

## The Relationship between COVID-19 and Preterm Birth During a Year of Pandemic; A Systematic Review

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### Abstract

**Aims:** The recent coronavirus disease 2019 (COVID-19) outbreak became a global health concern in 2020 and the effect this novel coronavirus disease is still unclear on pregnant women. The present systematic review aimed to study the relationship between COVID-19 in pregnant women and development of preterm birth.

**Instrument & Methods:** A systematic search of the published literature in PubMed, Scopus, and Google scholar was performed on every article addressing pregnant women regardless of the age or gestational age who were confirmed or suspected case of COVID-19 who gave birth and developed any type of neonatal adverse outcomes were included.

**Findings:** Seventeen studies entered the present systematic review from America, Europe, and Asia. A total number of 6251 deliveries from COVID-19 women were evaluated by these studies before excluding the possible studies with overlapping populations. The most common neonatal complication was preterm labor (11.9%). Other complications reported in more than one study included stillbirth (0.7%), PROM (12%), SGA (4%), and PPROM (5.4%). Moreover, the overall NICU admission was 173 neonates (25.2%).

**Conclusion:** Without considering the COVID-19 severity in pregnant women, the rate of preterm delivery as the most common neonatal complication is approximately 12% of live births which slightly greater than the previously reported global preterm rate in 2020.

### Keywords

Pregnancy [<https://www.ncbi.nlm.nih.gov/mesh/68011247>];

Premature Birth [<https://www.ncbi.nlm.nih.gov/mesh/?term=Preterm+Birth>];

COVID-19 [<https://www.ncbi.nlm.nih.gov/mesh/2052179>]

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## Introduction

The recent coronavirus outbreak has a considerable burden on almost every society and soon became a global health issue [1]. Similar to the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), the SARS-CoV-2 infection could occur at any age and some specific populations are at increased risk of developing coronavirus disease-2019 (COVID-19) including elderlies and those with chronic illnesses including hypertension, diabetes mellitus, and malignancies [2]. Despite more than one year of introducing the first case of COVID-19, the effect of SARS-CoV-2 infection is not clearly understood on pregnant women and pregnancy outcomes [3]. COVID-19 manifests with a wide range of clinical symptoms varying from asymptomatic or mild infection to severe respiratory failure and death. The most common manifestation include respiratory and flu-like symptoms as well as gastrointestinal symptoms including abdominal pain and diarrhea [4]. Moreover, laboratory abnormalities including lymphopenia and leukopenia alongside abnormal pulmonary imaging studies is present in most of the infected patients [5]. Based on recent reports, pregnant women infected with SARS-CoV-2 may experience such clinical and laboratory abnormalities, even more severe than the general population [6]. It has been demonstrated that pregnant women are more vulnerable to develop severe complications following viral infections during pandemics and seasonal viral infections such as Ebola and influenza infections [7]. During the SARS outbreak in 2003, more than half of the infected patients were women and the mortality rate was reported to be higher in males. Moreover, maternal and fetal outcomes were reported to worsen in infected pregnant women [8, 9]. Although available data about the effect of SARS and MERS on pregnancy is sparse; however, it seems that SARS-CoV-2 infection affect pregnant women similar to the previous coronavirus outbreaks. While young age and female gender are 2 factors associated with more favorable outcomes in SARS-CoV-2 infection; when pregnancy occurs, the outcome becomes negatively affected by these factors. It has been reported that infected pregnant women are at increased risk of developing severe infection requiring intensive care unit admission and mechanical support [6].

Regardless of the adverse effect of SARS-CoV-2 infection on pregnant women, the effect of infection on pregnancy outcome is limited. Moreover, our knowledge about the neonatal complications resulted from the previous coronavirus outbreaks including SARS and MERS is very limited and could not be used as a guideline for the current outbreak. Evenmore, the most recent systematic review and meta-analyses published in 2021 evaluating the effect of COVID-19 on pregnancy outcomes provided

controversial results [10-13]. Although these studies were conducted on published literature up to mid-2020; however, controversial results regarding the increased number of adverse pregnancy and neonatal outcomes including preterm labor and neonatal death rate are present [10-13]. Therefore, we aimed to evaluate the effect of maternal COVID-19 infection on neonatal outcomes reported in clinical studies published within the first year of introducing the SARS-CoV-2 pandemic as a global health concern.

