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Review of short-term and long-term adverse effects of covid-19 vaccination during pregnancy

Diana Ramasauskaite [a,*], Dominyka Grinciute [b]

[a] Center of Obstetrics and Gynaecology, Vilnius University Faculty of Medicine, PO: Santariškių 2, Vilnius, LT08661, Lithuania
[b] Vilnius University, Faculty of Medicine, Lithuania

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ABSTRACT

Background: The covid-19 pandemic sparked a debate about the safety of vaccines during pregnancy. However, pregnant women were excluded from the Pfizer-BioNTech vaccine phase 3 trials. As two years have passed since the first Covid-19 vaccine and more studies have been conducted, we want to evaluate the scientific literature to determine any actual risks in taking the vaccine during pregnancy.

Methods: We conducted literature research using PubMed and Google Scholar databases from January to April 2023. As the review considers short- and long-term adverse effects it was divided into two parts. The first part was conducted as a systematic review. The second concerning long-term negative effects due to lack of research is a literature review. The inclusion criteria for the systematic review part were singleton pregnancies, women vaccinated during pregnancy, and studies from 2020 and later. The most common short-term pregnancy adverse effects were included in the search: preterm delivery, small gestation age, intrauterine death, congenital defects, stillborn, fetal growth retardation, spontaneous abortion. Maternal immune activation was the primary concern for the long-term adverse effects and whether vaccination could cause it. The search terms included maternal immune activation, fetal neurodevelopment, neuropsychiatric disorders and the studies used were from 2019.

Results: Most studies showed no significant difference in short-term adverse effects between vaccinated and non-vaccinated women and their fetuses. However, the literature is insufficient to evaluate possible long-term adverse effects.

Conclusion: Available evidence supports the safety of administering SARS-CoV-2 vaccines to pregnant women, but further systematic reviews and meta-analyses are essential. Maternal immune activation caused by vaccination may impact a child's neurodevelopment and should be a concern for future studies.

1. Introduction

In November 2019, a new virus emerged in Wuhan, China. To this day, SARS-CoV-2 has claimed 6834981 lives, causing a worldwide pandemic and damaging economies [1,2]. To combat covid-19 disease, the first vaccine reached the market in December 2020 – Pfizer-BioNTech [3]. Typically, vaccine development takes about 5–10 years. However, there are steps to accelerate this process: clinical trial phases can be combined, phase III trials become shorter as there is a high number of new cases, and manufacturing may start before phase III trials. None of the steps are missing in the accelerated process, and all mandatory safety precautions are taken, thus, ensuring vaccine safety [4]. Certain groups, such as pregnant women, were excluded from covid-19 vaccine trials [5]. However, pregnancy is a risk factor for severe covid-19 illness and adverse pregnancy outcomes [6,7]. Therefore, when immunization is performed during pregnancy, the benefits to both mother and fetus should outweigh the risks.

Today pregnant women can safely be vaccinated with inactive or recombinant vaccines during pregnancy. The influenza and the Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) vaccines are strongly recommended in each pregnancy, with generally safe profiles [8,9]. Live, attenuated virus, and live bacterial vaccines pose a theoretical risk to the fetus and, thus, are contraindicated during pregnancy [10]. Although the influenza vaccine's safety and efficacy during pregnancy are proven, the uptake of this vaccine remains sub-optimal. From 2020 to 2022, 52 to 61% of pregnant persons in the United States reported receiving the influenza vaccine [11]. The coverage for pregnant women in the European Union ranged from 0.5 to 58.6% (median 25.0%) [12]. The most important factor influencing

* Corresponding author. Center of Obstetrics and gynaecology, Vilnius University Faculty of Medicine, PO: Santariškių 2, Vilnius, LT08661, Lithuania.
E-mail addresses: diana.ramasauskaite@santa.lt (D. Ramasauskaite), dominyka.grinciute@mf.stud.vu.lt (D. Grinciute).

