OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Date: Apr 18, 2022
To: "Nir Kugelman" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-655

RE: Manuscript Number ONG-22-655

Maternal and Neonatal Efficacy of Third (Booster) BNT162b2 Messenger RNA COVID-19 Vaccination During the Second Trimester of Pregnancy: A Prospective Study

Dear Dr. Kugelman:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 09, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics and Gynecology. If you opt to submit a revision, please also provide any maternal and neonatal outcomes that you have available.

2. Please group the antibody levels for maternal groups together and antibody levels for neonatal groups together in the abstract which will facilitate making comparisons between the primary vaccine series and booster groups. As written, it seems more like a comparison of the maternal with the neonatal antibody levels.

REVIEWER COMMENTS:

Reviewer #1:

In this original manuscript, the authors describe antibody levels after 3rd (booster) COVID vaccination and then compare these results with a historic cohort who received a full course of vaccination for COVID at similarly gestational ages. The study is well done, easy to follow, and of clinical importance. The authors acknowledge 1 of the 2 major limitations of the study - self-report COVID as they acknowledge that asymptomatic infection could have elevated antibody levels in this cohort (infection + vaccination). However, the major limitation is that the authors do not evaluate antibodies before the 3rd vaccination dose (i.e. at time of vaccination). When comparing the two cohorts, the report that there was elevated levels after booster could be higher levels of baseline antibodies before antibodies compared to the historic cohort. This should be discussed in this study. Other minor comments are described below.

Abstract:

Line 46: I think the authors means to say "121 patients?" A word appears missing; also the time intervals for measurement for the 2-dose group is not disclosed or compared here.
From a stylistic perspective, it does a little confusing to discuss those who only received 2 doses vs. those who received a 3rd dose. It might be easier to follow if these two distinct groups (which are defined in the methods part of the abstract) have distinct titles for clarification.

Introduction:
- Well-written; however this could be shortened or streamlined a bit and limit the number of studies discussed here
- Line 83-84: This would be conjecture and probably should be removed here. One could say, there is limited data that this response in pregnant women mirrors what the authors report in the non-pregnant population.
- Line 86-88: It would be helpful to report that this is a previously published group of control that is a comparison group; I would also clarify that this group during that previous study only have 2 doses.
- Line 88: Please change "at similar ages" to second trimester for clarification

Methods:
- Line 122: Why did the authors exclude the cohort that did not receive 3 doses? This could have been a more appropriate temporal control group as opposed to "historic controls."
- Line 122-123: The authors report that they excluded patients who reported a previous COVID infection. It is well know that there were high rates of asymptomatic infection amongst the omicron variant and its sub variant. Thus, it is possible, that many patients may not have "reported" infection, but could have in fact had infection. This skews the currently included cohort.
- Line 139: the authors report that this was a "post-hoc" analysis using historic controls. Was this a secondary aim added at the end? And not intended initially?
- Lines 147-148: The authors should clarify at all times that the 2 dose group is a historic control group.

Results:
- Line 166: Why did the 12 neonates without cord blood collected not have this collected. This should be added. Were only 121 approached and consented? Or did some refuse.
- In Table 1, the authors present both the current cohort and the historic cohort. The authors do not discuss the historic cohort until the last paragraph of the results. I would switch the Table columns and put the current prospective cohort first so as to not detract from results.
- I would exclude the outcome which is antibody levels (Maternal and neonatal) from the baseline characteristic table, especially as other characteristics association with these is discussed.
- The univariable and multivariable analyses for maternal and neonatal antibody levels are rather confusing when including characteristics. I think the discussion of maternal BMI and age detracts from the general direction of results. I would not start with those as the significant factors. The paragraph following demographics and the primary outcome - i.e. antibody levels for maternal and neonatal cohort - should be describing figure 2 and figure 3. The additional info about BMI and maternal age if included should be secondary to that. Or rather, these could just be discussed as covariates in multivariable analysis.
- The comparison with the historic cohort is appropriate.

Discussion:
- Line 229-232: For the prospective group in this study, there is no antibody levels prior to the 3rd vaccination dose. It is feasible that the results may reflect higher antibody levels prior to the 3rd dose of vaccination --> resulting in higher post-vaccination antibodies. This is a major limitation
- Similarly, any or all of the 121 patients included could have had asymptomatic omicron infection and thus skew the results
- Without a baseline antibody quantification, it is hard to attribute the cause and effect.

