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Review Article

Updating the impact of mRNA COVID-19 vaccine exposure during pregnancy on obstetric and neonatal outcomes

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ABSTRACT

Being a new vaccine platform, continuous monitoring of the mRNA COVID-19 vaccines in pregnant women is of critical importance. This systematic review and meta-analysis evaluate the maternal and neonatal outcomes associated with mRNA COVID-19 vaccination during pregnancy. We conducted a systematic search of PubMed, Embase, Cochrane Library, and clinical trial registries for studies published between December 2020 and July 2024. Studies were included if they assessed obstetric and neonatal outcomes following mRNA COVID-19 vaccination in pregnant women. Data were extracted and analyzed using a random-effects model to calculate pooled odds ratios (ORs) and 95 % confidence intervals (CIs). Fifteen studies met the inclusion criteria, encompassing 42,944 vaccinated and 183,733 unvaccinated pregnant women. mRNA vaccination was associated with a significant reduction in preterm delivery (OR 0.743, 95 % CI 0.607–0.911), fetal distress (OR 0.699, 95 % CI 0.546–0.893), neonatal congenital abnormalities (OR 0.712, 95 % CI 0.570–0.889), and NICU admissions (OR 0.718, 95 % CI 0.617–0.836). However, a slight increase in gestational diabetes risk was observed (OR 1.107, 95 % CI 1.054–1.162). mRNA COVID-19 vaccines are safe during pregnancy and associated with reduced risks of adverse obstetric and neonatal outcomes. An observed marginal increase in gestational diabetes risk underscores the need for continuous monitoring. These findings support the inclusion of pregnant women in vaccination campaigns and inform public health policies and clinical practices to improve maternal and neonatal health outcomes.

Introduction

The impact of mRNA COVID-19 vaccines on obstetric and neonatal outcomes is complex, necessitating ongoing surveillance to maintain public trust in vaccination during pregnancy. Understanding these effects is crucial for informed clinical decisions and public health policies. Evidence supports the safety and efficacy of COVID-19 vaccines in pregnant women, with positive maternal and neonatal outcomes reported. However, isolating the effects of mRNA vaccines is challenging due to comparisons with other vaccine types and a lack of comprehensive analyses. This study addresses these gaps by providing robust evidence on the safety and efficacy of mRNA COVID-19 vaccines in pregnancy. It exclusively analyzes high-quality studies comparing outcomes in mRNA-vaccinated pregnant women with unvaccinated controls, offering clear estimations of vaccine-attributed effects. Active and long-term surveillance is essential for continued trust and future mRNA vaccine development. Although growing evidence exists on the safety of these vaccines, there remains a critical need for continually updated data to promote vaccine trust and dispel misinformation [1–3].

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Pregnant women and children are typically excluded from routine vaccine clinical trials, making post-market vaccine surveillance a vital tool for assessing post-exposure outcomes and promoting vaccine trust and safety among this group. Preliminary short-term investigations of the BNT162b2 and mRNA-1273 vaccines have been inconclusive, with marginal and non-significant rates of obstetric effects reported on pregnancy and neonatal outcomes. [1,4–7]. This systematic review was conducted following the guides of the Cochrane Collaboration Handbook and PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [8] and using the Joanna Briggs Institute (JBI) methodology for systematic reviews to appraise the selected studies. This study aims to update the available evidence on maternal vaccination against COVID-19 and its impact on obstetric and neonatal outcomes.

Objectives

The primary objectives of this study are:

1. To evaluate the impact of in-utero mRNA COVID-19 vaccine exposure on obstetric outcomes.
2. To assess the neonatal outcomes following maternal mRNA COVID-19 vaccination during pregnancy.

Ethical considerations

The study did not require any ethical clearance application since no patient-related data or personal information were collected. Only peer-reviewed published high-quality data were extracted and used.

Methodology

This systematic review and meta-analysis followed the PRISMA 2020 guidelines (http://www.prisma-statement.org/) comprising of 3 main stages: identification, screening, and inclusion, Fig. 2. [8]. The comprehensive search was conducted across multiple electronic databases, including PubMed, Web of Science, and Scopus. MeSH terms were generated using the PICO framework, focusing on pregnant women, mRNA COVID-19 vaccines, and adverse health events (Fig. 1).

Eligibility criteria

Inclusions (PICO):

- Population (P); pregnant women vaccinated
- Intervention (I); mRNA COVID-19 vaccines
- Comparison group (C); unvaccinated pregnant women
- Outcome (O); general obstetric and neonatal health outcomes
- Published peer-reviewed, English-language studies between November 2019 and December 2023.

Exclusions:

- Studies not on mRNA COVID-19 vaccination during pregnancy.
- Efficacy or mechanistic studies.
- Publications in languages other than English.
- Predictive studies not conducted on humans.
- Studies without negative control groups.

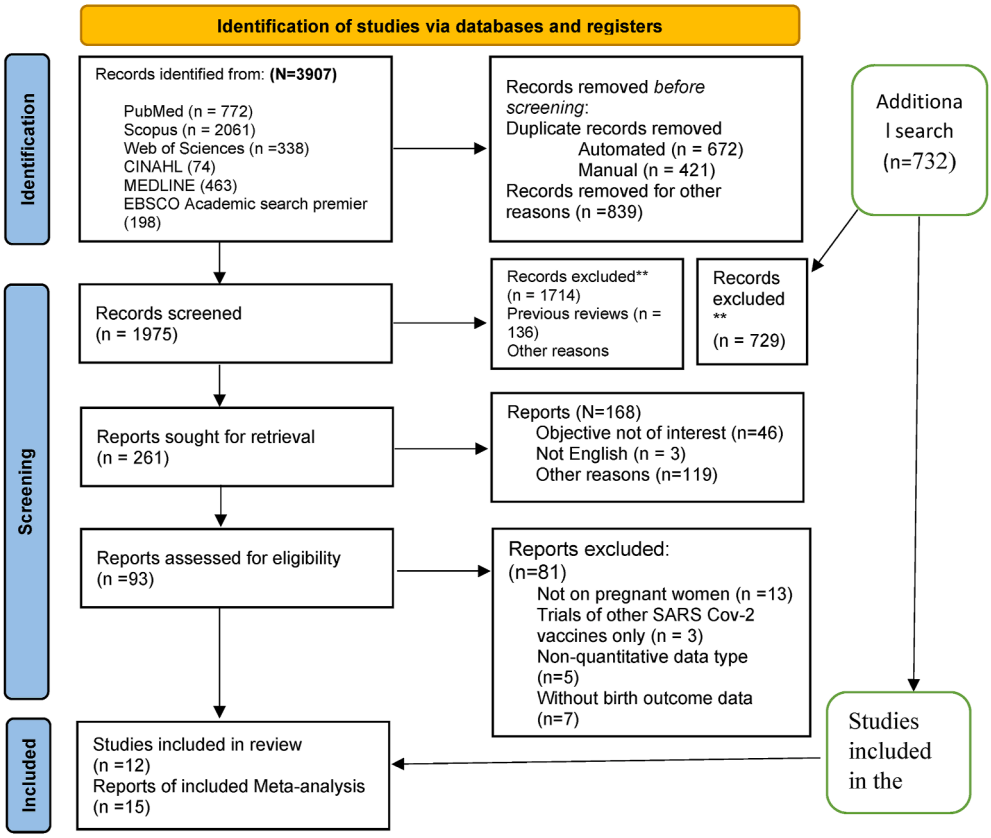


Fig. 1. PRISMA 2020 flowchart for identification and inclusion of articles in the systematic review and meta-analysis.

