EFFICACY, IMMUNOGENICITY AND SIDE EFFECT OF COVID-19 VACCINE ON PREGNANT AND LACTATING WOMEN: A SYSTEMATIC REVIEW

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Abstract

Purpose: To investigate the efficacy, immunogenicity, and side effect of Covid-19 vaccine on pregnant and lactating women. Methods: We obtained 1366 articles from 7 databases such as PubMed, Google Scholar, Sciencedirect, Cochrane Library, EU Clinical Trials Register, ClinicalTrials.gov, the WHO Clinical Trial Registry. The search terms were "Covid-19 Vaccine", "Sars-Cov-2 Vaccine", "Vaccine Efficacy", "Vaccine Immunogenicity", "Vaccine Side Effect", "Pregnant Women", and "Lactating Women". Study selection and study quality appraisal were guided by Joanna Briggs Institute (JBI). Results: Fifteen articles were included. Vaccinated pregnant women had lower risk of Covid-19 infection. Immune responses were detected in maternal blood, cord blood and breast milk. The T-cell had potential to against viral variants. Covid-19 vaccination resulted in low disruption among lactating women. There was no different of side effect between pregnant and nonpregnant women. Conclusions: Covid-19 vaccine lowered infection risk and robust immune responses among pregnant and lactating women.

Keywords: Covid-19 vaccines, Drug side effect, Pregnancy, Vaccine efficacy, Vaccine immunogenicity

Introduction

Covid-19 pandemic has created a massive global burden in the last 2 years. More than 216 million confirmed cases and 4.5 million deaths globally (World Health Organization, 2021b). Indonesia is one of the largest population countries has more than 4 million confirmed cases and 133 thousand deaths (World Health Organization, 2021b). Due to the Covid-19 prevention such as social and mobilization restriction resulted in great negative impact including social, mental and economic impact (Poudel & Subedi, 2020).

One hundred and twelve Covid-19 vaccine have been produced and pre and clinically tested to evaluate the efficacy, safety and immunogenicity (World Health Organization, 2021a). The finding showed that high efficacy was found on the Covid-19 vaccine using platform messenger RNA vaccine (Pfizer/BioNTech and Moderna), viral vector (Janssen and AstraZeneca) and inactivated virus (Sinovac and Sinopharm) (Garg et al., 2021). No pregnant and lactating women are included in phase III and only a few trials recruited them in phase IV trial (World Health Organization, 2021b). It raises concern about how the vaccine works on these subgroup.

In the beginning of vaccine administration in Indonesia, the pregnant and lactating women were not allowed receiving Covid-19 vaccine. However, Accumulating findings reported that the pregnant women were the subgroup with high risk of Covid-19 complications including maternal and neonatal morbidity as well as mortality (Di Mascio et al., 2020; Di Toro et al., 2021; Oncel et al., 2021; Rodrigues et al., 2020; Zaigham & Andersson, 2020). Therefore, prioritizing pregnant and lactating women as the target on Covid-19 vaccination is essential.

As a recommendation, European Board & College Obstetrics and Gynaecology (EBCOG) encouraged health professional and the government to administer the Covid-19 vaccine among pregnant and lactating women after explaining the benefits and risks (Martins et al., 2021). Consistently, Food and Drug Administration (FDA) in United States recommended mRNA vaccines (Pfizer/BioNTech, Moderna) and a non-replicating viral vector vaccine (Janssen) for aged above 12 years old including pregnant and lactating women (Centers for Disease Control prevention (CDC), 2021). CDC identified

no safety concern or adverse outcomes using Pfizer/BioNTech, Moderna, or Janssen COVID-19 vaccines among pregnant women (Centers for Disease Control prevention (CDC), 2021).

Despite the Ministry of Health of the Republic of Indonesia starts allowing Covid-19 vaccination using Sinovac, Pfizer/BioNTech and Moderna for pregnant women since August 2021 (COVID-19 Response Team Center, 2021), the trials are still on going and the published study on how vaccine works on the pregnant and lactating women is limited. The safety concern may influence women trust on the vaccine effectiveness (Skjefte et al., 2021). The robust information of the effectiveness of Covid-19 vaccine among pregnant and lactating women is needed to increase women trust and acceptance.

