Review Article

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A Meta-Analysis for Frequency of Miscarriage in Pregnant Women with COVID-19

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ABSTRACT

Background: Most pregnant women with COVID-19 develop less severe form of the disease, with few cases of severe maternal morbidity and mortality, or perinatal deaths. This meta-analysis was conducted to evaluate the frequency of miscarriage in pregnant women affected by the SARS-COV-2 infection.

Methods: A comprehensive search was performed in online databases to identify all relevant studies published up to 5th March 2021. Case-control studies and case series reported the frequency of miscarriage in pregnant women with COVID-19 was selected.

Results: A total of 22 studies with 8591 infected pregnant women and 141 abortions were selected. The frequency of miscarriage was 3.9% (95% CI 0.023-0.063) in infected pregnant women with COVID-19. It had the highest frequency in Asian (6.3%) followed by European (2.9%), West-Asian (2.5%) and Caucasian (2.3%) infected pregnant women. Moreover, stratified analysis by country showed that the frequency of miscarriage is the highest in Chinese (11.3%) followed by Italy (11.2%), India (2.7%), Turkey (2.2%), USA (1.2%) and France (0.9%) infected pregnant women.

Conclusion: Our pooled data revealed that the frequencies of miscarriage in pregnant women with SARS-COV-2 infection were 3.9%.

Introduction

Vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) and miscarriage are serious concerns in pregnant infected women.[1,2] However, the relationship between COVID-19 and risk of miscarriage remains unclear.[3] Since SARS-COV-2 presents similarities to severe acute respiratory syndrome coronavirus (SARS-COV) and Middle East Respiratory Syndrome-related coronavirus (MERS), it is likely that their effects on pregnancy are similar. A recent review suggested that COVID-19 appeared to be less lethal to mothers and infants than SARS and MERS but there may be an increased risk of pregnancy complications such as preterm birth after 28 weeks' gestation.[4] A review study indicated that COVID-19 can lead to fetal distress, miscarriage, respiratory distress and preterm delivery in pregnant women but does not infect newborns.[5]

The effects of SARS-CoV-2 in pregnancy were initially based on our previous experience with SARS-COV-1 and MERS.[6] A meta-analysis reported that the rate of miscarriage among infected women with SARS-COV-2, MERS-COV, and SARS-COV was 2.4%.[7] As our knowledge of COVID-19 increases, there is new data about risk and incidence of pregnancy complications in infected pregnant women. In women affected by COVID-19, occurrence of miscarriage appears higher in those affected in pregnancy compared with non-infected pregnant women. However, there was no reported data on frequency of miscarriage in pregnant women infected with COVID-19.[8] Thus, we carried out the current meta-analysis to estimate the frequency of miscarriage in pregnant women affected by the SARS-COV-2 infection.

Materials and Methods

Search Strategies: This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Moreover, this meta-analysis does not contain any studies with human participants performed by any of the authors. A comprehensive search was performed on PubMed/MEDLINE, Europe PMC, Google Scholar, EMBASE, Cochrane Library database, SciELO, Springer Link, Technology Journal database and Egyptian Knowledge Bank (EKB), Chinese Biomedical Database (CBD), China National Knowledge Infrastructure (CNKI) platforms, VIP, Chinese literature (Wan Fang) and China Science to identify all relevant studies on the incidence of miscarriage in pregnant women with SARS-COV-2 infection up to 5th March 2021. Combinations of following key words and Medical Subject Headings (Mesh) terms were used: (‘’COVID-19 virus disease’’ OR ‘’Severe Acute Respiratory Syndrome Coronavirus 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 (‘’pregnancy outcomes’’ OR ‘’neonatal outcomes’’) (‘’Miscarriage’’ OR ‘’Spontaneous Miscarriage‘’ OR ‘’Pregnancy Loss’’ OR ‘’Abortion’’). We restricted our search to human studies and published articles in English and Chinese. Moreover, the references of reviews and eligible studies were cross-checked to prevent missing of any eligible study which was not identified by primary search. Articles included in the current meta-analysis had no obvious overlap of subjects with other studies.

