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REVIEW

Risk Assessment of COVID-19 Vaccination Among Childbearing Women

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ABSTRACT

Background: *Recent studies have shown that pregnant women were more likely to experience COVID-19 complications than non-pregnant women, especially during the third trimester. Thus, the objective of the present systematic review is to investigate the literature so as to estimate the safety of COVID-19 vaccination during gestation, regardless of the trimester of pregnancy.*

Methods: *This systematic review was performed based on PRISMA statement and our search included four databases: Medline, PubMed, EMBASE and Google Scholar. Original studies were included. The following search terms were used: coronavirus disease, coronavirus, COVID-19, SARS-CoV-2, vaccine, vaccination, immunity, immunization, pregnancy, gestation, pregnant women, adverse outcomes, impact, safety, risk assessment and all possible combinations between them.*

Results: *The search strategy identified 153 unique items. After the initial screening process, 12 studies underwent full text review and five studies, which met all inclusion criteria, were ultimately included in our systematic review. All four studies claim that COVID-19 vaccination does not have a negative influence on pregnancy and can be beneficial for both the women and their newborns.*

Conclusions: *More clinical trials assessing pregnancy outcome and the value of COVID-19 vaccines in pregnant women are urgently needed. It is vital to determine the most appropriate timing of vaccination across the three trimesters of pregnancy in order to optimize the balance between vaccine efficacy and maternal and foetal safety. Future studies should evaluate the maternal–neonatal transfer of SARS-CoV-2 antibodies as well as long-term infant outcome after administration of the COVID-19 vaccine prenatally.*

Keywords: coronavirus disease, coronavirus, COVID-19, SARS-CoV-2, vaccine, vaccination, immunity, maternal immunization, pregnancy, gestation, pregnant women, adverse outcomes, impact, safety, risk assessment.

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BACKGROUND

In December 2019, a novel type of viral pneumonia emerged in Wuhan, China, which was later named coronavirus disease (COVID-19) (1). COVID-19 is caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which can lead to acute respiratory disease. This is associated with highly non-specific symptoms, including fever, dry cough and dyspnoea (2), which leads to severe illness and requires admission to hospital for supportive care in around one in five people (3).

As of December 2020, nearly 64 million people have been infected with the SARS-CoV-2 worldwide, with nearly 1.5 million deaths globally. The impact of this virus has continued to overwhelm hospital infrastructure and demanded remodeling of healthcare systems (4). In an attempt to stop the spread of COVID-19 pandemic, mass vaccination campaigns commenced worldwide. The first mRNA vaccine was initiated and, in July 2020, phases 2/3 of the leading vaccine (Pfizer-BioNTech, BNT162b2) began, prioritizing health care workers and high-risk populations such as elderly people and those with comorbidities (5). The BNT162b2 vaccine is based on a novel approach that utilizes mRNA to synthesize the spike protein of SARS-CoV-2, which is recognized by the immune system (6). Both Pfizer and Moderna have manufactured mRNA-based vaccines with 95% and 94.1% efficacy against SARS-CoV-2, respectively. Another type of COVID-19 vaccination has been manufactured by AstraZeneca using a viral vector. This has also demonstrated an early efficacy and this next-generation platform has previously been utilized for the Ebola vaccine and administered during pregnancy with an acceptable safety profile. As a result of this situation affecting the whole planet, approval of these vaccines had a crucial impact on the ongoing pandemic. However, there is a lack of data regarding COVID-19 vaccination during pregnancy (4).

According to the US Centers for Disease Control and Prevention (CDC), approximately 25% of women of reproductive age hospitalized with COVID-19 between 1 March and 22 August 2020 were pregnant (7). Accumulating evidence indicates that pregnant women are more likely to experience COVID-19 complications than non-pregnant ones, especially during the third trimester. Pregnant women with COVID-19 attending or admitted to hospital for any reason are less likely to manifest symptoms such as fever, dyspnoea, and myalgia, and are more likely to either be admitted to intensive care or require invasive ventilation than non-pregnant women of reproductive age. Pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, high maternal age, and high body mass index (BMI) are risk factors for severe COVID-19 in pregnancy. It has been suggested that pregnancies complicated by COVID-19 had a higher risk for caesarean delivery, foetal distress, preeclampsia and perinatal death. Also, pregnant women with COVID-19 are more likely to deliver preterm and not only do they have an increased risk of maternal death, but their babies are more likely to be admitted to the neonatal unit (8).

