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Fetal Complications in COVID-19 Infected Pregnant Woman: A Systematic Review and Meta-Analysis

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Abstract

Background Pregnancy is an immunocompromised state and, for this reason, a pregnant woman is at a higher risk of getting infected as compared with a healthy individual. There is limited data available regarding the impact of COVD-19 on pregnancy; however, the case of miscarriage due to placental infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in second trimester has already been reported.

Methods We searched for all published articles in PubMed, Science Direct, Cochrane, Scopus, and Embase. The literature search produced 167 relevant publications; 67 manuscripts were further excluded because they did not satisfy our inclusion criteria. Out of the remaining 100 articles, 78 were excluded after full text screening. Therefore, a total of 22 articles were eligible for review in our study.

Results Overall, these 22 studies included a total of 7,034 participants: 2,689 (38.23%) SARS-CoV-2 positive pregnant women, of which 2,578 (95.87%) were laboratory confirmed and 111 (4.13%) were clinically diagnosed. Among the positive patients, there were 174 (6.47%) cases of abortion, of them 168 (96.55%) were spontaneous abortions and 6 (3.45%) were missed. Most patients either reported mild symptoms of fever, cough, fatigue, and anosmia or they presented asymptomatic.

Conclusion Additional investigation and rigorous research are warranted to confirm placental pathology mechanisms concerning COVID-19 to protect maternal and fetal health.

Keywords
- coronavirus
- COVID-19
- pregnancy loss
- abortion
- pregnancy

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Introduction

COVID-19 infection is spread by respiratory droplets and is highly contagious.[1] It was first reported in Wuhan, China in December 2019 and the COVID-19 pandemic was declared by the World Health Organization on March 11, 2020.[2] COVID-19 enters the body via the nasal passage and infects pulmonary cells via the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor angiotensin-converting enzyme 2 (ACE2) and uses transmembrane serine protease 2 (TMPRSS2) for S protein priming.[3] Infection with SARS-CoV-2 is followed by viral replication and release of the virus, causing pyroptosis (inflammation-mediated programmed cell death occurring in response to a pathological stimulus).[4] Coronavirus is enveloped, nonsegmented, positive-sense ribonucleic acid usually causing respiratory distress in the infected patient.[5] However, evidence shows that coronavirus can cause harmful clinical effects on a wide spectrum of bodily systems. Since pregnancy is an immunocompromised state, a pregnant woman is at a higher risk of getting infected as compared with a healthy individual.[1] The modulations of the maternal immune system in pregnancy may affect the response to infections, and specifically to viruses.[6]

Mechanisms of damages of COVID-19 during pregnancy could be: a decrease in circulating natural killer (NK) cells[7]; increased progesterone hormone as a steroid hormone that has immunomodulatory properties[8]; alterations in the innate immune system, including the pattern recognition receptors Toll-like receptors (TLRs)[9]; a shift in CD4+ T cell population toward the Th2 phenotype over Th1[10]; also pregnancy is a hypercoagulable state with increased thrombin production and an increase in intravascular inflammation[11]; and the current reports indicate clinical manifestations of both widespread microvascular as well as large vessel thrombosis in patients infected with COVID-19.[12] But the fetal damages are explained by SARS-CoV-2 found on reverse transcription-polymerase chain reaction of swabs and biopsies following a spontaneous fetal loss at 19-week gestation[13] and in placental and umbilical cord biopsies.[14] Mechanisms of viral invasion of the placenta have yet to be established.

