

COVID-19 in pregnant women: a systematic review and meta-analysis on the risk and prevalence of pregnancy loss

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Received: August 3, 2023. Revised: October 1, 2023. Editorial decision: November 8, 2023.

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GRAPHICAL ABSTRACT

Pregnancy loss in women infected with SARS-CoV-2



An analysis of studies on the prevalence of early pregnancy loss in women infected with SARS-CoV-2 compared to pregnant women without SARS-CoV-2 infection showed no indications that SARS-CoV-2 infection increases risk of miscarriage. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio.

ABSTRACT

BACKGROUND: Pregnant women infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are more likely to experience preterm birth and their neonates are more likely to be stillborn or admitted to a neonatal unit. The World Health Organization declared in May 2023 an end to the coronavirus disease 2019 (COVID-19) pandemic as a global health emergency. However, pregnant women are still becoming infected with SARS-CoV-2 and there is limited information available regarding the effect of SARS-CoV-2 infection in early pregnancy on pregnancy outcomes.

OBJECTIVE AND RATIONALE: We conducted this systematic review to determine the prevalence of early pregnancy loss in women with SARS-Cov-2 infection and compare the risk to pregnant women without SARS-CoV-2 infection.

SEARCH METHODS: Our systematic review is based on a prospectively registered protocol. The search of PregCov19 consortium was supplemented with an extra electronic search specifically on pregnancy loss in pregnant women infected with SARS-CoV-2 up to 10 March 2023 in PubMed, Google Scholar, and LitCovid. We included retrospective and prospective studies of pregnant women with SARS-CoV-2 infection, provided that they contained information on pregnancy losses in the first and/or second trimester. Primary outcome was miscarriage defined as a pregnancy loss before 20 weeks of gestation, however, studies that reported loss up to 22 or 24 weeks were also included. Additionally, we report on studies that defined the pregnancy loss to occur at the first and/or second trimester of pregnancy without specifying gestational age, and for second trimester miscarriage only when the study presented stillbirths and/or foetal losses separately from miscarriages. Data were stratified into first and second trimester. Secondary outcomes were ectopic pregnancy (any extra-uterine pregnancy), and termination of pregnancy. At least three researchers independently extracted the data and assessed study quality. We calculated odds ratios (OR) and risk differences (RDs) with corresponding 95% CI and pooled the data using random effects meta-analysis. To estimate risk prevalence, we performed meta-analysis on proportions. Heterogeneity was assessed by I^2 .

OUTCOMES: We included 120 studies comprising a total of 168 444 pregnant women with SARS-CoV-2 infection; of which 18 233 women were in their first or second trimester of pregnancy. Evidence level was considered to be of low to moderate certainty, mostly owing to selection bias. We did not find evidence of an association between SARS-CoV-2 infection and miscarriage (OR 1.10, 95% CI 0.81–1.48; $I^2 = 0.0\%$; RD 0.0012, 95% CI –0.0103 to 0.0127; $I^2 = 0\%$; 9 studies, 4439 women). Miscarriage occurred in 9.9% (95% CI 6.2–14.0%; $I^2 = 68\%$; 46 studies, 1797 women) of the women with SARS CoV-2 infection in their first trimester and in 1.2% (95% CI 0.3–2.4%; $I^2 = 34\%$; 33 studies; 3159 women) in the second trimester. The proportion of ectopic pregnancies in women with SARS-CoV-2 infection was 1.4% (95% CI 0.02–4.2%; $I^2 = 66\%$; 14 studies, 950 women). Termination of pregnancy occurred in 0.6% of the women (95% CI 0.01–1.6%; $I^2 = 79\%$; 39 studies; 1166 women).

WIDER IMPLICATIONS: Our study found no indication that SARS-CoV-2 infection in the first or second trimester increases the risk of miscarriages. To provide better risk estimates, well-designed studies are needed that include pregnant women with and without SARS-CoV-2 infection at conception and early pregnancy and consider the association of clinical manifestation and severity of SARS-CoV-2 infection with pregnancy loss, as well as potential confounding factors such as previous pregnancy loss. For clinical practice, pregnant women should still be advised to take precautions to avoid risk of SARS-CoV-2 exposure and receive SARS-CoV-2 vaccination.

Keywords: SARS-CoV-2 / severe acute respiratory syndrome coronavirus 2 / COVID-19 / coronavirus disease 2019 / miscarriage / (early) pregnancy loss / ectopic pregnancy / abortion / spontaneous abortion / termination of pregnancy

When an overlap in data was expected, the study with most complete data was included.

Women were defined as having confirmed SARS-CoV-2 infection if they had confirmation through reverse transcription PCT (RT-PCR). Suspected SARS-CoV-2 infection was defined as women with a diagnosis based solely on clinical, serological, and radiological findings. We excluded studies when pregnancy loss data and/or having had SARS-CoV-2 infection was based on self-reporting.

Data extraction and study quality assessment

A structured data-extraction form was used, and data were extracted by multiple reviewers (J.v.B., J.K., M.S., M.V., B.C., E.K., M.v.W.). The data-extraction sheet of the main search from the PregCov group located in Birmingham was shared (J.Z. and S.T.), and all data extracted were cross-checked. We went back to the original studies to recheck the data (by J.v.B., E.K., M.v.W.) in case of discrepancies or missing data. The following study design characteristics were extracted: the first author's name, setting, year of publication, country of origin, and study design. The documented patient's characteristics were total number of patients included, number of patients included with confirmed SARS-CoV-2 infection, age of patients in years, BMI in kg/m², and other information about the patient spectrum including demographic characteristics, type of pregnancy loss, severity of COVID-19-related disease, previous miscarriages, smoking, and the week and/or trimester of gestation the pregnancy loss/termination occurred. The extracted data are also part of an open database (<https://cgf.cochrane.org/news/covid-19-coronavirus-disease-fertility-and-pregnancy>).

Methodological quality of included comparative cohort studies was assessed using the Newcastle-Ottawa Scale (Wells et al., 2000) for selection, comparability, and outcome ascertainment bias. As described previously (Allotey et al., 2020; Yap et al., 2020), studies achieving four stars for selection, two for comparability, and three for ascertainment of the outcome were considered to have a low risk of bias. Studies achieving two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have moderate risk of bias, and any study achieving one star for selection or outcome ascertainment, or zero for any of the three domains, was regarded as having a high risk of bias. The quality of prevalence studies was assessed using the validated tool by Hoy et al. (2012). The following domains were considered on risk of bias for external validity: population, sampling frame, selection, and non-response bias. The following domains were assessed on risk of bias for internal validity: data collection, case definition, reliability and validity, and mode of data collection, adequate follow up and appropriate numerator and denominator. The critical appraisal of included studies was carried out by three reviewers (J.v.B., E.K., M.v.W.).

GRADE was used to determine the certainty of the evidence; because all studies were observational the certainty of the evidence was initially set at 'low', with the possibility to be down or upgraded.

We excluded studies from the meta-analyses that reported on 10 or less cases, and those with 100% miscarriage in the first or second trimester in view of the selection bias. We excluded studies from the comparative meta-analysis when numerator and/or denominators were unclear and when SARS-CoV-2 infection was based on self-reporting.

Outcomes and definitions

Primary outcome was miscarriage ≤ 20 weeks of gestation, however, studies that reported pregnancy loss up to 22 or 24 weeks

were also included. Additionally, we included studies that defined the pregnancy loss to occur at the first and/or second trimester of pregnancy without specifying gestational age—this was an amendment to the review protocol. Second trimester miscarriages without a clear definition were included only when the study presented stillbirths and/or foetal losses separately from miscarriages. Miscarriage was stratified for gestational age (first trimester miscarriage up to 12 weeks of gestation and second trimester miscarriage above 12 weeks of gestation).

Secondary outcomes were EP, defined as any extra-uterine pregnancy, TOP, defined as an induced abortion, and recurrent miscarriage, defined as a spontaneous miscarriage after two previous spontaneous miscarriages. We evaluated EP for completeness as early pregnancy loss includes EP. We evaluated TOP/induced abortions to ensure induced abortions were distinguished from spontaneous abortions.

Statistical analysis

For studies comparing dichotomous outcomes in pregnant women with and without SARS-CoV-2 infection, we calculated odds ratios (OR) and risk differences (RDs) with corresponding 95% CI and pooled the data using random effects meta-analysis. To estimate the rate of miscarriage, EP, and TOP, we pooled proportions with 95% CI using DerSimonian and Laird random effects meta-analysis after transforming the data using Freeman-Tukey double arcsin transformation. Statistical heterogeneity between studies was reported as I^2 statistics, $I^2 > 50\%$ representing substantial heterogeneity. The impact of heterogeneity on pooled results was evaluated by calculating predictive intervals. We used the Metan and Metaprop routine in STATA for the analyses (StataCorp, 2019, Stata Statistical Software: Release 16, College Station, TX, USA: StataCorp LLC).

