

# Severe Acute Respiratory Syndrome Coronavirus 2 Infection Symptoms in Pregnancy and Maternal and Neonatal Complications Due to COVID-19: A Systematic Review

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### ABSTRACT

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pregnant women is associated with severe maternal and neonatal complications including maternal and newborn death. **Aims:** This review aimed to assess the SARS-CoV-2 infection symptoms during pregnancy as well as maternal and neonatal complications in Iran. **Settings and Design:** A developing and low-income country and a systematic review. **Materials and Methods:** International scientific databases including PubMed, Web of Science, Scopus and Google Scholar were searched in a systematic review manner. Two independent researchers were checked and identified articles from September 2019 to September 2022 based on eligibility criteria and quality appraisal. The results of review were reported in two sections including maternal and neonatal outcomes. **Statistical Analysis Used:** Descriptive statistics was used for statistical analysis. **Results:** Seventeen studies including 870 pregnant mothers with COVID-19 met the eligibility criteria and were reviewed. The main maternal consequences of COVID-19 were intensive care unit (ICU) admission, pre-term delivery, maternal death, pre-mature rupture of membranes, pre-eclampsia, intrauterine growth retardation and stillbirth. Neonatal ICU admission, newborn death, neonatal sepsis, low birth weight and respiratory distress syndrome, tachypnoea, asphyxia and pneumothorax were the most common outcomes of COVID-19 infection in offspring of pregnant subjects. **Conclusion:** Pregnant mothers with COVID-19 infection are at higher risk of being admitted to the ICU and mechanical ventilation and consequently maternal and neonatal death. Comparing the maternal and foetal consequences in different ethnicities, regions and countries may be related to the socioeconomic status of people and should be considered with respect to different determinants. Moreover, the maternal and neonatal complications due to COVID-19 infection in Iran and other developing countries seem to be higher than other countries.

**KEYWORDS:** Coronavirus infection, COVID-19, maternal, neonate, outcome

## INTRODUCTION

Coronavirus 2019 has affected more than millions of people in the world since it started. It was declared as a global pandemic by the WHO on 11 March 2020.<sup>[1]</sup> Severe acute respiratory syndrome coronavirus

2 (SARS-CoV-2) infection during pregnancy is related to mild or moderate disease in high-risk mothers and the

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morbidity and mortality rate is low.<sup>[2]</sup> Nevertheless, for some women, it has led to severe maternal and neonatal complications, including functional (cardiac) disorders, hyperglycaemia and neonatal complications such as tachypnoea and sepsis, and leads to the death of the newborn.<sup>[3,4]</sup> In addition, significant pathological changes are seen in placenta and umbilical cord in pregnancies with COVID-19 indicative of immunological responses of placenta and correlates to the intensive care unit (ICU) admission adverse neonatal outcomes increase.<sup>[5]</sup>

Pregnant women are a high-risk group that due to their sensitive immune system, and are more likely to be exposed to respiratory infections.<sup>[6]</sup> The infection may have a negative effect on the mother and the newborn.<sup>[7]</sup> Many studies have reported unfavourable outcomes of pregnancy in the women infected with COVID-19,<sup>[7-9]</sup> such as pre-term or caesarean birth,<sup>[10-16]</sup> pre-eclampsia,<sup>[13,15]</sup> stillbirth,<sup>[10,15,17]</sup> venous thromboembolism (VTE)<sup>[16]</sup> and pre-mature rupture of membranes (PROM).<sup>[15]</sup> Moreover, their babies are prone to foetal distress and more a higher incidence of admission to the neonatal unit.<sup>[10,18-20]</sup> The entire spectrum of maternal and neonatal consequences of COVID-19 infection in pregnancy and after delivery is still unknown and the vertical transmission is doubtful.<sup>[21-23]</sup>

Based on certain evidence, the noxious outcomes of COVID-19 in mothers and neonates are higher in low- and middle-income countries.<sup>[24,25]</sup> Therefore, due to the harmful consequences of COVID-19 infection for mother and her neonate,<sup>[21]</sup> especially in low-income countries,<sup>[24,25]</sup> this review was conducted to evaluate the common maternal and neonatal adverse consequences of mothers with COVID-19 during pregnancy and after delivery.

