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Coronavirus Infection during Pregnancy: A 1-Year Experience among Pregnant Egyptian Women

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Abstract

Objectives: This study aimed to investigate the effect of COVID-19 on fetal well-being and perinatal outcomes. *Methods*: Pregnant women with documented COVID-19 infection who visited the antenatal care clinic of El Shatby Maternity Hospital, Alexandria, Egypt, from May 2020 to May 2021 were selected and classified into three groups according to the illness severity: mild, moderate, and severe. Fetal well-being was examined using the umbilical and cerebral Doppler and nonstress test (NST). The estimated fetal weight and amniotic fluid volume were also evaluated. After delivery, the neonates were evaluated through Apgar scoring at 1 and 5 min, cord blood samples, and neonatal nasopharyngeal swabs. *Results*: Abnormal umbilical and cerebral Doppler findings, abnormal NST results, higher incidence of cesarean section (CS) and emergency CS, and poor perinatal outcomes were observed in severe cases. Moderate and mild maternal infections had neither an adverse perinatal outcome nor an effect on the mode of delivery. *Conclusion*: Severe COVID-19 infection can affect the perinatal outcome.

Keywords

Pregnancy, COVID-19, Fetus, Neonatal Infection

1. Introduction

Safe pregnancy and childbirth are significant public health issues during epidemics. The COVID-19 outbreak caused by SARS-CoV-2, may raise specific concerns among pregnant women because pregnancy brings physical changes that contribute to their susceptibility to viral respiratory infections. To date, scientific evidence about the increased susceptibility of pregnant women to

COVID-19 is unavailable; however, pregnancy appears to worsen the clinical course of COVID-19 compared with that of nonpregnant women of the same age. Laboratory evidence of patients with severe COVID-19 shows an exaggerated inflammatory response (similar to the cytokine release syndrome), which has been associated with critical and fatal illnesses. Whether the normal immunologic changes in pregnancy affect the occurrence and course of this response is unknown [1] [2] [3] [4].

The extent of vertical transmission (*in utero*, intrapartum, early postnatal period) remains unclear. Only a few well-documented cases of probable vertical transmission have been published [5] [6] [7].

This study aimed to investigate the effect of maternal infection on fetal well-being and neonatal outcomes and to what extent the severity of infection affects the fetus.

2. Materials and Methods

The study was conducted on pregnant women infected with SARS-CoV-2 during pregnancy between May 2020 and May 2021 to study their clinical presentation, obstetric examination, and neonatal outcome.

The study was approved by the ethics committee of Alexandria Faculty of Medicine, and informed consent was obtained from all patients.

The participants were divided into three groups according to the illness severity:

- *Mild illness*: Individuals with any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste, and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate illness*: Individuals who show evidence of lower respiratory disease during clinical assessment and have an oxygen saturation (SpO_2) ≥ 94% on room air at sea level.
- *Severe illness*: Individuals with SpO_2 < 94% on room air at sea level, an arterial partial pressure of oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) < 300 mm Hg, and a respiratory rate > 30 breaths/min [8].

At the time of infection, the patients were subjected to general and obstetric examination, and obstetric ultrasonography and umbilical and cerebral Doppler and nonstress test (NST) were used to determine the gestational age, estimated fetal weight, and amniotic fluid volume. The patients were followed up until delivery. Neonates were examined clinically. Apgar scores were recorded at 1 and 5 min, Apgar scores measure heart rate, respiratory effect, muscle tone, reflex irritability and color, and were used to assess the physical condition of newborns and the need for resuscitation. Cord blood samples were examined for acidemia. Neonatal nasopharyngeal swabs were also obtained.

3. Statistical Analysis

The data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 22) software.

The statistical test used as follows:

Arithmatic mean, standard deviation, for normally distributed data, comparison between two categorized parameters Chi square test was used. The level of significant was 0.05.

4. Results and Observations

From May 2020 to May 2021, 74 patients positive for SARS-CoV-2 infection during pregnancy documented by positive nasopharyngeal swabs and blood testing by polymerase chain reaction (PCR) were gathered.

Age, gravidity, and parity were not statistically significant (**Table 1**). The cases were divided into three groups according to the severity of infection and were followed up until delivery.

