Review on the efficiency of maternal to child antibody transfer after COVID-19 vaccination during pregnancy

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Abstract

Background: Newborns are at increased risk for severe COVID-19. Transplacental antibody transfer can provide newborns with a passive immunity, which is why vaccination of pregnant women is in the best interest of both mother and child. It is now recommended that pregnant women receive COVID-19 vaccination because of increased risk of severe COVID-19 disease complications during pregnancy.
Objectives: The aim of this review was to summarize currently available evidence on the efficiency of SARS-CoV-2-specific transplacental antibody transfer from mother to child after COVID-19 vaccination during pregnancy.
Design: Literature review
Data sources: ClinicalTrials.gov, Medline, ScienceDirect, bioRxiv, medRxiv, and PubMed from 1st January 2020 to 18th February 2022. An updated search was performed on 15th March 2022.
Methods: In the absence of clinical trials conducted on vaccination during pregnancy, electronic databases were searched for cohort studies reporting on antibody titers in mothers and infants after COVID-19 vaccination during pregnancy. The primary outcome was infant-to-mother IgG antibody transfer ratio (ATR). Secondary outcomes include ATR dependence on vaccination timing, and the difference in ATR between vaccination and natural SARS-CoV-2 infection during pregnancy.
Results: 10 studies were included, with an immunoglobulin G (IgG) ATR range of 0.34 to 2.6. The majority (6/10) reported transfer ratios around one. Four studies reported a significant association between mother and child antibody titers and timing of vaccination during pregnancy, with an optimal ART for vaccination during the late 2nd trimester, early 3rd trimester. Four studies recorded data comparing vaccination and natural infection during pregnancy and showed conflicting results regarding the comparison in ATR. However, all of these did establish higher antibody titers after vaccination as opposed to infection.
Conclusion: Although the data regarding the exact ATR and ideal timing for vaccination during pregnancy are inconclusive, this literature review supports maternal COVID-19 vaccination as a means to provide newborns with SARS-CoV-2-specific antibodies and showed higher overall vaccine-induced antibody titers in both mother and child, when compared to natural infection. Communicating these findings to pregnant women might encourage them to get vaccinated after being appropriately informed on the benefits and risks.

Abbreviations

COVID-19: coronavirus disease 2019
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
TR: transfer ratio
GA: gestational age
IgG: immunoglobulin G
IgM: immunoglobulin M
RBD: receptor binding domain
S protein: spike protein
RCT: randomized control trial
Abs: antibodies
nAbs: neutralizing antibodies
AU/mL: arbitrary units per milliliter blood

Layman summary

Both pregnant women and newborns are at increased risk for severe COVID-19. Newborns are at high risk to catch infectious diseases as their immune system is still developing. COVID-19 vaccination for pregnant mothers can protect them from infection and provide a passive immunity for their infant. The World Health Organization (WHO) recommends COVID-19 vaccination during pregnancy; however, studies looking into the efficiency of those vaccines in the transfer of antibodies through the placenta are limited. The objective of this literature review was to gather and review the existing literature on the efficiency of vaccine-induced antibody transfer, assessed through an infant-to-mother antibody ratio. A wide range of data sources were accessed in search for scientific papers, which were then assessed on content and quality. Information was gathered on antibody transfer ratios, along with potential determinants. All included papers showed mother-to-infant transfer of SARS-CoV-2-specific antibodies. The exact ratio at which this occurred was dependent on a number of variables, of which vaccination dose and timing were suggested as the most important. Further research will be necessary to determine the exact antibody transfer ratio, as well as the ideal timing and vaccine-targets to maximize neonatal immunity.

Introduction

On the 11th of March 2020, WHO declared the severe acute respiratory syndrome coronavirus 2 a pandemic (Centers for Disease Control and Prevention (CDC), 2022a). Since the first human infections in late 2019/early 2020, there have been over 418 million confirmed cases of COVID-19, leading to 5.8 million deaths (World Health Organization (WHO), 2022a). Pregnant women and young infants are at higher risk for severe illness with COVID-19 infection (Centers for Disease Control and Prevention (CDC), 2022b; Stafford, Parchem, & Sibai, 2021; Wang, Sibaii, Lee, J. Gill, & L. Hatch, 2021). The increased risk for pregnant mothers is due to physiological and mechanical changes that happen during pregnancy (Stafford et al., 2021). Furthermore, women with COVID-19 infection during pregnancy are more likely to experience preterm birth and stillbirth, along with other pregnancy complications (Stafford et al., 2021). WHO categorized pregnant women into the high-priority group for COVID-19 vaccination (World Health Organization (WHO), 2020). Newborn children are at increased susceptibility for infectious agents due to the fact that their immune system is not fully developed yet (Dong et al., 2020; Kim et al., 2020; Palmeira, Quinello, Ana, Zago, & Carneiro-sampaio, 2012). As a result of a slower immune response, vaccine-mediated prevention of infection at or soon after birth is bound to a few early-life vaccines, which does not include COVID-19 (Kollmann, Kampmann, Mazmanian, Marchant, & Levy, 2017). Young infants (<6 months old) are at increased risk for severe COVID-19 upon infection and are too young to be vaccinated (Adeyinka, Bailey, Pierre, & Kondamudi, 2021; World Health Organization (WHO), 2020). This is why they crucially rely on maternal antibodies for protection during early life. The active transfer of maternal immunoglobulins across the placenta is a known process, exploited in maternal vaccination to protect newborns against infectious diseases through short-term passive immunity (Palmeira et al., 2012). This adaptive mechanism could protect the newborn from infection during what is likely the most sensitive time of his or her life. Maternal vaccination has already been proven an effective means to prevent other infections such as pertussis, tetanus, and influenza, and is turning into a central component in the fight against newborn RSV infection (Kollmann et al., 2017; Palmeira et al., 2012). The question is whether this will also be the case for COVID-19 prevention.

Scientists all over the world have strived to develop a vaccine against COVID-19. A number of vaccines have been proven safe and effective, including those from Moderna, AstraZeneca, and Pfizer (World Health Organization (WHO), 2022b). However, none of the clinical trials undertaken for FDA approval included pregnant women, with much controversy regarding COVID-19 vaccination during pregnancy as a result

(Theiler et al., 2021). During the pandemic it became evident that pregnant women are at increased risk for severe COVID-19 and case-reports started providing evidence on vaccination safety during pregnancy. These findings lead to the reconsideration and final recommendation of COVID-19 vaccination during pregnancy. However, until recent recommendations, vaccination coverage among pregnant women has been low, and the number of studies reporting on vaccine-induced passive immunity in newborns is consequently limited (Lipkind et al., 2022).