## MATERIALS AND METHODS

This study is a systematic review on primary studies in Iran after the COVID-19 pandemic occurrence that assessed the maternal and/or neonatal outcomes of COVID-19 infection in pregnancy and after delivery. The review protocol of the current article is registered in PROSPERO with registration code of CRD42022370584. The scientific databases including Web of Science, PubMed, Scopus and Google Scholar were searched for finding the related sources. Table 1, showed the keywords and search strategy in different databases. Moreover, the references of published articles were evaluated for finding related and relevant articles and sources. The time limit used for articles was from starting the COVID-19 pandemic in September 2019–September 2022. Corona virus 2019, COVID19, pregnancy, consequence, outcomes, maternity, newborn

and delivery were the terms used in search strategy, and these terms were adjusted based on the MeSH. We searched all studies in English and Persian language, and all identified articles were entered into the Endnote software (Endnote X8, Thomson Reuters Co., New York, USA). The title and abstract of all sources were checked and duplicate sources were removed. The article search steps and the flowchart are shown in Figure 1.

### Inclusion and exclusion criteria

All observational studies that included women in the second and third trimesters of pregnancy with positive polymerase chain reaction (PCR) for COVID-19 infection were included in this review. Case report studies that reported the maternal and foetal outcomes of COVID-19 infection were included in this review. Studies that reported maternal and foetal death or other adverse consequences due to COVID-19 were included in this review. Laboratory and animal studies, reviews and other non-original studies, randomised clinical trials, other interventional studies, ongoing studies, conference abstracts, articles without available full text and duplicate studies in different databases were excluded from the study.

The eligibility criteria of the included study in this review were assessed by two different authors and were based on the research questions pertaining to maternal and foetal consequences of COVID-19, study design and study population, as well as the exposure/s and outcome/s of interest. Data extraction was conducted based on these items, and this process was done by two independent authors, SM and MD. Any disagreement between the two authors for selection of articles was settled by the third author (judge) for final decision in consultation with two other authors. Authors' names, year of study, study setting (city), maternal or foetal death, mother's age, neonatal and maternal outcomes such as stillbirth and pre-eclampsia, PROM and other related outcomes were extracted. Data related to the characteristics of mother and neonate as well as clinical features of COVID-19 during hospitalisation were recorded including laboratory tests, received treatments and perinatal and neonatal consequences in Iran.

Bias assessment and quality control of extracted articles were assessed using Cochrane checklist (Supplementary Material). Reporting was also conducted based on the PRISMA checklist. Two authors and an epidemiologist assessed the quality of the articles. The risk of bias and the quality of articles has been evaluated by STROBE checklist as a guideline for reporting observational studies. A random sequence generation and allocation concealment evaluation was used to evaluate selection bias in the articles included in this