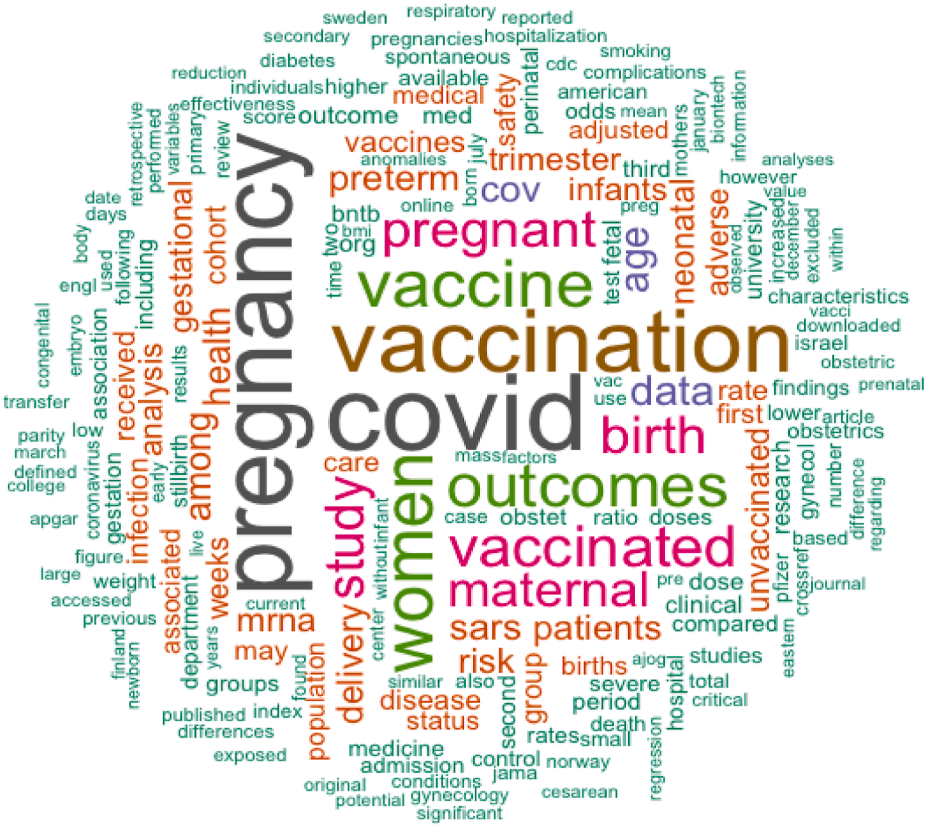


Fig. 2. Word clouds depict the most frequent terms in the selected studies' keywords. Larger fonts indicate higher frequency. "SARS-CoV-2″ and "COVID-19 vaccinations" were most common, followed by "COVID-19 mRNA," "vaccine safety" (notably Pfizer-BioNTech), and "obstetric outcomes."

Search strategy

A systematic search was performed using MeSH terms and Boolean combinations across databases including PubMed, Web of Science, and Scopus. The search strategy was adjusted for other databases as necessary detailed in supplementary file 1.

Search outcome and article selection

From the initial 3907 publications identified, duplicates were removed using RefWorks and manual checks. The remaining articles were screened for relevance, and 261 articles were selected for full-text review. After quality assessment using the JBI critical appraisal tool, 12 studies were included in the quantitative meta-analysis (Fig. 1). Screening process is detailed in supplementary file 2.

To pass the quality assessment, a quality score was agreed not to be less than 75 % using the appropriate study design tool. The JBI assessment was done by two researchers (FAM and OO). Grading conflicts were resolved through further mutual discussions with emphasis on the analytical methods used by the studies. Additional updated search done yielded 3 studies (Fig. 2). The overall number of the included studies are n = 15. In the current study, the Comprehensive Meta-Analysis (CMA) version 3 package was used of the meta-analysis. The main features of the selected studies are presented in Fig. 2 and Table 1.

Studies like 'myocarditis after BNT162b2 vaccination in Israeli adolescents' by Witberg et al. [9], vulvar aphthous ulcer in an adolescent after Pfizer-BioNTech (BNT162b2) COVID-19 vaccination by Wojcicki et al. [10] etc were rejected due to target group inconsistencies to the present study.

Data extraction and quality assessment

Data extraction was performed independently by two reviewers using a standardized data extraction form. Any discrepancies were resolved through discussion or consultation with a third reviewer. The quality of the included studies was assessed using the JBI critical appraisal tool, ensuring a rigorous evaluation of each study's methodology, data analysis, and results reporting.

Statistical analysis and synthesis

Statistical analyses were conducted using the Comprehensive Meta-Analysis (CMA) software. Odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated for each outcome of interest. Heterogeneity among studies was assessed using the I^2 statistic, and a random-effects model was applied to account for variability between studies.

Results

Characteristics of selected studies

The selected studies were conducted across various continents, with the majority being cohort studies. Most identified were conducted in the Middle East/Asia (6) followed by North America (5), lastly Europe (1) and Africa (1). Most studies were cohort studies (14) and a case–control study (1). Other characteristics are

Table 1
Study characteristics.

Study	Country	Design	Period	Vaccine type	Sample Size	Target population	Objective
[11]	Israel	Retrospective Cohort study	Jan –June2021	Pfizer BNT162b2 mRNA	4339	Postpartum women (Delivered between Jan and June 2021	To study the association between prenatal Pfizer-BioNTech COVID-19 vaccination, pregnancy course and outcomes.
[12]	Israel	Retrospective Cohort Study (Medical Centre)	Feb2021–July2021	Pfizer /BioNTech BNT162b2 mRNA	1894	Pregnant women	To compare adverse perinatal outcomes among (COVID-19–vaccinated and unvaccinated pregnant women
[13]	Israel	Population based Cohort Study	Mar2021–Oct2021	Pfizer-BioNTech (BN162b2)	24,288	Pregnant women	To examine whether BNT162b2 mRNA vaccination during pregnancy is associated with adverse neonatal and early infant outcomes among the newborns
[14]	Israel	Retrospective Cohort study	Mar–July2022	Pfizer-BioNTech BN162b2 mRNA vaccine	3700	Pregnant women	To compare obstetric and neonatal outcomes between vaccinated and non-vaccinated pregnant women with singleton pregnancies
[15]	Romania	Retrospective Cohort study	Jan2020– Jan2021	Pfizer BNT162b2 mRNA Moderna mRNA-1273	3094	Pregnancies (927) Spontaneous abortions (124)	To determine whether pregnant women vaccinated with an mRNA-type vaccine during the first trimester have higher risks of spontaneous abortion.
[16]	Australia	Retrospective multicenter cohort study	July 1, 2021 to March 31, 2022.	Pfizer-BioNTech BNT162b2 mRNA. Moderna mRNA; Janssen Ad26.COV2. S.; Oxford -AstraZeneca	32,536	Vaccinated and unvaccinated women for whom weeks 20–43 of gestation fell entirely within the 9-month data collection period	Aimed to measure the rate of COVID-19 vaccine uptake among women giving birth in Melbourne, Australia, and to compare perinatal outcomes by vaccination status.
[17]	Sweden & Norway	Registry based retrospective Study	Jan2021- Jan2022	mRNA Vaccines, Vector vaccines (BTN162b2, mRNA1273 & AZD1222)	157521 (Norway: 54112) (Sweden: 103409)	Pregnant women	To examine the risk of adverse pregnancy outcomes after vaccination against SARS-CoV-2 during pregnancy
[18]	United States	Retrospective cohort study	January 1, 2021, and December 31, 2021	Pfizer BNT162b2 mRNA & mRNA-1273	15,865	Vaccinated and unvaccinated pregnant patients	To compare frequency of perinatal death between pregnant patients who completed mRNA COVID-19 vaccination series and unvaccinated patients.
[19]	United States	Retrospective cohort study	Feb–Sept. 2021	Moderna & Pfizer BioNTech mRNA vaccines	1205	Vaccinated and non-vaccinated – hyper ovarian regnant women with hyperstimulation cycles	To assess whether COVID-19 mRNA vaccination is associated with controlled ovarian hyperstimulation or early pregnancy outcomes.
[20]	Israel	Retrospective cohort study	January and April 2021	(Pfizer–BioNTech BNT162b2	1775	Pregnant women	To evaluate the impact of Covid-19 vaccination (Pfizer–BioNTech BNT162b2) during the third trimester of pregnancy on maternal and neonatal outcomes
[21]	USA	Retrospective cohort study	May 17– October 24, 2020, and December 15, 2020–July 22, 2021	COVID-19 vaccine during pregnancy	46,079	Pregnant women	To evaluate risks for preterm birth (<37 weeks' gestation) and small-for-gestational-age (SGA) at birth (birthweight <10th percentile for gestational age) after COVID-19 vaccination (receipt of ≥1 COVID-19 vaccine doses) during pregnancy.
[22]	Israel	Retrospective cohort study	December 2020 and July 2021	Pfizer BioNTech (BNT162b2) or Moderna vaccines.	5618	Pregnant women	To examine the association between SARS-CoV-2 vaccination during pregnancy and maternal and neonatal outcomes in a large cohort study. Furthermore, to evaluate if the timing of vaccination during pregnancy is related to adverse outcomes.

