Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 2, pp. 3-12 July-December 2023
Mendoza RC, Ranile BM, Hernaez NAR. The Coronavirus Disease 2019 (COVID-19) Immunoglobulin (IgG) Levels Using Chemiluminescence Immunoassay (CLIA) Anti-S-RBD Test in Term Neonates Born to COVID-19 Fully Vaccinated Mothers.
https://doi.org/10.56964/pidspj20232402002

ORIGINAL ARTICLE

THE CORONAVIRUS DISEASE 2019 (COVID-19) IMMUNOGLOBULIN (IgG) LEVELS USING CHEMILUMINESCENCE IMMUNOASSAY (CLIA) ANTI-S-RBD TEST IN TERM NEONATES BORN TO COVID-19 FULLY VACCINATED MOTHERS

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1ST PLACE 2023 PIDSP RESEARCH CONTEST

ABSTRACT

Background: Though protective levels of neonatal SARS-CoV2 IgG still warrant further studies, maternal antibodies from COVID-19 vaccination may be the key to neonatal protection against COVID-19 related complications. This study aimed to correlate SARS-CoV2 IgG titers of term newborns delivered to fully vaccinated/boosted mothers with the time of dose completion to delivery and the type of COVID-19 vaccine received by the mothers.

Methodology: A single center prospective cohort study that utilized CLIA Anti-S-RBD IgG determination in cord blood was done. Kruskal-Wallis and Mann-Whitney U Test were used to determine significant differences between IgG titers from vaccine types and groups as to trimester when COVID-19 dose was completed. Spearman's rank was used to determine the correlation between IgG levels and interval of dose completion to delivery.

Results: All 177 newborns enrolled in the study had reactive results ($\geq$ 1 AU/ml) regardless of vaccine type received and trimester of maternal vaccination completion. The highest titers recorded per group was 19,340 AU/ml from the booster group and 5,960 AU/ml from the primary series group. The mRNA vaccinated group exhibited higher titers compared to other vaccine types regardless of the trimester completion for both groups.

Conclusions: A significant difference between IgG levels showed that higher titers were noted in the booster group compared to the primary series group across all trimesters. There was also a significant correlation between titer levels and time of dose completion to delivery with higher titers associated with more recent dose completion for both groups.

KEYWORDS: *SARS-CoV2 IgG S-RBD, COVID-19 Vaccine, Neonates*

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INTRODUCTION

The COVID-19 pandemic has already affected 452 million people globally with 3.6 million cases from the Philippines and counting as recorded by the World Health Organization (WHO). The increasing cases accounts for over 6 million COVID-19 related deaths with pregnant women having the greatest risk for severe to critical symptoms.[1,2,3,4] A systematic review and meta-analysis involving 67, 271 pregnant women concluded that their odds of intensive care unit admissions were significantly increased compared to the general reproductive age population. The risk increases in the presence of maternal co-morbidities with pre-eclampsia as the most common cause of morbidity and mortality.[5] Locally, a cross-sectional study conducted in Philippine General Hospital showed that maternal mortality rates due to severe COVID-19 was at 1.91 per 100 cases.[6]

Due to the increasing number of severe-critical COVID-19 among pregnant women, an emergency use authorization of COVID-19 vaccines was issued by WHO and was supported by international and local obstetrical societies. This emphasized the importance of vaccination during pregnancy amidst the pandemic.[7,8,9] These were the vaccine types approved for pregnant and lactating mothers: Messenger RNA (mRNA), inactivated, and viral vector vaccines.[10] Aside from maternal protection, this strong recommendation was due to several reports of symptomatic newborns of COVID-19 unvaccinated and infected mothers. It was noted that transplacental transmission of SARS-CoV2 was due to high levels of maternal viremia.[11] Multisystem Inflammatory Syndrome in Neonates (MIS-N), another entity of concern, is a post-infectious complication of COVID-19 infection. The passive transmission of maternal post-infectious antibodies was theorized to be one of the pathogenesis of MIS-N.[12] Thus studies on the vertical transfer of SARS-CoV2 IgG after maternal vaccination and the measurement of its levels using cord blood samples were conducted to emphasize the importance of maternal vaccination. Transplacental ratio studies between the newborns and mothers' antibodies showed direct correlation when tested.[13]

This study aimed to determine the correlation between the SARS-CoV2 Anti-S-RBD IgG levels in cord blood of term neonates and the time of maternal COVID-19 vaccine primary series or booster completion from delivery of mothers without history of COVID-19. This study also determined the neonate's demographic profile, mother's vaccination profile, and the difference between the median serum IgG levels across each trimester and vaccine type received.