The main vaccines included in this literature review are mRNA vaccines (Pfizer and Moderna). mRNA vaccines provide the genetic coding for the SARS-CoV-2 spike protein to the body. Once inside, the cells translate the mRNA into protein and display it on their cell surface where it is recognized by the immune system. Antibody-producing cells react to this antigen and start producing spike protein-specific antibodies. These antibodies attach to the virus and prevent it from infecting new cells. The coronavirus genome includes four main proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N). The S protein is a characteristic surface protein on the coronavirus envelope, which is used to attach and infect host cells. There are multiple domains on each monomer of the spike protein (which is a homotrimer): the receptor binding domain (RBD), S1 subunit, and S2 subunit. The RBD is the part of the spike protein that is responsible for docking onto the host cells and therefore the main target for antibodies produced after vaccination (Letko, Marzi, & Munster, 2020). During an immune response, the body will first show a rise in immunoglobulin M (IgM), the early infection response, and produce immunoglobulin G (IgG) thereafter, the sustained immune response. IgM can show whether someone has recently been infected, IgG is what you look for to identify long-lasting immunity. These IgM and IgG are part of the primary reaction of the body to SARS-CoV-2 infection. There are different types of antibodies that the immune system can produce: neutralizing and non-neutralizing antibodies. The main difference between both is that neutralizing antibodies inhibit infection of new cells, whereas non-neutralizing antibodies don't. Infection is prevented by binding to the virus in such a way that it can no longer infect the cell. For SARS-CoV-2 this can be achieved by blocking the RBD of the S protein so it can no longer attach to a human cell.
IgG is the only antibody class that can significantly cross the placenta. The rate at which this happens depends on multiple factors including 1) maternal antibody levels, 2) gestational age (GA), 3) placental integrity, and 4) antibody subtype (IgG1, IgG2, IgG3, IgG4) (Palmeira et al., 2012). A difference in efficiency of transplacental uptake between antibodies directed towards the S protein overall, or specifically the RBD, and between non-neutralizing and neutralizing antibodies is highly likely, but what those exact proportions are remains to be established proven.

Immunization during pregnancy can benefit both mother and child by protecting the mother against infection and providing a temporal postnatal protection of the infant through antibodies acquired across the placenta during pregnancy. The antibody transfer ratio (ATR) is used as a measure of vaccination efficacy to provide the neonate with this passive immunity, assessed by comparing antibody titers in mother and infant at birth. The ATR for vaccination is dependent on type of vaccine, the maternal antibody levels and timing of vaccination during pregnancy (Clements et al., 2020). In pursuit of the best possible early-life protection for neonates, the ideal combination of vaccine type and timing are sought to maximize the ATR. Optimal timing for COVID-19 vaccination during pregnancy is yet to be determined, along with the comparison of ATR for vaccination and natural infection.

Objectives

This literature review aims to gather information on the efficiency of transplacental antibody transfer from mother to fetus. The aim is to systematically review the efficiency of transplacental antibody transfer after COVID-19 vaccination during pregnancy. Secondary objectives include determining the ideal time window

for vaccination to acquire optimal antibody transfer and the difference in antibody transfer between vaccination and COVID-19 infection during pregnancy.

Methods

Search strategy

The search included six electronic databases with studies published between January 1st, 2020 and February 18th, 2022: ClinicalTrials.gov, Medline, ScienceDirect, PubMed, bioRxiv, and medRxiv. The combination of used search terms is provided the appendix. In addition, the reference lists of selected articles were searched manually for further articles. The used search terms are shown in the appendix.

Study selection

All English articles reporting on cohort studies and randomized control trials (RCT) were included. Studies were included if they included pregnant women a who had received at least one mRNA COVID-19 vaccination during pregnancy and reported antibody titers for both mother and infant at birth. Exclusion criteria were a) case reports or case-series, c) lack of antibody titers for infant, d) lack of authors mentioned, g) fail to report at least two of the following criteria: GA at birth, time between vaccination and birth, vaccine type, vaccination status ascertainment, study location, timing of study, average age of participants. Selections happened through title screening, followed by abstract screening, and lastly, a full-text screening.

The following data was collected from each paper: author name, publication date, study design and setting, sample size, vaccine type and assessment, gestational age (GA) at vaccination (both 1st and 2nd dose), time between vaccination and delivery (both 1st and 2nd dose), antibody type and essay, premature births, and outcomes (ATR, time dependence of ATR on vaccination, and comparison of ATR between vaccination and natural infection). When the ATR was not specifically reported, it was manually calculated using antibody titers in mother and infant.

Outcome measures

The primary outcome measure was efficiency of transplacental SARS-CoV-2-specific antibody transfer from mother to infant after maternal vaccination with an mRNA COVID-19 vaccine. Efficiency was defined using the ATR, which is the titer of SARS-CoV-2-specific IgG antibodies in the infant at birth divided by the titer in the mother at the same time-point. An active transfer of antibodies across the placenta is indicated by an ATR >1, which means antibody titers in the infant at birth exceed those in the mother. Secondary outcome measures were the association between ATR and GA at the time of COVID-19 vaccination, along with the difference in ATR between full- and preterm births. Multiple studies included COVID-19 positive, unvaccinated pregnant participants, which were used to evaluate the difference in ATR between dyads who were either vaccinated or naturally infected during pregnancy. Premature births were defined as children born at a GA under 37 weeks.

Antibody tests are used to determine the presence (qualitative) and amount (quantitative) of antibodies in the blood. There are different ways of measuring antibody titers, among which are immunoassays and, more specifically, neutralization assays. Immunoassays are based on the binding of the antibody to a specific antigen to detect and measure the presence of that antibody. Key to antibody quantification is the production of a measurable signal in response to the binding reaction. A virus neutralization assay looks specifically at the antibody's ability to neutralize the virus (prevention of infection). Neutralization assays are done by serially diluting the blood sample, incubating the dilutions with viral particles, and testing the

infectivity of the virus in each dilution. The neutralizing antibody titer can then be calculated by knowing which dilution achieves a certain level of neutralization. In the case of this review, antibody essays are used as a means to estimate the immune response induced by COVID-19 vaccination. Studies included reported antibody titers by total anti-SARS-CoV-2 IgG, anti-RBD, anti-S1, anti-S2, anti-N, and/or neutralizing antibodies. In the comprised studies, antibody levels (titers) were reported as: arbitrary units per milliliter (AU/mL) (Collier et al., 2021; Gray, Bordt, Atyeo, & Al., 2021; Mithal & Otero, 2021; Nir et al., 2022; Rottenstreich, Zarbiv, Oiknine-djian, & Zigron, 2021; Zdanowski & Wasniewski, 2021), inhibition percentage (Shen et al., 2022), and relative index value (Yang et al., 2022). AU/mL is the most common form of representing antibody titers. The inhibition percentage presented by Shen et al. is calculated using the fraction of binding between the RBD domain of the spike protein to the host cell receptor in a sample with antibodies and a negative control without antibodies. This fraction is subtracted from one and multiplied by 100. If the inhibition percentage is high, the fraction is small, this means that the level of free RBD was small and many antibodies were bound, therefore the antibody titer was high (Embregts et al., 2021). The relative index value used by Shen et al. is defined as the instrument readout of the test sample antibody value divided by the instrument cutoff value (mean readout of noninfected and nonvaccinated control samples+6 standard deviations (SDs)). It's hard to say whether these different assays are comparable to the ones represented by AU/mL. One could however argue that the primary outcome of interest is a ratio and therefore not subjective to measurement units.