We aimed to describe miscarriage before 20 weeks of gestation per registered first and second trimester pregnancy and stratified for time of gestation (before and after 12 weeks of gestation). The study specific and summarized effect measures were calculated using a random effect model. When available, recurrent pregnancy loss was summarized as prevalence and OR with 95% CI, as described above.

For the prevalence estimates, we performed subgroup analyses per year of publication (2020, 2021, and 2022), per study region according to geographic World Bank regions (<https://www.worldbank.org/>), and on the basis of the study size (below or at least 20) to evaluate small study bias. A generalized linear mixed model (GLMM) instead of Freeman-Tukey double arcsin transformation was used as sensitivity analysis for the primary outcomes and GLMM was applied when zero counts resulted in inconsistencies in the estimates.

Patient and public involvement

There was no patient or public involvement in the design and reporting of the present review.

Results

Search results

A total of 941 678 citations were identified after screening electronic databases from inception to 25 April 2022 (PregCOV-19 Living Systematic Review Consortium search). Subsequently, with the additional electronic search from inception to 10 March 2023, conducted to specifically address pregnancy loss, we identified an additional 32 521 studies. The databases we used for the extra search were PubMed, Google Scholar, and the LitCovid Database. After the removal of duplicates and irrelevant articles,

1336 studies remained for screening; 1139 studies were excluded based on screening titles and abstracts. After screening the remaining 197 full text articles, we excluded 77 studies (Fig. 1).

Finally, we included 120 studies comprising a total of 168 444 pregnant women registered with SARS-CoV-2 infection in first or second trimester of pregnancy (Adhikari et al., 2020; Ayed et al., 2020; Calderón et al., 2020; Chen et al., 2020, 2021; Curi et al., 2020; Delahoy et al., 2020; Diouf et al., 2020; Edlow et al., 2020; Emeruwa et al., 2020; Fox and Melka, 2020; Grechukhina et al., 2020; Hernández et al., 2020, 2023; Kayem et al., 2020; Lei et al., 2020; London et al., 2020; Mattar et al., 2020; Metkari and Palve, 2020; Nambiar et al., 2020; Omrani et al., 2020; Pirjani et al., 2020; Qiancheng et al., 2020; Sentilhes et al., 2020; Shah et al., 2020; Shmakov et al., 2022; Tug et al., 2020; Woodworth et al., 2020; Wu et al., 2020a; Yan et al., 2020; Crovetto et al., 2021; Damar Çakörca et al., 2021, 2022; D'Antonio et al., 2021; Deng et al., 2021; Devi et al., 2021; Donati et al., 2021; Erol et al., 2021; Fan et al., 2021; Foo et al., 2021; Gajbhiye et al., 2021; Guo et al., 2021; Hazari et al., 2021; Hcini et al., 2021; Jacoby et al., 2021; Jang et al., 2021; Kuzan et al., 2021; Lokken et al., 2021; Mahajan et al., 2021; Manasova et al., 2021; Metz et al., 2021; Mullins et al., 2021; Overtoom et al., 2022; Poon et al., 2021; Priyadharshini et al., 2021; Aabakke et al., 2021, 2023; Abedzadeh-Kalahrudi et al., 2021; Ajith et al., 2021; Akram et al., 2021; Anand et al., 2021; Arinkan et al., 2021; Basu et al., 2021; Burwick et al., 2021; Cardona-Pérez et al., 2021; Chaudhary et al., 2021; Saimin et al., 2021; Santhosh et al., 2021; Singh et al., 2021; Taghavi et al., 2021; Tanacan et al., 2021; Vizheh et al., 2021; Vouga et al., 2021; Vousden et al., 2021; Yassa et al., 2021; Yazihan et al., 2021; Ahmad et al., 2022; Al-Hajjar et al., 2022; Arakaki et al., 2022; Babic et al., 2022; Balachandren et al., 2022; Barris et al., 2022; Bhoora et al., 2022; Borges-Charepe et al., 2022; Cambou et al., 2023; Chung et al., 2022; Collins et al., 2022; Cosma et al., 2022; Daclin et al., 2022; Fallach et al., 2022; Grandone et al., 2022; Hamadneh et al., 2022; Haye et al., 2022; Khoiwal et al., 2022; Kiremitli et al., 2022; Kumari et al., 2022; Martínez-Varea et al., 2022; McCreary et al., 2022; Neelam et al., 2023; Péju et al., 2022; Qudsieh et al., 2022; Regan et al., 2022; Roza et al., 2022; Sahin et al., 2022a,b; Santos et al., 2022; Schell et al., 2022; Sekkarie et al., 2022; Souza et al., 2022; Sunder et al., 2022; Takemoto et al., 2022; Zellini et al., 2022; Ziert et al., 2022; Göklü et al., 2023; Hughes et al., 2023; Martínez-Baladejo et al., 2023; Poisson et al., 2023; Sertel and Demir, 2023; Tavakoli et al., 2023; Youssef et al., 2023). For studies with overlapping populations, we always selected the last most updated studies. In two cases both studies were included: Woodworth et al. (2020) had details on number of women in first and second trimester pregnancy that were lacking in Neelam et al. (2023); and Aabakke et al. (2021) had details on number of EP, but for all other outcomes we included the updated study (Aabakke et al., 2023).

Of the 120 included studies, 20 studies were cohort studies with a non-infected control group (Adhikari et al., 2020; Edlow et al., 2020; Pirjani et al., 2020; Cardona-Pérez et al., 2021; Crovetto et al., 2021; Donati et al., 2021; Erol et al., 2021; Gajbhiye et al., 2021; Jacoby et al., 2021; Metz et al., 2021; Taghavi et al., 2021; Tanacan et al., 2021; Yazihan et al., 2021; Balachandren et al., 2022; Cosma et al., 2022; Daclin et al., 2022; Fallach et al., 2022; Khoiwal et al., 2022; Souza et al., 2022; Sunder et al., 2022).

The details of the selection and review process are provided in Fig. 1.

Risk of bias assessment of included studies

Supplementary Tables S2 and S3 illustrate the results of the risk of bias assessment. Overall, half of the prevalence studies were judged to be at moderate risk of bias (60/120), 39% were judged to

be at low risk of bias (47/120), and 13 studies were judged to be of high risk of bias (13/120). In addition, 39% of cohort studies were judged to be at high risk of bias (7/18), 28% were judged to be at low risk of bias (5/18), and 33% were judged to be at medium risk of bias (6/18).

The following domains were considered as low risk of bias for external validity: representative of national population for relevant variables (population), representative of target population (sampling frame), some form of random selection was used to select the sample (selection bias), and more than 75% response rate in individuals with and without the outcome (non-response bias). The following domains were considered as low risk of bias for internal validity: all data were collected directly from the subjects, an acceptable case definition was used, the study instrument that measured the parameter of interest showed to have reliability and validity, the same mode of data collection was used for all subjects, the length of the shortest prevalence period of the parameter was appropriate and the paper provided appropriate numerators and denominators for the parameter of interest (Hoy et al., 2012).

Characteristics of included studies

The 120 included studies assessed 168 444 pregnant women with SARS-CoV-2 infection. Most studies were from the USA (23), Turkey (13), India (13), China (9), Iran (5), Italy (4), France (4), with five studies performed in multiple countries. The majority of the women diagnosed with SARS-CoV-2 were in their third trimester of pregnancy, with 18 233 women in their first or second trimester of pregnancy.

Most studies confirmed diagnosis on the basis of SARS-CoV-2 RT-PCR (105/120); 15 studies tested for SARS-CoV-2 using either RT-PCR or antibodies to confirm the presence of SARS-CoV-2; one study confirmed a COVID-19 disease diagnosis through reports in the official COVID-19 test surveillance system of Brazil (Takemoto et al., 2022) and one study confirmed diagnosis based on clinical signs (Curi et al., 2020).

The average age ranged from 23 to 36 years in women with SARS-CoV-2 infection and from 27 to 34 years in the control group without SARS-CoV-2 infection. One study specifically reported on an infertile population that conceived following fertility treatment (Cousins, 2020).

The average BMI ranged from 23 to 33 kg/m² in women with SARS-CoV-2 infection. Smoking was reported in 23 studies (Delahoy et al., 2020; Grechukhina et al., 2020; Kayem et al., 2020; WAPM, 2021; Aabakke et al., 2021; Cardona-Pérez et al., 2021; Crovetto et al., 2021; D'Antonio et al., 2021; Jacoby et al., 2021; Metz et al., 2021; Overtoom et al., 2022; Vouga et al., 2021; Vousden et al., 2021; Balachandren et al., 2022; Cosma et al., 2022; Daclin et al., 2022; Göklü et al., 2023; Hamadneh et al., 2022; Martínez-Varea et al., 2022; Hughes et al., 2023; Poisson et al., 2023; Souza et al., 2022; Martínez-Baladejo et al., 2023). One study reported on smoking marijuana (Edlow et al., 2020). Moreover, previous pregnancy loss was reported in two studies (Cosma et al., 2022; Sahin et al., 2022b). Characteristics of included studies are described in Supplementary Table S4.