[23]	USA	Retrospective delivery cohort	December 10, 2020, and April 19, 2021,	mRNA vaccine,	2002	pregnant patients.	To assess the safety and efficacy of COVID-19 vaccines in pregnant patients.
[24]	USA	Case-control test-negative design	July 1, 2021, and March 8, 2022	mRNA vaccine	1049	Infants younger than 6 months of age.	To assess the effectiveness of maternal vaccination during pregnancy against hospitalization for Covid-19 among infants younger than 6 months of age.
[25]	Tunisia	Retrospective cohort study	January 2021 to May 2022	mRNA vaccine	145	Parturients tested positive for COVID-19 during pregnancy and who needed hospitalization at any stage of gestation.	To assess the impact and effectiveness of vaccination among the pregnant population on maternal, obstetrical, and foetal outcomes.

detailed in Table 1. A summary of the characteristics is presented in Table 1 and Fig. 3.

Narrative results (systematic review)

The study examines the impact of COVID-19 vaccination during pregnancy on various obstetric and neonatal outcomes, with mixed findings reported across different studies.

Fetal Outcomes: Kugelman et al. and Rottenstreich et al. found no effect on intra-uterine fetal deaths. Hui et al. reported a significant protective effect against stillbirth (OR 0.18, CI 0.09–0.37), while Jarraya et al. found no significant effect. For intra-uterine growth retardation (IUGR), Hui et al. observed no significant impact, whereas Jarraya et al. reported a protective effect (OR 0.129, CI 0.029–0.581). [12,20,25,16]

Meconium-Stained Amniotic Fluid and Fetal Distress: Peretz-Machluv et al. and Wainstock et al. noted a significant association with meconium-stained amniotic fluid, while Jarraya et al. and Rottenstreich et al. did not. Jarraya et al. found no significant effects on fetal distress [11,14,20,25].

Preterm Birth: Results varied, with Jarraya et al., Hui et al., and Morgan et al. indicating a protective effect, while others, including Goldshtein et al., Kugelman et al., Peretz-Machluf et al., and Lipkind et al., showed no significant effect [11–14,16,18,20,21,25].

Pathological Complications: Wainstock et al. found no significant effect on pathological presentation, whereas Rottenstreich et al. reported an association with non-vertex presentation. Citu et al. found no significant effects on pregnancy-related complications. Mixed results were noted for gestational hypertension and diabetes [11,14,20].

Delivery Methods: Among eight studies on caesarean deliveries, results were mixed. Studies on vacuum delivery also showed mixed outcomes. Two studies on placental abruption found no significant effect.

Maternal Outcomes: Few studies assessed maternal outcomes, showing no differences in postpartum hemorrhage or fever between vaccinated and unvaccinated patients [15].

Neonatal Outcomes: Most studies reported no significant effect on outcomes like the 5-min Apgar score, congenital abnormalities, small for gestational age, neonatal complications, respiratory complications, low birth weight, birth weight $\geq$4000 g, neonatal hospitalization, and ICU hospitalization. Some studies suggested potential protective effects against congenital abnormalities and neonatal complications [11–14,16,17,20,22].

Trimester-Specific Outcomes: The review included trimester-specific data on preterm birth and small for gestational age (SGA), showing mixed results across studies [13,14,18,20,22,23,25].

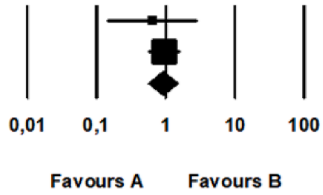
Meta-analysis

Maternal outcomes

The meta-analysis shows that mRNA COVID-19 vaccines significantly reduce the risk of preterm delivery (OR 0.743, 95 % CI 0.607–0.911, p = 0.004) and fetal distress (OR 0.699, 95 % CI 0.546–0.893, p = 0.004). There is also a significant association with gestational diabetes (OR 1.107, 95 % CI 1.054–1.162, p = 0.001). No significant associations were found for intrauterine fetal death (OR 0.556, 95 % CI 0.252–1.224, p = 0.145), intrauterine growth restriction (OR 0.727, 95 % CI 0.392–1.346, p = 0.310), placental abruption (OR 0.595, 95 % CI 0.294–1.204, p = 0.149), maternal postpartum fever (OR 0.911, 95 % CI 0.551–1.505, p = 0.716), maternal postpartum hemorrhage (OR 0.969, 95 % CI 0.821–1.142, p = 0.706), non-vertex presentation (OR 2.262, 95 % CI 0.408–12.535, p = 0.350), gestational hypertension (OR 1.092, 95 % CI 0.809–1.372, p = 0.449), vacuum delivery (OR 0.743, 95 % CI

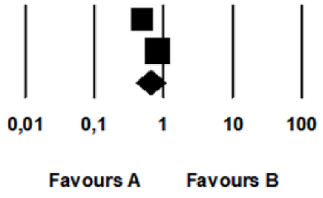
A

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Wainstock et al.	0,640	0,142	2,888	-0,581	0,562
Rottenstrich et al.	0,952	0,559	1,621	-0,181	0,856
	0,911	0,551	1,505	-0,364	0,716



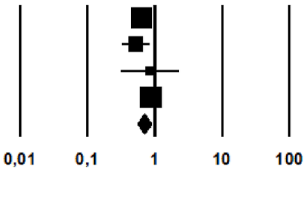
B

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Dick et al.	0,490	0,339	0,708	-3,798	0,000
Lipkind et al.	0,820	0,718	0,937	-2,918	0,004
	0,653	0,396	1,078	-1,666	0,096



C

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Peretz-Machluv et al.	0,630	0,484	0,820	-3,437	0,001
Wainstock et al.	0,520	0,323	0,837	-2,689	0,007
Jarraya et al.	0,836	0,313	2,232	-0,358	0,721
Rottenstreich et al.	0,876	0,672	1,142	-0,979	0,328
	0,699	0,546	0,893	-2,858	0,004



D

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Kugelman et al.	0,690	0,115	4,140	-0,406	0,685
Jarraya et al.	0,942	0,173	5,124	-0,069	0,945
Hui et al.	0,190	0,099	0,365	-4,976	0,000
Rottenstreich et al.	1,496	0,432	5,184	0,635	0,525
Dick et al.	0,870	0,498	1,520	-0,489	0,625
Morgan et al.	0,130	0,018	0,915	-2,050	0,040
Theiler et al.	1,033	0,058	18,399	0,022	0,982
	0,556	0,252	1,224	-1,458	0,145

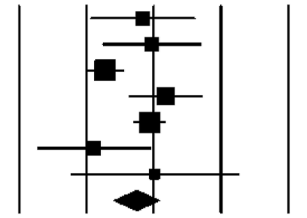


Fig. 3. A. Pooled association of maternal mRNA Covid-19 vaccine exposure and second trimester preterm delivery, B. Pooled association of maternal mRNA Covid-19 vaccine exposure and third trimester preterm delivery. C. Pooled association of maternal mRNA Covid-19 vaccine exposure and fetal distress, D. Pooled association of maternal mRNA Covid-19 vaccine exposure and intra-uterine fetal death. E. Pooled association of maternal mRNA Covid-19 vaccine exposure and intra-uterine fetal growth restrictions, F. Pooled association of maternal mRNA Covid-19 vaccine exposure and placental abruption. G. Pooled association of maternal mRNA Covid-19 vaccine exposure and gestational diabetes, H. Pooled association of maternal mRNA Covid-19 vaccine exposure and gestational hypertension. I. Pooled association of maternal mRNA Covid-19 vaccine exposure and maternal postpartum fever, J. Pooled association of maternal mRNA Covid-19 vaccine exposure and maternal postpartum haemorrhage. K. Pooled association of maternal mRNA Covid-19 vaccine exposure and non-vertex presentations, L. Pooled association of maternal mRNA Covid-19 vaccine exposure and preterm delivery. M. Pooled association of maternal mRNA Covid-19 vaccine exposure and vacuum delivery, N. Pooled association of maternal mRNA Covid-19 vaccine exposure and caesarean delivery.