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Abbreviations

ASD	Autism spectrum disorder
MIA	Maternal immune activation
CNS	Central nervous system
HPA	Hypothalamic-pituitary-adrenal
CRP	C reactive protein
MRI	Magnetic resonance image
GABA	Gamma-aminobutyric acid
ADHD	Attention deficit hyperactivity disorder
VAERS	Vaccine Adverse Event Reporting System
IL-1β	Interleukin-1beta
IP-10	The human interferon-inducible protein 10
IL-8	Interleukin 8
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor-alpha

maternal vaccination uptake is healthcare professional recommendation. During an outbreak, other factors can be associated with maternal vaccine uptake [13]. The most common and thoroughly investigated covid-19 vaccines are Pfizer-BioNTech, Moderna, AstraZeneca, and Johnson & Johnson. All these vaccines are inactive, thus, suggesting they should be safe during pregnancy. However, Pfizer-BioNTech and Moderna are mRNA vaccines, which is a relatively new technology in vaccine making, therefore, immunization with them may have some unforeseen risks [12]. Only three years have passed since the first vaccine, which raises another concern about long-term negative effects and insufficient time frame to evaluate them. Therefore, this review intends to discuss short-term and possible long-term fetal and maternal adverse effects of the new vaccines and widen the knowledge about vaccine counseling and safety during pregnancy.

2. Methods

We conducted literature research using PubMed and Google Scholar databases from 2023 January to 2023 April. As the review considers both short-term and long-term adverse effects it was divided into two parts. The first part was conducted as a systematic review. The second concerning long-term negative effects due to lack of research is a literature review. The inclusion criteria for the systematic review part were singleton pregnancies, women vaccinated during pregnancy, and studies from 2020 and later. The most common short-term pregnancy adverse effects were included in the search: preterm delivery, small gestation age, intrauterine death, congenital defects, stillborn, fetal growth retardation, and spontaneous abortion. Maternal immune activation was the primary concern for the long-term adverse effects and whether vaccination could cause it. The search terms included maternal immune activation, fetal neurodevelopment, and neuropsychiatric disorders. For the second part, articles from 2019 and later were used. Generic

