

REVIEW ARTICLE

Obstetrics

COVID-19 vaccine and pregnancy outcomes: A systematic review and meta-analysis

Luigi Carbone¹ | Maria Giuseppina Trinchillo¹ | Raffaella Di Girolamo¹ |
Antonio Raffone² | Gabriele Saccone¹ | Giuseppe Gabriele Iorio¹ | Olimpia Gabrielli¹ |
Giuseppe Maria Maruotti¹

¹Department of Neurosciences, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

²Division of Gynecology and Human Reproduction Physiopathology, Department of Medical and Surgical Sciences (DIMEC), IRCCS Azienda Ospedaliero-Universitaria di Bologna, S. Orsola Hospital, University of Bologna, Bologna, Italy

Correspondence

Raffaella Di Girolamo, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Via Sergio Pansini, 5, Naples 80131, Italy.
Email: raffaella.digirolamo95@gmail.com

Abstract

Objectives: To explore perinatal outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-vaccinated pregnant women compared with unvaccinated counterparts.

Methods: Search was conducted using Web of Science, Scopus, ClinicalTrial.gov, MEDLINE, Embase, OVID, and Cochrane Library as electronic databases. We included observational studies evaluating pregnant women undergoing SARS-CoV-2 vaccination and compared pregnancy and perinatal outcomes with those in unvaccinated women. Categorical variables were assessed using odds ratio (OR) with 95% confidence interval (CI), whereas for continuous variables, the results were expressed as mean difference with their 95% CI. All analyses were performed by adopting the random effect model of DerSimonian and Laird.

Results: There was no difference in the probability of having a small-for-gestational-age fetus (OR 0.97, 95% CI 0.85–1.09; $P = 0.570$), but we observed a reduced probability of a non-reassuring fetal monitoring, a reduced gestational age at delivery, and a reduced probability of premature delivery in vaccinated pregnant women versus unvaccinated ones.

Conclusion: The probability of small for gestational age is similar between vaccinated and unvaccinated pregnant women, and the former also had a slightly reduced rate of premature delivery.

KEYWORDS

coronavirus disease 2019, meta-analysis, pregnancy, preterm birth, severe acute respiratory syndrome coronavirus 2, small for gestational age, systematic review, vaccine

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has affected a huge number of people for 2 years worldwide, becoming the major public health issue and forcing healthcare facilities to reorganize

medical units, including obstetrical and gynecologic activities.¹⁻⁹ Pregnancy is considered an independent risk factor for adverse outcome in women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with increased rates of maternal mortality and intensive care unit admissions compared with

non-pregnant women, and also with increased rates of preterm deliveries (both spontaneous and iatrogenic), stillbirth, cesarean sections, and other pregnancy-related diseases.¹⁰⁻¹⁶ Recently, the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the Centers for Disease Control and Prevention declared that all pregnant women should be vaccinated to reduce maternal and fetal-neonatal morbidity and mortality.^{17,18} However, although it is growingly recognized that COVID-19 vaccination programs, including booster doses, are safe and open to pregnant women,^{19,20} Zavala et al.²¹ observed that, by September 2021, 17% of national policies still continued to recommend against the use of any COVID-19 vaccine during pregnancy, of which 25% were low- and middle-income countries, taking into consideration the lack of clinical trials, and developmental and reproductive toxicology data involving pregnant women. Moreover, there are still reports of a poor acceptance rate in this category of patients, mainly because of the maternal fear of consequences for fetal-neonatal health.²²⁻²⁴ In addition, although pregnancy and perinatal outcomes of SARS-CoV-2 infection have been largely investigated, little is still known about the impact of SARS-CoV-2 vaccine. Preliminary data on safety and immunization properties of SARS-CoV-2 vaccines in pregnant women seem to be reassuring, suggesting also that neonates born from vaccinated mothers may have antibodies against SARS-CoV-2.²⁵⁻²⁷ Furthermore, the US Centers for Disease Control and Prevention and the UK National Health Service considered safer the use of the Moderna or Pfizer-BioNTech vaccines, due to the rapidity of mRNA disintegration, although no adverse pregnancy-related outcomes seem to occur in clinical trials that evaluated other kind of vaccines, such as the J&J/Janssen COVID-19 vaccine.^{17,28} We therefore hypothesize that vaccines based on mRNA technology are safe and every pregnant woman should be strongly advised to get vaccinated. Therefore, in this scenario of continuing pandemic waves, with the Omicron variant as the last widely diffused and contagious one, the aim of this systematic review is to explore the maternal, fetal, and neonatal outcomes in COVID-19-vaccinated pregnant women compared with those not receiving COVID-19 vaccine.

2 | MATERIALS AND METHODS

2.1 | Study protocol

The present review was performed according to a protocol recommended for systematic review. The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement²⁹ and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).³⁰ PRISMA and MOOSE checklists are reported in Tables S1 and S2. It was also registered on PROSPERO (CRD42022319270). All review stages were conducted independently by three authors. In particular, three authors (OG, MGT, GGI) independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, and data extraction; RDG

and AR performed the data analysis. All disagreements were resolved by discussion with the senior author (GMM).

