Antibody Response to Coronavirus Disease 2019 (COVID-19) Vaccination in Pregnant Women and Transplacental Passage into Cord Blood in Phuket, Thailand

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Abstract

Background: Pregnant women are a vulnerable group for Covid-19 infection. The rates of pregnancy and neonatal adverse outcomes, such as mortality, hospital admission, intensive unit care admission, intubation, preeclampsia, abortion, low birth weight, preterm birth, neonatal intensive care unit admission, neonatal sepsis, neonatal death, and vertical transmission, have increased. Many health organizations encourage vaccination during pregnancy due to the safety and efficacy of vaccines in pregnant and lactating women. Infant neonatal immune responses from the mother are important. Many studies have found a good correlation between maternal serum and cord blood antibody levels. However, vaccination during pregnancy had very low coverage, especially in 2023, when COVID-19 became an epidemic infection. In Thailand, various types of Covid-19 vaccines were used, such as Sinovac, AstraZeneca, and mRNA vaccines (Pfizer and Moderna), with some individuals receiving mixed types.

Objectives: This study was designed to estimate the correlation of antibodies in pregnant women and cord blood among Thai pregnant women who received at least one dose of any Covid-19 vaccine both before and during pregnancy.

Methods: Between October 25 and November 9, 2023, the Labor Room of Vachira Phuket Hospital recruited forty low-risk pregnancies with a history of receiving at least one Covid-19 vaccine. We collected demographic data, maternal blood, and cord blood. COVID-19 Spike Protein IgG Quantitative Antibody (Alinity I SAR-CoV-2 IgG II Quant) was tested. Correlations and neonatal outcomes were analyzed.

Results: According to this study, the median of maternal serum SARS-CoV-2 IgG was 2805.00 (535.2, 43212.70) AU/mL, and the median of cord blood SARS-CoV-2 IgG was 4098.00 (479.30, 35085.30) AU/mL. The cord blood and maternal serum SARS-CoV-2 IgG levels at delivery were strongly positively correlated ($R = 0.953$, $P < 0.0001$).

Conclusion: The cord blood and maternal serum SARS-CoV-2 IgG levels at delivery were strongly positively correlated.

Keywords: SAR-CoV-2 Vaccine, Pregnancy, Cord blood, Correlation

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Introduction

The Covid-19 pandemic, which began in 2019, has highlighted pregnant women as a vulnerable group.1,2 Rates of hospital admission, intensive care unit admission, intubation, and mortality have increased compared to non-pregnant individuals.3-7 Adverse pregnancy and neonatal outcomes such as preeclampsia5, abortion, low birth weight, premature rupture of membranes, preterm birth7, neonatal intensive care unit admission, neonatal sepsis, and neonatal death were also more prevalent among Covid-19-infected pregnant women compared to those who were not infected. Several studies have reported vertical transmission and observed a hyperinflammatory process in placental and fetal tissues, which could potentially impact neonatal care in the future.

Vaccination during pregnancy has been strongly encouraged and recommended by many health organizations, including the WHO1, CDC4, ACOG8 and RTCOG9. Studies have shown that the safety and efficacy of vaccines in pregnant and lactating women are comparable to those in non-pregnant women, with some studies even reporting lower rates of fever.10

Innate neonatal immune responses and transplacental delivery from the mother are crucial.10 Many studies have found a strong correlation between maternal serum antibodies and cord blood antibody levels.11-13 However, even during the pandemic, vaccination coverage during pregnancy has been significantly lower compared to non-pregnant women; for instance, in 2021, only 16% of pregnant women in the USA received vaccinations during pregnancy.

In 2023, COVID-19 became an epidemic, and vaccination rates declined, especially among pregnant women. However, as of June 16, 2024, there had been 127,316 new cases reported worldwide within 28 days, as well as 31,205 new cases reported in Thailand from January to June 2024.14

In Thailand, various types of Covid-19 vaccines have been used, including Sinovac (SV), AstraZeneca (AZ), and mRNA vaccines (Pfizer and Moderna), with some individuals receiving mixed types. This study aims to estimate the correlation of antibodies in pregnant women and cord blood among Thai pregnant women who received at least one dose of any Covid-19 vaccine before or during pregnancy. It also seeks to determine the timing and type of vaccination that affect antibody titers and neonatal outcomes (length of hospital stay and newborn transfer to pediatric care).

Materials and Methods

The Vachira Phuket Hospital Research Ethics Committee (reference number VPE REC 009/2023 since July 21, 2023) approved this single-center study and conducted it in accordance with the Declaration of Helsinki and institutional review board guidelines. We obtained informed consent from all participants prior to enrollment. ClinicalTrials.gov

registered this study under the number NCT06259656.

