Obstetric Outcomes Following SARS-CoV-2 Infection Remote from Delivery: A Prospective Cohort Study

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ABSTRACT **Background:** Coronavirus disease 2019 (COVID-19) causes severe complications in 15% of patients, many of whom are pregnant. Most infected women continue their pregnancies until term even though severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replicates in the decidua.

Objectives: To assess the impact of SARS-CoV-2 infection remote from delivery on obstetric outcomes.

Methods: Women diagnosed with SARS-CoV-2 infection confirmed by polymerase chain reaction at least 14 days prior to delivery were enrolled prospectively and followed monthly until delivery. Their obstetric outcomes were compared to those of women who gave birth at our center during the year preceding the pandemic. The primary endpoint was a composite of hypertensive disorders of pregnancy, oligohydramnios, and fetal distress or meconium-stained amniotic fluid during labor. Other demographic and obstetric variables were also recorded.

Results: The obstetric outcomes of 143 patients were compared to those of 3565 patients who gave birth during the year preceding the pandemic. The composite rate of placental complications was significantly higher in the study group (58 [41%] vs. 593 [17%], respectively), with an odds ratio of 3.4 (95% confidence interval 2.4–4.7). There was also an increased rate of labor induction or advancing the elective cesarean date in the study group (37 [26%] vs. 601 [17%]). No significant differences were found in the Apgar score, cord pH or gestational age at infection.

Conclusions: The risk of placental complications remains greater in pregnant women infected with SARS-CoV-2 after acute illness resolution. Those patients should be monitored closely until delivery.

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KEY WORDS: hypertension disorders of pregnancy, intrauterine growth restriction, nonreassuring fetal status, meconium-stained fluid, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic in April 2020 and announced the end of the emergency phase in May 2023. The disease caused over 760 million cases of respiratory illness and 6.9 million deaths, although the actual numbers are thought to be even greater. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and usually presents with fever, sore throat, muscle aches, sneezing, or cough. The illness usually begins 5–6 days after exposure and lasts 1–14 days. Nearly 15% of patients experience severe morbidity, such as respiratory insufficiency or venous thromboembolism, with a high risk of mortality [1]. Individuals with advanced age; obesity; diabetes mellitus; hypertension; immune suppression; and heart, lung or kidney disease are at increased risk of severe disease, hospitalization, and mortality [2].

Pregnancy is traditionally considered a high-risk condition because of its physiological changes. Respiratory capacity is reduced during pregnancy [3], and the cardiovascular system suffers from volume overload [4], making coping with the disease more complicated. However, the immune shift to the predominant Th2 response favors a reduced inflammatory reaction and a decreased severity of COVID-19 compared with nonpregnant controls, at least during the second and third trimesters [3]. It is therefore not surprising that nearly 88% of pregnant women are diagnosed with asymptomatic infection, but 12% are symptomatic and need hospitalization, with 2% requiring admission to the intensive care unit (ICU) [5,6].

Data regarding obstetric complications began to accumulate early in the development of the COVID-19 pandemic. Preterm delivery rates were high, as were rates of low birth weight and cesarean section [7]. A significant portion of these acute complications were attributed later to the urgent

need to improve maternal hemodynamic status via iatrogenic delivery. Nevertheless, most pregnant women survive SARS-CoV-2 infection without significant consequences and proceed to usual labor and delivery at term. Because SARS-CoV-2 actively replicates in placental tissues, especially decidua [8], the influence of the virus on placental function during pregnancy progression is unclear.

The aim of our study was to determine the clinical impact of SARS-CoV-2 infection on placental function, with a particular focus on complications that arise during pregnancy and delivery when the acute COVID-19 episode is distant from delivery.

PATIENTS AND METHODS

This multicenter prospective cohort study was conducted from 20 July 2020 to 9 October 2022. The study was approved by the institutional review boards (IRB) of the participating health organizations in Israel: Tzafon Medical Center, Maccabi Health Services, and Leumit Health Care Services. Written informed consent was obtained from the participants.

