



Systematic Review

Maternal and Neonatal Complications, Outcomes and Possibility of Vertical Transmission in Iranian Women with COVID-19

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Abstract

Background: The emergence and fast spread of coronavirus disease 2019 (COVID-19) threatens the world as a new public health crisis. Little is known about its effects during pregnancy. This study aimed to investigate the clinical manifestations of COVID-19 on maternal and neonatal outcomes.

Methods: In this systematic review, PubMed, Scopus, Web of Science, and Google Scholar databases were searched focusing on pregnancy and perinatal outcomes of COVID-19.

Results: The initial search yielded 1236 articles, from which finally 21 unique studies, involving 151 pregnant women and 17 neonates, met the criteria. Mean \pm SD age of included mothers and mean \pm SD gestational age at admission were 30.6 ± 6.2 years and 30.8 ± 8.9 weeks, respectively. The common symptoms were fever, cough, fatigue, dyspnea and myalgia. The mortality rates of pregnant women and neonates were 28 out of 151 (18.5%) and 4 out of 17 (23.5%), respectively. Most of the neonates were preterm at the time of delivery. Three neonates had positive RT-PCR test on the first day after birth and three others on day two. On the average, neonate's PCR became positive on day 4 for the first time.

Conclusion: Early diagnosis of COVID-19 is crucial due to the possibility of the prenatal complications. Strict prevention strategies may reduce the risk of mother to infant transmission.

Keywords: COVID-19, Pregnancy, SARS-CoV-2, Systematic review, Vertical transmission

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Introduction

The emergence and fast spread of novel coronavirus disease 2019 (COVID-19) which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), threatens the world as a new public health crisis. As of January 16, 2021, there were nearly 94 million confirmed cases of SARS-CoV-2 infection with more than 2 million deaths worldwide according to the World Health Organization (WHO).¹ These numbers are increasing daily and crude mortality is estimated at 0.8–10.2% for the twenty countries currently most affected by COVID-19.²

It is critical to identify at-risk and vulnerable individuals for COVID-19 to avoid adverse outcomes with early preventive management. Although coronavirus can infect anyone, pregnant women are more susceptible to this virus due to physiological and immunological alterations during pregnancy.^{3,4} Currently, there is very limited knowledge about the various aspects of the coronavirus including during pregnancy and maternal and neonatal health before and after delivery. National-level as well as

global studies are now required to provide reliable data on the incidence of COVID-19 in pregnancy and its effects on the pregnant woman, fetus, and newborn.

The objective of the present systematic review was to evaluate the clinical characteristics of COVID-19 and maternal, fetal, and neonatal outcomes published in the literature in the Iranian population and answer the following issues: (i) describe the clinical characteristics of COVID-19 in pregnant women; (ii) discuss obstetric outcomes; (iii) describe the risk of vertical transmission; (iv) use this data to inform clinical practice and guide policy in maternity services; and (v) identify gaps in the existing knowledge.

Materials and Methods

Search Strategy

The present systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.⁵ PubMed, Scopus, Web of Science, and Google scholar

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databases were searched for studies on pregnant women and neonates with COVID-19 infection from December 1, 2019 until December 31, 2020.

For the search strategy, combinations of the following keywords and medical subject heading (MeSH) terms were used: “coronavirus OR COVID-19 OR COVID 19 OR SARS-CoV-2 OR n19-CoV”, “newborn OR neonatal OR child OR infants”, “pregnancy OR pregnant OR maternal OR mother”, “vertical transmission OR maternal–fetal transmission OR intrauterine transmission”. The above three combinations were searched alone or together, with also “Iran OR Iranian” keywords.

Study Registration

The protocol of this study review was registered with *Pajooeshyar* under registration number 93-3-94-50455. This study is classified as a systematic review and no institutional review board approval was required.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Only observational studies including case reports, case series and cohort studies were found eligible. (2) Participants must be pregnant with confirmed SARS-CoV-2 infection by RT-PCR or CT scan. (3) Study must take place in Iranian hospitals. (4) Neonates must be born to mothers with confirmed SARS-CoV-2 infection. (5) Only newborns who were not discharged after delivery were found eligible. (6) Skin to skin contact must be limited after birth and during breast feeding.

Exclusion criteria were as follows: review articles, opinion pieces or guidelines, articles pertaining solely to MERS-CoV, SARS-CoV or other viruses, non-peer-reviewed papers, unpublished reports, articles in which the date and location of the study were not specified, women with suspected COVID-19 which was not confirmed by laboratory tests.