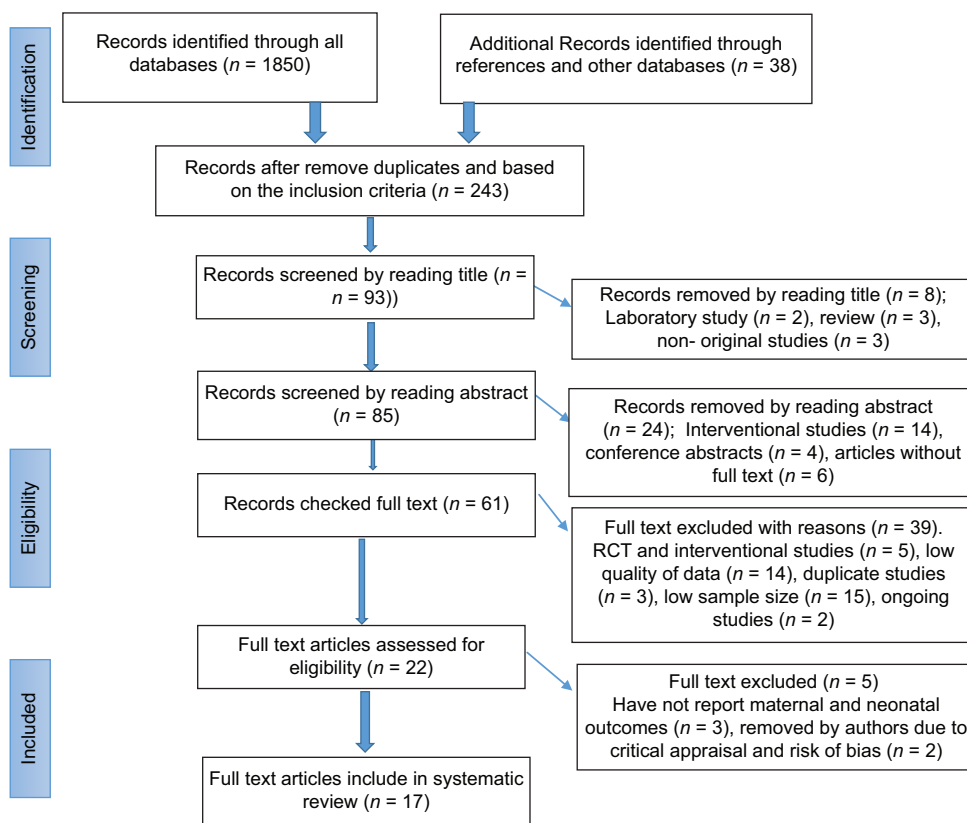


Figure 1: Flow diagram showing the selection of articles for the review process

Table 1 : The keywords and search strategy in different databases

Databases	Keywords/search strategy
PubMed/Medline	Maternal* OR maternal consequence* OR maternal complications* OR outcome* OR prenatal*AND newborn* OR neonatal complications* OR infant* OR consequence*[Mesh] OR coronavirus* OR covid-19* SARS-CoV-2*
Google Scholar	'Maternal outcome' AND 'neonatal outcome'
Scopus	Maternal consequence* OR maternal complications* AND neonatal complications*
Web of Science	'maternal outcome' AND 'neonatal outcome'

regular review. To evaluate performance bias, blinding performed on participants in each study was investigated and reported. Each of the final articles was evaluated for blinding the outcome in order to find detection bias. To determine reporting bias in each study, incomplete or selective outcome reporting was examined.

## RESULTS

Based on the initial search, 1850 articles and documents were retrieved using the applied keywords from 5 different databases and their references. Duplicate records were removed in Endnote software and according to the inclusion criteria 93 records title were remained. This

process was done by two authors independently. When a record was included according to title or abstract or in inconclusive situations between raters, the full text of paper was retrieved and assessed based on eligibility criteria. The literature searches and selection procedure are shown in Figure 1. During the screening procedure [Figure 1], in the first stage by checking titles 93 records were remained and after evaluation of abstracts and full text, finally 22 articles have eligibility criteria that 17 ones entered to review. Finally, after excluding 5 articles, 17 full-text articles were involved in a systematic review according to Table 2.

Finally, from all the included studies, 17 studies including 870 pregnant subjects with COVID-19 fulfilled the eligibility criteria and these articles including 15 cross-sectional and 2 case reports were reviewed that were published from 2019 to 2022. Majority of the involved studies were conducted in Tehran, the capital of Iran,<sup>[26-29]</sup> and the mothers' age varied from 19 to 42 years.

The main maternal and neonatal outcome in the included studies is shown in Table 2. According to these results, the maternal consequences of COVID-19 were ICU admission reported in nine studies,<sup>[27-35]</sup> pre-term delivery in six studies,<sup>[29-33,36]</sup> maternal death in four studies,<sup>[27-29,35]</sup> PROM in three studies,<sup>[26,33,37]</sup> pre-eclampsia,<sup>[30,38]</sup>

**Table 2: Main maternal and neonatal outcome in studies**

Subject	Outcome	Studies	Occurrence rate (%)
Maternal outcomes	Pre-term delivery	6 studies <sup>[29-33,36]</sup>	35.29
	Postpartum bleeding	1 study <sup>[33]</sup>	5.88
	ICU admission	9 studies <sup>[27-35]</sup>	52.94
	PROM	3 studies <sup>[26,33,37]</sup>	17.64
	Maternal death	4 studies <sup>[27-29,35]</sup>	23.53
	Pre-eclampsia	2 studies <sup>[30,38]</sup>	11.76
	IUGR	2 studies <sup>[19,37]</sup>	11.76
	Stillbirth	2 studies <sup>[29,32]</sup>	11.76
Neonatal outcomes	Newborn death	6 studies <sup>[29-31,36-38]</sup>	35.29
	Neonatal sepsis	5 studies <sup>[28-30,33,39]</sup>	29.41
	Low birth weight	8 studies <sup>[28,29,31,36-40]</sup>	47.06
	Tachypnoea	2 studies <sup>[28,36]</sup>	11.76
	NICU admission	7 studies <sup>[26,27,29-32,34]</sup>	41.17
	Asphyxia	2 studies <sup>[31,36]</sup>	11.76
	Pneumothorax	2 studies <sup>[27,37]</sup>	11.76
	RDS	3 studies <sup>[28,30,39]</sup>	17.65