Nine patients had infection before 20 weeks of gestation, and 66 patients were beyond 20 weeks of gestation. Among the early cases, one had severe infection, one had moderate infection, and seven had mild infection. Among the late cases, 10 had severe infection, 22 had moderate infection, and 33 had mild infection. These results were statistically insignificant ($X^2 = 2.479$, $P = 0.290$) (**Table 2**).

During follow-up, no statistical difference was found among the three groups with regard to the amniotic fluid volume ($X^2 = 4.22$, $P = 0.121$) (**Table 3**). Conversely, a statistically significant difference was found among the three groups regarding umbilical and cerebral Doppler results, where three cases in the severe group had both abnormal umbilical and cerebral Doppler results compared with one case of abnormal umbilical Doppler finding in the moderate group and no cases in the mild group ($X^2 = 12.623$, $P = 0.002^*$ for the umbilical Doppler results and $X^2 = 24.218$, $P = 0.001^*$ for the cerebral Doppler results) (**Table 4** and **Table 5**) (**Figure 1** and **Figure 2**).

Table 1. Distribution of the whole sample regarding basic demographic and clinical data.

	No	%
Age		
<25	22	29.73
25 - 30	36	48.65
>30	16	21.62
Range	22 - 35	
Mean ± SD	27.189 ± 3.842	
Gravidity		
Range	1 - 6	
Mean ± SD	2.824 ± 1.307	
Parity		
Range	0 - 4	
Mean ± SD	1.365 ± 1.015	

Table 2. Relation between the severity and time of catching infection.

Time of catching infection	Group						X^2 P
	Severe		Moderate		Mild		
Before 20 weeks	1	9.1	1	4.3	7	17.5	2.479 0.290
After 20 weeks	10	90.9	22	95.7	33	82.5	
Total	11	100.0	23	100.0	40	100.0	

Table 3. Relation between the severity and amount of liquor.

Amount of liquor	Group						X^2 P
	Severe		Moderate		Mild		
Normal	9	81.8	22	95.7	39	97.5	4.22 0.121
Diminished	2	18.2	1	4.3	1	2.5	
Total	11	100.0	23	100.0	40	100.0	

Table 4. Relation between the severity and umbilical Doppler.

Umbilical Doppler	Group						X^2 P
	Severe		Moderate		Mild		
Abnormal	3	27.3%	1	4.3%	0	0.0%	12.623 0.002*
Normal	8	72.7%	22	95.7%	40	100.0%	
Total	11	100.0%	23	100.0%	40	100.0%	

Table 5. Relation between the severity and cerebral artery Doppler.

Cerebral artery Doppler	Group						X^2 P
	Severe		Moderate		Mild		
Abnormal	4	36.4	0	0.0	0	0.0	24.218 0.001*
Normal	7	63.6	23	100.0	40	100.0	
Total	4	5.4	70	94.6	74	100.0	

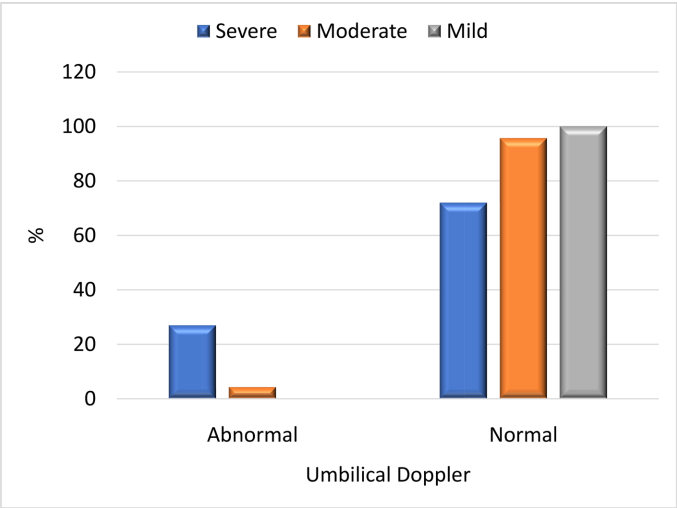

Figure 1. Relation between the severity and umbilical Doppler.