Analysis

This literature review provides a narrative synthesis of the available literature. The primary endpoint is the ATR after vaccination. When ATR was not directly provided in the research papers, it was calculated as mother IgG / umbilical cord IgG. A linear regression of ATR in relation to days between vaccination (or natural infection) and birth was calculated.

Results

Search results

During the search for research papers reporting on the efficacy of transplacental antibody transfer after SARS-CoV-2 vaccination during pregnancy, different internet sources such as PubMed, ScienceDirect, Medline, ClinicalTrial.gov, bioRxiv, and medRxiv were used. Forty-six records were retrieved through the database search. The searched key words are shown in the supplementary material.
Twenty-nine records were removed after title and abstract screening and six after examination of full text reports. Studies were excluded for different reasons: seven due to lack of vaccinated participants with the COVID-19 vaccine, six due to not being a cohort study or RCT, six due to lack of antibody titer measurements in mother and/or child, five duplicates, three due to being single-case studies, two due to exclusion of pregnant women, two due to exclusion of mRNA vaccines, two due being an animal studies, one due to the absence of information on GA at vaccination and average age of participants, one due to only partial gathering of maternal blood samples without matching them to the umbilical cord samples, one due to pregnancy through IVF, and finally. In total, ten critical cohort studies were identified, all confirming antibody transfer during pregnancy, with different transfer ratios (umbilical cord IgG / mother IgG)..

Study characteristics

Study characteristics are shown in Table 1.

There were eight primary cohort studies, each reporting on different cohorts (Beharier et al., 2021; Collier et al., 2021; Gray et al., 2021; Kugelman et al., 2021; Nir et al., 2022; Rottenstreich et al., 2021; Shen et al., 2022). All studies were peer-reviewed publications. Of the eight studies, five were based in Israel (Beharier

et al., 2021; Collier et al., 2021; Nir et al., 2022; Rottenstreich et al., 2021). This is likely due to the fact that the Ministry of Health in Israel recommended COVID-19 vaccination of pregnant women as of January 2021, whereas the CDC and the NHS only officially recommended COVID-19 vaccination during pregnancy in respectively August and October of that same year (Centers for Disease Control and Prevention, 2021; National Health Service (NHS), 2021; The Washington Post, 2021). Of the additional three papers, one was performed in Massachusetts, USA (Gray et al., 2021), another in New York, USA (Prabhu et al., 2021) and the third in Kaohsiung, Taiwan (Shen et al., 2022). There were three studies that weren't prospective cohort studies. One was a prospective case study, conducted in Illinois, USA (Mithal & Otero, 2021), the other two were retrospective cohort studies, from USA and Poland (Yang et al., 2022; Zdanowski & Wasniewski, 2021).

All papers clearly stated objective assessment of vaccination status, except for three papers: two where there was no indication on where the vaccination information was obtained at all (Beharier et al., 2021; Kugelman et al., 2021), and another where only self-reported vaccination is mentioned (Gray et al., 2021). The inclusion criteria regarding the number of COVID-19 vaccination doses differed per study. Some studies only included pregnant women who had received both COVID-19 vaccination shots (Kugelman et al., 2021; Nir et al., 2022; Rottenstreich et al., 2021; Zdanowski & Wasniewski, 2021), other studies included pregnant women with both one and/or two doses (Beharier et al., 2021; Collier et al., 2021; Mithal & Otero, 2021; Shen et al., 2022; Yang et al., 2022). Three studies explicitly indicated the absence of preterm deliveries (Shen et al., 2022; Yang et al., 2022; Zdanowski & Wasniewski, 2021), two studies mentioned (a minority of) preterm deliveries (Beharier et al., 2021; Gray et al., 2021). To assess whether studies included preterm deliveries when there was no clear mention of it, the inclusion criteria and average GA at birth were assessed. Three studies didn't mention preterm delivery but showed an average GA at birth of respectively 39.3 (SD 1.3), 38.7 (SD 1.3), 39.4 [IQR 38.3–40.7] (Kugelman et al., 2021; Nir et al., 2022; Rottenstreich et al., 2021), the other two studies didn't mention premature delivery nor average gestational age at birth (Collier et al., 2021; Mithal & Otero, 2021). The average maternal age was similar between studies and varied from 31 to 35. Race and ethnicity of the study population was not mentioned in five (5/10) of the studies (Nir et al., 2022; Rottenstreich et al., 2021; Shen et al., 2022; Zdanowski & Wasniewski, 2021). The other six primarily indicate either race or ethnicity. A comparison on race and ethnicity could therefore not be made between studies, although it is known that five (5/10) studies were conducted in Israel. One study collected samples from mothers before delivery, without clarification whether this is hours or days before delivery (Beharier et al., 2021). The number of women who were vaccinated during pregnancy and willing to provide umbilical cord samples varied widely between studies, with studies including 20 participants or less (Collier et al., 2021; Gray et al., 2021; Rottenstreich et al., 2021; Zdanowski & Wasniewski, 2021), to studies with over 100 participants (Kugelman et al., 2021; Yang et al., 2022).

Table 1. Study characteristics with primary and secondary results.