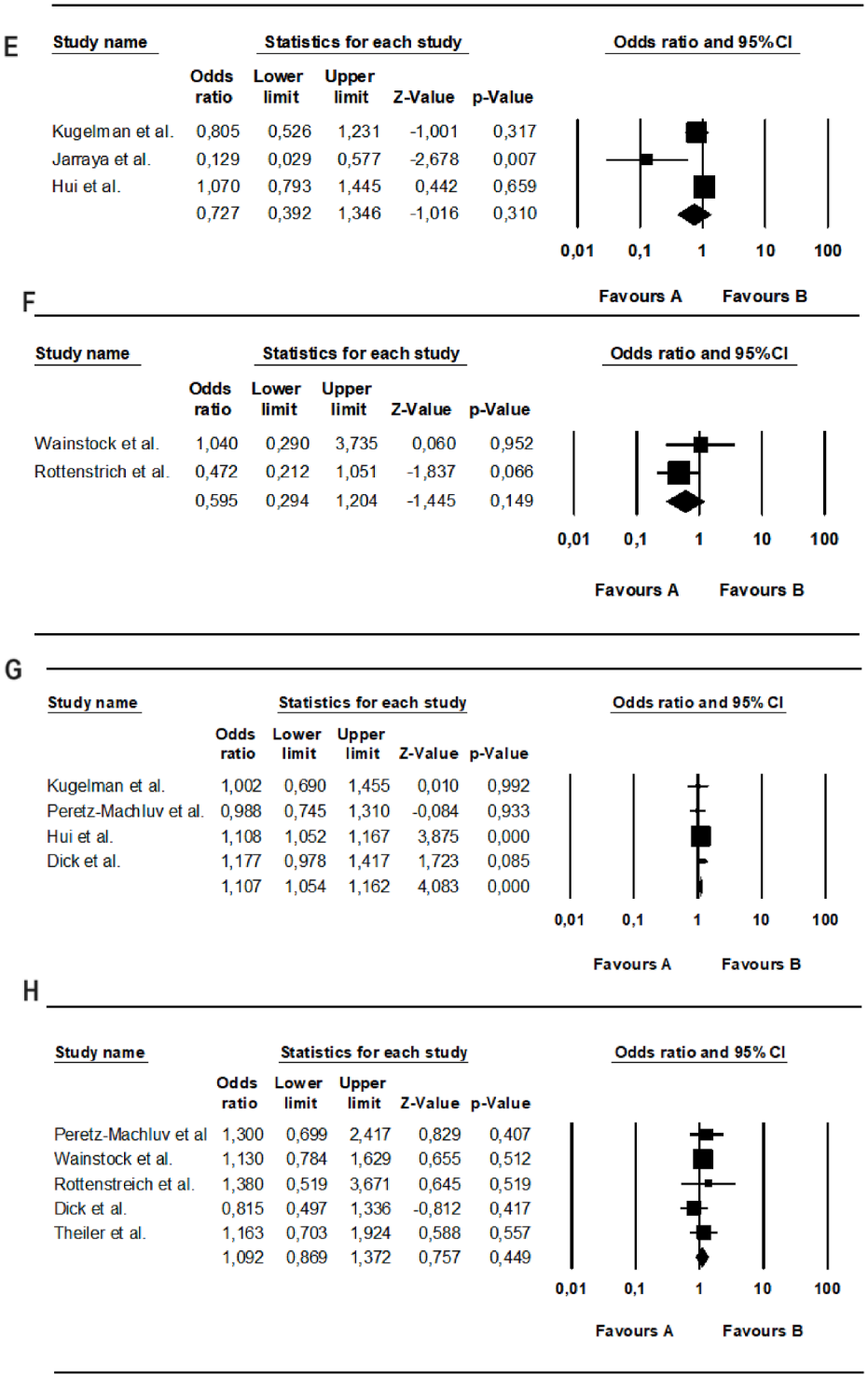


Fig. 3. (*continued*).

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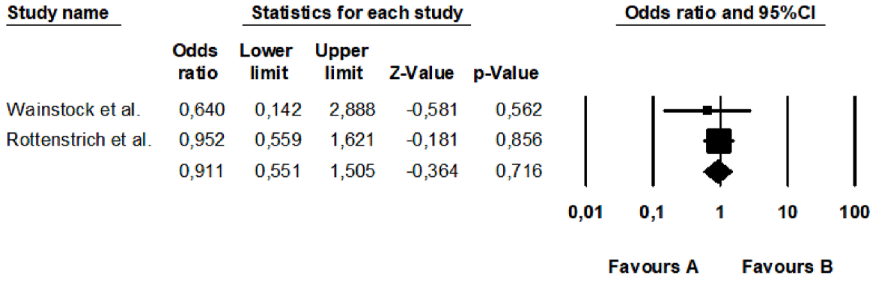

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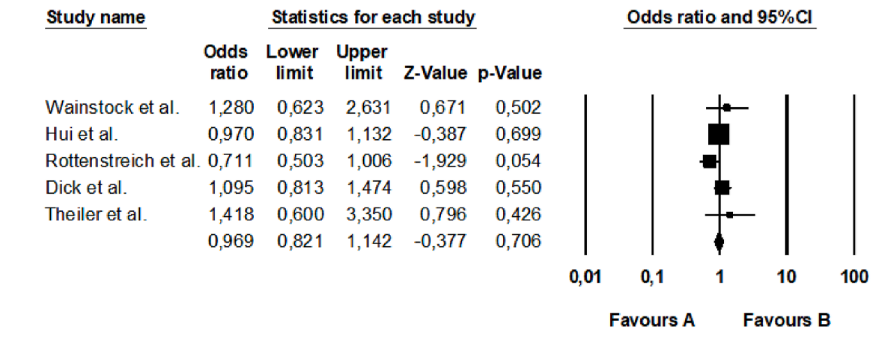

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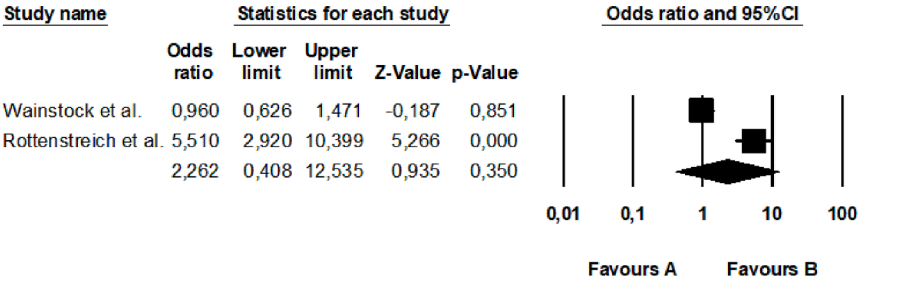

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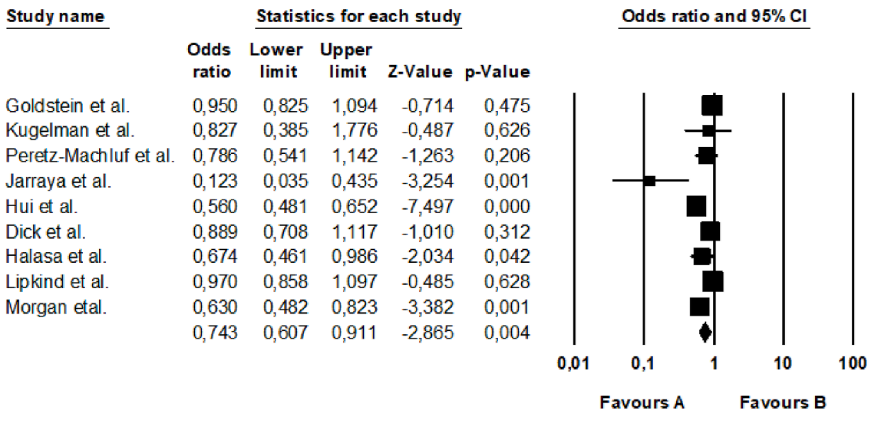