Outcomes in pregnant women with SARS-CoV-2 infection appear less severe compared with SARS and Middle East respiratory syndrome.[15] American Centers for Disease Control states that although hospitalization in the intensive care unit of COVID-19 affected pregnant patient is higher than nonpregnant, the mortality rate is similar to other nonpregnant patients. Since there is evidence that COVID-19 affects blood coagulation factors, it has the potential of adverse effect on pregnancy, particularly with the inherent hypercoagulability of gestation.[2] There had been a systematic review of published reports on COVID-19 which reported higher rates of preterm birth, preeclampsia, and perinatal death. The lack of data on spontaneous abortion due to COVID-19 in the first trimester prevents the inference of conclusive evidence for the effects of this infection during early pregnancy. But due to the scarcity of reliable data and misreporting of the information by the media has led pregnant women to take drastic choices such as voluntary abortion.[5] The wide range of COVID-19 symptoms, high rate of asymptomatic forms, and poor accuracy of nasopharyngeal swab testing have been the main barriers for understanding the prevalence of its infection and impact on a pregnant woman and the fetus.[5] Though we are aware that many viral infections are harmful to the fetus during the first trimester of pregnancy, what is the impact of COVID-19 on the fetus of the first trimester is still unknown.[5] There was a lack of study and reliable data to find the effect of COVID-19 on the first trimester and second trimester; however, there were some case reports of newborns with fetal distress requiring intensive care unit and stillbirth of COVID-19 affected pregnant women in the third trimester suggesting the possibility of pathology related to the placenta.[16] According to Yan et al, a retrospective study where 116 pregnant women were included resulted that SARS-CoV-2 infections during pregnancy is not associated with an increased risk of spontaneous abortion and spontaneous preterm birth. There is no evidence of vertical transmission of SARS-CoV-2 infection when the infection manifests during the third trimester of pregnancy.[17] The same conclusion was reported by the Cosma et al case–control study where 225 women were studied. COVID-19 did not seem to predispose to early pregnancy loss; its cumulative incidence did not show a difference between women with spontaneous abortion and women with ongoing pregnancy. COVID-19 appears to have a favorable maternal course at the beginning of pregnancy, consistent with what has been observed during the second and third trimesters.[5] In the Baud et al case report, the miscarriage during the first trimester due to SARS-CoV-2 infection appears related to placental infection as no other cause of miscarriage was identified. Limited data are available regarding the impact of COVD-19 on pregnancy; however, the case of miscarriage due to placental infection caused by SARS-CoV-2 in the second trimester has already been reported more than once.[16,18] An increasing number of miscarriage cases were reported during this pandemic. These cases of missed miscarriages were diagnosed clinically, supported by ultrasonographic evidence, before being diagnosed with COVID-19 infection. This could happen even in those cases where the patients were relatively asymptomatic or manifested mild symptoms of COVID-19 infection. However, the cause of the miscarriage was unknown, and SARS-CoV-2 infection as the causal factor could not be completely ruled out.[19] The position for pregnant women on this spectrum is unclear. The immune system adapts during pregnancy to allow for the growth of a semiallogenic fetus.[20]

Since December 2019 (when the pandemic started), several case studies and cohort studies have described the presentation and clinical course of COVID-19 in pregnancy. Therefore, the main aim of this study is to understand the role of COVID-19 infection in causing pregnancy complications specifically fatal outcomes.

Methods

This literature review is done for the period January 1, 2020 up to July 2021. We searched for articles in PubMed, Science

Direct, Cochrane, Scopus, and Embase. We used the following search terms "Pregnancy complications and/or COVID-19" and/or Fetal complications and/or SARS-CoV-2 and/or Pregnancy Complications and/or SARS-CoV-2. The search terms were kept broad to encompass all possibilities for applicable studies. Only articles published in the English language were included. Duplicates were removed manually. After eliminating duplicates, three investigators (D.S., R.A., and O.A.) independently reviewed all titles and abstracts. The full texts of articles regarded as potentially eligible for consideration were extracted and screened for further analysis. Thereafter, eligible articles were selected for final analysis according to predefined inclusion and exclusion criteria. Disagreements between the authors were resolved through consensus and active discussion. The exclusion criteria consisted of review articles, animal studies, elective abortion, studies published in a language other than English, and the absence or unclear reporting of pregnancy complication status in COVID-19 pregnant patients.

