



Meta-analysis of the frequency of intrauterine growth restriction and preterm premature rupture of the membranes in pregnant women with COVID-19

COVID-19'lu gebe kadınlarda intrauterin büyüme geriliği ve preterm erken membran rüptürünün sıklığı: Bir meta-analiz

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Abstract

The impact of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in pregnancy has yet to be determined. Some studies indicate that SARS-CoV-2 infection may be associated with a higher risk of adverse outcomes in pregnant women. Here, we performed a meta-analysis to estimate the frequency of intrauterine growth restriction (IUGR) and preterm premature rupture of the membranes (PPROM) in pregnant women with Coronavirus disease-2019 (COVID-19). A comprehensive search was performed in various databases, such as PubMed, Scopus, SciELO, MedRxiv, and Web of Science, to find all relevant studies published before 10 February 2021. Cross-sectional and consecutive case series reporting the pregnancy outcomes of COVID-19 were included. A total of 24 studies, including 8 studies on IUGR and 16 studies on PPRM, were selected. Pooled data showed that the frequencies of IUGR and PPRM in pregnant women with COVID-19 were 2.6% and 9.9%, respectively. Analyses stratified by ethnicity showed that the frequencies of IUGR in Asian and Caucasian COVID-19-infected pregnant women were 2.9% and 2.0%, respectively. Moreover, the frequencies of PPRM in Asian and Caucasian COVID-19-infected pregnant women were 10.2% and 5.8%, respectively. This meta-analysis showed that the frequencies of IUGR and PPRM in COVID-19-infected pregnant women were 2.6% and 9.9%, respectively. However, well-designed, large-scale and multicenter clinical studies are required to improve and validate these results.

Keywords: COVID-19, SARS-CoV-2, pregnancy, intrauterine growth restriction, preterm premature rupture of membranes

Öz

Şiddetli akut solunum sendromu-koronavirüs-2'nin (SARS-CoV-2) gebelikteki etkisi henüz bilinmemektedir. Bazı çalışmalar, SARS-CoV-2 enfeksiyonunun hamile kadınlarda artmış olumsuz sonuçlanım riski ile ilişkili olabileceğini göstermiştir. Burada, Koronavirüs hastalığı-2019'lu (COVID-19) hamile kadınlarda intrauterin büyüme geriliği (IUGG) ve preterm erken membran rüptürü (PERM) sıklığını tahmin etmek için bir meta-analiz gerçekleştirildi. 10 Şubat 2021'den önce yayınlanan tüm ilgili çalışmaları bulmak için PubMed, Scopus, SciELO, MedRxiv ve Web of Science'da kapsamlı bir arama yapıldı. Gebe kadınlarda COVID-19'un gebelik sonuçlarını bildiren kesitsel çalışmalar ve ardışık olgu serileri dahil edildi. İUGG üzerine 8 çalışma ve PERM üzerine 16 çalışma olmak üzere toplam 24 çalışma seçildi. Havuzlanmış veriler, COVID-19'lu enfekte kadınlarda İUGG ve PERM sıklığının sırasıyla %2,6 ve %9,9 olduğunu göstermiştir. Etnik kökene göre tabakalı analizler, Asyalı ve Kafkasyalı enfekte hamile kadınlarda İUGG sıklığının sırasıyla %2,9 ve %2,0 olduğunu göstermiştir. Ayrıca, Asyalı ve Kafkasyalı enfekte gebelerde PERM sıklığı sırasıyla %10,2 ve %5,8 idi. Bu meta-analiz, COVID-19 ile enfekte

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hamile kadınlarda İUGG ve PERM sıklığının sırasıyla %2,6 ve %9,9 olduğunu göstermiştir. Bununla birlikte, bu sonuçları iyileştirmek ve doğrulamak için iyi tasarlanmış, büyük ölçekli ve çok merkezli klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, gebelik, intrauterin büyüme geriliği, preterm erken membran rüptürü

Introduction

Since December 2019, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak has resulted in 120 million cases and over 2.2 million deaths worldwide^(1,2). Several viral infections are known to increase the risk of poor neonatal and maternal outcomes during pregnancy⁽³⁻⁵⁾. Maternal physiological changes in pregnancy have a significant impact on the coagulation and immune, respiratory, and cardiovascular systems of the fetus and may have positive or negative effects on Coronavirus disease-2019 (COVID-19) disease progression⁽⁶⁾. Some authors have indicated that two previous epidemics of SARS and Middle Eastern respiratory syndrome (MERS-CoV) were associated with adverse pregnancy and neonatal outcomes⁽⁷⁾. Our experiences in pregnancies complicated by infection with the previous coronaviruses have led us to believe that pregnant woman may be vulnerable to the adverse effects of COVID-19. Initial studies on pregnant women have revealed that COVID-19 significantly increases the risk of abortion, preterm birth, stillbirth, intrauterine growth restriction (IUGR), intrauterine death, low birth weight, and case fatality^(8,9). Some studies have also demonstrated that maternal COVID-19 could affect the oxygen supply of the fetus, leading to placental insufficiency, IUGR, fetal distress, and/or fetal demise⁽¹⁰⁾. Recent epidemiological and clinical studies have reported different results on the maternal and fetus outcomes of COVID-19⁽¹¹⁾. The current systematic review and meta-analysis aimed to evaluate these results and determine the frequency of IUGR and PROM in pregnant women with COVID-19.