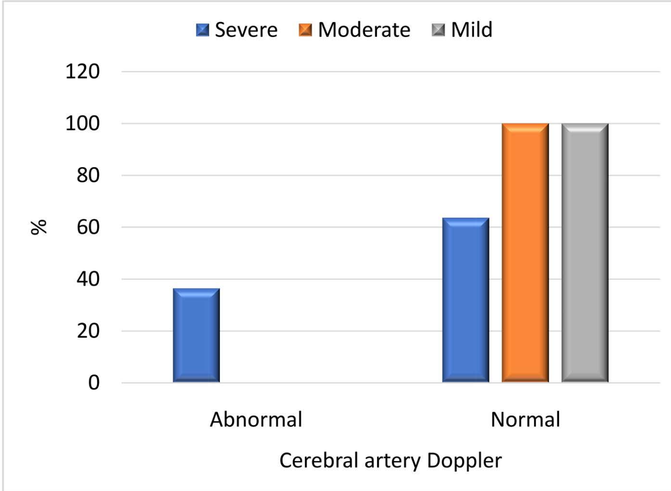

Figure 2. Relation between the severity and cerebral artery Doppler.

The results of the NST were also statistically significant, where the severe group had six cases with nonreactive NST results, four cases with late deceleration, and one case with variable deceleration compared with three cases with nonreactive NST results, one case with late deceleration, and two cases with variable deceleration in the moderate group. The mild group had seven cases with nonreactive NST results, no cases of late deceleration, and only two cases of variable deceleration ($X^2 = 32.59$, P = 0.001*) (Table 6, Figure 3).

Regarding delivery, only 1 case in the severe group had normal vaginal delivery compared to 10 cases of cesarean section (CS) of which 4 cases had emergency section due to fetal distress presented by late deceleration on the NST. The moderate group had 16 normal vaginal deliveries, 2 cases of induction of labor due to prelabor rupture of membranes, and 5 cases of CS, of which 1 had emergency CS due to late deceleration. The mild group had 33 cases of normal vaginal delivery, 4 cases of induction of labor (2 of them due to preeclampsia and one due to pregestational diabetes mellitus) and 4 cases of CS, of which 2 had a history of repeat section, 1 due to breech presentation and a large fetus, and 1 due to failed induction of labor due to prelabor rupture of membrane. These results were statistically significant ($X^2 = 30.0$, P = 0.001*) (Table 7, Figure 4).

After delivery, all neonates were examined. Ten neonates with abnormal 1-min Apgar score as well as 5-min Apgar score were delivered in the severe group, and three neonates in the moderate group showing abnormal 1-min Apgar score, with one of them continuing to have an abnormal 5-min Apgar score.

Four of the 10 neonates in the severe group had meconium aspiration. The mild group had eight neonates with an abnormal 1-min Apgar score, which became normal in the 5-min Apgar score. These results were statistically significant (1-min Apgar score, $X^2 = 25.204$, P = 0.001*; 5-min Apgar score, $X^2 = 59.258$, P = 0.001*) (Table 8 and Table 9) (Figure 5 and Figure 6).

Neonatal cord blood samples were tested for acidemia. Acidosis was noted in 10 neonates in the severe group, 2 in the moderate group, and only 1 in the mild group, which was statistically significant (X^2 = 48.380, P = 0.001*) (Table 10, Figure 7).

Table 6. Relation between the severity and nonstress test.

CTG	Group						X^2 P
	Severe		Moderate		Mild		
Normal	0	0.0	17	73.9	31	77.5	32.59 0.001*
Non reactive	6	54.5	3	13.0	7	17.5	
late deceleration	4	36.4	1	4.3	0	0.0	
variable deceleration	1	9.1	2	8.7	2	5.0	
Total	11	100.0	23	100.0	40	100.0	

Table 7. Relation between the severity and mode of delivery.

Mode of delivery	Group						X^2 P
	Severe		Moderate		Mild		
Normal vaginal	1	9.1	16	69.6	33	82.5	30.0 0.001*
Induction of labor	0	0.0	2	8.7	3	7.5	
Caesarean section	10	90.9	5	21.7	4	10.0	
Total	11	100.0	23	100.0	40	100.0	

Table 8. Relation between the severity and APAGAR at 1 min.