Results

The literature search produced 90 relevant publications in the PubMed database, 5 on ScienceDirect, and 72 on Scopus, and no results of Embase or Cochrane. All Google Scholar's results were repeated. After reviewing 167 articles manually by abstract screening, 67 manuscripts were further excluded because they did not satisfy our inclusion criteria. Out of the remaining 100 articles, 78 were excluded after full text screening. Therefore, 22 articles were eligible for review in our study. Details of included studies are listed in the table. The majority of papers arose from Asia. Of all of the studies included, 4 were case series reports, 6 case reports, 7 cohort studies, 4 cross-sectional, and 1 case–control study. Please find the information on all fatal outcome pregnancies reported in the literature that we included in our final quantitative analysis in ►Table 1.

Overall, these 22 studies included a total of 7,034 participants: 2,689 (38.23%) SARS-CoV-2 positive pregnant women, of which 2,578 (95.87%) were laboratory confirmed and 111 (4.13%) were clinically diagnosed. The clinical symptoms among pregnant women with laboratory-confirmed SARS-CoV-2 infection are presented in the table.

Symptoms

Symptoms most commonly reported were four: fever, cough, fatigue, and anosmia. Out of 3,512 patients, 15.19% had fever.[5,16–18,22–24,26–28,30,31] Out of 2,155, 28.19% presented with a cough and 16.6% developed fatigue from 307 cases.[5,16,17,19,22–24,26–28,30,31] Also, from 2,360 cases, 4.32% reported anosmia.[5,16,18,24,26,27,30] Six studies reported asymptomatic patients with COVID-19, so 34.3% from 1,892 cases.[19,23,24,26,28] There were three studies in which 89.11% reported mild disease of COVID-19.[24,26,28]

Only one study compared clinical symptoms between COVID-19 positive early pregnancy loss and pregnant group during the first trimester: fever, anosmia, ageusia, cough, arthralgia, diarrhea, and no cases of pneumonia were reported. Also, was noted no difference in the incidence of symptoms between the two groups.[5]

Vertical Transmission of SARS-COV-2 and Spontaneous Abortion

Martinez-Perez et al observed a significant increase in the stillbirth rate in the univariate analysis. It is an important point to highlight that two case reports confirmed positive SARS-CoV-2 in placental tissue samples and amniotic fluid.[34,37] Among the positive patients, there were 174 (6.47%) cases of abortion, of them 168 (96.55%) were spontaneous abortions and 6 (3.45%) were missed abortions. Comparing to United States 2021 abortion rate, which is reported as 20.8%,[38] there were also four cases of induced abortion owing to patient's concerns about COVID-19 and two cases of ectopic pregnancy. We have excluded these 6 cases from the analysis. Otherwise, three studies reported the use of lopinavir-ritonavir as therapy, so 6.23% of 593 cases.[21,28,31]

Assessment of Study Quality

For the quality assessment of included studies the Newcastle–Ottawa Scale was employed to ascertain the quality of studies by two reviewers (D.S.) and (R.A.). They independently assessed the methodologic quality of each study included: 7 cohort studies, 4 cross-sectional, and 10 observational studies were evaluated for the following three domains: quality of selection of cohorts (4 stars), comparability of cohorts (2 stars), and assessment of outcome (3 stars). One case–control study was assessed for quality of selection of cases and controls (4 stars), comparability of cases and controls (2 stars), and ascertainment of exposure (3 stars). We considered a total of 7 out of 9 stars to be a low risk of bias, 4 to 6 stars to be a moderate risk, and less than 4 stars to be a high risk of bias. In case of a disagreement, reviewers reached consensus by discussion with a third reviewer. The risk of bias assessment is shown in ►Table 2.

Discussion

SARS-CoV-2 Complicates the Pregnancy Utilizing ACE2 Receptor and Consequent Activation of the TMPRSS2 Enzyme

Coronavirus disease's clinical spectrum can range from asymptomatic presentation to pneumonia, heart failure, kidney injury, and eventually death. The SARS-CoV-2 utilizes the ACE2 receptor and consequent activation of the TMPRSS2 enzyme to gain entry into host cells and trigger an exaggerated inflammatory response via the release of cytokines ("cytokine storm"). These results in a severe form of COVID-19 infection which is associated with increased mortality and morbidity. An intact immune system is responsible for clearing infected cells and preventing further replication of the virus. A weakened immune system in pregnancy impacts viral clearance and therefore increases the susceptibility to develop an infection with SARS-CoV-2. Factors such as a preference of the humoral response over the cell-mediated response, a decrease in circulating NK cells, and alterations in the immune system and pattern recognition