Inclusion and Exclusion Criteria: The full text of primary studies was selected according to the following inclusion and exclusion criteria: 1) case series, case-control or cohort studies; 2) studies reported frequency of miscarriage in pregnant women with SARS-COV-2 infection; 3) studies with sufficient data to calculate the odds ratio (OR) with 95% confidence interval (CI). In addition, the following exclusion criteria were also used: 1) insufficient data; 2) non-human

or in vitro studies; 3) abstracts, case report, posters, editorials, reviews, conference papers, and previous meta-analyses and non-standard data presentation; and 4) overlapping and duplicated data.

Data Extraction: All titles and abstracts of the selected studies in the primary search were reviewed by two authors independently. They extracted the necessary data into a standardized form. A third author was involved to reach an agreement for all items when the authors were not in agreement. The information obtained from each article consisted of first author name, year of publication, country, ethnicity, total numbers of women with SARS-COV-2 infection, miscarriage, the trimester of miscarriage, and type of miscarriage (spontaneous, medical, and elective). The publication with the larger sample size was included in the meta-analysis if a duplicate publication was found or the same population was used in multiple studies. The corresponding author was contacted through email for any missing data.

Statistical Analysis: The frequency of miscarriage in pregnant women with SARS-COV-2 infection was assessed by odds ratios (ORs) with 95% confidence intervals (CIs). Using the Z-test, the significance of pooled ORs was determined and $P < 0.05$ defined as the significance threshold. Between-study heterogeneity was tested using the Q-statistic test, which $P \leq 0.10$ indicated significant heterogeneity crossing studies. To qualify the heterogeneity, the I^2 statistic was used (range of 0 to 100%: I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; I^2 = 75-100%, extreme heterogeneity). The results in the fixed-effect model (Mantel-Haenszel method) were selected when no significant heterogeneity existed; otherwise, the random-effect model (DerSimonian and Laird method) was employed. To assess potential publication bias, a visual inspection of the funnel plot was used. Besides, Egger's test was performed to assess the publication bias statistically, in which $P < 0.05$ was considered statistically significant. In the presence of publication bias, the Duval and Tweedie ''trim and fill'' method was used to adjust the bias.[9] Using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA), all of the statistical calculations were performed. Two-sided $P < 0.05$ were considered statistically significant.

Results

Our initial search yielded 592 studies up to 25 December 2020 as shown in figure 1. The search retrieved 311 items after eliminating duplicate articles. Upon check of the article titles and abstracts, 193 articles were excluded due to irrelevance to the meta-analysis scope. Of the remaining 118 articles that were assessed for eligibility in full-text screening, 91 did not meet inclusion criteria. Finally, a total of 27 studies including 22 studies with 8591 infected pregnant women and 141 miscarriages on miscarriage.[8,10-13,17-32]
were selected. The characteristics of studies included in the present meta-analysis are presented in table 1 and 2. The publication year of the selected studies was in 2020. All selected studies were published in English and Chinese. Of them, 8 studies were performed among Caucasians with 6087 infected women and 75 miscarriages, ten studies were from Asian women 650 infected women and 29 miscarriages, and one national wide study with 388 women and 6 miscarriages. The individual study sample sizes ranged from 3 to 4442 (Table 1). The studies were performed in Russia, Turkey, France, United States, Italy, United Kingdom, Iran, Kuwait, and China.

Quantitative Data Synthesis

Miscarriage: The summaries for frequency of miscarriage in women with SARS-COV-2 infection are shown in table 2. The frequency of miscarriage was 3.9% (95% CI 0.023-0.063, $P \leq 0.001$, Figure 2A) in infected women with COVID-19. Stratified analysis by ethnicity showed that the frequency of miscarriage was highest in Asian

