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Review article

COVID-19 and miscarriage: From immunopathological mechanisms to actual clinical evidence

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ABSTRACT

The association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the first half of pregnancy and pregnancy loss is still unknown. Infections by other coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), appear to increase the risk of miscarriage. The purpose of this study is to assess whether SARS-CoV-2 infection increases the risk of miscarriage. Firstly, a narrative review of the literature on animal and human studies was performed to analyze the immunopathological mechanisms of SARS-CoV-2 infection during preconception and early pregnancy, by which it may increase the risk of miscarriage. Secondly, a systematic review/meta-analysis of studies was conducted to assess the prevalence of miscarriage in COVID-19 patients diagnosed during pregnancy. Meta-analysis of proportions was used to combine data, and pooled proportions were reported. Seventeen case series and observational studies and 10 prevalence meta-analyses were selected for the review. The estimate of the overall miscarriage rate in pregnant women with COVID-19 was 15.3 % (95 % CI 10.94–20.59) and 23.1 (95 % CI 13.17–34.95) using fixed and random effect models, respectively. Based on the data in the current literature, the miscarriage rate (<22 weeks gestation) in women with SARS-CoV-2 infection is in the range of normal population. Well-designed studies are urgently needed to determine whether SARS-CoV-2 infection increases the risk of miscarriage during periconception and early pregnancy.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has been rapidly spreading all over the world, prompting the world health organization (WHO) to declare a pandemic on March 11, 2020 (Wu et al., 2020). COVID-19 had affected more than 170 million people worldwide, with a total of more than 3.5 million deaths (World Health Organization (WHO), 2021) by the end of May 2021. During the pandemic, treatment protocols have been rapidly established with the development of new drugs, including anti-SARS-CoV-2 monoclonal antibodies and antiviral medications (Mishra and Tripathi, 2021), and several COVID-19

vaccines have been introduced to prevent the spread of COVID-19. However, due to the safety concerns and difficulties in accessing vaccines, vaccine rollout has been slower than expected, and there are substantial regional differences in vaccination rates. In the U.S. and U. K., herd immunity is expected most likely by the third quarter of 2021 with improved vaccine supply. However, the emergence of SARS-CoV-2 variants and a possible fourth wave of Covid-19 may delay the timeline. Unfortunately, herd immunity may present temporary or limited regions. Therefore, we will face nationwide or regional herd immunity in the next few years, which can be temporary, or endemicity of COVID-19 (Sarun et al., 2021).

Predominantly, SARS-CoV-2 is transmitted through the respiratory

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route, with the virus suspended on droplets, or less commonly, aerosols. Other routes of transmission (from domestic pets and farm animals, fecal-oral, vertical, sexual, and blood-borne transmission) have already been studied and found to have little or no impact on disease spread (Meyerowitz et al., 2021). SARS-CoV-2 infection can occur without any clinical manifestation, with studies revealing varying proportions of asymptomatic patients ranging from 33 % to 89 % of laboratory-diagnosed cases. COVID-19 can cause mild or moderate disease in 81 % of cases, severe disease in 14 % of cases, and critical illness in 5% of patients, with the mortality rate being 2.3 % (Wu and McGoogan, 2020).

Pregnant women are at a higher risk of severe COVID-19-related illness. Pregnant women are more likely to be admitted to an intensive care unit (ICU) compared to non-pregnant women (10.5 versus 3.9 per 1000 cases; adjusted risk ratio [aRR] = 3.0; 95 % confidence interval [CI] = 2.6–3.4), to receive invasive ventilation (2.9 versus 1.1 per 1000 cases; aRR = 2.9; 95 % CI = 2.2–3.8) and extracorporeal membrane oxygenation (ECMO) (0.7 versus 0.3 per 1000 cases; aRR = 2.4; 95 % CI = 1.5–4.0), and to die (1.5 versus 1.2 per 1000 cases; aRR = 1.7; 95 % CI = 1.2–2.4) (Zambrano et al., 2020). However, the effect of COVID-19 on the first half of pregnancy has not been investigated well.

For decades, scientists have debated the association between viral infection and miscarriage. Among the known causes of miscarriage, chromosomal abnormalities, such as aneuploidy or triploidy, account for half of the cases, while obesity, endocrinopathies, thrombophilia (acquired or inherited), uterine anatomical abnormalities, and infections account for the other half (Pinar et al., 2018). During previous outbreaks of other coronaviruses, an increased risk of miscarriage has been reported in pregnant women with SARS-CoV and MERS-CoV. At the beginning of the COVID-19 pandemic, the potential obstetrical risk of pregnant women infected with SARS-CoV-2 was projected, considering a miscarriage rate (57 %, 4/7) observed in pregnant women infected with other coronaviruses, such as SARS-CoV (Favre et al., 2020), and the fact that the direct action of the virus or maternal immunological responses to the viral infection may cause trophoblast and placental damage (Giakoumelou et al., 2016). However, the first study on pregnant women with COVID-19 found no increased risk of miscarriage among these patients (Yan et al., 2020).

In this study, we aim to review possible immunopathological mechanisms of COVID-19 which may lead to pregnancy losses based on the literature of animal and human studies during the preconception period and the first half of pregnancy, and the current evidence of the COVID-19-impact on pregnancy losses by conducting a systematic review by a meta-analysis of studies that assessed the prevalence of miscarriages in pregnant women with COVID-19.

2. Immunopathological mechanisms of SARS-CoV-2 infection on pregnancy losses

2.1. SARS-CoV-2 infection

The SARS-CoV-2 virus is an enveloped positive-strand RNA virus. There are approximately 29 different viral proteins identified; the most important ones are the nucleocapsid (N), membrane (M), spike (S), and envelope (E) proteins. The capsid was formed outside the genome by N protein, and the genome is further packed by an envelope associated with structural proteins (M protein, S protein, and E protein) (Wang et al., 2020a). The angiotensin-converting enzyme 2 (ACE2) is the host receptor for SARS-CoV-2 cell entry. The S proteins are distributed uniformly on the virus surface, allowing for greater interaction with ACE2. After binding to ACE2, the cellular transmembrane serine protease 2 (TMPRSS2), located on the host cell membrane, promotes virus entry into the cell by activating the S protein (Wang et al., 2020a).

Initially, SARS-CoV-2 infects nasal epithelial cells and then spreads to bronchial epithelium and alveolar epithelial type II cells, which have ACE2 and TMPRSS2 expression. After reaching the pneumocytes, in

moderate/severe forms of COVID-19, an intense viral replication occurs, triggering local and systemic immune responses (Wang et al., 2020a). COVID-19 transmission and severity appear to be related to viral load in the upper and lower respiratory tracts, respectively (Cevik et al., 2021). Typically, viral respiratory pneumonia with critical hypoxemia is the most common clinical manifestation of severe COVID-19. During the acute phase of the disease, COVID-19 usually affects other organs, either directly or through systemic complications of the intense pulmonary inflammatory response known as a cytokine storm (Wang et al., 2020a).

2.2. SARS-CoV-2 infection on pregnancy

Interestingly, studies have revealed that a variety of extrapulmonary organs are potential binding targets for SARS-CoV-2. Furthermore, ACE2 proteins are expressed at various levels in organs such as the heart, kidney, liver, digestive tract, and brain (Dong et al., 2020). For decades, researchers have described the expression of ACE2 and TMPRSS2 in the endometrium, embryo, and various cell types of the human placenta, including syncytiotrophoblast, villous cytotrophoblasts, invasive and intravascular trophoblast, decidual cells, vascular smooth muscle of primary villi, and umbilical arterial and venous endothelium (Valdés et al., 2006; Vaz-Silva et al., 2009; Weatherbee et al., 2020). Recently, the expression of ACE2 and TMPRSS2 was detected in human trophoblast from early embryos as well as in all three trimesters of pregnancy (Cui et al., 2021). On the other hand, ACE2 and TMPRSS2 expression was negatively correlated with gestational age, with ACE2 and TMPRSS2 being highly expressed in first trimester trophoblastic tissues and little expressed or undetectable in the third-trimester placenta (Bloise et al., 2021). Therefore, the preconception and early pregnancy uterine environments are potentially vulnerable to SARS-CoV-2 infection. Thus, the occurrence of COVID-19 during the periconceptional period may increase the risk of miscarriage.