Reviewer #2:

Cohort study of pregnant women receiving a booster dose between 17-30 weeks and delivering at term, comparing to a prior cohort study of women receiving a primary vaccination series between 17-30 weeks and delivering at term, comparing IgG anti-S for women and neonates. The study finds that booster dose results in a higher maternal and neonatal antibody level.

Precis
--the timeline of the comparison (booster vs 2 dose regimen) is not clear - please clarify

Abstract
--line 36 - IgG to what antigen - anti-S?
--line 39 - "similar gestational age" - I know this becomes apparent later in the manuscript, but here, it is not clear if you are comparing women who get booster dose in 2nd tri vs both doses of primary vaccine series in 2nd tri - perhaps you could clarify here too?

--line 46. a little confused about the 121 and 109 neonates - can you clarify who are the 121 and who are the 109? also, can you include the number of pregnant women included in each cohort?
--conclusion of the abstract - it is important to qualify the findings that we don't know the immune correlates of protection - especially for the neonate. Ie - is more better?

Introduction
--no comments

Methods
--line 119 - how exactly did you know the patient was SARS-CoV-2 naive? Please clarify. a clinical history of symptomatic COVID19 infection is not adequate.
--line 118 - was the third dose due to timeline alone, or also because the patient may have been immunocompromised? Please clarify whether you included both groups of individuals, or only those who needed it due to the 6months elapsed, as combining women with differential indications for 3rd dose would not be appropriate
--how did you select the exposure time of 17-30 weeks for dose 3 ? was that a priori, or what the range was for this study ?
--line 141 - is the prior study published? if so please cite

Results
--are you able to show your placental transfer ratio by weeks of gestation of immunization for the booster? curious that the neonatal level is that much higher than the maternal on an aggregate level - would love to see if it varies by week of immunization.
--figures 2/3 - for each week that passed after the terminal vaccine dose - I feel this data is skewed as you did not have any women deliver immediately after the last dose of the vaccine, based on how I read your data. In reality if you had women deliver in every week after their terminal dose - you would first see an increase in antibody levels before you see the decrease. so to report that for every week that elapses since the last dose of vaccine, maternal and neonatal Ab levels drop by x%% does not completely capture the kinetics and will mislead some readers. can you rephrase to clearly explain this, and be clear that you are only talking about the ranges of xxx-yy weeks elapsed?

Discussion
--the points above also merit discussion here.

Reviewer #3:

Title, lines 81-82: Vaccine efficacy calculation depends on comparison of proportion with infection, serious infection, hospitalization or some other definition of infection with SARS. This study provides no clinical information re: infections, but rather, only titers. Should change the title to reflect change in immunogenicity, not direct evidence of change in infections. Could also compare titers to hypothetical levels of required for viral neutralization, but again that is not direct evidence of efficacy.

lines 4-6: In order to corroborate this statement, need to adhere to the comments re: Figs 2 and 3, to ensure that like times since last vaccine, BMI and maternal age are each equivalent.

Table 1: Since the comparison of titers vs virus or spike protein neutralizing frequently is shown vs titer on a log scale, should include Table or figure based on log scale of titer.

Figure 1: There are both fewer data points and more dispersion of them as maternal and neonatal AB levels increase. Should include the slope of the regression line (with CIs) and should include prediction intervals (not CIs) for the regression line. This would both quantify the 2x relationship of neonatal: maternal titers and provide the variation on that average relationship.

Fig 2: As can be seen from the figure, there are no data points prior to ~10 weeks duration for the 2nd dose cohort and few from ~ 6-10 weeks for the 3rd dose cohort. The comparison of slopes (i.e., rates of decline) should compare like with like in terms of duration, e.g., from 10 to 20 weeks duration. Also, for that subset of 2nd and 3rd dose cohorts, were the BMI and maternal age ages comparable, or is there a need for adjustment or matching to make them more equivalent? Also (lines 177-179, 184-189), it appears that these rates of decline were statistically indistinguishable, with the 3rd dose cohort starting at higher value. Also, should clarify for the reader that the decline only has occurred after a number of weeks, and the Authors are not suggesting a weekly decline in titers immediately following the 3rd dose, which would not make biological sense. Rather there would be an immune response, a peak value, then a decline, not an instantaneous peak coincident with the 3rd dose.