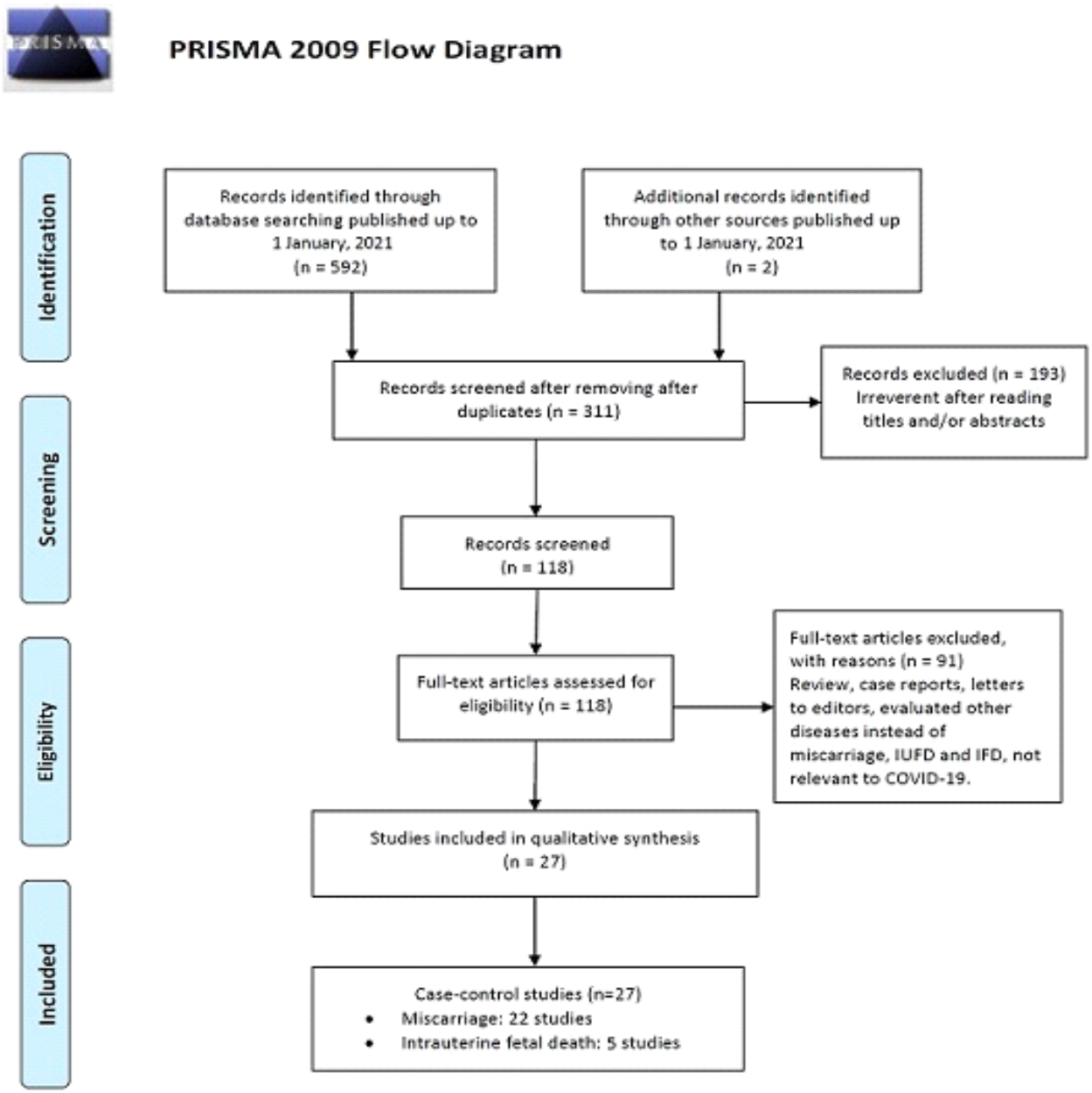

Figure 1. The Study Selection and Inclusion Process

(6.3%, 95% CI 0.032-0.122, P ≤ 0.001, Figure 2B), European (2.9%, 95% CI 0.012-0.065, P ≤ 0.001), West-Asian (2.5%, 95% CI 0.009-0.069, P ≤ 0.001) and Caucasian (2.3%, 95% CI 0.011-0.048, P ≤ 0.001, Figure 2B) infected pregnant women. Moreover, stratified analysis by country showed that the frequency of miscarriage was highest in Chinese (11.3%, 95% CI 0.054-0.221, P ≤ 0.001), Italy (11.2%, 95% CI 0.065-0.188, P ≤ 0.001), India (2.7%, 95% CI 0.012-0.057, P ≤ 0.001), Turkey (2.2%, 95% CI 0.013-0.038, P ≤ 0.001), USA (1.2%, 95% CI 0.004-0.036, P ≤ 0.001) and France (0.9%, 95% CI 0.004-0.021, P ≤ 0.001) infected pregnant women.