Table 1 All eligible studies to be included in our review

Authors	Location	Number of patients	Age	Gestational age on admission	COVID-19 diagnosis	Number of cases	Time of presentation	Outcomes
Yan et al, 2020[17]	China	116	30.8 (IQR 24–41)	38 + 0 (IQR 36 + 0–39 + 1) weeks	65 cases of laboratory-confirmed (qRT-PCR) and 51 cases of clinically diagnosed COVID-19 pneumonia	1 missed spontaneous abortion	5 + 2 weeks at presentation with fever and fatigue	Survived 76 discharged
Wong et al, 2020[19]	Malaysia	2	34	10-week period of amenorrhea (COVID-19 diagnosis time)	NPS/OPS for SARS-CoV-2 RT-PCR was positive	2 missed miscarriages	7-week and 1-day period of amenorrhea	Passed out product of conception 27 days after onset of symptoms
			38	12-week period of an amenorrhea	Antibody test for SARS-CoV-2 showed positive IgG and negative IgM NPS/OPS for SARS-CoV-2 RT-PCR which was positive		11-week period of an amenorrhea	Maternal survived
Buonsenso et al, 2020[21]	Italy	7	NA	6 patients < 37 weeks gestation	Positive (RT-PCR)	1 spontaneous abortion	8 weeks	Maternal survived
Chen et al, 2020[22]	Wuhan, China	118	31 years (IQR 28–34)	NA	84 (71%) had positive PCR testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 34 (29%) had suggestive findings on CT of the chest	9 (8%) abortion Of them, 3 spontaneous abortions	75 (64%) had been infected with SARS-CoV-2 in the third trimester	109/116 (94%) had been discharged, including all women with severe or critical disease. There were no deaths
Di Mascio et al, 2020[23]	73 centers from 22 countries	388	NA	30.6 ± 9.5 weeks	All pregnant women with laboratory-confirmed COVID-19 8% being diagnosed in the first, 22.2% in the second, and 69.8% in the third trimester of pregnancy	6 (2.3%) spontaneous abortions	First trimester of pregnancy	11.1% were admitted to ICU, and 6.4% requiring intubation 3 cases of maternal deaths
Mattar et al, 2020[24]	Singapore	16	23–36	First trimester, $n = 6$; second trimester, $n = 7$; third trimester, $n = 3$	All pregnant women with COVID-19 diagnosed by (RT-PCR)	2 spontaneous miscarriages	11 and 23 weeks	No maternal mortalities
Hachem et al, 2020[25]	France	1	21 years	20 weeks	RT-PCR positive	1 spontaneous abortion	20 weeks	Maternal survived
Shmakov et al, 2020[26]	Russia	66	30.3 ± 6.25	31.3 ± 10.4 (5–38 weeks)	All with PCR - confirmed SARS-CoV-2	4 (6.1%) spontaneous abortions	Before 20 weeks of gestation (2 before 12 weeks, 1 at 18 weeks, 1 medical abortion at 19th week for fetal abnormalities)	1 case of maternal death occurred on the 33rd day after the patient's admission to the hospital
Mayeur et al, 2020[27]	France	104	33.6 ± 4.1	16.9 ± 4.6 weeks	10 (11.3%) had symptoms related to COVID-19. 2 were positive on PCR test	15 (14.4%) spontaneous miscarriage	2 late spontaneous miscarriages. Both have not been tested for COVID-19	The first one was caused by a large subchorionic hematoma with a miscarriage at 19 weeks of gestational age. The second one occurred at 18 weeks of gestational age in a context of cervical insufficiency and chorioamnionitis
Sahin et al, 2021[28]	Turkey	533	28.04 ± 5.84 (17–47)	First trimester 130 (24.4) Second trimester 165 (30.9) Third trimester 238 (44.7)	All were laboratory-confirmed SARS-CoV-2 infection	12 (2.2%) miscarriages	NA	2 (0.4) maternal mortality

(*Continued*)