Despite this increased risk, and current deliberation by the US Food and Drug Administration (FDA) on whether to include pregnant women in clinical trials, pregnant women were not included in the initial COVID-19 vaccine trials (5). Also, no official recommendation was published to vaccinate pregnant women due to the lack of evidence regarding safety, since this population was excluded from phase II/III trial. Despite these recommendations and as a result of a sudden increase in morbidity and intensive care unit (ICU) admission in this population, the Israeli Ministry of Health decided not to withhold vaccination from pregnant women. Initially, the vaccine was available only to high-risk pregnant women; however, several weeks later, the recommendations have changed and the vaccine was recommended to all pregnant women at any gestational age due to the dramatic increase in morbidity caused by COVID-19 (9).

The worldwide COVID-19 pandemic continues to spread, causing substantial morbidity and mortality. To date, more than 80,000 pregnant women have been infected in the U.S. and the estimated global number of pregnant women infected with COVID-19 is likely to reach over one million this year (10). As a result of this, the World Health Organization (WHO), Centers for Disease Control (CDC), the American College of Obstetricians and Gynecologists (ACOG) and multiple national immunization advisory committees state that pregnant women, who are part of a high-risk group can be offered vaccination.

Since early on the pandemic, experts have consistently advocated for inclusion of pregnant women in trials of therapeutics and vaccines (11), while the German national vaccination commission (Ständige Impfkommission, STIKO) does not recommend vaccination for pregnant and breastfeeding women in general (12). Pregnant women now face a more difficult choice around vaccination than the general population (11). Their trimester, education level, employment status, and previous live births are important determinants for COVID-19 vaccine acceptance among the target population. Regarding psychosocial predictors, media/social media use, trust in the government, pharmaceutical industry, and healthcare professionals, partners, and the risk-benefit ratio were significant promoters of COVID-19 vaccine acceptance (13). Regardless of these factors, the safety of their unborn infant was the primary women's concern (14).

Crucial data for decision-making and counseling regarding COVID-19 vaccination in pregnancy are still limited. Thus, the aim of the present systematic review is to investigate the literature so as to estimate the safety of COVID-19 vaccination among pregnant women compared with unvaccinated pregnant women, regardless of the trimester of their pregnancy. ❑

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines were followed in order to conduct a systematic review of the literature (15).

Information sources

The search strategy for the review was primarily directed towards finding papers that have been published in journals and conference proceedings *via* widely accepted literature search engines and EMBASE, MEDLINE and Google Scholar databases. No language limits were applied and foreign texts were translated. Studies were included in the present systematic review if they had been published within the last two years. Specifically, the initial results were downloaded in October 2021, with updated searches being performed in January 2022.

Search strategy

Appropriate subject headings and special keywords were used for each database. These keywords and terms included the following subject headings: coronavirus disease, coronavirus, COVID-19, SARS-CoV-2, vaccine, vaccination, immunity, maternal immunization, pregnancy, gestation, pregnant women, adverse outcomes, impact, safety, risk assessment and all possible combination of these terms. Keywords and terms were searched for in the titles, abstracts and full texts of scientific studies.

Eligibility criteria

The present study was limited to articles that were written in English and representing the most recent literature. Every recent study that gave information about the safety of COVID-19 vaccination during pregnancy was included in the initial study selection. As for the characteristics of trial participants, every pregnant woman who was vaccinated against COVID-19 was included in the initial screening process. The following exclusion criteria were used: women who were either fully vaccinated (any number of doses) before pregnancy or after birth, or had undocumented COVID-19 disease or vaccine status, or had pre-admission COVID-19 virus disease or positive COVID-19 PCR test, or had a positive PCR test result during admission and hospitalisation; also, pregnant women were excluded from the present study if they had preg-

1. Women who were vaccinated before pregnancy
2. Women who were vaccinated after birth
3. Pregnant women who had undocumented COVID-19 disease
4. Pregnant women who had pre-admission COVID-19 virus disease
5. Pregnant women who had a positive COVID-19 PCR test
6. Pregnant women who had a positive PCR test result during admission or hospitalization
7. Women who had pregnancies complicated by foetal aneuploidy or genetic syndromes

