



COVID-19 VACCINE DURING PREGNANCY RESULTS OF TRANSPLACENTAL ANTIBODY TRANSFER TO INFANTS AND THROUGH BREAST MILK: A LITERATURE REVIEW

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Abstract

Background: This comprehensive literature review investigates the outcomes of administering the BNT162B2 COVID-19 vaccine during pregnancy, focusing on transmitting antibodies through both the placenta and breast milk to infants. The study evaluates existing research findings to provide a nuanced understanding of the immunological implications for newborns born to vaccinated mothers.

Methods: This literature review employed the PICO method to develop the review question, focusing on studies published between 2020 and 2023, identified through PubMed, Google Scholar, ScienceDirect, and Scopus using specific keywords related to antibody transfer, COVID-19 vaccine, neonatal immunity, and pregnancy. **Result:** Nine articles met the inclusion criteria. The review found that COVID-19 vaccination during pregnancy promoted transplacental antibody transfer to infants and the presence of antibodies in breast milk. **Conclusion:** The results of this study of the literature show that administering the mRNA vaccination in the latter half or third of pregnancy boosts IgA along with IgG levels through transplacental transmission or breastfeeding. BNT162b2 vaccination of mothers in the second trimester is recommended. Breastfeeding has advantages, but limited evidence suggests significant SARS-CoV-2 antibody transfer postpartum. Prospective mothers are urged to vaccinate pre-delivery and consider breastfeeding for antibody transfer.

Keywords: antibodies transfer, COVID-19 vaccine, neonatal immunity, pregnancy, SARS-CoV 2 antibodies

INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) received notification of several pneumonia cases. That were connected to Wuhan, China. Subsequent investigation identified a new coronavirus, named Coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). In January 2020, officially the epidemic was deemed a public health emergency of global significance. Pregnancy-related problems, death, and severe sickness are all increased when SARS-CoV-2 is contracted. It is strongly advised by both public health authorities and professional organizations that expecting moms should receive the COVID-19 vaccination (Cassidy *et al.*, 2023). Increasing evidence has



shown that receiving the COVID-19 messenger RNA (mRNA) immunization while pregnant is both safe and effective (Nir *et al.*, 2022)

While the recommendation is for COVID-19 immunization to be given to expectant mothers, there are instances where some individuals may opt for vaccination antepartum or choose not to get vaccinated altogether. Recent investigations propose that expectant mothers demonstrate a proficient humoral in reaction to SARS-CoV-2 vaccination (Collier *et al.*, 2021). Furthermore, studies indicate that vaccinating during pregnancy offers advantages to infants by reducing hospitalization rates due to COVID-19 (Halasa *et al.*, 2022).

Nevertheless, understanding Passive Immunity development through maternal vaccination against COVID-19 remains limited, along with characterization of maternal antibodies generated by vaccination in babies is insufficient. In light of the capability of maternal antibodies to SARS-CoV-2 IgG towards pass antepartum fetus (Treger *et al.*, 2022) and the existence of antibodies specific to SARS-CoV-2 in infant milk (Perl *et al.*, 2021). Based on the description above, The objective of this review is to investigate the location and outcome of antibodies produced by the SARS-CoV-2 vaccination in mothers of young children through transplacental antibody transfer and breast milk.

METHOD

This literature review implemented the PICO (Population, Intervention, Comparison, and Outcome) guideline to develop the review question.