The previous review reported the efficacy and safety of the Covid-19 vaccine on pregnant and lactating women (Garg et al., 2021). However, this study did not explore deeply the efficacy in terms of infection risk rate, humoral and cellular immune response as well as the possible adversity. We explored existing published studies to gain more information to be considered in vaccination decision making. Therefore, we conducted a review in order to identify the efficacy, immunogenicity and adversity of covid-19 vaccine among pregnant and lactating women.

Methods

Search strategy
Seven databases were explored in July/ August 2021 for peer-reviewed studies in written: PubMed, Google Scholar, Sciencedirect, Cochrane Library, EU Clinical Trials Register (EU-CTR), ClinicalTrials.gov, the WHO Clinical Trial Registry (WHO-CTR) from 2020 to 2019. PICO (population, intervention, comparator, and outcome) based on the Joanna Briggs Institute (JBI) guided the study selection (Tufanaru et al., 2017). This study followed The PRISMA (Preferred Reporting Items for Systematic Reviews and Analysis) in all review stages.

The search terms were "Covid-19 Vaccine", "Sars-Cov-2 Vaccine", "Vaccine Efficacy", "Vaccine Immunogenicity", "Vaccine Side Effect", "Pregnant Women", and "Lactating Women". Fifteen articles were included to evaluate the efficacy (disease infection, hospitalization risk, and death), immunogenicity (humoral and cellular immune response) and side effect or adversity of covid-19 vaccine on pregnant and lactating women. Figure 1 presented a detailed articles identification process.

Study selection and data extraction
All articles were added to Mendeley and duplications were excluded. The first and third author conducted study selection, screening, review, and data extraction. The second and third author assessed study quality. The disagreement solved by consensus. This study used PICO statement, the participant (pregnant and lactating women), intervention (Covid-19 vaccine), comparator (placebo, unvaccinated), outcomes (efficacy: covid-19 infection, hospitalization, and death risk; immunogenicity: humoral and cellular immune response; side effect or adversity). All articles were in English written and observational or intervention research. We excluded articles if had not been reviewed or preprint, and perspective studies such as editorials, commentary, narrative review or letter.

Study quality
The Joanna Briggs Institute (JBI) critical appraisal tools for cohort, cross-sectional, case control and case report study were used to assess study quality (Joanna Briggs Institute, 2021).

Synthesis of results
A narrative approach was conducted to explain study results: (1) Covid-19 vaccine characteristics used in pregnant and lactating women; (2) Covid-19 vaccine efficacy; (3) Immunogenicity; and (4) Side Effect.

Results

Covid-19 vaccine characteristics used in pregnant and lactating women
In total, there were 15 studies included in this review. The majority of the respondents including pregnant and lactating women received messenger RNA based Covid-19 vaccine (Moderna or BioNTech/Pfizer) (Baird et al., 2021; Beharier et al., 2021; Bookstein Peretz et al., 2021; Collier et al., 2021; Gill & Jones, 2021; Goldshtein et al., 2021; Gray et al., 2021; Guida et al., 2021; Jakuszko et al., 2021; Juncker et al., 2021; McLaurin-Jiang et al., 2021; Paul & Chad, 2021;

Shimabukuro et al., 2021; Zdanowski & Waśniewski, 2021)) and only one case report study used Inactivated Virus based Covid-19 vaccine (CoronaVac, Sinovac) (Soysal et al., 2021).

Five studies investigated pregnant women receiving the first dose of Covid-19 vaccine in the first, second or third trimester (Bookstein Peretz et al., 2021; Collier et al., 2021; Goldshtein et al., 2021; Gray et al., 2021; Shimabukuro et al., 2021) and five studies delivered vaccine at third trimester (Beharier et al., 2021; Gill & Jones, 2021; Paul & Chad, 2021; Soysal et al., 2021; Zdanowski & Waśniewski, 2021). Table 1. Presents the information of Covid-19 vaccine characteristics.