TABLE 1. Exclusion criteria

TABLE 2. Search terms used in the study

SARS-CoV-2		Vaccine		Assessment risk		Pregnancy
OR		OR		OR		OR
Corona virus		Vaccination		Safety		Gestation
OR	AND	OR	AND	OR	AND	OR
Corona virus disease		Immunity		Impact		Pregnant women
OR		OR		OR		
COVID-19		Immunization		Adverse outcomes		

nancies complicated by foetal aneuploidy or genetic syndromes. All vaccinated women who met the inclusion criteria were eligible and compared with unvaccinated pregnant women. So, all studies included both vaccinated for COVID-19 pregnant women and non-vaccinated ones, and differences in adverse maternal-foetal-neonatal outcomes between these two groups were estimated. ❑

RESULTS

The search strategy identified 153 unique records. After the initial screening process and after having read the titles and abstracts of all identified studies, 12 studies underwent full text review, of which seven were excluded as they did not meet all inclusion criteria: five of them because they compared pregnant women with non-pregnant ones and the remaining two studies because they included women who were positive for SARS-CoV-2 during pregnancy. Finally, five studies were found to meet the inclusion criteria, being ultimately eligible for the systematic review. They were conducted between 2020 and 2022 and their sample sizes were ranging from 213 to 15060. These studies were conducted across several continents, including three studies in Israel, one in the United Kingdom and one in Finland. Specifically, they were undertaken at two university-affiliated medical centres in Jerusalem, Israel [(The Shaare Zedek Medical Center (SZMC) and the Bikur Holim Medical Center (BHMC), a large state-mandated health care organization in Israel], the St George's University Hospitals National Health Service Foundation Trust, London, United Kingdom, and the local Helsinki committee. All studies aimed to determine the safety of COVID-19 vaccination during pregnancy.

COVID-19 vaccination and adverse maternal-foetal-neonatal outcomes

A cohort study conducted in the United Kingdom included 1368 pregnant women who gave birth at St George's University Hospitals National Health Service Foundation Trust, London, between March 1, 2020, and July 4, 2021. In total, 140 women received at least one dose of the COVID-19 vaccine and 1188 women did not; 85.7% received their vaccine in the third trimester of pregnancy and 14.3% in the second trimester. In total, 127 (90.7%) received a messenger RNA vaccine and 13 (9.3%) a viral vector vaccine. The uptake of COVID-19 vaccination and its determinants was the primary outcome of the study, and perinatal safety outcomes the secondary outcomes. We collected data on COVID-19 vaccination uptake, vaccination type, gestational age at vaccination, and maternal characteristics, including age, parity, ethnicity, in-