APAGAR at 1 min	Group						X^2 P
	Severe		Moderate		Mild		
Abnormal	10	90.9	3	13.0	8	20.0	25.204 0.001*
Normal	1	9.1	20	87.0	32	80.0	
Total	11	100.0	23	100.0	40	100.0	

Table 9. Relation between the severity and APAGAR at 5 min.

APAGAR at 5 min	Group						X^2 P
	Severe		Moderate		Mild		
Abnormal	10	90.9	1	4.3	0	0.0	59.258 0.001*
Normal	1	9.1	22	95.7	40	100.0	
Total	11	100.0	23	100.0	40	100.0	

Table 10. Relation between the severity and umbilical cord blood sample.

Umbilical cord blood sample	Group						X^2 P
	Severe		Moderate		Mild		
Normal	1	9.1	21	91.3	39	97.5	48.380 0.001*
Acidaemia	10	90.9	2	8.7	1	2.5	
Total	11	100.0	23	100.0	40	100.0	

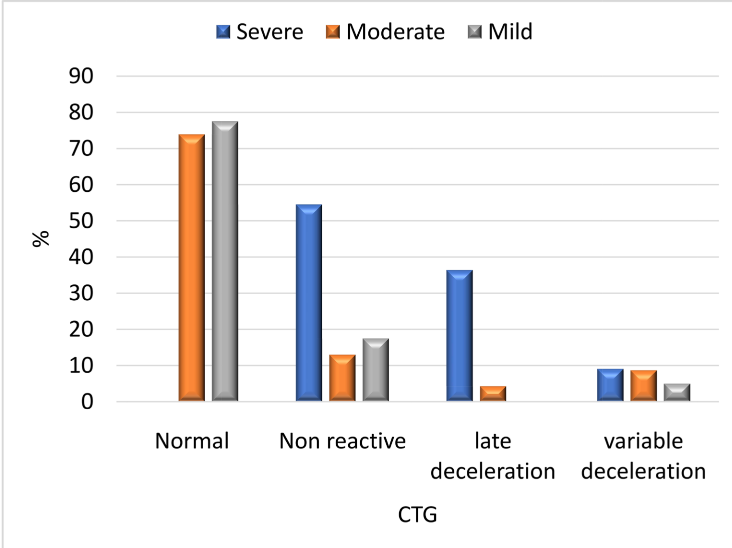

Figure 3. Relation between the severity and non stress test.

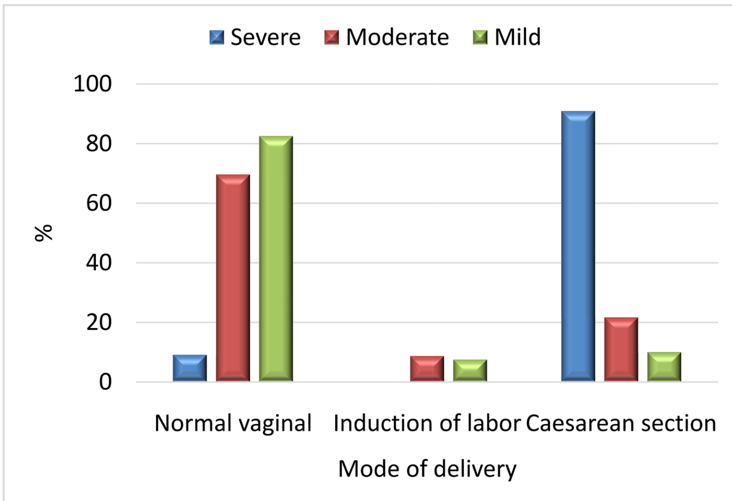

Figure 4. Relation between the severity and mode of delivery.

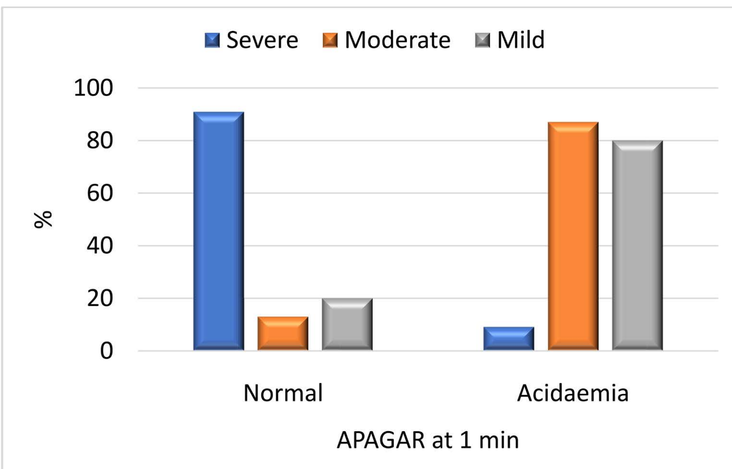

Figure 5. Relation between the severity and APAGAR at 1 min.