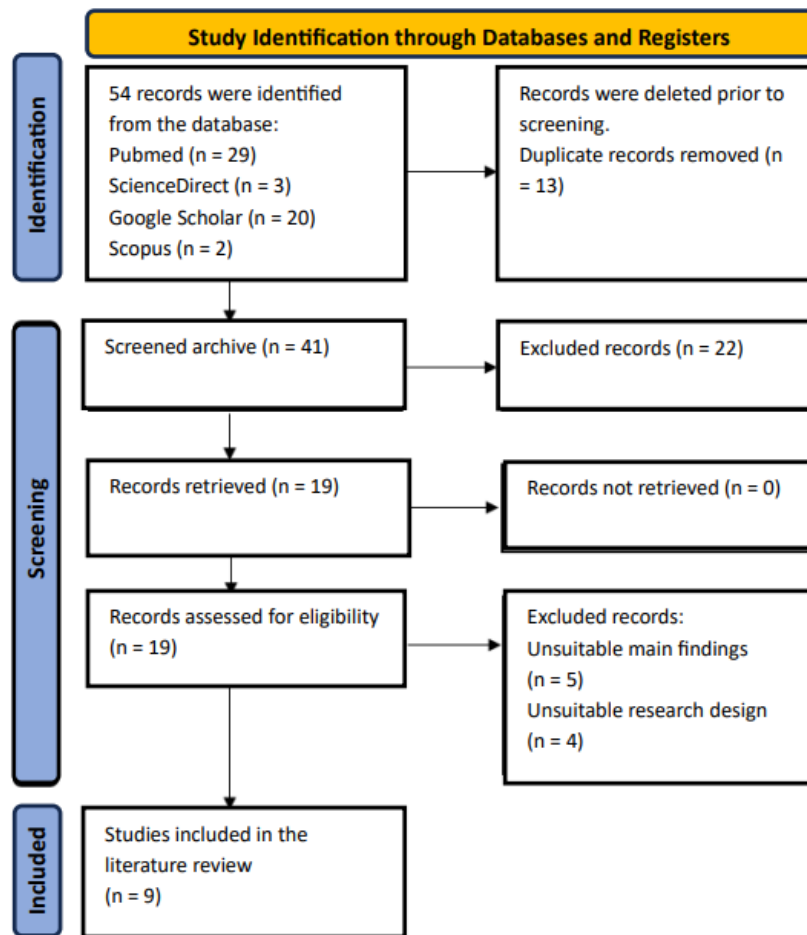
The question for this review: What is the result of COVID-19 vaccination during pregnancy on the transplacental transfer of antibodies to infants and through breast milk?

The breakdown of the PICO from the developed question is as follows.

Population	Intervention	Comparison	Outcome
Pregnant women who received the COVID-19 vaccine.	COVID-19 vaccination administered during pregnancy.	Pregnant women who did not receive the COVID-19 vaccine or antibodies	1. Presence of COVID-19 antibodies in infants through transplacental transfer. 2. Presence of COVID-19 antibodies in breast milk.

		through natural infection.	
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The researchers performed a literature review of ScienceDirect, Scopus, PubMed, and Google Scholar databases. Keywords were used to conduct a literature search such as "antibody transfer", "COVID-19 vaccine", "newborn immunity", "pregnancy", and "SARS-CoV 2 antibodies". Searches were limited to publications from 2020 to 2023 and screened based on predefined inclusion and exclusion criteria. Only English-language literature that was fully accessible or freely available online was included. A total of 54 articles were identified: 29 from PubMed, 3 from ScienceDirect, 20 from Google Scholar, and 2 from Scopus. After deduplication using the Elicit program, 13 duplicate records were removed, leaving 41 articles. Title and abstract screening resulted in the exclusion of 22 articles that did not meet the eligibility criteria, leaving 19. Of these, 18 were fully accessible to the researchers, and one was freely available online. Full-text screening excluded an additional 9 articles, 5 for addressing unrelated main findings and 4 for employing inappropriate research methodologies. The data were concisely synthesized and presented using narrative text and tables. To meet the study goals, descriptive there were analyzed along with group discussions, utilizing the retrieved data as well as pertinent references.



Picture 1. PRISMA Diagram Cycle

RESULT AND DISCUSSION

Nine literary works that have been considered share the following characteristics: they were released between 2020 and 2023. English was utilized in the nine literary works, eight of them were full texts accessible to researchers, and one can be summarized at no cost through the website. The nine included literature were case reports, cohort studies, cross-sectional, rapid reviews, and systematic reviews. By looking at the findings and discussion of each piece of included literature, this literature review design qualitatively descriptively analyzed the material. The researchers devised a table for the systematic extraction of pertinent data, in alignment with the specific themes under consideration in this overview of the literature. The compiled data within the table encompassed details such as the journal title, authorship, publication year, study design, geographical region, intervention/setting, and the primary outcomes derived from each study. While all the studies incorporated keywords such as pregnancy, the COVID-19 vaccination, the conveyance of antibodies, neonatal immunity, along SARS-CoV-2 antibodies, it is noteworthy that a subset of the included studies did not explicitly delve into

these topics. Nevertheless, it is imperative to underline that all studies retained the requisite data sought by the researchers.