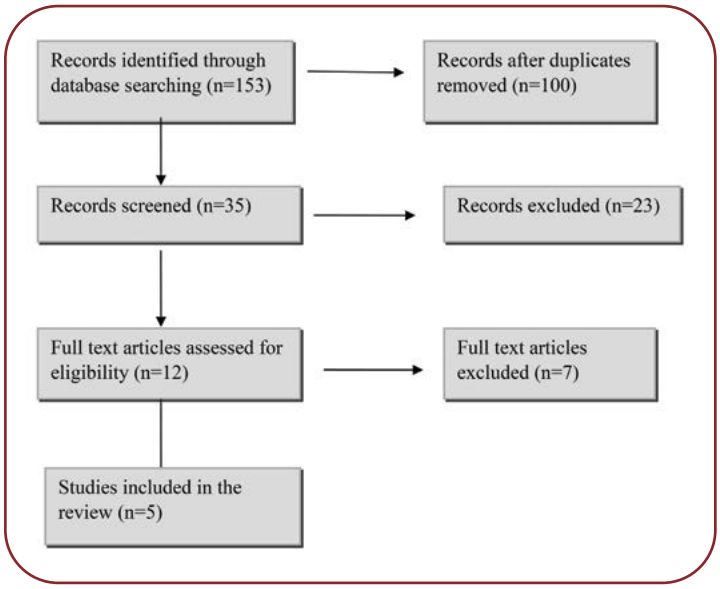

FIGURE 1. Selection process of included studies

dex of multiple deprivation score, and comorbidities, as well as about perinatal outcomes, including stillbirth (foetal death at ≥24 gestational weeks), preterm birth, foetal and congenital abnormalities and intrapartum complications. The results showed that the rates of adverse pregnancy outcomes of the 133 women who received at least one dose of a COVID-19 vaccine were similar to those of the unvaccinated pregnant women. Specifically, the rates of the two groups were as follows: stillbirth (0.0% *vs* 0.2%), foetal abnormalities (2.2% *vs* 2.5%), postpartum haemorrhage (9.8% *vs* 9.0%), caesarean delivery (30.8% *vs* 34.1%), small foetus for the gestational age (12.0% *vs* 12.8%), maternal high-dependency unit or intensive care admission (6.0% *vs* 4.0%), and neonatal intensive care unit admission (5.3% *vs* 5.0%). Intrapartum pyrexia (3.7% *vs* 1.0%) was significantly increased in the vaccinated group but the borderline statistical significance was dramatically reduced after excluding women with antenatal COVID-19 infection (16).

Another broader prospective observational study, which was conducted in Finland, used online questionnaires to study both vaccinated and unvaccinated pregnant women in order to compare the short-term outcomes between the two groups during pregnancy. Specifically, they used an online Google Forms questionnaire targeting groups on Facebook and WhatsApp. A second questionnaire was sent one month after the first one to obtain further information. The first questionnaire collected data about maternal age, last menstrual period, previous pregnancy loss, presence of any risk factors for COVID-19, whether they have received the COVID-19 vaccine and the gestational age at which they have received it, whether they were planning to be vaccinated soon and whether they have refused the vaccine or they were still considering it. In the second questionnaire, non-vaccinated women were asked to provide the reason for declining vaccination, and all women, regardless of their vaccination status, were asked if they had been diagnosed with any of the following pregnancy complications: vaginal bleeding, pregnancy loss during the first trimester (up to 13 weeks of gestation), pregnancy loss during the second trimester (14–28 weeks of gestation), gestational diabetes, premature birth, premature contractions, and foetal growth restriction. Overall, 432 women answered the first questionnaire and 326 the second one. Among them, 124 were vaccinated and 202 unvaccinated. Vaccination rate increased from 25.5% to 62% within a month. Maternal age, gestational age and number of children were similar in both groups. The results showed that the rates of pregnancy complications were similar between the vaccinated and unvaccinated groups (15.8% *vs* 20.1%). Specifically, the following complication rates were seen: foetal growth restriction (1.5% *vs* 0.0%), pregnancy loss up to 13 weeks (0.9 *vs* 0.8), postpartum bleeding (1.9 *vs* 5.6) and premature constructions (1.9 *vs* 3.2). Also, the risk of COVID-19 infection was found to be almost five times lower in the vaccinated group compared to the unvaccinated one (10).

Another retrospective cohort database study, which was conducted in Israel, included pregnant women (>18 years old) who gave birth at >24 weeks of gestation, between January and April 2021. In total, 712 of them received two doses of a COVID-19 vaccine and they were compared with 1063 unvaccinated women. The study objective was to evaluate the influence of COVID-19 vaccination during the third trimester of pregnancy on maternal and neonatal outcomes. The overall uptake of one or both vaccines was 40.2%. The results showed the following adverse maternal outcomes for vaccinated *vs* non-vaccinated pregnant women: delivery <34 gestational weeks 2.8% *vs* 2.8%, delivery <36 gestational weeks 1.0% *vs* 0.9%, meconium-stained amniotic fluid 14.5% *vs* 16.2%, chorioamnionitis 2.0% *vs* 2.4%, caesarean delivery 11.5% *vs* 7.6%, prolonged hospital stay 1.5% *vs* 2.4%, episiotomy 9.7% *vs* 10.5%, maternal ICU admission 0% *vs* 0% and postpartum haemorrhage 7.3% *vs* 10.0%. Overall, the combined adverse maternal outcome rates were 24.2% *vs* 23.6%. The neonatal outcomes of vaccinated versus unvaccinated women were as follows: 1-min Apgar score <7 4.2% *vs* 4.6%, 5-min Apgar score 2.9% *vs* 2.5%, intrauterine foetal death 0.7% *vs* 0.5%, meconium aspiration syndrome 0% *vs* 0%, mechanical ventilation 0.8% *vs* 1.5%, hypoglycaemia 2.4% *vs* 2.4%, sepsis 0.2% *vs* 0.1% and birth asphyxia 0.2% *vs* 0.9%. Overall, the combined adverse neonatal outcome rates were 7.9% and 11.4%. In summary, the rates of both maternal and neonatal outcomes were found to be similar between the two groups (17).