No definitive evidence of the vertical transmission of SARS-CoV-2 infection from mother to child is available in the existing data, but some pregnancy complications, such as premature birth, IUGR, and spontaneous abortion, through COVID-19-positive mothers have been reported.

Materials and Methods

Search Strategies

We performed a meta-analysis in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines (<http://www.prismastatement.org>). This meta-analysis does not contain any studies with human participants performed by any of the authors. Electronic databases, including PubMed/MEDLINE, Europe PMC, Google Scholar, EMBASE, Cochrane Library, SciELO, Springer Link, Technology Journal, Egyptian Knowledge Bank, Chinese Biomedical Database, the China National Knowledge Infrastructure platform, VIP, Chinese literature (Wan Fang), and China science, were comprehensively searched to identify all relevant studies

published up to 10 February 2021. Combinations of the following search terms were used (designed using English Medical Subject Headings keywords and Emtree terms): (“COVID-19 virus disease” OR “SARS -CoV-2” OR “SARS-CoV-2” OR “2019 novel coronavirus infection” OR “2019-nCoV infection” OR “coronavirus disease” OR “coronavirus disease-19” OR “2019-nCoV disease” OR “COVID-19 virus infection”) AND (“IUGR” OR “Intrauterine growth retardation” OR “IUGR”) AND (“Premature rupture of membranes” OR “Prelabor rupture of membranes” OR “PPROM”). We restricted our search to human studies and articles published in English, Farsi, and Chinese. An extra search was conducted in the reference lists of the included studies to avoid missing eligible studies that had not been identified in the primary search. The Centers for Disease Control and Prevention and World Health Organization websites were also evaluated.

Inclusion and Exclusion Criteria

The primary studies were selected according to the following inclusion criteria: 1) case series, case-control, or cohort studies; 2) studies reporting pregnancy outcomes in pregnant women with SARS-CoV-2 infection; 3) studies with sufficient data to calculate odds ratios (ORs) with 95% confidence intervals (CIs). The following exclusion criteria were also implemented: 1) insufficient data; 2) non-human or in vitro studies; 3) abstracts, case reports, non-consecutive case series, posters, editorials, reviews, conference papers, previous meta-analyses, and non-standard data presentations; and 4) overlapping and duplicated data.

Data Extraction

Two authors independently performed title-abstract screening on all primary studies. The full text of the selected articles was also screened, and all necessary data were extracted into a standardized form. In case of disagreement, a third author was involved to reach a consensus for all items. The following features were extracted for pooled estimation: name of the first author, year of publication, country of origin, ethnicity, total number of pregnant women with COVID-19, and numbers of reported PPROM and IUGR. The corresponding author was contacted by email for any missing data. The studies included in this current meta-analysis did not obviously overlap with the subjects in other studies. If a duplicate publication was found or the same population was used in multiple studies, the publication with the larger sample size was included in the meta-analysis.

Statistical Analysis

The frequency of IUGR and PPROM in pregnant women with SARS-CoV-2 infection was assessed by ORs with 95% CIs. The

significance of pooled ORs was determined using the Z-test; here, $p < 0.05$ defined as the significance threshold. Between-study heterogeneity was tested using the Q-statistic test; $p \leq 0.10$ indicated significant heterogeneity crossing studies. The I² statistic was used to qualify heterogeneity (range, 0-100%: I²=0-25%, no heterogeneity; I²=25-50%, moderate heterogeneity; I²=50-75%, large heterogeneity; I²=75-100%, extreme heterogeneity). If significant heterogeneity ($p < 0.1$) was detected, a random-effects model (i.e., the DerSimonian and Laird method) was selected to pool the data; otherwise, the fixed-effects model (i.e., the Mantel-Haenszel method) was employed. Visual inspection of the funnel plot was used to assess potential publication bias. Moreover, Egger's test was performed to assess the publication bias statistically, and $p < 0.05$ was considered statistically significant. If the publication bias tests indicated bias, the Duval and Tweedie "trim-and-fill" method was used to adjust this bias⁽¹²⁾. All of the statistical calculations were performed using comprehensive meta-analysis version 2.0 software (Biostat, USA). Two-sided p-values < 0.05 were considered statistically significant.