ICU=Intensive care, PROM=Pre-mature rupture of membranes, IUGR=Intrauterine growth retardation, NICU=Neonatal ICU, RDS=Respiratory distress syndrome

intrauterine growth retardation (IUGR)<sup>[19,37]</sup> and stillbirth in two studies<sup>[29,32]</sup> and postpartum bleeding in one study.<sup>[33]</sup> Neonatal ICU (NICU) admission was the most important of foetal consequences as reported in seven studies,<sup>[26,27,29-32,34]</sup> and low birth weight was in the second rank as reported in eight studies.<sup>[28,29,31,36-40]</sup> Moreover, newborn death was reported in six studies,<sup>[29-31,36-38]</sup> neonatal sepsis<sup>[28-30,33,39]</sup> in five studies and respiratory distress syndrome (RDS) in three studies.<sup>[28,30,39]</sup> In addition, tachypnoea,<sup>[28,36]</sup> asphyxia<sup>[31,36]</sup> and pneumothorax were reported in two studies.<sup>[27,37]</sup> Therefore, based on our results [Table 2], ICU admission, pre-term delivery and maternal death were the most common maternal outcomes of COVID-19 that were reported in 52.94%, 35.29% and 23.53% of the included population of this review, respectively. In addition, low birth weight, NICU admission and newborn death were the most common neonatal outcomes, reported in 47.06%, 41.17% and 35.29%, respectively.

The most common complaints [Table 3] included pregnant women were fever, cough, fatigue, body aches and headaches.<sup>[29,30,32,33,35,36]</sup> The most prevalent laboratory finding in women with COVID-19 was an increase in C-reactive protein (CRP).<sup>[30,33,36]</sup> Gastrointestinal symptoms were reported in Gragri *et al.*'s study.<sup>[31]</sup> Lymphopenia (62%), increased CRP (96.4%), lactate dehydrogenase (LDH) (48%), anaemia (21.4%) and liver enzymes (14.2%) were reported in Abedzadeh-Kalahroudi *et al.*'s study.<sup>[30]</sup> While CRP increase in Pirjani *et al.*'s study was (42%), leucocytosis (43%) and lymphopenia (46%).<sup>[33]</sup>

IUGR due to infection was caused by COVID-19 is reported in some studies.<sup>[30,32,37,40]</sup> Most of the patients

were infected in the third trimester of pregnancy,<sup>[30,32]</sup> but only one study showed the highest involvement in the first trimester of pregnancy.<sup>[40]</sup> Miscarriage was reported in Pakniat *et al.*'s study<sup>[26]</sup> in 6% of cases, and Pirjani *et al.* reported that two women had a miscarriage.<sup>[33]</sup> In two other studies, 12.1%<sup>[31]</sup> and 3.7%<sup>[30]</sup> of patients were admitted to ICU due to low oxygen saturation (SpO<sub>2</sub>) that more than half of them required respiratory ventilators.

## DISCUSSION

This review summarised and classified the most common complications, adverse effect and adverse outcomes of SARS-CoV-2 infection during pregnancy for mother and foetus. Maternal outcomes in this review were pre-mature birth, stillbirth, RDS, intrauterine foetal death and low birth weight in the third trimester.<sup>[26]</sup> The pre-mature birth complication in women with COVID-19 is more than the background risk.<sup>[30-32,34]</sup> In addition, the infant involvement in the first trimester of pregnancy was reported in one study.<sup>[41]</sup> In Samadi *et al.*'s study, eight pregnant women (3.1%) died due to COVID-19 severity.<sup>[35]</sup> Pre-mature birth<sup>[29,30,32,33,36]</sup> and stillbirth<sup>[32]</sup> were the most common impacts of the coronavirus on pregnancy as reported by most of the studies. Although, maternal death, PROM, IUGR and hospitalisation in the ICU<sup>[27,28,33]</sup> were mentioned in some studies, as pre-mature birth varied from 17.8%<sup>[29]</sup> to 34.5%<sup>[30]</sup> in the included studies.