Sensitivity Analysis: We carried out a sensitivity analysis through sequentially excluding an individual study to identify the effects of individual publication on the combined data. The significance of the pooled ORs was not influenced by excluding a single study, indicating that our data is statistically robust and was not dependent on an individual study.

Table 1. Characteristics of Studies Included in This Meta-Analysis for Miscarriage

Author	City (Country)	Ethnicity	Sample size	Miscarriage				
				No.	Trimester	Elective	Medical	Spontaneous
Shmakov et al.,	Russia	Caucasian	66	4	1st	-	-	4
Sahin et al.,	Ankara (Turkey)	Caucasian	533	12	1st	NA	NA	NA
Erol et al.,	Ankara (Turkey)	Caucasian	60	1	NA	NA	NA	NA
Sentilhes et al.,	Strasbourg (France)	Caucasian	54	1	1st	-	-	1
Kayem et al.,	France	Caucasian	617	5	1st	NA	NA	NA
Woodworth et al.,	US	Caucasian	4442	32	1st, 3rd	NA	NA	NA
Delahoy et al.,	13 States (US)	Caucasian	458	10	1st, 3rd	NA	NA	NA
Buonsenso et al.,	Italy	Caucasian	7	1	1st	-	-	1
Cosma et al.,	Italy	Caucasian	100	11	1st	-	-	11
Knight et al.,	UK	Caucasian	427	4	1st	NA	NA	NA
Di Mascio et al.,	WAPM	International	266	9	1st	3	-	6
Wu et al.,	Wuhan (China)	East Asian	23	3	1st	3	-	-
Yan et al.,	Wuhan (China)	East Asian	116	1	1st	-	-	1
Qiancheng et al.,	Wuhan (China)	East Asian	28	4	NA	-	4	-
Wong et al.,	Wuhan (China)	East Asian	12	4	1st	-	-	4
Chen et al.,	Wuhan (China)	East Asian	3	1	3rd	-	-	1
Chen et al.,	Wuhan (China)	East Asian	118	9	NA	4	2	3
Lei et al.,	Wuhan (China)	East Asian	13	1	1st	-	-	1
Ayed et al.,	Al-Jahra (Kuwait)	West Asian	185	3	NA	-	-	3
Pirjani et al.,	Babol (Iran)	West Asian	43	2	NA	NA	NA	NA
Nayak et al.,	Mumbai (India)	South Asian	141	6	NA	NA	NA	NA
Mahajan et al.,	Mumbai (India)	South Asian	879	17	NA	-	-	17

WAPM: The World Association of Perinatal Medicine; NA: Not available.

Publication Bias: Potential publication bias was estimated with the Begg's test and the Egger's test for literatures on miscarriage. The shape of the funnel plots and Egger's test showed that there was an evidence of publication bias for miscarriage in overall population ($P_{Begg's}$ = 0.427; $P_{Egger's}$ = 0.098). Thus, we performed the Duval and Tweedie non-parametric ''trim and fill'' method to adjust for publication bias for rs0011081 polymorphism. However, the outcomes showed that the current meta-analysis with and without ''trim and fill'' did not draw different results, indicating that the results of our study were stable and credible (Figure 3). Moreover, the Egger's test was performed to provide the statistical evidence of funnel plot ($P_{Begg's}$ = 0.427; $P_{Egger's}$ = 0.098) indicating that our pooled data were statistically robust and reliable.