Table 1. Data Extraction of Literature Search Results

No	Author	Title	Objective	Population	Intervention	Outcome and Result
1.	(Kugelman et al., 2022)	Maternal and Neonatal SARS-CoV-2 Immunoglobulin G Antibody Levels at Delivery After Receipt of the BNT162b2 Messenger RNA COVID-19 Vaccine During the Second Trimester of Pregnancy.	Cohort-study to assess antibody transfer in pregnant women vaccinated with two doses of COVID-19 vaccine.	Women with one pregnancy beyond 24 weeks gestation, vaccinated at least 7 days before, without prior COVID-19 infection.	Received second dose of COVID-19 vaccine at ≥ 24 weeks gestation.	Placental antibody transfer was observed, indicating successful transplacental passage of antibodies following full COVID-19 vaccination during pregnancy. Breast milk antibody presence was not assessed.



2.	(Nir et al., 2022)	Maternal-Neonatal Transfer Of SARS-Cov-2 Immunoglobulin G Antibodies Among Parturient Women Treated With BNT162b2 Messenger RNA Vaccine During Pregnancy.	Cohort-study comparing antibody transfer between vaccinated and COVID-19-recovered pregnant individuals.	Pregnant individuals who received Pfizer-BioNTech (BNT162b2) mRNA vaccine while conceiving compared to COVID-19-recovered pregnant females.	Pfizer-BioNTech (BNT162b2) mRNA vaccine during pregnancy.	Placental antibody transfer was present in vaccinated individuals, comparable to or greater than that in COVID-19-recovered pregnant individuals. Breast milk antibody presence was not evaluated.
3.	(Gray et al., 2021)	COVID-19 Vaccine Response In Pregnant And Lactating Women: A Cohort Study.	Cross-sectional study to determine antibody transfer after COVID-19 vaccination during various trimesters of pregnancy.	Pregnant women who received Pfizer or Moderna; first dose at mean 23.2 weeks, mostly in 2nd trimester (46%), 1st (13%), and 3rd (40%).	COVID-19 mRNA vaccination during 1st, 2nd, or 3rd trimester.	Antibodies were detected both in cord blood and breast milk, with measurable transplacental transfer and secretion into breast milk, regardless of trimester at the time of vaccination.

4.	(Muyldermans et al., 2022)	The Effects of COVID-19 Vaccination on Lactating Women: A Systematic Review of the Literature.	Systematic review to investigate antibody presence following various COVID-19 vaccines during pregnancy or lactation.	Pregnant or nursing women vaccinated with multiple COVID-19 vaccine types.	Pfizer, Moderna, AstraZeneca, Johnson & Johnson, or inactivated SARS-CoV-2 vaccines	Breast milk samples contained antibodies following various types of COVID-19 vaccination during pregnancy or lactation, but no data was provided on placental antibody transfer.
5.	(Cassidy et al., 2023)	Assessment of Adverse Reactions, Antibody Patterns, and 12-month Outcomes in the Mother-Infant Dyad after COVID-19 mRNA Vaccination in Pregnancy.	Cohort-study to study antibody transfer via breast milk following COVID-19 vaccination during pregnancy and postpartum booster.	Women vaccinated with COVID-19 mRNA vaccine during any pregnancy stage; some received third dose after delivery.	Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) during pregnancy, with possible postpartum booster.	Breast milk was shown to contain antibodies following mRNA vaccination during pregnancy and/or postpartum booster, but placental antibody transfer was not reported in this study.