Covid-19 vaccine efficacy
Only 1 study observed Covid-19 vaccine in term of Sars-Cov-2 infection risk after vaccination and disease symptoms between vaccinated and unvaccinated in infected pregnant women (Goldshtein et al., 2021). The risk of Covid-19 infection was significantly reduced in 11 to 27 days and 28 days or more after vaccination. However, no statistically significant difference of symptom between vaccinated and unvaccinated among infected pregnant women.

Covid-19 vaccine immunogenicity
Eight studies investigated how immune response to Covid-19 vaccine in pregnant women. The pregnant women received the vaccine in any trimester at three studies (Bookstein Peretz et al., 2021; Collier et al., 2021; Gray et al., 2021) and in third trimester at five studies (Beharier et al., 2021; Gill & Jones, 2021; Paul & Chad, 2021; Soysal et al., 2021; Zdanowski & Waśniewski, 2021).

In the maternal blood samples, humoral immune response including Immunoglobulin A (IgA), Immunoglobulin G (IgG) and Immunoglobulin M (IgM) specific Receptor Binding Domain (RBD) antigen (Beharier et al., 2021; Collier et al., 2021; Gray et al., 2021; Soysal et al., 2021), specific Sars-Cov-2 Spike (S1 or S2) (Beharier et al., 2021; Gray et al., 2021; Zdanowski & Waśniewski, 2021), specific Nucleocapsid (N) antigen (Beharier et al., 2021), Pseudovirus neutralizing antibodies (NT50) (Collier et al., 2021), and IgG unspecific antigen part (Bookstein Peretz et al., 2021; Gill & Jones, 2021). The antibodies were found higher in vaccinated pregnant women compared to naturally infected women (Collier et al., 2021; Gray et al., 2021). Two studies found that Covid-19 vaccine-induced humoral responses were not significantly different in any trimester (Bookstein Peretz et al., 2021; Gray et al., 2021). Only one study found that higher response of IgA specific Spike and RBD antigen in Moderna vaccine compare to BioNTech/Pfizer vaccines (Gray et al., 2021).

In the cord blood, humoral responses were detectable such as specific antibodies of viral Spike (Beharier et al., 2021; Gray et al., 2021; Zdanowski & Waśniewski, 2021), RBD (Beharier et al., 2021; Collier et al., 2021; Gray et al., 2021; Paul & Chad, 2021; Soysal et al., 2021), Pseudovirus neutralizing antibodies (NT50) (Collier et al., 2021), and unspecific antigen IgG (Gill & Jones, 2021). Lower IgG antibodies in the umbilical cord were found among pregnant women who delivered before receiving the second dose vaccine (Gray et al., 2021) and unvaccinated infected pregnant women (Collier et al., 2021). Detected humoral responses in the cord blood were significant correlated with humoral responses in maternal serum (Beharier et al., 2021). Antibodies transmission ratio maternal to cord blood were observed (Beharier et al., 2021; Soysal et al., 2021). The antibodies transmission maternal to fetal ratio did not differ between vaccinated and infected pregnant women (Beharier et al., 2021).

Collier et al. (2021) investigated the cellular responses and serology systems as well as responses to viral variant in vaccinated pregnant, non-pregnant and lactating women. The response of TH1 (IFN-γ) including CD4 T Cells, CD4 central memory T cells, CD8 T Cell and CD8 central memory T cells on antigen spike were not differ in vaccinated pregnant, non-pregnant and lactating women. Monocyte and neutrophil phagocytosis as well as antiviral complement activity also responded to the Covid-19 vaccine (Collier et al., 2021).
Among vaccinated pregnant, non-pregnant, lactating women and infant cord blood had a higher response of RBD antibodies against viral variants including wild-type USA-WA1/2020 and B.1.1.7 variant compare to B 1.351 variant. Pseudovirus neutralizing antibodies (NT50) had lower response to B.1.1.7 and B 1.351 variants than wild-type USA-WA1/2020. However, the response of TH1 (IFN-γ) including CD4 T Cells, CD4 central memory T cells, CD8 T Cell and CD8 central memory T cells against those variants were comparable (Collier et al., 2021).