Study Selection

Titles and abstracts were independently retrieved and reviewed for eligibility by two authors (H.F. and Z.H.) and non-relevant studies and studies that did not meet the inclusion criteria were excluded. After the initial screening, the remaining full texts were reviewed by O.K.G, and articles with insufficient data and duplicates were identified. Eligibility of the included studies and cases reported in case series were double checked at this stage. Then, all studies were divided into 3 major groups: maternal outcome, neonatal outcome and vertical transmission possibility.

Data Extraction, Quality Assessment and Outcome Measures

Two authors (Z.H. and H.F.) extracted the required information from selected studies. The extracted information included first author’s name, study type, number of participants for case series and cohort studies,

participant’s age, gestational age, clinical symptoms of mothers and newborns, laboratory finding of mothers and newborns, PCR tests results, imaging findings of both mothers and newborns, delivery type and protection strategies.

The methodological quality of the studies was assessed independently by the same two authors using the Joanna Briggs Institute (JBI) tool for case series and case reports.⁶

Data Analysis

Due to lack of data, we decided to perform a narrative systematic review without meta-analysis (SWiM). Central and descriptive statistics were reported for quantitative data. All statistical analyses were performed using the SPSS software (v. 26.0, Chicago, IL). We used a method presented by Hozo et al⁷ to estimate the median, average and standard deviation of some variables in cohort studies like WBC count.⁸

Results

Study Selection and Characteristics

The initial search yielded 1236 articles. Thirty-seven articles were duplicates, and 1133 articles were excluded following title and abstract screening. A total of 34 articles were removed due to lack of relevancy and 8 articles were removed because the maternal PCR was not positive or the newborns were discharged after delivery. Finally, 21 unique studies involving 168 participants met the criteria for full review (Figure 1).

Additionally, the study by Dorgalale et al⁹ was found eligible because the neonate returned to hospital with symptoms on the day he was discharged. In another case series by Schwartz et al,¹⁰ 10 cases were excluded because

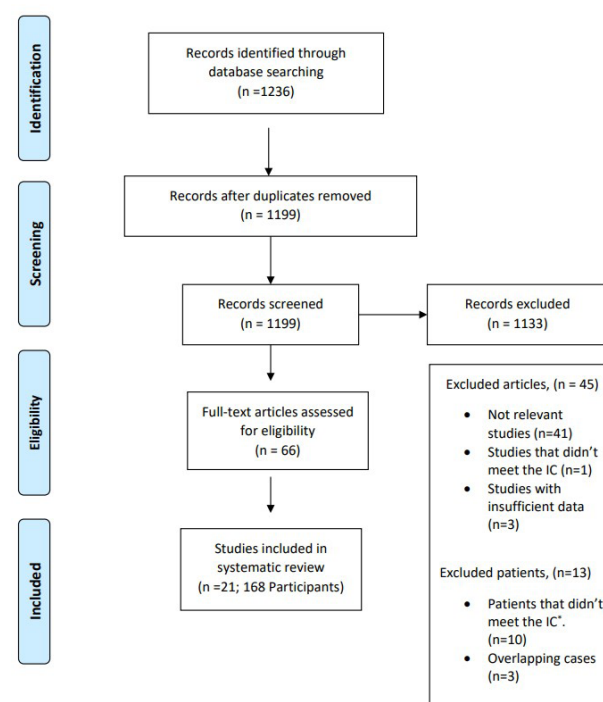


Figure 1. PRISMA Flowchart Showing Selection of Studies For review. IC, Inclusion criteria.

the mothers' RT-PCR was negative or not reported and one case was excluded because the neonate was discharged after delivery. The triplets reported by Farsi et al¹¹ were overlapping with one of the cases in the Schwartz et al¹⁰ case series.

Maternal Clinical Characteristics and Outcomes

To identify COVID-19 complications among Iranian pregnant women, 12 observational studies including 7 case reports, 2 case series and 3 cohort studies were

selected. Totally, 151 pregnant women were included in this study. The characteristics of these articles are shown in Table 1. The mean ± SD age of included mothers and gestational age at admission were 30.56 ± 6.28 years and 30.82 ± 8.9 weeks, respectively. Gestational age was not reported in one of the cohort studies and two other cohort studies only mentioned average gestational age for all of their participants. Out of 20 pregnant women, one was in the first trimester (5%), 4 were in their second trimester (20%) and the other 15 were in the third trimester (75%).