Author (country, year publication)	Study setting	Time period	No. dyads provided mother & cord serum		Preterm deliveries	Assessment of vaccination	Type of vaccine	Assessment of antibody titer	Outcomes			
			Vaccinated	Unvaccinated, infected					ATR vaccinated	ATR unvaccinated, infected	GA at vaccination	Time vaccination - delivery
Prospective cohort studies												
Beharier (Israel, 2021)	Multicenter consortium (8 hospitals), Israel	April 2020 – March 2021	86	65	Yes, a minority		Pfizer	Total SARS-CoV-2 IgG for S1, S2, RBD, and N	Total SARS-CoV-2 IgG: **± 1**[1,2]		TR<1 for infection < 30w GA	
Collier (Israel, 2021)	Multicenter records, Israel	April 2020 - March 2021	9	13	Not mentioned	Objective: medical records	Moderna, Pfizer	IgG for RBD nAbs, Non-nAbs	Anti-RBD IgG: **1.33**[2] nAbs: **0.32**[2]	Anti-RBD IgG: 0.47 nAbs: 1.09	1st dose: 17% < 14w 50% 14-28w 33% > 28w	2nd dose: 21 (14-36)d
Gray (USA, 2021)	2 care centers, Massachusetts, USA	December 2020 to March 2021	10		Yes, a minority	Subjective: self-reported	Moderna, Pfizer	nAbs, IgG to RBD-, and S-protein	Anti-RBD IgG: **0.91**[1,2*] Anti-S IgG: **0.78**[1,2*] nAbs: **0.5**[1,2*]		1st dose: 23.2 (16.3 - 32.1)w	1st dose: 36.5 (30-42)d 2nd dose: 14 (11-16)d
Kugelman (Israel, 2021)	Single medical center, Haifa, Israel	May - July 2021	114		Not mentioned, average GA: 39.3 ± 1.3		Pfizer	IgG for RBD	Total SARS-CoV-2 IgG: **2.6**[2]		1st dose: 21.9 ± 3.2w, 2nd dose: 24.9 ± 3.2w	2nd dose: 101± 21.0d
Nir (Israel, 2022)	Tertiary medical center, Israel	February - March 2021	64	11 (some also vaccinated)	Not mentioned, average GA: 38.7 ± 1.3	Objective: vaccinated with 2nd dose during study	Pfizer	IgG for RBD#	Anti-RBD IgG: **0.77**[2]	Anti-RBD IgG: 1.26 **	2nd dose: 33.5 ± 3.2w	2nd dose: 21.7± 11.0d
Rottenstreich (Israel, 2021)	Single medical center, Jerusalem, Israel	February 2021 → unclear	20		Not mentioned, average GA: 39.4 [38.3-40.7]	Objective: vaccinated with second dose during study	Pfizer	IgG for RBD and overall S-protein	Anti-RBD IgG: **0.34**[2] Anti-S IgG: **0.44**[2]			1st dose: 33 [30–37]d 2nd dose: 11 [9–15]d
Shen (Taiwan, 2022)	Single medical center, Kaohsiung, Taiwan		29 (26 double dose, 3 single dose)		No	Objective: medical records	Moderna, Pfizer	Neutralizing Abs	nAbs: **1.07**[1, WT] **0.99**[2, WT] **0.92**[1, D] **0.90**[2, D]		1st dose: 28.45 ± 2.64w 2nd dose: 33.31 ± 2.13w	1st dose: 70.0 ± 17.2d 2nd dose: 36.6 ± 14.3d

Prospective case series										
Mithal (USA, 2021)	Single medical center, Chicago, USA	January 2021 to March 2021	27 (22 two, 5 one dose)	Not mentioned	Objective: electronic health records	Pfizer, Moderna, Unknown (n=4)	IgG for RBD	Anti-RBD IgG: **1.0±0.6**[1,2***]	1st dose: 33 ±2w	2nd dose: 35 ±21d
Retrospective cohort studies										
Yang (USA, 2022)		March 2021 to October 2021	1321	No	Objective: electronic medical records	Pfizer, Moderna, Johnson & Johnson	IgG for S-protein ##	Anti-S IgG: **1 – 2**[2]	TR<1 for 2nd dose > 32w	
Zdanowski (Poland, 2021)	Provincial Specialist Hospital, Olsztyn, Poland	Still in progress	16	No	Objective: electronic medical records	Pfizer	IgG for N-protein and RBD	Anti-S IgG: **1.28**[2]	1st dose: 31.8±2.05w 2nd dose: 35.1±2.13w	1st dose: 59.5±14.5d 2nd dose: 38.5±14.7d

d: days; w: weeks; non-sign: not significant; []: interquartile range; ± is followed by a standard deviation
IgG: immunoglobulin G; RBD: receptor binding domain; S-protein: spike protein; N-protein: nucleocapsid protein; S1, S2: S1 and S2 subunit of the spike protein; nAbs: neutralizing antibodies
1: ATR after single vaccination dose; 2: ATR after two vaccination doses
WT: wild-type; D: delta SARS-CoV-2 variant
Infant antibody titers were measured from dried blood spots samples
use of relative index value for measurement of antibody titers
** HOWEVER, the maternal and blood cord SARS-CoV-2 IgG levels were significantly higher in vaccinated participants, compared to unvaccinated recovered participants. **All ATR values by Gray et al. are not significant. *** no distinction made between TR for single or double vaccinated women.

Primary outcome: infant-to-mother antibody ratio

All studies considered the effect of maternal COVID-19 vaccination during pregnancy and the resulting levels of SARS-CoV-2 specific antibodies in mother and infant. All studies found transplacental transfer of SARS-CoV-2 specific antibodies t, with four studies reporting active transfer (Collier et al., 2021; Kugelman et al., 2021; Yang et al., 2022; Zdanowski & Wasniewski, 2021).

As shown in Table 1, five studies only presented anti-S IgG ATR or anti-RBD IgG ATR, two additionally showed neutralizing antibody ATR. One study (Shen et al.) only present neutralizing antibody ATR and two studies (Beharier et al. and Kugelman et al.) only present total anti-SARS-CoV-2 IgG ATR. This is important to keep in mind as the transplacental transfer capacity might differ between specific antibodies.

Six studies showed an ATR of approximately one (between 0.8 and 1.3) (Beharier et al., 2021; Collier et al., 2021; Mithal & Otero, 2021; Nir et al., 2022; Shen et al., 2022; Zdanowski & Wasniewski, 2021). Two studies found lower values of 0.5, and 0.44 and 0.34 (Gray et al., 2021; Rottenstreich et al., 2021). The values reported by Gray et al. were however not statistically significant. Two different studies reported higher transfer ratio values of 2.6 and 1-2 (Kugelman et al., 2021; Yang et al., 2022). Remarkable is that the two studies with high values are also the two studies with the largest number of participants. Furthermore, Collier et al. reported separate ATR for SARS-CoV-2 RBD antibodies and neutralizing antibodies with respective values of 1.33 and 0.32.

