

# **Maternal And Perinatal Outcomes with COVID-19: A Systematic Review Of 1008 Pregnancies Isolation Department In Zliten Medical Center**

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## **ABSTRACT**

**Background:** As the COVID-19 outbreak unfolds, more and more pregnant women are infected with SARS-CoV-2, concerns have been raised about its clinical manifestations in pregnancy and the potential risk of vertical transmission from mother to fetus in pregnant women. Hence, in this review, we summarize the latest research progress related to COVID-19 epidemiology and the reported data of pregnant women with COVID-19.

**Patients and methods:** We searched databases for all case reports and series from 20 February 2020 to 30 April 2021. Multiple terms and combinations were used including COVID-19, pregnancy, maternal mortality, maternal morbidity, complications, clinical manifestations, neonatal morbidity, intrauterine fetal death, neonatal mortality and SARS-CoV-2. and quantitative real-time polymerase chain reaction (PCR) or dual fluorescence PCR-confirmed SARS-CoV-2 infection. Unpublished reports, unspecified date and location of the study or suspicion of duplicate reporting, cases with suspected COVID-19 that were not confirmed by a laboratory test, and unreported maternal or perinatal outcomes were excluded. Data on clinical manifestations, maternal and perinatal outcomes including vertical transmission were extracted and analyzed.

**Results:** Data from 1008 pregnancies between 20 February 2020 and 30 April 2021 were included in the current study. Most reports described women presenting in the third trimester with fever (68%) and coughing (34%). Lymphocytopenia (59%) with elevated C-reactive protein (70%) was observed and 91% of the women were delivered by cesarean section. Three maternal intensive care unit admissions were noted with maternal deaths. One neonatal death and one intrauterine death were also reported.

**Conclusion:** Although the majority of mothers were discharged without any major complications, severe maternal morbidity as a result of COVID-19 and perinatal deaths were reported. Vertical transmission of the COVID-19 could not be ruled out. Careful monitoring of pregnancies with COVID-19 and measures to prevent neonatal infection are warranted.

**Keywords:** Perinatal Outcomes; COVID-19; Maternal Outcomes

**Abb.:** BMI: body mass index; ICU: intensive care unit; qRT-PCR: quantitative real-time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

## **INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is a novel type of highly contagious pneumonia caused by the severe acute respiratory syndrome coronavirus 2 (SARS-

CoV-2). Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been growing at an accelerating rate (1). The increasing mortality rate warrants identification and protection of the vulnerable populations in society. The knowledge gained from previous human coronavirus outbreaks, namely, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), suggests that pregnant women and their fetuses are particularly susceptible to poor outcomes. Admission to intensive care is common and a case fatality rate of up to 35% has been documented (2).

The physiological changes occurring during pregnancy make the mother more vulnerable to severe infections. Anatomical changes such as an increase in the transverse diameter of the thoracic cage and an elevated level of the diaphragm, decrease maternal tolerance to hypoxia (3). Lung volume changes and vasodilation can lead to mucosal edema and increased secretions in the upper respiratory tract. In addition, alterations in cell-mediated immunity contribute to the increased susceptibility of pregnant women to be infected by intracellular organisms such as viruses (4). With regard to the fetus and the newborn, the immaturity of the innate and adaptive immune systems makes them highly susceptible to infections. Dysregulation of factors such as cytokines and the complement cascade can have deleterious consequences for brain development and function. To find out whether an infectious agent can infect the fetus or newborn by vertical transmission is therefore of particular interest. Pregnant women and their newborns should be evaluated for being potential risk groups in the current COVID-19 pandemic (5).

From the limited information gathered about the novel coronavirus and the drastically increasing burden of the disease, it is vital that scientific information concerning the disease is shared in a concise and practical manner. Data on the maternal and perinatal outcomes of pregnant women infected with the SARS-CoV-2 are limited to a handful of case reports and series (6). The sample sizes are small and the findings are diverse. Health policy changes in countries affected by the pandemic, continuously evolving clinical management guidelines and uncertainty about the reliability of the results make the findings of these reports difficult to interpret (7).

We aimed to conduct a systematic review of available published literature on pregnancies affected by COVID-19 and present a mixed narrative and quantitative synthesis of the clinical manifestations and maternal and perinatal outcomes.