Recruitment and inclusion criteria: From October 25 to November 9, 2023, the Labor Room at Vachira Phuket Hospital recruited forty low-risk pregnant women with a history of receiving at least one dose of a Covid-19 vaccine. Data collection: Maternal blood and demographic data were recorded on case report forms in the labor room, while cord blood was collected at delivery. Both samples were sent to the laboratory for analysis. COVID-19 Spike Protein IgG Quantitative Antibody (Alinity I SAR-CoV-2 IgG II Quant) levels were assessed using Chemiluminescent Microparticle Immunoassay (CMIA). Details on route of delivery and neonatal outcomes were manually recorded on case report forms prior to maternal discharge. After completion of all forty cases, data from the case report forms were transferred to a computer for analysis by the principal investigator.

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics software version 28 (IBM Corporation, New York, NY, USA). Descriptive statistics were used to characterize the demographic data of the study population, presented as median (min, max) and mean (SD). The correlation between cord blood and maternal serum SARS-CoV-2 IgG levels was assessed using Spearman's rank correlation coefficient. Associations between variables of interest, such as the time between vaccination and birth, type of vaccination, and neonatal outcomes (including length of hospital stay and transfer to the neonatal care department), were analyzed using simple and linear regression analysis.

Results

Study population

Table 1 summarizes the demographic data of forty pregnant and newborn participants. The median age was 29.63 years (range: 18.58 to 43.16 years), gestational age at delivery was 39 weeks (range: 37.14 to 41.29 weeks), and the mean body mass index (BMI) was 23.25 ± 4.43 kg/m2. Among the participants, 52.5% were primigravida, and 75% underwent cesarean delivery. Only one participant, at 17 weeks gestation, received an mRNA vaccine. Furthermore, 77.5% had a history of Covid-19 infection, with three reporting it during pregnancy. The duration from vaccination to delivery ranged from 163 to 892 days, with a median of 661.3 days.

Primary Outcome

The study discovered that the average SARS-CoV-2 IgG level in a mother's blood was 2805.00 AU/mL (range: 535.2 to 43212.70 AU/mL), and the average level in a baby's cord blood was 4098.00 AU/mL (range: 479.30 to 35085.30 AU/mL). There was a strong positive correlation between cord blood and maternal serum SARS-CoV-2 IgG levels at delivery ($R = 0.953$, $P < 0.0001$), as depicted in Figure 1.

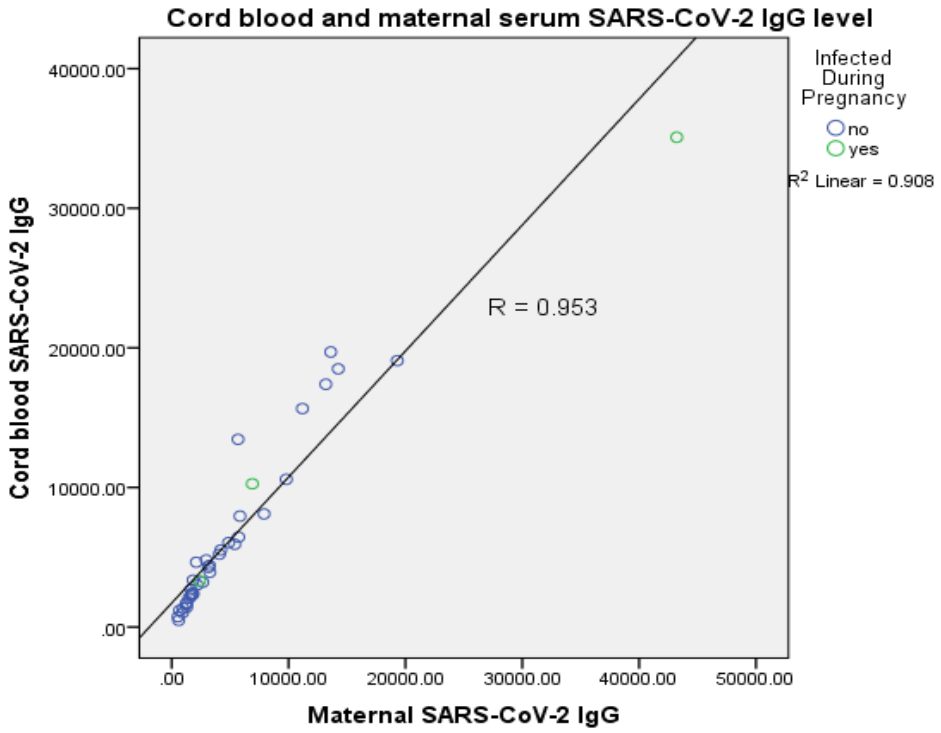
Table 1: Demographic Data (n=40)