Secondary outcome: vaccination timing and association to transfer ratio

Different studies found a significant association between the vaccination timing and ATR or infant antibody levels at birth (Kugelman et al., 2021; Mithal & Otero, 2021; Zdanowski & Wasniewski, 2021). These studies indicated a positive effect of increasing GA at the time of vaccination and subsequent ATR at birth. Although Rottenstreich et al. did not specify the effect of GA at vaccination on ATR, they did show an increase in both mother and child IgG levels for higher GA at vaccination. Zdanowski et al. however point out that the increase of IgG levels with GA at vaccination is time-limited by showing a decrease in ATR following vaccination (1st and 2nd dose) past a certain GA. Mithal et al. similarly showed that the infant-to-mother antibody ratio increases with increasing GA at vaccination, though the average maternal and infant IgG levels significantly decreases per additional week from second vaccination to birth in women vaccinated in their second trimester. Finally, Yang et al. clearly stated that the average ATR ranged between 1 and 2 for much of the time period of maternal vaccination initiation and dropped below 1 once vaccination initiation took place later than 32 weeks of gestation.

The studies by Nir et al. and Shen et al. did not find a significant correlation between timing of second vaccination dose and cord antibody levels at birth. However, Shen et al. only compared time intervals in the third trimester. Gray et al. and Collier et al. didn't mention any analysis on the association between vaccination timing and mother and child antibody titers at birth, however Gray et al. do mention that there was no difference observed in mother antibody titers between vaccinations in each trimester of pregnancy. The study by Beharier et al. reported on the association of final ATR and GA at infection with SARS-CoV-2 during pregnancy, and not vaccination. They found a significant increase in ATR at birth for participants infected prior to 30 weeks GA.

Comparison of one and two vaccine doses

Shen et al. also compared antibody titers between both pregnant women who received either one or two vaccine doses and found that the antibody titers in mothers and infants who received only one dose during pregnancy were significantly lower. Furthermore, the reported ATR for the one and two dose group was respectively 1.07 and 0.99, although the confidence intervals of both values overlapped and the number of cases in the single dose group was 3. Gray et al. reported antibody transfer ratios for both groups combined, although it is important to remark that nine out of ten participants had received two vaccine doses prior to delivery. They also showed that a lowest cord antibody titers where from the participant that delivered between first and second vaccine doses, with the first dose a little over 2 week prior to delivery. For the second low value, the mother was close to receiving the booster vaccine, indicating that vaccination timing might be an essential determinants of ATR. Finally, Mithal et al. and Yang et al. reported a significant increase in spike protein IgG levels for infants born to mothers who received their second vaccination dose before delivery.

Secondary outcome: Inclusion of parturient women who had COVID-19 during pregnancy

Multiple studies also included pregnant women who had had COVID-19 during pregnancy and were not vaccinated (Beharier et al., 2021; Collier et al., 2021; Gray et al., 2021; Nir et al., 2022). Collier et al. showed a lower for anti-RBD IgG immune response for both mother and infant for the group with SARS-CoV-2 infection during pregnancy compared to that elicited from the vaccinated dyads. The ATR for the vaccinated and infected dyads were respectively 1.33 and 0.47 (Table 1). However, for neutralizing antibodies this was respectively 0.32 and 1.09 after vaccination and natural infection during pregnancy. Nir et al. found the exact opposite anti-RBD IgG: higher ATR after SARS-CoV-2 infection compared to vaccination during pregnancy, respectively 1.26 and 0.77. In the study by Nir et al the mean time interval between second vaccination and delivery was 21.7 (±11.0) days and 92.5 (±75.8) days between a positive COVID-19 PCR test and delivery. For the study by Collier et al. this was respectively 21 days (IQR, 14-36) and 41 days (IQR, 15-140) (Figure S1). Nir et al. also state higher absolute vaccine-induced antibody titers, when compared to women with COVID-19 during pregnancy. This is in line with the findings from Gray et al., which showed that all IgG levels in the mothers were significantly higher in the vaccinated group compared to the group with prior SARS-CoV-2 infection. Unfortunately there weren't enough dyads in the study by Gray et al. that had gone through COVID-19 during pregnancy that contributed umbilical cord samples at birth to the study to compare ATRs to the vaccinated group.

The findings from Beharier et al. indicated that the ATR for vaccinated mothers exceeded those from mothers who had COVID-19 during their third trimester of pregnancy. Furthermore, Beharier et al. found that the comparison of IgG titers between vaccinated mothers and infants, and those with passed SARS-CoV-2 infection during pregnancy varied depending on the specific antibody. Maternal IgG for S1 and RBD were significantly higher for vaccinated mothers, while infant IgG for S1 and RBD did not differ from infants from mothers who had COVID-19. Maternal and infant IgG for S2 and N were significantly higher for dyads who experience SARS-CoV-2 infection, compared to vaccination during pregnancy.

Discussion

Summary of findings

The included studies showed SARS-CoV-2-specific ATR ranging between 0.34 to 2.6. Six studies showed a significant ATR between 0.8 and 1.3. Two studies showed significantly higher ATR, ranging up to 2.6 (Kugelman et al., 2021; Yang et al., 2022), and finally, one study showed significant values under 0.5 (Rottenstreich et al., 2021). Factors found to influence ATR are GA at time of vaccination and number of vaccination doses. The results suggest there might be an optimal GA at around 32 week, however further

analysis is needed to confirm this finding. Double-dose vaccination was proven more efficient in providing higher ATR when compared to single dose vaccinated women. Studies in this review included separate ATR for different antibody types (anti-S, anti-RBD, anti-N, and neutralizing vs non-neutralizing antibodies), suggesting differences in the efficiency of transplacental uptake per specific antibody. This means that the highest possible neonatal protection is provided by maximizing both maternal antibody titers and ATR. The ATR was boosted by complete vaccination and ideal timing of vaccination doses. The importance of which antibodies are elicited by the vaccine is not to be neglected, as different ATR were found for different types of antibodies. This suggests that efficiency at which some antibodies attach to-, and cross the placenta depends on their particular structure. The implications for protective effect of these differences depend on the different roles of each antibody (different anti-S antibodies, neutralizing vs non-neutralizing antibodies) in the immune response of the infant against SARS-CoV-2 infection. This remains yet to be determined. Regarding the ideal timing of vaccination, there seem to be two contradictory trends: 1) increasing GA at time of vaccination provides better ATR by giving the antibodies more time to produce and transfer across the placenta, 2) increasing time between vaccination and delivery reduces the ATR. The second trend could be explained through the reasoning that after reaching their highest titer, antibodies will start to decrease in the mother over time, which leads to lower concentrations in the blood stream, and therefore less available antibodies at the placenta. This suggests that an ideal time point for vaccination would be provided by balancing out both trends. Finally, results for ATR of infection induced- versus vaccine induced antibodies are contradictory, but absolute antibody titers in both mother and infant are consistently higher after vaccination across studies.