Fig 3: Similarly to Fig 2, need to provide more information re: the respective slopes of the two regression lines (which

appear to be statistically indistinguishable). Also, there is scant data available for 3rd vaccine < 10 weeks duration and essentially none for 2nd vaccine < 10 weeks. Again, should compare similar duration times for regression analysis of neonatal 2nd vs 3rd doses. Also, should clarify for the reader that the rate of weekly decline does not begin at the time of the dose, but rather the only data allows for that estimate beginning weeks after the dose, thus avoiding confusion that the max titer coincides with the inoculation.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "Patients with obesity" instead of "obese patients," "Women with disabilities" instead of "disabled women," "women with HIV" instead of "HIV-positive women," "women who are blind" instead of "blind women."

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis,

abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

7. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

8. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make sure there are no inconsistencies between the abstract and the manuscript, and that the abstract has a clear conclusion statement based on the results found in the manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. In your abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate

confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001").

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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Please make sure your references are numbered in order of appearance in the text.

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If your article is accepted, you will receive an email from the Editorial Office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision.

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 09, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

[redacted]

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28th April 2022

To: Torri D. Metz, MD

Associate Editor

Obstetrics and Gynecology

Dear Prof. Metz,

Re: Manuscript ONG-22-655

Title: Maternal and Neonatal Efficacy of Third (Booster) BNT162b2 Messenger RNA COVID-19 Vaccination During the Second Trimester of Pregnancy: A Prospective Study

Revised Title: Maternal and Neonatal SARS-CoV-2 Immunoglobulin G Levels Following the Third (Booster) BNT162b2 Messenger RNA COVID-19 Vaccination During the Second Trimester of Pregnancy

Thank you for considering our manuscript for publication in *Obstetrics and Gynecology***.**
We have studied the reviewer's and editor's comments carefully and made all the necessary corrections. A track changes version of the manuscript is attached to demonstrate the changes made.
Attached is the revised manuscript with a point-by-point response to the comments.
We hope you will find the revised version suitable for publication.

Reply to the comments:

Editor:

Comment:

1. If you opt to submit a revision, please also provide any maternal and neonatal outcomes that you have available.

Response: We appreciate the editor's comment. As requested, maternal and neonatal outcomes were provided by creating an additional Table (lines 388-390):

Table 2. Comparison of maternal and neonatal outcomes between pregnant women vaccinated with the third and second BNT162b2 mRNA COVID-19 vaccine during the second trimester of pregnancy

Outcome		**Booster Group n=121**	**2-dose Group n=121**	**p-value**
Mode of birth	Spontaneous vaginal birth No. (%)	85 (70.2)	94 (77.7)	0.237
	Vacuum assistance No. (%)	4 (3.3)	1 (0.8)	
	Cesarean birth No. (%)	32 (26.5)	26 (21.5)	
Preterm birth < 37 weeks		9 (7.4)	9 (7.4)	0.808
Intrauterine fetal death No. (%)		0 (0)	0 (0)	1
Birthweight ≤ 2500 grams No. (%)		8 (6.6)	4 (3.3)	0.377
Birthweight ≥ 4000 grams No. (%)		4 (3.3)	6 (4.9)	0.752
5-minute Apgar score ≤ 7 No. (%)		1 (0.8)	0 (0)	1
Neonatal intensive care unit admission No. (%)		4 (3.3)	5 (4.1)	1

We also added the outcomes that were collected in the Materials and Methods:

"Further data were extracted from patients' charts following birth including intrauterine fetal death, mode of birth, neonatal sex, neonatal weight, 5-minute Apgar score, and neonatal intensive care unit admission." (lines 112-114)

Moreover, we related to the absence of differences between the groups in the Results:

"Furthermore, maternal and neonatal outcomes were similar between the groups (Table 2)." (lines 185-186)

Comment:

2. Please group the antibody levels for maternal groups together and antibody levels for neonatal groups together in the abstract which will facilitate making comparisons between the primary vaccine series and booster groups. As written, it seems more like a comparison of the maternal with the neonatal antibody levels.