In the current review, the most common maternal and neonatal complications of COVID-19 in Iran were similar to other studies.<sup>[42]</sup> Considering maternal ICU admissions and maternal deaths during COVID-19

**Table 3: The characteristics of entered study in systematic review**

D	Author	City	Year	Participant	Type of study	Mother's age	Cough	Headache	Myalgia	Fatigue	Diarrhoea	Shortness of breath
1	Taghavi et al. <sup>[32]</sup>	Hormozgan	2021	110	Descriptive	30.45±4.22	+	-	+	+	+	+
2	Pirjani et al. <sup>[33]</sup>	Tehran	2020	199	Descriptive	30.9±6.3	+	-	+	-	-	+
3	Abedzadeh-Kalahroudi et al. <sup>[30]</sup>	Tehran	2021	160	Cohort	31.6±6.1	+	-	-	-	-	+
4	Chaichian et al. <sup>[27]</sup>	Tehran	2021	14	Series case	31	+	-	+	-	-	+
5	Vizheh et al. <sup>[37]</sup>	Isfahan	2021	599	Descriptive	31.1±5.8	+	-	-	-	-	-
6	Moaya et al. <sup>[36]</sup>	Tehran	2021	120	Descriptive case series	-	+	-	-	-	-	-
7	Samadi et al. <sup>[35]</sup>	Qom	2021	256	Descriptive	29.5±6.03	+	+	+	+	+	+
8	Mohaghegh et al. <sup>[29]</sup>	Tehran	2021	15257	Descriptive	29.7±5.9	+	-	-	-	-	-
9	Rashidi et al. <sup>[40]</sup>	Tehran	2022	38	Cross sectional	31.6±7.3	+	-	-	-	-	+
10	Saleh Gargari et al. <sup>[31]</sup>	Tehran	2022	182	Descriptive	29.3±6.15	+	+	+	+	+	+
11	Farhadi et al. <sup>[28]</sup>	Tehran	2022	118	Cross sectional	30.29±4.92	-	-	-	-	-	-
12	Azh et al. <sup>[26]</sup>	Qazvin	2021	133	Descriptive	27.09±5.67	+	-	+	-	-	-
13	Asadi et al. <sup>[53]</sup>	Gorgan	2020	100	Descriptive	30.2±5.67	-	-	-	-	-	-
14	Alipour et al. <sup>[34]</sup>	Qom	2020	165	Retrospective cohort	29±4.3	+	-	-	-	-	-
15	Jenabi et al. <sup>[38]</sup>	Hamedan	2022	90	Case-control study	29.47±5.64	+	+	+	+	+	+
16	Kazemi Aski et al. <sup>[54]</sup>	Tehran	2021	40	Case-control study	25.2±6.2	+	-	-	-	-	-
17	Sheikhahmadi et al. <sup>[39]</sup>	Sanandaj	2021	8	Case series	30±5.4	+	-	-	-	-	-
<b>D Add NICU Maternal outcome Neonatal outcome</b>												
1	+	-	-	-	Hydroxychloroquine/antibiotic	Pre-term delivery	-	-	-	-	-	-
2	-	+	4	1	Chloroquine/ritonavir/lopinavir	Postpartum bleeding ICU admission	-	-	-	-	-	Neonatal sepsis
3	-	+	6	9	Antibiotic	Pre-term delivery PROM	-	-	-	-	-	RDS sepsis newborn death
4	-	+	1	2	Atazanavir/favipiravir/chloroquine/steroid//antibiotic	Abort-eclampsia Foetal distress death of mother intubation	-	-	-	-	-	Pneumomediastinum
5	-	+	-	1	Antibiotic	In pre-mature rupture of membranes, pre-mature delivery, intrauterine growth retardation/necrotising//meconium/sepsis/ptl/PROM/UUGR	-	-	-	-	-	LBW enterocolitis/pneumothorax
6	+	-	-	1	Antibiotic	Pre-term delivery/placental involvement	-	-	-	-	-	LBW baby/Neonatal asphyxia Tachypnoea
7	+	33	33	5	Ceftriaxone Remdesivir/azithromycin/hydroxychloroquine	Death of mother increased length of hospitalisation	-	-	-	-	-	Death of mother increased length of hospitalisation
8	+	3	3	2	Antibiotic	Pre-term delivery death of mother stillbirth the ventilator ICU admission mechanical ventilation, maternal mortality	-	-	-	-	-	Death of a baby sepsis
9	-	-	-	-	Antibiotic	Abortion bleeding hysterectomy pre-mature	-	-	-	-	-	low birth weight RDS

Contd...