TABLE 3. Characteristics of included studies

Study-year	Design	Country	Sample size	Tools	Main results
Blakeway *et al* (2022)	RCT	UK	1368	Data on COVID-19 vaccination uptake, vaccination type, gestational age at vaccination, and maternal characteristics as well as further data on perinatal outcomes were collected.	The results show that the rates of adverse pregnancy outcomes in vaccinated women were similar to those in unvaccinated pregnant women.
Bleicher *et al* (2021)	RCT	Finland	326	This study used online questionnaires in both COVID-19 vaccinated and unvaccinated pregnant women in order to compare the short-term outcomes between the two groups during pregnancy.	The rate of pregnancy complications was similar between vaccinated and unvaccinated groups (15.8% *vs* 20.1%), respectively.
Rottenstreich *et al* (2022)	RCT	Israel	1775	This study compared COVID-19 vaccinated pregnant women with unvaccinated ones in order to evaluate the impact of COVID-19 vaccination during the third trimester of pregnancy on maternal and neonatal outcomes.	Both maternal and neonatal outcomes were found to be similar between the two groups, with no increase or decrease in adverse outcomes.
Beharier *et al* (2021)	RCT	Israel	213	Maternal and foetal blood samples were collected prior to delivery and from the umbilical cord following delivery. Serum IgG and IgM titers were measured using the Milliplex MAP SARS-CoV-2 Antigen Panel.	There were no differences between correlation slopes of the SARS-CoV-2–infected group and the vaccinated group for any type of antibodies, suggesting similar placental antibody transfers.
Goldshtein *et al* (2021)	RCT	Israel	15060	Documented SARS-CoV-2 infection 28 days or more after the first vaccine dose was the primary outcome. Tests are freely offered to all Israeli citizens, and therefore, no referral is required. The following pregnancy- and birth-related complications were examined as exploratory outcomes.	The hazards of infection were 0.33% *vs* 1.64% in the vaccinated and unvaccinated groups, respectively. Vaccine-related adverse events were not severe for any woman.

Maternal and foetal antibodies against SARS-CoV-2 in infected and vaccinated uninfected pregnant women

A multicenter study performed in eight medical centers across Israel included three study groups of pregnant women: vaccinated subjects (n = 86), PCR-confirmed SARS-CoV-2-infected during pregnancy (n = 65), and unvaccinated non-infected controls (n = 62). Maternal and foetal blood samples were collected from those groups prior to delivery and from the umbilical cord following delivery, respectively. Serum IgG and IgM titters were measured using the Milliplex MAP SARS-CoV-2 Antigen Panel. A gradual rise in IgG humoral response (anti-S1, -S2, -BD, and -N) was detected during the first 45 days after infection. In the same period, vaccinated participants who received the first BNT162b2 dose showed a rapid IgG response to S1, S2, and RBD but not N, resulting in high titter values by day 15 after the first dose. A further rise in IgG was observed following the second dose. At the time of delivery, maternal IgG for S1 and RBD were significantly higher in vaccinated women, while IgG for S2 and N were significantly higher in PCR-positive women. Foetal IgG for S2 and N were significantly lower in cord blood samples of vaccinated women, while foetal IgG for S1 and RBD did not differ from those of PCR-positive women. There were no differences between the

correlation slopes of the SARS-CoV-2–infected group and the vaccinated group for any type of antibodies, suggesting similar placental antibody transfer following SARS-CoV-2 infection and vaccination (11).