Response: We embraced the editor's comment and as suggested, revised the results section to facilitate making the comparison:

"Median (IQR) maternal antibody titers were higher in the booster group (4485 (2569-9702) AU/ml) compared to the 2-dose group (1122 (735-1872) AU/ml) (P<0.001). Furthermore, neonatal antibody titers were higher in the booster group (8773 (5143-18830) AU/ml) compared to the 2-dose group (3280 (2087-5754) AU/ml) (P<0.001)." (lines 51-54)

Reviewer #1:

Comment:

In this original manuscript, the authors describe antibody levels after 3rd (booster) COVID vaccination and then compare these results with a historic cohort who received a full course of vaccination for COVID at similarly gestational ages. The study is well done, easy to follow, and of clinical importance. The authors acknowledge 1 of the 2 major limitations of the study - self-report COVID as they acknowledge that asymptomatic infection could have elevated antibody levels in this cohort (infection + vaccination). However, the major limitation is that the authors do not evaluate antibodies before the 3rd vaccination dose (i.e. at time of vaccination). When comparing the two cohorts, the report that there was elevated levels after booster could be higher levels of baseline antibodies before antibodies compared to the historic cohort. This should be discussed in this study. Other minor comments are described below.

Response: We thank the reviewer for this important comment. We agree that the fact that maternal SARS-CoV-2 IgG antibodies were not evaluated prior to the third vaccination is a major limitation of our study. However, all of the women received the third mRNA COVID-19 Pfizer vaccine at least five months after their second mRNA COVID-19 Pfizer vaccination so it may be assumed the baseline antibody levels were relatively low. In accordance with the reviewer's comment, with added the limitation to the discussion section:

"Another limitation of our study was that maternal SARS-CoV-2 IgG antibodies were not evaluated prior to the third vaccination. Therefore, it is possible the results may reflect higher antibody levels preceding the third dose, resulting in higher post-vaccination antibodies compared to the 2-dose group." (lines 260-262)

Comment:

Abstract:

Line 46: I think the authors means to say "121 patients?" A word appears missing; also the time intervals for measurement for the 2-dose group is not disclosed or compared here.

Response: We thank the reviewer for pointing out our mistake and revised to “121 women” (line 46)

In addition, as suggested the time intervals for measurement for the 2-dose group was disclosed in the Methods and Results sections of the abstract:

“Present data were compared to data from a previous study of pregnant women who received their second vaccine dose (2-dose group) at **17-30 weeks of pregnancy**.“(lines 44-45)

“The 2-dose group included 121 women and 107 neonates with antibody levels measured at a mean±SD of 14.6±2.6 weeks after the second dose.” (lines 49-50)

From a stylistic perspective, it does a little confusing to discuss those who only received 2 doses vs. those who received a 3rd dose. It might be easier to follow if these two distinct groups (which are defined in the methods part of the abstract) have distinct titles for clarification.

Response:

We thank the reviewer for this paramount comment and for clarification we defined two distinct groups in the methods section of the abstract:

“Prospective cohort of women admitted to delivery ward who received the third vaccine dose (**booster group**) at 17-30 weeks of pregnancy, and were not previously infected with COVID-19. Maternal and neonatal antibody levels were measured upon admission to birth and in the umbilical blood after birth. Present data were compared to data from a previous study of pregnant women who received their second vaccine dose (**2-dose group**) at 17-30 weeks of pregnancy.” (lines 41-45)

We also adopted to the reviewer’s suggestion throughout the manuscript and defined the two distinct groups in the Materials and Methods for the use of this terminology in the Results and Discussion sections.

In addition, we used the same terminology for the two groups in Table 1 and Table 2.

Introduction:

- Well-written; however this could be shortened or streamlined a bit and limit the number of studies discussed here

Response: We appreciate the reviewer's comment. Accordingly, the introduction was shortened substantially, and the numbers of studies discussed were limited. We believe it is more streamlined now.

Comment:

Line 83-84: This would be conjecture and probably should be removed here. One could say, there is limited data that this response in pregnant women mirrors what the authors report in the non-pregnant population.

Response: We embraced the reviewer's comment and removed the conjecture. As offered we revised the first sentence in the last paragraph of the introduction:

"There is limited data regarding the immunologic response in pregnant women following the administration of the third BNT162b2 mRNA COVID-19 vaccine during pregnancy." (lines 76-77)

Comment:

- Line 86-88: It would be helpful to report that this is a previously published group of control that is a comparison group; I would also clarify that this group during that previous study only have 2 doses.