Table 3: Contd...

D	Sore throat	Fever	Add ICU	Drug	Add NICU	Maternal outcome	Neonatal outcome
10	+	+	22	Hydroxychloroquine Enoxaparin sodium Lopinavir/ritonavir antiviral drug Corticosteroid	11	Pre-term delivery Foetal distress maternal ICU ad mission IUGR	Death of a Newborn asphyxia
11	-	-	31	Antiviral therapy	34	Convulsions Maternal death Pneumomediastinum	Pre-mature infants Sepsis RDS Hospitalisation in NICU Seizure/TTN/neonatal abstinence syndrome
12	+	-	4	Antiviral therapy		Pre-mature rupture of membranes, maternal death/IUGR	
13	-	-				Pre-mature labour pre-term	
14	-	-				Foetal stress Pre-mature birth	
15	+	+		Antibiotic		Pre-eclampsia Pre-term labour	LBW Neonatal death RDS RDS LBW Sepsis
16							
17	-	+					

ICU=Intensive care unit, PROM=Pre-mature rupture of membranes, IUGR=Intrauterine growth retardation, NICU=Neonatal ICU, RDS=Respiratory distress syndrome, LBW=Low birth weight, TTN=Transient tachypnoea of the newborn

pandemic in different studies, the results of this review and other studies appear reassuring.<sup>[28,30]</sup> Studies have shown that SARS-CoV-2 infection during pregnancy increases the risk of pre-term or caesarean birth,<sup>[10-16]</sup> pre-eclampsia,<sup>[13,15]</sup> stillbirth,<sup>[10,15,17]</sup> VTE,<sup>[16]</sup> PROM<sup>[15]</sup> and admission to NICU.<sup>[10]</sup> Moreover, the laboratory results such as increased CRP,<sup>[36]</sup> alanine transaminase and aspartate aminotransferase<sup>[32]</sup> as well as maternal and foetal consequences following COVID-19 were reported in many studies. As per one study,<sup>[27]</sup> all infants' PCR was positive, and in another study,<sup>[26]</sup> only one baby had positive PCR for COVID-19.

However, women in pregnancy encounter physiological variations that increase their vulnerability to severe respiratory infections and complications due to diseases such as COVID-19 infections.<sup>[43,44]</sup> It is considered that pregnant women are not at higher risk for COVID-19 infection than other people, but mothers during pregnancy with symptomatic COVID-19 may experience higher adverse consequences than other people. Based on some studies, an inequality is seen in pregnant women in different countries based on the income level and mothers in low- and middle-income countries are challenged with important struggles.<sup>[45]</sup> Moreover, the COVID-19 virus type is related to the maternal and foetal consequences. However, Delta variant infection during pregnancy is related to increased risk of placental dysfunction and foetal abortion than other variants.<sup>[46,47]</sup> A case report showed probability for placental dysfunction and foetal disorders due to Delta-variant SARS-CoV-2 infection during pregnancy not necessarily proportional to the disease severity.<sup>[47]</sup>

ICU admission, pre-term delivery and maternal death were reported in 52.94%, 35.29% and 23.53%, respectively, as the most common maternal outcomes of COVID-19. Moreover, low birth weight, NICU admission and newborn death were reported in 47.06%, 41.17% and 35.29%, respectively, as the most common neonatal outcomes in this review. Severe-critical disease and adverse perinatal outcomes were reported to 24.1% in Delta, 13.3% in pre-Delta and 1.8% in Omicron.<sup>[46]</sup> The severe consequences of COVID-19 including mother and neonatal death as well as pre-term delivery and NICU admission were higher in Iranian people in comparison to other studies in developed countries. This difference could be due to diversity in COVID-19 vaccination schedule and types and delayed access to effective drugs.