Six studies reported immune responses among vaccinated lactating women (Baird et al., 2021; Collier et al., 2021; Gray et al., 2021; Guida et al., 2021; Jakuszko et al., 2021; Juncker et al., 2021). Sars-Cov-2 specific IgG and IgA antibodies were detected in serum and breastmilk of lactating women (Baird et al., 2021; Collier et al., 2021; Gray et al., 2021; Guida et al., 2021; Jakuszko et al., 2021; Juncker et al., 2021). The lack of vaccine induced IgM was observed (Gray et al., 2021; Jakuszko et al., 2021). The IgG and IgA antibodies increased after the first dose and more sharply increased after the

second dose (Baird et al., 2021; Collier et al., 2021; Guida et al., 2021; Jakuszko et al., 2021; Juncker et al., 2021). In contrast, Gray et al. (2021) reported IgG robustly induced after the first and second dose but not for IgA antibodies. Breastmilk antibodies were positively associated with serum antibodies (Jakuszko et al., 2021).

Side Effect
Ten studies reported Covid-19 vaccine side effects on pregnant and lactating women (Bookstein Peretz et al., 2021; Collier et al., 2021; Gill & Jones, 2021; Goldshtein et al., 2021; Gray et al., 2021; McLaurin-Jiang et al., 2021; Paul & Chad, 2021; Shimabukuro et al., 2021; Soysal et al., 2021; Zdanowski & Waśniewski, 2021). Various symptoms were concluded. The most vaccine side effects were fever, headache, general weakness, stomachache, muscle pain, arthralgia, injection site pain, nonspecific pain, rash or allergic reaction but not anaphylaxis (Collier et al., 2021; Gray et al., 2021). Three studies observed more frequent symptoms after second dose (Collier et al., 2021; McLaurin-Jiang et al., 2021; Shimabukuro et al., 2021). These symptoms ended less than 1 day (Goldshtein et al., 2021). The side effects were similar between vaccinated pregnant and non-pregnant women (Gray et al., 2021; Shimabukuro et al., 2021) except vomiting and nausea in pregnant women (Shimabukuro et al., 2021).

No maternal, neonatal or breastfeeding severe adverse event was reported (Collier et al., 2021; Gill & Jones, 2021; McLaurin-Jiang et al., 2021; Paul & Chad, 2021; Soysal et al., 2021; Zdanowski & Waśniewski, 2021). However, low cases of severe complications were observed including intrauterine growth restriction, preeclampsia, stillbirth, maternal death, obstetric pulmonary embolism, low birth weight, spontaneous abortion, ectopic pregnancy, preterm birth, congenital anomalies, vaginal bleeding, uterine contraction, and premature rupture of amnion membrane (Bookstein Peretz et al., 2021; Goldshtein et al., 2021; Shimabukuro et al., 2021). On the other hand, no severe complications different between vaccinated and unvaccinated pregnant women in terms of intrauterine growth restriction, preeclampsia, stillbirth, maternal death, obstetric pulmonary embolism, and low birth weight (Goldshtein et al., 2021). The adverse events in pregnant women which first or second dose in any trimester were not different (Bookstein Peretz et al., 2021).

Discussions

We synthesized the data of 15 studies regarding Covid-19 vaccine efficacy, immune response and side effect after receiving the Covid-19 vaccine among pregnant and lactating women. Due to the heterogeneity of the study designs, we could not conduct meta-analysis. Previous review observed the efficacy and safety of Covid-19 vaccine among pregnant and lactating women (Garg et al., 2021). This review did not show the covid-19 vaccine's potential efficacy in terms of infection risk rate and immune response in detail.