Response: We agree with the reviewer's comment. Accordingly, the last sentence of the introduction was revised:

"We also compared these antibody levels to a previously published control group of pregnant women who received only two BNT162b2 mRNA COVID-19 doses during the second trimester." (lines 80-82)

Comment:

- Line 88: Please change "at similar ages" to second trimester for clarification

Response: As suggested “at similar ages” was changed to “second trimester”. (lines 81-82)

Methods:

Comment:

- Line 122: Why did the authors exclude the cohort that did not receive 3 doses? This could have been a more appropriate temporal control group as opposed to "historic controls."

Response: We appreciate the reviewer’s comment and agree that it could have been interesting to demonstrate the antibody upsurge by comparing women who received the booster dose with women who did not receive it. However, at the time of the study the majority of women admitted to the delivery room which received only two vaccines doses had received them around conception. Since such a long period had past, it most likely that maternal and neonatal antibody levels would have been very low at birth. The recruitment of women who received two vaccine doses in the second trimester at the era the study was conducted in would have provided a very low sample size with insufficient statistical power. The use of the historical control group allowed the comparison with a relatively high number of women vaccinated with two doses in the second trimester.

Comment:

- Line 122-123: The authors report that they excluded patients who reported a previous COVID infection. It is well know that there were high rates of asymptomatic infection amongst the omicron variant and its sub variant. Thus, it is possible, that many patients may not have "reported" infection, but could have in fact had infection. This skews the currently included cohort.

Response: We agree with the reviewer’s comment. Therefore, this is mentioned as one of the limitations of the study:

“We assumed that women were not infected relying on previous tests that were done; however, some women may have asymptomatic or mild illness without confirmed

diagnosis. Our laboratory uses an antibody test that also recognizes IgG to nucleocapsid protein, thus an occult natural infection may have led to an increased immune response in some women." (lines 256-259)

In addition, during the period of the omicron variant COVID-19 tests (PCR or antigen) were very accessible to the public in Israel an even provided by the government. People were tested not only due to symptoms but also after exposure to infected people, for isolation reduction, prior to vacations, etc. As a result, the majority of women included in this study had several COVID-19 tests in the months prior their birth. We added these indications to the Materials and Methods:

"Pregnant women over 24 weeks of their singleton gestation expected to give birth within three days, who were vaccinated with the third BNT162b2 (Pfizer-BioNTech) mRNA COVID-19 vaccination (booster group) at 17-30 weeks of pregnancy and were not known to be previously infected (negative results in all previous COVID-19 tests that were done due to symptoms, exposure to infected people, for isolation reduction, prior to vacations, etc.) with the virus, were enrolled and recruited consecutively upon admission to the delivery room." (lines 92-97)

Comment:

- Line 139: the authors report that this was a "post-hoc" analysis using historic controls. Was this a secondary aim added at the end? And not intended initially?

Response: We appreciate with the reviewer's comment. The analysis using the historic control was a secondary aim which was intended initially. Accordingly, we rephrased the sentence:

"Next, an analysis was done to compare the present study group to a matched group who received the second BNT162b2 mRNA COVID-19 vaccine dose (2-dose group) at 17-30 weeks of gestation." (lines 120-121)

Comment:

- Lines 147-148: The authors should clarify at all times that the 2 dose group is a historic control group.

Response: As suggested, we clarified that the 2-dose group is a historic control group:

“A comparison was done between characteristics of the booster group to the historic control 2-dose group using the Chi Square test for the categorical variables and Independent t- test or Mann-Whitney, as appropriate, for the continuous variables.” (lines 133-136)

Results:

Comment:

- Line 166: Why did the 12 neonates without cord blood collected not have this collected. This should be added. Were only 121 approached and consented? Or did some refuse.

Response: We thank the reviewer for this comment. As suggested we added this to the results section:

“Umbilical blood was collected from 109 neonates. Of 12 neonates whose antibody titers were not measured, 11 did not have samples obtained and one sample was not analyzed owing to insufficient amount of blood.” (lines 168-170)

In addition, only 121 women who were eligible for the study were approached and they all consented to participate in the study. Accordingly, we revised the first sentence of the results section:

“Between October 2021 to February 2022, 121 women found eligible were recruited consecutively to the study.” (lines 167-168)

Comment:

- In Table 1, the authors present both the current cohort and the historic cohort. The authors do not discuss the historic cohort until the last paragraph of the results. I would switch the Table columns and put the current prospective cohort first so as to not detract from results.