2.2 | Literature search and study selection

The literature search was conducted using Web of Science, Scopus, ClinicalTrials.gov, MEDLINE, Embase, OVID, and Cochrane Library as electronic databases. The studies were identified with the use of a combination of the following text words: "coronavirus" OR "COVID-19 pandemic" OR "SARS-CoV-2" OR "COVID-19" AND "vaccine" OR "vaccination" OR "COVID-19 vaccine" OR "SARS-CoV-2 vaccine" AND "pregnancy" OR "pregnant" OR "pregnant women" OR "during pregnancy" OR "pregnancy outcome" OR "adverse outcome" from December 2019 to February 28, 2022. Review of articles also included the abstracts of all references retrieved from the search. Duplications were removed using Endnote online software and also manually. Only English-language studies were considered for inclusion. Unpublished or non-peer-reviewed studies were not included. Given that, for ethical reasons, no randomized controlled studies were planned in pregnant women, we included in our systematic review all observational studies that evaluated the population of women undergoing SARS-CoV-2 vaccination during the COVID-19 pandemic and compared pregnancy, maternal, and fetal-neonatal outcomes with those of non-vaccinated pregnant women. We excluded case reports and studies without control groups or that considered non-pregnant women as controls, as well as studies focusing only on immunogenic properties or intrinsic adverse events of vaccines against SARS-CoV-2 infection.

2.3 | Risk of bias assessment

The risk of bias and quality assessment of the included studies were performed using the Newcastle-Ottawa Scale (NOS).^{31,32} The NOS score was used to evaluate the included studies, and judgment on each one was passed according to three issues: selection of the study group, comparability between groups, and ascertainment of exposed/unexposed cohorts.

2.4 | Data extraction

Data were extracted from the included studies without modifications. A data extraction sheet based on the Cochrane data extraction template for non-randomized controlled trials was used (<https://dplp.cochrane.org/data-extraction-forms>). The main data extracted for our systematic review were: first authors' names and publication year, study design, study location, period considered in the analysis, sample size, inclusion and exclusion criteria, type of vaccine, general features of included populations (age, body mass index, race, previous disease, obstetrical history, number of fetuses, trimester of vaccination) as well as various maternal, fetal, and neonatal outcomes.

2.5 | Outcomes

The primary outcome was the evaluation of risk of small-for-gestational-age fetuses for pregnant women receiving SARS-CoV-2 vaccine. Other gestational diseases, delivery outcomes, neonatal birth weight, and fetal-neonatal conditions were considered as secondary outcomes.

2.6 | Statistical analysis

Prevalence of SARS-CoV-2 vaccination according to trimester of pregnancy was calculated as the number of pregnant women vaccinated in that specific trimester: first, second, and third, respectively. Also, the association between the prevalence of sociodemographic or adverse pregnancy outcome with SARS-CoV-2 vaccine was assessed using odds ratio (OR) with 95% confidence interval (CI), whereas for continuous variables, results were expressed as mean difference (MD) with their 95% CI. All analyses were performed by adopting the random effect model of DerSimonian and Laird. Statistical heterogeneity among included studies was evaluated by the inconsistency index I^2 . In detail, heterogeneity was classified as: null for $I^2 = 0\%$, minimal for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$, and high for $I^2 \geq 75\%$. Egger's test and tests for funnel plot asymmetry to assess potential publication bias were not used when the total number of publications included for each outcome was less than 10, as the tests lack power to detect real asymmetry in this case. Comprehensive Meta-Analysis (BIostat, Englewood, NJ, USA) and REVIEW MANAGER 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) were used as data analysis software. A *P* value less than 0.05 was considered significant.

3 | RESULTS

3.1 | Study selection and study characteristics

We identified 1037 articles, 40 of which were assessed with respect to their eligibility for inclusion and nine studies were included in the systematic review (Table 1; Figure 1). Excluded studies and reason for exclusion are reported in Table S3.

These nine studies included 40728 pregnant women, 21297 (52.3%) of which received the COVID-19 vaccine, while 19431 (47.7%) pregnant women did not receive it. The majority of studies were performed in Israel³³⁻³⁷ and the USA^{38,39}; one study was performed in Romania⁴⁰ and another in the UK.⁴¹ Only two studies were prospective,^{38,40} whereas the others were retrospective observational analyses. Only three studies evaluated cohorts of women including vaccines others than mRNA-based: Blakeway et al.⁴¹ also described 13 women vaccinated with the AstraZeneca vaccine, and Theiler et al.³⁹ and Citu et al.⁴⁰ observed one woman and 58 women, respectively, who were vaccinated with Janssen.

The results of the quality assessment of the included studies using NOS scale are presented in Table S4. The included studies showed an overall good score regarding the selection of the study groups and for ascertainment of the outcome of interest.