MATERIALS AND METHODS

Study Design and Subjects

This was a single center prospective cohort study on term neonates born to COVID-19 fully vaccinated or boosted mothers who delivered in a tertiary hospital from July to September 2022. To avoid discrepancies in the IgG titers, mothers with documented or prior history of COVID-19 infection during the course of pregnancy were excluded. To avoid delays in the neonatal resuscitation, newborns with poor APGAR and those who experienced adverse events during the perinatal period such as, asphyxiation or Intrauterine Fetal Demise (IUFD) were also excluded. Hemolyzed specimens that could not be read by the machine, or untoward events during the intrapartum course (e.g., umbilical cord detached from placenta, placenta adhered to the uterus) causing insufficient cord blood samples were considered dropouts.

Definition of Terms

- **Fully Vaccinated Mother:** A mother who has completed the recommended course of COVID-19 vaccination at least 2 weeks from delivery.
- **COVID-19 Booster:** an additional COVID-19 vaccine dose after completing the initial full course vaccination.

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- **Term Newborn**: A newborn who is ≥ 37 weeks age of gestation by Ballard scoring.
- **Reactive CLIA Anti-S-RBD IgG:** Defined as a value of ≥ 1 arbitrary unit per ml (AU/ml)
- **Documented COVID-19 Maternal Infection:** A SARS-CoV2 RT-PCR and/or Rapid Antigen Test (RAT) positive (+) result during pregnancy either for screening purposes or if the mother developed symptoms.

Sample Size and Sampling

A 95% confidence interval was estimated to quantify the difference in mean serum COVID-19 IgG levels. The researcher set the margin of error to be no more than 50 AU/ml. The sample size computation was based on the standard deviation (SD) of a previous study by Kashani-Ligumsky, L., et. al. which had a mean serum IgG level of 224.7 U/ml and a standard deviation of 64.3.[14]

In this study, a power of 80% was considered with α=0.05 (1-0.95), then z=1.96. Given these, the study needed at least 27 IgG titer readings per group for the following sets of comparisons: mothers who completed their vaccination and had booster in the 1st, 2nd, and 3rd trimester to have an actual power of 80.06%. The comparisons were done per trimester to minimize the effect of time as a confounding variable. Therefore, a total of 162 neonates were needed in this study obtained by quota sampling for the study to be 95% confident with an estimate within 50 units of the true mean serum SARS-CoV2 IgG levels in AU/ml, and considering a power of 80% for every comparison to be done.

Data Collection

Once an expectant mother arrived at the labor room or emergency room, the researcher or his co-investigator interviewed and reviewed the mother's prenatal and vaccination history for screening and were documented in the data collection sheet. The mother's vaccine/booster card was requested to validate the vaccination status. If a mother met the criteria, the research protocol and objectives of the study were then explained, and consent was obtained. The attending obstetrician and pediatrician were informed of the study and the mother's decision. In the event the mother was unable to consent for certain reasons (i.e. in active labor/labor pains, exhaustion), the husband/partner or legal guardian of the newborn signed the consent in her stead.