Association between receipt of BNT162b2 mRNA vaccine and risk of SARS-CoV-2 infection among pregnant women

A retrospective cohort study within the pregnancy registry of a large state-mandated health care organization in Israel included 7530 vaccinated and 7530 matched unvaccinated women, of which 46% and 33% were in the second and third trimester, respectively, with a mean age of 31.1 years. The primary outcome was documented SARS-CoV-2 infection 28 days or more after the first vaccine dose. SARS-CoV-2 infection was defined as a positive real-time PCR test result obtained from a nasopharyngeal swab. The tests are freely offered to all Israeli citizens and therefore, no referral is needed. Both asymptomatic and symptomatic patients were included in the study. In addition, the following pregnancy- and birth-related complications were examined as exploratory outcomes. Among infected women, they described the proportion of subjects in the vaccinated and unvaccinated groups who required hospitalization. There were 118 SARS-CoV-2 infections in the vaccinated group and 202 in the unvaccinated one. Among infected women, 88 of 105 (83.8%) were symptomatic in the vaccinated group *vs* 149 of 179 (83.2%) in the unvaccinated one. During the 28 to 70 days of follow-up there were 10 infections in the vaccinated group and 46 in the unvaccinated one. The hazards of infection were 0.33% *vs* 1.64% in the vaccinated and unvaccinated groups, respectively, representing an absolute difference of 1.31%. Vaccine-related adverse events were reported by 68 patients and none was severe. The most common symptoms included headache (n = 10, 0.1%), general weakness (n = 8, 0.1%), non-specified pain (n = 6, <0.1%), and stomach ache (n = 5, <0.1%). Three of these women were also infected with SARS-CoV-2 near vaccination; a manual review of their symptoms indicated that they were more likely associated with the infection rather than the vaccine. None of the reports indicated prolonged fever. According to the exploratory outcomes, the rates in vaccinated and unvaccinated women were as follows: SARS-CoV-2-associated hospitalization 0.2% *vs* 0.3%, abortion 1.7% *vs* 1.6%, intrauterine growth restriction 0.5% *vs* 0.5%, preeclampsia 0.3% *vs* 0.3%, maternal death 0% *vs* 0%, obstetrics pulmonary embolism 0% *vs* 0% and preterm birth (<37 weeks) 5.6% *vs* 6.0% (18). ❑

DISCUSSION

Despite the fact that COVID-19 infection in pregnancy has been associated with significant adverse maternal and neonatal outcomes in multiple studies, most pregnant women were still confused about COVID-19 vaccination during pregnancy. Sociodemographic factors associated with increased vaccination rates in pregnancy include older age, higher level of maternal education, non-smoking, use of infertility treatment and lower gravidity (19). In addition, a recent study conducted in the United States on a similar study population explored COVID-19 vaccination acceptance among pregnant, non-pregnant and breastfeeding women, indicating that non-pregnant women were most likely to accept vaccination (76.2%), with breastfeeding women the second most likely to accept it (55.2%) and pregnant women having the lowest rate of vaccine acceptance (44.3%) (20).

The most recent findings give clinicians confidence that COVID-19 vaccination during pregnancy is protective against maternal SARS-CoV-2 infection and that no pattern of adverse maternal or birth outcomes is evident after vaccination. Specifically, the first study of the present systematic review supports the safety of COVID-19 vaccination in pregnancy. In that study cohort, less than one-third of eligible women received the COVID-19 vaccination during pregnancy. This rate was much lower than that for non-pregnant women, despite the known increased risk of severe COVID-19 in pregnant women. Also, pregnancy outcomes were found to be similar to those for unvaccinated pregnant women (16).

Similarly, the second study showed that the short-term composite pregnancy complications rate following vaccination against COVID-19 using the Pfizer-BioNTech, BNT162b2 mRNA vaccine was not increased compared to the non-vaccinated group. Moreover, vaccine was shown to have significantly reduced the risk of COVID-19 infection from 6.5% to 1.5%. Thus,

this study supported that mRNA vaccination during pregnancy did not seem to increase the rate of pregnancy complications and it was effective in the prevention of COVID-19 infection (9).