3.2 | Synthesis of the results

Complete general and demographic analysis of study populations was reported in Table 2. We observed that pregnant women who underwent the vaccination were slightly, but significantly, older than those who did not undergo vaccination (OR 0.79, 95% CI 0.14-1.45; *P* = 0.020) and more frequently had a history of miscarriage (OR 1.28, 95% CI 1.06-1.55; *P* = 0.009). Furthermore, Caucasian ethnicity appeared to be associated with vaccination (OR 1.76, 95% CI 1.20-2.58; *P* = 0.004), while women with black ethnicity seemed to refuse it (OR 0.40, 95% CI 0.19-0.81; *P* = 0.010). In the pooled analysis of other anamnestic factors, we did not observe other statistically significant differences (Table 2).

Stratifying per trimester we observed that the majority of the women were vaccinated during the third trimester (Table 3). Looking to maternal outcomes, we noticed that the gestational age at delivery was slightly reduced in pregnant women who were vaccinated compared with unvaccinated women (MD -0.13, 95% CI -0.21 to -0.04; *P* = 0.003) (Figure 2) but actually, SARS-CoV-2 vaccine is associated with a reduced probability of premature delivery (OR 0.88, 95% CI 0.78-0.98; *P* = 0.020) (Figure 3; Table 4). There is no difference in the probability of having a small-for-gestational-age fetus between vaccinated and unvaccinated women (OR 0.97, 95% CI 0.85-1.09; *P* = 0.570), but we observed a reduced probability of a non-reassuring fetal monitoring in pregnant women who received the SARS-CoV-2 vaccine (OR 0.69, 95% CI 0.51-0.94; *P* = 0.020) (Figure 4; Table 5). There were no statistically significant differences in all other explored maternal and fetal-neonatal outcomes between vaccinated and unvaccinated pregnant women.

4 | DISCUSSION

The SARS-CoV-2 vaccine is not associated with increased risk of having a small-for-gestational-age fetus.

Moreover, we found that vaccination was associated with a reduced probability of premature delivery, although the gestational age at delivery seemed slightly lower when compared with that in unvaccinated pregnant women. Furthermore, we observed reduced probability of non-reassuring fetal monitoring in vaccinated women. The pooled analysis of the nine included studies showed also that the prevalence of older and white pregnant women was higher among vaccinated than unvaccinated women, as well as for women with a previous history of miscarriages. In contrast, black women had a lower prevalence in the vaccinated group.

As far as we know, the present study represents the first pooled analysis for the evaluation of maternal, fetal, and neonatal outcomes

TABLE 1 General features of studies included in the systematic review

Authors	Location	Period considered	Study design	Sample size (cases vs control)	Inclusion criteria	Exclusion criteria	Vaccine type
Rottenstreich et al. (2022)	Israel	January 2021–April 2021	Retrospective	1775 (712 vs 1063)	All women aged 18 years or older, with no documented previous positive SARS-CoV-2 PCR test, who delivered during study period	Undocumented COVID-19 disease or vaccine status, pre-admission COVID-19 virus disease or a positive PCR test resulting during admission and hospitalization	Pfizer-BioNTech
Blakeway et al. (2021)	UK	March 2021–July 2021	Retrospective	1328 (140 vs 1188) of which 524 (131 vs 393) after exclusion of COVID-19 affected cases and PSM	Pregnant women with known vaccination status	Vaccinated entirely before pregnancy or after birth, pregnancies complicated by fetal aneuploidy and genetic syndromes	109 Pfizer-BioNTech; 18 Moderna; 13 Oxford-AstraZeneca
Wainstock et al. (2021)	Israel	January 2021–June 2021	Retrospective	4399 (913 vs 3486)	Women who delivered singletons at the hospital unit in the period considered	Diagnosed COVID-19 in the past, multiple gestations or unknown vaccination status and pregnancy follow-up information	Pfizer-BioNTech
Theiler et al. (2021)	USA	December 2020–April 2021	Retrospective	2002 (140 vs 1862) of which 1790 (138 vs 1652) after exclusion of COVID-19 affected cases	Women aged 16–55 years with a delivery event at a hospital in the period considered	Women who opted out to use their medical records for research	127 Pfizer-BioNTech; 12 Moderna; 1 Janssen
Shanes et al. (2021)	USA	January 2021–April 2021	Prospective	200 (84 vs 116)	Women who received vaccine delivering during study period	NS	mRNA vaccine
Goldshstein et al. (2022)	Israel	March 2021–September 2021	Retrospective	24 190 (16 738 vs 7452) of which 20864 (15 637 vs 5227) after exclusion of COVID-19 affected cases and IPTW	All singleton live births during study period	Records with no mother-offspring linkage were excluded because it was not feasible to assess their prenatal exposure status Non-singleton live births	Pfizer-BioNTech
Beharier et al. (2021)	Israel	April 2020–March 2021	Retrospective	158 (92 vs 66)	Age of 18 years or older and a willingness to participate and provide informed consent	Pregnant women with active maternal COVID-19 disease at delivery	Pfizer-BioNTech
Dick et al. (2022)	Israel	December 2020–July 2021	Retrospective	5618 (2305 vs 3313)	Women with singleton deliveries	Multiple pregnancy, vaccination before pregnancy, COVID-19 infection during or before pregnancy, or unknown timing of vaccination	Pfizer BioNTech or Moderna vaccines
Citu et al. (2022)	Romania	May 2021–December 2021	Prospective	702 (173 vs 529)	Women in the third trimester	NS	115 Pfizer BioNTech; 58 Janssen

