

Review

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Covid-19 vaccination and pregnancy: a systematic review of maternal and neonatal outcomes

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Abstract

Objectives: Although the vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov-2) is considered safe during pregnancy, vaccine hesitancy among pregnant women is high. The results of published observational studies addressing the issue of Covid-19 vaccination's efficacy and safety during pregnancy need to be summarized.

Content: This systematic review compares the incidence of major maternal and neonatal outcomes between SARS Cov-2 vaccinated and unvaccinated pregnant women. The included studies enrolled pregnant women of any age and any trimester. Medline-Pubmed, Scopus, Cochrane Library, and grey literature were searched until the 28th of May 2022, and 2,947 studies were found.

Summary: Seven observational cohort studies, enrolling 67,274 pregnant women, were selected. When comparing vaccinated and unvaccinated pregnant women, SARS Cov-2 vaccines were not associated with major maternal and neonatal adverse events. The rate of SARS Cov-2 infections among vaccinated pregnant women compared to unvaccinated is significantly reduced by 43%.

Outlook: SARS Cov-2 vaccination in pregnant women is effective and safe. The results are promising, but caution is advised due to some limitations: only observational studies addressing this issue were found. Parallely, the

enrolled populations and the intervention (vaccination type and the number of doses) were not homogeneous.

Keywords: COVID-19; infant; newborn; obstetrics; pregnancy; vaccination.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov-2) is a strain of coronavirus provoking the Coronavirus Disease 2019 (Covid-19). The ongoing global pandemic since January 2020 has led to severe morbidity and mortality around the world; over 300 million confirmed cases and over 5.5 million deaths [1]. Pregnant women infected by SARS Cov-2 are at increased risk for hospitalization, Intensive Care Unit (ICU) admission, mechanical ventilation, and death, particularly during the 3rd trimester [2]. Likewise, they are prone to still-birth and thromboembolic events [3–7]. SARS Cov-2 infection may increase the incidence of gestational hypertensive disorders such as preeclampsia and preterm delivery. Both these entities have been associated with inflammatory mechanisms [8]. During pregnancy, altered hormone levels lead to subsequent alterations of immune function, resulting in increasing pregnant's susceptibility to viral infections [9, 10]. Pregnancy's immune modifications may decrease the potency of cell-mediated immune responses to infection [11, 12]. CD4+ and CD8+ lymphocytes' levels, as well as inflammatory cytokines' levels, have been found decreased during gestation [13].

The Center for Disease Control and Prevention (CDC) officially acknowledges that pregnant women or recently pregnant women (namely for at least 42 days following the end of pregnancy) are at an increased risk for a severe form of Covid-19, preterm birth, and stillbirth [3, 14]. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal and Fetal Medicine (SMFM) agree with CDC, stating that pregnancy is a risk factor for developing a severe SARS Cov-2 infection [15, 16].

In late-2020 two messenger RNA (mRNA) vaccines (BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna) were approved for emergency use against SARS Cov-2. Both vaccines have been found effective during randomized

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trials, but no trial initially included pregnant and/or lactating women [12, 17]. Likewise, between late-2020 and mid-2021, different countries approved and initiated the general population's vaccination with viral vector vaccines, such as the AZD1222 (Oxford AstraZeneca), the Ad26.COV2-S (Janssen Biotech), the rAd26-S/rAd5-S (Gam-COVID-Vac, Sputnik V), and the AD5-nCOV (Convidecia). Inactivated vaccines, such as the PiCoVacc (Sinovac COVID-19 vaccine), were also introduced. However, no studies regarding these vaccines among pregnant women were conducted [18–20]. Theoretically, vaccines that do not contain a live attenuated virus are considered safe during pregnancy [21]. However, vaccine hesitancy among pregnant women is high and limited data is available because pregnant women were initially excluded from Covid-19 vaccine trials [22]. Currently, randomized studies enrolling pregnant women have already started, and the first results are expected during 2022 [23].

Preliminary non-randomized studies which enrolled pregnant healthcare workers proved the efficacy of Covid-19 vaccines and the presence of antibodies in the umbilical cord blood and breast milk, and no safety issues were met [24]. ACOG states that vaccination against SARS Cov-2 is safe for pregnant women. All pregnant, lactating, or recently pregnant women over 12 years old should be vaccinated preferably with mRNA vaccines over the Ad26.COV2-S (Janssen Biotech). A third dose is advised only in pregnant women who can be considered immunocompromised [16]. SMFM agrees with the above statement [25].

At present, there are published observational studies which address the issue of Covid-19 vaccination among pregnant women. Thus, the need to summarize their results was evident. Therefore, we have conducted a systematic review of maternal and neonatal outcomes after the vaccination against SARS Cov-2.

Methods

This systematic review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [26], and it is in line with the PRISMA checklist (see Supplementary Material).

Inclusion and exclusion criteria

We searched for either Randomized Controlled Trials (RCTs) or Observational prospective and retrospective studies comparing the maternal and neonatal adverse events of Covid-19 vaccination (any vaccine, any dose) during pregnancy (any trimester). Our study group included vaccinated pregnant women and our control group unvaccinated

pregnant women. Our primary outcomes were Thromboembolic events (both maternal and neonatal), Preterm delivery, stillbirth. Our secondary outcomes were SARS Cov-2 infection, Birthweight, Small-for-Gestational Age (SGA) neonates <5th and 10th percentile, Neonatal death, Maternal hemorrhage. We excluded studies that assessed serum antibodies' levels after vaccination or SARS Cov-2 infection. Table 1 shows our study's exact inclusion and exclusion criteria.

Search strategy and sources

The research strategy was designed based on the Peer Review of Electronic Search Strategies (PRESS) checklist [27] using free text and Medical Subject Heading (MeSH) terms and their synonyms. Search terms were “pregnancy”, “covid-19” and “vaccines” with synonyms and alternatives. No more terms were used since we decided to conduct a widely open search to gather all potentially appropriate studies. No filters, geographical, publication status, language, and year restrictions were applied.

The following databases were searched by two reviewers (C-GK, GK) independently: Medline-Pubmed, Scopus, Cochrane Library, Clinicaltrials.gov, openGrey, and EU Clinical Trials Register.

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Studies including pregnant women of any trimester/gestational week and any age in both study-arms	Studies including non-pregnant women are excluded. If a study includes pregnant women in one study-arm and non-pregnant in other(s) study-arm(s), it is excluded
Covid-19 vaccination (any vaccine, 1st dose, 2nd dose, booster-3rd dose) <u>compared to</u> no vaccination	Studies, where the intervention does not constitute a Covid-19 vaccine (any vaccine, any dose), are excluded. Equally, studies where the comparator arm does not contain unvaccinated pregnant women, are excluded
Covid-19 vaccination may be administered at any trimester/gestational week during pregnancy	Studies, where covid-19 vaccination is administered before pregnancy (pre-conceptionally) or after pregnancy (postpartum), are excluded
Studies that assess at least one of our primary and secondary outcomes (cited in the main text)	Studies that did not assess any of our primary and secondary outcomes were excluded. Studies that assessed serum antibodies' levels after vaccination are excluded
Studies of any language, any geographical location, any publication status, any year of publication.	Studies conducted on animals. Studies whose full text could not be retrieved by any means were excluded
Study types: RCTs ^a , and prospective and retrospective cohort studies.	Any other type of study is excluded.

