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Original article

Comparison of Clinical and Laboratory Criteria of Neonates Born to SARS-CoV-2 Infected Mothers in Second and Third Trimester of Pregnancy

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ABSTRACT

Aims*. To verify clinical, laboratory, and outcomes of neonates born SARS-CoV-2 infected pregnant women in second and third trimesters and assess the relation of the timing of infection to neonatal outcomes.* ***Methods****. A cross-sectional study recruited 126 neonates admitted to the neonatal care unit (NCU) whose mothers had confirmed SARS-CoV-2 infection; divided into groups I (72/126) and II (54/126) based on second and third-trimester infection, respectively. Neonatal data were collected, including gender, gestational age at delivery, birth weight, indication, and number of days for admission to NCU; blood parameters, and biochemical and inflammatory markers.* ***Results****. A trend of prematurity and low birth weight was reported in group I. APGAR score and admission days to NCU were comparable. Sepsis was frequently reported among admitted neonates, irrespective of group. Group I showed non-significant elevated neutrophil count while C-reactive protein was insignificantly higher in group II. Group, I had a trend of 2.5 odds ratio OR for low birth weight, 1.75 OR for more prolonged admission, while group II had 3.14 odds for elevated C-reactive Protein II.* ***Conclusion****. Low birth weight and longer NCU admission were common among second-trimester newborns; however, a favorable neonatal outcome was reported irrespective of the timing of maternal infection.*

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INTRODUCTION

Uncertainty surrounds the effects of Acute respiratory syndrome-coronavirus 2(SARS-CoV-2) infection in pregnancy; which is linked to adverse maternal outcomes yet few are known regarding its relation with newborn outcomes [1,2].

Given the negative consequences of COVID-19 on pregnancy, a comprehensive understanding of the effects of COVID-19 on newborn outcomes is highly needed [3]. The perinatal effects are diverse from prematurity, fetal distress, respiratory distress, and even death [2]. Many confounders affected the perinatal complications as maternal co-morbidities, the severity of maternal infection [3], and the timing of infection during pregnancy [4].

The relation of the timing of maternal infection with the adverse neonatal outcome is acknowledged in many infections; Rubella virus, for example, if contracted in the first trimester, can lead to fetal loss and congenital rubella syndrome; this transplacental spread will decrease in the second trimester with few fetal consequences to rise again during the last month of gestation [5]. Early in the pandemic, there was a sharp rise in first-trimester abortion, mostly due to the uncertainty of the viral transport and its consequences on growing fetuses [6,7], this rise was reduced and settled with reassuring reports. Although immunization programs have lowered infections globally, vaccine hesitancy in pregnant is frequent [8].

A Recently published systematic review demonstrated that the percentage of infected newborns was low; 6% [9]. COVID -19 showed geographical dysparency; multiple areas of the globe witnessed high mortality rates adding to the negative consequences of COVID-19 on pregnancy [10]. For that, a comprehensive understanding of the effects of COVID-19 on newborn outcomes is highly needed. In this study, we examine the risk of adverse birth outcomes for pregnant women

exposed to SARS-CoV-2 infection by relating the time of maternal infection to the clinical and laboratory outcomes among a group of Iraqi women.

METHODS

Study design and setting

An observational, cross-sectional study was conducted at the central child teaching hospital's neonatal ward over six months (April 2021-October 2021). The central child teaching hospital is a tertiary center, one of the largest pediatric hospitals in Baghdad-Iraq.

Data collection procedure

The study recruited neonates less than 48 hours admitted to the neonatal care unit (NCU) and whose mothers were all not received any dose of COVID-19 vaccines and had a positive history of COVID-19 diagnosis during the second and third trimesters (2^{nd} and 3^{rd}) of pregnancy confirmed by polymerase chain reaction (RT-PCR). Exclusion criteria: 1). Neonates aged 48 hours or more, 2). Vaccinated mothers against COVID-19, 3). Maternal medical -co-morbidities like premature rupture of membrane, hypertension, diabetes mellitus, anemia, current history of infection, and autoimmune diseases, and 4). Those who refused to give informed consent and those who had missing data.