Abbreviations: COVID-19, coronavirus disease 2019; IPTW, inverse probability of treatment weights; NS, not specified; PCR, polymerase chain reaction; PSM, propensity score matching; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

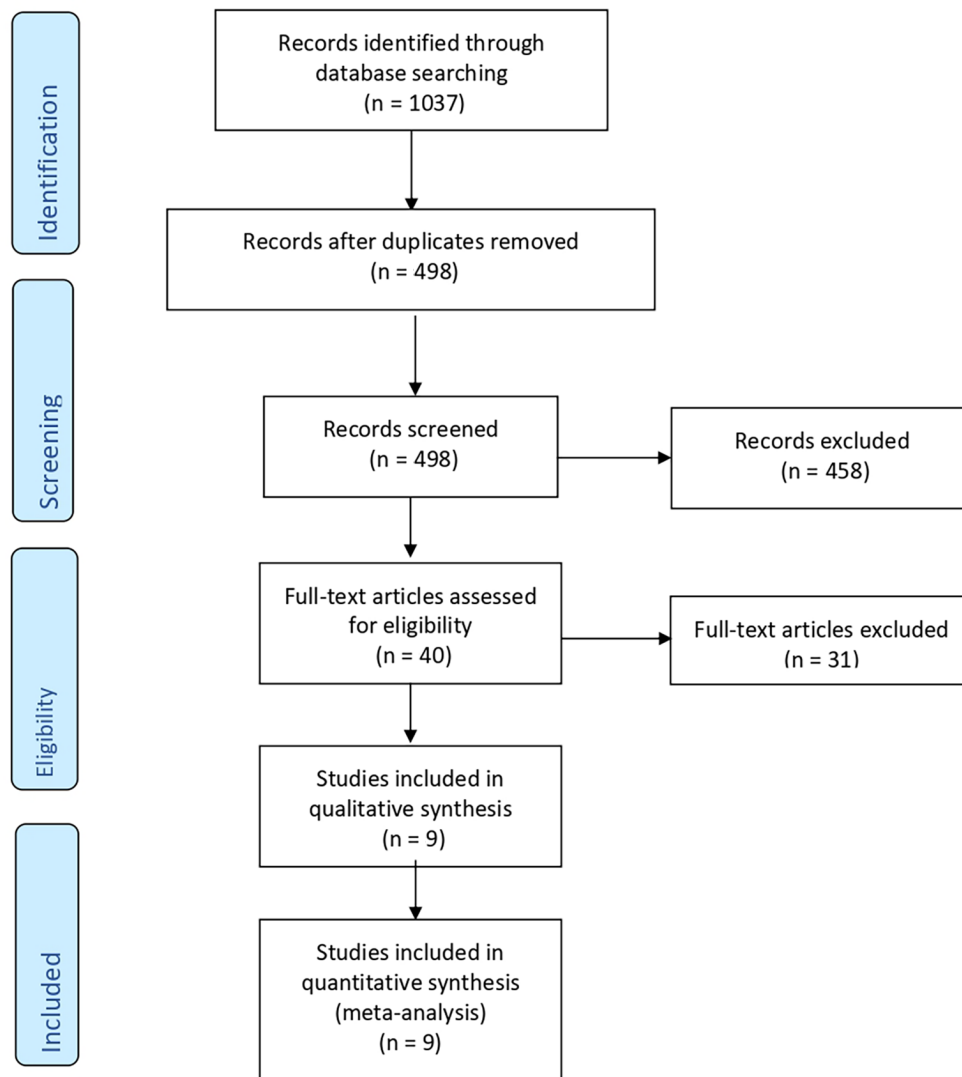


FIGURE 1 Flow diagram of studies identified in the systematic review.

in women undergoing SARS-CoV-2 vaccination, after exclusion of cases affected by SARS-CoV-2 infection during pregnancy, compared with unvaccinated pregnant women. The main strengths of our analysis are the adherence to PRISMA guidelines and the large number of outcomes considered. The review protocol was not registered a priori. Limitations lie in the observational design and heterogeneity among studies, as well as in the reduced number of studies considering some of the outcomes evaluated. Moreover, more than half of included studies come from a single country, and therefore directionality of the results could be skewed according to local obstetrical policies. Moreover, the differences among the populations of vaccinated and unvaccinated, especially in terms of age, history of miscarriage and ethnicity, could be considered a confounding factor. However, all the effects should eventually determine an increase in perinatal complications of vaccinated pregnant women, which has not been observed, apart from the black ethnicity, which was shown less frequently among vaccinated pregnant women, and we do know that black race is usually linked to increased adverse pregnancy outcomes.⁴²⁻⁴⁴

The results of our study reinforce the idea that receiving the SARS-CoV-2 vaccine during pregnancy is not associated with increased probability of adverse outcomes for both mothers and fetus/neonates.