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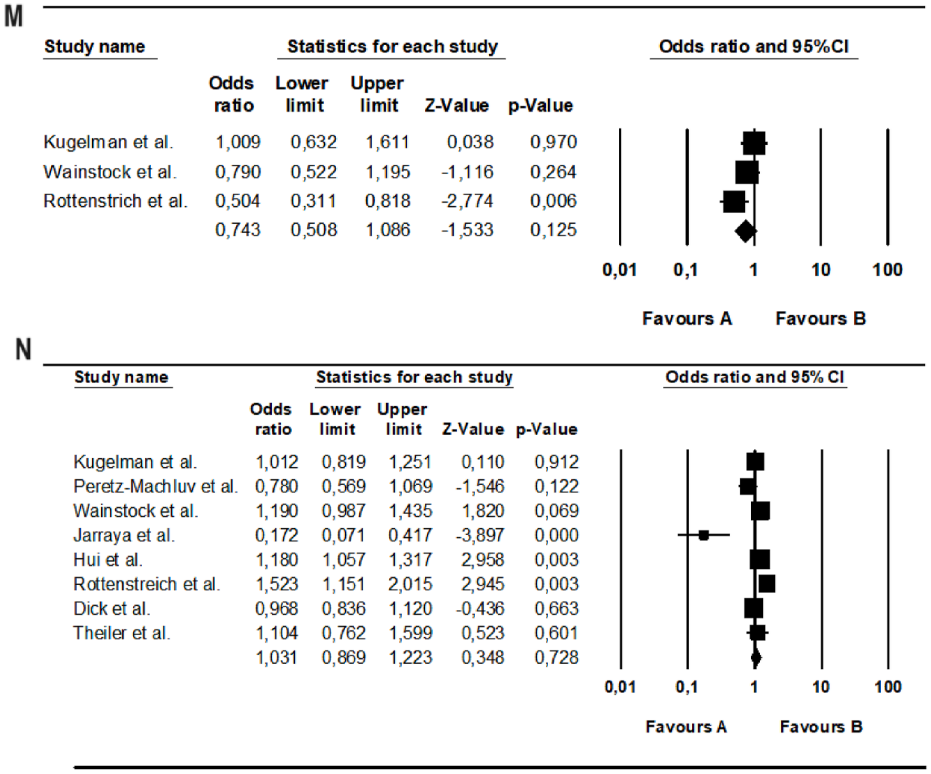

Fig. 3. (*continued*).

0.508–1.086, p = 0.125), and caesarean delivery (OR 1.031, 95 % CI 0.869–1.223, p = 0.728). Fig. 3A–N presents the forest plots for these outcomes. This comprehensive analysis highlights the benefits and risks associated with mRNA COVID-19 vaccination during pregnancy, providing valuable insights for healthcare providers and policymakers.

Meta analysis for the neonatal outcomes

The meta-analysis indicates that maternal mRNA COVID-19 vaccination significantly reduces the risk of congenital abnormalities (OR 0.712, 95 % CI 0.570–0.889, p = 0.003), NICU hospitalization (OR 0.718, 95 % CI 0.617–0.836, p = 0.000), and preterm delivery (OR 0.743, 95 % CI 0.607–0.911, p = 0.004). Marginal but non-significant reductions were observed for third-trimester small for gestational age (SGA) (OR 0.922, 95 % CI 0.846–1.006, p = 0.068). No significant associations were found for other adverse neonatal outcomes, including 5-min Apgar score (OR 0.805, 95 % CI 0.629–1.030, p = 0.085), newborn respiratory complications (OR 0.717, 95 % CI 0.460–1.118, p = 0.142), all-cause neonatal complications (OR 0.718, 95 % CI 0.617–1.100, p = 0.277), and overall SGA (OR 0.979, 95 % CI 0.917–1.044, p = 0.510). Fig. 4A–J presents the forest plots for these outcomes.

General discussions

The systematic review and meta-analysis aimed to investigate the impact of prenatal mRNA COVID-19 vaccine exposure on obstetric and neonatal outcomes. The analysis encompassed a comprehensive evaluation of various outcomes across 15 studies (Table 1, Fig. 1). The findings from our analysis (Figs. 3A-4J) have suggested that receiving the mRNA COVID-19 vaccine during pregnancy does not seem to increase the likelihood of experiencing adverse outcomes for both the mother and the newborn except for potential association with gestational diabetes (Fig. 3G). However, potential added benefit in the form of reductions in certain adverse maternal and neonatal outcomes were observed which outweighs the risk.

From the analysis, a potential protective effect of prenatal mRNA COVID-19 vaccine exposure against fetal distress with 30 % reduction (Fig. 3C), fetal congenital abnormalities with 28 % reduction (Fig. 4D), NICU hospitalizations with 28 % reduction (Fig. 4H) and preterm birth with 25 % reduction (Fig. 4I) was observed, which was evidenced by the significant reduction of odds in the meta-analysis (Figs. 3C, 4D and 4H, 4I). In addition, it was also demonstrated that other neonatal adverse outcomes such as intrauterine fetal death, and intrauterine fetal growth restriction were not significantly associated with prenatal mRNA COVID-19 vaccine. An increased risk of gestational diabetes was found to be associated with mRNA COVID-19 vaccine in pregnancy. Other adverse maternal and neonatal outcomes such as placental abruption, gestational hypertension, maternal post-partum fever, maternal post-partum hemorrhage, non-vertex presentation, vacuum delivery, caesarean delivery, 5-min APGA, low birth weight, newborn respiratory complications, all-cause neonatal complications and full-term small for gestational age (SGA) were not found to be associated with exposure to *prenatal* mRNA COVID-19 vaccine. These observations did not significantly change in a sensitivity analysis using fixed effect model for outcomes with tau square statistics less than 25 % (supplementary 3, not included in the main text).

The decline in preterm births may stem from preventing complications that are linked to infection with COVID-19, such as severe maternal respiratory issues or pre-eclampsia/eclampsia. This decrease could also be attributed to systemic inflammation avoidance which is associated with infection by COVID-19 or different general immune response [16]. During pregnancy, maternal SARS-CoV-2 infection has been linked to immune activation in the maternal and fetal compartments that can lead to