Pregnant women aged 18 to 55 years who were infected with SARS-CoV-2 at least 14 days before the end of their pregnancy and who sought medical treatment at our medical facilities were enrolled. SARS-CoV-2 infection was confirmed by polymerase chain reaction by a nasopharyngeal swab and was documented by any approved medical laboratory. Originally, we recruited women of any gestational age and with any pregnancy result, but due to the extremely low enrollment rate, terminations of pregnancy and miscarriages were removed from the final statistics.

The control group included all women who gave birth at our medical center during 2019, the year preceding the COVID-19 pandemic. Because of the clear tracing of clinical cases of SARS-CoV-2 infection with the first documented case in our country on 27 February 2020, all delivery cases during 2019 can be safely defined as not being infected with this specific virus.

SARS-CoV-2-positive patients were monitored monthly for maternal physical status as well as fetal well-being and growth via ultrasound.

The primary endpoint was the combined rate of placental complications, defined as a composite of hypertensive disorders of pregnancy, oligohydramnios, and suspicion of fetal distress or meconium-stained amniotic fluid during labor. In addition, maternal demographic characteristics, gestational age at diagnosis and delivery, disease symptoms, delivery type, newborn weight, Apgar scores, and neonatal ICU admissions were recorded.

STATISTICAL ANALYSIS

The target population is approximately 4000 pregnant women per year. Assuming that the rate of SARS-CoV-2 infection during pregnancy was 15% [9], 85 patients in the study group were required for 80% power (5% two-sided α). Due to the incredible importance attributed to COVID-19 research during the study period and the noninvasive study design, the size of the study group was approved by the IRB to be expanded to 300 participants.

The baseline characteristics and outcomes of the study groups were compared via Student's *t*-test or the Wilcoxon two-sample test for continuous variables and chi-square or Fisher's exact test for categorical variables. Controlling for background characteristics was performed via multivariable logistic regression.

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

The study was terminated when COVID-19 testing in Israel transitioned to self-implementation, resulting in inconsistent documentation of the infection timing.

In total, 157 patients infected with SARS-CoV-2 (53% of the intended sample size but still above the minimum required) participated in the study. None of the study group patients were hospitalized in the ICU and 33 (21%) were asymptomatic**.** The most common symptom was muscle cramps (43, 29%), and fever was recorded in 4 patients (3%). Twelve patients (8%) in the study group required close follow-up due to suspected fetal growth restriction. Sixteen patients (10%) in the study group were infected between weeks 22 and 26 of gestation, while 141 (90%) were infected from week 27 until term.

The obstetric outcomes were available for 143 patients in the study group. These outcomes were compared with those of 3565 patients who gave birth at our medical center in 2019, resulting in a final statistical power of 96%. Maternal characteristics are presented in Table 1, and the neonatal characteristics are presented in Table 2. Patients with SARS-CoV-2 were older and more obese than those in the control group were. There were 6 twins (4%) in the study group and 86 (2.5%) in the control group.

The maternal study outcomes are presented in Table 3, and the neonatal outcomes are presented in Table 4. In

Table 1. Maternal demographic characteristics

Maternal variables	Controls (N=3565)	Study (N=143)	*P*-value
Maternal age in years	29.8 ± 5.4	31.4 ± 5.5	< 0.001
Residency			
City > 20,000 citizens	1841 (52%)	78 (55%)	0.44
Town > 1500 citizens	949 (27%)	31 (22%)	
Village ≤ 1500 citizens	766 (21%)	33 (23%)	
Unknown	9 (0.3%)	1 (0.7%)	
Nationality			
Jewish	2023 (57%)	98 (68.5%)	0.017
Arab	1501 (42%)	43 (30%)	
Other	41 (1.2%)	2 (1%)	
Maternal weight in kg at delivery	76.6 ± 13.1	81.1 ± 15.9	0.003
Parity	1.74 ± 0.52	1.94 ± 1.69	0.82

The values are presented as the means ± standard deviations or numbers (%)

Table 2. Newborn demographic characteristics

Newborn variable	Controls (N=3651)	Study (N=149)	*P*-value
Newborn sex			
Male	1911 (52%)	73 (49%)	0.42
Female	1740 (48%)	76 (51%)	

The values are presented as numbers (%)