In this review, fourteen studies evaluated RNA based vaccines (Moderna or BioNTech Pfizer) and only 1 study observed inactivated virus based vaccine (CoronaVac, Sinovac). Due the limited study evaluated inactivated virus based vaccine, it was not possible to compare the efficacy and immunogenicity with other vaccine platforms. We found a study that reported the covid-19 vaccine reducing the risk of covid-19 infection (Goldshtein et al., 2021). The immune responses were detected through maternal blood, cord blood and breastmilk samples. Humoral and cellular responses actively stimulated after vaccine injection after first dose and robustly increased second dose. Moderna or BioNTech Pfizer against covid-19 virus variant was reported (Collier et al., 2021). Therefore, RNA based vaccines are potentially beneficial for risker subpopulation such as pregnant and lactating women.

Antibodies transmitted from maternal to cord blood were evaluated and humoral antibodies of the cord blood were associated with maternal blood antibodies after covid-19 vaccination (Beharier et al., 2021; Soysal et al., 2021). Antibodies could be able to transmit vertically from mother to the infant (Albrecht & Arck, 2020) and this passive immunity had been produced successfully from maternal immunization including pertussis, influenza and tetanus toxoid immunization (Blanchard-Rohner & Eberhardt, 2017; Chu & Englund, 2017; Vygen-Bonnet et al., 2020). In this review also found that higher antibodies in the umbilical cord among pregnant women who delivered after receiving the second dose. It is indicated that completing covid-19 vaccine dose during pregnancy has more positive benefits for infant immunity.

Common side effects were fever, headache, pain, weakness and arthralgia. Low cases of adverse events were reported. In contrast, no significant difference between vaccinated and unvaccinated pregnant women (Goldshtein et al., 2021). Furthermore, there is no difference in humoral immune response and side effect of receiving vaccine compared at any trimester (Bookstein Peretz et al., 2021; Gray et al., 2021). These findings could be considered to determine the appropriate time for receiving Covid-19 vaccination during pregnancy.

Food and Drug Administration (FDA) in United States considered the safety and efficacy as well as approved the use of mRNA based vaccine (Pfizer/BioNTech, Moderna) and a non-replicating viral vector vaccine (Janssen) on pregnant and lactating women (Centers for Disease Control prevention (CDC), 2021). Regardless of the vaccine benefits, European Board & College Obstetrics and Gynaecology (EBCOG) recommends that health care professional to explain risk and benefit of covid-19 vaccination before delivering the vaccine (Martins et al., 2021). Therefore, pregnant and lactating women are allowed to decide whether to receive vaccine.

According to the Minister of Health of the Republic of Indonesia regulation, the Covid-19 vaccine including Sinovac, Pfizer/BioNTech and Moderna are allowed for pregnant women since August 2021 (COVID-19 Response Team Center, 2021). The effectiveness of the Covid-19 vaccine may increase vaccine acceptance in Indonesia (Harapan et al., 2020). These review findings could be the useful information of vaccine adventages to support the expanse of the Covid-19 vaccination and increase trust among pregnant and lactating women in Indonesia.

To our knowledge, this study is the first systematic review of efficacy, immunogenicity and side effects of the Covid-19 vaccine among pregnant and lactating women. The limitation of this review is the findings are obtained only from published articles. These articles have various study designs and a small population that could not generalize the findings. Due to limited published studies, the Covid-19 vaccine included is only Pfizer/BioNTect, Moderna and Sinovac. Further study may include different study design with a larger sample size, longer follow-up duration, and evaluate other vaccine platforms to establish more safety data for pregnant and lactating women.

Conclusions

The covid-19 vaccines reduce risk of infection and develop humoral and cellular immune responses. The health care professional should explain potential risks and benefits to the pregnant and lactating women before deciding to receive the Covid-19 vaccine. Future study need to include more study samples and various vaccine platforms to generalize the safety concern of Covid-19 vaccine among pregnant and lactating women.