The SARS-CoV2 S-RBD CLIA IgG levels were taken immediately after delivery of the placenta through cord blood samples (4-5 ml) from the umbilical vein obtained aseptically by the researcher and placed in a red-top tube. The samples were sent to the medical technologist on duty for centrifugation while another trained medical technologist ran the test. For optimal results, the specimens should be free of fibrin, red blood cells, or other contaminants that may cause inconsistent results. The samples were tested using MAGLUMI® CLIA SARS-CoV2 S-RBD IgG test which has a clinical specificity of 99.6% and clinical sensitivity of 100%. This assay uses an indirect CLIA for the quantitative determination of IgG antibodies to SARS-CoV2 and utilizes the MAGLUMI® fully-auto CLIA analyzer. An IgG titer of ≥ 1 AU/ml was considered reactive for this study. The sample is mixed along with the buffer and magnetic microbeads coated with S-RBD recombinant antigen, then incubated to form immune-complexes. After precipitation, the sample undergoes several wash cycles and treatment until a chemiluminescent reaction occurs. This reaction was measured using a photomultiplier wherein the light signal was measured as relative light units (RLUs) which was proportional to the concentration of S-RBD IgG in the sample. Manual errors in handling and labeling the samples were avoided by using the provided barcode labels attached on the test tubes. Quality control (negative and positive) was done to achieve satisfactory levels based on acceptable analyte values within the laboratory's control range. If ever these values do not fall within the range, a repeat measurement was done and if ever the repeat still did not fall within the acceptable range the results were not reported and the following troubleshoot methods were done: the

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material's expiry date was checked, maintenance was performed, if test kit instructions were followed, rerun the assay with fresh quality specimens, or to contact technical support or distributor for assistance.

After processing, the samples were discarded to the infectious waste disposal as per institutional protocol. The mother's type of vaccine, months from dose completion to delivery, newborns' demographics, SARS-CoV2 IgG S-RBD result, and interpretation were then entered in the data collection sheet.

Data Analysis and Statistical Considerations

Descriptive statistics such as mean, standard deviation (SD), median, interquartile range (Q1-Q3), minimum and maximum values were reported to describe the numerical variables under clinical profile of neonates. The same were used to present the following: serum SARS-CoV2 IgG levels of term neonates in AU/ml; and time in months from vaccination completion or booster to delivery. Frequency distribution and percentage were used to present the categorical variables with frequency counts under vaccination profile of mothers. Mann-Whitney U Test was used to determine if there was a significant difference between two groups in terms of serum SARS-CoV2 IgG levels of term neonates in AU/ml. Kruskal-Wallis Test was used to determine if there was a significant difference among 3 groups in terms of serum SARS-CoV2 IgG levels of term neonates in AU/ml. Spearman's Rank Correlation was used to determine if there was a significant correlation between SARS-CoV2 IgG levels in AU/ml and time in months from vaccination completion to delivery; and also between IgG levels and time in months from booster to delivery.

For all tests, a confidence interval was set at 95%, comparison and association significance at <0.05, all hypotheses were tested at 0.05 level of significance.

Ethical Issues

This study was approved by the research technical committee and the institutional ethics review committee of Cebu Doctors' University Hospital, Protocol Code: 2-2022-011. Written informed consents were obtained from the mothers prior to enrollment of the newborns. Letter of request for sponsorship was sent to Mr. Artis L. Pinote, the CEO of LabSolutions Technologies, Inc. and Distributor of SNIBE MAGLUMI® SARS-CoV2 CLIA S-RBD IgG who provided the test kits used in this study. The researcher shouldered the cost of processing and storage of the samples. The author and co-authors declared that they had no conflicts of interests in the conduct of this study.

Data Privacy

All personal information of the subjects were held confidential in accordance to the Data Privacy Act of 2012. Only the researcher and the co-authors knew the identity of the subjects and were able to review the data. All documents containing the subjects' data were safely secured in a locker accessible only to the researcher and all the data collected were used for the sole purpose of this study. After the study was finalized and all data were encoded, tallied, and treated, all documents with the subjects' personal data were discarded and shredded.

RESULTS

During the study period, a total of 260 newborns (3 sets of twins) were born to 257 mothers. From the 260 newborns, 57 were excluded from the study due to the following exclusion criteria: Prematurity (21), mothers with documented history of COVID-19 infection (16), mother's RT-PCR was positive on admission (13), Intrauterine fetal demise (3), incomplete maternal COVID-19 vaccination (2), and unvaccinated mothers (2). From the remaining 203 eligible newborns, 26 were considered drop-outs due to the following reasons: eligible but group's sample size quota was reached (19), hemolyzed specimens (3), umbilical cord detached from placenta (2), and

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placenta adhered to the uterus (2); ending with 177 subjects in the study. All eligible mothers enrolled in this study signed the informed consent and were informed of their respective results. The 177 newborns delivered had a mean Ballard score of 38.07 weeks AOG, 102 (42.37%) were male and 75 (57.63%) were female.