6.	(Beharier et al., 2021)	Efficient Maternal To Neonatal Transfer Of Antibodies Against SARS-Cov-2 And BNT162b2 Mrna COVID-19 Vaccine.	Cohort-study to compare maternal and fetal humoral response following antenatal BNT162b2 vaccination versus natural SARS-CoV-2 infection.	Pregnant women grouped into vaccinated (n=86), infected (n=65), and unvaccinated controls (n=62) across 8 Israeli medical centers; blood samples taken at delivery.	BNT162b2 mRNA vaccination during pregnancy.	Maternal IgG (anti-S, RBD) from BNT162b2 crossed placenta with near-maternal levels in fetus within 15 days; transfer lower in 3rd vs. 2nd trimester infection; fetal IgM only detected in infection group; breast milk data not reported.
7.	(Sajadi et al., 2023)	Maternal Transfer Of Iga And Igg SARS-Cov-2 Specific Antibodies Transplacentally And Via Breast Milk Feeding.	Cross-sectional study to evaluate antibody transfer in vaccinated breastfeeding mothers.	Mother-infant pairs; mothers breastfed and were vaccinated before or after delivery.	COVID-19 vaccination before or after delivery during breastfeeding.	Both placental and breast milk antibody transfer were confirmed, with antibodies detected in cord blood and breast milk of mothers vaccinated during pregnancy or postpartum.

8.	(Ghorbani et al., 2023)	Effectiveness, Immunogenicity and Safety of COVID-19 Vaccination in Pregnant Women: A Rapid Review Study.	Rapid review study to determine antibody transfer from mRNA and inactivated vaccines during pregnancy.	Pregnant women who received Sinopharm BIBP (inactivated), Pfizer-BioNTech (BNT162b2), or Moderna (mRNA-1273).	Vaccination with mRNA or inactivated COVID-19 vaccines during pregnancy.	Antibodies were present in both the placenta and breast milk following administration of either mRNA or inactivated COVID-19 vaccines during pregnancy, supporting dual routes of passive immunity.
9.	(Kigel et al., 2023)	Maternal Immunization During the Second Trimester with BNT162b2 mRNA Vaccine Induces a Robust IgA Response in Human Milk: A Prospective Cohort Study.	Cohort-study to compare antibody levels in breast milk between vaccinated postpartum women and pre-pandemic controls.	73 women vaccinated with Pfizer-BioNTech (BNT162b2) during 2nd or 3rd trimester; compared to 16 breast milk samples from pre-pandemic controls.	Pfizer-BioNTech (BNT162b2) during 2nd or 3rd trimester of pregnancy.	Antibodies were detected in the breast milk of women vaccinated with mRNA vaccines during the second or third trimester, whereas pre-pandemic control samples lacked such antibodies. Data on placental transfer was not reported.

Before delving into the data regarding the placenta and breast milk as routes for the transmission of maternal antibodies, it is crucial to underscore that as of now, there is no proven correlation to immunity towards COVID-19 disease or SARS-CoV-2 infection (Krammer, 2021). Vaccines and natural infections both provide protection through various mechanisms. The assessment of individual elements, like the antibody response, is more straightforward compared to measuring cellular immune responses. As a result, much of the research in this field has predominantly concentrated on studying antibody responses (Jorgensen, Burry and Tabbara, 2022). The vaccination's efficacy may be correlated with quantities of antibodies that specifically neutralize SARS-CoV-2, based on many published research (Khoury *et al.*, 2021). Based on the literature reviewed, the safety of COVID-19 vaccination during pregnancy is examined efficacy administration while expecting to transfer immunity from mother to baby through both transplacental transmission and breast milk.

From Table 1. Research studies exploring the concept of antibody transfer from mothers to infants, as depicted in Table 1, were conducted in various countries, including Israel ($n = 4$), the USA ($n = 1$), Iran ($n = 2$), Spain ($n = 1$), Brazil ($n = 1$), Italy ($n = 1$), Poland ($n = 1$), Portugal ($n = 1$), Singapore ($n = 1$), and The Netherlands ($n = 1$). These studies investigated the effectiveness of administering the COVID-19 vaccine's efficacy on the presence of antibodies in infants.

A total of nine studies were identified that evaluated transplacental antibody transfer and the transfer via breast milk to infants. The initial discussion related to research reports that exclusively mention the transfer of antibodies to infants through the transplacenta includes studies numbered 1, 2, and 6. Studies numbered 3, 7, and 8 reported both transplacental and breast milk antibody transfer. Studies numbered 4, 5, and 9 exclusively reported the transfer of antibodies through breast milk without discussing transplacental transfer. In addition, study number 6 reported fetal IgM response detected only in the infection group.