The renin-angiotensin system (RAS) is composed of a set of peptides, enzymes and receptors involved in the pregnancy process. The components of the RAS are distributed throughout the uteroplacental unit. Angiotensinogen, renin, ACE, angiotensin I, angiotensin II and angiotensin receptors (type 1 and type 2) are found in the placenta, uterus (endometrium and myometrium), fetal membranes and amniotic fluid. In early pregnancy, high levels of estrogens stimulate hepatic production of angiotensinogen, consequently raising plasma and uterine levels. Studies have shown that changes in the RAS are related to obstetric complications such as pre-eclampsia (Qi et al., 2020; Anton and Brosnihan, 2008).

ACE2 and TMPRSS2 are highly expressed in human endometrial stromal cells during the secretory phase and required for decidualization of human endometrial stromal cells (Vaz-Silva et al., 2009). In addition, ACE2 is also an important component of the human placental renin-angiotensin system (RAS), which is upregulated in the first trimester and involved in endometrial neovascularization during the peri-implantation period as well as placental development (Qi et al., 2020). Throughout pregnancy, the expression of the placental RAS is decreased. When recurrent miscarriage women were compared to fertile women, the expression of RAS components was found to be dysregulated (Qi et al., 2020). The SARS-CoV-2-ACE2 complex negatively regulates ACE2, resulting in a decrease in plasma levels of angiotensin-(1–7), which, in turn, potentiates vasoconstriction and the hypercoagulable state, contributing to reproductive failures and other obstetrical complications (Narang et al., 2020).

2.3. SARS-CoV-2 infection and pregnancy loss

Increased risk of embryo implantation failure and miscarriage has been reported during the periconceptional period in women with COVID-19. It was speculated that the reproductive failure was due to systemic inflammation and interference with trophoblast-endometrium molecular signaling rather than a direct action of SARS-

CoV-2 at the implantation site (Sills and Wood, 2020). The immunopathology of COVID-19, accompanied by high levels of IL-6, IL-8, TNF-alpha, and other cytokines, would result in unbalanced Th1/Th2 immune responses. Consequently, the “cytokine storm” of COVID-19 induces a hypercoagulable state that is detrimental to normal in-utero blastocyst/fetal development (toxic endometrial microenvironment and hypoperfusion secondary to microthrombus formation), as well as an unfavorable uterine immune response to embryo implantation (Sills and Wood, 2020). Indeed, abnormalities in the maternal immune response during peri-implantation and early pregnancy, with a predominant pro-inflammatory response (Th1 and Th17), and thrombophilic conditions have been linked to recurrent implantation failure and miscarriage (Yang et al., 2010; Kwak-Kim et al., 2014; Liu et al., 2020).

SARS-CoV-2 has been found in various body fluids (Bora et al., 2020), including blood (Chang et al., 2020; Wang et al., 2020b), cerebrospinal fluid (Huang et al., 2020; Moriguchi et al., 2020), pericardial fluid (Farina et al., 2020), pleural fluid (Mei et al., 2020), urine (Zheng et al., 2020), semen (Li et al., 2020), saliva (To et al., 2020), and eye tissues (Bora et al., 2020; Xie et al., 2020). Plasma SARS-CoV-2 RNA was detected in 27 % of hospitalized participants and 13 % of outpatients with COVID-19. Furthermore, the viral load (as measured by a nasopharyngeal sample, posterior oropharyngeal saliva or endotracheal aspirate or plasma) of COVID-19 patients was associated with disease severity (worse respiratory disease severity, lower absolute lymphocyte counts, and increased markers of inflammation, including C-reactive protein and IL-6) and mortality (Fajnzylber et al., 2020). Although the dynamics of SARS-CoV-2 during the active phase of the disease need to be elucidated further, endometrial, decidual, and placental infection is possible via the hematological spread of SARS-CoV-2. Indeed, placental SARS-CoV-2 infection was described through molecular and immunohistochemical assays, as well as electron microscopy. The presence of SARS-CoV-2 was confirmed in a 22-week placenta, primarily being localized to syncytiotrophoblast cells at the maternal-fetal interface, with the presence of maternal antibody response in the blood (Hosier et al., 2020).

According to a recent meta-analysis by Sharps et al., studies of placental morphological changes observed in pregnant women diagnosed with COVID-19 are mostly conducted in the third trimester. SARS-CoV-2 was found in 21 % of placental samples from the COVID-19 cases. Maternal vascular malperfusion (46 % of cases; 95 % CI 38.0 %–54.0 %), fetal vascular malperfusion (35.3 % of cases; 95 % CI 27.7 %–43.0 %), and evidence of inflammation in the placentas (villitis 8.7 % of cases, intervillitis 5.3 % of cases, chorioamnionitis 6% of cases) were the most common pathologies of affected placentas. Other placental changes observed in the second and third-trimester placentas include fibrin deposition, infarction, and vascular and intervillous thrombosis (Sharps et al., 2020). Placental changes are more frequent in severe COVID-19 cases but have been reported in patients with mild COVID-19 and even in asymptomatic cases (Ferraiolo et al., 2020).

A case study of a 26-year-old pregnant woman in the third trimester with one living child and a history of one first-trimester spontaneous abortion was published in August 2020. In the eighth week of pregnancy, she presented with an asymptomatic COVID-19. The ultrasound evaluation revealed a fetal demise at 13 weeks of gestation (corresponding with 10-week 5-day size). The virus was detected in the first-trimester cytotrophoblast and syncytiotrophoblast 6 weeks after the detection of the virus from the respiratory tract, although the repeat throat swab was negative. The fetus had extensive bilateral pleural effusion and subcutaneous edema, indicating hydrops fetalis. Moreover, SARS-CoV-2 was found in amniotic fluid (via RT-PCR) and fetal membranes (by immunofluorescence of spike proteins). Histopathology of the placenta revealed prominent avascular villi with extensive perivascular fibrin deposition, lysis of local syncytiotrophoblast, extensive decidual fibrin deposition, and large dilated and engorged blood vessels. The presence of a large number of leukocytes, including polymorphonuclear leukocytes, in the decidual bed and intervillous space

indicated widespread inflammation (Shende et al., 2021). Later, a spontaneous abortion of twin fetuses at the 13th week of gestation was reported in a 28-year-old pregnant woman with mild COVID-19. Fetal infection with SARS-CoV-2 was confirmed using PCR, immunofluorescence, and viral replication in fetal organs (lung and kidney) and placenta, which was consistent with an in-utero transmission of SARS-CoV-2 and highly associated with a hyperinflammatory process (Valdespino-Vázquez et al., 2021).

Therefore, based on the data in the current literature, SARS-CoV-2 infection during the preconception period and the first half of pregnancy may increase the risk of miscarriage. According to the immunopathological mechanisms, reproductive failure is caused by a pro-inflammatory maternal immune response (systemic and/or uterine), thromboembolic events, or a direct action of the virus in the uterine environment (endometrium, decidua, and trophoblast) (Fig. 1). Moreover, the risk appears to be higher in patients with the severe form of COVID-19 but also in asymptomatic women. Based on evidence from studies prior to COVID-19 and other studies with conditions similar to SARS-CoV-2 infection, it is necessary to assess whether the current literature supports the hypothesis that SARS-CoV-2 infection in the preconception period and in the first half of pregnancy increases the risk of miscarriage.

3. Systematic review and meta-analysis of the prevalence of miscarriage in pregnant women with COVID-19

3.1. Materials and methods

3.1.1. Study design

This study aimed to systematically review the risk of miscarriage in pregnant women who had COVID-19 during the first half of their pregnancy. The review was carried out in accordance with the statement on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Liberati et al., 2009; Page et al., 2021). The following search strategies were used to explore the PUBMED and EMBASE databases: COVID-19 or coronavirus disease 2019 or SARS-CoV-2, and miscarriage or abortion or pregnancy outcomes. The search was restricted to papers written in English.