We initially recruited 130 cases; only 126 cases were eligible. The cases were divided into two groups according to which trimester the mother gets COVID-19. Group I (72/126): neonates whose mothers were diagnosed with COVID -19 during the second trimester of pregnancy. Group II (54/126): neonates whose mothers were diagnosed with COVID-19 during the third trimester of pregnancy. Two sets of data were collected: maternal and neonatal data. Maternal data included: the mother's age, weight, and height for calculation of body mass index (BMI), mode of delivery, gestational age at the time of delivery, and symptoms of COVID-19. Neonatal data included: neonate gender, birth weight, clinical symptoms at the time of admission, diagnosis at the time of admission to ICU, and the number of admission days; and laboratory characteristics (complete blood count with differential, renal function tests, liver function, C reactive protein, PCR for SARS-COV2 were collected and compared between both. The institutional review board of Mustansiriyah university gave the study approval issued (IRB number: 126 on 20-march-2021). All enrolled cases gave informed consent before embarking on the study, and the declaration of Helsinki was followed.

Statistical analysis

Data normality was checked by Shapiro-Wilk Test. Continues data were expressed as means and standard deviations(M±SD). Categorical variables were expressed as numbers and percentages. Student's t-test tested the difference between continuous variables and the Chi-square test between categorical variables. Logistic regression was constructed to estimate the Odds Ratio (OR) for various neonatal outcomes versus the time of maternal infection. All tests were done by Med Calc version 20; P-value <0.05 was significant for all tests.

Results

About 126 neonates whose mothers had confirmed diagnosis of COVID-19 during the 2^{nd} and 3^{rd} trimesters of pregnancy were included. Female neonates (59.1%) outnumbered males (40.1%); no vertical transmission of SARS-CoV-2 was found in this study as none of the neonates tested positive for RT-PCR.

The demographic criteria of seropositive mothers were presented, and no significant differences were reported regarding maternal age, BMI, gestational age at delivery, and mode of delivery. All women were symptomatic at the time of infection; they reported fever and cough, and loss of taste was higher among group I, and shortness of breath was higher in group II; however, both were insignificant as shown in table 1.

Table 1. Maternal demographic criteria

Parameters	2nd Trimester N=72	3rd Trimester N=54	P-value
Maternal age (mean± SD)	28.75±7.07	29.88±6.55	0.84
Maternal BMI (mean± SD)	28.35±2.56	29.83±4.12	0.14
Gestational age at delivery (mean± SD)	34.83±3.61	35.22±3.07	0.66
Mode of the delivery. N, (%) Vaginal delivery C-section	 48 (75) 24 (25)	 18 (33.3) 36 (66.6)	0.80
Maternal presenting symptoms. N (%) Fever Cough Loss of taste SOB	 72(100) 66(91.7) 42(58.3) 18(25)	 54(100) 54(100) 12(22.2) 18(33.3)	0.07

Neonatal demographic criteria showed a trend of preterm delivery and low birth weight was reported in group **I**; however, both were statistically insignificant. Neonatal sex, APGAR score at 5- minutes, and admissions days to NCU were all comparable in both groups as seen in table 2.

Table 2. Comparison of neonatal demographic criteria according to timing of maternal infection

Parameters	Group I 2nd Trimester N=72	Group II 3rd Trimester N=54	P-value
Gestational age at birth Term Preterm	 **30 (41.6 %)** **42 (58.4%)**	 **12 (22.2 %)** **42 (77.7 %)**	**0.56**
Birth weight (mean± SD)	**2.18±0.88**	**1.97±0.77**	**0.721**
Neonate sex Male Female	 **30(42.9%)** **42(57.1%)**	 **18(38.1%)** **36(61.9%)**	**0.704**
5-min APGAR score (mean± SD)	**6.42±2.391**	**6.22±2.2791**	**0.91**
5-min APGAR score APGAR >7 APGAR <7	 **54(75%)** **18(25%)**	 **36(66.6%)** **18(33.4%)**	**0.72**
No. of admission days (mean± SD)	**18.250±10.762**	**18.555±8.1870**	**0.44**

Table 3 shows the indication for neonatal admission to NCU, they were not significantly different by the timing of maternal infection. Sepsis was the common indication for admission seen in (42.9%).