## Instrument and Methods

### Literature Search Strategy and Selection Criteria:

The present systematic review protocol approved by Mashhad University of Medical Sciences Ethic committee by code IR.MUMS.REC.1399.209. The main purpose of the present systematic review based on the PICO tool formulated as (P) any pregnant women regardless of the age or gestational age who were confirmed case of COVID-19 based on molecular tests or imaging studies as well as the pregnant women who were clinically suspected to have COVID-19 disease but were not tested or underwent imaging studies; (I) gave birth; (CO) neonatal adverse outcomes including premature rupture of amniotic membrane (PROM), Preterm premature rupture of the membranes (PPROM), preterm labor, neonatal death or stillbirth, low birth weight, small for gestational age (SGA) and other severe neonatal conditions including pneumonia sepsis. Therefore, a systematic search of the published literature in PubMed, Scopus, and Google scholar was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Two independent researchers searched the databases until March 5, 2021, with the combination of keywords including SARS-CoV-2 infection and pregnancy outcomes (supplementary 1). Moreover, the researchers cross-checked the references of each article for any relevant studies. The inclusion criteria consisted of any English language article on human subjects addressing pregnant women infected with COVID-19 and reporting their perinatal outcomes or complications. Any types of review articles, as well as small case reports or case series (reporting  $\leq 10$  deliveries), were excluded.

After retrieving the primary studies, overlapped and duplicated articles were excluded and the quality of remained studies evaluated by Newcastle-Ottawa scale. A total number of 405 studies entered the article evaluation phase and after removing the duplicated references, 240 results remained. After screening the title and abstract of these studies, 59 articles were meet the inclusion criteria and entered the full-text evaluation phase. Among these articles, 17 articles remained and entered the final analysis.

## Findings

Among the 17 studies entered the present systematic review [14-30], 3 of them were case-control studies [14, 15, 29] (Table 1).

These 17 studies were from 3 continents including America, Europe, and Asia. Only one study from china

[17] evaluated infants born with cesarean section, and the rest of 16 studies both vaginal delivery and cesarean section (Table 2). While 15 articles studied pregnant women with a confirmed diagnosis of COVID-19 with molecular or imaging studies, 2 studies included suspected cases of COVID-19 [27, 28, 30].

**Table 1)** Case control studies addressing the relationship between maternal COVID-19 and neonatal outcomes.

Author	Location	Date	Number of deliveries from infected mothers	Mode of delivery	COVID-19 confirmation method	Number of Neonatal uninfected outcome mothers	Comments
Liao et al. [14]	Hubei, China	20 January – 2 March	10	Vaginal delivery	Confirmed* or suspected COVID-19	53	Preterm birth: 1/10 (10%) Neonatal death: 0/10 (0%) One neonate had hyaline membrane disease, which successfully treated
Prabhu et al. [15]	USA	20 March	70	Vaginal delivery and cesarean section	Only confirmed cases *	605	Stillbirth: 1/70 (1%) Preterm birth: 11/70 (15%) Preterm birth rate and live birth were not different among groups.
Yang et al. [29]	Hubei, China	13 January – 18 March	65	Vaginal delivery and cesarean section	Only confirmed cases *	11013	PROM: 4/65 (6%) Preterm birth: 9/65 (14%) Pregnant women with COVID-19 had an increased risk of preterm delivery.