Acknowledgement

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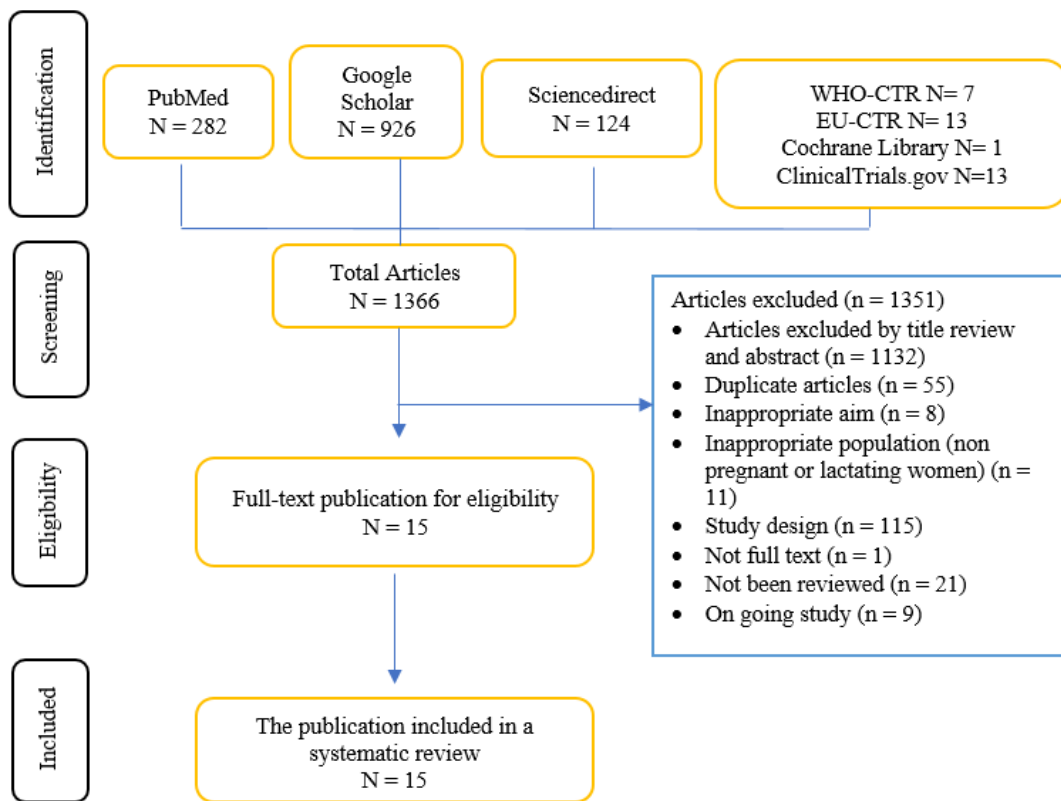
Figure 1. Articles Identification Flow Chart

Here is an example of a table

Table 1. Data Extractions

Article, country	Design and comparator	Participants	Races/ subgroup population	Samples	Intervention	Outcomes
(Juncker et al., 2021), Netherlands	Prospective longitudinal study	26 lactating women	Unidentified	• Breast milk • Blood samples	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	Sars-Cov-2 specific IgA antibodies in human milk and IgG in serum
(Guida et al., 2021), Italy	Cohort prospective observational study	10 lactating women with no previously Covid-19 infection	Unidentified	• Breast milk • Blood samples	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	Anti-Sars-Cov-2 S antibodies
(Gray et al., 2021), United State	Cohort study	84 pregnant, 31 lactating women, 16 non-pregnant reproductive age women	White, Black, Asian, Multiracial Other	• Breast milk • Blood samples • Cord blood	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer) or 1273 (Moderna)	Sars-Cov-2 receptor binding domain (RBD), S1, and S2 and Sars-Cov-2 spike.
(Collier et al., 2021)	An exploratory, descriptive, prospective cohort study	30 Pregnant, 16 lactating, 57 non-pregnant or lactating women aged 18 to 45.	White, Black, Asian, Other	• Breast milk • Blood samples • Cord blood	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer) or 1273 (Moderna)	• Humoral and cellular immune activation and response on viral variant.
(Goldshtein et al., 2021), Israel	Retrospective cohort study	7530 vaccinated and 7530 unvaccinated pregnant women	Jewish Ultra-orthodox Arab	Electronic health record from the comprehensive database of the Maccabi Healthcare Services.	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Sars-Cov-2 infection • Adverse event after vaccination.
(Zdanowski & Waśniewski, 2021), Poland	Retrospective preliminary study	16 pregnant women	Unidentified	• Blood and umbilical cord	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Specific nucleocapsid (N) antigen antibodies • Antibodies against Sars-Cov-2-Spike (S)-RBD
(Beharier et al., 2021), Israel	Multicenter study	86 Vaccinated, 62 unvaccinated, and 65 unvaccinated with Sars-Cov-2 infection pregnant	Jewish Arab Other	• Maternal prior to delivery • Umbilical cord blood following delivery	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Serum IgG and IgM (S1, S2, RBD, N)