^aRCTs, randomized controlled trials.

PROSPERO (International Prospective Register of Systematic Reviews) database was likewise searched for ongoing SRMAs. Abstracts of conferences and meetings of Neonatal, Perinatal, and Obstetric Societies were also searched. The last searches were conducted on the 28th of May 2022.

Study selection and data extraction

Two reviewers (C-GK, GK) conducted study selection and data extraction separately. In case of discrepancies, a third reviewer (GM) was involved, settling the issue through discussion and consensus. Mendeley© (v.1.19.8) was used as a reference manager, and duplicates were removed. Predefined collection forms proposed by Cochrane collaboration for Intervention Reviews [28] were used for data extraction. In case of questions about study eligibility or data provided by the studies, the paper authors were contacted. The reviewers initially conducted pilot-calibration exercises for this process.

A list of the outcomes and variables for which data were sought was predefined (Supplementary Material, Table 1).

Definitions

Thromboembolic events (both arterial and venous) were a composite outcome, including myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism (obstetrical) [29]. Preterm delivery was defined as the delivery before 37 completed weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period [30] [Late preterm: between 34 0/7 and 36 6/7 [31]; Moderate preterm: between 32 0/7 and 33 6/7 [31]; Very preterm: between 28 0/7 and 31 6/7 [30]; Extremely preterm: <28 completed weeks of gestation [30]. Stillbirth was defined as the death after the 20th gestational week [32, 33].

SARS Cov-2 infection was defined as a positive real-time polymerase chain reaction (PCR) test result acquired from nasopharyngeal swabs [12]. Birthweight was defined as the weight of the newborn in grams. Birthweight was defined as low if it was less than 2,500 g. It was defined as extremely low if it was less than 1,500 g [34]. SGA neonates were defined as birthweight below the 5th or 10th percentile for gestational localized anthropometric newborn curves (World Health Organization 1995) [34]. Likewise, defined as >2 standard deviations below the mean for weight and/or length for gestational age [34]. Neonatal death was defined as the death of the newborn during the first month of life (1–30 days). Early neonatal death was defined as the death of the newborn during the first week of life (1–7 days). Late neonatal death was defined as the death of the newborn between the 8th and 30th day of life [32, 33]. Hemorrhage (obstetrical) was defined as a hemorrhagic macroscopic event that led to a loss of 1000 mL of blood or more [35].

Risk of bias assessment

We used the ROBINS-I Cochrane Tool for assessing the risk of bias in non-randomized studies [36]. Studies with low/moderate risk of bias were included in the quantitative synthesis. A sensitivity analysis was conducted for studies with serious/critical risk of bias. Graphics visualizing the risk of bias were created using the Robvis tool [37]. Two reviewers (C-GK and GK) independently conducted the risk of bias

assessment, and the experienced third reviewer (GM) settled any discrepancies.

Synthesis

The treatment effect of all outcomes (primary and secondary) was measured using mean/median, SD/IQR with 95% Confidence Interval (CI) for quantitative data, and Odds Ratio (OR) with 95% CI for dichotomous data. The above were calculated using RevMan (v.5.4.1) software.

First, a robust qualitative synthesis was conducted. Second, we conducted a quantitative synthesis with RevMan (v.5.4.1). Different forest plots were created. Statistical heterogeneity was evaluated using the Higgins I^2 test and Chi-Squared Cochran Q-test ($\alpha=0.1$). When I^2 was over 75%, quantitative synthesis was prohibited. Mantel-Haenszel method was applied for dichotomous data and the Inverse Variance method for quantitative data. The fixed-effects model was adopted if $I^2<50\%$, while the random-effects model was applied if $I^2\geq 50\%$ (or $p>0.1$). In case of persistent statistical heterogeneity, we removed the studies creating this heterogeneity by conducting sensitivity analysis (excluding studies of high risk of bias). Subgroup analyses were performed based on the type of vaccine. In case of missing data, we tried to contact the authors (maximum 3 times) by e-mail. No imputation method was necessary.

Publication bias was planned to be assessed if ≥ 10 studies were available per outcome. RevMan 5.4.1 was planned to be used to create funnel plots. R-Studio (v.1.2.50.42) was planned to be used to conduct the Egger's and rank correlation test.

Quality of evidence

An assessment of the quality of evidence for each outcome was performed separately by two reviewers (C-GK and GK) using the GRADE reporting system (Grading of Recommendations Assessment Development and Evaluation System) [38]. Any discrepancies were resolved by the third reviewer (GM). The assessment was conducted using the online tool GRADEpro GDT [39].

Results

Study selection

Figure 1 depicts the study selection process. 2947 studies were potentially appropriate after the duplicates' removal. 2580 were excluded by screening the title and the abstract, and 367 were full text examined. Seven observational cohort studies (four retrospective and three prospective) were finally selected [40–46], enrolling 67,274 women, from which 19,871 vaccinated pregnant women were matched to 24,328 unvaccinated pregnant controls. Studies that appear to meet the inclusion criteria, but were finally excluded, are presented in Supplementary Material, Table 2 [47–54].