Vertical transmission of COVID-19 is reported in two studies by Zamaniyan *et al.*<sup>[48]</sup> and Abedzadeh-Kalahroudi *et al.*<sup>[30]</sup> Zamaniyan *et al.*'s study<sup>[48]</sup> showed a positive test of SARS-CoV-2 for amniotic fluid and neonatal

nasal and throat swabs. There were cases of confirmed vertical transmission of SARS-CoV-2 between mother and offspring, and it is related to the severity of maternal COVID-19.<sup>[49]</sup> The WHO classified the COVID-19 transmission from mother to child into three types including *in utero*, intrapartum and early post-natal.<sup>[49]</sup> However, the congenital infection rate is reported <2% of all maternal infections and varied from 0.1% in North America to 5.7% in Latin America and the Caribbean regions.<sup>[49]</sup> The mechanism of SARS-CoV-2 effect during pregnancy on foetus is based on the angiotensin-converting enzyme 2 receptors and serine protease TMPRSS2 of the placenta.<sup>[44,50,51]</sup> However, the maternal immunoglobulin M of SARS-CoV-2 may affect the foetus due to ischaemic injury to the placenta, without requiring placental cell infection.<sup>[44,52]</sup>

This review has some limitations as data of neonate screening for COVID-19 infection using PCR on cord blood, amniotic fluid, nasopharyngeal swab and urine analysis were reported in only some studies. Moreover, data of mother comorbidities were not available, and we could not report on this important aspect. In addition, the relevance of these findings to pregnancies following assisted conception cannot be ascertained.

## CONCLUSION

Based on this review, the main maternal consequences of COVID-19 were ICU admission, pre-term delivery, maternal death, PROM, pre-eclampsia, IUGR and stillbirth. While NICU admission, newborn death, neonatal sepsis, low birth weight and RDS, tachypnoea, asphyxia and pneumothorax were the most common outcomes of COVID-19 infection in women during pregnancy. Therefore, pregnant women with COVID-19 infection are at higher risk ICU admission and mechanical ventilation and consequently maternal and neonatal death. Moreover, the effect of vertical transmission of COVID-19 infection should be looked into in larger studies. In addition, comparing the maternal and foetal consequences in different ethnicities, regions and countries and socioeconomic status of people and should be evaluated as determinants. The maternal and neonatal complications due to COVID-19 infection in Iran and other developing countries appear to be higher than other countries.

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## Conflicts of interest

There are no conflicts of interest.

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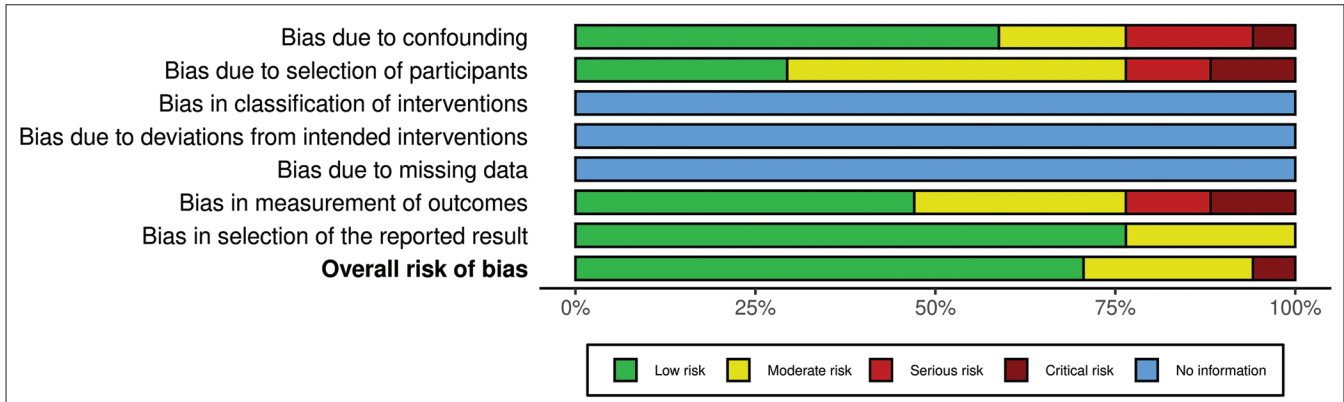
## Supplementary Material