Table 1. Vaccination profile of mothers

Mothers' Vaccination Profile	N=176		
	Mean (SD)	Median (Q1-Q3)	Min-Max
Time *in months* from primary series completion to delivery	9.47 (4.12)	10.00 (7-12)	1-17
Time *in months* from booster to delivery	5.23 (2.99)	5.00 (3-8)	0.60-13
	No.	**%**	
Completed COVID-19 Vaccination			
Without booster	92	52.27	
With booster	84	47.73	
COVID-19 Primary Series Completion			
Prior to pregnancy	22	12.5	
At 1st trimester	29	16.48	
At 2nd trimester	14	7.95	
At 3rd trimester	27	15.34	
COVID-19 Booster Completion			
At 1st trimester	27	15.34	
At 2nd trimester	30	17.05	
At 3rd trimester	27	15.34	
Type of COVID-19 vaccine			
Inactivated	64	36.36	
mRNA	68	38.64	
Viral Vector	44	25	

Table 1 presents the mothers' vaccination profile, trimester of dose completion, and distribution of vaccine types. On average, the time in months from primary series completion to delivery was at 9.47 months (SD 4.12) and 5.23 months (SD 2.99) for the booster group. There were 176 eligible mothers (1 mother of term twins), 92 (52.27%) had only completed the primary series while 84 (47.73%) mothers received booster shots. Only the primary series completed during 2nd trimester sub-group was not able to fulfill the minimum required quota of 27 samples (14, 7.95%). Because of this, a non-parametric test was used utilizing the median of the IgG titers. The distribution of vaccine type amongst the mothers shows that 38.64% received the mRNA vaccine, 36.36% with inactivated vaccine, and 25% received the viral vector vaccine.

Table 2. Serum SARS-CoV2 IgG levels of neonates using CLIA Anti-S-RBD test in AU/ml

Neonates' COVID-19 IgG Titer	N=177		
	Mean (SD)	Median (Q1-Q3)	Min-Max
Serum IgG *in AU/ml* for ALL neonates	763 (1705)	467 (195-794)	5.4 – 19,340
Serum IgG *in AU/ml* for neonates of primary series group	398.7 (639.9)	277.9 (89-503.5)	5.4 – 5,690
Serum IgG *in AU/ml* for neonates of booster group	1,167 (2323)	731 (450-971)	100 – 19,340
Qualitative Assessment	**N**	**%**	
Reactive CLIA Anti S-RBD IgG	177	100.00	
Non-Reactive CLIA Anti S-RBD IgG	00	00.00	

Table 2 presents the neonates' IgG levels for both primary series and booster group. All 177 cord blood samples showed reactive results with the highest recorded from the primary series group at 5,690 AU/ml and 19,340 AU/ml from the booster group.

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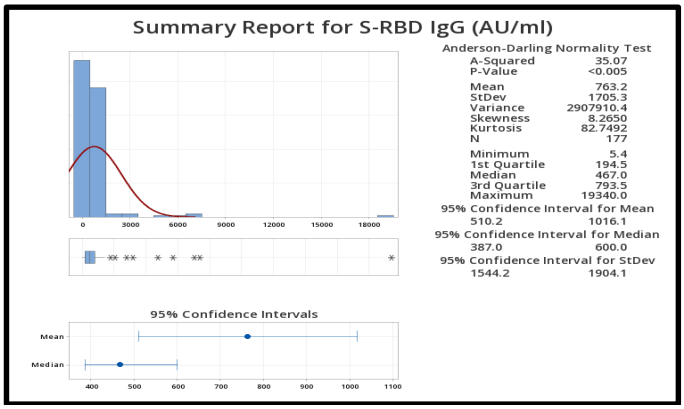

Figure 1. Serum SARS-CoV2 IgG levels of neonates in AU/ml

Figure 1 shows the population distribution in terms of IgG levels which shows an asymmetrical distribution and a mean IgG of 763.2 AU/ml. A standard deviation of 1,705 AU/ml, tells us how spread out the data are from the mean and that the values vary widely. About 25% of the neonate's titer readings were less than or equal to 194.5 (Q1). Median titer is 467 AU/ml which means that half of the sampled neonates had IgG titers below this value. About 25% of the IgG titers in the sampled population are greater than 793.5 AU/ml, i.e., 75% of the neonates considered in this study had titers of 793.5 and below (Q3).