The definition of miscarriage differed between studies and is reported in Supplementary Table S5. Seven studies defined miscarriage as pregnancy loss up to 24 weeks (Calderón et al., 2020; Emeruwa et al., 2020; Wu et al., 2020a; Akram et al., 2021; Poisson et al., 2023; Regan et al., 2022; Sertel and Demir, 2023).

One study provided mean gestational age for pregnancy loss in the second trimester (Schell et al., 2022). Forty-six studies did not provide a definition of miscarriage (Adhikari et al., 2020; Chen

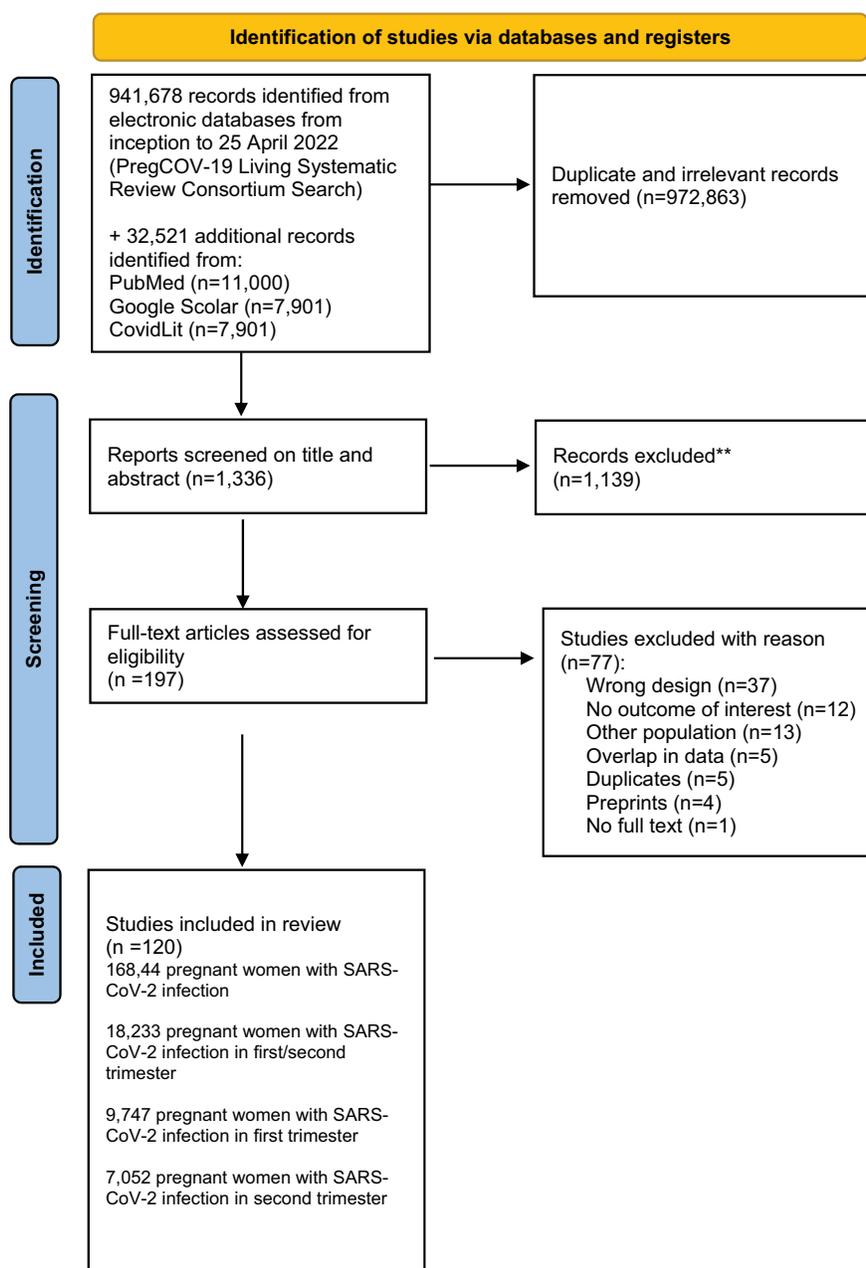


Figure 1. PRISMA flowchart of selection of studies for a systematic review and meta-analysis on the risk and prevalence of pregnancy loss in pregnant women infected with SARS-CoV-2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

et al., 2020; Curi et al., 2020; Edlow et al., 2020; Emeruwa et al., 2020; Hernández et al., 2020; Sentilhes et al., 2020; Martínez-Baladejo et al., 2023; Metkari and Palve, 2020; Omrani et al., 2020; Pirjani et al., 2020; Ajith et al., 2021; Anand et al., 2021; Abedzadeh-Kalahroudi et al., 2021; Basu et al., 2021; Cardona-Pérez et al., 2021; Chaudhary et al., 2021; Crovetto et al., 2021; Donati et al., 2021; Guo et al., 2021; Jang et al., 2021; Saimin et al., 2021; Mahajan et al., 2021; Mullins et al., 2021; Overtoom et al., 2022; Poon et al., 2021; Priyadharshini et al., 2021; Tanacan et al., 2021; Yazihan et al., 2021; Vizheh et al., 2021; Vousden et al., 2021; Ahmad et al., 2022; Arakaki et al., 2022; Babic et al., 2022; Chung et al., 2022; Cosma et al., 2022; Daclin et al., 2022; Hamadneh et al., 2022; Sahin et al., 2022a; Souza et al., 2022; Zelini et al., 2022; Qudsieh et al., 2022; Regan et al., 2022; Santos et al., 2022; Ziert et al., 2022; Youssef et al., 2023).

Miscarriage in women with SARS-CoV-2 infection versus non-infected controls

Eleven studies reported on miscarriage in the first or second trimester of pregnancy and had data on number of women in their first or second trimester of pregnancy with SARS-CoV-2 infection versus non-infected pregnant controls (Edlow et al., 2020; Crovetto et al., 2021; Donati et al., 2021; Erol et al., 2021; Taghavi et al., 2021; Tanacan et al., 2021; Yazihan et al., 2021; Balachandren et al., 2022; Cosma et al., 2022; Fallach et al., 2022; Souza et al., 2022). In the women with SARS-CoV-2 infection the average age was 30.4 (SD 3.0) years, and the average BMI was 25.3 kg/m² (SD 4.7) versus 27.3 (SD 3.5) years and 25.0 kg/m² (SD 5.1), respectively, in non-infected controls. Two studies were excluded from the meta-analysis: one study because presence of SARS-CoV-2 infection was based on self-reporting, which was an

exclusion criterium (Balachandren et al., 2022), and the other study because miscarriage was only mentioned in the flowchart with unclear data in the control group (Donati et al., 2021).

Of the nine included studies, four studies were judged to have a low risk of bias (Crovetto et al., 2021; Tanacan et al., 2021; Yazihan et al., 2021; Fallach et al., 2022), two studies had a moderate risk of bias (Taghavi et al., 2021; Souza et al., 2022), and three a high risk of bias (Edlow et al., 2020; Erol et al., 2021; Cosma et al., 2022) (Supplementary Table S2).

The OR for miscarriage in SARS-CoV-2 infected women versus non-infected controls was 1.10 (95% CI 0.81–1.49; $I^2 = 0.0\%$; 9 studies, 5984 women; moderate quality evidence; Fig. 2a). This corresponds to an RD of 0.0004 (95% CI –0.0070 to 0.0079; $I^2 = 0.0\%$; 9 studies, 5984 women; Fig. 2b). No stratified analyses were performed in view of the limited number of studies and lack of heterogeneity ($I^2 = 0$). The majority of women were likely at the end of the first trimester; given a miscarriage rate of 10% in uninfected controls, the risk of a miscarriage in women with SARS-CoV-2 infection is between 9.3% and 10.8%.