Table 1. Characteristics of Included Studies to Evaluate the Maternal Outcome of COVID-19

Study Type	First Author (Ref)	Number of Participants (n)	MA (y)	Maternal Mortality (Count)	ICU Admission (Count)	Ventilator Support (Count)	GA at Admission (wk)	Delivery			
								C/S	NVD	Still Pregnant	
Case reports	Jafari ¹²	1	26.00	0	N/R	N/R	36.00	1	0	0	
	Karami ¹³	1	27.00	1	1	0	34.00	0	1	0	
	Khodamoradi ¹⁴	1	36.00	0	N/R	N/R	37.00	1	0	0	
	Mohammadi ¹⁵	1	26.00	0	N/R	N/R	8.00	0	0	0	
	Soleimani ¹⁶	1	30.00	0	1	0	21.20	0	0	0	
	Taghizadieh ¹⁷	1	33.00	0	N/R	1	34.00	1	0	0	
	Zamaniyan ¹⁸	1	22.00	1	1	1	32.00	1	0	0	
Total	7	28.57	2	3	2	28.89	4	1	0		
Case series	Gheysarzadeh ¹⁹										
	Case1	1	30.00	0	N/R	0	40.00	0	1	0	
	Case2	1	42.00	0	N/R	0	40.00	1	0	0	
	Case3	1	30.00	0	N/R	0	22.00	0	0	1	
	Case4	1	27.00	0	N/R	0	34.00	0	0	1	
	Hantoushzadeh ²⁰										
	Case1	1	39.00	1	1	1	36.00	1	0	0	
	Case2	1	39.00	1	N/R	1	33.80	1	0	0	
	Case3	1	49.00	1	1	1	28.00	1	0	0	
	Case4	1	39.00	1	N/R	1	24.00	0	0	0	
	Case5	1	34.00	1	1	1	36.00	1	0	0	
	Case6	1	34.00	1	N/R	1	24.00	0	0	0	
	Case7	1	44.00	1	N/R	1	30.80	1	0	0	
Case8	1	29.00	1	1	1	38.50	1	0	0		
Case9	1	29.00	1	1	1	30.50	0	0	0		
Total	13	35.77	9	5	9	32.12	7	1	2		
Cohorts	Amini Moghadam ²¹	15	30.00	15	N/R	N/R	N/R	0	0	0	
	Pirjani ⁸	66	30.90	0	4	N/R	32.60	0	0	0	
	Sattari ²²	50	29.20	2	4	N/R	28.40	10	14	0	
	Total	131	30.15	17	8	N/R	30.79	10	14	2	
Total		151	30.56 (6.28)	28 (18.5%)	16 (10.5%)	11 (7.28%)	30.82 (8.9)	21 (13.9%)	16 (10.5%)	2 (1.3%)	

GA, Gestational age; ICU, Intensive care unit; MA, Maternal age; C/S, Cesarean section; NVD, Normal vaginal delivery Totals are presented as number (percentage) or average (Standard deviation).

The mortality rate in pregnant women was 28 out of 151 (18.5%). Only 16 patients were reported to be admitted to the Intensive Care Unit (ICU) but unfortunately, ICU admission was not reported in most cases and the exact number is bigger than 16. Due to this fact, we did not consider this variable in our study.

The most common symptoms among our participants were fever ($n = 102$, 67.5%), cough ($n = 84$, 55.6%), fatigue ($n = 68$, 45%), dyspnea ($n = 65$, 45%) and myalgia ($n = 39$, 25.8%). Gastrointestinal symptoms such as nausea ($n = 14$, 1%), vomiting ($n = 14$, 1%) and diarrhea ($n = 7$, 0.5%) were also present in some patients. All symptoms and clinical and laboratory data have been summarized in [Table 2](#) and [Table S1](#) (see [Supplementary file 1](#)^{8,12-22}).

Systolic and diastolic blood pressures were mostly low with mean \pm SD of 110.46/74.46 \pm 12.86/6.46 mmHg which was lower than the normal blood pressure 120/80 mm Hg. The mean \pm SD of white blood cells (WBC) count was 10.8 \pm 4.97 $\times 10^9$ /L and within the normal range of 4.5–11 $\times 10^9$ /L. After applying the Hozo et al⁷ method to the study by Pirjani et al,⁸ the estimated average and standard deviation of WBC count of all participant were 11.8 \pm 4.68 $\times 10^9$ /L. Then, we compared WBC counts between dead and live mothers and the outcome is abstracted in [Table 3](#).