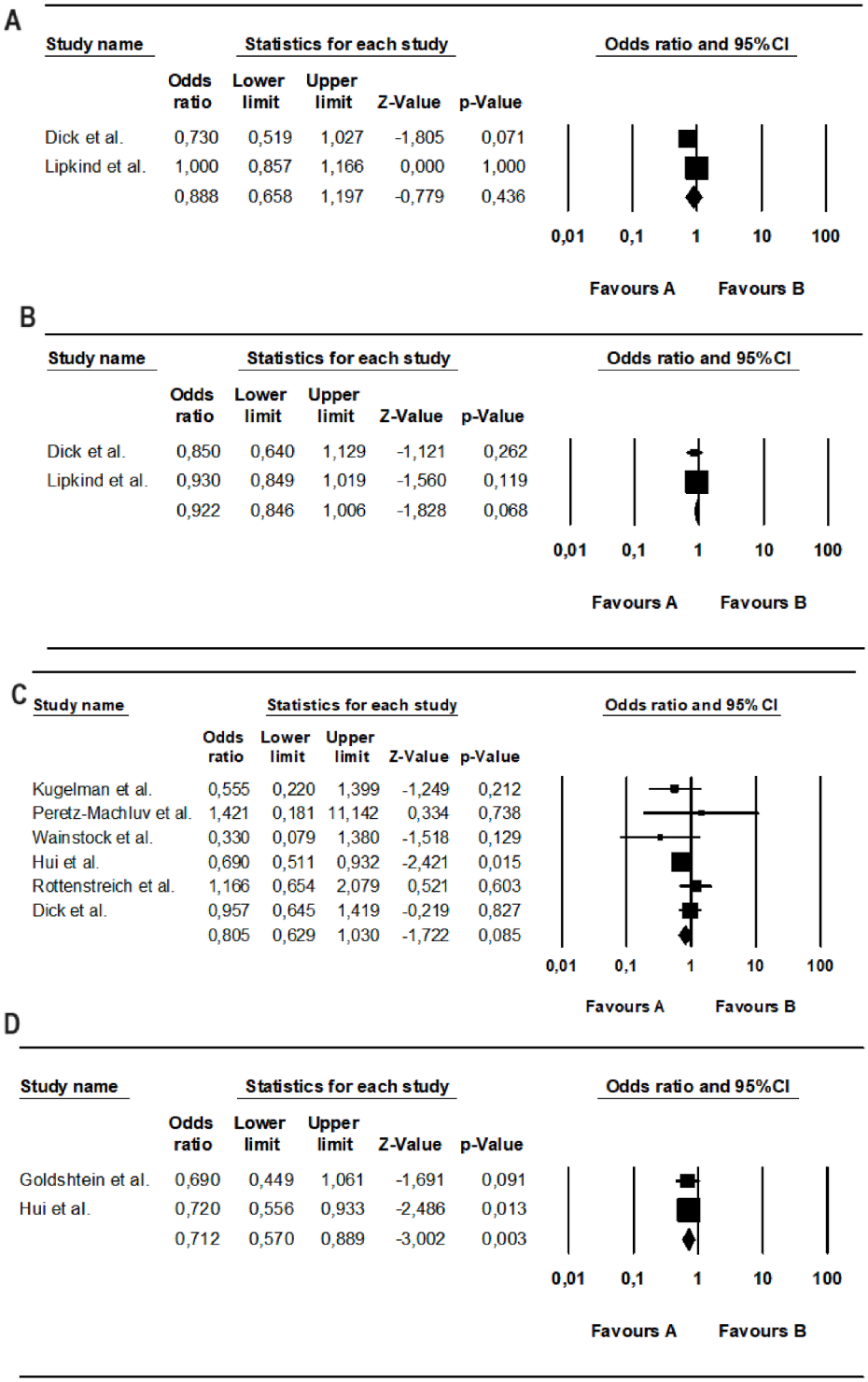

Fig. 4. A. Pooled association of maternal mRNA Covid-19 vaccine exposure and 2nd trimester SGA, B. Pooled association of maternal mRNA Covid-19 vaccine exposure and 3rd Trimester SGA. C. Pooled association of maternal mRNA Covid-19 vaccine exposure and 5-min APGA, D. Pooled association of maternal mRNA Covid-19 vaccine exposure and congenital abnormalities. E. Pooled association of maternal mRNA Covid-19 vaccine exposure and low birthweight, F. Pooled association of maternal mRNA Covid-19 vaccine exposure and newborn respiratory complications. G. Pooled association of maternal mRNA Covid-19 vaccine exposure and all-cause neonatal complications, H. Pooled association of maternal mRNA Covid-19 vaccine exposure and neonatal intensive care unit admission (NICU). I. Pooled association of maternal mRNA Covid-19 vaccine exposure and preterm delivery, J. Pooled association of maternal mRNA Covid-19 vaccine exposure and Small for gestational age (SGA).

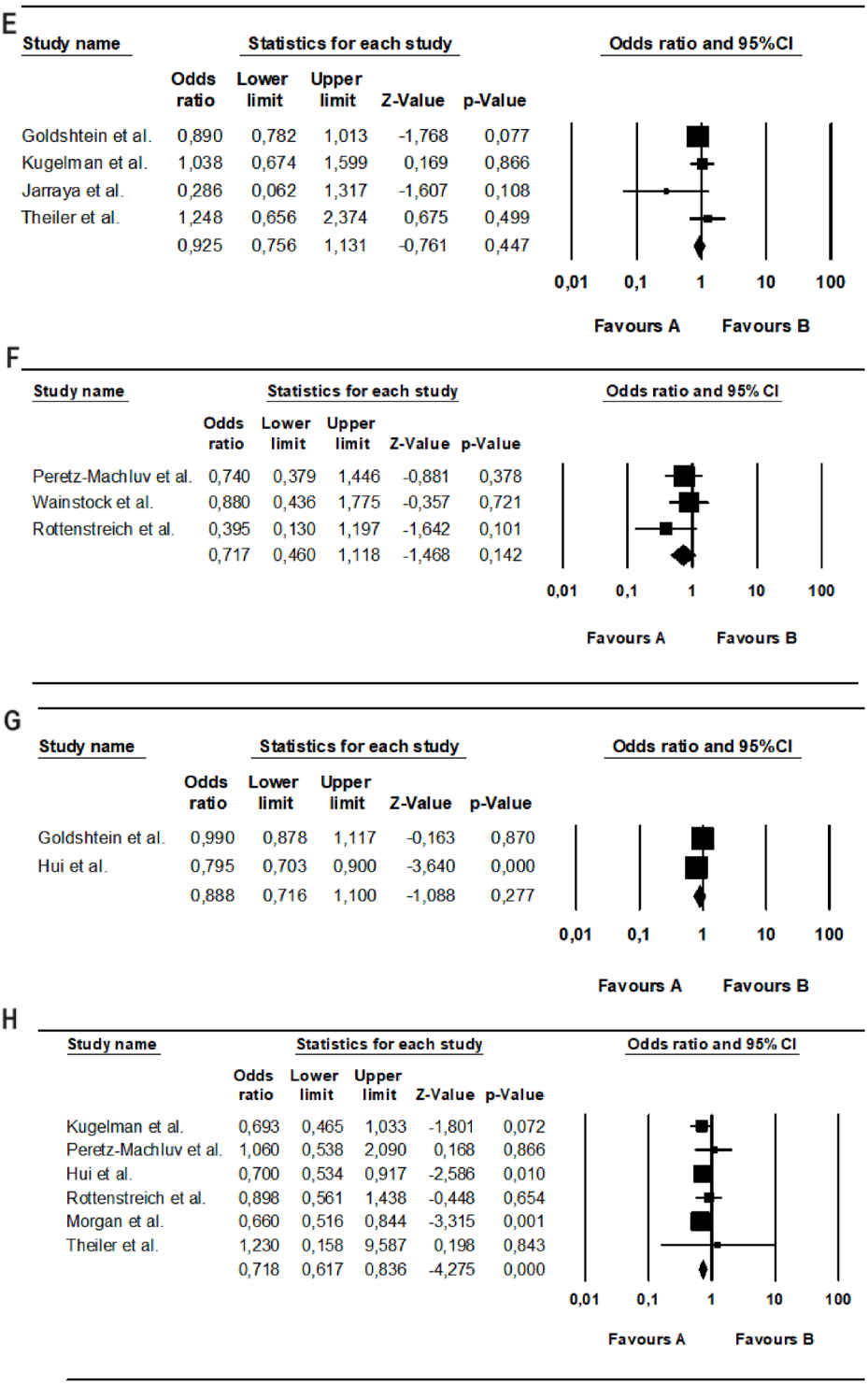

Fig. 4. (*continued*).

adverse fetal outcomes. Vaccination aims to decrease this immune activation and thus reduce adverse perinatal outcome [25–27]. COVID-19 vaccines are found to be linked to a decreased chance of maternal COVID-19 infection/severity from infection. Induction of comparable immune response in pregnant women was found with the two doses of mRNA COVID-19 vaccine which is associated with transmissions of antibodies to the newborn [28,29]. By activating the innate immune response, antibodies play a role in protecting