Proportion of first trimester miscarriage in women with SARS-CoV-2 infection

Miscarriage occurring in the first trimester was reported by 46 studies that included 1797 women diagnosed with SARS-CoV-2 infection in the first trimester (Curi et al., 2020; Edlow et al., 2020; Erol et al., 2021; Hernández et al., 2020, 2023; Grechukhina et al., 2020; Mattar et al., 2020; Metkari and Palve, 2020; Qiancheng et al., 2020; Shah et al., 2020; Tug et al., 2020; Wu et al., 2020a; Yan et al., 2020; Arinkan et al., 2021; Chen et al., 2021; Deng et al., 2021; ESHRE Working Group, 2021; Fan et al., 2021; Hazari et al., 2021; Guo et al., 2021; Jacoby et al., 2021; Jang et al., 2021; Kuzan et al., 2021; Lokken et al., 2021; Manasova et al., 2021; Santhosh et al., 2021; Singh et al., 2021; Yassa et al., 2021; WAPM, 2021; Al-Hajjar et al., 2022; Balachandren et al., 2022; Barris et al., 2022; Bhoora et al., 2022; Borges-Charepe et al., 2022; Cosma et al., 2022; Fallach et al., 2022; Khoiwal et al., 2022; Kiremitli et al., 2022; Kumari et al., 2022; McCreary et al., 2022; Sahin et al., 2022b; Santos et al., 2022; Schell et al., 2022; Shmakov et al., 2022; Souza et al., 2022; Sunder et al., 2022).

In women with SARS-CoV-2 infection in their first trimester, the miscarriage rate was 9.9% (95% CI 6.2–14.0%; $I^2 = 68.4\%$; 46 studies, 1797 women; Fig. 3). There was substantial heterogeneity in the reported miscarriage estimates. The heterogeneity could partly be explained by differences in geographical region; in five studies from South Asia with 10 or less women in their first trimester of pregnancy, the miscarriage prevalence was between 10% and 60%. Subgroup analyses according to study size and year of publication resulted in overlapping estimates. Table 1 reports on overall, sensitivity, and subgroup results.

Proportion of second trimester miscarriage in women with SARS-CoV-2 infection

In 33 studies, the proportion of second trimester miscarriage could be retrieved (Adhikari et al., 2020; Curi et al., 2020; Grechukhina et al., 2020; Lei et al., 2020; Pirjani et al., 2020; Shah et al., 2020; Santhosh et al., 2021; Yan et al., 2020; Arinkan et al., 2021; Deng et al., 2021; ESHRE Working Group, 2021; Guo et al., 2021; Kuzan et al., 2021; Lokken et al., 2021; Manasova et al., 2021; Sunder et al., 2022; Yassa et al., 2021; Al-Hajjar et al., 2022; Barris et al., 2022; Bhoora et al., 2022; Borges-Charepe et al., 2022; Fallach et al., 2022; Khoiwal et al., 2022; Kumari et al., 2022; McCreary et al., 2022; Roza et al., 2022; Sahin et al., 2022b; Santos et al., 2022; Schell et al., 2022; Shmakov et al., 2022; Souza et al., 2022; Hernández et al., 2023; Martínez-Baladejo et al., 2023). Second

trimester miscarriage was usually defined as loss before 20 or 22 weeks. Two studies that did not provide a definition were also included as number of women in their second trimester and number of miscarriages during second trimester were provided (Curi et al., 2020; Souza et al., 2022).

The miscarriage rate in women with SARS-CoV-2 infection during the second trimester was 1.2% (95% CI 0.5–2.0%; $I^2 = 57\%$; 33 studies; 3159 women; Fig. 4 and Table 1). There was moderate heterogeneity in the reported miscarriage estimates between the studies. The proportion of second trimester miscarriages seemed to vary by size of the included study ($P = 0.004$) and was 2.9% (95% CI 0.0–8.6%) in studies that included <20 women and 1.1% (95% CI 0.2–2.6%) in studies with at least 20 women (Table 1). Subgroup analyses according to year of publication and geographical region resulted in overlapping estimates (respectively, $P = 0.09$ and $P = 0.24$) (Table 1).

Additional analysis to estimate the prevalence of miscarriage in women with SARS-CoV-2 infection

In 42 studies, the number of miscarriages and number of women with SARS-CoV-2 infection and number of women in either first or second trimester was reported, but miscarriage rates could not be extracted for the first and second trimester separately. Supplementary Figure S1 provides an overall average for all studies that reported on miscarriage per number of women in either first or second trimester pregnancies. For the studies with incomplete trimester information the miscarriage rate in women that became infected at any time during their first or second trimester of pregnancy was 5.7% (95% CI 3.8–7.9%; $I^2 = 92\%$; 42 studies, 2909 women), and in the studies with trimester information 4.2% (95% CI 2.6–6.2%; $I^2 = 77\%$), leading to a total average of 4.9% (95% CI 3.6–6.4%; $I^2 = 88\%$; 92 studies). When assuming an equal distribution of women over the first and second trimester, the overall expected total chance to have a miscarriage would be twice these estimates; on basis of the calculated total average (95% CI of 3.61–6.44) this would be between 7.2% and 12.9%. This is in line with the sum of our reported first and second trimester estimates for miscarriage rate of 9.9% and 1.2%, respectively.

Proportion of ectopic pregnancy in women with SARS-CoV-2 infection

We found 18 studies that reported on EP (Calderón et al., 2020; Chen et al., 2020; Curi et al., 2020; Metkari and Palve, 2020; Shah et al., 2020; Tug et al., 2020; Aabakke et al., 2021; Devi et al., 2021; Gajbhiye et al., 2021; Guo et al., 2021; Hazari et al., 2021; Singh et al., 2021; Balachandren et al., 2022; Bhoora et al., 2022; Khoiwal et al., 2022; Kumari et al., 2022; Martínez-Varea et al., 2022; Souza et al., 2022) but only for 15 studies could the number of women that were included in their first or second trimester of pregnancy be retrieved (Chen et al., 2020; Curi et al., 2020; Metkari and Palve, 2020; Shah et al., 2020; Tug et al., 2020; Aabakke et al., 2021; Guo et al., 2021; Hazari et al., 2021; Singh et al., 2021; Balachandren et al., 2022; Bhoora et al., 2022; Khoiwal et al., 2022; Kumari et al., 2022; Martínez-Varea et al., 2022; Souza et al., 2022). One study was excluded in view of an unexpectedly high number of EP suggesting extreme selection bias (four cases in seven women in their first trimester) (Metkari and Palve, 2020).

The EP rate in women with SARS-CoV-2 infection was 1.4% (95% CI 0.02–4.2%; $I^2 = 65.8\%$; 14 studies, 950 women; Fig. 5). The heterogeneity was moderate to severe. In view of the limited number of studies we did not do subgroup analyses per geographical region on EP rate. The proportion of EP varied by size of study ($P = 0.01$) and was 1.0% (95% CI 0.0–3.4%) in 10 studies that included more than 20 women and 9.4% (95% CI 0.08–26.4) in