For inclusion, articles published between December 1, 2019, and March 31, 2021, were considered. There were no attempts made to contact the study authors in order to identify missing and confusing data. Further, the EndNote X9 (Clarivate Analytics US LLC, Philadelphia, United States) was used as reference management software. In addition, a manual search of the references found in the selected articles and reviews was performed. Two reviewers (MBC and CTMBC) went over the titles and abstracts and screened duplicates independently for potential eligibility. They then read the entire text to determine final eligibility. Discrepancies were resolved through discussion and consensus, with the assistance of the third reviewer (ANMC), if necessary.

3.1.2. Statistical analysis

The authors, the date of publication, the study design, the total number of pregnant women, the total number of pregnant women diagnosed with COVID-19 in the first half of pregnancy, and the number of abortions were extracted. The data were initially analyzed in the form of a table using descriptive statistics.

In a meta-analysis, individual studies were pooled, and overall estimates of miscarriage prevalence were calculated using fixed and random effect models. The heterogeneity of the results was assessed using the Cochran's Q test and the I^2 inconsistency measure test. Publication bias was evaluated using Egger's and Begg's test with the funnel plot. MedCalc® Statistical Software version 19.8 (MedCalc Software Ltd, Ostend, Belgium) was used for statistical analyses.

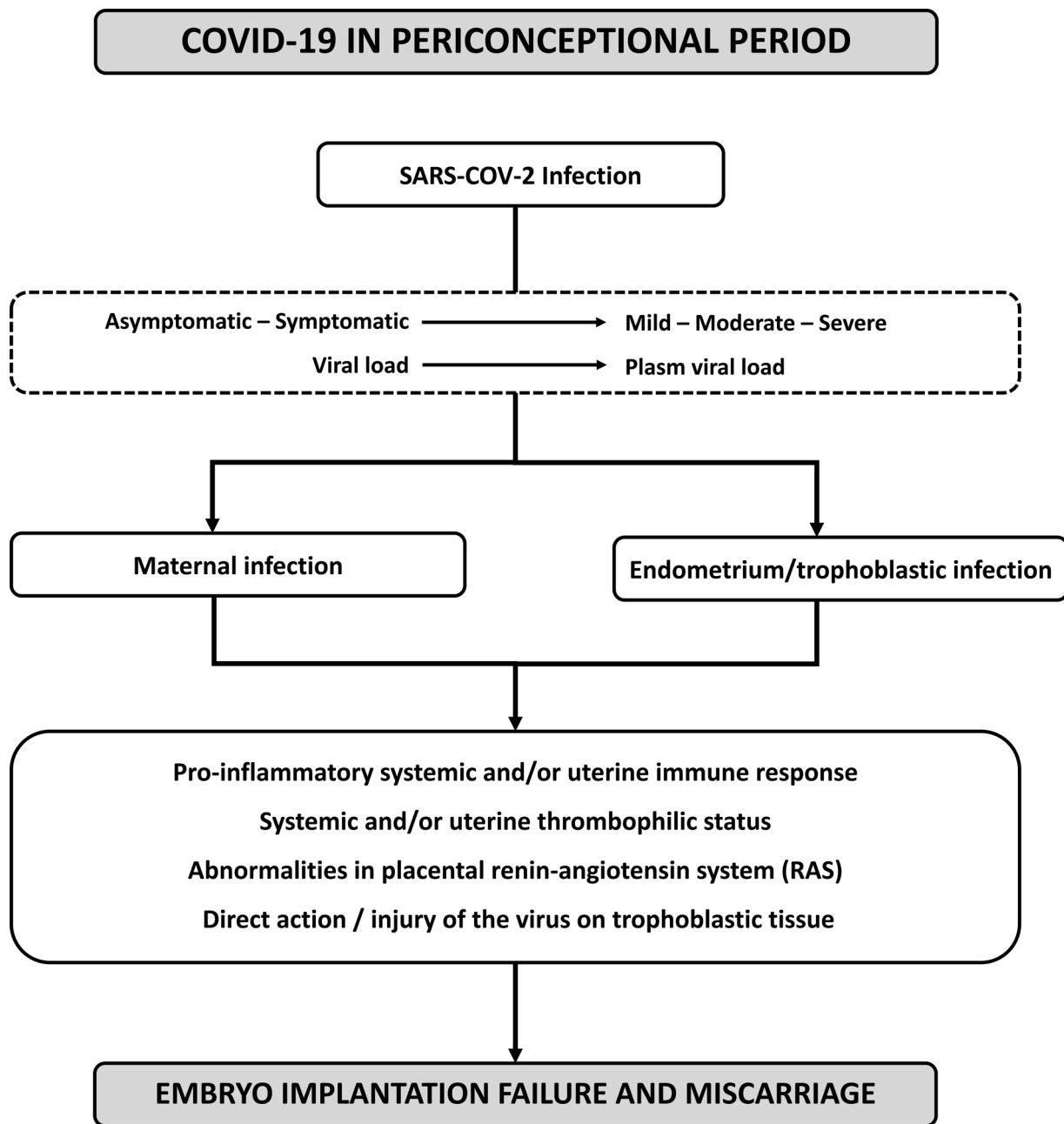


Fig. 1. Possible immunopathological mechanisms that may increase the risk of embryo implantation failure and miscarriage in women infected with SARS-CoV-2.

3.2. Results

3.2.1. Study selection and characteristics

In PubMed/Medline and EMBASE, the electronic search yielded 887 and 208 records, respectively. A total of 980 studies were obtained after downloading 1095 studies to the EndNote X9 Library Program after excluding duplicate records (115 duplicate records). Following an initial evaluation of titles and abstracts, 25 studies were excluded due to non-English language and 892 for other reasons (review articles, case reports, animal research, letters, exception to the letter reporting data on miscarriage in pregnant women with COVID-19). Sixty-three publications were chosen for a full-text review, excluding forty-six original articles that did not contain data on the prevalence of miscarriage in pregnant women with COVID-19 or were literature reviews. Finally, 17 studies were evaluated in the systematic review (6 case series studies, 6 retrospective cohort studies, and 7 prospective cohort studies), and 10

out of 17 studies were included in the meta-analysis of proportions (4 case series studies, 2 retrospective cohort studies and 4 prospective cohort studies) (Fig. 2) (Adhikari et al., 2020; Ayed et al., 2020; Chen et al., 2020; Curi et al., 2020; Delahoy et al., 2020; Grechukhina et al., 2020; Knight et al., 2020; Mattar et al., 2020; Nayak et al., 2020; Shmakov et al., 2020; Wong et al., 2020; Yan et al., 2020; D’Antonio et al., 2021, Group 2021, Guo et al., 2021; Sahin et al., 2021; Singh et al., 2021). All included studies were published from April 17, 2020, to February 20, 2021. Table 1 shows the characteristics of included studies. Subgroup analysis was done in women who miscarried before 12 weeks of gestation (8 studies) and those who miscarried before 22 weeks of gestation (3 studies). The study by Mattar et al. was included in both subgroup analyses since the study described 6 cases of COVID-19 in pregnant women <12 weeks and total of 7 cases in pregnant women <22 weeks gestation.