Table 3. Comparison of serum SARS-CoV2 IgG levels of neonates depending on maternal vaccination

	Computed Values			
Trimester Completed	**Primary Series**	**w/ Booster**	**p***	**Interpretation**
First trimester	N=29, η_1=147.7	N=24, η_2=540.0	<0.001	**Significant difference**
Second trimester	N=14, η_1=302	N=30, η_2=726	<0.001	**Significant difference**
Third trimester	N=27, η_1=690	N=27, η_2=991	0.004	**Significant difference**
All Titers, regardless of time	N=93, η_1=277.9	N=84, η_2=730.5	<0.001	**Significant difference**

Vaccine Type	**Inactivated**	**mRNA**	**viral vector**	**P****	**Interpretation**
Vaccine Type, regardless of booster and time	N=65, η_1=332	N=68, η_2=653	N=44, η_3=357	0. 001	**Significant difference**

**Median values compared; Comparison done with Mann-Whitney U Test; significant at <0.05*
***Median values compared; Comparison done with Kruskal-Wallis Test; significant at <0.05*

Table 3 presents the results comparing the average serum IgG levels between mothers who completed the primary series and those who got booster shots. All p-values were <0.05, the differences between the median IgG levels of each population were all statistically significant. The average IgG levels of neonates from the booster group were significantly higher regardless of trimester (730.5 vs 277.9 AU/ml; p-value <0.001). This table also presents the comparison between the average serum IgG levels across the three vaccine types. With p-value of 0.001, the differences between the median IgG levels of each population across all groups was statistically significant. The average IgG level is significantly higher among mothers who received mRNA vaccines.

Table 4. Relationship between serum COVID-19 IgG levels (AU/ml) and time (months) from vaccination to delivery

IgG levels (AU/ml) and time (months)	**Correlation coefficient ρ (95% CI for ρ)**	**p-Value ***	**Interpretation**
Completed Vaccination w/o Booster	-0.627 (-0.745, -0.470)	<0.001	**Significant relationship**
Completed Vaccination w/ Booster	-0.487 (-0.642, -0.292)	<0.001	**Significant relationship**

**Relationship tested using Spearman's Rank Correlation; significant at <0.05*

Table 4 presents the relationship between SARS-CoV2 IgG levels (AU/ml) and time in months from primary series or booster completion to delivery. Since the p-values for both groups were <0.001, the association between time from dose completion to delivery and the IgG levels were statistically significant. Which means a higher IgG titer was associated with more recent vaccinations with respect to the date of delivery. It must be noted however that this correlation does not imply a causal relationship (cause and effect) between the two measurements. This relationship is presented in the

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following matrix plots for the primary series group (Figure 2) and booster group (Figure 3).

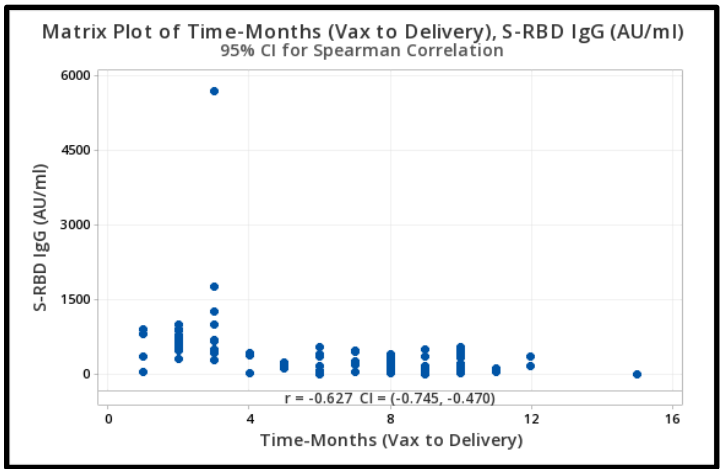

Figure 2. SARS-CoV2 IgG levels (AU/ml) and time (months) from primary series completion to delivery