The first study demonstrated that mothers who obtained the COVID-19 mRNA vaccination from Pfizer-BioNTech (BNT162b2) in a double dose during their second trimester developed antibodies against COVID-19. These mother's

antibodies were passed through the placenta and into the newborns, as evidenced by antibody levels in newborns that were on average 2.6 times higher than in their mothers at delivery. All mothers in the study had positive COVID-19 antibody levels at delivery. Additionally, a favorable association was shown between mother as well as newborn antibody levels, meaning that mothers with higher antibody levels tended to have newborns with higher antibody levels as well. This data shows that mRNA vaccination during pregnancy confers protection for both mothers and infants through placental antibody transfer.

The second investigation's findings by Nir et al. align with the first study's findings. Nir's study looked at females who got the Pfizer BioNTech mRNA (BNT162b2) vaccination in two doses within 14 days before giving birth. It furthermore found efficient transmission of the mother's SARS-CoV-2 antibodies (IgG) towards the newborn via the placenta. Similar to the first study, a favorable association was seen between the concentrations of mother blood and neonatal cord blood of these antibodies. Additionally, vaccinated mothers were found to have significantly higher levels of their blood samples including cord blood from neonates with SARS-CoV-2 IgG opposed to mothers who had simply recovered from COVID-19 naturally. This reinforces the conclusion that mRNA vaccination during pregnancy confers high levels of antibody protection against COVID-19 in newborns.

In the sixth study, the multivariable analysis indicated that babies conceived to third-trimester individuals carrying the SARS-CoV-2 virus, as opposed to early pregnancy, were less likely to be born with neutAb or anti-S IgG+. Conversely, maternal vaccination before delivery was associated with increased odds of infants possessing neutAb or anti-S IgG+ from birth, as opposed to those not vaccinated (Lacourse et al., 2023)."

Next, research numbers fourth, fifth, and ninth exclusively report the sole way that antibodies are given to babies via breast milk. As reported by Muyldermans *et al.* (2022), a pregnant woman injected along mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) or ChAdOx1 nCoV-19 (Oxford - AstraZeneca) or JNJ-78436735 (Johnson & Johnson) as or the SARS-CoV-2 entire virus inactivation, with no specific dosage and semester of pregnancy, at least



during pregnancy has great potential to transfer antibodies to infants through breast milk. In the fifth research, expectant mothers were immunized with COVID-19 mRNA using Moderna's mRNA-1273 nor Pfizer-BioNTech's BNT162b2 at any time while gestation, with 2-3 doses (Cassidy *et al.*, 2023).

The ninth study examined 62 breastfeeding women who had gotten the COVID-19 mRNA vaccination while in the third or second trimester of pregnancy. Notably, the study found that vaccination with two doses regarding the Pfizer-BioNTech vaccination (BNT162b2) prompted high levels of IgA antibodies against COVID-19 in breast milk, especially colostrum milk produced shortly after birth. The highest IgA levels were seen when, in the subsequent trimester, the second vaccination dosage was administered. Since IgA antibodies protect mucous membranes and are present in milk throughout lactation, this implies that vaccination during pregnancy could offer defense to infants via breastfeeding. These IgA antibodies are being transferred underscoring the importance of maternal vaccination for infant health.

In contrast to studies exclusively reporting antibody transfer via either the transplacental or breast milk routes, evidence was uncovered indicating that pregnant women receiving the vaccine during the 1st, 2nd, or 3rd trimester, or throughout the gestational phase, demonstrated antibody transfer through both transplacental and breast milk pathways to infants, as seen in studies numbered 3, 7, and 8, as delineated in Table 1.