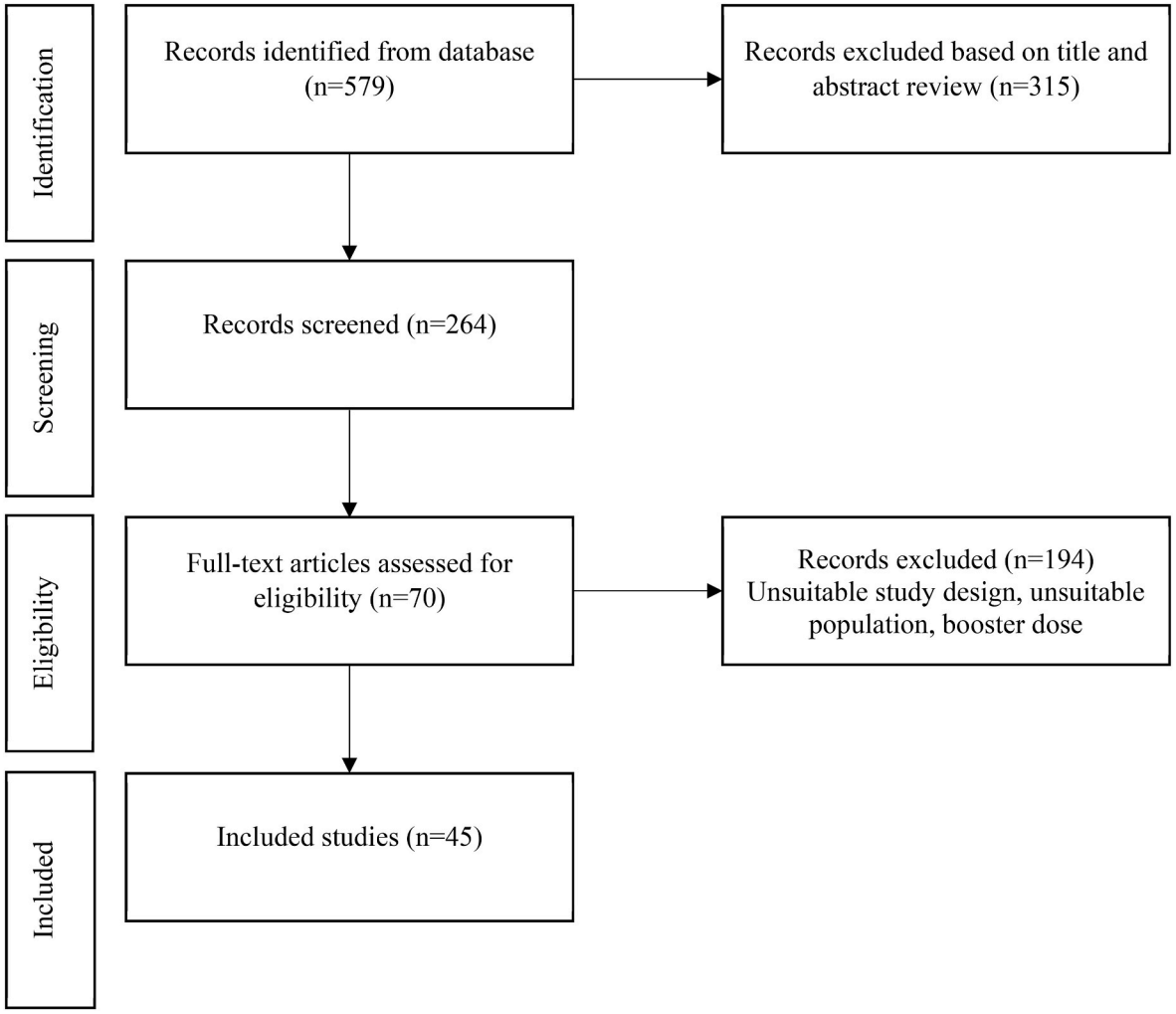

Fig. 1. Flow diagram presents the number of studies excluded at each stage.

vaccination side effects such as arm pain, swelling at the injection site, fatigue, and headache were excluded from the review (Fig. 1).

3. Covid-19 vaccine fetal and maternal adverse effects

To this day, vaccine acceptance among pregnant women is relatively low. Only around 49% of pregnant women are willing to be vaccinated. The highest vaccine acceptance was found in Africa (61%), lower in Asia (49%), then the Americas (46%), and the lowest in Europe/Oceania (45%). However, the vaccine uptake rate provided in the literature should be evaluated with caution, for example, the mentioned acceptance in Africa evaluates only the uptake in South Africa and Ethiopia and, therefore, should not be generalized for the whole continent [14]. Lack of knowledge about the vaccine and its effect on the fetus were the most common reasons for vaccine hesitancy [15–17]. We have reviewed 24 studies about the vaccine's maternal and fetal adverse effects. Most tested were mRNR vaccines: Pfizer-BioNTech (24 studies) and Moderna (16 studies). Six studies included the AstraZeneca vaccine, five included Johnson & Johnson, and one added the Sinovac vaccine. The most common investigated adverse fetal effects were small gestation age at birth (below 10th percentile), preterm birth (less than 37th gestation week), spontaneous abortion, congenital malformations, newborn hospitalization, neonatal death, fetal growth restriction, stillbirth, abnormal fetal heart rate, reduced fetal movement, and neonatal infection. Postpartum bleeding (estimated blood loss of $>$ 1000 ml and/or hemoglobin drop of $\geq$3 g/dl), hypertensive disease, vaginal bleeding, pre-labor rupture of membranes, gestational diabetes, endometritis, blood transfusion, a caesarian delivery, and intensive care unit admission were the main discussed maternal adverse effects. Women vaccinated during the third trimester had a higher rate of elective cesarean deliveries [18]. 2023 D.T. Covas recommends using the Pfizer-BioNTech vaccine as it has the lowest risk of adverse effects [19]. A single study found small gestation age higher compared to previously published studies [20]. 2022 A. Carmona et al. noticed more congenital microcephaly cases in vaccinated mothers' newborns. However, the authors admit that microcephaly diagnosis highly depends on the measurement methods and may be temporary due to cranial molding at birth or other reasons [21]. The risk of preterm delivery may be higher for women vaccinated with Pfizer-BioNTech or Moderna during the second trimester [22]. Reduction in stillbirth and preterm delivery was observed in vaccinated women. However, these women were also of higher socioeconomic class and older. Therefore, they may be more used to caring for their health [23]. 2022 A. Mascolo et al. singled out spontaneous abortion as the most common pregnancy adverse effect. The study also noticed that Moderna and AstraZeneca vaccines have the highest rates of spontaneous abortion, and Pfizer-BioNTech has the lowest one. However, the authors did not compare their findings with the general population incidence of spontaneous abortion [24]. One study shows that vaccinated women had higher rates of elective cesarean deliveries [18] (Table 1).