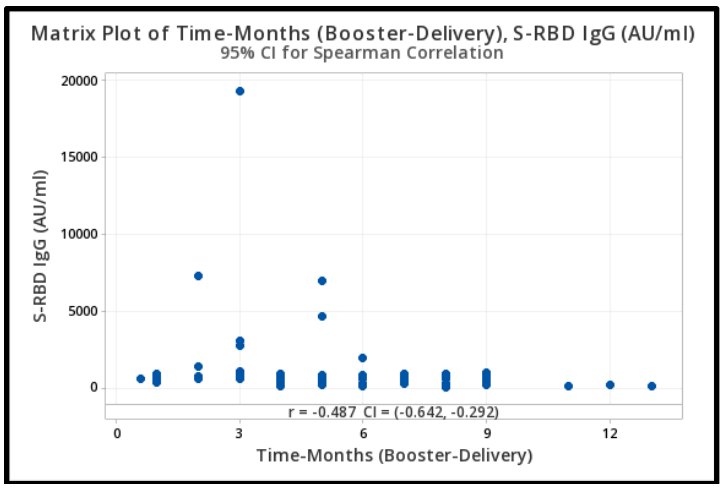

Figure 3. SARS-CoV2 IgG levels (AU/ml) and time (months) from booster completion to delivery

DISCUSSION

Until now, the COVID-19 pandemic still has its infectious and post-infectious effects on the pediatric population even after the roll out of vaccinations for age 5 years old and above implying that the younger and more vulnerable population remain at risk.[15] Cardiovascular manifestations such as arrhythmias, AV blocks to severe complications such as cardiac dysfunction leading to shock and death were documented in a case series conducted on newborns of unvaccinated mothers with maternal COVID-19 infection during the course of pregnancy.[12] Vaccination has proven to have been the solution to lessen both maternal and neonatal morbidity and mortality. As of March 2023, 79 million Filipinos had already completed the primary series while only 24 million received booster shots.[16]

The protective antibody level of SARS-CoV2 has not yet been fully established; However, benefits of maternal COVID-19 vaccination on newborns delivered to vaccinated mothers showed that it decreases the risk of hospital admissions. This was evident in the case-control test negative study by Halasa et. al., which assessed the effectiveness of maternal COVID-19 mRNA vaccination against hospitalization and their infants younger than 6 months old. The study showed that overall effectiveness of maternal COVID-19 vaccination was at 52% as it reduced the risk for hospitalization (COVID or non-COVID related admissions) by 80%. There was also a decrease in pediatric ICU admissions by 70% for COVID-19 related cases and 47% in non-COVID-19 cases. Overall, the study concluded that complete maternal COVID-19 vaccination was associated with a reduced risk of hospitalization for COVID-19 and critical illness among infants younger than 6 months.[17]

This single center prospective cohort study has demonstrated that maternal antibodies to SARS-CoV2 were passed on to the fetus as exhibited by a reactive result on all cord blood samples, regardless of which trimester vaccination was completed or which type of vaccine or booster was given. The results of this study were in congruent with the prospective cohort study by Sourouni et. al. that showed a 100% reactivity to SARS-CoV2 IgG antibodies from cord blood samples of mRNA vaccinated mothers.[18] In another similar prospective cohort study by Kugelman et. al., which involved newborns of both vaccinated and boosted mothers during the third trimester, the results were similar to this study as the booster group had significantly higher antibody titers. The mothers in their study were presumed to have no prior infection to COVID-

19 based on their clinical history alone, like our study. One limitation to their study was the test kits used also detects antibodies to nucleocapsid indicating that natural infection despite being asymptomatic may have altered some of their results.[19]

In a large observational study by Lo Sasso et. al, they determined the SARS-CoV2 IgG Anti-S-RBD titers of the following groups: mRNA vaccinated without prior COVID-19 infection, COVID-19 recovered, and COVID-19 recovered with vaccination. Those in the COVID-19 recovered group had the lowest antibody titer, with the highest belonging to the vaccinated without prior infection group indicating the S-RBD's specificity to antibodies after vaccination.[20] The significance of anti-spike protein S1 and S2 (anti-S) after vaccination, particularly the receptor binding domain (RBD) was identified to be responsible in eliciting robust immune response while on the other hand elevated levels of anti-nucleocapsid (Anti-N) were prominent in patients with prior infection.[21,22] In this study, the test kits used were the MAGLUMI® CLIA SARS-CoV2 S-RBD IgG which has a clinical specificity of 99.6% and sensitivity of 100%.