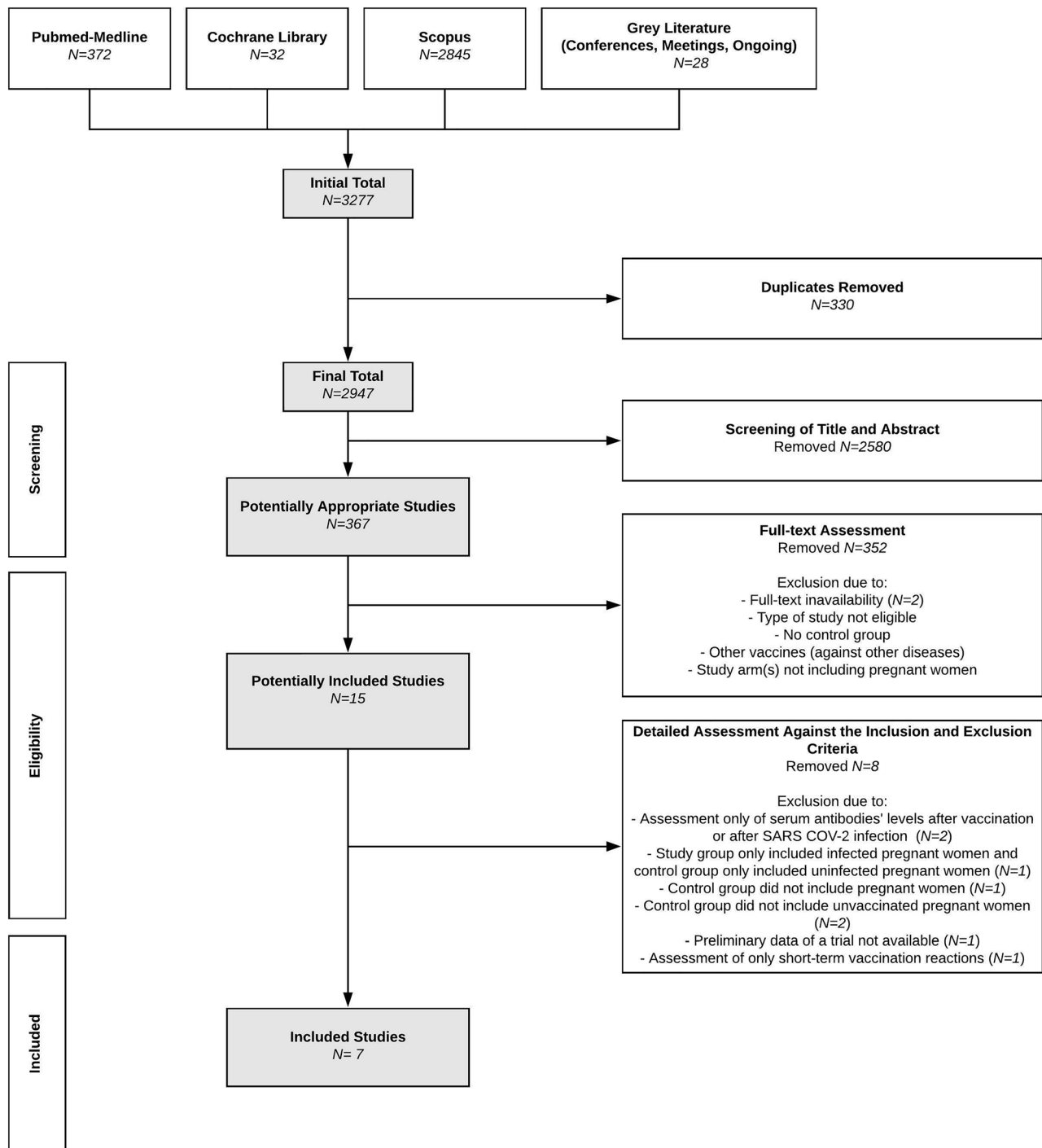


Figure 1: Study selection process.

Study characteristics

Table 2 summarizes the characteristics of the included studies.

Five studies were conducted in Israel [40–43, 46], one in the USA [44], and the last one in the UK [45].

All the included studies administered the BNT162b2 (Pfizer-BioNTech) vaccine. However, five studies included exclusively women vaccinated with the BNT162b2 (Pfizer-BioNTech) [40–43, 46], while only two included women vaccinated with two or more different vaccines. Blakeway et al. included women vaccinated with BNT162b2

Table 2: Characteristics of the included studies.

Reference/ type of study	Number	Inclusion criteria	Exclusion criteria	Trimester of vaccination	Type of vaccine	Number of doses	Outcomes
Wainstock et al. 2021 [46]	- 913 vaccinated - 3,486 unvaccinated - TOTAL 4399	- ≥ 16 years old - Singleton - 2nd and 3rd trimester	- SARS ² Cov-2 infection in the past - unknown vaccination status - Unknown pregnancy follow-up	- 2nd and 3rd	- BNT162b2 (Pfizer-BioNTech)	- 1st: 155 - 2nd: 758	- SGAb <5th percentile - Gestational age at delivery - Birthweight - Postpartum hemorrhage - Preeclampsia/Eclampsia - Type of delivery - Newborn respiratory complications - Placental abruption - Apgar score <7 at 5min - Oligohydramnios/ Polyhydramnios - Meconium - Non-reassuring fetal monitoring - Maternal postpartum fever - Newborn fever
Blakeway et al. 2021 [45]	- 133 vaccinated - 399 unvaccinated - Total 532	- Clear vaccination status - Complete maternal and fetal outcome data	- Vaccination before or after pregnancy - Women with pregnancies complicated by fetal aneuploidy or genetic syndromes	- 2nd and 3rd	- BNT162b2 (Pfizer-BioNTech) 127 - AZD1222 (oxford AstraZeneca) 13	- 1st: 114 - 2nd: 26	- SARS Cov-2 infection - Stillbirth (≥24 weeks) - SGA <10th percentile - Birthweight z-score - Fetal abnormalities - Postpartum hemorrhage (blood loss ≥1L) - Type of delivery - Chorioamnionitis - Placental abruption - Maternal postpartum fever - NICU admission - High-dependency unit admission
Beharier et al. 2021 [40]	- 92 vaccinated - 66 unvaccinated - Total 158	- ≥ 18 years old - Informed consent	- SARS Cov-2 infection in the past - active maternal SARS Cov-2 infection at delivery	- Any	- BNT162b2 (Pfizer-BioNTech)	- Not defined	- Preterm birth < 37 weeks - Gestational age at delivery - Birthweight - NICU admission
Theiler et al. 2021 [44]	- 140 vaccinated - 1862 unvaccinated	- 16–55 years old - Any dose - Any trimester	- Location restrictions	- Any	- BNT162b2 (Pfizer-BioNTech) 127	- 1st: BNT162b2 (Pfizer-BioNTech) 30, mRNA-1273 (moderna) 6, Ad26.COV2-S (janssen biotech) 1	- SARS Cov-2 infection - Stillbirth (≥24 weeks) - Maternal death - Birth ≥ 37 gestational week

Table 2: (continued)

Reference/ type of study	Number	Inclusion criteria	Exclusion criteria	Trimester of vaccination	Type of vaccine	Number of doses	Outcomes
Bleicher et al. 2021 [41] Prospective cohort	-	Total 202	-	-	- mRNA-1273 (moderna) 12 - Ad26.COV2-S (janssen biotech) 1	- 2nd: BNT162b2 (Pfizer-BioNTech) 97, mRNA-1273 (moderna) 6	- Preterm death < 37 weeks - Preterm 24 0/7–31 6/7 - Preterm <24 - Late preterm - Birthweight <2,500 g - Birthweight <1,500 g - Gestational hypertension - Preeclampsia/Eclampsia - Early neonatal death (for birthweight ≥ 2,500 g and GA ≥ 37 weeks) - Postpartum hemorrhage ≥ 1L - Postpartum hemorrhage with transfusion - Transfusion - Type of delivery - Uterine rupture - Apgar <7 at 5min (for birthweight ≥ 2,500 g and GA ≥ 37 weeks) - Hypoxic ischemic encephalopathy - Birth trauma - Thromboembolism - Stroke - NICU admission (within 1 day of birth, for birthweight ≥ 2,500 g and GA ≥ 37 weeks) - Maternal ICU ^d admission - SARS Cov-2 infection - Preterm birth < 37 weeks - FGR ^e (not defined) - Pregnancy loss up to 13 weeks - Pregnancy loss 14–28 weeks - Gestational hypertension - Fetal abnormalities - Antepartum hemorrhage (not defined) - Premature contractions
	-	202 vaccinated 124 unvaccinated Total 326	- Any age Pregnant at enrollment - Proper/complete data	- 1st, 2nd and 3rd	- BNT162b2 (Pfizer-BioNTech)	- 1st: 78 - 2nd: 124	