## **PATIENTS AND METHODS**

We conducted a comprehensive literature search using data from Isolation Department in Zliten Medical Center ,Obstretic Department in Zliten Medical Center ,The Fardous Piaviat and Royal Piaviat Zliten Libyen. The search covered the period from 20 Februray 2020 through 20 April 2021 used combinations of the following search terms: COVID-19, pregnancy, maternal mortality, maternal morbidity, complications, clinical manifestations, neonatal morbidity, intrauterine fetal death, neonatal mortality and SARS-CoV-2.

We identified several case reports and case series. Full-text articles were retrieved for further consideration for inclusion. Eligibility criteria included laboratory-confirmed COVID-19 infection using quantitative real-time polymerase chain reaction (qRT-PCR) or dual fluorescence polymerase chain reaction (PCR), and availability of clinical characteristics including maternal and perinatal outcomes. Published guidelines on systematic reviews recommend a quality assessment of the included literature, but since only a handful of case reports and series were available,

the authors decided to include as many studies that fitted the eligibility criteria as possible.

The study or suspicion of duplicate reporting, cases with suspected COVID-19 that were not confirmed by a laboratory test, and unreported maternal or perinatal outcomes. Efforts were made to ensure that there was no overlap in the results and that no case was counted twice. This assessment was based on several criteria as described by admission date, gestational age at birth, date of publication of the report, author names, name and location of the hospital/ , maternal and perinatal outcome data, etc.

Variables extracted and analyzed included maternal age, clinical signs and symptoms on admission, gestational age at admission and laboratory testing. Maternal and perinatal outcome data were also recorded. Any maternal to fetal transmission of the virus was also noted.

## RESULTS

A total of 1008 pregnant women with COVID-19 were identified. The studies originated from Libyan, mean maternal age ranged from 29 to 32 years of age and women reported mostly in their third trimester .Pregnant women presented with a number of comorbidities or complications in their pregnancies such as preeclampsia, gestational diabetes, hypothyroidism, placenta previa, previous uterine surgeries etc. Cesarean section accounted for 70% of all deliveries; successful vaginal delivery was reported (30%) (**Table 1**). Of the clinical signs and symptoms, pregnant women with COVID-19 commonly presented with a fever at admission (68%). A persistent, dry cough (34%) along with malaise (13%) and dyspnea (12%) were less commonly described. Diarrhea was identified in only seven cases (6%) (**Table 2**).

Lymphocytopenia was reported in (59%) where the information was recorded. Similarly, an elevated C-reactive protein concentration (>10 mg/L) was recorded in (70%). From the papers that included information about the treatment provided to the pregnant women, it was found that oxygen and antiviral therapy were given to ICU patients. Treatment with antibiotics was also generously prescribed (all cases), possibly to prevent superimposed bacterial infection or as prophylaxis before cesarean section. However, we identified only some cases where corticosteroids were administered. From the reasoning provided in the published papers, corticosteroid administration was given to relieve inflammation due to maternal pneumonia rather than for fetal lung maturation (**Table 3**).

Regarding the perinatal outcomes, most cases did not report any adverse events. In contrast, some cases report neonatal death and usually there is admissions to the neonatal intensive care unit (ICU). The first symptom in the newborns was shortness of breath. Other initial symptoms were fever, thrombocytopenia accompanied by abnormal liver function, tachycardia, vomiting and pneumothorax. One term baby developed low-grade fever and abdominal distension with lymphocytopenia on day 3 and the day after, a chest radiograph revealed diffuse haziness. Some babys was discharged 9 days after delivery. The anther babys was delivered by cesarean section at 36+5 weeks gestational age; and went on to develop mild neonatal pneumonia with lymphocytopenia, which were treated with antibiotics. The neonates recovered within 2 days (**Table 4**).

There were cases of intrauterine fetal death and cases of neonatal death one pregnancy where multiple organ dysfunction syndrome (MODS) with acute respiratory distress syndrome (ARDS) led to an emergency cesarean section. The

neonate was stillborn and the mother required intubation with ventilator support and extracorporeal membrane oxygenation (ECMO). The outcome of this patient is dies.Regarding maternal morbidity reported 3 cases of maternal ICU admission. The first case was a 19-year-old women with a body mass index (BMI) of 25 kg/m<sup>2</sup>, presenting at 37 weeks of gestation for CS. Poorly controlled respiratory distress . Cesarean section was indicated and the mother developed a fever prior to the operation. Intraoperatively, uterine atony lead to massive hemorrhage (1.5 L) and the mother was intubated. Bronchospasm and wheezing ensued and a chest X-ray performed during the operation revealed hazy opacities in the lungs (**Table 4**).