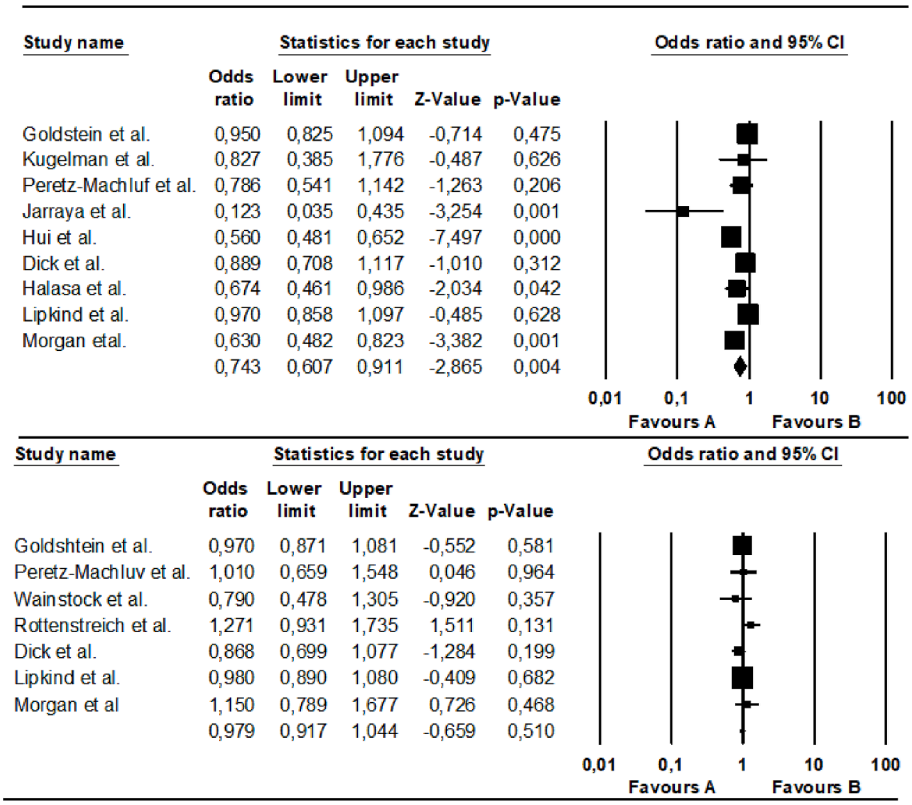

Fig. 4. (*continued*).

the mother and the fetus against COVID-19 infection through the Fc-domain [30]. Previous review studies showed the association between any type of COVID-19 vaccination exposure including mRNA COVID-19 vaccine in pregnancy and peripartum outcomes but they did not find any significant protective effect on preterm birth [31].

Based on our analysis, we have robust evidence to support the safety of prenatal mRNA COVID-19 vaccine and advocate for its advantages in reducing the occurrence of preterm birth and fetal distress. It was found that individuals who received the mRNA vaccine showed a significantly reduced likelihood of having meconium-stained amniotic fluid, indicating a protective influence of the vaccine against this event. As an indicator of fetal distress, meconium-stained amniotic fluid is recognized [14,32].

An increased risk of gestational diabetes is found with the mRNA COVID-19 vaccine exposure. Our investigation of previous studies did not reveal a direct link between the mRNA COVID-19 vaccine and gestational diabetes. However, we observed mRNA vaccine-associated hyperglycemia, with several suggested mechanisms to explain the phenomena in some studies. The natural immune response of the body to viral infections can facilitate beta cell destruction in the pancreas which is linked to abnormal glucose metabolism [33,34]. MDA5(melanoma differentiation-associated protein 5), a protein to recognize pathogens, plays a significant role in controlling the initial immune response of the body to SARS-CoV-2 infection [35]. It is suggested that MDA5 detects RNA from mRNA COVID-19 vaccine which can stimulate type 1 interferon production that can hamper the insulin production, conversion of proinsulin, and the function of mitochondria taking place in beta cells of the pancreas [36]. This can cause dysregulation of effective blood sugar levels in the body and lead to hyperglycemia, but further studies are warranted to get specific molecular mechanisms.

Neonatal intensive care admission could stem from multiple sources of congenital abnormalities, neonatal infection, stressful labor, etc. The observed decrease in neonatal abnormalities in due to maternal vaccination partly justifies the subsequent reduction in the observed neonatal intensive care admissions among the vaccinated mothers. This observation is in sync with other studies [37].

Our study provided a comprehensive overview of COVID-19 acceptance and hesitancy among pregnant women throughout the world. Some studies reported a positive trend with high acceptance and low hesitancy rates, while some others revealed mixed results with similar acceptance and hesitancy rates. On the other hand, several studies from different areas of the world including Asia, Europe, and North America pointed out low acceptance and high hesitancy rates. This highlights the significance of targeted educational efforts and information access so that vaccine hesitancy can be addressed, and vaccination uptake can be promoted in this demographic.

The uptake of vaccine among pregnant women is on the rise but still low, with only a minor portion being fully vaccinated when it is time to deliver. Pregnant mothers usually hesitate to try something unfamiliar or new during pregnancy because of their concerns about the potential harm to their offspring. It is crucial to address the low vaccination rates among pregnant individuals to safeguard the health of both mother and offspring [38,39].

Strength: Our updated search strategy reviewed over 3900 records, including all high-quality studies assessed by the JBI critical appraisal tool. We used meta-analysis techniques to provide precise estimates of mRNA COVID-19 exposure's impact on pregnancy and neonatal outcomes, aiding decision-making for pregnant individuals and healthcare professionals.

Limitations: The studies were limited to a few countries, affecting geographical generalizability. Excluding some high-

quality studies without comparison groups may have missed important insights. Further studies are recommended to validate the results.

Clinical and Policy Implications: The findings offer robust evidence for healthcare providers to support the safety and benefits of mRNA COVID-19 vaccines during pregnancy, aiding in counseling and addressing vaccine safety concerns. Public health agencies can use this evidence to develop policies promoting maternal vaccination and addressing vaccine hesitancy.

Conclusion: This systematic review and meta-analysis provide robust evidence that mRNA COVID-19 vaccines are safe during pregnancy, reducing preterm delivery, fetal distress, congenital abnormalities, and NICU admission. However, the association with gestational diabetes requires vigilant post-vaccine surveillance and further research. The findings inform public health policy, guide clinical practices, and shape future vaccine development strategies.

Data availability

Supplementary data is attached.

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Declaration of competing interest

The researchers have no conflicting interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2025.07.022.