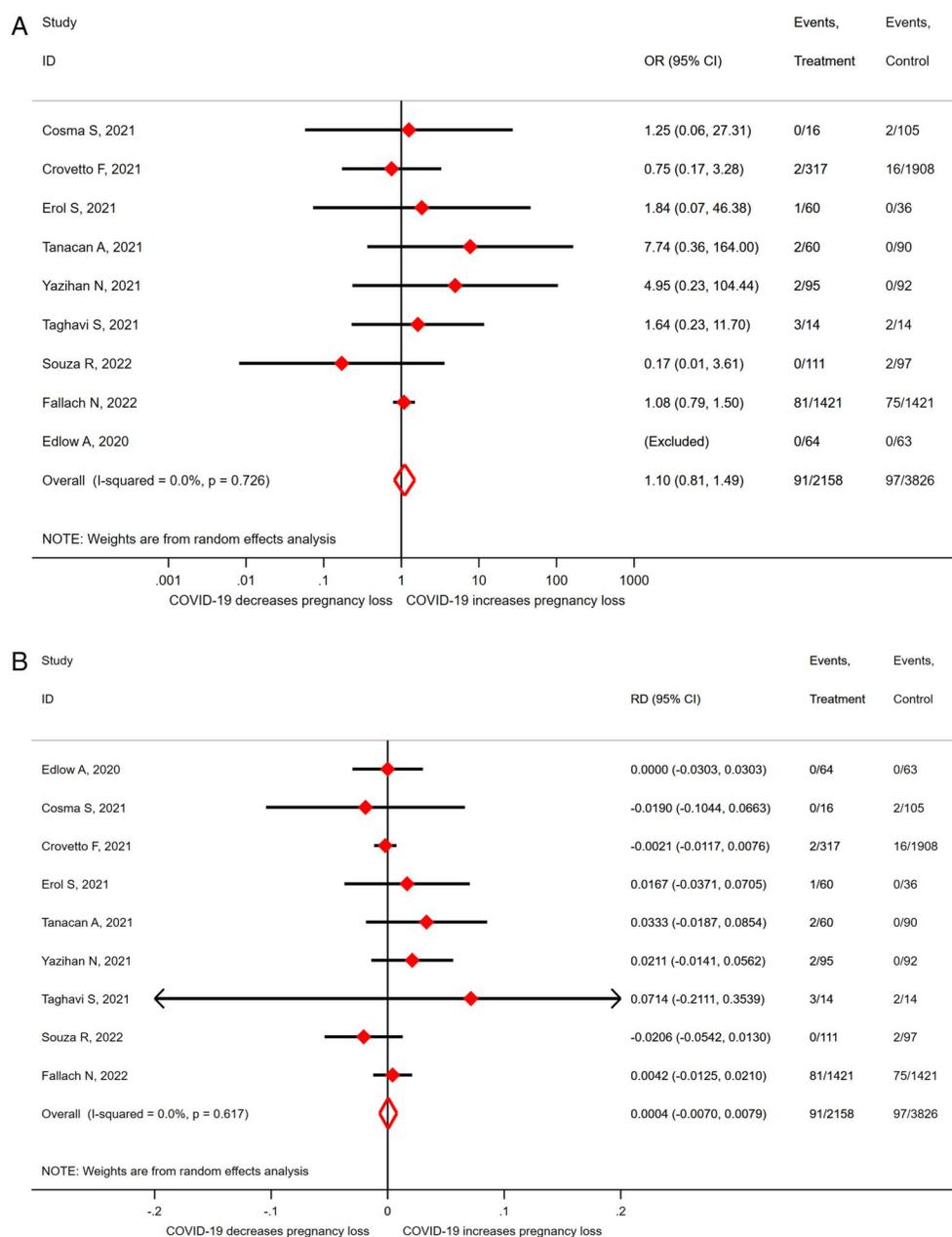


Figure 2. Odds ratio (A) and risk difference (B) for miscarriage in pregnant women with SARS-CoV-2 versus without SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; OR, odds ratio; RD, risk difference.

studies with <20 women. Year of publication (2020, 2021, and 2022) did not affect EP rates ($P = 0.41$).

Proportion of termination of pregnancy in women with SARS-CoV-2 infection

We found 49 studies that reported on TOP (Adhikari et al., 2020; Ayed et al., 2020; Chen et al., 2020; Curi et al., 2020; Edlow et al., 2020; Grechukhina et al., 2020; Hernández et al., 2020; Lei et al., 2020; London et al., 2020; Mattar et al., 2020; Nambiar et al., 2020; Pirjani et al., 2020; Qiancheng et al., 2020; Sentilhes et al., 2020; Shah et al., 2020; Wu et al., 2020a; Anand et al., 2021; Arinkan et al., 2021; Crovetto et al., 2021; Deng et al., 2021; Devi et al., 2021; Donati et al., 2021; Erol et al., 2021; Fan et al., 2021; Foo et al., 2021; Gajbhiye et al., 2021; Guo et al., 2021; Hcini et al., 2021; Jacoby et al., 2021; Jang et al., 2021; Kuzan et al., 2021; Mahajan et al., 2021; Santhosh et al., 2021;

Tanacan et al., 2021; Vouga et al., 2021; Yazihan et al., 2021; Arakaki et al., 2022; Balachandren et al., 2022; Bhoora et al., 2022; Borges-Charepe et al., 2022; Cambou et al., 2023; Cosma et al., 2022; Fallach et al., 2022; Khoiwal et al., 2022; Poisson et al., 2023; Sahin et al., 2022b; Sekkarie et al., 2022; Shmakov et al., 2022; Souza et al., 2022; Aabakke et al., 2023) and, of these, 43 studies reported on the number of women in their first and/or second trimester of pregnancy (Adhikari et al., 2020; Ayed et al., 2020; Chen et al., 2020; Curi et al., 2020; Edlow et al., 2020; Grechukhina et al., 2020; Hernández et al., 2020; Lei et al., 2020; London et al., 2020; Mattar et al., 2020; Nambiar et al., 2020; Pirjani et al., 2020; Qiancheng et al., 2020; Sentilhes et al., 2020; Shah et al., 2020; Wu et al., 2020a; Crovetto et al., 2021; Deng et al., 2021; Donati et al., 2021; Erol et al., 2021; Fan et al., 2021; Foo et al., 2021; Guo et al., 2021; Jacoby et al., 2021; Jang et al., 2021; Kuzan et al., 2021; Santhosh et al., 2021; Tanacan et al., 2021; Yazihan et al., 2021;

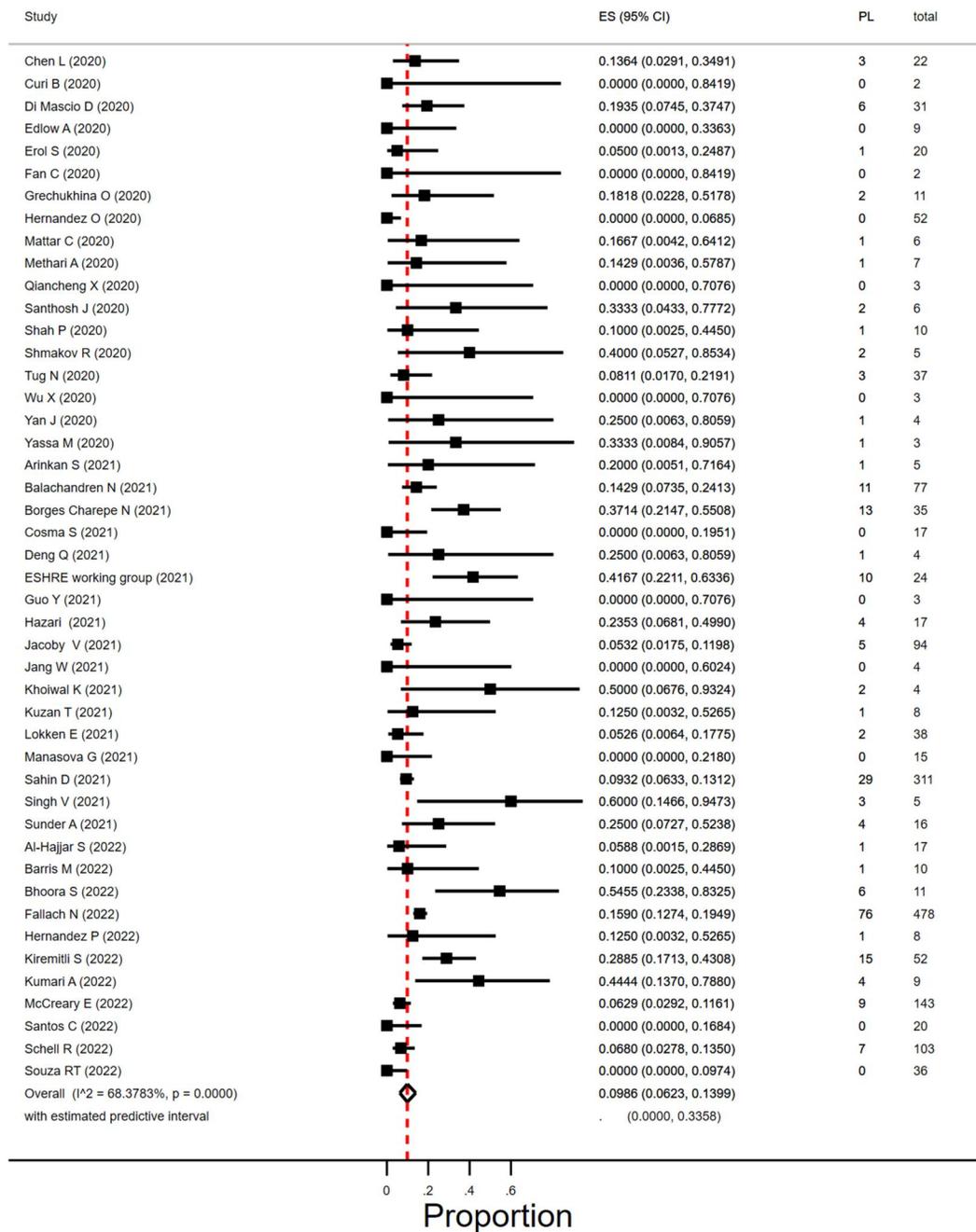


Figure 3. Proportion of miscarriage in pregnant women with SARS-CoV-2 in the first trimester. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ES, estimate of proportion; PL, pregnancy loss.

Arinkan *et al.*, 2021; Arakaki *et al.*, 2022; Balachandren *et al.*, 2022; Bhoora *et al.*, 2022; Borges-Charepe *et al.*, 2022; Cambou *et al.*, 2023; Cosma *et al.*, 2022; Fallach *et al.*, 2022; Khoiwal *et al.*, 2022; Sahin *et al.*, 2022b; Sekkarie *et al.*, 2022; Shmakov *et al.*, 2022; Souza *et al.*, 2022; Aabakke *et al.*, 2023; Poisson *et al.*, 2023). Four studies were excluded, two studies as only one woman was in her first or second trimester of pregnancy (London *et al.*, 2020; Sentilhes *et al.*, 2020) and two studies as all of the women registered with an infection in their first or second trimester of pregnancies were TOP pregnancies (Qiancheng *et al.*, 2020; Wu *et al.*, 2020a). The overall proportion of termination in SARS-CoV-2 infected pregnancies was 0.6% (95% CI 0.01–1.6%; $I^2 = 79%$; 39 studies; 1166 women; Fig. 6). Reason for TOP was only provided in a few early studies; in one early Chinese study two women asked for TOP owing to fear of SARS-CoV-2 effect on the

pregnancy (Fan *et al.*, 2021); in two studies TOP was medically indicated (Donati *et al.*, 2021; Fan *et al.*, 2021).