In the third study, the authors assessed the impact of SARS-CoV-2 BNT162b2 mRNA vaccination in the third trimester on maternal and neonatal outcomes. Women who received both doses of the vaccine were older and had higher rates of previous miscarriages, CD and fertility treatments. Maternal outcomes were comparable and the uptake of the COVID-19 vaccine was not associated with poorer maternal outcomes. However, the authors found that the uptake of two doses of the vaccine was associated with a higher rate of elective cesarean delivery and a lower rate of vacuum assisted vaginal delivery (VAVD). By contrast, the risk of composite neonatal outcomes was lower. Thus, even in the setting of pre-existing conditions the vaccine would still be recommended, as that study supported that the uptake of COVID-19 vaccination during the third trimester of pregnancy was not associated with an increased risk of adverse maternal outcomes and lowered the risk of adverse neonatal outcomes (17).

According to the fourth study, there is a robust maternal humoral immune response coupled with a rise in protective antibodies in the foetal circulation as early as 15 days after the first BNT162b2 mRNA vaccination. The results further showed that mid-pregnancy SARS-CoV-2 infection resulted in prolonged maternal and foetal humoral immunity presented at the time of delivery (10).

In the last study, approximately 69% of pregnant women in the health fund had received the first dose of the vaccine. The benefit from the vaccine may be somewhat attenuated among this population compared with the general public, because pregnant women have been generally advised to take extra precautions during the pandemic and to adhere particularly strongly to social distancing guidelines, regardless of the vaccination status. In this retrospective cohort study of pregnant women, BNT162b2 mRNA vaccination was associated with a significantly lower risk of SARS-CoV-2 infection compared with no vaccination (18).

All of the above mentioned studies support COVID-19 vaccination during pregnancy, since not only does it not have a negative impact on perinatal outcomes, but it also may be beneficial and protective for pregnant women. Currently, the Royal College of Obstetricians and Gynaecologists (RCOG) does not specify any stage of gestation at which to avoid COVID-19 vaccination but mentions that pregnant women can choose to delay vaccination until 12 weeks of gestation in low-risk situaions: COVID-19 vaccines can be given at any time in pregnancy (12).

Another significant factor that should be considered is the gestational period in which pregnant women should get vaccinated so as to have the greatest protection. Recently, Mithal *et al* found that the antibody transfer ratio seemed to increase with latency from vaccination, suggesting that earlier vaccination may produce greater infant immunity (21). Studies on other vaccinations supported that placental transfer ratios increased when there was a longer time between maternal infection and delivery (22). However, some other studies have found that the Tdap vaccine may be more effective when administered during the second trimester of pregnancy (23).

Some side effects have been correlated with COVID-19 vaccines, such the association between thrombosis and the AstraZeneca vaccine (24). Although these events are rare, the intensive coverage of COVID-19 side effects on social media and other platforms might have had a negative influence on decisions of the public regarding vaccine safety (25). Pregnant women should be informed of their risk of severe COVID-19-associated illness and the warning signs of severe COVID-19. To reduce the risk of acquiring SARS-CoV-2 infection, pregnant women should limit unnecessary interactions with people who might have been exposed to or are infected with SARS-CoV-2 as much as possible. When they go out or interact with others, pregnant women should wear a mask, keep social distance, avoid people who are not wearing a mask, and wash their hands frequently. In addition, they should take measures to ensure their general health, including staying up to date with annual influenza vaccination and prenatal care.

Providers who care for pregnant women should be familiar with guidelines for medical management of COVID-19, including considerations for management of COVID-19 in pregnancy. As the COVID-19 vaccine is relatively new, advice on vaccination changes very often. When vaccination first started in the United

Kingdom, many pregnant women turned to their midwives and obstetricians for advice, but given the lack of clear guidance at that point, it was difficult for healthcare professionals to counsel these women (26). ❑

CONCLUSIONS

COVID-19 vaccination does not seem to lead to an increased risk during pregnancy but it can have a beneficial and a protective impact on pregnant women and their infants. However, more clinical trials assessing pregnancy outcomes and the efficacy of COVID-19 vaccines in pregnant women are urgently needed. It is crucial to determine the most appropriate timing of vaccination across all three trimesters in order to optimize the balance between vaccine efficacy and maternal and foetal safety. Furthermore, with the aim of providing evidence-based recommendations, future studies should evaluate maternal-neonatal transfer of SARS-CoV-2 antibodies as well as long-term infant outcome after administration of a COVID-19 vaccine during pregnancy. ❑