Average WBC count in patients who expired due to COVID-19 was 11.94 $\times 10^9$ /L in comparison to 12.75 $\times 10^9$ /L among survivors. The study by Sattari et al²² was excluded from this comparison because it did not report this variable separately for live and dead patients. Also, the mean \pm SD of lymphocyte percentage in all participant was 17.98% \pm 8.51 and it was lower than normal (20–40%). Interestingly, lymphocyte percentage was lower in deceased patients with the mean \pm SD of 7.63% \pm 1.68 versus 23.67% \pm 8.96 in survivors.

The mean \pm SD of O₂ saturation percentage was 86.95 \pm 11.2% which was low. Deceased mothers also had lower SPO₂ with the mean \pm SD of 76.38 \pm 8.69 versus 92.25% \pm 6.7 in survivors. The mean \pm SD of creatinine level (1.07 \pm 1.42 mg/dL) was within the normal range. BUN and creatinine were only high in patients with reported kidney injuries like the patient with acute kidney injury (AKI) and acute tubular necrosis reported by Taghizadieh et al.¹⁷

The mean \pm SD of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 48.64 \pm 36.67 IU/L and 32.5 \pm 35.53 IU/L, respectively. Deceased patients had much lower levels of AST and ALT than survivors. Average AST among deceased participants was 45.76 \pm 20.5 IU/L versus 72.67 \pm 53 IU/L in survivors. The mean \pm SD of ALT in deceased patients was 40.62 \pm 19.2 IU/L versus 113.77 \pm 147 IU/L in survivors ([Table 3](#)). The prothrombin time (PT), partial thromboplastin time (PTT) and D-dimer levels were also measured in our study but unfortunately, the published data was not adequate to report.

Acute respiratory distress syndrome (ARDS) ($n = 19$, 12.5%), coagulopathies ($n = 11$, 7.2%) and cardiovascular

problems ($n = 8$, 5%) were the most common complications that our participants experienced. Cardiovascular complications mostly consisted of cardiopulmonary collapse and right heart failure. At least 6 out of 8 patients who developed cardiovascular complications died due to COVID-19. The dead/live status of two other patients in the study by Sattari et al²² was not reported. Common complications and prescribed medications have been summarized in [Tables S2](#) and [S3](#), respectively (see [Supplementary file 1](#)).^{8,12-22}

Neonatal Complications

Eight studies including seven case reports and one case series were selected that determined the neonatal complication of SARS-CoV-2 in newborns born to infected mothers. The characteristics of these selected studies have been summarized in [Table 4](#). Totally, 17 neonates were included in this study. The female/male ratio was 7/10 and the mean \pm SD of gestational age was 33.09 \pm 3.86 weeks. Most of the neonates were preterm at the time of delivery (82.3%). The mean \pm SD of birth weight was 2047.19 \pm 971.57 grams.

Five neonates had an Apgar score lower than 7 one minute after delivery while only one neonate had an Apgar score lower than 7 five minutes after delivery. The mean \pm SD of Apgar score one and five minutes after birth were 6.79 \pm 1.76 and 7.86 \pm 1.65, respectively. SARS-CoV-2 specific RT-PCR test was positive in 14 neonates. Fifteen neonates were delivered by cesarean section and in at least five patients, COVID-19 was reported as the main culprit. The neonatal mortality rate was 4 out of 17 (23.5%).

[Table S4](#) of [Supplementary file 1](#) summarizes the clinical findings and symptoms of the newborns.^{9,10,11,18,23-26} Eleven (64.7%) neonates were transferred to NICU after delivery and 14 (82.3%) neonates developed respiratory distress syndrome (RDS). No case of sepsis was reported and we did not observe any other significant adverse complications among them except two cases of pulmonary hemorrhage reported by Sagheb et al and Rashidian et al.²⁶ Ten neonates had COVID-19-related findings in their CT-scan or chest X-ray (CXR). Laboratory finding of the newborns is listed in [Table S5](#).^{9,10,23,24} Four patients had low lymphocyte counts and other significant changes were not reported in other tests.