Results

As shown in Figure 1, 484 articles were found in different databases and manual searches; these articles were published up to 10 January 2020. Duplicate articles were removed, and 241 articles remained. All of these articles were screened by

reading their abstracts/titles, and another 128 studies were eliminated. Of the remaining studies, 89 articles were excluded because they were reviews, meta-analyses, or non-consecutive case reports or did not report the necessary data. Finally, a total of 24 studies, including 8 studies on IUGR with 2,504 infected pregnant women and 60 IUGR cases⁽¹³⁻²⁰⁾ and 16 studies on PPROM with 1,469 infected pregnant women and 91 PPROM cases^(15,20-34), were selected. The characteristics of the studies included in the present meta-analysis are presented in Table 1. The publication year of the selected studies was 2020. All selected studies were published in English and Chinese. Among the studies on IUGR, five were performed among Caucasians, two were conducted among Asians and one was conducted among a mixed population. Among the studies on PPROM, nine studies were performed among Asians, four were conducted among Caucasians, and one was conducted among Latin-Americans. The studies were performed in the United States, France, Turkey, Iran, India, Spain, Peru, and China.

IUGR

Summaries of the frequency of IUGR in pregnant women with SARS-CoV-2 infection are shown in Table 2. The pooled data showed that the frequency of IUGR in COVID-19-infected women was 2.6% (95% CI: 0.021-0.034, $p \leq 0.001$, Figure 2A). Analyses stratified by ethnicity showed that the frequencies of IUGR among Asian and Caucasian pregnant women were 2.9% (95% CI: 0.020-0.042, $p \leq 0.001$) and 2.0% (95% CI: 0.014-0.031, $p \leq 0.001$, Figure 2B), respectively. Moreover, the frequency of IUGR among North-American women was 2.5% (95% CI: 0.016-0.040, $p \leq 0.001$).

PPROM

Table 2 presents the summaries of the frequency of PPROM among SARS-CoV-2-infected pregnant women. The pooled data showed that the frequency of PPROM among pregnant women infected with COVID-19 was 9.9% (95% CI: 0.058-0.164, $p \leq 0.001$, Figure 3A). Analyses stratified by ethnicity showed that the frequencies of PPROM among Asian and Caucasian infected pregnant women were 10.2% (95% CI: 0.056-0.181, $p \leq 0.001$, Figure 3B) and 5.8% (95% CI: 0.011-0.248, $p \leq 0.001$, Figure 3C), respectively. Moreover, the frequency of PPROM among Chinese women was 10.6% (95% CI: 0.072-0.155, $p \leq 0.001$).

Between-study Heterogeneity and Sensitivity Analysis

As shown in Table 1, significant between-study heterogeneity was noted in the overall population for PPROM (I²=79.27, $PH \leq 0.001$) but not for IUGR (I²=34.02, $PH = 0.157$). Subgroup analysis by ethnicity demonstrated no decrease in heterogeneity. However, subgroup analysis among Chinese women revealed that the country of origin may be a source of heterogeneity in the current meta-analysis (Table 2). We performed a sensitivity analysis to evaluate the stability of the results by sequentially

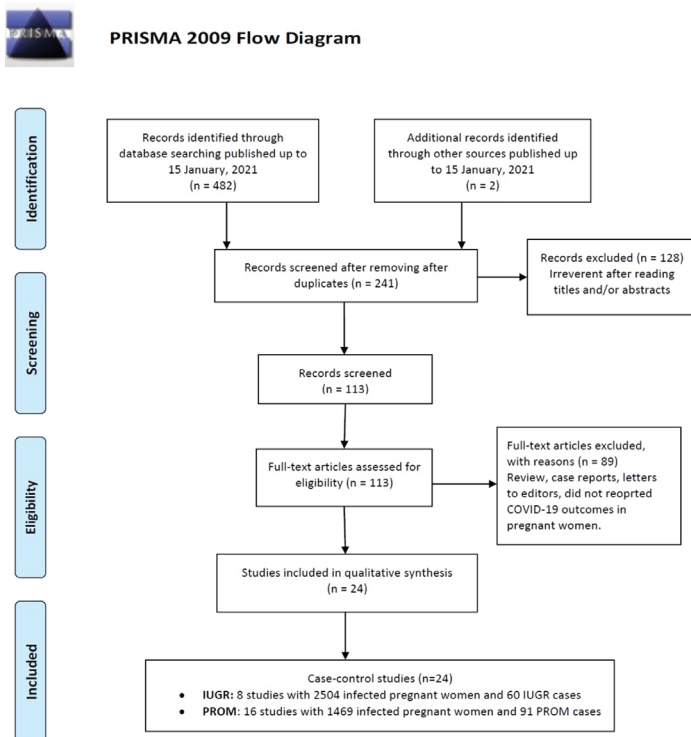


Figure 1. Study selection and inclusion process

IUGR: Intrauterine growth restriction, PPROM: Preterm premature ruptures of membranes, COVID-19: Coronavirus disease-2019