A possible explanation for the difference in ATR might be the timing of vaccination during pregnancy. This is a likely reasoning for the low ATR observed by Beharier et al., as the average number of days between both first and second dose vaccination and delivery was low (respectively 33 and 11 days). However, when comparing the papers with the most extreme ATR values to one another, this doesn't seem to be the case. The results from Gray et al., and Yang et al. had a respective ATR of 0.5 and 1-2 and showed the same percentage of participants receiving their vaccine in the 2nd or 3rd trimester. However, the ATR published by Rottenstreich et al. were approximately 0.34 and 0.44 (for anti-S and anti-RBD-specific IgG) and in this study, the mean gestational age at 1st vaccination and 2nd vaccination was respectively 35 and 38 weeks. The late stage at which the participants were vaccinated is a likely explanation for the lower values in ATR that were observed by Rottenstreich at al., but this doesn't hold for the ATR of 0.5 from Gray et al. However, Gray et al. reported their ATR of 0.5 was non-significant. Figure S1 in the supplementary material shows the ATR as a function of time between 2nd vaccination dose and delivery. There is an increasing trend in ATR with more time between vaccination and birth.

Although many papers discuss ideal timing for COVID-19 vaccination during pregnancy, it is important to take into consideration that early vaccination helps to ensure complete vaccination by the time of delivery. There is no certainty that women will not deliver prematurely, and the majority of papers in this review only include women without premature delivery. Furthermore, early vaccination provides protection throughout the pregnancy, which minimizes the risk for severe COVID-19, and is best for the unborn child (Yang et al., 2022).

The papers comparing antibody titers in mother and infant after single or double vaccination before delivery showed a clear consensus on higher values following two-dose vaccinations for both mother and child at the time of birth. However, when it came specifically to ATR the findings by Nir et al. and Collier et al. were very contradicting. The lower number of days between SARS-CoV-2 infection and delivery in the study by Nir et al. (on average 12 weeks) the most likely reason for why the ATR is low. According to the findings in this literature review (Fig. 1), ART increases with increasing time between vaccination and/or infection and delivery. This is also in line with the findings by Beharier et al. that indicated a positive

association between ATR and earlier timing of infection. They found that SARS-CoV-2 infection during the second trimester confers the highest ATR from mother to child. The timing of SARS-CoV-2 infection in the study by Nir et al. could therefore be seen as favorable for the ATR, compared to that in the study by Collier et al. To put these differences into context, it is also important to know that even though the infant-to-mother ratio of antibodies in the study by Nir et al is higher for women with COVID-19 during pregnancy than for vaccinated women, the absolute values for both mother and infant were higher after vaccination, which was consistent with findings from Gray et al. Overall, all papers evaluating antibody titers for both infected and vaccinated pregnant women do agree that vaccinated women and/or their newborns have higher IgG titers after vaccination, when compared to SARS-CoV-2 infection during pregnancy. However, it is important to keep in mind that there might be some bias regarding vaccination status, as some studies only mention self-reported vaccination status.

Although there was quite some variation between studies, all studies report detectable SARS-CoV-2-specific antibodies in infants at birth after vaccination during pregnancy. This strengthens recommendations on maternal vaccination to protect neonates against severe COVID-19. The ATR at birth is variable and influenced by vaccination vs natural infection, type of antibody targeted through vaccination, vaccination timing, number of vaccination doses, and maternal antibody titers. The combined findings across studies indicate ATR is highest when mothers had undergone complete vaccination during pregnancy, with the second dose provided roughly between 25 and 30 weeks of GA. These findings attest to the importance of full vaccination along with careful consideration. These findings are supported by a recent paper by Halasa et al. assessing the protective effects of a 2-dose mRNA vaccination during pregnancy against COVID-19 in infants, which reported a 61% effectiveness of maternal vaccination against COVID-19 hospitalization in infants <6 months old. They also showed a higher effectiveness of early completion of vaccination during pregnancy when compared to late completion (respectively 32% and 80%) (Halasa, Olson, Staat, & Newhams, 2022).

Finally, the findings in this review focused on de-novo vaccination of pregnant women against SARS-CoV-2, however we are approaching a period in which most women will already have undergone full COVID-19 vaccination and/or COVID-19 itself. Therefore, the question of whether or not to vaccinate pregnant women and which time-window would provide their unborn children with the optimal protection will be one relating to booster vaccination doses. The study by Yang et al. suggest that for cases with prepregnancy SARS-CoV-2 infection and/or vaccination before or at early pregnancy stages, a potential sustained immune response combined with a booster vaccine during pregnancy, might make the discussion on timing of COVID-19 vaccination obsolete. This is due to the finding that primary vaccination series, with a subsequent booster dose was associated to the highest antibody titers in both mothers and infants. However, it is important to keep in mind that there were only 20 (out of 1321) participants who had received a booster vaccination before delivery and that the association between the reaction to a booster dose and sustained immunity remains to be proven.

Strengths and limitations of literature review and included papers

Key strengths to this review are the extensive search strategy, with distinct in- and exclusion criteria, and a standardized assessment and appraisal of the included studies. The major limitation to this literature review is the relatively small number of papers reporting on ATR of SARS-CoV-2-specific antibodies after vaccination during pregnancy. This was expected at the start of the search, as the recommendation of COVID-19 vaccination for pregnant women was only recent. A limiting factor in the search for studies was the limitation to English studies, as COVID-19 is a global pandemic. Another important limitation is the variation in outcome representation (the differences in types of antibodies measured), which reduces the comparability between papers. Although incomparability is reasonable due to the fact that the outcome

of interest is a ratio and not an absolute antibody titer. Finally, the majority of publications didn't specify whether they included dyads with premature delivery, and when they did, there was no specification of ATR for these participants. Therefore, there was no way to correct for premature delivery in this literature review, which might bias the results as premature deliveries are more likely to show lower antibody titers in the mother, which could lead to a lower ATR for the newborn.

To my knowledge, this is the first review article providing an overview of the available literature on the efficiency of vaccine-induced antibody transfer in pregnant women.

Unanswered questions for future research

The exact ATR, along with the gestational timing remain to be confirmed. Knowing the ideal timing for vaccination is essential for the preparation of vaccination campaigns to provide optimal immunity for both mother and child. The challenge might lie in finding the balance between protecting the mother from infection throughout her pregnancy and maximizing antibody transfer and absolute titers for the infant. Furthermore, the majority of studies attested to the positive association between maternal antibody titers and ATR for the neonate. However, a higher ATR might mean a reduction in antibodies available for the mother's own immune defenses. This is however speculation and has not been shown in the included studies. These papers assessed transferability of antibodies to the infant, but the protective effect thereof is yet to be further assessed. Additional research is needed to provide evidence that newborns from vaccinated mothers are at reduced risk for severe COVID-19. Finally, larger and more diverse studies are required to obtain generalizability of the results to all pregnant women.