Demographic Data (n=40)	
Maternal age (years)	29.63 (18.58,43.16)
Gestational age at birth (weeks)	39.00 (37.14,41.29)
Body mass index (kg/m2)	23.25+/-4.43
Privigravida	21 (52.5%)
Route of delivery, cases (%)	
Cesarean section	30 (75%)
Normal labor	8 (20%)
Vacuum extraction	2 (5%)
Vaccination Data	
Type of vaccine	
Inactivated vaccine*	23 (57.5%)
mRNA	1 (2.5%)
Mixed type	16 (40%)
Number of vaccines	3 (1,5)
1	1 (2.5%)
2	9 (22.5%)
3	15 (37.5%)
4	14 (35%)
5	1 (2.5%)
Duration since last vaccine to delivery (days) n=40	661.5 (163,892)
History of Covid-19 infection	31 (77.5%)
one time	9 (72.5%)
two times	2 (5%)
Duration since last infection to delivery (days) n = 31	566 (45,860)
Duration since last vaccination or infection to delivery (days)	533 (45,796)

Median (min,max), mean ± standard deviation

*SinoVac(SV) or AstraZeneca(AZ) Vaccine

Figure 1: Correlation between maternal serum and cord blood antibodies levels (n=40)



All pregnant participants had low-risk term pregnancies. Table 2 summarizes the neonatal outcomes. The average birth weight was 3236.00 ± 452.50 grams, and the Apgar score at 1 minute was 9 (range: 8 to 9). However, a high percentage (42.5%) of neonates required transfer to the neonatal department, with discharge diagnoses including early neonatal sepsis (EONS) (15%), congenital pneumonia (12.5%), transient tachypnea of the newborn (TTNB) (12.5%), and shock (2.5%). All cases of early neonatal sepsis tested negative on hemoculture. The median length of neonatal hospital stay was 3 days (range: 3 to 21 days).

Table 2: Outcome

Outcome (n=40)	
Maternal serum SARS-CoV-2 IgG (AU/mL)	2805.00 (535.2,43212.70)
Cord blood SARS-CoV-2 IgG (AU/mL)	4098.00 (479.30,35085.30)
Neonatal Outcome (n=40)	
Apgar score at 1 min	9 (8,9)
Birth weight (grams)	3236.00 +/-452.50
Newborn transfer, case (%)	17 (42.5%)
TTNB	5 (12.5%)
EONS	6 (15%)
Pneumonia	5 (12.5%)
Shock	1 (2.5%)
Oxygen therapy, case (%)	14 (35%)
Oxygen box	6 (15%)
HHHFNC	6 (15%)
ETT	2 (5%)
Newborn LOS (days)	3 (2,21)

Median (min,max), mean ± standard deviation

TTNB: Transient tachypnea of the newborn, EONS: Early-onset neonatal sepsis, HHHNFC: Heated humidified high flow nasal cannula

The maternal antibody titer levels showed a trend towards an increase with the number of vaccinations, but this trend did not reach statistical significance (p = 0.116). However, the type of vaccine and the number of Covid-19 infections were statistically significantly associated with antibody levels (p = 0.017 and p = 0.025, respectively), as shown in Table 3. Specifically, the mRNA vaccine group and pregnant individuals with a history of more infections demonstrated significantly higher antibody levels compared to other groups.

Table 3: Association Between Maternal Antibody Levels and Number of Vaccines, Type of Vaccine, and Number of Infections

	Maternal serum SARS-CoV-2 IgG (AU/mL)	p-value*	p-value** (Post Hoc)
Number of vaccines (n=40)		p=0.116	-
1			
2	1636.5 (1636.5,1636.5)		
3	2074.2 (535.2,5719.7)		
4	7555.2 (984.2,43212.7)		
5	5473.7 (599.6,14246.3)		
	7898.2 (7898.2,7898.2)		
Type of vaccine (n=40)		p=0.009	p = 0.017
Inactivated vaccine			
mRNA	1797.9 (535.2,9805.5)		
Mix type			
	19302.1 (19302.1,19302.1)		
	5134.3 (599.6,43212.7)		
Number of infections (n=40)		p=0.002	p = 0.025
0			
1	2174 (676,14246.3)		
2	3142.2 (535.2,19302.1)		
	22806.9 (2401,43212.7)		

*Kruskal Wallis test (median (min,max))

**Post Hoc Analysis with interval between last vaccination or last infection to deliver

Correlations between maternal antibody levels and various variables were analyzed, revealing a correlation coefficient of 0.389 between maternal serum SARS-CoV-2 IgG and neonatal length of hospital stay, indicating a weak positive relationship that is statistically significant ($p < 0.05$). The 95% confidence interval for this correlation was 0.013.