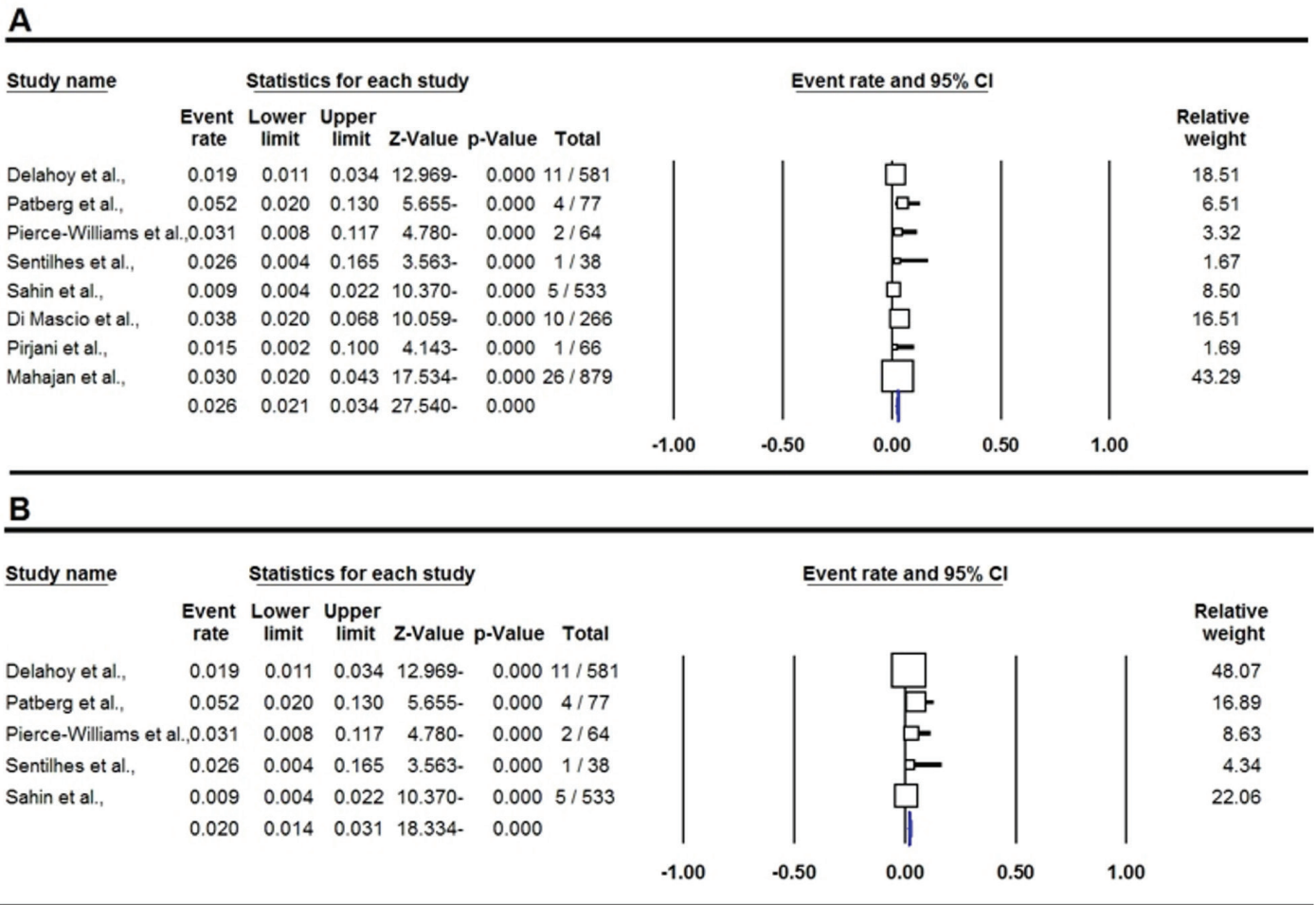


Figure 2. Forest plots of the frequency of IUGR in pregnant women infected with SARS-CoV-2 in the (A) overall and (B) Caucasian populations

IUGR: Intrauterine growth restriction, CI: Confidence interval, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

removing each study and then recalculating the corresponding ORs. The data from the sensitivity analysis revealed that none of the studies changed the pooled ORs for IUGR and PPRM, thereby indicating that our combined data are reliable.