Table 3. Maternal outcomes

Maternal variable	Controls (N=3565)	Study (N=143)	*P*-value
Delivery week	39.3 ± 1.85	38.67 ± 2.53	< 0.001
Delivery type			
Spontaneous delivery	2588 (72%)	102 (71.3%)	< 0.001
Vacuum delivery	256 (7%)	0 (0%)	
Elective cesarean delivery	187 (5%)	21 (15%)	
Urgent cesarean delivery	552 (15%)	20 (14%)	
Proactive delivery*	601 (17%)	37 (26%)	0.005
Fetal distress	332 (9%)	21 (15%)	0.03
Oligohydramnios	113 (3%)	12 (8%)	0.0028
Meconium	24 (1%)	26 (18%)	< 0.0001
Hypertensive diseases of pregnancy	81 (2%)	12 (8%)	0.0002
Placental abruption	89 (3%)	7 (5%)	0.097
Placental complications combined**	**593 (17%)**	**58 (41%)**	**< 0.0001**

The values are presented as the means ± standard deviations or numbers (%)
*Proactive delivery: labor induction or advancing the elective cesarean date
**Primary outcome

Table 4. Neonatal outcomes

Newborn variable	Controls (N=3651)	Study (N=149)	*P*-value
Birth weight	3239 ± 539	3139 ± 551	0.01
Apgar at 1 minute	8.49 ± 1.26	8.52 ± 1.24	0.45
Apgar at 5 minutes	9.28 ± 1.16	9.27 ± 1.19	0.49
Apgar < 7 at 5 minutes	56 (2%)	3 (2%)	0.51
Cord pH	7.29 ± 0.08	7.30 ± 0.08	0.02

The values are presented as the means ± standard deviations or numbers (%)

the study group, proactive delivery (labor induction or advancing the elective cesarean date) occurred more frequently (37, 26%) than it did in the control group (601, 17%). Gestational age at birth was slightly lower (38.67 vs. 39.3 weeks), and the mean birth weight was lower by approximately 100 grams.

The combined rate of placental complications was significantly greater in the study group (41% vs. 17% in the control group). Logistic regression was used to adjust our results for patient age and nationality. The odds ratio for placental complications was 3.4 (95% confidence interval 2.4–4.7). No significant differences were observed in the Apgar score or umbilical cord pH. We found no correlation between any adverse pregnancy outcome and the gestational age at which SARS-CoV-2 infection occurred.

DISCUSSION

PRINCIPAL FINDINGS

Our study was designed to follow pregnant women who had been diagnosed with SARS-CoV-2 infection at least 14 days before delivery. The results clearly demonstrate that the obstetric outcomes of these women can still be worse than usual even if the acute phase of infection has already passed. Oligohydramnios, hypertensive disorders, and lower birth weight are clear signs of placental insufficiency. An increased need for labor induction or planning

elective cesarean in advance and increased incidence of intrapartum nonreassuring fetal heart rate tracings and meconium-stained amniotic fluid confirm that observation.

Our results align with findings from similar studies. In a U.S. study, rates of hypertensive disorders of pregnancy were higher among patients exposed to SARS-CoV-2 [10]. An investigation from Mozambique reported elevated preeclampsia biomarkers among women infected with SARS-CoV-2 who experienced perinatal loss [11]. In Brazil, researchers noted high rates of preeclampsia and HELLP syndrome among the SARS-CoV-2-infected population [12]. Italian investigators reported a significant association between intrauterine growth restriction and SARS-CoV-2 infection among pregnant women [13]. Conversely, some studies failed to establish an association between placental disorders and SARS-CoV-2 infection [14].

The key substance linking COVID-19 with placental disorders is angiotensin-converting enzyme 2 (ACE2). This protein is expressed in the lungs, kidneys, vascular endothelium, decidua, and trophoblast. It plays a central role in the renin-angiotensin system while counterbalancing its associated angiotensin-converting enzyme (ACE) in regulating cardiovascular homeostasis [15]. During pregnancy, this balance shifts toward ACE2, reducing systemic vascular resistance; impairments in this balance are associated with preeclampsia development [15]. SARS-CoV-2 has a high affinity for human ACE2 via its spike protein, exploiting it for cell entry [3]. This situation downregulates ACE2 expression within infected cells, shifting the ACE/ACE2 balance toward vasoconstriction and promoting intrauterine malperfusion, which leads to preeclampsia, fetal growth restriction, and other signs of placental insufficiency [16].