References

[1] Ellington S, Olson CK. Safety of mRNA COVID-19 vaccines during pregnancy. Lancet Infect Dis 2022;22(11):1514–5. https://doi.org/10.1016/S1473-3099(22)00443-1.
[2] Joudeh AI, Lutf AQ, Mahdi S, Tran G. Efficacy and safety of mRNA and AstraZeneca COVID-19 vaccines in patients with autoimmune rheumatic diseases: a systematic review. Vaccine 2023;41(26):3801–12. https://doi.org/10.1016/j.vaccine.2023.05.048.
[3] Sharif N, Alzahrani KJ, Ahmed SN, Dey SK. Efficacy, immunogenicity and safety of COVID-19 vaccines: a systematic review and meta-analysis. Front Immunol 2021;12:714170. https://doi.org/10.3389/fimmu.2021.714170.
[4] Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, et al. Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 vaccine pregnancy registry 2020–21. Res Square 2021. Preprint, https://doi.org/10.21203/rs.3.rs-798175/v1.
[5] Cirillo N, Doan R. The association between COVID-19 vaccination and Bell's palsy. Lancet Infect Dis 2022;22(1):5–6. https://doi.org/10.1016/S1473-3099(21)00467-9.
[6] Shahsavarinia K, Mahmoodpoor A, Sadeghi-Ghyassi F, Nedayi A, Razzaghi A, Zehi Saadat M, et al. Bell's palsy and COVID-19 vaccination: a systematic review. Med J Islam Repub Iran 2022;36:85. https://doi.org/10.47176/mjiri.36.85.
[7] Wan EYF, Chui CSL, Lai FTT, Chan EWY, Li X, Yan VKC, et al. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. Lancet Infect Dis 2022;22(1):64–72. https://doi.org/10.1016/S1473-3099(21)00451-5.
[8] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
[9] Witberg G, Magen O, Hoss S, Talmor-Barkan Y, Richter I, Wiessman M, et al. Myocarditis after BNT162b2 vaccination in Israeli adolescents. N Engl J Med 2022:NEJMc2207270. https://doi.org/10.1056/NEJMc2207270. Published online October 19.
[10] Wojcicki AV, O'Flynn O'Brien KL. Vulvar aphthous ulcer in an adolescent after Pfizer-BioNTech (BNT162b2) COVID-19 vaccination. J Pediatr Adolesc Gynecol 2022;35(2):167–70. https://doi.org/10.1016/j.jpag.2021.10.005.
[11] Wainstock T, Yoles I, Sergienko R, Sheiner E. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. Vaccine 2021;39(41):6037–40. https://doi.org/10.1016/j.vaccine.2021.09.012.
[12] Kugelman N, Riskin A, Kedar R, Riskin-Mashiah S. Safety of COVID-19 vaccination in pregnant women: a study of the adverse perinatal outcomes. Int J Gynaecol Obstet 2023;161(1):298–302. https://doi.org/10.1002/ijgo.14599.
[13] Goldshtein I, Steinberg DM, Kuint J, Chodick G, Segal Y, Shapiro Ben David S, et al. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes. JAMA Pediatr 2022;176(5):470–7. https://doi.org/10.1001/jamapediatrics.2022.0001.
[14] Peretz-Machluf R, Hirsh-Yechezkel G, Zaslavsky-Paltiel I, Farhi A, Avisar N, Lerner-Geva L, et al. Obstetric and neonatal outcomes following COVID-19 vaccination in pregnancy. J Clin Med 2022;11(9):2540. https://doi.org/10.3390/jcm11092540.
[15] Citu IM, Citu C, Gorun F, Sas I, Bratosin F, Motoc A, et al. The risk of spontaneous abortion does not increase following first trimester mRNA COVID-19 vaccination. J Clin Med 2022;11(6):1698. https://doi.org/10.3390/jcm11061698.
[16] Hui L, Marzan MB, Rolnik DL, Potenza S, Pritchard N, Said JM, et al. Reductions in stillbirths and preterm birth in COVID-19-vaccinated women: a multicenter cohort study of vaccination uptake and perinatal outcomes. Am J Obstet Gynecol 2023;228(5):585.e1–585.e16. https://doi.org/10.1016/j.ajog.2022.10.040.
[17] Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, et al. Association of SARS-CoV-2 vaccination during pregnancy with pregnancy outcomes. JAMA 2022;327(15):1469–77. https://doi.org/10.1001/jama.2022.3271.
[18] Morgan JA, Biggio JR, Martin JK, Mussarat N, Elmayan A, Chawla HK, et al. Pregnancy outcomes in patients after completion of the mRNA coronavirus disease 2019 (COVID-19) vaccination series compared with unvaccinated patients. Obstet Gynecol 2023;141(3):555–62. https://doi.org/10.1097/AOG.0000000000005072.
[19] Aharon D, Lederman M, Ghofranian A, Hernandez-Nieto C, Canon C, Hanley W, et al. In vitro fertilization and early pregnancy outcomes after coronavirus disease 2019 (COVID-19) vaccination. Obstet Gynecol 2022;139(4):490–7. https://doi.org/10.1097/AOG.0000000000004713.
[20] Rottenstreich M, Sela HY, Rotem R, Kadish E, Wiener-Well Y, Grisaru-Granovsky S. Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. BJOG 2022;129(2):248–55. https://doi.org/10.1111/1471-0528.16941.
[21] Lipkind HS, Vazquez-Benitez G, DeSilva M, Vesco KK, Ackerman-Banks C, Zhu J, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth - eight integrated health care organizations, United States, December 15, 2020-July 22, 2021. MMWR Morb Mortal Wkly Rep 2022;71(1):26–30. https://doi.org/10.15585/mmwr.mm7101e1.
[22] Dick A, Rosenbloom JI, Gutman-Ido E, Lessans N, Cahen-Peretz A, Chill HH. Safety of SARS-CoV-2 vaccination during pregnancy- obstetric outcomes from a large cohort study. BMC Pregnancy Childbirth 2022;22(1):166. https://doi.org/10.1186/s12884-022-04505-5.
[23] Theiler RN, Wick M, Mehta R, Weaver AL, Virk A, Swift M. Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. Am J Obstet Gynecol MFM 2021;3(6):100467. https://doi.org/10.1016/j.ajogmf.2021.100467.
[24] Maternal vaccination and risk of hospitalization for Covid-19 among infants - PubMed. Accessed December 7, 2024. https://pubmed.ncbi.nlm.nih.gov/35731908/.
[25] Jarraya A, Kammoun M, Amouri S, Elleuch S, Khanfir F, Chaabene K, et al. Impact of COVID-19 vaccination among pregnant women requiring hospital admission: prospective observational research. Ital J Gynaecol Obstet 2023. https://doi.org/10.36129/jog.2022.53. Published online June 1.
[26] WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol 2021;57(2):232–41. https://doi.org/10.1002/uog.23107.
[27] Di Mascio D, Sen C, Saccone G, Galindo A, Grünebaum A, Yoshimatsu J, et al. Risk factors associated with adverse fetal outcomes in pregnancies affected by coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19. J Perinat Med 2020;49(1):111–5. https://doi.org/10.1515/jpm-2020-0539.
[28] Atyeo C, DeRiso EA, Davis C, Bordt EA, De Guzman RM, Shook LL, et al. COVID-19 mRNA vaccines drive differential antibody Fc-functional profiles in

pregnant, lactating, and nonpregnant women. Sci Transl Med 2021;13(617): eabi8631. https://doi.org/10.1126/scitranslmed.abi8631.
[29] Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol 2021;225(3):303.e1–303.e17. https://doi.org/10.1016/j.ajog.2021.03.023.
[30] Schäfer A, Muecksch F, Lorenzi JCC, Leist SR, Cipolla M, Bournazos S, et al. Antibody potency, effector function, and combinations in protection and therapy for SARS-CoV-2 infection in vivo. J Exp Med 2021;218(3):e20201993. https://doi.org/10.1084/jem.20201993.
[31] Watanabe A, Yasuhara J, Iwagami M, Miyamoto Y, Yamada Y, Suzuki Y, et al. Peripartum outcomes associated with COVID-19 vaccination during pregnancy: a systematic review and meta-analysis. JAMA Pediatr 2022;176(11): 1098–106. https://doi.org/10.1001/jamapediatrics.2022.3456.
[32] Oliveira CPL, Flôr-de-Lima F, Rocha GMD, Machado AP, Guimarães Pereira Areias MHF. Meconium aspiration syndrome: risk factors and predictors of severity. J Matern Fetal Neonatal Med 2019;32(9):1492–8. https://doi.org/10.1080/14767058.2017.1410700.
[33] Sakurai K, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, et al. Type 1 diabetes mellitus following COVID-19 RNA-Based vaccine. J Diabetes Investig 2022;13 (7):1290–2. https://doi.org/10.1111/jdi.13781.
[34] Aida K, Nishida Y, Tanaka S, Maruyama T, Shimada A, Awata T, et al. RIG-I- and MDA5-initiated innate immunity linked with adaptive immunity accelerates beta-cell death in fulminant type 1 diabetes. Diabetes 2011;60(3): 884–9. https://doi.org/10.2337/db10-0795.
[35] Yin F, Wu Z, Xia X, Ji M, Wang Y, Hu Z. Unfolding the determinants of COVID-19 vaccine acceptance in China. J Med Internet Res 2021;23(1):e26089. https://doi.org/10.2196/26089.
[36] Blum SI, Tse HM. Innate viral sensor MDA5 and coxsackievirus interplay in type 1 diabetes development. Microorganisms 2020;8(7):993. https://doi.org/10.3390/microorganisms8070993.
[37] Norman M, Magnus MC, Söderling J, Juliusson PB, Navér L, Örtqvist AK, et al. Neonatal outcomes after COVID-19 vaccination in pregnancy. JAMA 2024;331(5):396–407. https://doi.org/10.1001/jama.2023.26945.
[38] Stock SJ, Carruthers J, Calvert C, Denny C, Donaghy J, Goulding A, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med 2022;28(3):504–12. https://doi.org/10.1038/s41591-021-01666-2.
[39] Iacobucci G. Covid-19 and pregnancy: vaccine hesitancy and how to overcome it. BMJ 2021;375:n2862. https://doi.org/10.1136/bmj.n2862.