**Table 2)** Studies addressing the relationship between maternal COVID-19 and neonatal outcomes.

Author	Location	Date	Number of deliveries	Mode of delivery	COVID-19 confirmation method	Perinatal outcome
1 Martínez-Perez et al. [16]	Spain	12 March – 6 April	82	Vaginal delivery and cesarean section	Only confirmed cases*	PROM: 18/82 (21%) PPROM: 7/82 (8%) Preterm: 15/82 (18%) NICU admission: 19/52 (23%) Apgar score < 5 at 5min: 3/82 (3.6%)
2 Khan et al. [17]	Hubei, China	25 January – 15 February	17	Cesarean section	Only Confirmed cases **	Preterm: 3/17 (17%) Neonatal pneumonia: 5/17 (30%) Neonatal death: 0/17 (0%) Stillbirth: 0/17 (0%)
3 Woodworth et al. [18]	16 Jurisdictions in the USA	29 March – 14 October	4527	Vaginal delivery and cesarean section	Only confirmed cases *	Pregnancy loss: 32/4527 (0.7%) Preterm: 506/3912 (12.9%) ICU admission: 279/2995 (9.3%)
4 Delahoy et al. [19]	13 states of USA	1 March – 22 August	458	Vaginal delivery and cesarean section	Only confirmed cases *	Preterm birth: 56/445 (12.6%) Pregnancy loss: 10/458 (2.2%) In hospital death: 2/448 (0.4 %)
5 Khoury et al. [20]	USA	13 March – 12 April	247	Vaginal delivery and cesarean section	Only confirmed cases *	Preterm birth: 34/233 (14%) NICU: 61/237 (25.7%) Sepsis: 1/241 (0.04%) RDS: 14/241 (5.8%) Still birth: 2/247 (0.8 %)

**Table 2)** Studies addressing the relationship between maternal COVID-19 and neonatal outcomes.

6	<b>Knight <i>et al.</i></b> [21]	UK Obstetric Surveillance System	1 March – 14 April	427	Vaginal delivery and cesarean section	Only confirmed cases *	Pregnancy loss: 4/427 (1%) Stillbirth: 3/427 (1%) Neonatal death: 2/427 (1%) Preterm birth: 31/427 (26%)
7	<b>Remaeus <i>et al.</i></b> [22]	Sweden	19 March – 26 April	68	Vaginal delivery and cesarean section	Only confirmed cases *	Stillbirth: 1/68 (1%) Preterm birth: 14/68 (21%) SGA: 3/67 (4%) NICU admission: 12/67 (18%)
8	<b>Liu <i>et al.</i></b> [23]	Hubei, China	31 January – 21 February	19	Vaginal delivery and cesarean section	Only confirmed cases *	PROM: 3/19 (15%) Preterm birth: 2/19 (11%) Neonatal death: 0/19 (0%)
9	<b>Pierce-Williams <i>et al.</i></b> [24]	Twelve hospitals from 4 regions in the USA	5 March – 20 April	64	Vaginal delivery and cesarean section	Only confirmed cases *	Preterm: 19/64 (25%) PPROM: 1/64 (1%) NICU admission: 21/64 (63%) Stillbirth: 0/64 (0%) IUGR: 2/64 (3%)
10	<b>Savasi <i>et al.</i></b> [25]	A multicenter study from Italy	23 February – 28 March	57	Vaginal delivery and cesarean section	Only confirmed cases *	Preterm birth: 12/57 (21%) NICU admission: 9/57 (16%) Neonatal death: 0/57 (0%)
11	<b>Sentilhes <i>et al.</i></b> [26]	France	1 March – 3 April	54	Vaginal delivery and cesarean section	Confirmed* or suspected COVID-19	Preterm birth: 5/54 (23.8%) Fetal death: 1/54 (1.9%) SGA: 2/54 (9.5%) NICU admission: 3/54 (14%)
12	<b>Villalaín <i>et al.</i></b> [27]	Spain	28 February – 10 May	54	Vaginal delivery and cesarean section	Confirmed* or suspected COVID-19	Still birth: 0/54 (0%) SGA: 2/54 (2%) IUGR: 0/54 (0%) Preterm birth: 4/54 (7.4%) NICU admission: 1/54 (5%)
13	<b>Zhang <i>et al.</i></b> [28]	Hubei, China	30 January – 1 March	18	Vaginal delivery and cesarean section	Only confirmed cases *	Preterm birth: 3/18 (17%) PROM: 4/18 (22%) Neonatal death: 0/18 (0%)
14	<b>Yan <i>et al.</i></b> [30]	China	20 January – 24 March	99	Vaginal delivery and cesarean section	Confirmed* or suspected COVID-19	Fetal distress: 9/99 (10.6%) Preterm birth: 21/99 (21.2%) PROM: 6/99 (6.1%) NICU admission: 47/99 (47%) Neonatal death: 1/99 (1%)

A total number of 6251 deliveries from COVID-19 women were evaluated by these studies before excluding the possible studies with overlapping populations. Based on these 6251 deliveries, the most common neonatal complication was preterm labor (11.9%). Other complications reported in more than one study included stillbirth (0.7%), PROM (12%), SGA (4%), and PPRM (5.4%).