Compared to other types, mRNA vaccines exhibited higher antibody levels in this study. This finding was supported by Lau et. al.'s comparative study on the kinetics of neutralizing and SARS-CoV2 antibodies after inactivated and mRNA vaccination. Lau's study concluded that mRNA vaccines showed significant antibody response compared to the inactivated vaccines.[23] This study also showed the significant relationship between the time of vaccine completion or booster from the time of delivery. A shorter time in months (1-2 months) from vaccine or booster completion to the time of delivery wherein peak SARS-CoV2 IgG titers achieved was observed. This is congruent with the longitudinal study by Naaber et. al., in which peak SARS-CoV2 IgG Anti-S-RBD titers were noted at 1 week and 6 weeks after the 2nd dose of mRNA vaccination. It was good to note that antibodies in their study, declined and reached a nadir of 2-25% (median of 7%) from peak levels by 6 months post-vaccination, indicating the importance of booster vaccination to augment antibody titers.[24] This was supported by Shook et. al who concluded that majority of the newborns delivered to vaccinated mothers had higher and more persistent anti-S antibodies even at six months old. [25]

This study emphasizes the significant effect of booster vaccines on the antibody titers. Furthermore, all mothers enrolled in this study had no documented or known history of COVID-19. This study has several limitations. It was conducted as a single center study only in a private institution and may not represent the local population. Screening of mothers for previous history of COVID-19 was based on history and retrieval of previous positive RT-PCR or RAT results. Therefore, some mothers with mild symptoms or those who previously had asymptomatic course may have been enrolled to the study possibly affecting some of the results. This study utilized a quota sampling method and during the study period, one group's quota was not reached (primary series 2nd trimester) thus utilizing the median of each IgG in non-parametric testing was used instead of the parametric tests.

CONCLUSION

The study showed that all samples were reactive to SARS-CoV2 IgG. The average IgG levels of neonates of the booster group were significantly higher compared to the primary series group regardless of which trimester it was completed. In addition, significantly higher titers of SARS-CoV2 IgG were noted among neonates whose mothers were vaccinated with mRNA vaccines. Lastly, there was a significant correlation between IgG titer levels of neonates and time from vaccination/booster completion to delivery with higher titers associated in more recent dose completion with respect to time of delivery.

RECOMMENDATIONS

Future research with a multi-center design involving government hospitals to get a better representation of the local population is recommended. Another recommendation is to compare the IgG titers of

newborns born to mothers who are fully vaccinated without prior history of COVID-19 infection, COVID-19 recovered mothers or with prior history, and COVID-19 recovered with vaccination to assess which group has the best antibody response. A longitudinal study on the newborns in this study to reassess their IgG titers and status or condition at 3 and 6 months old would have been ideal.

ACKNOWLEDGEMENTS

To Mr. Alex Phil Ponce, for his contribution in the statistical analysis of this study.

To Dr. Samuel Yu, Chairman – Department of Pediatrics, for allowing the researcher to conduct this study.

To Dr. Ma. Asuncion Tremedal, Chairman – Department of OB-GYN and the Obstetrics and Gynecology Consultants, for allowing the researcher to interview and extract cord blood samples on their patients.

To Dr. Alma Malilong, Chairman – Department of Pathology and Mrs. Marmi Sesaldo, Chief Medical Technologist - CDUH, for allowing the researcher to utilize their equipment, for the processing and storage of the specimens.

To Mr. Artis Pinote, CEO of LabSolutions Technologies, Inc. and Distributor of SNIBE MAGLUMI® SARS-COV2 S-RBD IgG, for graciously providing the test kits used in this study.

CONFLICT OF INTEREST

None declared.

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