The reduced probability of preterm birth is attributable to the weight of the data from Goldshtein et al.,³⁵ which provided the larger data set included in our pooled analysis. Indeed, it could be hypothesized that women who accepted the vaccination were at the same time self-managing their pregnancy in a safe way (i.e. reducing physical stressors), thereby reducing the risk of various complications of pregnancy, such as preterm birth. Lipkind et al.⁴⁵ observed no increased risk of preterm birth in vaccinated pregnant women compared with their unvaccinated counterparts; in addition, they showed that the prevalence of preterm birth was lower after two doses than after one dose and observed an adjusted OR less than 1 for vaccination in the third trimester, which is consistent with our results. Furthermore, the finding of a reduced probability of non-reassuring fetal heart rate could find explanation in a more preventive

TABLE 2 General characteristics of study populations expressed as mean difference and pooled odds ratio (with their 95% confidence intervals)

	Studies	Pregnancies	MD (95% CI)	P value	I ²
Age, years	9	40728	0.79 (0.14–1.45)	0.020	98%
BMI	2	6946	0.17 (–1.07 to 1.42)	0.780	98%
	Studies	Pregnancies (n ₀ /N ₀ vs n ₁ /N ₁)	Pooled OR (95% CI)	P value	I ²
Obesity	6	2115/18816 vs 2273/15580	0.97 (0.90–1.04)	0.380	0%
Pre-existing disease	3	473/16970 vs 494/9380	0.92 (0.79–1.07)	0.290	0%
History of miscarriage	2	271/885 vs 382/1592	1.28 (1.06–1.55)	0.009	0%
IVF	4	370/18676 vs 268/14752	2.07 (0.97–4.41)	0.060	93%
Nulliparity	4	6315/19895 vs 4034/13690	1.05 (0.91–1.20)	0.510	68%
Caucasian ethnicity	2	208/280 vs 2079/3050	1.76 (1.20–2.58)	0.004	27%
Black-Caribbean ethnicity	2	8/280 vs 200/3050	0.40 (0.19–0.81)	0.010	0%
Asian ethnicity	2	23/280 vs 294/3050	0.72 (0.46–1.13)	0.150	0%
Mixed ethnicity	2	15/280 vs 284/3050	0.43 (0.13–1.44)	0.170	63%
Twin pregnancy	4	22/1905 vs 61/7959	1.50 (0.86–2.59)	0.150	0%
Smoking	5	879/19415 vs 785/13881	0.81 (0.47–1.39)	0.440	78%
Pregestational or gestational diabetes	8	826/21213 vs 937/18959	1.19 (0.96–1.47)	0.100	61%

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; IVF, in vitro fertilization; MD, mean difference; OR, odds ratio. Statistically significant values are put in bold.

TABLE 3 Pooled proportions for COVID-19 vaccination stratified per trimester of pregnancy

	Studies	Pregnancies (n/N)	Pooled proportions % (95% CI)	I ²
First trimester	6	1863/20981	0.78 (0.50–6.00)	99.6%
Second trimester	6	9980/20981	10.64 (0.06–35.50)	99.9%
Third trimester	6	9138/20981	88.11 (57.80–99.90)	99.9%

Abbreviation: CI, confidence interval.

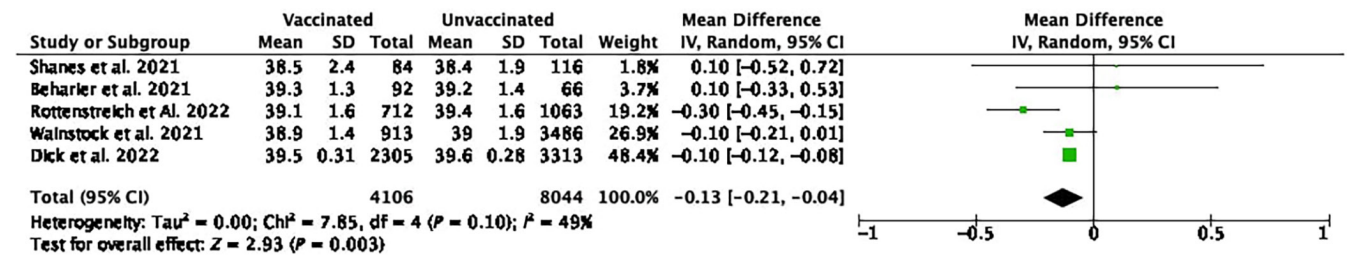


FIGURE 2 Forest plot for the mean difference of gestational age at delivery.