Table 2. Summary Frequency Estimates for Miscarriage in the Infected Women with COVID-19

Subgroup	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
		I^2 (%)	P_H	Prevalence	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall									
	Random	86.91	≤ 0.001	0.039	0.023-0.063	-12.166	≤ 0.001	0.214	0.022
Ethnicity									
Caucasian	Random	88.54	≤ 0.001	0.023	0.011-0.048	-9.722	≤ 0.001	0.591	0.265
Asian	Random	79.68	0.001	0.063	0.032-0.122	-7.375	≤ 0.001	0.436	0.165
European	Random	82.10	≤ 0.001	0.029	0.012-0.065	-8.101	≤ 0.001	0.386	0.770
West Asian	Fixed	26.66	0.243	0.025	0.009-0.069	-0.6811	≤ 0.001	NA	NA
Country									
Chinese	Random	61.02	0.017	0.113	0.054-0.221	-5.050	≤ 0.001	1.000	0.920
USA	Random	89.41	0.002	0.012	0.004-0.036	-7.836	≤ 0.001	NA	NA
India	Random	64.54	0.093	0.027	0.012-0.057	-8.972	≤ 0.001	NA	NA
Turkey	Fixed	0.00	0.770	0.022	0.013-0.038	-13.530	≤ 0.001	NA	NA
France	Fixed	0.00	0.449	0.009	0.004-0.021	-11.380	≤ 0.001	NA	NA
Italy	Fixed	0.00	0.791	0.112	0.065-0.188	-6.744	≤ 0.001	NA	NA