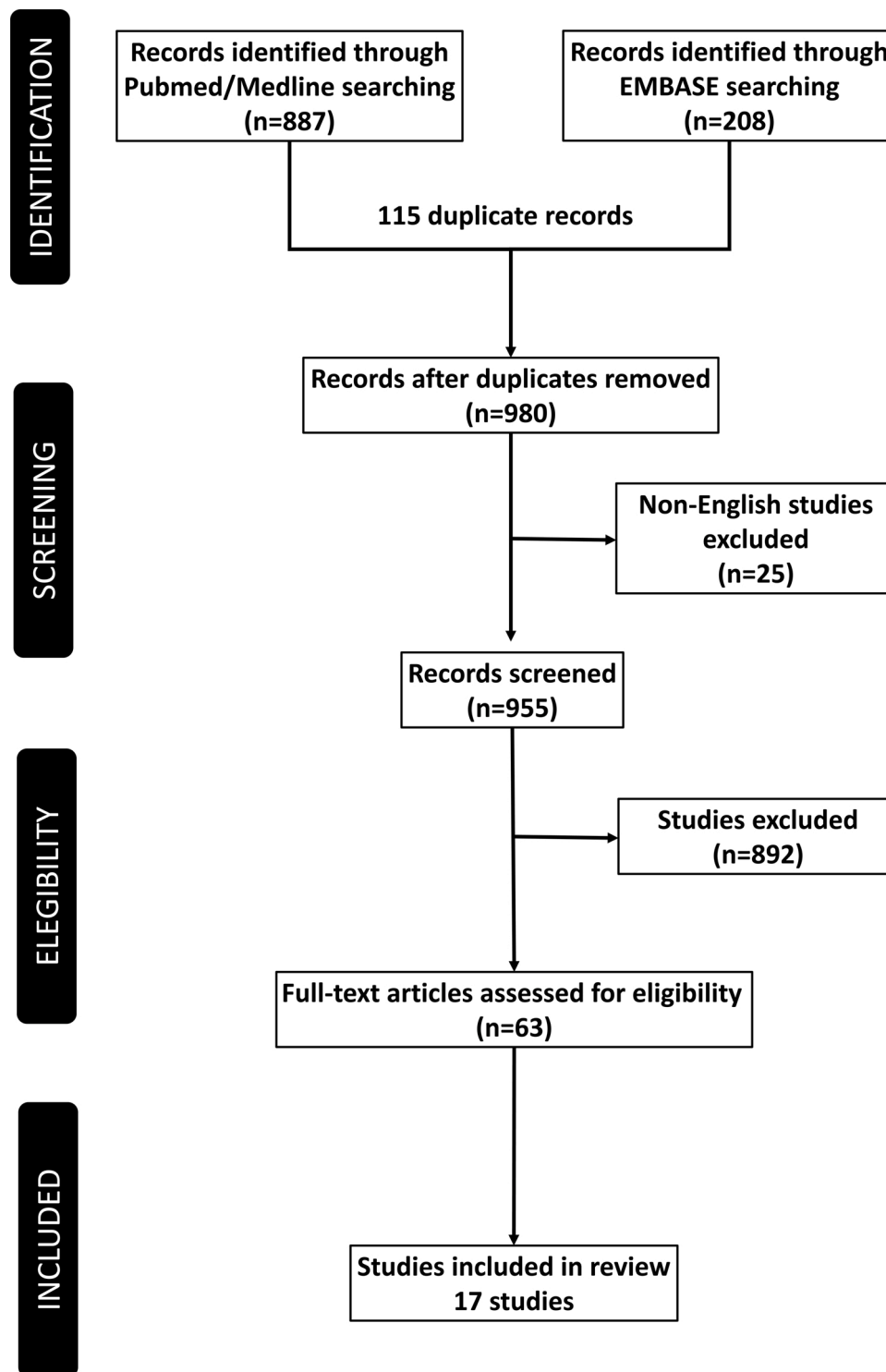


Fig. 2. Flowchart summarizing the study search and selection process.

3.2.2. Descriptive analysis

Chen et al. were the first to describe miscarriage as a possible pregnancy outcome in COVID-19 pregnant women ($n = 118$). In this group of patients (Wuhan City, China), there were three spontaneous abortions, two ectopic pregnancies, and four induced abortions (all due to patients' concerns about COVID-19). The authors did not report the number of COVID-19 cases per trimester, being impossible to calculate the miscarriage rate. Pregnant women with non-severe COVID-19 had all of their losses in the first half of their pregnancy (Chen et al., 2020).

Another six studies included in this review described miscarriages in pregnant women infected with COVID-19, but the miscarriage rate could not be determined due to a lack of accurate data on the total number of pregnant women infected with SARS-CoV-2 in the first half of pregnancy (Adhikari et al., 2020; Ayed et al., 2020; Delahoy et al., 2020; Nayak et al., 2020; D'Antonio et al., 2021; Guo et al., 2021).

In a case series study of 116 patients, Yan et al. reported the miscarriage rate in pregnant women with COVID-19 for the first time. Before the 20th week of gestation, 8 out of 116 pregnant women were

Table 1
Characteristics of the included studies.

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
Chen et al., 2020	Apr. 17, 2020 (China)	CSS ^b (n = 118)	NA	There were 3 spontaneous abortions, 2 ectopic pregnancies, and 4 induced abortions. All pregnancy losses were in patients with non-severe COVID-19. Symptomatic patients (all pregnant women were hospitalized for pneumonia).
Yan et al., 2020	Apr. 23, 2020 (China)	CSS (n = 116)	12.5 % (1/8) (0.32–52.65)	8 out of 116 cases presented before 24 weeks' gestation. One case (12.5 %, 1/8) was complicated with a missed spontaneous abortion at 5 ⁺² weeks. Symptomatic patients (all pregnant women were hospitalized for pneumonia).
Knight et al., 2020	June 8, 2020 (United Kingdom)	PCS ^c (n = 427)	18.2 % (4/22) (5.19–40.28)	The study included 22 (5 %) patients <22 weeks, 60 (14 %) 22–27 weeks, 64 (15 %) 28–31 weeks, 106 (25 %) 32–36 weeks, 142 (33 %) ≥37 weeks, 30 (7%) peripartum, and 3 (0.7 %) missing data. Four women had a miscarriage, at a range of 10–19 weeks gestation. Symptomatic patients (all pregnant women were admitted to hospital with confirmed SARS-CoV-2 infection).
Nayak et al., 2020	July 7, 2020 (India)	RCS ^d (n = 977)	N/A	Total 977 pregnant women were included. 141 patients had

Table 1 (continued)

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
Wong et al., 2020	Aug. 14, 2020 (Malaysia)	CSS (n = 7)	100 % (2/2) (15.81–100)	COVID-19 [6 miscarried (4.25 %, 6/141) and 1 had an ectopic pregnancy] and 836 patients were COVID negative [33 miscarried (3.94, 33/836) and 3 had ectopic pregnancies]. The number of pregnant women infected per trimester is unknown. Authors reported 465 COVID-19 cases (from 12 March 2020 to 25 May 2020). Seven of these cases were pregnant women (2 in the 1 st trimester, 3 in the 2 nd trimester and 2 in the 3 rd trimester). Two of the cases who were in their 1 st trimester had miscarriages. The other 5 cases have no reported adverse pregnancy.
Curi et al., 2020	Aug. 18, 2020 (USA)	CCS (n = 33)	0% (0/2) (0–84.19)	33 COVID-19-positive symptomatic pregnant patients, 2 (6.1 %) in the first trimester, 9 (27.2 %) in the second trimester, and 22 (66.7 %) in the third trimester.
WAPM (World Association of Perinatal Medicine) Working Group on COVID-19, 2021	Aug. 26, 2020 (Multinational)	RCS (n = 338)	19.4 % (6/31) (7.45–37.47)	Six of the 31 pregnant women with the first-trimester infection had miscarriages, including 5/23 (21.7 %) symptomatic and 1/8 (12.5 %) asymptomatic patients. 3 out

(continued on next page)

Table 1 (continued)

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
Delahoy et al., 2020	Sep. 25, 2020 (USA)	PCS (n = 458)	NA	of 338 patients (1.1 %) had a termination of pregnancy. Pregnancy losses occurred among both symptomatic and asymptomatic hospitalized women with COVID-19. Four pregnancy losses (3 in symptomatic and 1 in asymptomatic patients) occurred at <20 weeks' gestation. 54.5 % were asymptomatic. The number of pregnant women infected per trimester is unknown.
Grechukhina et al., 2020	Oct. 7, 2020 (USA)	CSS (n = 83)	18.2 % (2/11) (2.28–51.78)	11 (13.2 %) patients were in the 1 st trimester, 37 (44.6 %) in the 2 nd trimester, and 35 (42.2 %) in the 3 rd trimester. 2 (mild disease) out of 11 (10 mild and 1 severe disease) 1 st trimester pregnant women had miscarriage and 1 had a therapeutic abortion. Miscarriages occurred in symptomatic patients.
Mattar et al., 2020	Nov. 1, 2020 (Singapore)	PCS (n = 16)	14.3 % (1/7) (0.36–57.87)	6 (37.5 %) patients in the 1 st trimester, 7 (43.8 %) in 2 nd trimester and 3 (18.7 %) in 3 rd trimester. Three patients (18.8 %) were asymptomatic, while 13 (81.2 %) had mild respiratory symptoms. One woman miscarried (11 th week) among the 7 patients with