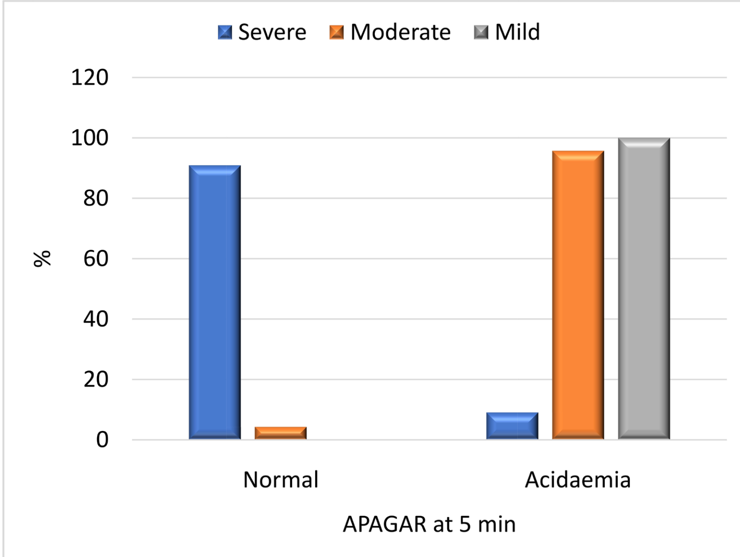

Figure 6. Relation between the severity and APAGAR at 5 min.

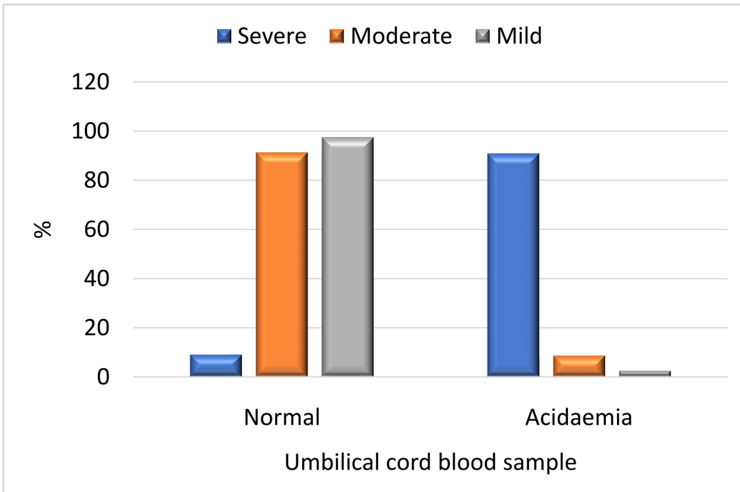

Figure 7. Relation between the severity and umbilical cord blood sample.

Regarding neonatal infection documented through neonatal nasopharyngeal swabs, the percentage positivity was 18.2% (2 of 11) among infants born to women with documented severe infection identified ≤14 days before delivery. This result was statistically significant ($X^2 = 11.77$, $P = 0.003$) (Table 11, Figure 8). The two neonates were born premature, and one of them had fever on the third day of life.

Neonates born to women who had moderate infection as well as those with mild infection <14 days before delivery gave birth to neonates whose tests were negative and who were admitted in the neonatology unit for nothing but the need for isolation of an otherwise asymptomatic infant (Table 11).

Neonates born to women with severe, moderate, or mild infection >14 days before delivery had negative cord blood PCR and nasopharyngeal swab results (Table 11, Figure 9).

Table 11. Relation between the severity and neonatal nasopharyngeal swabs.