Publication Bias

We performed the Begg’s and Egger’s tests to detect potential publication bias. As shown in Figure 4, the symmetrical funnel plot indicated a significant publication bias for IUGR (PBeggs=0.035; PEggers=0.707) in the overall population but not for PPRM (PBeggs=0.444, PEggers=0.512). Egger’s test was performed to provide statistical evidence of the funnel plot (Table 2). The Duval and Tweedie non-parametric “trim-and-fill” method was used to adjust for publication bias. Meta-analyses with and without using the “trim-and-fill” method did not result in different conclusions (Figure 4A).

Discussion

The impact of COVID-19 on pregnancy outcomes remains poorly understood^(1,35,36). The clinical course of COVID-19 in pregnant women has been reported to be similar to that in non-pregnant

women⁽³⁷⁾. Patberg et al.⁽¹⁴⁾ found in a retrospective study that the frequency of fetal vascular malperfusion abnormalities was significantly higher in pregnant women than in non-pregnant women with COVID-19 by using a multivariable model adjusted for maternal age, ethnicity, preeclampsia, mode of delivery, IUGR/FGR, and oligohydramnios. Placental abnormalities, such as maternal vascular malperfusion, in pregnant women with COVID-19 have also been associated with IUGR^(27,38,39). Studies on pregnant women during previous outbreaks of SARS and MERS observed an increased risk of IUGR. Thus, surveillance of IUGR in women with SARS-CoV-2 infection is recommended because IUGR is often observed in ongoing pregnancies with SARS-CoV-2^(37,38).

The incidence of IUGR among pregnant women has been reported to be between 4% and 7%⁽⁴⁰⁾. A recent cohort study involving 4.451 Chinese women found that the incidence of IUGR was 22.4% in women with severe preeclampsia and 18.6% in women with chronic hypertension with superimposed preeclampsia⁽⁴¹⁾. Diriba et al.⁽⁴²⁾ performed a meta-analysis on the maternal outcomes of coronavirus infection (i.e., SARS-

Table 1. Characteristics of the studies included in this meta-analysis

First author	City (country)	Ethnicity	Pregnancies or neonate	Number of reports
IUGR				
Delahoy et al. ⁽¹³⁾	13 States (USA)	Caucasian	581	11
Patberg et al. ⁽¹⁴⁾	New York (USA)	Caucasian	77	4
Pierce-Williams et al. ⁽¹⁵⁾	Pennsylvania (USA)	Caucasian	64	2
Sentilhes et al. ⁽¹⁶⁾	Strasbourg (France)	Caucasian	38	1
Sahin et al. ⁽¹⁷⁾	Ankara (Turkey)	Caucasian	533	5
Di Mascio et al. ⁽¹⁸⁾	WAPM	Mixed	266	10
Pirjani et al. ⁽¹⁹⁾	Babol (Iran)	West Asian	66	1
Mahajan et al. ⁽²⁰⁾	Mumbai (India)	South Asia	879	26
PPROM				
Pierce-Williams et al. ⁽¹⁵⁾	Pennsylvania (USA)	Caucasian	64	1
Shanes et al. ⁽²⁷⁾	USA	Caucasian	16	1
Martnez-Perez et al. ⁽²⁹⁾	Spain	Caucasian	82	18
Egerup et al. ⁽²⁸⁾	Copenhagen (Denmark)	Caucasian	28	0
Dávila-Aliaga et al. ⁽³⁰⁾	Peru	Latin	114	17
Yan et al. ⁽³¹⁾	Wuhan (China)	Asian	116	6
Yang et al. ⁽³²⁾	Wuhan (China)	Asian	65	4
Yang et al. ⁽³³⁾	Wuhan (China)	Asian	27	1
Hu et al. ⁽³⁴⁾	Wuhan (China)	Asian	6	2
Chen et al. ⁽²¹⁾	Wuhan (China)	Asian	9	2
Zhu et al. ⁽²²⁾	Wuhan (China)	Asian	9	3
Li et al. ⁽²³⁾	Wuhan (China)	Asian	16	2
Liu et al. ⁽²⁴⁾	Guangzhou (China)	Asian	13	1
Zhang et al. ⁽²⁶⁾	Qianjiang (China)	Asian	16	3
Hantoushzadeh et al. ⁽²⁵⁾	Iran	West Asian	9	1
Mahajan et al. ⁽²⁰⁾	Mumbai (India)	South Asia	879	29