4. Covid-19 vaccine long-term vaccine adverse effects

Discussing the possible long-term effects of maternal immunization on the child is also essential. The most troubling possibility is that the maternal disease may impact the child's neurodevelopment and predispose psychiatric disorders such as psychosis, depression, anxiety, schizophrenia, cognitive deficits, sensory-motor deficits, and autism spectrum disorder (ASD) [40–42]. Such a connection between maternal infections and neurodevelopmental disorders has been noticed previously. Adverse neurodevelopmental outcomes of the offspring are most commonly associated with pathogens that typically do not cross the placenta and are upper respiratory tract infections, such as influenza [43,44]. There are a few potential mechanisms for how covid-19 can affect offspring's neurodevelopment. It can be via vertical transmission, by causing adverse pregnancy effects, which are associated with neurological risk (preterm birth, fetal growth restriction, or miscarriage), or via maternal immune activation (MIA) [43,45]. Vertical transmission of covid-19 is rare even in unvaccinated mothers; therefore, it is irrelevant in this review [46–48]. MIA is our primary concern when discussing the vaccine's long-term adverse effects. Activation of the maternal immune system has been linked to the long-term risk of neuropsychiatric disorders in both animal and human models [41,44,49]. It is known that mRNA vaccines elicit a strong immune response, type I interferon is produced along with multiple inflammatory cytokines [50,51]. This raises the question of whether maternal immune activation caused by vaccines may predispose similar long-term effects as the infection itself.

MIA is the rise of inflammation mediators in the mother's body during an infection. These inflammation mediators can cross the placenta entering the fetal bloodstream, triggering placental and fetal brain immune activation [43,52]. Immune mediators, such as cytokines, chemokines, and neurotrophins, play a role in the development of the central nervous system (CNS) by regulating neurons and glial cells migration, differentiation, apoptosis, synaptogenesis, synaptic maturation, and plasticity [52,53]. During the early stages of development, microglia is the main source of cytokines in the fetus. Maternal inflammation mediators activate fetal microglia, inducing the overproduction of proinflammatory cytokines, thus, interrupting fetal neurodevelopment. Increased maternal cytokines may also affect the hypothalamic-pituitary-adrenal (HPA) axis, which is vital to hormonal pregnancy regulation. The HPA axis is responsible for concentrations of glucocorticoids and progesterone. Dysregulation in these hormones can additionally affect fetal development [43,52].

2021 S. Gee et al. studied cord blood changes during maternal covid-19 infection. During maternal infection, the fetal immune system responds by releasing proinflammatory cytokines: Interleukin-1β (IL-1β), the human interferon-inducible protein 10 (IP-10), and interleukin 8 (IL-8). Even after the maternal infection is cleared, the fetal immune response persists, thus, presenting a risk of future cognitive and behavioral deficits and neuropsychiatric disorders [48,49]. The increase of interleukin 6 (IL-6) was also observed in pregnant women with covid-19 and their newborns 2 h after the birth. The increase in IL-6 is associated with decreased cognitive abilities 12 months after birth [54]. IL-6 and IL-1β are also considered important factors in the development of ASD [55,56]. Cytokines associated with schizophrenia are IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α), which were all reported to increase during covid-19 infection [56,57]. C reactive protein (CRP) is another inflammation marker increasing during the infection. 2022 A. Suleri et al. published a large-scale prospective cohort study evaluating MIA by measuring CRP in the first 18 weeks of gestation and assessing good quality magnetic resonance images (MRI) of the child's brain at age 10 [58]. A direct association between continuous MIA and lower cerebellar volume was found. In animal studies, the reduction of GABA-ergic and Purkinje cells was also observed in the cerebellum. The decrease in cerebellum volume may be related to ASD, attention deficit hyperactivity disorder (ADHD), developmental dyslexia, and atypical social-behavioral development [58,59]. Considering vaccines may affect the child's neurological development through maternal inflammation, they may also be able to influence it differently depending on the timing of the vaccination. Elevated IL-8 levels during the first trimester are more likely to manifest as externalizing symptoms: aggression and impulsivity. However, maternal inflammation during the second trimester is associated with internalizing symptoms: withdrawal, sorrow, and anxiety [60].

5. Conclusion

Available evidence supports the safety of administering SARS-CoV-2 vaccines to pregnant women, but further systematic reviews and meta-analyses are essential. To this day, not enough time has passed since the beginning of covid-19 pandemic to evaluate possible long-term

Table 1
Reviewed studies concerning maternal and fetal adverse effects after vaccination with covid-19 vaccines. Includes studied vaccines, evaluated outcomes, and observed adverse effects.