Table 1 (continued)

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
Sahin et al., 2021	Nov. 1, 2020 (Turkey)	PCS (n = 533)	9.2 % (12/130) (4.86–15.57)	COVID-19 before 22 weeks. 130 (24.4 %) patients were in the 1 st trimester, 165 (30.9 %) in the 2 nd trimester and 238 (44.7 %) in the 3 rd trimester. 165 out of 533 (30.9 %) were asymptomatic.
Adhikari et al., 2020	Nov. 19, 2020 (USA)	RCS (n = 3374)	NA	252 SARS-CoV-2 positive and 3122 SARS-CoV-2 negative pregnant women. The authors report the number of miscarriages in each group [7/272 (3 %) in SARS-CoV-2 positive group vs. 87/3122 (3 %) in SARS-CoV-2 negative group], but the number of pregnant women infected per trimester is unknown.
Shmakov et al., 2020	Nov. 29, 2020 (Russia)	PCS (n = 66)	40 % (2/5) (5.27–85.34)	5 (7.6 %) patients in the 1 st trimester, 7 (10.6 %) in the 2 nd trimester, and 54 (81.8 %) in the 3 rd trimester. Abortions before 20 weeks of gestation occurred in 4 cases (6.1 %) out of 66: 2 spontaneous abortions before 12 weeks of gestation in women with a mild form of Covid-19, one spontaneous abortion at 18 th week in a woman with severe infection, and one medical abortion at 19 th week for fetal abnormalities.
Ayed et al., 2020	Dec. 2, 2020 (Kuwait)	RCS (n = 185)	NA	21 (11.4 %) patients in the

(continued on next page)

Table 1 (continued)

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
Guo et al., 2021	Jan. 18, 2021 (China)	CSS (n = 20)	NA	1 st trimester, 64 (34.6 %) in 2 nd trimester and 95 (51.3 %) in 3 rd trimester. Three patients had a miscarriage at the 13 th (1 patient) and 14 th week of gestation (2 patients). The authors did not specify the number of patients diagnosed with COVID-19 before 22 weeks. Therefore, it was not possible to determine the miscarriage rate. 3 (15 %) patients in the 1 st trimester, 2 (10 %) in the 2 nd trimester, and 15 (75 %) in the 3 rd trimester. There was one case with induced abortions in the 1 st trimester (8w2d) and one with ectopic pregnancy (4w2d). 5 (3.8 %) patients were in the 1 st trimester, 2 (1.5 %) were in the 2 nd trimester, and 125 (94.7 %) were in the 3 rd trimester. 86 pregnant women (65.1 %) were asymptomatic, and 45 (34.1 %) had mild symptoms. Only one (0.8 %) had severe COVID-19. 208 high-risk patients and 679 low-risk patients were included. The incidence of miscarriage in high-risk
Singh et al., 2021	Feb. 6, 2021 (India)	RCS (n = 132)	60 % (3/5) (14.66–94.73)	5 (3.8 %) patients were in the 1 st trimester, 2 (1.5 %) were in the 2 nd trimester, and 125 (94.7 %) were in the 3 rd trimester. 86 pregnant women (65.1 %) were asymptomatic, and 45 (34.1 %) had mild symptoms. Only one (0.8 %) had severe COVID-19.
D'Antonio et al., 2021	Feb. 20, 2021 (Multinational ^b)	RCS (n = 887)	NA	208 high-risk patients and 679 low-risk patients were included. The incidence of miscarriage in high-risk

Table 1 (continued)

Author, year	Date ^a (Country)	Type of Study (No. of patients)	Miscarriage rate (%) (95 % CI)	Comments
				pregnancies was compared to that of low-risk pregnancies [5.3 % (11/208) vs. 1.6 % (11/679), p = 0.008]. The correct miscarriage rate cannot be calculated. The number of COVID-19 cases in patients < 22 weeks in each group has not been reported.

^a Date, the date of online publication.

^b CSS, case series study published by a letter to the editor.

^c PCS, prospective cohort study.

^d RCS, retrospective cohort study.

^e Multinational study by the World Association of Perinatal Medicine. Cases are from Argentina, Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and the USA.

tested positive for COVID-19. The miscarriage rate among these eight pregnant women was 12.5 % (n = 1/8, 95 % CI 0.32–52.65) (Yan et al., 2020). Other authors have reported the following miscarriage rates (<22 weeks of gestation): 18.2 % (n = 4/22, 95 % CI 5.19–40.28) (Knight et al., 2020), and 14.3 % (n = 1/7, 95 % CI 0.36–57.87) (Mattar et al., 2020).

Early miscarriage rates (<12 weeks) in pregnant women with COVID-19 diagnosed in the first trimester were 100 % (n = 2/2, 95 %CI 15.81–100) (Wong et al., 2020), 0% (n = 0/2, 95 %CI 0–84.19) (Curi et al., 2020), 19.4 % (n = 6/31, 95 %CI 7.45–37.47) (WAPM (World Association of Perinatal Medicine) Working Group on COVID-19, 2021), 18.2 % (n = 2/11, 95 %CI 2.28–51.78) (Grechukhina et al., 2020), 16.7 % (n = 1/6, 95 %CI 0.42–64.12) (Mattar et al., 2020), 9.2 % (n = 12/130, 95 %CI 4.86–15.57) (Sahin et al., 2021), 40 % (n = 2/5, 95 %CI 5.27–85.34) (Shmakov et al., 2020) and 60 % (n = 3/5, 95 %CI 14.66–94.73) (Singh et al., 2021).

The study of the World Association of Perinatal Medicine (WAPM) group was the only one that determined the miscarriage rate based on the presence of COVID-19 symptoms in pregnant women. When symptomatic pregnant women (21.7 %, n = 5/23) were compared to asymptomatic pregnant women (12.5 %, n = 1/8) (p = 0.568), the miscarriage rates were not significantly different. In addition, pregnant women at high obstetric risk who had COVID-19 in the first half of pregnancy had a higher miscarriage rate than pregnant women at low obstetric risk (5.3 % vs. 1.6 %, p = 0.008) (D'Antonio et al. 2021).

3.2.3. Meta-analysis

3.2.3.1. Total group analysis. To estimate the prevalence of miscarriage (<22 weeks) in patients with COVID-19, a total of 223 cases from 10 studies were pooled for the meta-analysis. The pooled proportion of miscarriage before 22 weeks gestation in pregnant women with COVID-19 was 15.3 % (95 % CI 10.95–20.59) and 23.1 % (95 % CI 13.17–34.95) using fixed and random effects models, respectively (Fig. 3). The

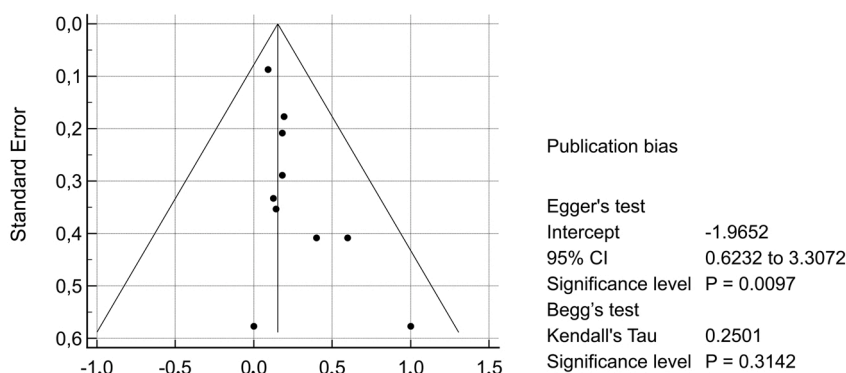
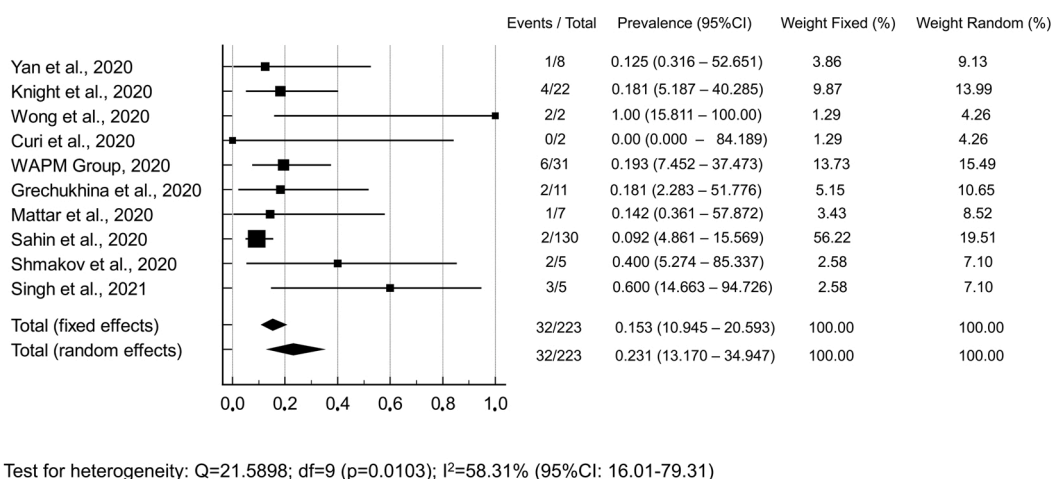