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Taghavi et al[32]	-	-	?	?	?	-	-	-
Reihaneh Pirjani et al[33]	-	+	?	?	?	+	+	+
Masoumeh Abedzadeh-Kalahroudi et al[30]	X	!	?	?	?	+	-	+
Shahla Chaichian, et al[27]	+	+	?	?	?	!	+	+
Maryam Vizheh et al,[37]	-	-	?	?	?	+	+	+
Moaya Mansoureh et al[36]	+	+	?	?	?	X	-	+
Parisa Samadi,, et al[35]	+	+	?	?	?	+	+	+
Zaynab Mohaghegh, et al[29]	+	X	?	?	?	+	+	+
Batool Hossein Rashidi et al[40]	X	+	?	?	?	X	+	-
Soraya Saleh Gargari , et al[31]	+	-	?	?	?	+	+	+
Roya Farhadi, et al [28]	+	-	?	?	?	-	+	+
Nizal Aj, et al[26]	+	-	?	?	?	-	-	-
Roya Ismailpour Astrakhi, et al[53]	+	-	?	?	?	-	+	+
Zahra Alipor, et al[34]	+	-	?	?	?	+	+	+
Ensiyeh Jenabi ,et al[38]	+	-	?	?	?	+	+	+
Sudabeh kazemi, et I[54]	X	!	?	?	?	-	+	-
Shobo Sheikahmadi, et al[39]	!	X	?	?	?	!	+	!

Domains:  
D1: Bias due to confounding.  
D2: Bias due to selection of participants.  
D3: Bias in classification of interventions.  
D4: Bias due to deviations from intended interventions.  
D5: Bias due to missing data.  
D6: Bias in measurement of outcomes.  
D7: Bias in selection of the reported result.

Judgement  
! Critical  
X Serious  
- Moderate  
+ Low  
? No information

Supplementary Material 1: ROBINS-i(1)



Supplementary Material 1: ROBINS-i(2)

**Supplementary Material 1: ROBINS-i(3)**

<b>Study</b>	<b>Confounding</b>	<b>Selection</b>	<b>D3</b>	<b>D4</b>	<b>D5</b>	<b>Information</b>	<b>Reporting</b>	<b>Overall</b>
Taghavi <i>et al</i> <sup>[32]</sup>	Moderate	Moderate	No information	No information	No information	Moderate	Moderate	Moderate
Reihaneh Pirjani <i>et al</i> <sup>[33]</sup>	Moderate	Low	No information	No information	No information	Low	Low	Low
Masoumeh Abedzadeh-Kalahroudi <i>et al</i> <sup>[30]</sup>	Serious	Critical	No information	No information	No information	Low	Moderate	Low
Shahla Chaichian, <i>et al</i> <sup>[27]</sup>	Low	Low	No information	No information	No information	Critical	Low	Low
Maryam Vizheh <i>et al</i> , <sup>[37]</sup>	Moderate	Moderate	No information	No information	No information	Low	Low	Low
Moaya Mansoureh <i>et al</i> <sup>[36]</sup>	Low	Low	No information	No information	No information	Serious	Moderate	Low
Parisa Samadi, <i>et al</i> <sup>[35]</sup>	Low	Low	No information	No information	No information	Low	Low	Low
Zaynab Mohaghegh, <i>et al</i> <sup>[29]</sup>	Low	Serious	No information	No information	No information	Low	Low	Low
Batool Hossein Rashidi <i>et al</i> <sup>[40]</sup>	Serious	Low	No information	No information	No information	Serious	Low	Moderate
Soraya Saleh Gargari, <i>et al</i> <sup>[31]</sup>	Low	Moderate	No information	No information	No information	Low	Low	Low
Roya Farhadi, <i>et al</i> <sup>[28]</sup>	Low	Moderate	No information	No information	No information	Moderate	Low	Low
Nizal Aj, <i>et al</i> <sup>[26]</sup>	Low	Moderate	No information	No information	No information	Moderate	Low	Low
Roya Ismailpour Astrakhi, <i>et al</i> <sup>[53]</sup>	Low	Moderate	No information	No information	No information	Moderate	Moderate	Moderate
Zahra Alipor, <i>et al</i> <sup>[34]</sup>	Low	Moderate	No information	No information	No information	Moderate	Low	Low
Ensiyeh Jenabi, <i>et al</i> <sup>[38]</sup>	Low	Moderate	No information	No information	No information	Low	Low	Low
Sudabeh Kazemi, <i>et al</i> <sup>[54]</sup>	Serious	Critical	No information	No information	No information	Moderate	Low	Moderate
Shobo Sheikhhahmadi, <i>et al</i> <sup>[39]</sup>	Critical	Serious	No information	No information	No information	Critical	Low	Critical