Vertical Transmission

Periodical neonatal RT-PCR tests plus vaginal secretions, umbilical cord blood and amniotic fluid and neonates' urine, feces and gastric juice tests for SARS-CoV-2 antigens were used to determine the possibility of vertical transmission of SARS-CoV-2. Totally, 14 newborns had positive RT-PCR test. Three newborns were positive on day 1, whereas six neonates had a negative result on day 1 ([Table S6](#)).^{9-11,18,23-26} On the average, the neonate's PCR test became positive on day 4 for the first time. Amniotic fluid test was positive in three mothers and SARS-CoV-2 antigens were also detected in vaginal secretion of an

Table 2. Laboratory and Examination Findings of Included Pregnant Mothers

Study type	First Author	Systolic Pressure	Diastolic Pressure	RR	HR	WBC (x10 ⁹ /L)	Lymph percentage	CRP	SpO2	BUN	Cr	ESR	AST	ALT	Plt	PT	PTT	D-dimer		
Case Reports	Jafari ¹²	N/R	N/R	N/R	N/R	N/R	N/R	N/R	92.00	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R		
	Karami ¹³	100.00	60.00	37.00	110.00	10.00	7.20	31.00	93.00	N/R	2.80	54.00	52.00	68.00	40.00	N/R	N/R	2.00		
	Khodamoradi ¹⁴	110.00	70.00	20.00	92.00	N/R	N/R	N/R	94.00	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	800.00	
	Mohammadi ¹⁵	96.00	74.00	27.00	N/R	3.20	N/R	N/R	95.00	7.00	0.80	N/R	123.00	283.00	359.00	N/R	N/R	N/R		
	Soleimani ¹⁶	110.00	70.00	N/R	98.00	N/R	N/R	N/R	76.00	N/R	10.00	N/R	N/R	N/R	N/R	N/R	N/R	N/R		
	Taghizadeh ¹⁷	100.00	66.00	36.00	N/R	11.00	N/R	N/R	94.00	N/R	6.80	N/R	78.00	46.00	N/R	16.00	36.00	N/R		
	Zamaniyan ¹⁸	N/R	N/R	26.00	118.00	7.80	*	32.90	85.00	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R		
	Case reports avg	103.20	68.00	29.20	104.50	8.00	7.20	31.95	89.86	7.00	5.10	54.00	84.33	99.28	199.50	16.00	36.00	401.00		
	Gheysarzadeh ¹⁹																			
	Case1		115.00	75.00	18.00	95.00	N/R	N/R	2.00	97.00	N/R	N/R	13.00	N/R	N/R	N/R	N/R	N/R	N/R	
Case2		110.00	70.00	20.00	90.00	7.70	18.00	3.00	96.00	N/R	1.00	20.00	N/R	N/R	359.00	N/R	N/R	N/R		
Case3		120.00	80.00	19.00	100.00	6.20	19.00	N/R	94.00	N/R	0.80	125.00	17.00	12.30	199.00	N/R	N/R	N/R		
Case4		120.00	80.00	14.00	86.00	6.10	34.00	N/R	N/R	N/R	0.60	N/R	N/R	N/R	196.00	N/R	N/R	N/R		
Hantoushzadeh ²⁰																				
Case1		N/R	N/R	N/R	N/R	26.00	8.50	210.00	85.00	N/R	0.60	N/R	172.00	126.00	145.00	N/R	N/R	N/R		
Case2		130.00	80.00	N/R	N/R	9.40	9.00	45.00	60.00	N/R	0.60	N/R	80.00	62.00	275.00	N/R	N/R	N/R		
Case3		120.00	80.00	N/R	N/R	16.40	7.00	81.90	62.50	N/R	0.70	N/R	66.00	38.00	380.00	N/R	N/R	N/R		
Case4		N/R	N/R	N/R	N/R	7.00	9.00	117.50	65.00	N/R	0.90	N/R	29.00	18.00	177.00	N/R	N/R	N/R		
Case5		N/R	N/R	N/R	N/R	20.30	8.50	64.00	72.50	N/R	0.80	N/R	40.00	17.00	305.00	N/R	N/R	N/R		
Case6		N/R	N/R	30.00	130.00	13.30	7.70	56.00	83.00	N/R	6.00	N/R	28.00	26.00	206.00	N/R	N/R	N/R		
Case7		N/R	N/R	N/R	N/R	7.00	5.00	25.00	55.00	N/R	0.60	N/R	160.00	143.00	224.00	N/R	N/R	N/R		
Case8		110.00	70.00	N/R	N/R	8.00	N/R	18.00	70.00	N/R	0.50	N/R	60.00	40.00	68.00	N/R	N/R	N/R		
Case9		125.00	80.00	N/R	N/R	3.80	6.80	41.00	85.00	N/R	0.80	N/R	52.00	68.00	51.00	N/R	N/R	N/R		
Case series avg		118.75	76.88	20.20	100.20	10.93	12.05	60.31	77.08	N/R	1.16	52.67	70.40	55.03	215.42	N/R	N/R	N/R		
Cohorts	Amini Moghadam ²¹	N/R	N/R	N/R	N/R	12.10	*	N/R	78.00	N/R	0.90	N/R	27.00	30.00	171.00	N/R	N/R	N/R		
	Pirjani ¹⁸	110.00**	N/R	18.00**	94.00**	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R		
	Sattari ²²	N/R	N/R	N/R	N/R	10.60	19.50	1.84	91.60	N/R	0.77	N/R	N/R	23.40	217.00	N/R	N/R	N/R		
Cohorts avg	110.00	N/R	18.00	94.00	10.95	19.50	1.84	88.46	88.46	N/R	0.80	N/R	27.00	24.92	206.38	N/R	N/R	N/R		
Total		110.46 (12.86)	73.46 (6.46)	18.88 (3.15)	94.97 (11.56)	10.80 (4.97)	17.98 (8.51)	13.00 (7.13)	86.95 (11.2)	7.00 (1.42)	1.07 (1.42)	53.00 (51.23)	48.64 (36.67)	32.50 (35.53)	207.58 (84.18)	16.00	36.00	401.00		