NA: Not applicable

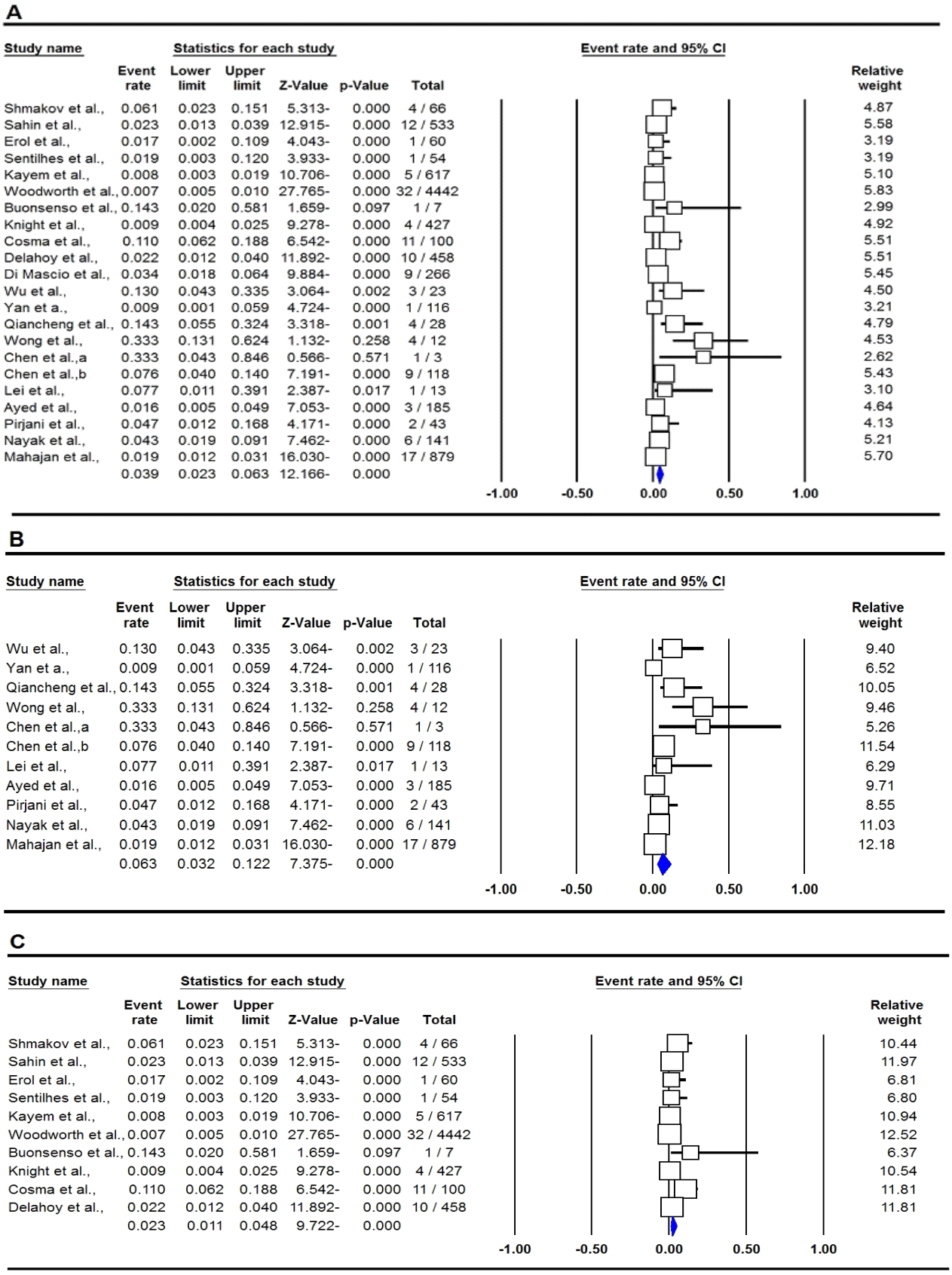

Figure 2. Forest Plots for Frequency of Miscarriage in Pregnant Women with SARS-COV-2. A: Overall; B: Asian and C: Caucasian

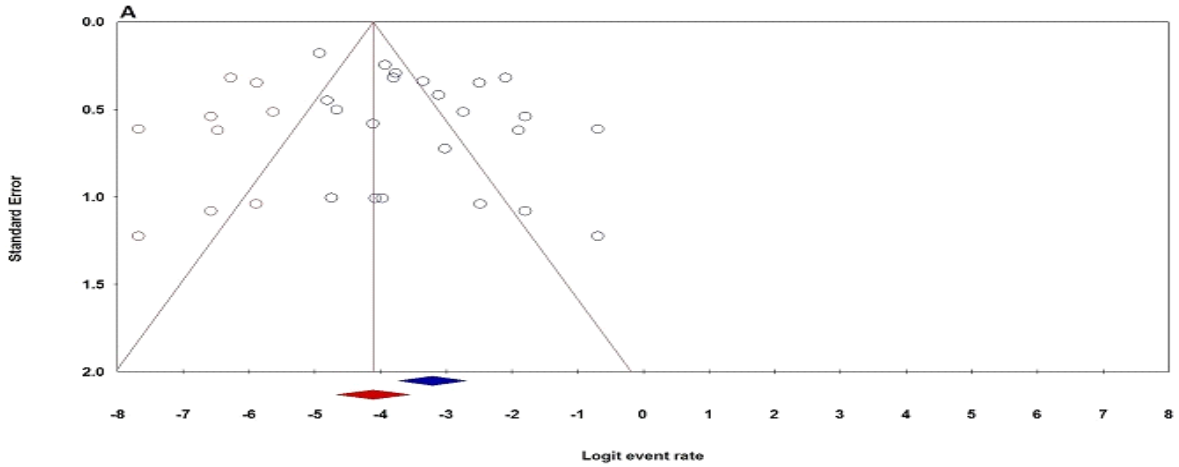

Figure 3. Begg's Funnel Plot for Publication Bias Test for Frequency of Miscarriage in Pregnant Women with SARS-COV-2

Discussion

It was estimated that miscarriage occurs in 8-15% of clinically recognized pregnancies and approximately in 30% of all pregnancies.[33-35] Harb et al., in a prospective cohort study and meta-analysis showed that the rates of miscarriage were as follows: White 9.5%, Asian 11%, Black 12.5%, Chinese 3.7%, and Mixed 10.3% in UK.[36] The current data do not suggest a high risk of abortion or premature gestational loss, amniotic fluid abnormality, cyanosis, and congenital defects in neonates of pregnant women infected with COVID-19.[5] Moreover, no study has reckoned the rate of miscarriage in infected pregnant women with COVID-19.[37-41] Some studies described that the SARS-COV infection during pregnancy was associated with high incidences of spontaneous miscarriage.[8,26] Hachem et al., reported the first report of a second-trimester miscarriage as an inaugural manifestation of COVID-19. Baud et al. reported a second-trimester miscarriage in a patient with symptomatic COVID-19.[42] In one study, it was noted that four out of seven (57%) women who presented during first trimester sustained spontaneous miscarriage, likely attributed to maternal respiratory failure and hypoxemia caused by SARS-related acute respiratory illness.[26] Moreover, it was suggested the risk of miscarriage was unlikely to be due to transplacental infection, as there was an absence of viral particles in the products of conceptions.[26] However, Rana et al., described a case of miscarriage during the first trimester due to SARS-COV-2 infection related to placental infection.[43]