Table 2: (continued)

Reference/ type of study	Number	Inclusion criteria	Exclusion criteria	Trimester of vaccination	Type of vaccine	Number of doses	Outcomes
Goldshstein et al. 2021 [42]	- 7,530 vaccinated	- Any age	- SARS Cov-2 infection preconceptionally	- Not defined	- BNT162b2 (Pfizer- BioNTech)	- Not defined	- SARS Cov-2 infection
Retrospective cohort	- 7,530 unvaccinated	- Any trimester	- Vaccination preconceptionally				- SARS Cov-2 hospitalization
	- Total 15060	- Pregnant at enrollment	- Joined the database less than a year preconception				- Spontaneous abortion < 20 weeks
			- Matched unvaccinated women who were subse- quently vaccinated				- Stillbirth (≥20 weeks)
							- Maternal death
							- Preterm birth < 37 weeks
							- IUGR ^f (not defined)
							- Gestational age at delivery
							- Birthweight
							- Preeclampsia/Eclampsia
							- Thromboembolism (obstet- rical pulmonary embolism)
Dagan et al. 2021 [43]	- 10,861 vaccinated	- ≥16 years old	- History of SARS Cov-2 infection	- Not defined	- BNT162b2 (Pfizer- BioNTech)	- Not defined	- SARS Cov-2 infection
Prospective cohort	- 10,861 unvaccinated	- Vaccinated be- tween 20/12/2020 to 3/6/2021	- Home confinement due to medical reasons				- SARS Cov-2 symptomatic disease
	- Total 21722	- Member of the registry for at least 1 complete year	- Healthcare worker Interaction with the health- care system in the previous 2 days before enrollment				- SARS Cov-2 severe disease
			- Missing data				

^aSARS, Severe Acute Respiratory Syndrome; ^bSGA, small-for-Gestational Age; ^cNICU, neonatal intensive care unit; ^dICU, intensive care unit; ^eFGR, fetal growth restriction; ^fIUGR, intrauterine growth restriction.

(Pfizer BioNTech) and AZD1222 (Oxford AstraZeneca) [45], and Theiler et al. enrolled women vaccinated with BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2-S (Janssen Biotech) [44].

Regarding the populations, two studies included only women vaccinated at the 2nd and 3rd trimesters [45, 46], while three studies included women vaccinated at any trimester [40, 41, 44]. Two of the included studies did not define the trimester of vaccination [42, 43]. Three studies did not specify the specific number of vaccinated participants who received one or two doses [40, 42, 43].

Concerning the primary outcomes, thromboembolic events were assessed by Theiler et al. and Goldshtein et al. (pulmonary embolism) [42, 44]. Theiler et al. also assessed the incidence of stroke [44]. Preterm delivery (<37 gestational weeks) was examined by four studies [40–42, 44], while Theiler et al. assessed late preterm deliveries (34 0/7–36 6/7), preterm deliveries between 24 0/7 to 31 6/7 gestational weeks, and deliveries below the 24th gestational week [44]. Stillbirth $\geq$ 24 gestational weeks was assessed by Theiler et al. and Blakeway et al. [44, 45], while Goldshtein et al. assessed stillbirths $\geq$ 20 gestational weeks [42].

Regarding the secondary outcomes, SARS Cov-2 infection rates were assessed by five studies [41–45], and hospitalization rates by only one [42]. Birthweight was examined by four studies [40, 42, 45, 46]. Theiler et al. divided the birthweight to “low birthweight” (<2,500 g) and to “extremely low” (<1,500 g) [44]. Wainstock et al. also studied the incidence of SGA neonates <5th percentile [46]. Likewise, Blakeway et al. examined SGA neonates’ <10th percentile rates [45]. Early neonatal death (within the first 7 days of life) was addressed by Theiler et al. [44], while no study assessed total neonatal death rates as an outcome. Hemorrhage as an outcome was investigated in different forms: Bleicher et al. examined antepartum hemorrhagic events [41], and Wainstock et al. the postpartum ones [46]. Theiler et al. assessed the transfusion rates, the postpartum bleedings which needed transfusion (as a composite outcome), and the incidence of any maternal hemorrhage with blood loss greater than 1L [44]. The latter was also examined by Blakeway et al. [45].

Risk of bias assessment

The ROBINS-I Cochrane Tool [36] for the risk of bias assessment of observational studies was used for the assessment. The results (traffic light plots and weighted summary plots) are presented in Table 3 and Figures 2 and 3.

Most issues were met in the “confounding”, “measurement of outcomes” and “selection of the reported

result” domains. Overall, as far as the outcomes of interest are concerned, Bleicher et al. is of “Serious” risk of bias (<25%) [41], and the other studies are of “Moderate” risk of bias (>75%) [40, 42–46]. Bleicher et al. recruitment method, which was based on social media accounts, negatively affects the “selection of participants” domain. Parallely, all studies have issues regarding “confounding”, as they are observational, and the matching process was not always successful since population imbalances are present. Besides, all studies were open-label and not blinded, affecting the “measurement of outcomes” domain. However, the methods used are comparable across the intervention groups, which somehow “fixes” this parameter. Due to the nature of the intervention (vaccine), bias due to “deviations from intended interventions” is low.

Qualitative synthesis

Thromboembolic events

Goldstein et al.’ study reported no incidence of obstetrical pulmonary embolism (the study assessed only this type of thromboembolic event) [42]. In contrast, Theiler et al. noted two cases of thromboembolism in the unvaccinated group (2/1,580), and no cases in the vaccinated group (0/129). The writers did not define the type of thromboembolic events [44]. Parallely, Theiler et al. separately assessed the incidence of stroke. Two incidents were reported in the unvaccinated group vs. no incident in the vaccinated group (2/1,581 vs. 0/129 respectively) [44]. No significant results were reported [42, 44].