Conclusion

This literature review provides evidence of the maternal transfer vaccine-induced antibodies through the placenta to their unborn child, with an ATR ranging between 0.34 to 2.6, depending on the number of vaccination doses and their respective timing. Fortunately, all studies, regardless of whether participants had undergone single or double vaccination, did show SARS-CoV-2-specific antibody titers in the newborn infants. The exact infant-to-mother ratio at which this happens remains uncertain. Unlike vaccines that promote preexisting immunity, such as those against the flu and pertussis, the time dependence of the vaccine for the production of "new" SARS-CoV-2 antibodies is unresolved. Thus, as the prevalence of SARS-CoV-2 continues to spread, the antibody transfer kinetics after vaccination during pregnancy will become an important topic for future studies. These studies will likely be focused on the ideal timing and antibody-targets of booster vaccinations, as many future pregnancies will be in women who have already undergone full vaccination and/or been naturally infected.

References

Adeyinka, A., Bailey, K., Pierre, L., & Kondamudi, N. (2021). COVID 19 infection: Pediatric perspectives. *JACEP Open*. https://doi.org/10.1002/emp2.12375

Beharier, O., Mayo, R. P., Raz, T., Sacks, K. N., Schreiber, L., Suissa-cohen, Y., … Kovo, M. (2021). Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *The Journal of Clinical Investigation*, *131*(13), 1–9. https://doi.org/10.1172/JCI150319

Centers for Disease Control and Prevention. (2021). New CDC Data: COVID-19 Vaccination Safe for Pregnant People. Retrieved February 23, 2022, from https://www.cdc.gov/media/releases/2021/s0811-vaccine-safe-pregnant.html

Centers for Disease Control and Prevention (CDC). (2022a). CDC Museum COVID-19 Timeline. Retrieved February 21, 2022, from https://www.cdc.gov/museum/timeline/covid19.html

Centers for Disease Control and Prevention (CDC). (2022b). COVID-19 Vaccines While Pregnant or Breastfeeding. Retrieved February 21, 2022, from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html

Clements, T., Rice, T. F., Vamvakas, G., Barnett, S., Barnes, M., Donaldson, B., … Holder, B. (2020). Update on Transplacental Transfer of IgG Subclasses: Impact of Maternal and Fetal Factors. *Frontiers in Immunology*, *11*(September), 1–17. https://doi.org/10.3389/fimmu.2020.01920

Collier, A. R. Y., McMahan, K., Yu, J., Tostanoski, L. H., Aguayo, R., Ansel, J., … Barouch, D. H. (2021). Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women. *JAMA - Journal of the American Medical Association*, *325*(23), 2370–2380. https://doi.org/10.1001/jama.2021.7563

Dong, Y., Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., … Tong, S. (2020). Epidemiology of COVID-19 among children in China. *Pediatrics*, *145*(6). https://doi.org/10.1542/peds.2020-0702

Embregts, C. W. E., Verstrepen, B., Langermans, J. A. M., Böszörményi, K. P., Sikkema, R. S., de Vries, R. D., … GeurtsvanKessel, C. H. (2021). Evaluation of a multi-species SARS-CoV-2 surrogate virus neutralization test. *One Health*, *13*. https://doi.org/10.1016/j.onehlt.2021.100313

Gray, K., Bordt, E., Atyeo, C., & Al., E. (2021). Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. *American Journal of Obstetrics and Gynecology*, (September), 225–303.

Halasa, N. B., Olson, S. M., Staat, M. A., & Newhams, M. M. (2022). *Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19 – Associated Hospitalization in Infants Aged*. *71*(7), 264–270.

Kim, L., Whitaker, M., O'Halloran, A., Kambhampati, A., Chai, S. J., Reingold, A., … Kawasaki, B. (2020). Hospitalization Rates and Characteristics of Children Aged < 18 Years Hospitalized with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1–July 25, 2020. In *Morbidity and Mortality Weekly Report* (Vol. 69).

Kollmann, T. R., Kampmann, B., Mazmanian, S. K., Marchant, A., & Levy, O. (2017). Protecting the Newborn and Young Infant from Infectious Diseases: Lessons from Immune Ontogeny. *Immunity*, *46*(3), 350–363. https://doi.org/10.1016/j.immuni.2017.03.009

Kugelman, N., Nahshon, C., Shaked-Mishan, P., Cohen, N., Sher, M. L., Gruber, M., … Kedar, R. (2021). 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. *JAMA Pediatrics*, 1–6. https://doi.org/10.1001/jamapediatrics.2021.5683

Letko, M., Marzi, A., & Munster, V. (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiology*, *5*(4), 562–569. https://doi.org/10.1038/s41564-020-0688-y

Lipkind, H. S., Vazquez-Benitez, G., DeSilva, M., Vesco, K. K., Ackerman-Banks, C., Zhu, J., … Kharbanda, E. O. (2022). Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth — Eight Integrated Health Care Organizations, United States, December 15, 2020–July 22, 2021. *MMWR. Morbidity and Mortality Weekly Report*, *71*(1), 26–30. https://doi.org/10.15585/mmwr.mm7101e1

Mithal, L. B., & Otero, S. (2021). Cord blood antibodies following maternal coronavirus disease 2019 vaccination during pregnancy. *American Journal of Obstetrics and Gynecology*, (225), 192–194. https://doi.org/10.1016/j.ajog.2021.03.035

National Health Service (NHS). (2021). NHS encourages pregnant women to get COVID-19 vaccine. Retrieved February 23, 2022, from https://www.england.nhs.uk/2021/10/nhs-encourages-pregnant-women-to-get-covid-19-vaccine/

Nir, O., Schwartz, A., Toussia-Cohen, S., Leibovitch, L., Strauss, T., Asraf, K., & Doolman, R. (2022). Maternal-neonatal transfer of SARS-CoV-2 immunoglobulin G antibodies among parturient women treated with BNT162b2 messenger RNA vaccine during pregnancy. *American Journal of Obstetrics and Gynecology*, *4*(100492).

Palmeira, P., Quinello, C., Ana, L., Zago, A., & Carneiro-sampaio, M. (2012). IgG Placental Transfer in Healthy and Pathological Pregnancies. *Clinical and Developmental Immunology*, *2012*, 13. https://doi.org/10.1155/2012/985646

Prabhu, M., Murphy, E. A., Sukhu, A. C., Yee, J., Singh, S., Eng, D., … Yang, Y. J. (2021). Antibody Response to

Coronavirus Disease 2019 (COVID-19) Messenger RNA Vaccination in Pregnant Women and Transplacental Passage Into Cord Blood (preprint). *American College of Obstetricians and Gynecologists*, *138*(2), 2019–2021.