To determine the frequency of miscarriage in women with SARS-COV-2 infection, a meta-analysis and systematic review was carried out. To the best of our knowledge, this may be the largest meta-analysis on the frequency of abortion in pregnant women with COVID-19 infection published so far. A total of 22 articles with 8591 confirmed women with COVID-19 and 141 miscarriages cases were analyzed. The pooled data showed that the frequency of abortion was 3.9% (approximately 2.3% to 6.3% of infected women) in the infected women with COVID-19 in overall population. Stratified analysis showed that miscarriage had highest frequency in Asian (6.3%) followed by European (2.9%), West-Asian (2.5%) and Caucasian (2.3%) infected pregnant women. Besides, stratified analysis by country showed that the frequency of miscarriage is the highest in Chinese (11.3%) followed by Italy (11.2%), India (2.7%), Turkey (2.2%), USA (1.2%) and France (0.9%) infected pregnant women. Diriba et al., described that the rate of miscarriage for COV infection was 14.5% as

follows: 2.4% for COVID-19 and 38.1% for SARS-COV.[7] Castro et al., in an overview described that there are no data on miscarriages in women with COVID-19. MERS-COV did not present miscarriages; however, SARS-COV had a high miscarriage rate of 39%.[44] Di Mascio revealed that the pooled frequency of first trimester miscarriage for SARS infection was 64.7% (95% CI 37.9-87.3). However, there was no data on miscarriage for COVID-19 and MERS infection occurring during the first trimester.[45] Dashraath et al., in a meta-analysis showed that the maternal outcomes in SARS-COV-2 are more favorable than SARS-COV and MERS-COV infections, with lower morbidity and mortality, with case fatality rates of 18%, 25%, and 0%, respectively.[46] Selim et al. in a publication described that SARS infection (but not SARS-COV-2 infection) has been associated with a higher risk for intrauterine growth retardation, premature births, and spontaneous abortion.[47] Amaral et al., in a review based on 70 studies described a total of 7 miscarriages as follows: Spontaneous miscarriage (n = 1), threatened miscarriage (n = 1), medical miscarriage (n = 4), and induced miscarriage (n = 1).[48] Ghayda et al., based on 11 case series studies with 104 pregnant women with COVID-19 reported that there were 3 (2.9%) cases with abortion.[49] There were no neonatal deaths. In a series of 55 pregnant women with COVID-19, it was found that fetal complications of COVID-19 included miscarriage (2%).[46] This meta-analysis showed that 3.8% of pregnant women with COVID-19 might experience miscarriage, which was higher than 0.7% to 2.9% widely reported in previous meta-analysis.

The present study has a considerable strength. The large study sample and the huge number of miscarriages enabled reliable estimation of the trends in miscarriages globally. However, a number of limitations of this meta-analysis study should be mentioned. First, we were unable to accurately estimate the frequency of miscarriage in pregnant women with COVID-19 with 110 abortions. Second, all of the studies included in this study were performed on Caucasian and Asian pregnant women with COVID-19. Thus, our pooled data are not generalizable to other ethnicity. Further studies with larger sample sizes with different ethnicity are necessary. Third, the studies included in the current meta-analysis were published in English and Chinese language so, a number of potential data published in other languages studies might be neglected. Fourth, we detected some degrees of heterogeneity, which might stem from difference in ethnicity, trimester of miscarriage, and type of miscarriage. Fifth, there was evidence of publication bias in Begg's and Egger's tests in overall population, which was unavoidable due to the limited databases searched and only English and Chinese studies included. Finally, in this study we could not address many important questions, including the extent of asymptomatic or mild infection and the effect of COVID-19 on miscarriage, age and history of previous miscarriages due to the lack of data in primary studies.

Conclusion

In summary, the current study results revealed that the frequency of miscarriage in the infected women with COVID-19 was 3.9%. Stratified analyses suggest that Asian infected pregnant women had highest frequency of miscarriage when compared to other ethnic group, although further data is needed to approve our findings.

Conflict of Interests

Authors have no conflict of interests.

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