Fig. 3. Miscarriage (<22 weeks) prevalence in pregnant women with COVID-19 (all studies included, meta-analysis and funnel plot).

included studies showed significant heterogeneity, with I^2 being 58.3 % (95 % CI 16.01–79.31, $P = 0.010$) (Fig. 3). Additionally, modest publication bias was noticed (Egger's test, 95 % CI 0.623–3.307, $P = 0.0097$; Begg's test Kendall's tau -0.2501, $P = 0.314$).

3.2.3.2. Subgroup analysis. A total of 8 studies investigating the COVID-19 cases in pregnant women <12 weeks gestation were included in this analysis. To estimate the prevalence of early miscarriage (<12 weeks) in patients with COVID-19, a total of 192 cases were pooled for the meta-analysis. The pooled proportion of miscarriage before 12 weeks gestation in pregnant women with COVID-19 was 14.9 % (95 % CI 10.3–20.6) and 26.7 % (95 % CI 13.1–43.0) using fixed and random effects models, respectively (Fig. 4). However, the included studies showed substantial heterogeneity, with I^2 being 67.2 % (95 % CI 30.93–84.47, $P = 0.003$) (Fig. 4) and the modest publication bias (Egger's test, 95 % CI 0.5066–3.7294, $P = 0.0182$; Begg's test Kendall's tau 0.3706, $P = 0.1992$).

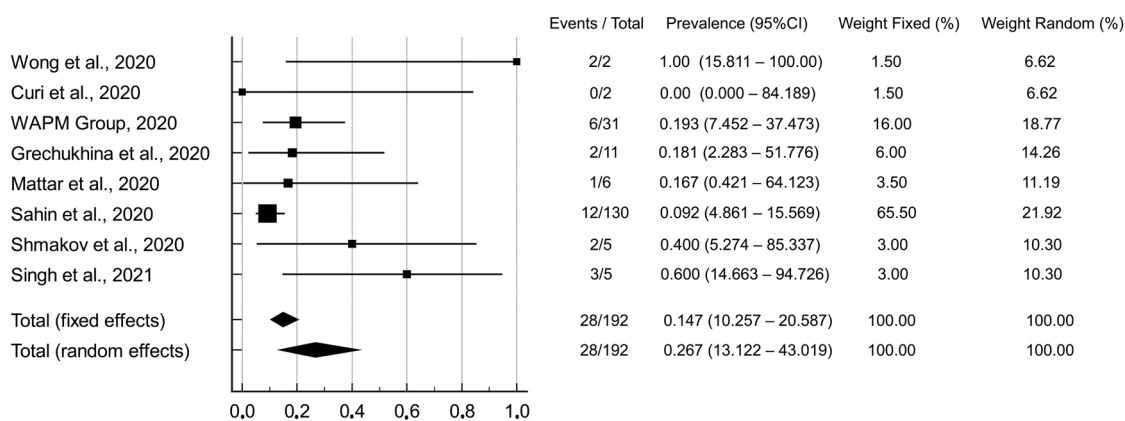
Three studies included pregnant women under 22 weeks gestation without specifying weeks miscarriage being <12 weeks. To estimate the prevalence of miscarriage (<22 weeks) in patients with COVID-19, a total of 37 cases were pooled for the meta-analysis. The pooled proportion of miscarriage before 22 weeks gestation in pregnant women with COVID-19 was 18.5 % (95 % CI 8.04–33.98) using both fixed and random effects models, respectively. The included studies showed low heterogeneity, with I^2 being 0% (95 % CI 0.0 to 0.0, $P = 0.977$) (Fig. 5). Additionally, publication bias was not noticed (Egger's test, 95 % CI -4.3006 to 3.4832, $P = 0.40$; Begg's test Kendall's tau -0.3333, $P =$

0.6015).

3.3. Discussion

The research on the effects of viral respiratory infections on pregnancy, particularly during the first half of pregnancy, has been inconsistent. At the beginning of the COVID-19 pandemic, it was speculated that SARS-CoV-2 infection could increase the risk of miscarriage based on small studies conducted during previous SARS and MERS outbreaks (Favre et al., 2020). The maternal influenza A subtype H1N1 infection can be fatal to pregnant women, inducing inflammatory immune responses similar to SARS-CoV-2 infection. A meta-analysis of 17 studies involving 2,351,204 cases published recently found that H1N1 infection increased the risk of stillbirth (Relative risk = 3.62, 95 % CI: 1.60–8.20) (Wang et al., 2021). In addition, a large Norwegian study noted that maternal influenza-like illness during pregnancy increases the risk of miscarriage (Adjusted hazard ratio = 2.28 [95 % CI 1.45–3.59]) (Gunnes et al., 2020).

Miscarriage is an unintentional pregnancy loss happening before 12 weeks (early miscarriage) or between 12 and 22 weeks (late miscarriage). The overall miscarriage rate before 20 weeks gestation ranges from 10 % to 26 % (Practice Committee of the American Society for Reproductive Medicine, 2012; American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology, 2018; Dugas and Slane, 2021) with the rate increasing with the woman's age, reaching around 53 % in women aged 45 and up (Kolte et al., 2015; Pinar et al., 2018). In this study, the pooled proportion of miscarriage



Test for heterogeneity: $Q=21.3708$; $df=7$ ($p=0.0033$); $I^2=67.25\%$ (95%CI: 30.93-84.47)