Neonatal nasopharyngeal swabs	Group						X^2 P
	Severe		Moderate		Mild		
Negative	9	81.8	23	100.0	40	100.0	11.77 0.003*
Positive	2	18.2	0	0.0	0	0.0	
Total	11	100.0	23	100.0	40	100.0	

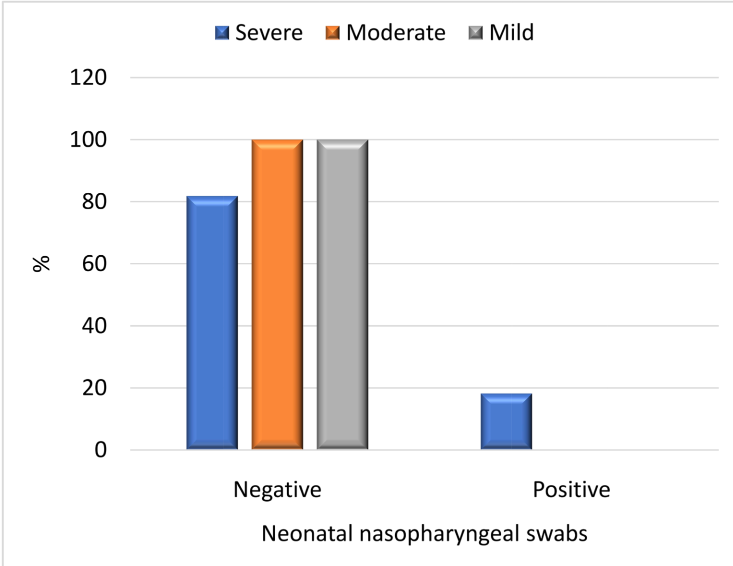

Figure 8. Relation between the severity and neonatal nasopharyngeal swabs.

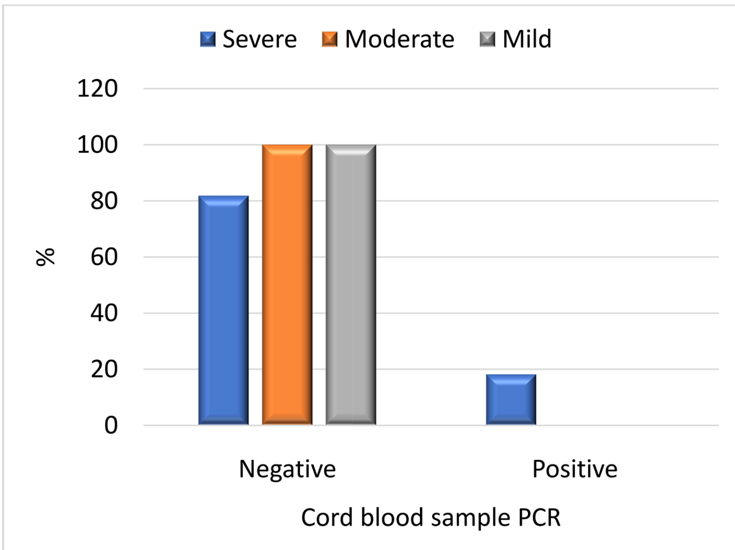

Figure 9. Relation between the severity and cord blood sample PCR.

Finally, abnormal umbilical and cerebral Doppler findings, abnormal NST results, higher rate of CS and emergency CS, abnormal neonatal Apgar scores, higher incidence of neonatal acidemia, and higher possibility of neonatal infection were observed in severe cases, especially if maternal infection was identified ≤14 days before delivery. No cases of miscarriage or congenital birth defects were reported, and there were no cases of stillbirth.

4. Discussion

Publications on COVID-19 during pregnancy have risen steeply through individual case reports, case series, observational studies, and systematic reviews. After 1 year of work, it was found that COVID-19 infection can affect the fetus and the course of pregnancy, delivery, and perinatal outcome only if severe.

The effects on the fetus have been studied by several researchers. Some studies have hypothesized that maternal respiratory failure and hypoxia may transiently reduce uterine placental blood flow [8] [9]. Others considered fetal hypoxia as a direct sequela of placental damage. Gagneur *et al.* [10] reported two cases of stillbirth that were preceded by fetal heart deceleration, whereas Wong *et al.* [11] and Jeong *et al.* [12] described placental infarction in three cases in the absence of any maternal comorbidity that can cause such finding [12]. Accordingly, they postulated that SARS-CoV-2 is mainly implicated in the thrombotic injury observed in such case reports. The vascular tropism of COVID-19 has recently gained much interest, and several of its multiorgan manifestations have been attributed to its endothelial tropism. Such endothelial tropism is accounted for by the high load of angiotensin-converting enzyme 2 (ACE2) and furin [13] [14], which are important viral checkpoints in the endothelium. The placenta is a vascular organ, in which furin plays an important role in its differentiation, that heavily expresses ACE2 and angiotensin 1-7, making it an important target for the vascular tropic effect of COVID-19.