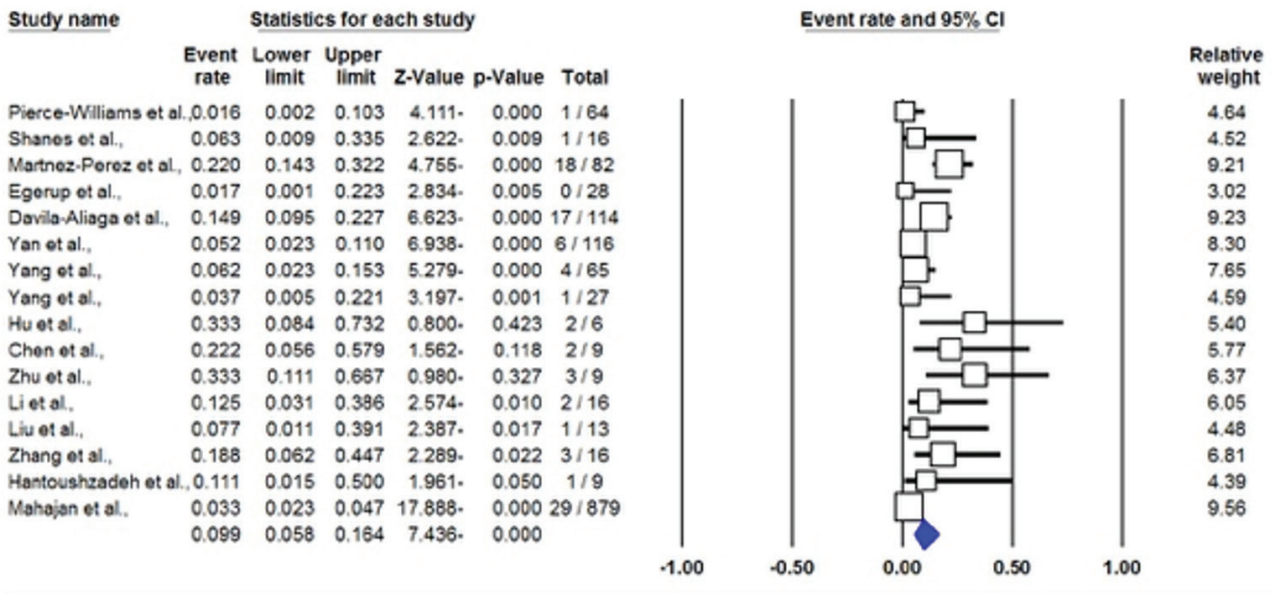
IUGR: Intrauterine growth restriction, PPROM: Preterm premature rupture of membranes, WAPM: World Association of Perinatal Medicine

Table 2. Summary of the frequencies of IUGR and PPROM among pregnant women with COVID-19

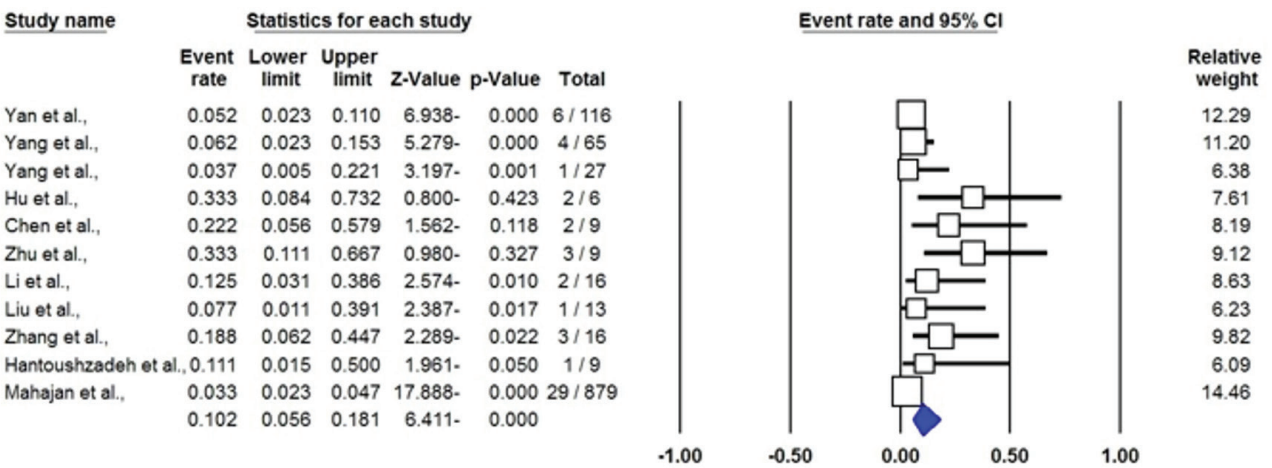
Subgroup	Type of model	Heterogeneity		Odds ratio				Publication bias	
		I ² (%)	P _H	Frequency	95% CI	Z _{test}	P _{OR}	P _{Begg}	P _{Eggers}
IUGR									
Overall	Fixed	34.02	0.157	0.026	0.021-0.034	-27.540	≤0.001	0.035	0.707
Caucasian	Fixed	43.85	0.129	0.020	0.014-0.031	-18.132	≤0.001	0.806	0.590
Asian	Fixed	0.00	0.506	0.029	0.020-0.042	-18.00	≤0.001	1.000	0.718
US	Fixed	36.63	0.206	0.025	0.016-0.040	-14.828	≤0.001	1.000	0.478
PPROM									
Overall	Random	79.27	≤0.001	0.099	0.058-0.164	-7.436	≤0.001	0.444	0.512
Caucasian	Random	74.98	0.007	0.058	0.011-0.248	-3.252	0.001	0.734	0.051
Asian	Random	70.82	≤0.001	0.102	0.056-0.181	-6.411	≤0.001	0.371	0.004
Chinese	Random	47.81	0.053	0.106	0.072-0.155	-9.618	≤0.001	0.465	0.205

