregnancy. Approximately 15 million babies are born preterm annually worldwide, indicating a global preterm birth rate of about 11% in studies pre-pandemic period. [37,38]

The iatrogenic preterm delivery, also called provider-initiated preterm birth is a relevant term that is defined as a birth that occurs before 37 weeks of gestation because of to a planned delivery in the absence of spontaneous labor. There have been conflicting data on perinatal outcomes in systematic reviews there was a reduction in preterm birth at less than 37 weeks (OR 0.89, 95% CI 0.81-0.98) and 34 weeks (OR 0.56, 95% CI 0.37-0.83) for iatrogenic births and in singleton pregnancies. The reduction in preterm births in regions with high mitigation measures against SARS-CoV-2 infection is likely driven by a reduction in iatrogenic births [39], in contrast with the conclusion of other two systematic reviews that claimed that Iatrogenic preterm birth is the main adverse obstetric outcome [40,41]

The patients who presented with a thrombosis-related risk factors (such as thrombophilia) received low molecular weight heparin or unfractionated heparin, which may have aided in maintaining the pregnancy and minimizing thrombotic events induced by the virus. It should also be noted that the only patient that suffered from severe COVID-19 (Stage D) was delivered preterm at 36 weeks to prevent harm to herself and her unborn child due to complications of her psychiatric illness.

The main debate on deciding a cesarean section in the absence of obstetrical causes, is to prevent vertical transmission to the baby. In our result the mode of delivery by a Cesarean section or spontaneous vaginal delivery did not show a statistically significant number of delivery-related complications 38 of 80 (48%) vs 41 of 80 (52%). Mode of delivery was dictated by the obstetric indication not because of the infection status.

We found no evidence of vertical transmission from the 8 SARS-CoV-2–positive women who gave birth while infected. No virus was detected in amniotic fluid, placentas, or cord blood, and none of the newborns tested positive. Such results were in line with the conclusions from large international systematic reviews. [42,43] A meta-analysis on COVID-19-pregnancy-related placental pathologies shows no typical placental changes. [44] Another systematic review failed to clarify the route of infection in SARS-Cov-2-positive neonates but there is no sufficient evidence to exclude the possibility of vertical transmission for COVID-19 based on the current available data. [45]

Preeclampsia as an outcome was not observed in the included patients. In one systematic review with Seventeen observational studies with low to moderate risk of bias, reported on 2,769 pregnant women with a positive SARS-CoV-2 PCR test and 13,807 with a negative test, higher odds for preeclampsia (OR 1.30; 95% CI 1.09-1.54) [46]

Screening and testing pregnant patients for Covid-19 is a question often asked particularly in those admitted to hospital for any reason. Therefore, universal testing of pregnant patients presenting to the hospital should be strongly considered as an important measure to prevent in-hospital and community transmission of COVID-19. [47] This strategy seems needed as more than two-thirds of identified pregnant women have no symptoms. [48]

It is interesting to note in the results that the pregnancy-related complications in asymptomatic was in stage A: 40 of 81 (49%) vs stage C (severe disease) 4 of 81 (4.9%). We hypothesize the explanation may be due to either the sample size was not large enough, or the asymptomatic covid-19 patients may have others risk factors that we could not adjust for in this study.

The vaccination data was not collected for the study that started in May 2020. To explore perinatal outcomes in SARS-CoV-2 vaccinated pregnant women comparing with unvaccinated counterparts a systematic review conclusion reported no difference in the probability of having a small for gestational age fetus (OR 0.97, 95% CI 0.85-1.09; p=0.570) [49], while in another systematic review of 23 studies including 117,552 COVID-19 vaccinated pregnant people, almost exclusively with mRNA vaccines, there was no evidence of a increased risk of pregnancy related outcomes including miscarriage, earlier gestation at birth, placental abruption, pulmonary embolism, postpartum haemorrhage, maternal death, intensive care unit admission[50]

Implications in practice to women admitted to hospital, including maternity units, to be offered testing for SARS-CoV-2 on admission, because the majority of pregnant ladies are asymptomatic. Pregnant patients tested positive for Covid-19 can be managed according to public health guidelines. A particular emphasis on assessing the risk factors (other than covid-19 positive test) associated with pregnancy-related complications to plan the delivery. [48]

The strength of this study is the prospective design of 81 positively confirmed pregnant ladies for covid-19 who were followed up till delivery or loss of pregnancy perinatally.

Limitations of this study are the relatively small number of pregnant women evaluated, the small number of women with Stage C or D COVID-19, and the lack of a non-infected control group. This study is biased toward women with high-risk pregnancies, because our center is a tertiary care center catering to high-risk pregnancies.

Further studies are suggested to investigate risk factors for pregnancy-related complications in positively confirmed pregnant ladies for covid-19 in an adequately powered sample size to avoid type 2 statistical error, using logistic regression modelling for which the dependent outcome is (pregnancy-related complications or no complications) and the independent predictors as risk factors so the risk of pregnancy related complications attributed to covid-19 can be confidently quantified after adjusting for other risk factors such as found in a systematic review in pregnancy, the maternal risk factors associated with severe COVID-19 were: age 35 years and older, OR 1.83 (95% CI 1.27–2.63); BMI 30 kg/m2 and above, OR 2.37 (95% CI 1.83–3.07); chronic hypertension, OR 2.0 (95% CI 1.14–3.48); and pre-existing diabetes, OR 2.12 (95% CI 1.62–2.78). [51]

Conclusions

Despite the small sample size, the observed local perinatal outcomes were in line with studies conducted internationally elsewhere for the main outcome measures that have been investigated. We did not observe an unusual frequency of adverse complications due to SARS-CoV-2 infection in a high-risk obstetric population regardless of stage of infection or gestational age. Vertical transmission did not occur in the patients who delivered while positive for the virus. More studies with larger sample sizes will be needed to confirm these results.

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