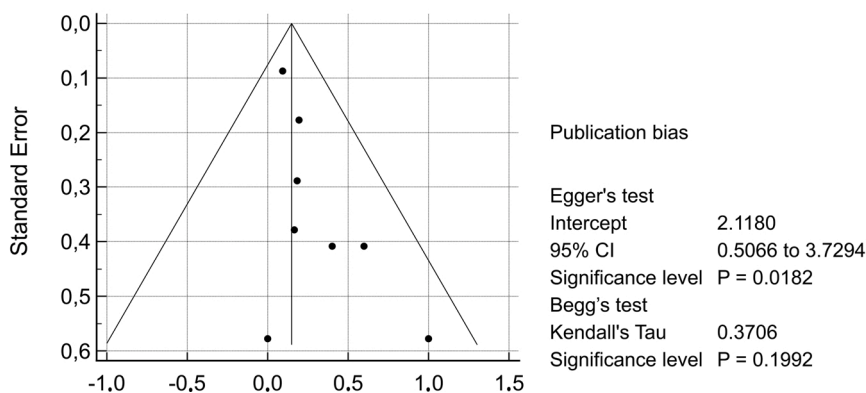


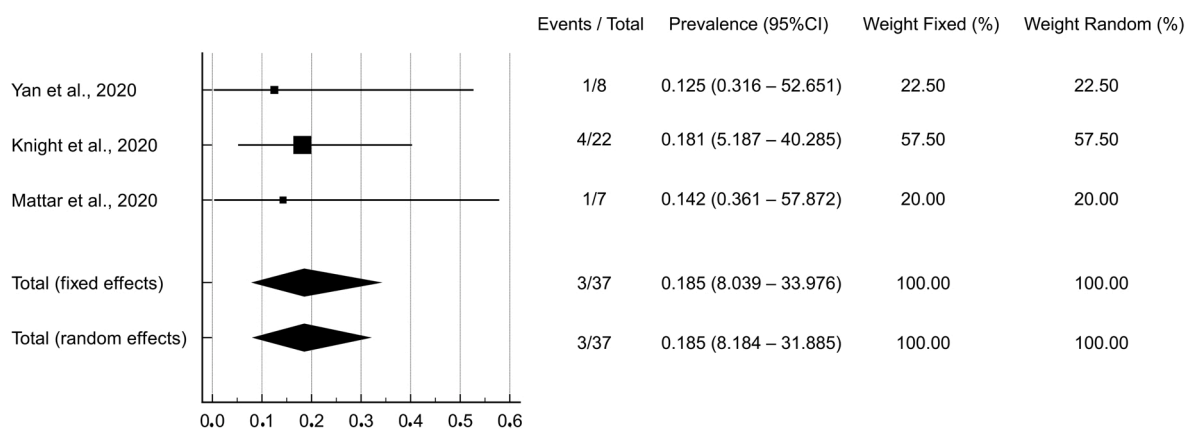
Fig. 4. Subgroup analysis for early miscarriage (<12 weeks) prevalence in pregnant women with COVID-19 (meta-analysis and funnel plot).

(<22 weeks) in pregnant women with COVID-19 was 15.3 % (95 % CI 10.95–20.59) and 23.1 % (95 % CI 13.17–34.95) using fixed and random effects models, respectively. Thus the miscarriage rate of COVID-19 cases seems to be in the range of the normal pregnant population. Since most studies were case series studies without proper controls or only including COVID-19 cases, we were not able to compare miscarriage rates between COVID-19 positive and negative pregnant women. The findings should be interpreted cautiously, given the small number of cases and the heterogeneity among the included cases.

Contrary to findings of influenza infection, earlier COVID-19 studies did not demonstrate an association between COVID-19 and miscarriages. The impact of the pandemic environment on the miscarriage rate in two cohorts of pregnant women has been studied in Montreal, Quebec, Canada, at two different times. A retrospective cohort study was conducted to compare the miscarriage rate of all asymptomatic women (without performing universal screening) in the first trimester during the study period ($n = 113$, March 13 until May 6, 2020) with that of pregnant control women ($n = 172$, from March 1 to May 17, 2019), approximately 1 year earlier. There was no significant difference in the total number of pregnancy losses (defined as the sum of biochemical abortions, 1st-trimester abortions, and blighted ova) (22.1 % vs. 16.9 %, $p = 0.32$) or in each type of miscarriage. The weakness of this study stems from the lack of universal screening for SARS-CoV-2 infections in the study group. Furthermore, there were no cases of COVID-19 reported

in the study group (Rotshenker-Olshinka et al., 2021). The cumulative incidence of COVID-19 was also compared in women who had miscarriages ($n = 100$) and those who were pregnant at the time of the study (controls, $n = 125$). No difference was detected in the cumulative incidence of COVID-19 between the miscarriage group (11/100, 11 %) and controls (12/125, 9.6 %) ($p = 0.73$) (Cosma et al., 2021). Based on these studies, SARS-CoV-2 infection during the first trimester of pregnancy does not seem to predispose to early pregnancy loss.

Interestingly, the presence of symptoms during the acute phase of COVID-19, plasma viral load, disease severity, and the presence of obstetrical risk factors appear to increase the risk of miscarriage in pregnant women infected with SARS-CoV-2. However, the studies included in this review did not adequately assess the relationship between the clinical features of pregnant women with COVID-19 and the risk of miscarriage, and the majority of them are small cohorts or case series studies to assess the risk of miscarriage in pregnant women infected with SARS-CoV-2. Additionally, the vast majority of studies evaluating the impact of COVID-19 on pregnancy have limited descriptions of perinatal complications, and only a few studies have evaluated the effects of COVID-19 during the periconceptional period. Therefore, there is an urgent need for well-designed studies, considering the clinical manifestation of COVID-19 and determining whether SARS-CoV-2 infection during the periconceptional period increases the risk of miscarriage.



Test for heterogeneity: $Q=0.04646$; $df=2$ ($p=0.977$); $I^2=0.00\%$ (95%CI: 0.00-0.00)

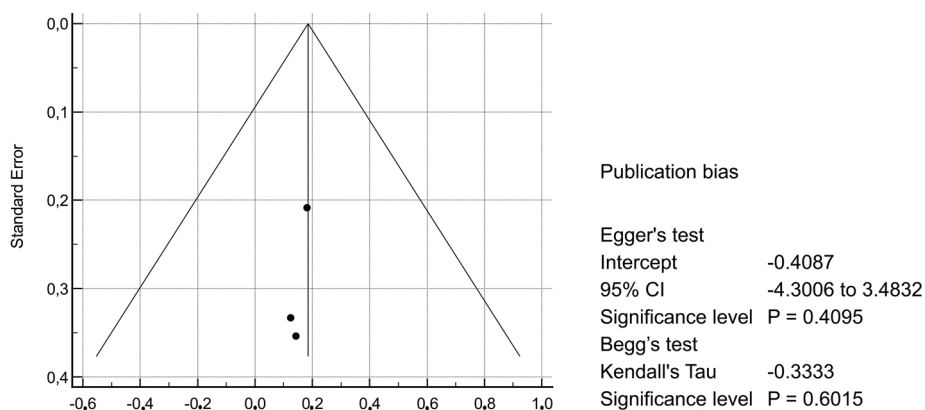


Fig. 5. Subgroup analysis for miscarriage (<22 weeks) prevalence in pregnant women with COVID-19 (meta-analysis and funnel plot).

Declaration of Competing Interest

The authors report no declarations of interest.

References

Adhikari, E.H., et al., 2020. Pregnancy outcomes among women with and without severe acute respiratory syndrome coronavirus 2 infection. *JAMA Netw Open*. 3, e2029256.

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology, 2018. ACOG practice bulletin no. 200: early pregnancy loss. *Obstet. Gynecol.* 132, e197–e207.

Anton, L., Brosnihan, K.B., 2008. Systemic and uteroplacental renin–angiotensin system in normal and pre-eclamptic pregnancies. *Ther. Adv. Cardiovasc. Dis.* 2, 349–362.

Ayed, A., et al., 2020. Maternal and perinatal characteristics and outcomes of pregnancies complicated with COVID-19 in Kuwait. *BMC Pregnancy Childbirth* 20, 754.

Bloise, E., et al., 2021. Expression of severe acute respiratory syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-fetal interface in pregnancies complicated by preterm birth or preeclampsia. *Am. J. Obstet. Gynecol.* 224, 298.e1–298.e8.

Bora, I., et al., 2020. Persistence of SARS-CoV-2 in body fluids: a bystander or whistle blower. *Iran. J. Microbiol.* 12, 370–375.

Cevik, M., et al., 2021. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2, e13–e22.

Chang, L., et al., 2020. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. *Emerg. Infect. Dis.* 26, 1631–1633.

Chen, L., et al., 2020. Clinical characteristics of pregnant women with covid-19 in Wuhan, China. *N. Engl. J. Med.* 382, e100.

Cosma, S., et al., 2021. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. *Am. J. Obst. Gynecol.* 224, 391.e1–391.e7.

Cui, D., et al., 2021. Single-cell RNA expression profiling of SARS-CoV-2-related ACE2 and TMPRSS2 in human trophoctoderm and placenta. *Ultrasound Obstet. Gynecol.* 57, 248–256.

Curi, B., et al., 2020. Coronavirus infection in a high-risk obstetrical population of the South Bronx, New York. *Am. J. Obst. Gynecol. MFM* 2, 100203.

D'antonio, F., et al., 2021. Maternal and perinatal outcomes in high vs low risk-pregnancies affected by SARS-CoV-2 infection (phase-2): the WAPM (World Association of Perinatal Medicine) working group on COVID-19. *Am. J. Obst. Gynecol. MFM* 3, 100329.