This study also identified correlation coefficients of -0.473 and -0.512 between maternal serum SARS-CoV-2 IgG levels and the interval since the last vaccine or infection (n=40) and since the last infection (n=31), respectively, indicating a moderate negative relationship with statistical significance (p-values = 0.007 and 0.001, respectively). This suggests that longer intervals since vaccination or infection are associated with lower antibody levels. However, there was no statistically significant correlation (p =

0.466) between maternal antibody levels and the interval since the last vaccination (r = -0.119).

Even with intervals as long as 892 days after the last vaccine or 860 days after the last infection, maternal antibody levels remained positive at 1636 and 984 AU/mL, respectively.

Table 4: Association Between Maternal Antibody Levels and Neonatal Outcomes

	Newborn transfer to neonatal department care		
	No (n=23)	Yes (n=17)	p-value
Maternal serum SARS-CoV-2 IgG level (AU/mL)	3996 (535,19302)	7425 (676,43212)	*p = 0.034
Interval since last infection or vaccination (Days)	574 (160,785)	515 (45,796)	*p = 0.808

*Mann-Whitney U test

Due to the high rate of newborn transfer to the neonatal department, serum antibody levels were analyzed in this study. It was found that the maternal antibody levels in the newborn transfer group were significantly higher than those in the non-transfer group (p = 0.034).

Discussion

The cord blood and maternal serum SARS-CoV-2 IgG levels at delivery were strongly positively correlated, indicating passive immunity to newborns. COVID-19 Spike Protein IgG Quantitative Antibody (Alinity I SAR-CoV-2 IgG II Quant) in this study was tested using Chemiluminescent Microparticle Immunoassay (CMIA), which detects antibodies against the receptor binding domain (RBD) on the SARS-CoV-2 spike protein. A positive result suggests recent or prior SARS-CoV-2 vaccination or infection. IgG presence indicates some level of immunity to the virus, though the degree of protection against future COVID-19 illness is uncertain.

Higher maternal antibody levels appeared to be associated with an increased risk of newborn transfer to the neonatal department, but it cannot be conclusively determined whether the elevated antibody levels resulted from vaccination or infection. The median interval from the last vaccination to delivery was 661.5 days (range: 163 to 892 days), approximately two years. Due to concerns about vaccine side effects, especially among Thai pregnant women, despite encouragement from many health organizations for vaccination during

pregnancy, most pregnant women in Thailand declined vaccination. In this study, only one participant received the vaccine during pregnancy, while 31 had a history of infection. It is possible that the high antibody levels observed were due to natural infection.

Table 5: Association Between Neonatal Hospital Length of Stay (LoS) and Maternal Covid-19 Infection During Pregnancy

	LoS (days)	p-value	Maternal Antibody Level (AU/mL)	p-value
Vaccination during pregnancy		P=0.800		p=0.950
Yes (n=1)	3		2401	
No (n=39)	3 (2,21)		2955.2(535.5,43212.7)	
Infection during pregnancy		p=0.093		p=0.144
Yes (n=3*)	15 (3,21)		6897.7(2401,43212.7)	
No (n=37)	3 (2,8)		2654.8(535.2,19302.1)	
Infection during pregnancy with no vaccination during pregnant		p=0.003		p=0.051
Yes (n=2)	18 (15,21)		25055.2(6897.7,43212.7)	
No (n=38)	3 (2,8)		2527.9(535.2,19302.1)	

Mann-Whitney U test

*45,153,160 days before delivery

In this study, a high rate of newborn transfer to the neonatal department care and early neonatal sepsis was observed. One particularly interesting finding, which may have clinical importance and warrants further study, is that only one participant (case no. 8 at 17 weeks gestational age, or 163 days before delivery) received Covid-19 vaccination during pregnancy. Additionally, only three participants (case no. 8, 12, and 15 at gestational ages of 17, 33, and 18 weeks, respectively) had a history of Covid-19 infection during pregnancy. Cases no. 12 and 15 were associated with prolonged neonatal hospital stays of 15 and 21 days, respectively. Further analysis was conducted and is presented in Table 5. The findings suggest that prolonged hospital stays of newborns may be associated with maternal Covid-19 infection during pregnancy, particularly

among those who did not receive Covid-19 vaccination.

Conclusion

This study found a strong positive correlation between cord blood and maternal serum SARS-CoV-2 IgG levels at delivery, but it cannot be conclusively determined whether the elevated antibody levels resulted from vaccination or infection.

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