In the third study it is reported, that the umbilical cord with the lowest levels of RBD along with SARS-CoV-2 spike resistance of IgG antibodies proteins belonging to a mother whose two initial vaccinations were administered in between, having obtained her first dosage just seventeen days before giving birth. This indicates that having both doses may be crucial for maximizing the transfer of immune protection to the baby (Gray *et al.*, 2021). Notably, the amount of S-specific IgG1 transferred increased noticeably to the cord over time after the booster dose. IgA and IgM antibodies against RBD in breastmilk did not increase significantly after either vaccine dose. However, IgG1 antibodies against RBD rose significantly from baseline (V0) to after the second dose (V2), but not from baseline to following the initial dosage (V1). This suggests that the subsequent vaccine dose

boosts the transfer of IgG antibodies to breast milk, while IgA antibody transfer remains consistent but unboosted (Gray *et al.*, 2021). However, other research reported, that high-titer anti-spike IgA presence was actually present in the nares of babies whose moms had antepartum vaccinations was also an unexpected finding (Sajadi *et al.*, 2023).

The primary outcomes from the seventh study conducted by Sajadi *et. al.* (Table 1) regarding the transfer of antibodies through both transplacental and breast milk routes suggest that infants who are fed with breast milk develop anti-spike IgG antibodies throughout the body only become mothers are present received the vaccination during pregnancy. As a result, the most effective approach for providing both systemic and local anti-SARS-CoV-2 antibodies to babies seems to involve immunization during pregnancy, then nursing.

The eighth study by Ghorbani *et al.* (2023), it is reported that vaccination against COVID-19 throughout pregnancy poses not at danger of virus transmission to babies throughout breastfeeding, since the vaccines do not contain live virus. Moreover, antibodies produced after breast milk may guard newborns against vaccinations. Overall, the study demonstrated that vaccination is effective in pregnant women - it helps them develop strong COVID-19 immunity, enabling the transmission of shielding antibodies to young children through breastfeeding and the placenta.

Maternal IgG by attaching to newborn Fc receptors, antibodies are transported from the mother to the fetus through the placenta. (FcRn) (Borghi *et al.*, 2020). This literature review demonstrated this transplacental antibody transfer - mothers vaccinated against SARS-CoV-2 antepartum passed anti-spike IgG and IgA antibodies to their infants. Additionally, consistent with prior research, the review found that vaccination during pregnancy can elicit suppressing SARS-CoV-2-related antibodies in infant milk, thereby conferring protection to infants (Narayanaswamy *et al.*, 2022).

This is one of the few literature reviews that examine the effects of the SARS-CoV-2 vaccine and the transfer of antibodies to infants via placenta and breast milk. The included studies had geographically diverse populations spanning 10 countries globally. They examined the transmission of antibodies across the



placenta as well as breastmilk, demonstrating the existence alongside the capacity of antibodies to fend against SARS-CoV-2 in newborns. This review provides real-world answers to pressing questions from physicians and mothers about The COVID-19 vaccine during gestation. The implications extend beyond just this pandemic - the objective evidence generated can guide strategies to optimize maternal and infant health outcomes in potential future disease outbreaks. These globally representative data lay the groundwork for evidence-based pandemic planning and management.

This research has flaws too. Reporting bias could skew findings since COVID-19 cases in babies and breastmilk get more attention. Also, cherry-picking some examples to support hypotheses is questionable.

CONCLUSION AND SUGGESTION

This study offers supporting evidence indicating that the administration of giving pregnant women an mRNA vaccination in either the second or third trimesters increases vaccine-specific IgA and IgG levels through either transplacental transmission or breastfeeding. Therefore, thus recommend the BNT162b2 mRNA vaccination administered to mothers in the subsequent trimester as the most advisable approach. While breastfeeding holds numerous advantages for infants, there is a lack of substantial evidence suggesting a significant transmission of SARS-CoV-2-specific antibodies from mothers who received vaccinations to their offspring if vaccination occurs postpartum. Therefore, prospective mothers are encouraged to consider receiving the vaccine before delivery and contemplate breastfeeding if parents wish to give their babies antibodies particular to SARS-CoV-2.

DECLARATION

Conflict of Interest

The authors confirm that there are no conflicts of interest to disclose.

Authors' Contribution

The author designed the study, selected and reviewed the relevant literature, and synthesized the findings. The manuscript was entirely drafted, critically reviewed, and edited by the author.

Ethical Approval

This study did not use Ethical Approval.

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Data Availability

All data discussed in this study are included in the manuscript. The analyzed datasets can be obtained from the corresponding author upon reasonable request.

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