Table 1 (*Continued*)

Authors	Location	Number of patients	Age	Gestational age on admission	COVID-19 diagnosis	Number of cases	Time of presentation	Outcomes
Michel et al, 2021[29]	France	1	40	16 weeks and 4 days	SARS-CoV-2 serology positive	1 spontaneous miscarriage	NA	Maternal survived
D'Antonio et al, 2021[30]	22 countries	887	208 (34.16 ± 6.8),679 (31.39 ± 5.5)	208 (30.26 ± 9.8),679 (29.65 ± 9.6)	All were laboratory-confirmed SARS-CoV-2 infection	11 spontaneous miscarriages	Before 22 weeks of gestation	3 cases of maternal deaths
Baud et al, 2020[16]	Switzerland	1	28	19 weeks' gestation	Nasopharyngeal swab was positive (RT-PCR)	1 miscarriage	2 days after admission	Maternal survived
Cosma et al, 2021[5]	Turin, Italy	225	125 (33.7 ± 4.7), 100 (35.5 ± 4.7)	12–13 weeks approximately	23 (10.2%) had a positive test result (anti-SARS-CoV-2 IgG and IgM antibodies)	100 spontaneous abortions (12 had COVID-19)	NA	No severe cases or hospital admission because of COVID-19-related symptoms were recorded, both in women who had ongoing pregnancies and in those with early pregnancy loss
Sentilhes et al 2020[31]	France	54	30.6 ± 6.2	37.4 ± 4.7 weeks	54 symptomatic pregnant women with COVID-19 during the study period; 38 had positive RT-PCR results for SARS-CoV-2	1 miscarriage	NA	5 were (9.3%) admitted to the ICU, all owing to COVID-19 respiratory symptoms
Rana et al, 2021[18]	Rawalpindi, Pakistan	1	30	10 weeks and 6 days of gestation	rRT-PCR positive	1 miscarriage	14 days later admission	Maternal survived
la Cour et al, 2021[32]	Denmark	1,356	1,019 (31.71, SD 4.52), 36 (32.96, SD 5.22)	11–14 weeks	18 had SARS-CoV-2 antibodies	3 missed abortions at the nuchal translucency scan	First trimester	Maternal survived
Ayed et al, 2020[33]	Kuwait	185	31 years (IQR: 27.5–34)	29 weeks (IQR: 18–34)	All were positive by RT-PCR assay of nasopharyngeal swab specimens	3 miscarriages	2 cases at 14 weeks and 1 case at 13 weeks	Maternal survived
Shende et al, 202q[34]	India	1	26-year- old	7.6 weeks	Nasopharyngeal swab by RT-PCR	1 fetal demise	8 weeks	Maternal survived. Presence of SARS-CoV-2 in the placenta from an asymptomatic mother in the first trimester
de Vasconcelos Gaspar and Santos Silva, 2021[35]	Portugal	1,962	36 (SD 4.100)	40 weeks (IQR 3)	12 (0.61%) SARS-CoV-2 positive	1 stillbirth	20 weeks	None had severe or critical illness due to SARS-CoV-2
Martinez-Perez et al, 2021[36]	Spanish	1,009	32.6 (246 cases) and 32.5 (763 cases)	38 + 1 (246 cases) and 38 + 6 (763 cases)	246 positive cases, $n = 218$ were asymptomatic at delivery	3/246 stillbirth	NA	The infected group had 4.5% miscarriage risk
Pulinx et al, 2020[37]	Belgium	1 (gravida 2 para 1)	30-year-old	22 weeks	Positive for SARS-CoV-2 RT-PCR on a nasopharyngeal swab	1 fetal demise, fetus two showed fetal heart rate decelerations	24 weeks	Both placental tissue samples and amniotic fluid tested positive for SARS-CoV-2 RT-PCR

Abbreviations: CT, computed tomography; ICU, intensive care unit; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; NPS/OPS, nasopharyngeal swabs and oropharyngeal swabs; PCR, polymerase chain reaction; qRT-PCR, quantitative reverse transcriptase-polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Table 2 Risk of bias assessment for included studies