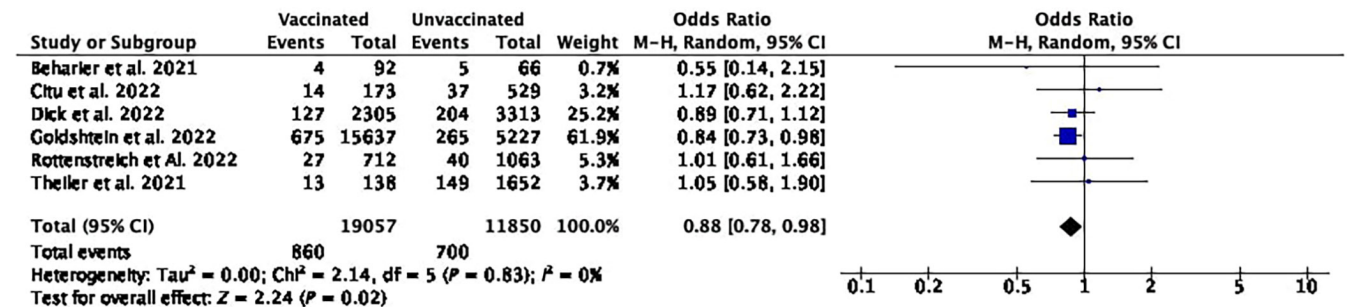


FIGURE 3 Forest plot for the odds ratio of preterm delivery.

TABLE 4 Pooled odds ratio (95% confidence intervals) for the maternal outcome of women undergoing COVID-19 vaccination compared with unvaccinated women

Maternal	Studies	Pregnancies	MD (95% CI)	P value	<i>I</i> ²
Gestational age at delivery	5	12 150	-0.13 (-0.21 to -0.04)	0.003	49%
Length of hospitalization	3	4267	0.00 (-0.03 to 0.03)	1.00	0%
	Studies	Pregnancies (<i>n</i> ₀ / <i>N</i> ₀ vs <i>n</i> ₁ / <i>N</i> ₁)	Pooled OR (95% CI)	P value	<i>I</i> ²
Premature delivery	6	860/19 057 vs 700/11 850	0.88 (0.78–0.98)	0.020	0%
Gestational hypertension/ pre-eclampsia	6	126/4381 vs 517/11 231	1.19 (0.86–1.65)	0.300	52%
Placental abruption	4	16/1929 vs 54/5471	0.66 (0.38–1.16)	0.150	0%
Vaginal delivery	5	1506/1978 vs 5004/6710	0.96 (0.81–1.13)	0.600	32%
Instrumental vaginal delivery	5	85/2067 vs 333/7123	0.87 (0.59–1.28)	0.480	53%
Cesarean section	6	754/4372 vs 1955/10 436	1.09 (0.92–1.28)	0.330	55%
Postpartum fever	3	30/1756 vs 53/4942	1.18 (0.55–2.54)	0.670	41%
Postpartum hemorrhage	6	162/4372 vs 329/10 436	0.98 (0.80–1.20)	0.840	2%
Maternal ICU admission	3	8/981 vs 12/3108	2.36 (0.96–5.78)	0.060	0%
Chorionamnionitis	2	14/843 vs 28/1456	0.79 (0.42–1.50)	0.470	0%
Transfusions	2	28/850 vs 224/2715	1.31 (0.85–2.02)	0.220	0%

Abbreviations: CI, confidence interval; ICU, intensive care unit; MD, mean difference; OR, odds ratio. Statistically significant values are put in bold.

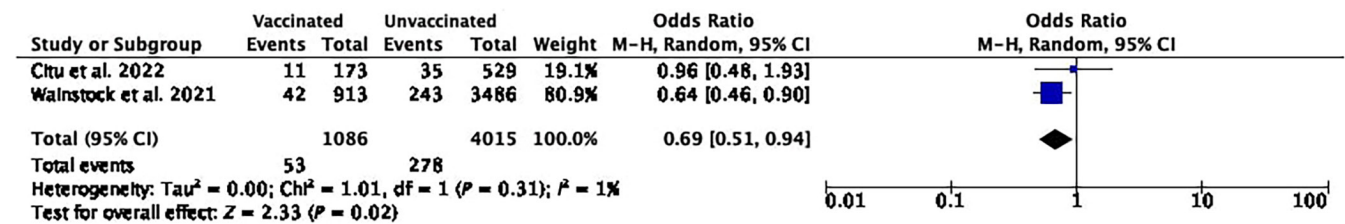


FIGURE 4 Forest plot for the odds ratio of non-reassuring fetal monitoring.