Table 3: The association of causes of admission of the neonates with the timing of maternal infection

Neonatal diagnoses	Timing of maternal COVID-19		P-value
	Second trimester N=72, (%)	Third trimester N=54, (%)	
Sepsis	30 (41.6)	24 (44.4)	0.899
RDS	18 (25)	24(44.4)	0.350
Pneumonia	12 (16.7)	6 (11.1)	0.719
Asphyxia	6 (8.3)	0	0.375
TTN	6 (8.3)	0	0.375

RDS: respiratory distress syndrome, TTN: Transient tachypnea of the newborn

The hematological parameters showed hemoglobin and total WBC were comparable. Neutrophil count, blood urea, and serum creatinine show a trend of higher numbers in group **I** while lymphocytes and platelets were higher in group **II**. Inflammation biomarkers C-reactive protein and neutrophilia to lymphocyte ratio (N/L) ratio show higher levels in group **II** without meaningful differences as shown in table 4.

Table 4. Laboratory findings for neonate on the admission

Parameters	2nd Trimester N=72(mean ±SD)	3rd Trimester N=54(mean ±SD)	P-value
Hb	13.19±2.20	13.33±3.28	0.218
Total WBC Count	12.81±8.12	12.81±5.79	0.34
Neutrophils	7.14±5.96	6.02±4.18	0.33
Lymphocyte	4.12±1.78	6.37 ±2.52	0.27
N/L ratio	2.02 ± 1.73	2.10 ± 2.08	0.55
Platelets	232.75 ± 157.19	321.11 ±193.75	0.51
Blood urea	4.98±2.68	4.10±2.88	0.80
Serum creatinine	44.85±16.57	35.89±21.25	0.43
C-reactive protein	30.28±11.015	39.96±20.79	0.13

Hb: hemoglobin, WBC: white blood cell, N/L: Neutrophil/Lymphocyte ratio

Neonates born to mothers who got the infection in the 3rd trimester had 3.14 odds for elevated C-reactive Protein CRP, while neonates born to mothers who got the infection in the 2nd trimester had 2.5 OR for low birth weight,1.75 OR for longer admission and 1.5 OR low 5-minute APGAR score as seen in table 5.

Table 5. The odds ratio for the time of maternal infection with various neonatal outcome

Variable	Odds Ratio	95% CI	P- value
5-min. APGAR score for group I	1.5	0.2233 to 10.076	NS
Reference is group II			
No. of admission days for group I	1.75	0.2422 to 12.642	NS
Reference is group II			
Low birth weight for group I	2.5	0.3571 to 17.50	NS
Reference is group II			
C-reactive Protein For group II	3.14	0.2380 to 41.50	NS
Reference is group I			

DISCUSSION

Our data highlighted a trend of higher incidence of premature labor (PL), and low birth weight (LBW) among group I, and comparable APGAR score and admission days to NCU among both groups. Sepsis was the most frequently reported morbidity among admitted neonates. Group, I had a trend OR for low birth weight, longer admission, and low 5-Minute APGAR score. Odds for elevated C-reactive Protein were higher for group II.

None of our enrolled cases was asymptomatic and non-had severe infection necessitating intensive care unit ICU admission. Ayed et al.'s study discussed that 39% of cases infected in the second trimester were asymptomatic, and 42% were symptomatic; fever was the most presented symptom in line with our result. About 10% of their cases had severe infections that required ICU admission. Dileep et al. recruited 200 pregnant at the third trimester; mild to asymptomatic course of infection affect 74% of pregnant, and 26% had moderate to severe infections [11,12].

Enrolled neonates showed a trend of premature delivery, especially in group II; Dileep A et al. study showed that PL complicated 30.56% of their cases; they discsed severity of maternal infection to result in an increased risk ratio (RR) of PL by 5.7[12].

Gulersen et al. declared that later infection time (from 34 to less than 37 weeks) was linked with PL; OR 2.9, P= 0.006, and the severity of the infection were not influential to PL risk, [13].

Piekos et al. examined 18 335 COVID-19 infected mothers grouped according to the trimester of the infection. They confirmed that timing of maternal infection represents the major predictor of gestational age at delivery. Neonates delivered to infected mothers in the 1st and 2nd trimesters were at risk of being delivered prematurely; they highlighted the younger gestational age at contracting infection the greater risk of premature labor. However, they agreed with Gulersen et al. by denying the role of severe infection in participating in PL [14].