The observed placental damage was explained by long-standing viremia, as reported by Chen *et al.* [15] during the first SARS outbreak, which showed that the RNA of SARS-CoV-2 can be detected in up to 50% of blood samples and can last up to 1 week. However, further studies are needed to correlate the degree of placental damage with the duration and degree of viremia.

Other researchers have shown that placental malperfusion, even without gross visible pathology in the placenta, is not an uncommon event, with resultant risk of fetal distress [16].

In our study, abnormal umbilical and cerebral Doppler results were observed in three cases in the severe group, which reflects placental insufficiency, compared to only one case of abnormal umbilical Doppler results in the moderate group and no cases in the mild group. Unfortunately, histopathological examination of the placenta was not performed; therefore, we could not differentiate whether the fetal hypoxia was due to placental pathology or maternal hypoxia, which is considered a limitation in our study.

Placental pathology causes fetal hypoxia, which can affect the neonatal outcomes. Some researchers observed neonates with meconium staining with a subsequent risk of meconium aspiration prevalent in pregnancies complicated with fetal hypoxia [17]. Among the neonates in this study, four were born with meconium-stained amniotic fluid and aspirated meconium in the severe group.

Regarding delivery, previous studies in pregnant women with other types of viral pneumonia have shown an increased risk of preterm labor [18].

In a prospective observational study done on women infected by COVID-19 virus admitted in the gynecology obstetrics department of the University Hospital of Marrakesh, researchers found that the clinical, biological and radiological presentation of COVID-19 infection in pregnant and post-partum women was not different from general population. Pregnant and post-partum women don't seem to be more at risk to develop severe features of the disease. They also concluded that vertical transmission via placenta is possible and COVID-19 infection may cause premature labor, premature rupture of membranes, preeclampsia or fetal distress [19].

In our study, only two cases of preterm labor due to the poor condition of the mother without any obstetric indication were found. The literature reviewed reported information for 201 newborns; 71 of them were delivered preterm before 36 weeks of gestation, representing about 35.3%. This percentage is high when compared to that of our results, but it was not consistently clear whether early delivery was induced in light of obstetric indications or maternal SARS-CoV-2 infection [20].

In our study, no cases of miscarriage or early pregnancy loss were noted in pregnancies with COVID-19, which is consistent with previous results [21].

The perinatal outcomes also agreed with the previous results. Adverse perinatal outcomes were more common in patients with severe or critical disease than in those with mild or moderate disease. An observational cohort study of all pregnant patients at 33 US hospitals with a singleton gestation and a positive result on a SARS-CoV-2 virologic test evaluated maternal characteristics and outcomes across disease severity. The data suggested that adverse perinatal outcomes were more common in patients with severe or critical disease than that in asymptomatic patients with SARS-CoV-2 infection. The perinatal outcomes for those with mild to moderate illness were similar to those observed in asymptomatic patients with SARS-CoV-2 infection [22].

Although vertical transmission of SARS-CoV-2 is possible, current data suggest that it is rare [23].

A review of 101 infants born to 100 women with SARS-CoV-2 infection at a single US academic medical center found that two infants (2%) had indeterminate SARS-CoV-2 PCR results, which were presumed to be positive; however, the infants exhibited no evidence of clinical disease. It is reassuring that most infants received negative PCR results after rooming with their mothers and directly breastfeeding (the mothers in this study practiced appropriate hand and breast hygiene) [24].

In our study, 2 out of 72 neonates had positive nasopharyngeal swabs (2.7%), which is consistent with previous reports. Their mothers had severe infections <14 days before delivery.

5. Conclusion

After one year of work, we found that SARS-CoV-2 infection with pregnancy can affect the fetus, the course of pregnancy, delivery and perinatal outcome only if severe.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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