The proportion of TOP seemed to vary by size of the included study ($P = 0.005$) and was 2.5% (95% CI 0.01–7.6%) in studies that included <20 women and 1.3% (95% CI 0.39–2.5%) in studies with at least 20 women. Geographical regions did not differ in TOP rates ($P = 0.28$), nor did year of publication (2020, 2021, and 2022) ($P = 0.28$).

Discussion

Findings in context

In this systematic review, we found no evidence for an association of SARS-CoV-2 infection in early pregnancy with pregnancy

Table 1. Sensitivity and subgroup analyses for miscarriage in pregnant women with SARS-CoV-2 infection.

	Study N	Prevalence (95% CI)	I ²	Subgroup heterogeneity
First trimester miscarriage	46	9.86% (6.23–13.99)	68.4%	
Sensitivity analysis with GLMM		10.02% (6.71–14.51)		
Sensitivity analysis fixed effect		7.85% (6.32–9.50)		
Sensitivity analysis with CC (0.5)		10.77% (7.69–13.85)		
Predictive interval		0–33.6%		
By World Bank region				P = 0.0003
North America	8	6.24% (3.61–8.87)*	0.0%	
East Asia and Pacific	9	7.13% (0.02–19.27)	0.0%	
Europe and West Asia	13	13.98% (6.71–22.83)	75.6%	
Middle East and North Africa	5	14.70% (10.25–19.67)	13.6%	
South Asia	5	30.58% (11.70–52.66)	38.4%	
World, other regions	6	6.90% (0.00–22.83)	85.4%	
By study size, no of patients				P = 0.23
<20	33	10.93 (4.91–16.94)	50.0%	
≥20	13	9.73 (5.07–14.39)	74.1%	
By publication year				P = 0.80
2020	18	6.86 (1.56–14.30)	40.7%	
2021	17	12.81 (6.24–20.76)	71.8%	
2022	11	11.01 (4.84–18.83)	82.0%	
Second trimester miscarriage	33	1.24% (0.38–2.42)	58.8%	
Sensitivity analysis with GLMM		1.16% (0.73–2.43)		
Sensitivity analysis fixed effect		0.57% (0.28–0.87)		
Sensitivity analysis with CC (0.5)		1.58% (0.73–2.43)		
Predictive interval		0–3.8%		
By WB region				P = 0.24
North America	7	0.69% (0.00–1.99)	69.9%	
East Asia and Pacific	5	0.00% (0.00–5.22)	0%	
Europe and West Asia	8	1.12% (0.20–2.84)	0%	
Middle East and North Africa	4	8.75% (0.00–29.98)	72.5%	
Latin-America and Caribbean	4	0.77% (0.00–4.08)	67.2%	
South Asia	4	3.83% (0.00–22.17)	54.6%	
World, other regions	1	3.23% (0.08–16.70)		
By study size, no of patients				P = 0.004
<20	18	2.91 (0.00–8.60)	31.3%	
≥20	15	1.13 (0.18–2.60)	78.1%	
By publication year				P = 0.09
2020	10	2.87 (0.00–10.95)	37.0%	
2021	11	1.13 (0.00–3.68)	40.7%	
2022	12	0.45 (0.00–1.96)*	46.7%	

* Unstable proportion owing to incorrect back transformation, recalculated with GLMM.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GLMM, generalized linear mixed models; CC, continuity correction.

loss. We found that pregnant women in the first or second trimester of pregnancy with SARS-CoV-2 infection were not at increased risk for a miscarriage compared to pregnant women without the infection. On average, first trimester miscarriage occurred in 1 in 10 pregnant women (10%) with SARS-CoV-2 infection and second trimester miscarriage in 12 of 1000 pregnant women (1.2%) with SARS-CoV-2 infection. These data suggest an overall miscarriage rate of 11%. This is in line with the estimate of the studies for which miscarriage rate per first and second trimester could not be extracted separately. These miscarriage rates also correspond to what would be expected in women without SARS-CoV-2 infection.

We found EP to occur in of 1.4% in early pregnancies. This compares to the overall rate of EP of 1–2% found in the general population (Panelli et al., 2015). The average proportion of TOP in women with SARS-CoV-2 infection was 0.6%.

Prevalence estimates showed substantial heterogeneity for first trimester miscarriage and moderate heterogeneity for second trimester miscarriage. For first trimester miscarriages, the prevalence differences between geographical region were largely caused by high prevalence in some small studies. Overall, study size and year of publication did not have significant effects on the estimates. Part of the heterogeneity in the first trimester

could possibly be related to inclusion or exclusion of biochemical pregnancies, i.e. pregnancies diagnosed based on hCG. This would suggest that actual early miscarriage rates may be larger than estimated. On the other hand, in hospital-based studies selection bias is feasible, as women may be more inclined to visit the hospital in case of a miscarriage than when the pregnancy is ongoing, particularly when the pandemic was at the highest. For second trimester miscarriages the prevalence differed by study size and was highest in the smaller studies, with no significant effect of geographical region or year of publication. For EP heterogeneity was moderate, while it was substantial for TOP. TOP estimates varied by sample size of the individual study. Health care provider uncertainty of the effect of SARS-CoV-2 infection on mother and child may have increased the rate of TOP early in the pandemic (Wu et al., 2020b). On the other hand, lower abortion access because of COVID-19 pandemic-related restrictions may have resulted in a decrease in TOP (Cousins, 2020).

How SARS-CoV-2 could be related to pregnancy loss

There is a known association of some viral infections with foetal malformation and pregnancy complications. Particular

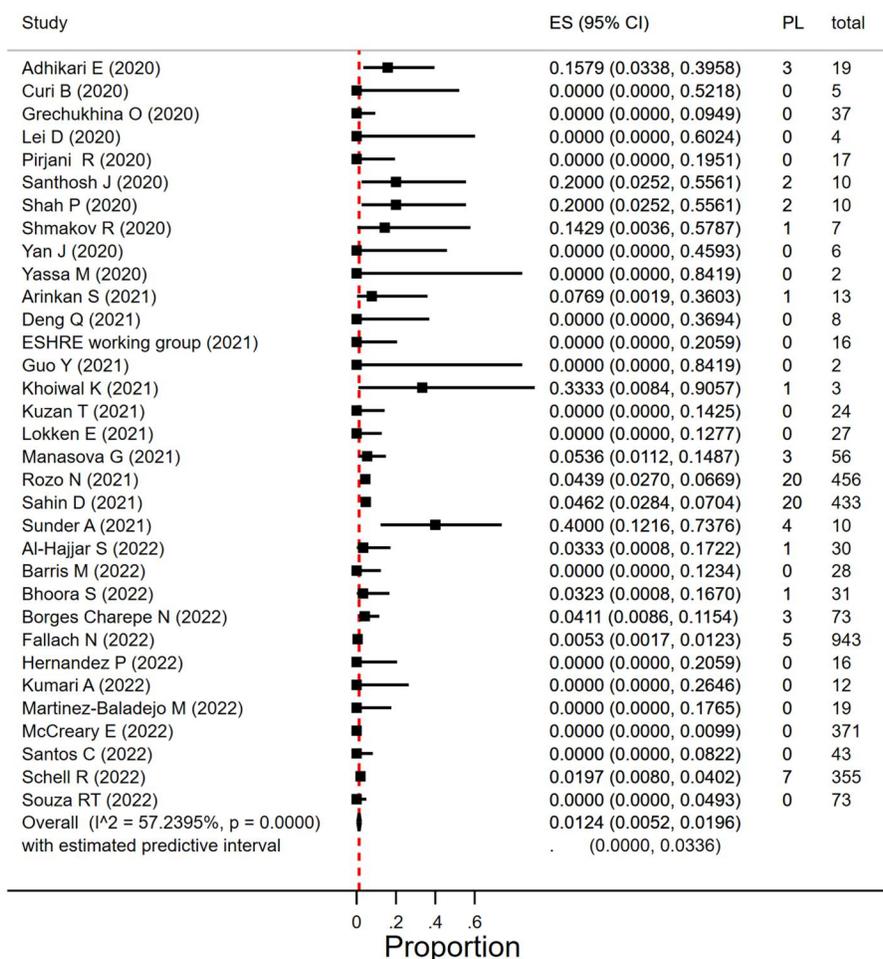


Figure 4. Proportion of miscarriage in pregnant women with SARS-CoV-2 infection in the second trimester. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ES, estimate of proportion; PL, pregnancy loss.

viruses can infect several cellular components of the placenta, such as trophoblasts, and can affect placental function, which may result in pregnancy complications such as preterm birth, miscarriage, and intrauterine growth restriction (Racicot and Mor, 2017). Also, it has been suggested that the adverse pregnancy outcomes following SARS-CoV-2 infection might be caused by an inflammatory cytokine imbalance (Vesce et al., 2022).