	Study design	Vaccine	Evaluated outcomes	Significant adverse effects
H. S. Lipkind [6]	Retrospective cohort study	Pfizer-BioNTech, Moderna, Johnson & Johnson	Small gestation age at birth Preterm birth	–
E. O. Kharbanda [25]	Case-control surveillance	Pfizer-BioNTech, Moderna, Johnson & Johnson	Spontaneous abortion	–
I. Goldshtein [5]	Population-based cohort study	Pfizer-BioNTech	Preterm birth Small gestation age at birth Congenital malformations Neonatal death	–
M. Rottenstreich [18]	Multicenter retrospective cohort study	Pfizer-BioNTech	Postpartum bleeding Endometritis Blood transfusion Caesarian delivery Intensive care unit admission	Vaccinated women had higher rates of elective cesarean deliveries
I. Bleicher [26]	Prospective observational study	Pfizer-BioNTech	Preterm birth Spontaneous abortion Fetal growth restriction Hypertensive disease Vaginal bleeding Gestational diabetes	–
S. B. Peretz [27]	Observational case-control study	Pfizer-BioNTech	Preterm birth Spontaneous abortion Newborn hospitalization Neonatal death Vaginal bleeding Pre-labor rupture of membranes	–
M. Sadarangani [28]	Observational cohort study	Pfizer-BioNTech, Moderna	Spontaneous abortion Stillbirth Abnormal fetal heart rate Reduced fetal movement Vaginal bleeding	–
D. T. Covas [19]	Observational cross-sectional study	Pfizer-BioNTech, AstraZeneca, Sinovac/Bhutan, Johnson & Johnson	Spontaneous abortion Neonatal death Vaginal bleeding	–
A. L. Arulappen [20]	Retrospective cohort study	Pfizer-BioNTech, Moderna	Small gestation age at birth Spontaneous abortion Congenital malformations Fetal growth restriction	Higher incidence of small gestation age compared to previously published studies
A. Carmona [21]	Multicenter prospective cohort study	Not mentioned	Small gestation age at birth Preterm birth Congenital malformations Neonatal death Stillbirth Neonatal infection	A higher number of congenital microcephaly
H. Blakeway [29]	Cohort study	Pfizer-BioNTech, Moderna, AstreZeneca	Preterm birth Congenital malformations Stillbirth	–
T. Wainstock [30]	Retrospective cohort study	Pfizer-BioNTech	Small gestation age at birth	–
D. B. Fell [31]	Population-based retrospective cohort study	Pfizer-BioNTech, Moderna	Small gestation age at birth Preterm birth Stillbirth	–

(*continued on next page*)

Table 1 (*continued*)

	Study design	Vaccine	Evaluated outcomes	Significant adverse effects
M. E. Trostle [32]	Descriptive study	Pfizer-BioNTech, Moderna	Small gestation age at birth Preterm birth Spontaneous abortion Congenital malformations Fetal growth restriction	–
M. C. Magnus [33]	Retrospective cohort study	Pfizer-BioNTech, Moderna, AstraZeneca	Small gestation age at birth Preterm birth	–
R. Peretz-Machluf [34]	Retrospective cohort study	Pfizer-BioNTech	Small gestation age at birth Preterm birth Hypertensive disease	–
A. Dick [22]	Retrospective cohort study	Pfizer-BioNTech, Moderna	Preterm birth	The risk of preterm delivery may be higher for women vaccinated with Pfizer-BioNTech or Moderna during the second trimester
P. L. Moro [35]	Review of reports to the Vaccine Adverse Event Reporting System (VAERS)	Pfizer-BioNTech, Moderna	Preterm birth Spontaneous abortion Congenital malformations Stillbirth Vaginal bleeding	–
G. Favre [36]	Multicenter prospective cohort study	Pfizer-BioNTech, Moderna	Preterm birth Spontaneous abortion	–
L. Hui [23]	Retrospective multicenter cohort study	Pfizer-BioNTech, Moderna	Preterm birth Congenital malformations Stillbirth	–
N. Kugelman [37]	Retrospective equivalence cohort study	Pfizer-BioNTech	Preterm birth Fetal growth restriction	–
O. Mansour [38]	Retrospective cohort study	Pfizer-BioNTech, Moderna	Spontaneous abortion	–
A. Mascolo [24]	Descriptive study	Pfizer-BioNTech, Moderna, AstraZeneca, Johnson & Johnson	Spontaneous abortion	Moderna and AstraZeneca have higher spontaneous abortion rates than Pfizer-BioNTech
C. Calvert [39]	National, population-based, matched cohort study	Pfizer-BioNTech, Moderna, AstraZeneca	Spontaneous abortion	–

adverse effects. Maternal immune activation caused by vaccination may impact a child's neurodevelopment and should be a concern for future studies.

CRediT authorship contribution statement

Diana Ramasauskaite: Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision, Project administration. **Dominyka Grinciute:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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