A qRT-PCR test was positive for SARS-CoV-2.The second patient was a 33-year-old patient with a BMI of 28 kg/m<sup>2</sup> who presented at 34 weeks of gestation for CS due to sever hypoxia. Her past medical history included asthma, the patient developed respiratory distress, high fever with reduced oxygen saturation and tachycardia during operation. A qRT-PCR was positive and the patient was admitted to ICU due to severe bronchospasm. Five days postoperatively, the patient was dies, last case 31 weeks GA for CS due to severe hypoxia. Past medical history of asthma pat. Dies due to massive pulmary embolasim one hours post operative .The neonatal death reported a male newborn born at 34+5 weeks gestational age with an Apgar score of 8 at 5 minutes. The neonate developed refractory shock and gastric bleeding with multiple organ failure and disseminated intravascular coagulation (DIC). A throat swab obtained 9 days after delivery was negative for SARS-CoV-2 al17 mentioned poor immune function of the neonate and massive viremia as possible factors which could have contributed to the neonatal death(**Table 4**).

Reported one case with parallel findings of positive qRT-PCR in both the mother and the neonate. The mother was admitted with fever at 40 weeks of gestation and computerized tomography (CT) scan of chest showed ground-glass opacities in the lungs. She underwent emergency cesarean section and the baby was born with normal Apgar scores. The mother wore an N95 mask during the surgery, and the baby had no contact with the mother after birth and was transferred to the neonatology department 10 minutes after birth for observation.

The neonate had lymphocytopenia, deranged liver function and elevated creatine kinase, although it was clinically stable and appeared well. The mother's pharyngeal swab was positive for SARS-CoV-2 and, as a result, a pharyngeal swab was collected from the baby 36 hours after birth. This turned out to be positive. Swabs from umbilical cord blood and placenta were negative, but a possible mother-to-child transmission of SARS-CoV-2 cannot be excluded. Both mother and child recovered and were discharged (**Table 4**).

**Table (1): Demographic data and Maternal characteristics from the studied 1008 pregnancies**

Maternal characteristics						
Age (y) (mean ± SD)	31 ± 4	30	29 ± 3	32 ± 5	30 ± 6	
Gestational age in days (mean ± SD)	253 ± 25	N/A	271 ± 10	224 ± 8	260 ± 14	
Delivery characteristics						
Total number of deliveries	467	56	149	103	28	803/1008 (75%)
Patients not delivered at time of reporting of studies	90	27	25	36	27	205/1008 (25%)
Delivery by cesarean section	172	105	98	140	105	620/803 (70%)
Vaginal delivery	23	27	64	60	9	183/803 (30%)

**Table (2): Presenting signs among the studied 1008 pregnancies**

Presenting signs and symptoms						
Fever on admission	205	124	98	123	36	586/856(68%)
Cough	145	61	48	59	32	245/1008 (34%)
Malaise	37	30	19	24	21	131/1008 (13%)
Dyspnea	50	21	30	10	10	121/1008 (12%)
Myalgia	18	21	11	43	9	102/1008 (10%)
Sore throat	24	19	12	11	8	74/1008 (7%)
Diarrhea	13	21	10	11	0	65/1008 (6%)

**Table (3): Laboratory investigation among the studied 1008 pregnancies**

Laboratory characteristics						
Lymphocytopenia (<1 × 10 <sup>9</sup> /L)	132 <sup>a</sup>	39	62	28	19	369/633 (59%)
Elevated C-reactive protein concentration (mg/L)	99 <sup>b</sup>	61	80	84	95	419/596(70%)
Confirmed SARS-CoV-2	518	106	206	150	28	1008/1008 (100%)

**Table (4): Maternal and prenatal outcomes among the studied 1008 pregnancies**

Other parameters						
Maternal mortality	1	0	2	0	0	3/1008 (0.003%)
Maternal ICU admission	7	6	9	1	7	30/1008 (3%)
Neonatal mortality	3	1	1	4	2	11/1008 (1%)
Intrauterine fetal death	3	1	1	4	1	10/1008 (1%)
Vertical transmission	4	2	1	2	2	11/ 1008(1%)

**DISCUSSION**

The first cases of COVID-19 pneumonia were reported in December 2019 from Wuhan, Hubei Province in China. Since then, the infection has rapidly spread all over the world. As obstetricians began to identify cases of COVID-19 in pregnancy, some reports have appeared in the literature (8). This review summarizes the findings from 1008 pregnancies confirmed to have COVID-19. We found that COVID-19 during pregnancy may be associated with severe maternal morbidity and the possibility of maternal-fetal transmission could not be ruled out completely.