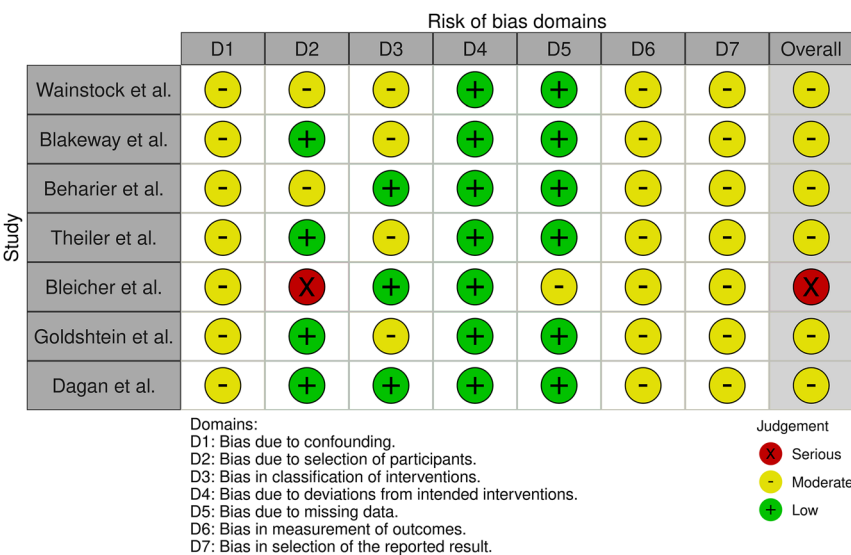
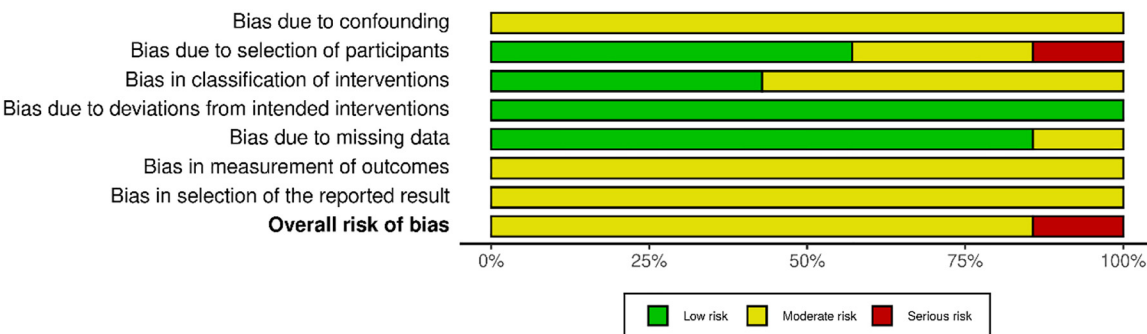
Preterm delivery

The incidence of preterm delivery below 37 weeks did not differ significantly between vaccinated and unvaccinated pregnant women. Bleicher et al. reported no incidence, while Beharier et al. noted 4/92 cases in the vaccinated and 5/66 cases in the unvaccinated groups. Likewise, Goldshtein reported 77/7,530 cases and 85/7,530 cases, respectively. Theiler et al. tried to distinguish women with a history of SARS Cov-2 infection and women without a history of infection (vaccinated and unvaccinated). Similarly, no statistically significant results were found [40–42, 44].

Likewise, Theiler et al. assessed different sub-categories for the same outcome, following the same methodology. The incidence of preterm deliveries between 24 0/7–31 6/7 gestational weeks, below the 24th gestational week, and the incidence of late preterm

Table 3: Risk of bias assessment for the included studies for all outcomes.

	Overall bias	Confounding bias	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Wainstock et al. [46]	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate
Blakeway et al. [45]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
Beharier et al. [40]	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Theiler et al. [44]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
Bleicher et al. [41]	Serious	Moderate	Serious	Low	Low	Moderate	Moderate	Moderate
Goldshtein et al. [42]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
Dagan et al. [43]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate


Figure 2: Traffic light plot for the risk of bias assessment of the included studies – all outcomes (ROBINS-I cochrane tool).

Figure 3: Weighted summary plot for the risk of bias assessment of the included studies – all outcomes (ROBINS-I cochrane tool).

deliveries (34 0/7–36 6/7) did not differ significantly between the vaccinated and unvaccinated women (even when the writers divided the groups into “past-infection” and “no past infection” subgroups) [44].

Stillbirth

The rate of stillbirth ≥ 24 gestational weeks was assessed by Blakeway et al. and Theiler et al., showing no statistically significant differences (respectively: 0/133 in vaccinated and 1/399 in unvaccinated; 0/140 in vaccinated and 6/1862). Subsequently, Blakeway et al. excluded women with antenatal SARS Cov-2 infection, and the results remained unaltered [44, 45].

Equal results were extracted for the rate of stillbirth ≥ 20 gestational weeks (Goldshtein et al. 1/7,530 cases in the vaccinated group and 2/7,530 cases in the unvaccinated group) [42].

SARS Cov-2 infection

Theiler et al. and Bleicher et al. noted a statistically significant decrease of SARS Cov-2 infections in the vaccinated group. Theiler et al. noted 2/140 in vaccinated vs. 210/1862 cases in unvaccinated ($p=0.03$). Bleicher et al. noted 3/202 in vaccinated vs. 8/124 cases in unvaccinated ($p=0.024$) [41, 44]. Blakeway, on the contrary, found no statistically significant difference [45].

SARS Cov-2 infection probability (118 cases in the vaccinated group, and 202 in the unvaccinated) in Goldshtein et al. differs significantly between vaccinated and unvaccinated women (Odds Ratio OR 0.58, 95% CI 0.46 to 0.73, $p<0.001$). Goldshtein et al. also noted a non-significant difference between the two groups during the first ten days after vaccination (adjusted Hazard Ratio aHR 0.96, 95% CI 0.69 to 1.33, $p=0.79$), and a significant 54% hazard reduction in the vaccinated group during 11–27 days after vaccination, and 78% hazard reduction during 28 days or more after vaccination (respectively: aHR 0.46, 95% CI 0.31 to 0.67, $p<0.001$, and aHR 0.22, 95% CI 0.11 to 0.43, $p<0.001$). Regarding infections, 105/118 in the vaccinated group and 179/202 in the unvaccinated group were symptomatic, while 13/118 infected women in the vaccinated group and 23/202 women in the unvaccinated group needed hospitalization. The latter results were not statistically significant [42]. Dagan et al.’s results are analogous; cumulative incidence curves in both groups are similar until the 14th day after vaccination. After the 14th day the infection rates in the vaccinated group started to decline sharply. Vaccine effectiveness was 67% (95% CI 40–84%) in 14–20 days after

the first dose, 71% (95% CI 33–94%) in days 21–27 after the first dose, and 96% (89–100%) in days 7–56 after the second dose. Likewise, SARS Cov-2 infection probability differs significantly between vaccinated and unvaccinated women (Odds Ratio OR 0.55, 95% CI 0.45 to 0.68, $p<0.001$) [43].