	Newcastle–Ottawa Scale: cohort studies					
Study ID	**Selection**	**Comparability**	**Outcome**	**Total score**	**Judgment**	**Support of judgment**
Di Mascio et al, 2020 [23]	****	*	**	******* (7)	Low risk	Quote: "multinational, cohort study on all consecutive pregnant women with laboratory- confirmed COVID-19 from February 1, 2020 to April 30, 2020 from 73 centers from 22 different countries," comment: this type of cohort study according to AHRQ standard has good quality, and they had the maximum of selection criteria
Mattar et al, 2020 [24]	****		***	******* (7)	Low risk	Quote: "Prospective observational study of 16 pregnant patients admitted for COVID-19 to 4 tertiary hospitals in Singapore," comment: this type of cohort study according to AHRQ standard has good quality, and they had the maximum of selection criteria
Sahin et al, 2021 [28]	***		***	****** (6)	Low risk	Quote: "prospective cohort study was conducted on pregnant women," comment: this type of cohort study according to AHRQ standard has good quality, and they explained data with statistical analysis
D'Antonio et al, 2021 [30]	****	*	***	******** (8)	Low risk	Quote: "multinational retrospective cohort study involving women with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection from 76 centers from 25 countries," comment: this type of cohort study according to AHRQ standard has good quality, and they had a sufficient follow-up
Sentilhes et al 2020 [31]	****		***	******* (7)	Low risk	Quote: "retrospective, single-center study includes all consecutive pregnant women," comment: this type of cohort study according to AHRQ standard has good quality, and they had the maximum of selection criteria
la Cour et al, 2021[32]	****	*	***	******** (8)	Low risk	Quote: "Cohort study of 1,019 women with a double test," comment: this type of cohort study according to AHRQ standard has good quality, and they had the maximum of selection criteria
Martinez-Perez et al, 2021 [36]	****	*	***	******** (8)	Low risk	Quote: "multicenter prospective study in pregnancy based on a universal antenatal screening program for SARS-CoV-2 infection," comment: this type of cohort study according to AHRQ standard has good quality, and they had the maximum of selection criteria
	Newcastle–Ottawa Scale: case–control study					
Study ID	**Selection**	**Comparability**	**Exposure**	**Total score**	**Quality**	**Support of judgment**
Cosma et al, 2021 [5]	**	*	***	****** (6)	Low risk	Quote: "women with spontaneous abortion (case group, $n = 100$) and those with ongoing pregnancy (control group, $n = 125$)," comment: this type of case–control study according to AHRQ standard has fair quality, but they had an acceptable response rate
	Newcastle–Ottawa Scale: cross-sectional studies					
Study ID	**Selection**	**Comparability**	**Outcome**	**Total score**	**Quality**	**Support of judgment**
Shmakov et al, 2020 [26]	**	*	***	****** (6)	Low risk	Quote: "66 women with polymerase chain reaction (PCR) - confirmed SARS-CoV-2 and their 42 neonates were included in the prospective observational study," comment: this type of cross- sectional study according to AHRQ standard has fair quality, but they mentioned the sample size and percentage of respondents and explained data with statistical analysis
Mayeur et al, 2020 [27]	*****		*	****** (6)	Low risk	Quote: "single center, retrospective study from December 2019 to March 2020 based on a phone call interview using a specific questionnaire sheet," comment: this type of cross-

(*Continued*)

Table 2 (*Continued*)