The results can also be interpreted by regions to reduce the chance of overlapping populations and duplicated patients. Among the 17 studies, 6 were from the Hubei province in China with overlapping study recruitment dates. Among these 6 articles, the Yan *et al.* study chose their study population from Hubei and outside the Hubei province<sup>30</sup>. This study with the largest population size from China demonstrated that preterm birth (21.2%), fetal distress (10.6%), PROM (6.1%), and neonatal death (1%) were the common complications among COVID-19 infected women and 47% of the neonates born to these mothers had been admitted in NICU admission<sup>30</sup>. By considering the infant population from the other 5 studies in China, the overall number of infants

born to infected mothers will be 219 neonates<sup>[14]</sup> [17,23,28]. Among them, 15% had preterm labor as the most common complication. Yang *et al.* highlighted this finding in their case-control study indicating that COVID-19 infection in pregnant women increases the risk of preterm birth.

The largest study conducted by Woodworth *et al.* on 16 Jurisdictions in the USA reported that 12.9% of infants born from COVID-19 infected mothers are preterm and pregnancy loss occurs in less than 1 percent of infected mothers (0.7%)<sup>[18]</sup>.

The Knight *et al.* study has the largest population from the UK Obstetric Surveillance System demonstrating that preterm birth (26%), pregnancy loss (1%), neonatal death (1%), and stillbirth (1%) are the common complications in COVID-19 infected mother<sup>[21]</sup>. While the population overlap is possible for the 2 studies from Spain; by excluding these 2 studies and considering the rest of the studies from Europe, the overall preterm birth percentage will be 10%<sup>[16, 17, 21, 22, 25, 27]</sup>.

By considering the largest study from the USA, the 6 studies China and European studies excluding the 2

Spanish articles, the percentage of preterm labor will be 12% [14, 16-18-22-24-28, 30].

Regardless of the preterm birth rate as the most common complication, the overall NICU admission was 173 (25.2%) with the highest percentage of admission reported by Pierce-Williams *et al.* study from the USA (63%) [24]. The highest percent of preterm labor among pregnant women was reported by Pierce-Williams *et al.* on 12 institutions from the USA and a single study from France (25% and 23.8% respectively) [24, 26]. The lowest percent of preterm delivery was reported from a study evaluating both confirmed and suspected COVID-19 cases from Spain (6%) [27]. The highest percentage of pregnancy loss has been reported in the Delahoy *et al.* study evaluating pregnant women from 13 different USA states from March 1 to August 22 (2%) [19] (13 states,). The highest percentage of PROM has been reported by Martínez-Perez *et al.* from Spain (21%) and the lowest percentage was reported by Pierce-Williams *et al.* from the USA (1%) [16]. While the Sentilhes *et al.* study from France reported the highest percentage of SGA (9.5%), the Villalaín *et al.* study reported the lowest percentage (2%) on Spanish women [26, 27]. Other studies from USA reported higher rate of preterm birth (15%, 14% and 25% respectively) [15, 20, 24]. The results of the studies from the USA should be interpreted with caution as there is recruitment period overlap and some studies have been conducted in similar states.

## Discussion

The present study demonstrated that among the evaluated studies preterm labor is the most common neonatal complication varying from 1% to 26% of deliveries from COVID-19 infected mothers while other complications including neonatal death, PROM, and stillbirth occurs less frequently.

Similar to the other viral infections, the SARS-CoV-2 can provide disease with variable severity depending on many factors mainly the host's immune system. Pregnancy is a complicated physiological phenomenon with many unclear aspects especially its effect on the maternal immune system. The adaptation of the immune system during pregnancy results in an altered immune response [8]. The previous coronavirus infections had a considerable rate of adverse maternal outcomes and mortality rate. Although the clinical evidence for complications of previous coronavirus infections on pregnancy is limited; however, SARS and MERS were both correlated with increased preterm birth, IUGR, and perinatal death [9]. A national cohort study during the early days of the outbreak from the UK reported that the risk factors of hospitalization for COVID-19 among women are similar to the rest of the population [21]. The largest study addressing the effect of COVID-19 on pregnant women was reported from the US, including 91412 pregnant. This study

demonstrated that pregnancy is associated with an increased risk of hospitalization, mechanical ventilation, and ICU admission [31]. However, the effect of SARS-CoV-2 on the postpartum period seems to be a little different.