Birthweight

Wainstock et al. found no statistically significant differences between the birthweight of newborns derived from vaccinated and unvaccinated mothers (mean $3,224 \pm 472$ vs. $3,227 \pm 465$, $p=0.87$). Newborns derived from mothers who were vaccinated with two doses had significantly lower birthweight compared to newborns derived from mothers who were vaccinated with one dose (mean difference -133 g, $p=0.004$). Likewise, newborns derived from mothers who were vaccinated with two doses had significantly lower birthweight compared to newborns derived from unvaccinated mothers (mean difference -105 g, $p=0.01$). No statistically significant difference was noted when comparing those newborns from mothers vaccinated with one dose to newborns from unvaccinated mothers [46].

Beharier et al. and Goldshtein et al. equally found no statistically significant difference concerning the birthweight [40, 42]. Blakeway et al. calculated the z-score of the birthweight of newborns derived from vaccinated and unvaccinated mothers, and noted no significant difference, even when they excluded those newborns from mothers with antenatal SARS Cov-2 infection [45].

Theiler et al. investigated the rates of newborns with low and extremely low birthweight ($<2,500$ g and $<1,500$ g, respectively). No statistically significant difference was found. Similar results were obtained when they calculated the above rates in the “no infection” and “infection” subgroups [44].

SGA neonates

No differences were found regarding the incidence of SGA neonates below the 5th and the 10th percentile originated from vaccinated and unvaccinated mothers [45, 46]. Equally, the results remained the same even when Blakeway et al. excluded the newborns derived from mothers with antenatal SARS Cov-2 infection [45]. Parallely, Wainstock et al. found no difference between the two-doses vaccinated group vs. the one dose vaccinated group, the two-doses vaccinated group vs. the unvaccinated group, and the one-dose vaccinated group vs. the unvaccinated group [46].

Neonatal death

Theiler et al. tried to investigate the early neonatal death rate (within 7 days from birth), but no incidence occurred [44].

Maternal hemorrhage

Postpartum hemorrhage without exact definitions was investigated by Wainstock et al., who noted no significant decrease in postpartum bleeding incidents in the unvaccinated group (OR 1.28, 95% CI 0.62 to 2.62; Adjusted OR 1.46, 95% CI 0.63 to 3.38) [46]. Theiler et al. and Blakeway et al. investigated the incidence of postpartum hemorrhage with blood loss greater than 1L. No significant results were found, even when Blakeway et al. excluded pregnant with antenatal SARS Cov-2 infection, and even when Theiler et al. divided the vaccinated and unvaccinated participants into “no infection” and “infection” subgroups [44, 45]. Theiler et al. also assessed the transfusion rates and a composite outcome, including postpartum bleeding events that needed a transfusion. These results were not significant [44]. Finally, antepartum hemorrhage was only evaluated by Bleicher et al., who found equally no difference regarding these events’ rates between the two groups [41].

Quantitative synthesis

For the quantitative synthesis, we created two subgroups: those studies assessing BNT162b2 (Pfizer-BioNTech) exclusively (“BNT162b2 Pfizer-BioNTech” subgroup), and those assessing multiple types of vaccines (“Multiple Vaccines” subgroup). Since Bleicher et al.’s study was of serious risk of bias, it was not included in the quantitative analysis. Publication bias was not conducted since less than ten studies were available for each outcome.

In the “BNT162b2 Pfizer-BioNTech” subgroup, we note a statistically significant decrease of 44% of the odds of infection among vaccinated women compared to unvaccinated women ($n=36,782$, pooled OR 0.56, 95% CI 0.48 to 0.66, $p<0.001$, $I^2=0\%$). In the “Multiple Vaccines” subgroup, we note a statistically significant decrease of 79% of the odds of infection among vaccinated women compared to unvaccinated women ($n=40,112$, pooled OR 0.21, 95% CI 0.08 to 0.57, $p=0.002$). However, we note a significant statistical heterogeneity in this subgroup ($I^2=81\%$) and overall ($I^2=72.6\%$). After sensitivity analysis, we removed the study, which created the statistical heterogeneity (in the above subgroup and overall). The rate of infections among the vaccinated women compared to unvaccinated is significantly reduced

by 43% ($n=38,110$, pooled OR 0.57, 95% CI 0.49 to 0.66, $p<0.001$). The overall statistical heterogeneity is $I^2=0\%$ (Figure 4).

The pooled effect estimate for preterm deliveries, stillbirth, birthweight, SGA neonates, and maternal hemorrhage is not statistically significant. The forest plots are available in Supplementary Material (Supplementary Material, Figures 1–5).

Strength of evidence GRADE reporting system

We defined the number of studies for each outcome, the studies’ design, and we evaluated the inconsistency across studies measuring the same outcome. We also assessed if the outcome was examined directly across studies (indirectness), if the results were precise enough across studies (imprecision), the presence/absence of publication bias, of a large effect, of plausible confounding, and of a dose-response gradient. Results are depicted in Table 4.

The only outcome that was judged as of “High” strength of evidence was the rate of covid-19 infections after vaccination only with BNT162b2 (Pfizer-BioNTech). The following outcomes were judged as of “Moderate” strength of evidence: Covid-19 infection rates, and Birthweight (in grams), while Preterm delivery (<37 gestational weeks), Stillbirth, and SGA (<10 th percentile) were judged as of “Low” strength for evidence. Postpartum hemorrhage and thromboembolic events were judged as of “Very low” strength of evidence”. We note that the assessment was conducted only for the “Moderate” and “Low” risk of bias studies.

Discussion

This systematic review suggests that the vaccination against SARS Cov-2 in pregnant women is effective and safe.

Concerning the effectiveness, SARS Cov-2 infection rates were significantly lower among vaccinated pregnant women in all studies included. The quantitative meta-analysis revealed a 43% statistically significant reduction of infections’ rates among vaccinated pregnant women compared to non-vaccinated ones (OR 0.57, 95% CI 0.49 to 0.66, $p<0.001$). This decrease was similar (44% decrease, OR 0.56, 95% CI 0.48 to 0.66, $p<0.001$) among those pregnant women who were exclusively administered the BNT162b2 (Pfizer-BioNTech) vaccine. Likewise, it is worth noting that the BNT162b2 (Pfizer-BioNTech) vaccine’s effectiveness was time-dependent; it was increased during the time