						sectional study according to AHRQ standard has fair quality, but they mentioned the sample size and percentage of respondents and explained data with statistical analysis
Ayed et al, 2020 [33]	**		***	***** (5)	High risk	Quote: "retrospective national-based study, we analyzed the medical records of all pregnant women infected with SARS-CoV-2 and their neonates," comment: this type of study is only descriptive and not have comparable group
de Vasconcelos Gaspar and Santos Silva, 2021 [35]			***	*** (3)	High risk	Quote: "retrospective descriptive study, in order to evaluate the obstetric results on pregnant women," comment: this type of cross-sectional study does not justify the sample size and only descriptive
	Newcastle–Ottawa Scale: other observational studies					
Study ID	**Selection**	**Comparability**	**Exposure**	**Total score**	**Quality**	**Support of judgment**
Yan et al, 2020[17]	**		***	***** (5)	High risk	Quote: "Clinical records were retrospectively reviewed for 116 pregnant women," comment: this type is a case series study, and it is only a group selected of patients and only descriptive
Wong et al, 2020[19]	*		*	** (2)	High risk	Quote: "We would like to highlight 2 cases of first trimester miscarriage in COVID-19 infected pregnant mothers," comment: this type of two patients in a case series does not have sufficient data about selection and no applied to comparability
Buonsenso et al, 2020[21]			*	* (1)	High risk	Quote: "observational study of neonates born to mothers," comment: this type of study does not have sufficient data
Chen et al, 2020[22]	*		*	* (2)	High risk	Quote: "pregnant patients represented 0.24% of all reported patients with COVID-19," comment: this type is a case series study with 118 patients, but is only a group selected of patients and only descriptive
Hachem et al, 2020[25]				0	High risk	Quote: "We report an unusual case of a second-trimester miscarriage," comment: this type of one case report in the report study does not have sufficient statistical data
Michel et al, 2021[29]				0	High risk	Quote: "Data about obstetric complications of maternal infection by SARS-CoV-2 remain sparse," comment: this type of one case report in the report study does not have sufficient data
Baud et al, 2020[16]				0	High risk	Quote: "We present a case of miscarriage," comment: this type of one case report in the report study does not have sufficient data
Rana et al, 2021[18]				0	High risk	Quote: "report a case of miscarriage during the first trimester due to SARS-CoV-2 infection," comment: this type of one case report in the report study does not have sufficient data
Shende et al, 2021[34]				0	High risk	Quote: "report a case of a pregnant woman in the first trimester who tested positive for SARS-CoV-2 at 8 weeks of gestation," comment: this type of one case report in the report study does not have sufficient data
Pulinx et al, 2020[37]				0	High risk	Quote: "we describe a case of a known SARS-CoV-2-positive woman giving preterm birth to two fetuses with SARS-CoV-2 positive testing in placental tissue and amniotic fluid," comment: this type of one case report in the report study does not have sufficient data

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

receptors such as the TLRs result in a decreased response to coronavirus disease.[7–10,39] During pregnancy, the presence of a fetus alters respiratory function as there is an increase in tidal volume, decreased functional residual capacity due to a reduction in chest volume, and a reduction in the total lung capacity. A reduced total lung capacity impairs the lung's ability to clear infections, therefore increasing the susceptibility to develop severe respiratory secretions.[39]

Miscarriage Likely Occurred due to Placental Abruption and Maternal Preeclampsia with Thrombocytopenia and Coagulopathy

Pregnant women demonstrated enhanced levels of the ACE 2 receptors on organs, such as the placenta, uterus, and kidneys, to allow for proper fetal growth and regulation of angiotensin-II levels. This high expression of ACE2 reveals that the SARS-CoV-2 virus can potentially infect the placenta and result in placental dysfunction and severe pregnancy complications.[40] Wong et al discuss two cases of first trimester miscarriages in pregnant mothers infected with COVID-19. Although SARS-CoV-2 follows vertical transmission and interacts with fetal ACE2 receptors resulting in fetal death and abortion, the two patients in the study by Wong et al reported no signs of vertical transmission. Reports indicate that the spontaneous miscarriage in both these patients resulted from SARS-related hypoxic respiratory illness.[19] In addition, Wastnedge et al discuss a series of case reports studying the placentas of pregnant women infected with COVID-19 sustaining miscarriage in the second trimester. A high number of SARS-CoV-2 receptors were expressed in the placental and umbilical cord biopsies in these patients. Reports indicate that the miscarriage likely occurred due to placental abruption and maternal preeclampsia with thrombocytopenia and coagulopathy. Also, electron microscopy in these patients revealed particles of the virus in the cytosol of placental cells.[39] In addition, Poisson and Pierone's case report indicates extensive fetal vascular malperfusion and parenchymal infarcts resulting in a severe loss of a significant percentage of chorionic villi in the placental examination.[41]