CLINICAL IMPLICATIONS

At the beginning of the COVID-19 pandemic, the primary emphasis was on acute disease complications. In the case of pregnancy, acute illness was linked to high rates of preterm delivery and cesarean section; however, both complications were mostly consequences of severe acute maternal morbidity. As the pandemic continued, more evidence of long-term sequelae emerged, linking SARS-CoV-2 infection to chronic disease [17]. In the case of pregnancy, the chronic state of the disease includes viral propagation marks in uterine, trophoblastic, and fetal tissues [8], as well as maternal and fetal sequelae, which we identified in our study. A fair inference is that women infected with SARS-CoV-2 during pregnancy should receive close surveillance for signs of hypertension, fetal growth restriction, or other signs of placental insufficiency.

STRENGTHS

The prospective design and the fact that enrollment was performed after the acute phase of the infection ended were strengths of our study. As is well known, any acute infection promotes increased production of interleukin (IL)-1, IL-6, interferons and tumor necrosis factor (TNF), which stimulate the host acute-phase response, such as vasodilation, T- and B-cell activation, phagocytic cell migration, and fever. This mechanism is self-propagating. For example, T- and B-cell stimulation by the synergism of IL-1 and TNF is much stronger at 39°C than at 37°C. An important part of the acute-phase reaction is the release of lipid-derived mediators such as prostaglandin (PG) E2 and thromboxane, which are involved in labor stimulation and placental dysfunction syndromes, respectively [18]. Unsurprisingly, the acute phase of COVID-19, especially high fever, is associated with an increased risk of spontaneous preterm delivery and fetal distress leading to iatrogenic delivery. This effect is nonspecific for SARS-CoV-2 infection and was neutralized in our study by starting patient enrollment at least 14 days after the infection diagnosis. Our results describe the pure effects of SARS-CoV-2 on pregnancy progression and placental complications.

LIMITATIONS

The enrollment process was interrupted by changes in SARS-CoV-2 screening and diagnostic indications, which limited our ability to achieve the intended sample size. In addition, none of the enrolled patients were infected during the first half of pregnancy, making discussions regarding teratology and miscarriages following SARS-CoV-2 infection impossible. Furthermore, we did not address potential influences from different SARS-CoV-2 variants. Despite these limitations, the study group size was above the minimum required for statistical significance, and the results aligned with similar studies worldwide, validating our findings as credible contributions to global knowledge about SARS-CoV-2 infection and COVID-19.

CONCLUSIONS

We found an association between SARS-CoV-2 infection and obstetrical complications, particularly placental insufficiency, which can develop when the acute illness is over. Pregnant women infected with SARS-CoV-2 should be monitored closely until delivery to prevent possible adverse maternal and fetal outcomes.

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One cannot be deeply responsive to the world without being saddened very often.

Erich Fromm (1900–1980), psychoanalyst and author

Capsule

Immuno-molecular features and therapeutic implications of brain metastases in clear cell renal cell carcinoma patients

Brain metastases are a serious complication of clear cell renal cell carcinoma (ccRCC) and are associated with poor prognosis. **Roodhooft** and colleagues performed a comprehensive immunologic and molecular characterization of brain metastases from patients with ccRCC to better understand their biology and identify potential therapeutic targets. The investigators found that brain metastases exhibit a distinct tumor microenvironment compared with primary renal tumors. Metastatic lesions demonstrated altered immune-cell infiltration, including differences in T-cell populations and immune checkpoint expression. Several immunosuppressive pathways were enriched within the brain metastatic niche, suggesting mechanisms by which tumor cells evade immune surveillance after colonizing the central nervous system. Molecular profiling revealed changes in gene-expression programs related to inflammation, immune regulation, angiogenesis, and tumor adaptation to the brain environment. The authors also identified heterogeneity among metastatic lesions, indicating that not all brain metastases share the same immune landscape or therapeutic vulnerabilities.

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