Rottenstreich, A., Zarbiv, G., Oiknine-djian, E., & Zigron, R. (2021). Efficient Maternofetal Transplacental Transfer of Anti- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Antibodies After Antenatal SARS-CoV-2 BNT162b2 Messenger RNA Vaccination. *Clinical Infectious Diseases*, *73*, 1909–1912. https://doi.org/10.1093/cid/ciab266

Shen, C. J., Fu, Y. C., Lin, Y. P., Shen, C. F., Sun, D. J., Chen, H. Y., & Cheng, C. M. (2022). Evaluation of Transplacental Antibody Transfer in SARS-CoV-2-Immunized Pregnant Women. *Vaccines*, *10*(1), 1–12. https://doi.org/10.3390/vaccines10010101

Stafford, I. A., Parchem, J. G., & Sibai, B. M. (2021). The coronavirus disease 2019 vaccine in pregnancy: risks, benefits, and recommendations. *American Journal of Obstetrics and Gynecology*, *224*(5), 484–495. https://doi.org/10.1016/j.ajog.2021.01.022

The Washington Post. (2021, January 7). *Israel recommends coronavirus vaccine for pregnant women, marking a shift as some countries reassess risk*.

Theiler, R. N., Wick, M., Mehta, R., Weaver, A. L., Virk, A., & Swift, M. (2021). Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. *Obstet Gynecol MFM*, *3*(6). https://doi.org/10.1016/j.ajogmf.2021.100467

Wang, Y., Sibaii, F., Lee, K., J. Gill, M., & L. Hatch, J. (2021). Increased Risk of Severe COVID-19 Disease in Pregnancy in a Multicenter Propensity Score-Matched Study. (preprint). *MedRxiv*, *1*(165), 1–13.

World Health Organization (WHO). (2020). WHO SAGE Roadmap for Prioritizing Uses of Covid-19 Vaccines in the. *Who*, (October).

World Health Organization (WHO). (2022a). Coronavirus (COVID-19) Dashboard. Retrieved February 20, 2022, from https://covid19.who.int/

World Health Organization (WHO). (2022b). COVID-19 advice for the public: Getting vaccinated. Retrieved February 20, 2022, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

Yang, Y. J., Murphy, E. A., Singh, S., Sukhu, A. C., Wolfe, I., Adurty, S., … Prabhu, M. (2022). Association of Gestational Age at Coronavirus Disease 2019 (COVID-19) Vaccination, History of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, and a Vaccine Booster Dose With Maternal and Umbilical Cord Antibody Levels at Delivery. *Obstetrics & Gynecology*, *139*(3), 373–380. https://doi.org/10.1097/aog.0000000000004693

Zdanowski, W., & Wasniewski, T. (2021). Evaluation of SARS-CoV-2 Spike Protein Antibody Titers in Cord Blood after COVID-19 Vaccination during Pregnancy in Polish Healthcare Workers : Preliminary Results. *Vaccines*, *9*(675). https://doi.org/10.3390/vaccines9060675

Supplementary Material

Key terms used for paper search in all databases except for bioRxiv and medRxiv:

((SARS-CoV-2 [Title/Abstract]) OR (COVID-19 [Title/Abstract])) AND ((vaccination [Title/Abstract]) OR (vaccine [Title/Abstract])) AND ((pregnancy [Title/Abstract]) OR (pregnant women [Title/Abstract])) AND ((antibody [Title/Abstract]) OR (immunity [Title/Abstract])) AND ((transplacental [Title/Abstract]) OR (antibody transfer [Title/Abstract]) OR (passive immunity [Title/Abstract])) AND ((newborn [Title/Abstract]) OR (neonate [Title/Abstract])).

Key terms used for paper search in bioRxiv and medRxiv:

Abstract or title: “"COVID-19, vaccination, pregnancy, transfer, antibodies"

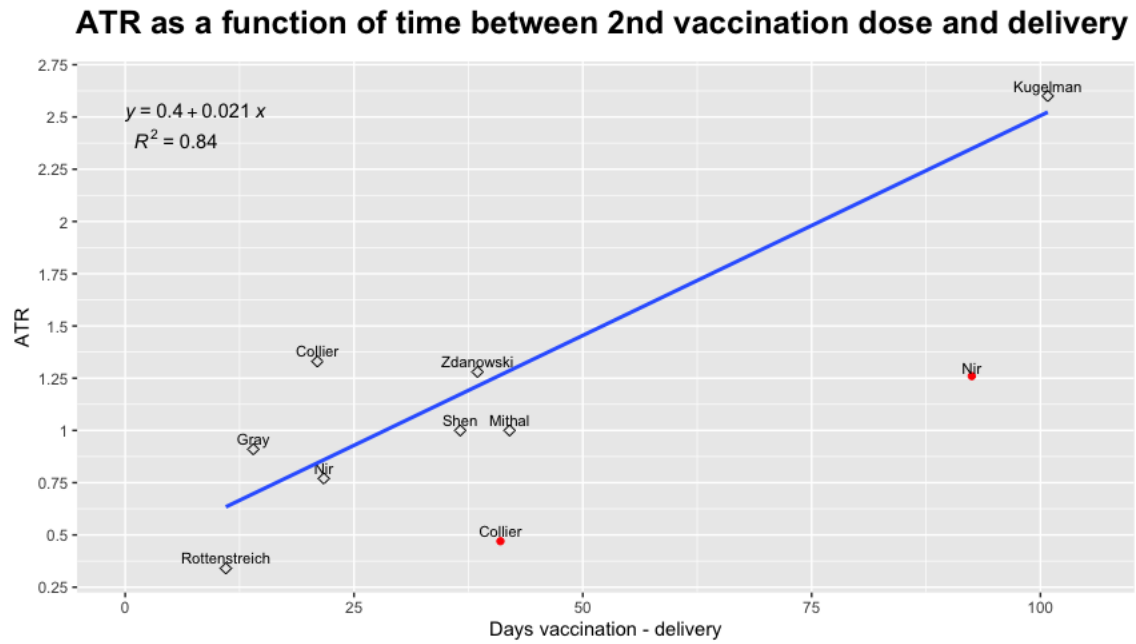

Figure S1. Scatter plot showing ATR values as a function of time between 2nd vaccination and delivery for each study. Red dots represent ATR resulting from natural infection. The x-axis was chosen as a measure for vaccination timing instead of GA at 2nd dose vaccination due to the lesser number of papers publishing GA at 2nd dose. The papers by Prabhu et al., Beharier et al., and Yang et al. did not present average time between 2nd vaccine dose and delivery and are therefore not shows in the figure. She graph shows an overall increasing ATR with increasing time between vaccination and delivery. More time between vaccination and delivery means more time for the antibodies to be produced and absorbed across the placenta.