management by obstetrical practitioners, with the aim of avoiding any suspected risky situations. Nonetheless, we decided to cumulate the data between pregestational and gestational diabetes, considering it as a maternal factor affecting the choice to vaccinate more than a consequence of the vaccine. This decision depends mainly on two reasons: first, there is heterogeneity among the included studies in what they reported, that is if the diabetes was gestational or pregestational, and in the way they reported, mainly in third trimester, so that it is difficult to prove that diabetes is a consequence of the vaccine, given that according to guidelines the diagnosis is made around 24–28 weeks at latest.⁴⁶ In detail, Dick et al.,³⁴ Citu et al.,⁴⁰ and Wainstock et al.³⁷ describe only gestational diabetes mellitus but it is not specified whether it is diagnosed before or after the vaccine uptake; Beharier et al.³³ and Rottenstreich et al.³⁶ cumulate gestational and pregestational diabetes mellitus; Goldshtein et al.,³⁵ Blakeway et al.,⁴¹ and Theiler et al.³⁹ differentiate pregestational and gestational diabetes mellitus but the last is not mentioned in the subgroup analyses without COVID-19-affected pregnant women, so we took into consideration only the pregestational one.

Indeed, our results are in accordance with two other systematic reviews and meta-analyses, by Ma et al.⁴⁷ and by Pratama et al.⁴⁸ Ma et al.,⁴⁷ performed a pooled analysis of existing literature considering

19 078 vaccinated and 21 848 unvaccinated pregnant women, and showed that SARS-CoV-2 vaccination appeared to be protective against both the infection and hospitalization due to the infection itself. Pratama et al.,⁴⁸ in addition to showing similar maternal-fetal and neonatal outcomes between vaccinated and unvaccinated pregnant women, observed a significantly reduced risk of infection only after 10 days from vaccination. However, in contrast to them, we excluded studies that did not properly differentiate (eventually performing subgroup analysis) women affected by SARS-CoV-2 infection during pregnancy from those who had not been affected among the vaccinated and unvaccinated cohorts. In this regard, in fact, we think that the occurrence of COVID-19 during pregnancy could change the management of the cases and therefore pregnancy outcomes could be different, skewing the results.

Apart from being safe in relation to obstetrical and perinatal outcomes, SARS-CoV-2 vaccines are being studied also regarding intrinsic adverse events; Bookstein Peretz et al.⁴⁹ showed that non-pregnant women suffer more from adverse events than pregnant women after both first and second doses of vaccine; in addition, they found a lower antibody titer in pregnant women compared with non-pregnant women. Instead, Gray et al.²⁵ and Collier et al.²⁶ observed similar levels of antibodies between pregnant and non-pregnant

TABLE 5 Mean difference and pooled odds ratio (with 95% confidence intervals) for fetal and neonatal outcomes of pregnant women undergoing COVID-19 vaccination compared with those who remained unvaccinated

Fetal	Studies	Fetuses (n_0/N_0 vs n_1/N_1)	Pooled OR (95% CI)	P value	I^2
Stillbirth	4	25/3288 vs 45/6631	0.96 (0.58–1.57)	0.860	0%
SGA	6	1255/19871 vs 866/14011	0.97 (0.85–1.09)	0.570	15%
Non-reassuring fetal monitoring	2	53/1086 vs 278/4015	0.69 (0.51–0.94)	0.020	1%
Oligohydramnios	2	31/1086 vs 127/4015	0.90 (0.60–1.34)	0.610	0%
Polyhydramnios	2	12/1086 vs 37/4015	1.15 (0.60–2.23)	0.670	0%
Meconium-stained amniotic fluid	2	130/1625 vs 336/4549	0.78 (0.58–1.03)	0.080	32%
Abnormal presentation	2	43/1086 vs 155/4015	1.02 (0.73–1.45)	0.890	0%
Neonatal	Studies	Infant born	MD (95% CI)	P value	I^2
Neonatal birth weight	5	12 652	-2.74 (-30.86 to 25.37)	0.850	61%
	Studies	Infant born (n_0/N_0 vs n_1/N_1)	Pooled OR (95% CI)	P value	I^2
NICU admission	4	41/1073 vs 82/3174	0.94 (0.63–1.40)	0.760	0%
5-min Apgar <7	5	69/4241 vs 157/10043	0.95 (0.69–1.29)	0.740	1%
Respiratory complications	3	16/1798 vs 76/5078	0.67 (0.31–1.46)	0.310	16%
Fever	2	4/1086 vs 13/4015	1.05 (0.34–3.24)	0.930	0%
Jaundice	2	203/16349 vs 87/6290	0.91 (0.32–2.55)	0.850	90%
LBW	2	686/15775 vs 368/6879	0.89 (0.77–1.03)	0.120	0%
VLBW	2	51/15775 vs 56/6879	0.78 (0.22–2.81)	0.710	75%

Abbreviations: CI, confidence interval; LBW, low birth weight; MD, mean difference; NICU, neonatal intensive care unit; OR, odds ratio; SGA, small for gestational age; VLBW, very low birth weight. Statistically significant values are put in bold.

women, showing also that vaccine-induced immunity was higher than infection-induced and that antibodies were also found in umbilical cord blood and breast milk.