Preterm labor is a challenging issue regarding the effect of COVID-19 infection on postpartum complications. Regardless of the COVID-19 infection, it has been reported that 15 million neonates are born preterm each year [32]. The most recent study evaluating the global rate of preterm birth has reported an approximate rate of 11% of birth occurring before 37 weeks of pregnancy [32]. Preterm labor has been related to various socio-demographic and medical risk factors [33]. While two-thirds of preterm births occur without a well-known risk factor, the rests happen because of specific factors including maternal medical condition [33]. It has been demonstrated that systemic maternal infections, as well as intrauterine infections, are associated with preterm delivery. Although the mechanism behind preterm labor induced by viral agents is not clearly understood; however, a well-known example of preterm labor caused by viral infection is the influenza infection [34]. Our study demonstrated preterm labor is the most common complication reported in pregnant women infected with SARS-CoV-2. However, we demonstrated that by summing up the preterm births from the studies addressing neonatal complications in mothers infected with COVID-19, the rate of preterm labor seems to be slightly higher than the global preterm rate before the COVID-19 outbreak (12% versus 11%) [32, 33]. Such finding has been addressed in recently published literature comparing the overall preterm delivery before and after the COVID-19 outbreak. A study by Wood *et al.* reports no significant reduction in the preterm birth rate at the hospital system in the US during the COVID-19 pandemic [35]. However, Matheson *et al.* study suggested an association between lockdown and reduced preterm birth rates in Australia without increases in stillbirth or SGA neonates [36]. Other studies addressed the effect of COVID-19 on other neonatal complication before and after the pandemic. Stowe *et al.* study demonstrated that Stillbirth deliveries in a European health registry declined during 2016-2019, which was consistent with Office for National Statistics during the same period [37]. Yang *et al.* Demonstrated that the prevalence of cesarean sections and PROM were higher during the COVID-19 pandemic period compared with women before the pandemic. However, other pregnancy outcomes were not different before and after the pandemic [38].

Regardless of such studies addressing the prevalence of neonatal complications before and after the outbreak, there are limited data on case control studies comparing the infected pregnant women with uninfected. There were only 3 case control studies with small sample size indicating controversial

results regarding to the adverse neonatal outcomes [14, 15, 29]. Liao *et al.* case-control study revealed that perinatal adverse outcomes including premature rupture of membranes, premature delivery, and neonatal asphyxia dose not differ among infected and uninfected pregnant women [14]. While the Prabhu *et al.* study evaluating 70 American pregnant women with COVID-19 reported slightly similar preterm rate with Yang *et al.* study on 65 infected Chinese pregnant women (15% versus 14%), the Prabhu *et al.* stated that preterm delivery is associated with COVID-19 infection while the Yang *et al.* did not report such relationship [14, 29]. A possible explanation could be their widely different control group population (605 women in Prabhu *et al.* study versus 11013 in Yang *et al.* study) [15, 29].

A possible limitation about our resent review could be ignoring the disease severity. In the present systematic review, we did not consider the pregnant women's disease severity as the disease severity was not similarly assessed across different studies. Women with critical COVID-19 has been reported to deliver at an earlier mean gestational age [24]. Also, it has been reported that women with more severe symptoms are more likely to have cesarean delivery [20]. Even more, the cesarean section has been related to increased NICU admission risk and clinical deterioration [16].

## Conclusion

the present systematic review on the neonatal complications during COVID-19 pandemic demonstrated that without considering the disease severity in pregnant women, the rate of preterm delivery as the most common neonatal complication is approximately 12% of live births which slightly greater than the previously reported global preterm rate in 2020 (11%). Further case control studies are warranted to evaluate the effect of COVID-19 infection and adverse neonatal outcomes.

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