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REFERENCES

1. **Hui DS, I Azhar E, Madani TA, et al.** The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020;91:264-266.
2. **Wang Y, Li X, Ren L, et al.** Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2019;395:10223.
3. **Lim SM, Allard NL. Devereux J, et al.** The COVID Positive Pathway: a collaboration between public health agencies, primary care, and metropolitan hospitals in Melbourne. *The Medical Journal of Australia* 2022.
4. **Craig AM, Hughes BL, Swamy GK, et al.** Coronavirus disease. Vaccines in pregnancy. *Am J Obstet Gynecol MFM* 2021;3:100295
5. **Polack FP, Thomas SJ, Kitchin N, et al.** Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;383:2603-2615.
6. **Pardi N, Hogan MJ, Naradikian MS, et al.** Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. *J Exp Med* 2018;4;215:1571-1588.
7. **Delahoy MJ, Whitaker M, O'Halloran A, et al.** Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19—COVID-NET, 13 states, March 1–August 22, 2020. *MMWR Morb Mortal Wkly Rep* 2020;25;69:1347-1354.
8. **Allotey J, Stallings E, Bonet M, et al.** Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020;1;370:m3320.
9. **Bleicher I, Kadour-Peero E, Sagi-Dain L, et al.** Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study. *Vaccine* 2020;22;39:6535-6538.
10. **Beharier O, Plitman Mayo R, Raz T, et al.** Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *J Clin Invest* 2021;131:150319.
11. **Heath PT, Le Doare K, Khalil A.** Inclusion of pregnant women in COVID-19 vaccine development. *Lancet Infect Dis* 2020;20:1007-1008.
12. **American College of Obstetricians and Gynecologists' Immunization, I.D., and Public Health Preparedness Expert Work Group.** *Vaccinating Pregnant and Lactating Patients Against COVID-19* 2021.
13. **Riad A, Jouzová A, Üstün B, et al.** COVID-19 Vaccine Acceptance of Pregnant and Lactating Women (PLW) in Czechia: An Analytical Cross-Sectional Study. *Int J Environ Res Public Health* 2021;18:13373.
14. **Geoghegan S, Stephens LC, Feemster KA, et al.** This choice does not just affect me. Attitudes of pregnant women toward COVID-19 vaccines: a mixed-methods study. *Hum Vaccin Immunother* 2021;3:3371-3376.
15. **Moher D, Liberati A, Tetzlaf J, et al.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Thembj* 2009;339.
16. **Blakeway H, Prasad S, Kalafat E, et al.** COVID-19 vaccination during pregnancy: coverage and safety. *Am J Obstet Gynecol* 2021;226:236.e1-236.
17. **Rottenstreich M, Sela HY, Rotem R, et al.** Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. *BJOG* 2021;129:248-255.
18. **Goldshtein I, Nevo D, Steinberg DM, et al.** Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. *JAMA* 2021;24;326:728-735.
19. **Theiler RN, Wick M, Mehta R, et al.** Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. *Am J Obstet Gynecol MFM* 2021;3:100467 .
20. **Sutton D, D'Alton M, Zhang Y, et al.** COVID-19 vaccine acceptance among pregnant, breastfeeding, and nonpregnant reproductive-aged women. *Am J Obstet Gynecol MFM* 2021;3:100403.
21. **Mithal LB, Otero S, Shanes ED, et al.** Cord blood antibodies following maternal coronavirus disease 2019 vaccination during pregnancy. *Am J Obstet Gynecol* 2021;225:192-194.
22. **Madhi SA, Polack FP, Piedra PA, et al.** Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med* 2020;383:426-439 .
23. **Eberhardt CS, Blanchard-Rohner G, Lemaître B, et al.** Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. *Clin Infect Dis* 2016;62:829-836.
24. **Bookstein Peretz S, Regev N, Novick L, et al.** Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. *Ultrasound Obstet Gynecol* 2021;58:450-456.
25. **Solís Arce JS, Warren SS, Meriggi NF, et al.** COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries. *Nat Med* 2021;27:1385-1394.
26. **Wang EW, Parchem JG, Atmar RL, et al.** SARS-CoV-2 Vaccination During Pregnancy: A Complex Decision. *Open Forum Infect Dis* 2021;10;8:ofab180.