HR, heart rate; RR, respiratory rate; WBC, white blood cell count; Lymph, lymphocyte percentage; CRP, C-reactive protein; SpO2, pulse oximeter oxygen saturation; BUN, blood urea nitrogen; Cr, creatinine level; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Plt, platelet count; PT, prothrombin time; PTT, partial thromboplastin time; N/R, not reported.

Normal ranges and units: WBC count (4.4×10⁹/L–11×10⁹/L); lymphocyte percentage (20%–40%); CRP (<1 mg/dL), SPO2 (>95%), BUN (7 mg/dL–20 mg/dL), Cr (0.84 mg/dL–1.21mg/dL), ESR (<20 mm/h), AST (<31U/L), ALT (<31U/L), Plt (165–415×10⁹/L).

*These findings were reported as lymphocyte count.

**These findings were presented as median and IQR, to estimate the mean and standard deviation we considered median as mean and standard deviation to be IQR/1.35. because these variables seemed to have normal distribution.

Table 3. Comparison of Expired Pregnant Mothers and Surviving Participants

Maternal Mortality	WBC, Mean (SD)	Lymphocyte, n (%)	SpO ₂ , n (%)	Cr, Mean (SD)	AST, Mean (SD)	ALT, Mean (SD)
No (75)	12.75 (4.78)	23.67 (8.96)	92.25 (6.7)	3.33 ²³	72.67 (53)	113.77 (147)
Yes (26)	11.94 (3.26)	7.63 (1.68)	76.38 (8.69)	1.11 (0.6)	45.76 (20.5)	40.62 (19.2)

SD, standard deviation; WBC, white blood count; SpO₂, oxygen saturation; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Numbers are presented as Mean (standard deviation) or number (%).

infected mother. Eleven neonates were transferred to NICU and skin to skin contact was limited. The cases reported by Dorgalale et al.⁹ discharged after birth had contact with their mother for half a day.

Discussion

In this review, the most common symptoms among pregnant women included fever, cough, and myalgia. However, kidney injuries, cardiovascular complication and coagulation problems were the most important complications that caught our attention. It was found that pregnant women who expired or developed IUFD had an average lower SpO₂, indicating that women with more severe lung involvement were at higher risk of maternal and neonate mortality than those with mild lung involvement. This finding is consistent with a study by Turan et al.²⁷ Therefore, it seems that pregnant women with severe symptoms and low oxygen saturation need special care, while women with mild symptoms usually do not face serious problems.