The mean birth weight of admitted newborns was below average regardless of the trimester of contracting the infection. Our results were in good agreement with earlier studies, that reported that low birth weight was observed following contracting COVID-19 regardless of the trimester of infection. Moreover, they speculated that the increased risk of PL also contributed to smaller-sized infants' [14,15].

Most of the born infants had a favorable APGAR score that exceeded 7 in the majority. Even days of admission were comparable in both groups. Fortunately, no maternal or neonatal death was reported, and no positive RT-PCR was seen among any neonates, in line with many studies that showed good feto-maternal outcomes [16,17]. Admission to NCU was more frequent among cases whose mothers were infected in the 2nd rather than the 3rd trimester based on Ayed et al. study. The leading causes for admission were prematurity, neonatal jaundice, and transient tachypnea of newborns. While the current study showed that sepsis, RDS, and pneumonia were the leading indications for admission [11].

Tug et al. addressed the effect of pregnancy on the course and outcome of COVID-19 they confirmed; that the disease severity increases significantly among pregnant as pregnancy advances [18,19].

Regarding the lab finding and inflammatory biomarkers, both groups showed comparable and statistically insignificant results. The data regarding infected neonates are scarce and very conflicting. Vakili et al. discussed that most neonates with confirmed RT-PCR test were asymptomatic, and the accompanied blood biochemical test was diverse, ranging from normal WBC counts to leukopenia, while others showed lymphopenia. Interestingly, CRP, ESR, and coagulation profiles were within normal limits [20,21].

Group, I neonates had a trend of LBW with an OR of 2.5 and 1.75 for ICU admission. Dileep A et al. showed that LBW complicated 17.0% of their cases, and ICU admission was recorded in 33% of the neonates. They suggested severity of maternal infection increases the risk ratio (RR) of LBW by 9 and admission to ICU by 29.3 compared to mild cases. The fact that all our enrolled cases were mildly symptomatic may explain the disparity in our results [22].

Piekos et al. disused that infected mothers gave birth to LBW neonates across all trimesters. Interestingly 3rd trimester infection was linked to small gestational age infants [14]. The reduced placenta efficiency as pregnancy approaches term with the superadded infection may be the cause [19]. Multiple adverse neonatal outcomes were higher among 2nd-trimester infection 5mintue APGAR score, days of admission to NCU, and LBW risk. A proposed mechanism by which enhanced stress on the placenta arises in a gestational age-dependent way after SARS-CoV-2 infection is; overexpression of angiotensin-converting enzyme 2 (ACE2) in the placenta during the first trimester of pregnancy is a probable mechanism that may explain why SARS-CoV-2 infections result in poorer outcomes [23].

The SARS-CoV-2 spike protein binds with ACE2 for entrance into human cells and ACE2 placental concentrations are dependent on weeks of gestation, with the greatest levels found in early pregnancy and virtually become unnoticeable near term. This discrepancy suggests an increased likelihood of placental infection by SARS-CoV-2 via ACE2 coupling earlier in pregnancy [24]. Which explains the high Odds ratio for adverse neonatal outcome among 2nd trimester born infants. However, an intrauterine infection during the 3rd trimester can lead to ACE2-expressing by the neutrophils and monocytes (macrophages) invading the placenta, which increases the risk of fetal distress, which is supported by our result in higher CRP in our 3rd trimester born neonates [25]. The strength of the current study relies on the fact that all pregnant mothers were unvaccinated so we eliminated acquired immunity. since the majority of reported COVID-19 cases were mild-moderately infected so as our cases pregnant; we think the current result mirrors an honest picture of the consequences of feto-maternal infection. Many acknowledge the stress and uncertainty that have accompanied the emerging virus; having a study that was conducted locally with favorable and reassuring outcomes may ease many concerned mothers. The limitations of the study: A small-sized study, in addition to being a single-center study.

CONCLUSION

Newborns of second-trimester infected mothers were more likely to have a low birth weight, low APGAR scores, and a longer NCU stay, whereas newborns of the third-trimester infection had a higher CRP. Regardless of the timing of the maternal infection, a good neonatal outcome was observed. More close monitoring is warranted in the early neonatal period.

Disclaimer
The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest
There are no financial, personal, or professional conflicts of interest to declare.

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