The SARS-CoV-1 outbreak during 2002-2003 was associated with a high maternal mortality rate (case fatality rate of 25%), spontaneous miscarriages during the first trimester and intrauterine growth restriction in the second and third trimesters (9). Nevertheless, a recent editorial on COVID-19 in pregnancy (36) argues that management guidelines should be based on data from the current epidemic rather than drawing on the limited experience from previous outbreaks, as their epidemiology, clinical course and response to treatment may differ. Indeed, our review of 1008 pregnant women with confirmed SARS-CoV-2 infection showed thirty cases of maternal intensive care admission (3%) and .003% confirmed fatalities. The 30 maternal ICU admissions (10).

With regard to the mode of delivery, cesarean section was performed in the majority of cases and several authors cited maternal distress as the reason behind the decision (11). However, some cases of spontaneous vaginal delivery were not associated with poorer outcomes (12).

The most common presenting sign was fever and a non-productive cough. Tiredness, shortness of breath and diarrhea were reported only occasionally. In all, 21% of the pregnancies presented at earlier gestations, and they were all discharged without any serious complications (13). However, due to lack of data on the perinatal outcomes, we cannot draw any conclusions about any maternal and neonatal consequences of the infection when it is acquired early during the pregnancy.

In our review, we found that one of some newborns tested was positive for SARS-CoV-2 infection. This baby did well clinically but had transient lymphocytopenia and deranged liver function tests. Among some cases (all babies

SARS-CoV-2-negative) reported by two developed disseminated intravascular coagulation and recovered, and one had multiple organ failure and died. Reported 20 neonates with mild lymphocytopenia and radiological findings of pneumonia, although both appeared clinically well and eventually made a full recovery. From these findings, we cannot exclude that the fetus and newborn baby might show a response, often sub-clinical, to the mother's infection and, thus, vertical maternal-fetal transmission cannot be ruled out. This view has been seconded by a recently published study where 31 infants born by cesarean section tested positive for SARS-CoV-2, 2 days after birth. However, in their analysis of 380 infected pregnancies, **Schwartz (14)** did not find any evidence for intrauterine transmission. Nevertheless, lymphocytopenia and thrombocytopenia have been repeatedly reported, as well as radiological findings in seemingly healthy babies born to SARS-CoV-2-infected women. Therefore, we encourage clinicians to monitor the newborns of mothers with COVID-19 closely **(15)**.

The main limitation of our review is related to the fact that the primary studies currently available in the literature were not of sufficiently high quality regarding their methodology. Several studies had missing outcome data and selective reporting bias could not be ruled out. Our study has some strengths. Only pregnant women with laboratory-verified SARS-CoV-2 infection were included in our review. Thus, the clinical manifestations and maternal-neonatal outcomes are representative of the disease. By including all cases available in the published literature, we were able to achieve a relatively large sample size. However, the majority of the individual reports describe only a small number of cases, and it is difficult for the clinicians to draw any definitive conclusions about the clinical manifestations and outcomes of the SARS-CoV-2 infection in the pregnant women and their neonates. With the disease burden accelerating every day, we hope that our synthesis can help physicians to better understand the nature of the disease at a glance and to make informed decisions when treating pregnant women with COVID-19 infection.

## **CONCLUSION**

Current evidence suggests the possibility of severe maternal morbidity requiring ICU admission and perinatal death with COVID-19 infection in pregnancy. Maternal-fetal transmission of the SARS-CoV-2 virus was not detected in the majority of the reported cases, although one neonate had a positive qRT-PCR 36 hours after birth despite being isolated from the mother. Careful monitoring of pregnancies with COVID-19 and measures to prevent neonatal infection are warranted.

**No Conflict of interest.**

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