Pregnant women are susceptible to AKI.²⁸ Additionally, coronavirus could cause kidney injuries.²⁹ AKI was present in three patients two of whom expired. In the case reported by Taghizadeh et al,¹⁷ a pregnant mother developed acute tubular necrosis, and the most possible reason to explain her condition was COVID-19. Fortunately, this patient was treated by hemodialysis. Kidney injuries were associated with an increase in creatinine levels while creatinine level was normal in other patients who did not experience renal involvement. It seems that in severe illness, AKI was more severe than in mild patients and BUN and creatinine levels were also higher in the first group. Also, another study reported three kidney injuries in 99 people.³⁰ On the contrary, the study by Wang et al on 116 patients did not find any relation between COVID-19 and AKI.³¹ Finally, it can be concluded that even if pregnancy with COVID-19 and kidney injuries are related, pregnancy does not seem to have a major impact on the incidence of kidney injuries related to COVID-19. However, more studies are required to make a reliable statement. Nevertheless, hemodynamic monitoring of pregnant women with COVID-19 is necessary.

COVID-19 is associated with myocarditis, ACS, heart failure and arrhythmia. Systemic inflammation following COVID-19 may causes these cardiovascular consequences in patients.³² In our study, eight pregnant women had cardiovascular problems, six of whom

expired. In a case-series reported by Hantoushzadeh et al, four patient developed cardiopulmonary collapse, none of whom had a history of underlying disease associated with cardiovascular problems.²⁰ In a study by Karami et al, a pregnant mother with COVID-19 was diagnosed with right heart hypertrophy,¹³ which may be due to increased pulmonary artery pressure. In a study on 799 patients with COVID-19 in Wuhan, heart failure was found in 24% of all patients and 49% of those who died.³³ Another study on 138 patients reported 17% arrhythmias in COVID-19 patients.³⁴ Considering the death rate of 75% for patients who had cardiovascular problems in our study, it seems that cardiovascular problems are a risk factor for the poor prognosis of COVID-19 in pregnant women.

One of the cases that caught our attention was in the study by Mohammadi et al who reported an ovarian vein thrombosis in a pregnant woman with COVID-19.¹⁵ It is well known that pregnancy is a risk factor for increased coagulation. In addition, several studies have shown the link between COVID-19 and coagulation problems. For example, according to Nishiga et al, coagulation complications were more common in patients with COVID-19 but mostly did not meet the criteria of disseminated intravascular coagulation (DIC). The systemic inflammation and hypercoagulable state may be the cause of these coagulation complications.³² In our study, there were eleven patients with coagulopathies (three with DIC, three with thrombosis or emboli and five others whose exact condition was not reported).

Platelet counts were normal in all patients but the average platelet count was a little bit higher in patients who experienced coagulation problems, although within the normal range. In a review article by Wool et al, they found that COVID-19 patients had a slightly higher platelet count in comparison to the control group.³⁵ Unfortunately, we did not have enough data for D-dimer levels, PT and PTT, so we cannot judge conclusively. Nevertheless, we recommend risk assessment for coagulopathies like DVT and imaging modalities like MRA and CTA for pregnant women with COVID-19.

Fourteen preterm deliveries were reported out of the 17 included neonates, which is significantly high. In a recent systematic review by Di Toro et al, the prevalence of preterm delivery was reported to be 23% among 684 newborn.³⁶ This difference could be due to the small number of participants in our study or selection bias. But we should not miss the fact that most of the included