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		women age 18 years or older				
(Jakuszko et al., 2021), Poland	Cohort study	32 breastfeeding health worker	Unidentified	• Maternal serum • Breast milk	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Serum IgG (S1 domain of the spike protein and Receptor binding domain (RBD) • IgA (S1 domain of the spike protein) • IgM (Nucleocapsid protein)
(Baird et al., 2021); Portland, Oregon, United State	A longitudinal cohort study	7 lactating health workers	Unidentified	• Breast milk	Dose 1 and 2 of mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer) or mRNA 1273 (Moderna)	IgG and IgA (Spike protein and Receptor binding domain (RBD)
(Soysal et al., 2021), Turkey	Case report	32-years-old pregnant health careworker	Unidentified	• Maternal blood • Cord blood	Inactivated virus vaccine (CoronaVac, Sinovac)	• Anti -receptor binding domain (RBD) of Sars-Cov-2 spike protein antibody • Sars-Cov-2 infection
(Gill & Jones, 2021), Minnesota, United State	Case report	34-years-old pregnant health worker	Unidentified	• Maternal blood • Cord blood	Dose 1 and 2 of mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Serum IgG • Sars-Cov-2 infection • APGAR score
(Paul & Chad, 2021), United State	Case report	36-weeks 3 days pregnant health worker	Unidentified	• Cord blood •	mRNA-based Covid-19 vaccine mRNA 1273 (Moderna)	• Serum IgG (Anti - receptor binding domain (RBD) of Sars-Cov-2 spike protein antibody) • Sars-Cov-2 infection
(McLaurin-Jiang et al., 2021)	Cross-sectional study	4455 Lactating women aged 18 years old or above	• Asian	• Online questionnaire (InfantRisk Center website, Facebook, and Twitter).	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Impact of Covid-19 vaccine on maternal activities

					or 1273 (Moderna)	• Child symptom • Breast milk intensity
(Shimabukuro et al., 2021), united state	Longitudinal study	35691 pregnant women and non-pregnant women age 16 to 54 years old	• White • Black • Asian • Other races	• Online survey using v-safe after vaccination health checker surveillance system, the v-safe pregnancy registry and the Vaccine Adverse Event Reporting System (VAERS)	Dose 1 or 2 of mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer) or mRNA 1273 (Moderna)	• Local and systemic reactogenicity • Pregnancy outcomes • Neonatal outcomes
(Bookstein Peretz et al., 2021), Israel	Observational case control study	390 pregnant women and 260 non-pregnant women completed 2 dose of mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	Unidentified	• First Digital questionnaires of demographic data, medication, medical history, history of Sars-Cov-2 infection, timing of Covid-19 vaccine doses and side effect. • Second Digital questionnaire for pregnancy and delivery outcomes • Serology blood test for Sars-Cov-2 receptor binding domain (RBD) IgG 2	mRNA-based Covid-19 vaccine BNT162b2 (BioNTech/Pfizer)	• Pregnancy and Non-pregnancy side effect • Obstetric symptom • Current pregnancy and delivery outcomes

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