Chowdhury et al's study evaluate 12 cases of miscarriage, diagnosed by an ultrasound scan, at 11 weeks or more due to COVID-19 from March 2020 to July 2020 in a single hospital in Dhaka, Bangladesh. The miscarriage was supposed to be due to SARS-CoV-2 virus-induced damage of the placental barrier via hypoxemia. The miscarriage resulted from viral damage and the consequent induction of a placental inflammatory reaction, acute chorioamnionitis, and intervillous.[1] Yet, the effect sizes of all of these studies are too small to statistically conclude that the SARS-CoV-2 virus is the main culprit in causing miscarriages in pregnant women.

As discussed earlier, SARS-CoV-2 utilizes the ACE2 and the resultant activation of the TMPRSS2 enzyme to gain entry into host cells leading to the coronavirus disease.

COVID-19 Infection in Pregnant Women May More Likely Cause Late Pregnancy Complications and Vertical Transmission

However, overall, evidence reported so far regarding COVID-19 infection and pregnancy demonstrates that the TMPRSS2 enzyme may only be expressed after 24 weeks of pregnancy and only in the extravillous trophoblast. As a result, COVID-19 infections in pregnant women may more likely cause late pregnancy complications and vertical transmission as opposed to problems in the first trimester, such as spontaneous or missed abortions. Furthermore, the mild increase in the spontaneous or missed abortions rate may not be because of the SARS-CoV-2 virus itself but due to individual's intense physical and mental stresses from the pandemic. These stressors then cause a release of large amounts of cortisol, which could potentially affect the pregnancy, especially in the early trimester. Yet, at this time, there is limited data available regarding the vertical transmission of SARS-CoV-2 infection. Although recent studies have reported cases of anti-SARS-CoV-19 immunoglobulins in newborns, there are limitations, such as the lack of placental and amniotic fluid examination.[42]

Pregnancy is a vulnerable period, particularly the early period; therefore, it is essential to be vigilant and provide the best maternal care to ensure successful maternal and fetal outcomes. However, as the COVID-19 pandemic is still in progress worldwide, it is vital to assess more extensive studies from a wide range of patient populations and health care settings.

Lessons Learned

One of the main crucial lessons learned from conducting this comprehensive literature review is that the early pregnancy complications, such as spontaneous or missed abortions, may not have been increased by the COVID-19 infection. As demonstrated by a few studies, the main reason for an increased rate of spontaneous or missed abortions, if any, is due to the environment of the pandemic itself, affecting health care quality and access.[43] As a result, this increased rate was mainly observed in minority populations, such as African American populations, where there already exists a severe health care disparity.[43] Thus, to effectively lower the rate of fatal fetal complications in COVID-19-infected pregnant women and maternal mortality, it is best to address the public health aspect of the COVID-19 pandemic instead of clinical management of COVID-19 itself.

Strengths

We conducted a sensitive and comprehensive search strategy to reduce the risk of missing relevant studies. We adhered to rigorous quality appraisal, which was independently assessed by pairs of reviewers and discrepancies solved by consensus.

Limitations

Our literature search was restricted to publications in English. Although we included a comprehensive number of

outcomes, we cannot rule out the possibility that some associations were spurious.

Conclusion

In conclusion, many current studies included in our comprehensive literature review have shown that there is no increased risk of fetal fatal outcomes in pregnant women infected with COVID-19 infection. Pregnant patients can present with mild disease symptoms such as fever, cough, fatigue, and anosmia. However, almost half of the infected pregnant women were asymptomatic. The expressions of the TMPRSS2 enzyme are higher during the third trimester. There is a theoretical possibility of an increased risk of late pregnancy complications and vertical transmission due to the COVID-19 infection. Recent case reports indicate extensive fetal vascular malperfusion and parenchymal infarction resulting in a severe loss of a significant percentage of chorionic villi in the placental examination. However, additional investigation and rigorous research are warranted to confirm placental pathology mechanisms concerning COVID-19 to protect maternal and fetal health.

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Conflict of Interest

The authors indicate no potential conflicts of interest.

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