Table 4. Characteristics of Included Neonates to Determine the Neonatal Outcomes

First Author	Gender		Neonatal Mortality	GA at Delivery	Birth Weight	Apgar1	Apgar5	DOL at Discharge	Delivery		CS due to COVID-19	PCR
	Female	Male							C/S	NVD		
Bordbar ²⁴	0	1	0	Term	4300.0	8.00	9.00	4.00	1	0	0	1
Dorgalaleh ⁹	0	1	0	Term	N/R	N/R	N/R	16.00	1	0	0	1
Farsi, ¹¹ case 1	1	0	1	30.00	1320.0	4.00	7.00	Died	1	0	0	0
Farsi, case 2	0	1	0	30.00	1600.0	5.00	7.00	37.00	1	0	0	1
Farsi, case 3	1	0	1	30.00	1200.0	6.00	7.00	Died	1	0	0	0
Parsa ²⁵	1	0	0	37.00	3500.0	9.00	10.00	28.00	1	0	0	1
Rashidiann ²⁶	0	1	1	39.00	3545.0	9.00	10.00	1.00	1	0	0	0
Sagheb, ²³ case 1	0	1	0	31.00	1550.0	7.00	8.00	60.00	1	0	0	1
Sagheb, case 2	0	1	0	33.50	1930.0	7.00	8.00	N/R	1	0	1	1
Schwartz, ¹⁰ case 1	0	1	0	34.00	1800.0	4.00	5.00	7.00	1	0	0	1
Schwartz, case 2	0	1	0	31.00	1660.0	7.00	8.00	21.00	0	1	0	1
Schwartz, case 3	1	0	1	28.00	900.0	N/R	N/R	Died	1	0	0	1
Schwartz, case 4	1	0	0	34.00	2000.0	9.00	10.00	7.00	1	0	1	1
Schwartz, case 5	1	0	0	32.00	2300.0	5.00	5.00	12.00	1	0	1	1
Schwartz, case 6	0	1	0	28.00	900.0	N/R	N/R	N/R	0	0	0	1
Schwartz, case 7	0	1	0	33.00	1900.0	7.00	7.00	14.00	1	0	1	1
Zamaniyan ¹⁸	1	0	0	32.00	2350.0	8.00	9.00	.00	1	0	1	1
Total	7 (41)	10 (59)	4 (23.5)	33.09 (3.86)	2047.19 (971.57)	6.79 (1.76)	7.86 (1.65)	20.60 (17.19)	15 (88.2)	1 (0.05)	5 (29.4)	14 (82.3)

GA, gestational age; DOL, day of life; CS, caesarean section; NVD, normal vaginal delivery; PCR, polymerase chain reaction. Total is presented as number (percentage) or Mean (standard deviation).

mothers in our study had symptomatic SARS-CoV-2 infection and two maternal deaths were reported. Still birth and preterm delivery rates have increased during the SARS-CoV-2 pandemic.³⁷ Also, maternal COVID-19 could somehow cause preterm delivery. Mean birthweight was also low and this finding was due to preterm delivery plus a triplet reported by Zamaniyan et al with low birthweight.

RDS was the most common finding among included neonates which is consistent with previous studies.³⁸ Lymphocytopenia was found in three newborns. In a cohort study in the US, none of the neonates had considerable complications and all RT-PCR tests resulted negative.³⁹ It should be considered that 14 newborns in our study had positive RT-PCR tests indicating that lymphocytopenia and RDS may be secondary to SARS-CoV-2 infection among these neonates. Interestingly, anuria was reported in one,¹¹ and pulmonary bleeding was reported in two neonates^{23,26} which were not mentioned in other studies. Overall, it seems that maternal COVID-19 does not have a direct neonatal impact other than preterm delivery or fetal distress (not found in our study) and the prevention strategies to reduce the risk of mother to infant transmission should be considered.⁴⁰

Three neonates had positive RT-PCR test on the first day of life and three others were positive on day two. On the average, the neonate's PCR became positive on day 4 for the first time. Raschetti et al⁴¹ suggested a vertical transmission with probability of 30%. The results of the current study show that even after excluding participants whose skin to skin contact protections and breastfeeding protocols were not reported, the risk of vertical transmission is still more considerable than our current expectations. But more studies are required to confirm this finding. Nevertheless, what is for sure is the need for extra care for SARS-CoV-2 infected pregnant women and adoption of alternative strategies for breastfeeding and adhering to protection protocols.

The included articles only belong to one country and our findings could be used to compare outcomes from different parts of the world. Case reports are mostly about special patients with special complications, and the Hantoushzadeh et al²⁰ case series was not a consecutive case series and only expired pregnant women were included in that study. The cohort study by Amini Moghadam et al²¹ also had the same problems and their participants were not randomly selected. Up to the present time, two cohort studies by Sattari et al²² and Pirjani et al⁸

have selected random cases. One of the major limitations was the fact that many variables were not mentioned in all of the articles.

In conclusion, early diagnosis of COVID-19 disease is crucial in pregnant women, because there is a possibility of worsening complications in the mother and fetus, and also to use the prevention strategies to reduce the risk of mother to infant transmission.

Authors' Contribution

ZH: Project development. MG: Manuscript editing. BHR: Project development. OK and HF: Data collection and management. MZ: Data management and manuscript writing.

Conflict of Interest Disclosures

None.

Ethical Statement

This manuscript was performed in accordance with Helsinki declaration. All patients' data were kept confidential. This study was approved by Tehran University of Medical Science's ethical committee.

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Supplementary Materials

Supplementary file 1 contains Tables S1-S6.

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