Delahoy, M.J., et al., 2020. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 - COVID-NET, 13 states, March 1–August 22, 2020. *MMWR Morb. Mortal. Wkly. Rep.* 69, 1347–1354.

Dong, M., et al., 2020. ACE2, PMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Biomed. Pharmacother.* 131, 110678.

Dugas, C., Slane, V.H., 2021. Miscarriage. *StatPearls [Internet]*. StatPearls Publishing, Treasure Island (FL), 2021 Jan.

Fajnzylber, J., et al., 2020. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat. Commun.* 11, 5493.

Farina, A., et al., 2020. SARS-CoV-2 detection in the pericardial fluid of a patient with cardiac tamponade. *Eur. J. Intern. Med.* 76, 100–101.

Favre, G., et al., 2020. 2019-nCoV epidemic: what about pregnancies? *Lancet* 395, e40.

Ferraiolo, A., et al., 2020. Report of positive placental swabs for SARS-CoV-2 in an asymptomatic pregnant woman with COVID-19. *Medicina (Kaunas)* 56, 306.

Giakoumelou, S., et al., 2016. The role of infection in miscarriage. *Hum. Reprod. Update* 22, 116–133.

Grechukhina, O., et al., 2020. Coronavirus disease 2019 pregnancy outcomes in a racially and ethnically diverse population. *Am. J. Obst. Gynecol. MFM* 2, 100246.

- Gunnes, N., et al., 2020. Seasonal and pandemic influenza during pregnancy and risk of fetal death: a Norwegian registry-based cohort study. *Eur. J. Epidemiol.* 35, 371–379.
- Guo, Y., et al., 2021. Case series of 20 pregnant women with 2019 novel coronavirus disease in Wuhan, China. *J. Obstet. Gynaecol. Res.* 47, 1344–1352.
- Hosier, H., et al., 2020. SARS-CoV-2 infection of the placenta. *J. Clin. Invest.* 130, 4947–4953.
- Huang, Y.H., et al., 2020. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav. Immun.* 87, 149.
- Knight, M., et al., 2020. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ* 369, m2107.
- Kolte, A.M., et al., 2015. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. *Hum. Reprod.* 30, 495–498.
- Kwak-Kim, J., et al., 2014. Immunological modes of pregnancy loss: inflammation, immune effectors, and stress. *Am. J. Reprod. Immunol.* 72, 129–140.
- Li, D., et al., 2020. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. *JAMA Netw. Open.* 3, e208292.
- Liberati, A., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339, b2700.
- Liu, H., et al., 2020. Why are pregnant women susceptible to covid-19? An immunological viewpoint. *J. Reprod. Immunol.* 139, 103122.
- Mattar, C.N., et al., 2020. Pregnancy outcomes in COVID-19: a prospective cohort study in Singapore. *Ann. Acad. Med. Singap.* 49, 857–869.
- Mei, F., et al., 2020. First detection of SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction assay in pleural fluid. *Chest* 158, e143–e146.
- Meyerowitz, E.A., et al., 2021. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. *Ann. Intern. Med.* 174, 69–79.
- Mishra, S.K., Tripathi, T., 2021. One year update on the COVID-19 pandemic: where are we now? *Acta Trop.* 214, 105778.
- Moriguchi, T., et al., 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94, 55–58.
- Narang, K., et al., 2020. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. *Mayo Clin. Proc.* 95, 1750–1765.
- Nayak, A.H., et al., 2020. Impact of the coronavirus infection in pregnancy: a preliminary study of 141 patients. *J. Obstet. Gynaecol. India* 70, 256–261.
- Page, M.J., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71.
- Pinar, M.H., et al., 2018. Early pregnancy losses: review of nomenclature, histopathology, and possible etiologies. *Fetal Pediatr. Pathol.* 37, 191–209.
- Practice Committee of the American Society for Reproductive Medicine, 2012. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil. Steril.* 98, 1103–1111.
- Qi, R., et al., 2020. The role of the renin-angiotensin system in regulating endometrial neovascularization during the peri-implantation period: literature review and preliminary data. *Ther. Adv. Endocrinol. Metab.* 11, 2042018820920560.
- Rotshenker-Olshinka, K., et al., 2021. COVID-19 pandemic effect on early pregnancy: are miscarriage rates altered, in asymptomatic women? *Arch. Gynecol. Obstet.* 303, 839–845.
- Sahin, D., et al., 2021. Updated experience of a tertiary pandemic center on 533 pregnant women with COVID-19 infection: a prospective cohort study from Turkey. *Int. J. Gynaecol. Obstet.* 152, 328–334.
- Sarun, Charumilind, et al., 2021. When Will the COVID-19 Pandemic End? <https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/when-will-the-covid-19-pandemic-end>.
- Sharps, M.C., et al., 2020. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. *Placenta* 101, 13–29.
- Shende, P., et al., 2021. Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. *Hum. Reprod.* 36, 899–906.
- Shmakov, R.G., et al., 2020. Clinical course of novel COVID-19 infection in pregnant women. *J. Matern. Fetal. Neonatal. Med.* 1–7. Online ahead of print.
- Sills, E.S., Wood, S.H., 2020. An experimental model for peri-conceptual COVID-19 pregnancy loss and proposed interventions to optimize outcomes. *Int. J. Mol. Cell. Med.* 9, 180–187.
- Singh, V., et al., 2021. Maternal and neonatal outcomes of COVID-19 in pregnancy: a single-centre observational study. *Cureus* 13, e13184.
- To, K.K., et al., 2020. Consistent detection of 2019 novel coronavirus in saliva. *Clin Infect Dis.* 71, 841–843.
- Valdés, G., et al., 2006. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathological pregnancies. *Placenta* 27, 200–207.
- Valdespino-Vázquez, M.Y., et al., 2021. Fetal and placental infection with SARS-CoV-2 in early pregnancy. *J. Med. Virol.* 93, 4480–4487.
- Vaz-Silva, J., et al., 2009. The vasoactive peptide angiotensin-(1-7), its receptor Mas and the angiotensin-converting enzyme type 2 are expressed in the human endometrium. *Reprod. Sci.* 16, 247–256.
- Wang, M.Y., et al., 2020a. SARS-CoV-2: structure, biology, and structure-based therapeutics development. *Front. Cell. Infect. Microbiol.* 10, 587269.
- Wang, W., et al., 2020b. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 323, 1843–1844.
- Wang, R., et al., 2021. The effect of influenza virus infection on pregnancy outcomes: a systematic review and meta-analysis of cohort studies. *Int. J. Infect. Dis.* 105, 567–578.
- WAPM (World Association of Perinatal Medicine) Working Group on COVID-19, 2021. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. *Ultrasound Obstet. Gynecol.* 57, 232–241.
- Weatherbee, Ba.T., et al., 2020. Expression of SARS-CoV-2 receptor ACE2 and the protease TMPRSS2 suggests susceptibility of the human embryo in the first trimester. *Open Biol.* 10, 200162.
- Wong, T.C., et al., 2020. Miscarriage risk in COVID-19 infection. *SN Compr. Clin. Med.* 2, 1449–1452.
- World Health Organization (WHO), 2021. WHO Coronavirus Disease (COVID-19) Dashboard (Accessed 31 May 2021). <https://covid19.who.int/>.
- Wu, Z., McGoogan, J.M., 2020. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 323, 1239–1242.
- Wu, Y.C., et al., 2020. The outbreak of COVID-19: an overview. *J. Chin. Med. Assoc.* 83, 217–220.
- Xie, H.T., et al., 2020. SARS-CoV-2 in the ocular surface of COVID-19 patients. *Eye Vis.* 7, 23.
- Yan, J., et al., 2020. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *Am. J. Obstet. Gynecol.* 223, 111.e1–111.e14.
- Yang, K.M., et al., 2010. Women with multiple implantation failures and recurrent pregnancy losses have increased peripheral blood T cell activation. *Am. J. Reprod. Immunol.* 63, 370–378.
- Zambrano, L.D., et al., 2020. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22–October 3, 2020. *MMWR Morb. Mortal. Wkly. Rep.* 69, 1641–1647.
- Zheng, S., et al., 2020. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January–March 2020: retrospective cohort study. *BMJ* 369, m1443.