A review on 11 pregnant women infected with Middle East Respiratory Syndrome coronavirus (MERS-CoV) reported adverse outcomes in over 90% of the presented cases; there was no information related to placental infection (Alfaraj et al., 2019).

A study investigating the pregnancy and perinatal outcomes of pregnant women with SARS in 2002 reported that 57% of the patients had a miscarriage, while case fatality rate was 25%. Placental tissues and cord blood were negative for SARS-CoV in this study (Wong et al., 2004).

Viruses can directly infect the foetus at specific times during gestation. This can result in severe birth defects or even pregnancy loss (Racicot and Mor, 2017; Badr et al., 2020). How viruses cross the placental barrier and reach the foetus remains largely unknown. A proposed mechanism involves infection of extravillous trophoblasts and/or direct infection of maternal immune cells. Other possible routes of vertical transmission include direct infection of the syncytium or via inflammation-mediated disruption of the syncytiotrophoblast layer, thus damaging the

placental barrier and allowing for transmission (Megli and Coyne, 2022). Results from a systematic review on mother-to-child transmission in SARS-CoV-2 infection confirmed vertical transmission of the virus could occur, although the absolute numbers were low and transmission was rare (Allotey et al., 2020).

Several case studies have reported on SARS-CoV-2 positive placental tissue in the second trimester using a variety of assays before 20 weeks of gestation (Baud et al., 2020; Michel et al., 2021). SARS-CoV-2-related placentitis, which is an inflammation of the placenta caused by infection with SARS-CoV-2 and is characterized by increased perivillous fibrin deposition, histiocytic intervillitis, and villous trophoblast necrosis (Mithal et al., 2022), has been associated with pregnancy loss and stillbirth (Stenton et al., 2022). On the other hand, another study found no placental differences between SARS-CoV-2 infected and non-infected women and suggested that maternal SARS-CoV-2-related respiratory failure and the resulting hypoxia is the major risk factor for pregnancy loss and stillbirth (Suhren et al., 2022). In addition, SARS-CoV-2 infection can trigger a cytokine storm, which may lead to both an inflammatory response in the foetus and to placental damage with consecutive foetal growth retardation, preterm birth, and miscarriage (Cavalcante et al., 2021).

The MaterCov study investigated the impact of SARS-CoV-2 infection on subclinical placental thrombosis and maternal

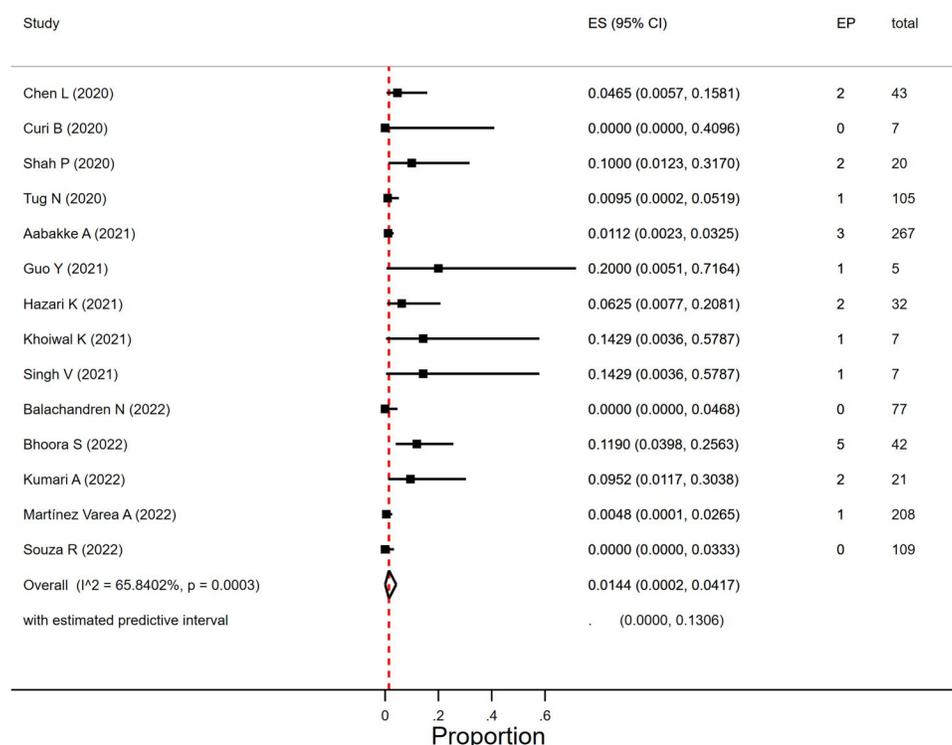


Figure 5. Proportion of ectopic pregnancies in women with SARS-CoV-2 infection in the first or second trimester. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; EP, ectopic pregnancy; ES, estimate of proportion.

thrombotic factors. They found an increased risk of developing obstetric complications in pregnant women with SARS-CoV-2, such as intrauterine growth restriction and stillbirth. However, there were no more placental pathologies identified in pregnant women infected by SARS-CoV-2 compared to pregnant women without infection (Carbannel et al., 2022).

Given that SARS-CoV-2 infection during pregnancy is associated with more severe maternal disease than in SARS-CoV-2-infected non-pregnant women of reproductive age as well as associated with an increase in adverse perinatal outcomes such as stillbirth and preterm delivery with infection in later pregnancy, pregnant women should be advised to take precautions to avoid risk of SARS-CoV-2 exposure and receive a COVID-19 vaccine to reduce the risk of severe disease.

There is no reason to speculate that SARS-CoV-2 should be associated with abnormal fertilization and implantation outside the uterus. One study reported that SARS-CoV-2 can infect human embryos *in vitro* (Montano et al., 2022); it remains to be elucidated whether this finding has any implications *in vivo*.

Comparison with existing data

A recent European study (Balachandren et al., 2022) suggested that women who had SARS-CoV-2 infection in the first trimester had a higher risk of early miscarriage. The authors found an early miscarriage rate of 14% in the 'presumed infected' group (11/77 [95% CI 6–22]), 5% in the 'uncertain' group (15/295 [95% CI 3–8]), and 8% in the 'presumed uninfected' group (212/2669 [95% CI 7–9], $P = 0.02$). After adjusting for age, BMI, ethnicity, smoking status, gestational age at registration and the number of previous miscarriages, they found the risk of early miscarriage to be higher among women with presumed SARS-CoV-2 infection in the first trimester compared to those with no infection (relative

rate 1.7, 95% CI 1.0–3.0, $P = 0.06$). This study used self-reported data on diagnosis of SARS-CoV-2 and pregnancy outcomes, which may have resulted in higher reporting of miscarriage in the presumed infected group.

Two systematic reviews and meta-analyses reported on the proportion of miscarriage in women with SARS-CoV-2. One review included seven cases-series and concluded higher miscarriage rates were found in infected women (Kazemi et al., 2021), the other review included 17 studies, both case-series and cohort studies, and suggested miscarriage rates were comparable to non-infected women (Cavalcante et al., 2021). A recent systematic review and meta-analysis reported, among several other outcomes, that there was no significant difference in the rates of total miscarriage between SARS-CoV-2-infected and non-infected pregnant women (Jeong and Kim, 2023). In this review, the denominator included women in their third trimester both in the infected and non-infected controls, thus not allowing a fair comparison.

A systematic review on foetal demise, including stillbirths and late miscarriages following SARS-CoV-2 infection, concluded that most cases with late miscarriages (between 14 and 22 weeks) and stillbirths presented with placental abnormalities associated with potential transplacental SARS-CoV-2 infection, which may cause placental insufficiency and foetal hypoxia. The review included mostly case studies and case series (Alcover et al., 2023).

Study strengths and limitations

The strength of this systematic review and meta-analysis is the review process that combined the extensive search of the PregCov consortium with specific searches, which enabled us to include a large population of pregnant women with and without SARS-CoV-2 infection during the first and second trimester.