IUGR: Intrauterine growth restriction, PPROM: Preterm premature ruptures of membranes, CI: Confidence interval, COVID-19: Coronavirus disease-2019

A



B



C

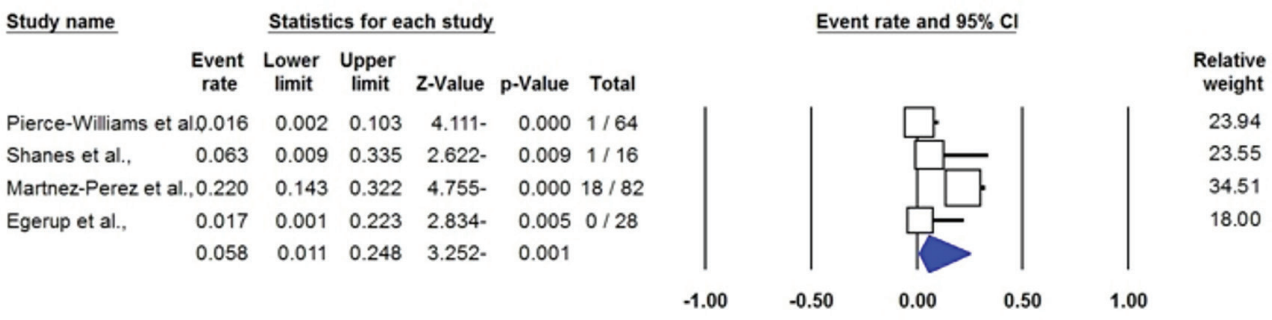


Figure 3. Forest plots of the frequencies of PPROM in pregnant women with SARS-CoV-2 infection in the (A) overall, (B) Asian, and (C) Caucasian populations

PPROM: Preterm premature rupture of the membranes, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, CI: Confidence interval

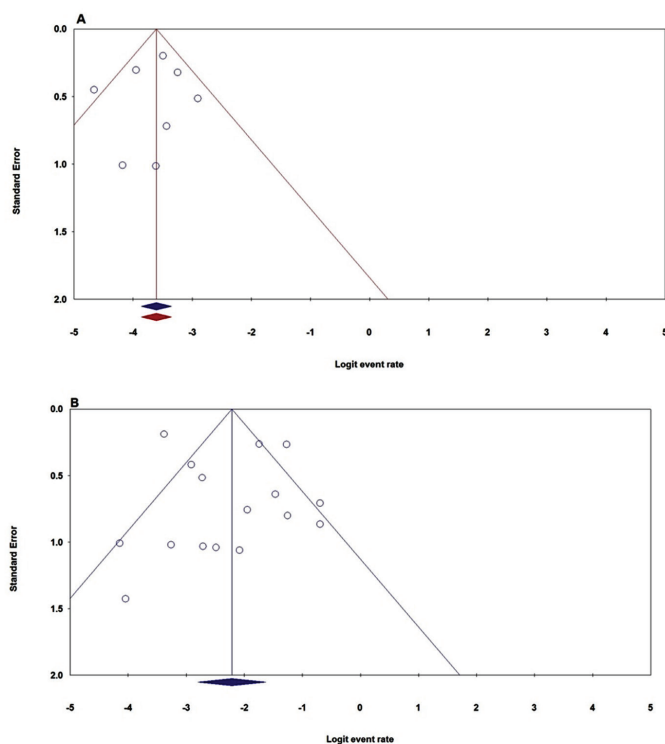


Figure 4. Begg's funnel plot to test for publication bias test on the frequencies of (A) IUGR and (B) PPROM in pregnant women with SARS-CoV-2

PPROM: Preterm premature rupture of the membranes, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, IUGR: Intrauterine growth restriction