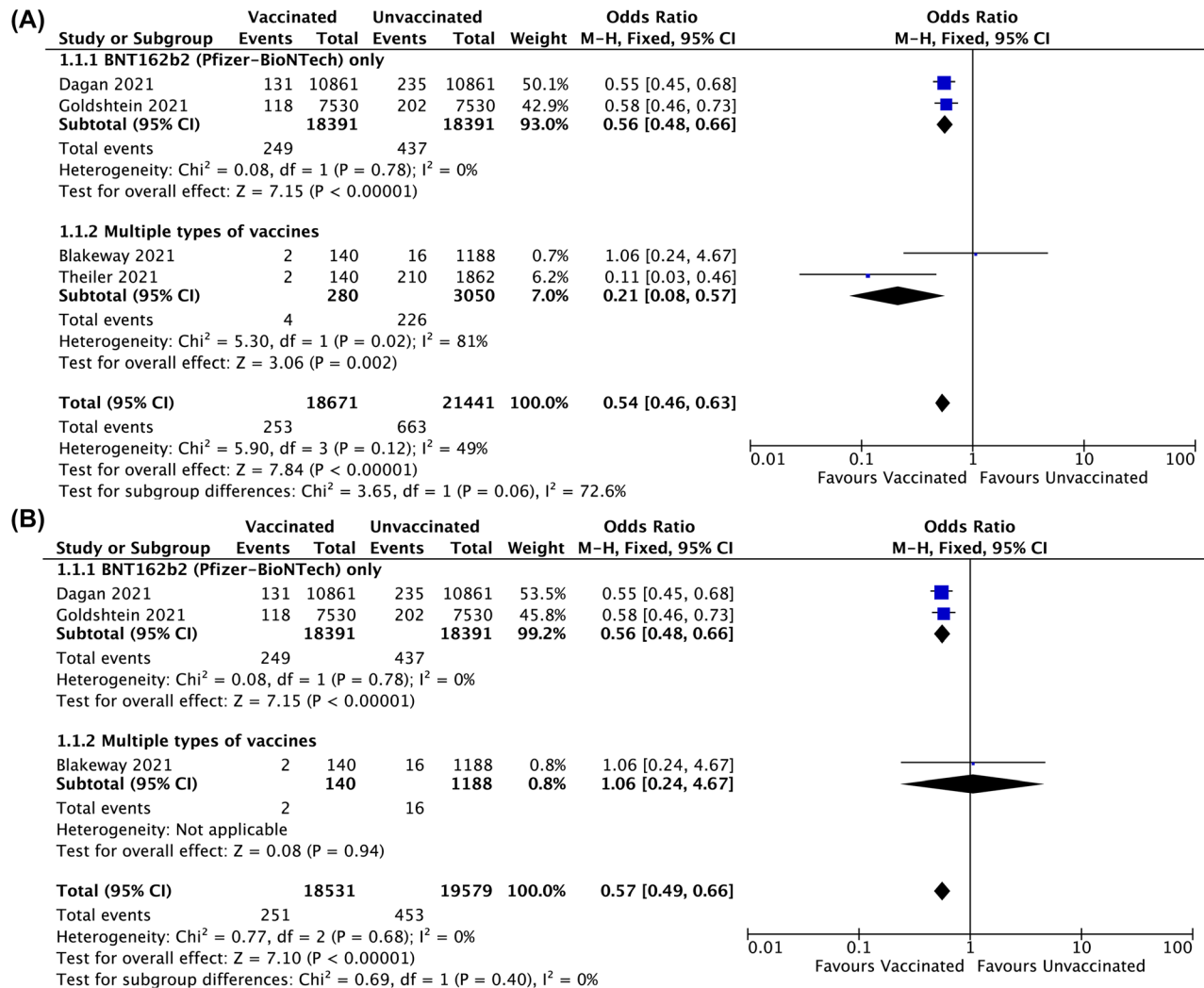


Figure 4: SARS Cov-2 infection odds. Before (A) and after (B) sensitivity analysis.

after the first dose and, especially, after the second dose. However, the risk reduction of SARS Cov-2 infection seems to be lower than this among the general population [42, 43].

Regarding safety, vaccines against SARS Cov-2 were not proved to be associated with major maternal and neonatal adverse events. The studies included in this systematic review noted no differences between vaccinated and unvaccinated pregnant women as far as the following outcomes are concerned: thromboembolic events, preterm delivery, stillbirth, birthweight, SGA neonates, neonatal death, and maternal hemorrhage. Regarding birthweight, it must be outlined that this outcome cannot simply be compared as it is since the fetus' growth depends on the gestational week. Indeed, birthweight percentiles associate the birthweight of a newborn with the gestational age at birth. However, none of the authors, who assessed the above outcome, used birthweight percentiles. Thus, in our

synthesis, we could not use percentiles as well. Only Blakeway et al. calculated the z-score of the birthweight (derived from the birthweight percentiles) and noted no significant difference [45].

Besides, it is essential to address the fact that the studies included assessed a variety of outcomes, in addition to those predefined and assessed by this systematic review. Since these additional outcomes were not defined as outcomes of interest of the present review, the authors could not include them in their meta-analysis (this could mean a violation of the protocol). The complete list of outcomes assessed by each included study is available in Table 2. However, it is meaningful to comment that no statistically significant differences were noted between vaccinated and unvaccinated pregnant women regarding these additional outcomes. Thus, overall, there is evidence that vaccines against SARS Cov-2 are safe during pregnancy.

Table 4: Summary of findings for RCTs after evaluation with GRADE reporting system.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence, GRADE	Relative effect (95% CI ^a)	Anticipated absolute effects		№ of patients	
				Risk with no-vaccination	Risk difference with vaccination against SARS Cov-2	Vaccination	No vaccination
Covid-19 infection	38,110 (3 observational studies)	⊕⊕⊕○ Moderate	OR ^b 0.57 (0.49–0.66)	23 per 1.000	10 fewer per 1.000 (12 fewer to 8 fewer)	251/18,531 (1.4%)	453/19,579 (2.3%)
Covid-19 infection after vaccination only with BNT162b2 (Pfizer-BioNTech)	36,782 (2 observational studies)	⊕⊕⊕⊕ High	OR 0.56 (0.48–0.66)	14 per 1.000	6 fewer per 1.000 (7 fewer to 5 fewer)	437/18,391 (2.4%)	249/18,391 (1.4%)
Thromboembolic events	16,770 (2 observational studies)	⊕○○○ Very low	OR ^b 2.44 (0.12–51.08)	0 per 1.000	0 fewer per 1.000 (0 fewer to 11 more)	0/7,659 (0.0%)	2/9,111 (0.0%)
Preterm delivery (<37 gestational weeks)	17,220 (3 observational studies)	⊕⊕○○ Low	OR 0.92 (0.70–1.21)	10 per 1.000	1 fewer per 1.000 (3 fewer to 2 more)	94/7,762 (1.2%)	94/9,458 (1.0%)
Stillbirth (20th gestational week or more)	17,594 (3 observational studies)	⊕⊕○○ Low	OR 0.73 (0.14–3.70)	1 per 1.000	0 fewer per 1.000 (1 fewer to 2 more)	1/7,803 (0.0%)	9/9,791 (0.1%)
Stillbirth (24th gestational week or more)	2,534 (2 observational studies)	⊕⊕○○ Low	OR 1.01 (0.12–8.59)	3 per 1.000	0 fewer per 1.000 (3 fewer to 23 more)	0/273 (0.0%)	7/2,261 (0.3%)
Birthweight, grams	4,557 (2 observational studies)	⊕⊕⊕○ Moderate	Mean 0.02 g (–33.10 to 33.15)		Mean 0.02 g higher (33.1 lower to 33.15 higher)	1,005	3,552
SGA (small for gestational age) below the 10th percentile	4,931 (2 observational studies)	⊕⊕○○ Low	OR 0.82 (0.58–1.16)	46 per 1.000	8 fewer per 1.000 (19 fewer to 7 more)	42/1,046 (4.0%)	179/3,885 (4.6%)
Postpartum hemorrhage	6,933 (3 observational studies)	⊕○○○ Very low	OR 1.22 (0.80–1.87)	21 per 1.000	5 more per 1.000 (4 fewer to 18 more)	29/1,186 (2.4%)	123/5,747 (2.1%)
Postpartum hemorrhage >1L	2,534 (2 observational studies)	⊕○○○ Very low	OR 1.20 (0.70–2.03)	41 per 1.000	8 more per 1.000 (12 fewer to 39 more)	19/273 (7.0%)	93/2,261 (4.1%)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ^aCI, confidence interval; ^bOR, odds ratio. GRADE working group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