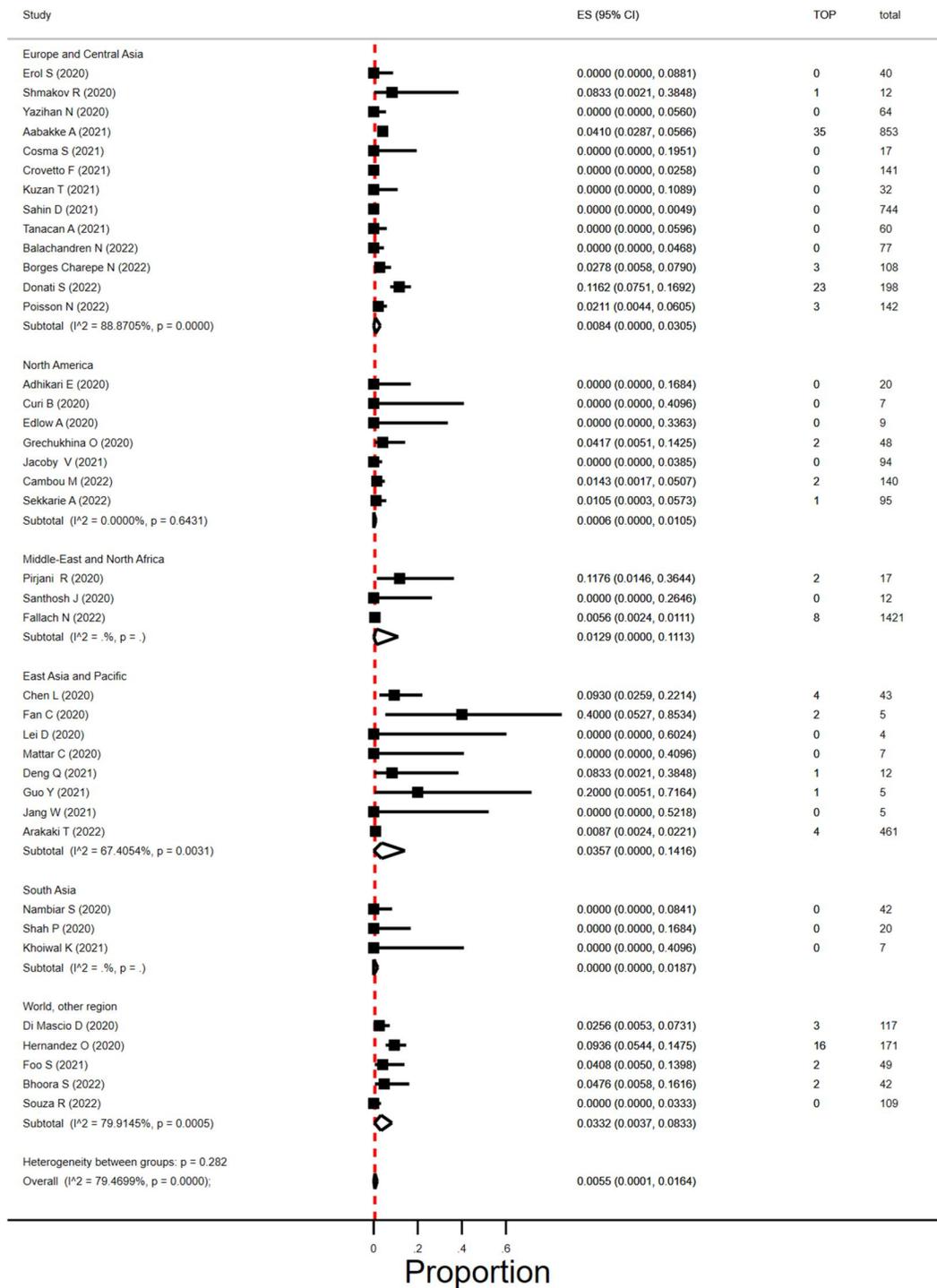


Figure 6. Proportion of termination of pregnancies in women with SARS-CoV-2 infection in first or second trimester in different geographical regions. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TOP, termination of pregnancy; ES, estimate of proportion.

Our review has several limitations. Most included studies were hospital-based studies such that selection bias towards more severe infections seems likely. On the other hand, if the prevalence of miscarriage is not clearly higher in the women with more severe COVID-19, then it is very unlikely it will be higher in infection with mild symptoms. The majority of studies did not include very early pregnancies, i.e. before 5 or 6 weeks of gestation. This implies that we cannot make a statement on the

possible effect of SARS-CoV-2 infection on biochemical pregnancy. However, as the majority of biochemical pregnancies miscarry owing to chromosomal abnormalities, and as comparable viral infections, such as influenza, only increased miscarriage rates later in pregnancy, it does not seem likely that SARS-CoV-2 is associated with very early miscarriage (Dawood et al., 2021). The effect estimates have large 95% confidence boundaries and there was high heterogeneity across studies in first trimester

miscarriage. This could only partly be explained by small study effect and may further be explained by differences in definition of miscarriage and differences in gestational age at which women were included in the cohorts and registries. Therefore, uncertainties remain for key outcomes that require further evidence. Furthermore, different variants of SARS-CoV-2, treatment of pregnant women with COVID-19 and access to vaccines could have affected outcomes but could not be studied as detailed data on variants, treatment and prevention in women in their first or second trimester of pregnancy was usually lacking. SARS-CoV-2 variants differed between 2020 and 2022, however, prevalence estimates for 2020, when no treatment was available yet, overlapped with prevalence estimates for 2021 and 2022. Meanwhile, a large proportion of vaccinated women could only be expected in the studies published in 2022. The overlapping estimates between 2020, 2021, and 2022 suggest there is no large impact of variants of SARS-CoV-2, treatment of pregnant women with COVID-19 and access to vaccines on pregnancy loss. Additionally, data on prior pregnancy history, such as previous pregnancy loss, were mostly not available. These could be important confounders when assessing the risk of miscarriages.

Relevance for clinical practice and research

In order to provide better risk estimates more studies are needed. These are preferably well-designed prospective studies that include pregnant women with and without SARS-CoV-2 infection at conception and early pregnancy, and consider the association of clinical manifestation and severity of COVID-19 disease with pregnancy loss, as well as potential confounding factors such as previous pregnancy loss. In SARS-CoV-2-infected women with a miscarriage, foetal karyotyping could be carried out to exclude a genetic factor.

Even though the WHO has declared an end to the COVID-19 pandemic as a global health emergency, women are at risk of SARS-CoV-2 infection. Pregnant women should be advised to take precautions to avoid risk of SARS-CoV-2 exposure and to be vaccinated with a COVID-19 vaccine.

Conclusion

There are still many unknowns regarding SARS-CoV-2 infection in early pregnancy. Reassuringly, based on currently available evidence, there are no indications that SARS-CoV-2 infection in early pregnancy increases the risk of miscarriages. In order to provide better risk estimates, well-designed studies are needed.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

Data collected including data on pregnancy loss is available at <https://cgf.cochrane.org/news/covid-19-coronavirus-disease-fertility-and-pregnancy>. Dissemination to participants and related patient and public communities: The PregCov-19 LSR Group will disseminate the findings through dedicated websites: www.birmingham.ac.uk/research/who-collaborating-centre/pregcov/index.aspx and <https://cgf.cochrane.org/news/covid-19-coronavirus-disease-fertility-and-pregnancy> as well as through social media.

Acknowledgements

We would like to acknowledge the following members of the PregCOV-19 Living Systematic Review Consortium: Elena Stallings, Magnus Yap, Shaunak Chatterjee, Tania Kew, Luke Debenham, Anna Clavé Llavall, Anushka Dixit, Dengyi Zhou, Rishab Balaji, Xiu Qiu, Mingyang Yuan, Dyuti Coomar, Siang Ing Lee, Vanessa Brizuela, Nathalie Jeanne Nicole Broutet, Edna Kara, Anna Thorson, Olufemi Taiwo Oladapo.

Authors' roles

M.v.W. and E.K. conceptualized the study. J.A., S.T., M.B., C.K., J.Z., L.M., H.K., A.K., E.v.L., E.K., and M.v.W. are members of the PregCOV-19 Living Systematic Review Consortium. M.G. and A.C. advised on the protocol. J.A., S.T., and J.Z. shared data from this infrastructure. J.B., B.C., J.K., M.S., M.V., M.v.W., and E.K. performed literature searches, selected studies, and extracted data. M.v.W. conducted the analyses. J.Z. gave statistical advice. All authors contributed to the interpretation and writing of the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author is the guarantor of the data (M.v.W.) and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been disclosed.

Funding

The presented work on pregnancy loss received no specific funding. However, it was facilitated by the infrastructure of the PRegCOV-19 Living Systematic Review Consortium that was partially supported by the German Federal Ministry of Health (BMG) COVID-19 Research and development support to the World Health Organization (WHO) and UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a co-sponsored programme executed by WHO. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Conflict of interest

Authors declare that partial funding by WHO and HRP for the infrastructure of the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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