CoV-2, MERS-CoV, and SARS-CoV) and found that the rates of preterm birth (<37 weeks of gestation), preeclampsia, miscarriage, PPROM, and FGR were 14.3%, 5.9%, 14.5%, 9.2%, and 2.8%, respectively. The pooled data revealed that the incidence rates of PPROM and FGR among pregnant women with SARS-CoV-2 infection were 8.9% and 1.2%, respectively. Moreover, the group showed that the incidence rates of PPROM and FGR among pregnant women with SARS-CoV infection were 12.5% and 12.5%, respectively. The current meta-analysis revealed found that the frequency of IUGR in COVID-19 infected pregnant women was 2.6%. This incidence is lower than that determined by others in previously published studies on healthy and infected women⁽⁴⁰⁻⁴²⁾. Biasucci et al.⁽¹¹⁾, in a study among 375 Italian pregnant women, demonstrated that COVID-19 was not associated with poorer clinical outcomes and/or with higher rates of preterm birth and IUGR in infected pregnant women compared with non-infected pregnant women. PPROM is defined as the rupture of the fetal membrane prior to the onset of labor at less than 37 weeks of gestation. The incidence of PPROM has been reported to be approximately 3%⁽⁴⁰⁾. However, this incidence varies by ethnicity and region. A retrospective cohort study reported that the incidence of PROM among African-Americans was 29.5%; another study

showed that the incidence of PROM in Rochester, NY, USA, was 12.0%⁽⁴³⁾. In 2019, Sae-Lin and Wanitpongpan⁽⁴⁴⁾ reported that the incidence of PPROM over a 5-year period in Thailand was 2.93%. Our pooled data showed that the frequency of PPROM was 9.9% in COVID-19-infected pregnant women; this figure is substantially higher than that indicated in previous research. Subgroup analysis by ethnicity showed that the respective frequencies of PPROM in COVID-19-infected pregnant women were 10.2% in Asians and 5.8% in Caucasians. This frequency was 10.6% in Chinese women. Rodrigues et al.⁽⁴⁵⁾ performed a systematic review including 3,985 COVID-19-infected pregnant women and found that the most frequent obstetric conditions include gestational diabetes (4.5%), PPROM (2.7%), preeclampsia/eclampsia/HELLP syndrome (1.7%), fetal distress (1.1%), gestational hypertension (0.6%), fetal growth restriction (0.4%), placenta previa/placental abruption/placenta accreta (0.4%), and oligohydramnios/polyhydramnios (0.2%). Chi et al.⁽⁴⁶⁾, in a meta-analysis including 230 women with COVID-19 and 156 newborns, showed that 8.49% (9/106) of the newborns had PPROM. Della Gatta et al.⁽⁴⁷⁾ conducted a review of six studies including 51 pregnant women and found PPROM in at least 9 of 34 patients (26%). Akhtar et al.⁽⁴⁸⁾ performed a meta-analysis and determined that the most common maternal/fetal complications included intrauterine/fetal distress (14%) and PPROM (8%). Moreover, the group found that COVID-19 infection in pregnancy leads to increased risk of pregnancy complications, such as preterm birth and PPROM, and may even lead to maternal death in rare cases. Yang et al.⁽³²⁾, in a study based on the Maternal and Child Health Information System of Wuhan, China, showed no significant difference in the incidence of PPROM between the confirmed and free COVID-19 groups. Zhang et al.⁽²⁶⁾, in a case-control study among pregnant women with and without COVID-19 in Hubei, China, reported no significant difference between pregnant women in terms of gestational diabetes, severe preeclampsia, PPROM, fetal distress, meconium-stained amniotic fluid, premature delivery, neonatal asphyxia, and procedures for severe post-partum bleeding. Our meta-analysis presents potential limitations. First, all of the included studies were performed among Caucasian and Asian pregnant women with COVID-19. Thus, our pooled data are not generalizable to other ethnicities. Further studies with larger sample sizes in different ethnicities are necessary to confirm our findings. Second, the studies included in the current meta-analysis were published in English and Chinese; thus, a number of potentially significant data published in other languages may have been excluded. Finally, in the current meta-analysis, we could not answer some important questions, such as the extent of asymptomatic or mild infection and the effect on IUGR and PPROM, because of the lack of data in primary studies. In summary, this meta-analysis showed that the frequencies of IUGR and PPROM in COVID-19-infected pregnant women were 2.6% and 9.9%, respectively. Analyses stratified by

ethnicity revealed that the frequencies of IUGR and PPROM were higher in Asian COVID-19-infected pregnant women than in Caucasian COVID-19-infected women. Given that most studies on COVID-19 included cases with early stages of the disease and that the selected reports were restricted to China, further well-designed studies with larger sample sizes including different populations may be required to obtain more accurate estimates.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.B., D.A.S., M.K.Z., Design: R.B., D.A.S., M.K.Z., Data Collection or Processing: M.K.Z., Analysis or Interpretation: S.R.M., H.N., Literature Search: M.N., A.J., S.A.D., F.F., Writing: M.N., R.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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