Interestingly, it was also observed that the length of the time interval from vaccination to delivery influences the antibody titer in a directly proportional manner.^{50,51}

Likewise, an interesting objective for future research would be to clarify the impact of different vaccination timing on perinatal outcomes: Dick et al.³⁴ showed an increased preterm birth rate and lower overall gestational age at delivery in women vaccinated during the second trimester compared with unvaccinated pregnant women. Goldshtein et al.³⁵ observed no differences in the rate of preterm delivery, small-for-gestational-age neonate, and any congenital malformation between pregnant women vaccinated during the first trimester and unvaccinated pregnant women. Nevertheless, our results reflect the outcomes after second (mainly attributable to Goldshtein et al.³⁵) and third trimesters compared with unvaccinated pregnant women. However, no studies have yet evaluated directly the comparison of perinatal outcomes between trimesters.

Regarding the risk of miscarriage for first-trimester vaccination, Magnus et al.⁵² observed no increased risk, in accordance with Kharbanda et al.⁵³ and Zauche et al.⁵⁴ However, none of these studies could be included in our meta-analysis for various reasons (Table S3).

Another hint could be represented by the comparison among one or more doses, especially when we are going to consider the booster

doses during pregnancy²⁰; in this regard, only Wainstock et al.³⁷ performed a subgroup analysis, observing no differences in the rate of pregnancy-related hypertensive disorders, cesarean delivery, small for gestational age and neonatal respiratory complications, but a reduced birth weight and lower gestational age at delivery in pregnant women with only one dose compared with those with two doses. Currently, a booster dose is recommended by various guidelines on the management of COVID-19 during pregnancy.⁵⁵

The last two big waves of the pandemic have been dominated by the Delta and Omicron variants, with the former associated with a more severe course of infection during pregnancy compared with the pre-Delta variants⁵⁶ and the last that showed a milder infection but still increased prevalence of adverse outcomes in the unvaccinated pregnant women, next to a tremendous increase in contagiousness,⁵⁷ which again put under strain the healthcare systems involved in the management of affected cases. In our meta-analysis, we still observed differences among vaccinated and unvaccinated women in relation to their medical history or personal features (age, ethnicity), which demonstrates again the need for intervention at a national level with a large informative campaign and a proficient, expert, and non-directional but very exhaustive counseling by general practitioners and obstetricians, reinforced by real world data and pooled analyses with overall large samples showing the safety of mRNA vaccines towards maternal and fetal/neonatal health, to ensure that pregnant women would have all the useful and needed information to take their decision in an autonomous but very conscious way.^{58,59} Magee et al.⁶⁰ calculated in 11 the number of

pregnant women needed to vaccinate (NNV) to prevent a SARS-CoV-2 infection, in 206 the NNV to prevent a symptomatic infection, as well as in 176 the NNV to prevent a preterm birth.

Additional studies with larger samples and longer follow ups are needed to uncover the doubts in relation to all the aspects of vaccination, from immunogenicity to adverse events and obstetrical and perinatal outcomes. However, the current findings support the safety of mRNA vaccines regarding pregnancy and delivery complications. In this scenario, it is of paramount importance that governments adopt all the needed strategies to inform this subgroup of the population that the consequences of the disease may be significantly more severe than the potential and unproven consequences of the vaccine, which are causing pregnant women's avoidance. Furthermore, reporting of the acceptance/refusal of the vaccine against SARS-CoV-2 in all obstetrical and delivery settings will help to acquire more data on the safety of it, to be shared as soon as possible.

In conclusion, the probability of small for gestational age and other adverse perinatal outcomes is similar between vaccinated and unvaccinated pregnant women, who did not acquire COVID-19 during pregnancy. Furthermore, the rate of preterm delivery seems reduced among vaccinated pregnant women compared with their counterparts. These data strengthen the safety of the mRNA vaccines during pregnancy and should be used during professional counseling. Further data are needed to explore the impact of multiple doses (included booster) on perinatal outcomes and the difference between trimesters, taking into account the interval from vaccination to delivery.

AUTHOR CONTRIBUTIONS

LC, GS, and GMM contributed to study conception, study design, methods supervision, manuscript preparation, and whole study supervision. MGT contributed to data extraction, data analysis, and manuscript preparation. RDG contributed to study conception, study design, study methods, data extraction, data analysis, and manuscript preparation. AR contributed to study design, data analysis, manuscript preparation, and methods supervision. GGI contributed to study conception, study design, study methods, data analysis, and manuscript preparation. OG contributed to study design, study methods, data analysis, and manuscript preparation. GMM contributed to study conception, study design, methods supervision, manuscript preparation, and whole study supervision. All authors approved of the final of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

CONFLICT OF INTEREST

The authors reports no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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