As far as other studies are concerned, few addressed similar research questions. Shimabukuro et al. compared maternal and neonatal adverse events between vaccinated pregnant women and published incidence in the general population (no population matching) and found no safety issues regarding vaccination of pregnant women during the 3rd trimester [54]. These results are in line with our findings. Charepe et al. studied short-term vaccination events in vaccinated lactating and non-lactating women. No differences between the groups were found [48]. Bookstein-Peretz et al. assessed short-term events after vaccination

between vaccinated pregnant and vaccinated non-pregnant women (local pain, swelling, fever, etc.) and reported lower rates of myalgia, arthralgia, axillary lymphadenopathy, and headache among vaccinated pregnant women after the administration of two doses. Paresthesia had higher rates among vaccinated pregnant women [55]. Kachikis and al., who only enrolled vaccinated pregnant and lactating women, likewise studied short-term reactions and reported that vaccines were well-tolerated and noted no differences regarding vaccination reactions between groups. Our systematic review did not assess short-term outcomes [51].

Limitations and strengths

This systematic review has some limitations. First, no clinical trials addressing this issue were found. As a result, we only included observational studies (both retro- and prospective), which are *de facto* prone to biases. All the studies included were non-randomized and not blinded. Furthermore, the number of included studies was small. The interventions and populations were mixed; the use of different types of vaccines and administering a different number of doses is indeed problematic, while many studies marked population imbalances. The administration of the vaccines' doses mainly concerned the 2nd and the 3rd trimester, failing thus to measure the impact of the 1st trimester's administration. Moreover, studies that tried to assess the incidence of outcomes between populations who were administered one or two doses, failed to do so due to insufficient power to detect differences. Our systematic review failed to thoroughly investigate vaccination's impact on the incidence of our primary outcome (thromboembolic events). Although concerns were reported globally concerning the association between vaccines against SARS Cov-2 and thromboembolic events, only two studies assessed the incidence of similar events [42, 44], limiting the possibility to make safe conclusions for pregnant populations. Besides, we failed to acquire preliminary data from an ongoing study [50]. We were informed that Pfizer currently conducts a phase 2/3 trial among pregnant women, but no results were likewise available [23].

Besides, in pregnant women, the assessment of the vaccine's effects may be biased since, generally, pregnant women are more precautious, especially during the pandemic, as far as social distancing is concerned, independently from their vaccination status. Most studies were conducted during lockdown periods or periods with implemented social distancing. This fact may attenuate the vaccine's beneficial effect. Unvaccinated women are more prone to undergo testing more often, increasing the incidence of SARS Cov-2 infections among them. Parallely, herd immunity may protect both vaccinated and unvaccinated populations. It must be noted that socioeconomic differences are observed between vaccinated and unvaccinated pregnant women, suggesting that vaccination status is not entirely due to hesitancy [44]. It is important to underline that obstetric events and neonatal complications have a psychological impact on women, influencing their desire to participate in this type of study.

Despite the above limitations, this systematic review has some essential strengths. We strongly believe that the

studies included are the best possible that a researcher could find. Our work is genuinely comprehensive; the research question was specific, and our search strategy was broad to secure the inclusion of every appropriate study that could potentially answer our research question. The methodology followed was proposed by the Cochrane Handbook, while no violations of our protocol were noted. The risk of bias assessment was conducted using the appropriate tools, while sensitivity and subgroup analyses were performed wherever a quantitative synthesis was conducted. Finally, to our best knowledge, this is the first systematic review addressing the issue of maternal and neonatal adverse events on vaccinated pregnant women compared to unvaccinated.

Implications for the future

The above results need to be confirmed by larger studies with more homogeneous populations, especially regarding the administration of SARS Cov-2 vaccines during the 1st trimester of pregnancy. The larger populations will permit the observation of more minor differences between potential subgroups of the pregnant population (two doses vs. one dose, three doses vs. two, administration during specific trimesters, same vaccine type, etc.), and the eradication of potential population imbalances. During the conduction of this systematic review the third booster dose was proposed for those pregnant women who are immunocompromised [16,25]. Thus, the need to evaluate the safety and efficacy of the third dose in this specific subgroup is essential. In addition, a newer vaccine NVX-CoV2373 (Nuvaxovid by Novavax), which contains the spike protein of SARS Cov-2, was approved by the European Medicines Agency (EMA) [56]. This vaccine may be used among pregnant women, and new studies should address this issue.

Apart from the above, pregnant women's vaccination may protect the fetus and the newborn. Beharier et al. reported that protective antibodies were present in the fetal circulation 15 days after the administration of the first dose. At the same time, SARS Cov-2 infection likewise led to fetal humoral immunity at delivery [40]. Humoral immunity was significantly lower in vaccinated pregnant women compared to vaccinated non-pregnant women [47]. Binding and neutralizing antibodies were found in breast milk and the cord blood of infants born to mothers vaccinated against Covid-19 with mRNA vaccines [57]. Lactating women who were vaccinated showed an increase in SARS Cov-2 antibodies in their breast milk [58–60]. More studies

need to define further the immunity duration and the significance of these results.

Conclusions

Covid-19 vaccination during pregnancy seems to significantly decrease SARS Cov-2 infection rates in vaccinated pregnant women compared to non-vaccinated. Furthermore, there is no association between vaccines against SARS Cov-2 and major maternal and neonatal adverse events. The results are promising, but caution is advised due to the limitations of the studies included. Studies with larger and more homogeneous populations are needed.

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Competing interest: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

Registration and protocol: The protocol of this study was submitted to the PROSPERO database with registration number CRD42022310413. There were no amendments regarding our initial protocol.

Data availability: Upon request.

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