Response: We embraced the reviewer’s comment and switched the table columns in Table 1 as suggested. (lines 369-376)

Comment:

- I would exclude the outcome which is antibody levels (Maternal and neonatal) from the baseline characteristic table, especially as other characteristics association with these is discussed.

Response: As suggested by the reviewer the maternal and neonatal antibody levels were excluded from Table 1. For the emphasize of these important outcomes and in accordance with one of the editor's comments we revised the results section (similarly to the abstract) as follows:

"The present study group was compared to the 2-dose group which included 121 women and 107 neonates with SARS-CoV-2 IgG levels measured at a mean± standard deviation of 14.6±2.6 weeks after the second vaccine. No significant differences were found between demographic and clinical characteristics (Table 1). Furthermore, maternal and neonatal outcomes were similar between the groups (Table 2). Median (IQR) maternal SARS-CoV-2 IgG antibody titers were significantly higher in the booster group (4485 (2569- 9702) AU/ml) compared to the 2-dose group (1122 (735- 1872) AU/ml) (P<0.001). Furthermore, neonatal SARS-CoV-2 IgG antibody titers were significantly higher in the booster group (8773 (5143-18830) AU/ml) compared to the 2-dose group (3280 (2087- 5754) AU/ml) (P<0.001). The comparison of SARS-CoV-2 IgG antibody levels between the groups is demonstrated in Figure 3 and Figure 4." (lines 182-191)

Comment:

- The univariable and multivariable analyses for maternal and neonatal antibody levels are rather confusing when including characteristics. I think the discussion of maternal BMI and age detracts from the general direction of results. I would not start with those as the significant factors. The paragraph following demographics and the primary outcome - i.e. antibody levels for maternal and neonatal cohort - should be describing figure 2 and figure 3. The additional info about BMI and maternal age if included should be secondary to that. Or rather, these could just be discussed as covariates in multivariable analysis.

- The comparison with the historic cohort is appropriate.

Response: We embraced the reviewer's comment and agree that the results section should focus more on our main results. Hence, as suggested we described the comparison between the study group and the historic cohort after the demographics and the primary outcome. In addition, as suggested we only discussed the multivariable analysis with the different characteristics since these findings are secondary in our study. We removed the description of the univariable analysis findings.

Discussion:

Comment:

- Line 229-232: For the prospective group in this study, there is no antibody levels prior to the 3rd vaccination dose. It is feasible that the results may reflect higher antibody levels prior to the 3rd dose of vaccination --> resulting in higher post-vaccination antibodies. This is a major limitation

Response: We thank the reviewer for this important comment. We agree that the fact that maternal SARS-CoV-2 IgG antibodies were not evaluated prior to the third vaccination is a major limitation of our study. However, all of the women received the third mRNA COVID-19 Pfizer vaccine at least five months after their second mRNA COVID-19 Pfizer vaccination so it may be assumed the baseline antibody levels were relatively low. In accordance with the reviewer's comment, with added the limitation to the discussion section:

"Another limitation of our study was that maternal SARS-CoV-2 IgG antibodies were not evaluated prior to the third vaccination. Therefore, it is possible the results may reflect higher antibody levels preceding the third dose, resulting in higher post-vaccination antibodies compared to the 2-dose group." (lines 260-262)

Comment:

- Similarly, any or all of the 121 patients included could have had asymptomatic omicron infection and thus skew the results

Response: We agree with the reviewer's comment. Therefore, this is mentioned as one of the limitations of the study:

"We assumed that women were not infected relying on previous tests that were done; however, some women may have asymptomatic or mild illness without confirmed diagnosis. Our laboratory uses an antibody test that also recognizes IgG to nucleocapsid protein, thus an occult natural infection may have led to an increased immune response in some women." (lines 256-259)

In addition, during the period of the omicron variant COVID-19 tests (PCR or antigen) were very accessible to the public in Israel an even provided by the government. People were tested not only due to symptoms but also after exposure to infected people, for isolation reduction, prior to vacations, etc. As a result, the majority of women included in this study had several COVID-19 tests in the months prior their birth. We added these indications to the Materials and Methods:

"Pregnant women over 24 weeks of their singleton gestation expected to give birth within three days, who were vaccinated with the third BNT162b2 (Pfizer/BioNTech) mRNA COVID-19 vaccination (booster group) at 17-30 weeks of pregnancy and were not known to be previously infected (negative results in all previous COVID-19 tests that were done due to symptoms, exposure to infected people, for isolation reduction, prior to vacations, etc.) with the virus, were enrolled and recruited consecutively upon admission to the delivery room." (lines 92-97)

Comment:

- *Without a baseline antibody quantification, it is hard to attribute the cause and effect.*

Response: We agree with the reviewer's comment and therefore described this limitation in detail in the Discussion.

Reviewer #2:

Cohort study of pregnant women receiving a booster dose between 17-30 weeks and delivering at term, comparing to a prior cohort study of women receiving a primary vaccination series between 17-30 weeks and delivering at term, comparing IgG anti-S for women and neonates. The study finds that booster dose results in a higher maternal and neonatal antibody level.

Comment:

Precis

--the timeline of the comparison (booster vs 2 dose regimen) is not clear - please clarify

Response: We appreciate the reviewer's comment and rephrased the Precis for clarification:

"Maternal and neonatal SARS-CoV-2 Immunoglobulin G titers following BNT162b2 messenger RNA COVID-19 booster vaccination during second trimester of pregnancy were higher compared to two-dose vaccination." (lines 4-6)

Abstract

Comment:

--line 36 - IgG to what antigen - anti-S?

Response: As suggested by the reviewer we clarified in the Objective of the Abstract that the IgG is to antigen- S:

"To evaluate maternal and neonatal SARS-CoV-2 **S** Immunoglobulin G (IgG) antibody levels" (line 37)

Comment:

--line 39 - "similar gestational age" - I know this becomes apparent later in the manuscript, but here, it is not clear if you are comparing women who get booster dose in 2nd tri vs both doses of primary vaccine series in 2nd tri - perhaps you could clarify here too?

Response: We appreciate the comment and in accordance with the response to a previous comment by reviewer #1, we revised the sentence for clarification:

"Objective*:* To evaluate maternal and neonatal SARS-CoV-2 S Immunoglobulin G (IgG) antibody levels at birth, following third BNT162b2 messenger RNA (mRNA) COVID-19 vaccine during the second trimester of pregnancy; and compare them to women who received two vaccine doses **during the second trimester**." (lines 37-40)

Comment:

--line 46. a little confused about the 121 and 109 neonates - can you clarify who are the 121 and who are the 109? also, can you include the number of pregnant women included in each cohort?

Response: We thank the reviewer for the comment. In accordance with previous comments of Reviewer #1 we corrected the sentence (added women after 121) and included the numbers of women and neonates included in the historical cohort:

"Between October 2021 and February 2022, antibody levels **were measured in 121 women and 109 neonates** at mean± standard deviation (SD) of 15.3±3.9 weeks after booster vaccination. Neonatal titers measured two times higher than maternal titers; with inverse correlation between maternal and neonatal titers at birth and time interval from third vaccination. **The 2-dose group included 121 women and 107 neonates** with antibody levels measured at a mean±SD of 14.6±2.6 weeks after the second dose." (lines 46-50)

Comment:

--conclusion of the abstract - it is important to qualify the findings that we don't know the immune correlates of protection - especially for the neonate. Ie - is more better?

Response: We appreciate the comment and revised the conclusion (the conclusion of the main manuscript was revised as well) as suggested:

"*M*aternal and neonatal SARS-CoV-2 IgG antibody titers following second trimester maternal BNT162b2 mRNA COVID-19 vaccination, were significantly higher after the

booster vaccine, compared to the two-dose vaccination. While there is uncertainty if antibody levels correlate with protection, this data supports the importance of mRNA COVID-19 booster vaccination during the second trimester to restore maternal and neonatal protection against the ongoing COVID-19 pandemic." (lines 55-59)

Methods

--line 119 - how exactly did you know the patient was SARS-CoV-2 naive? Please clarify. a clinical history of symptomatic COVID19 infection is not adequate.

Response: We appreciate the reviewer's important comment. During the period of the omicron variant COVID-19 tests (PCR or antigen) were very accessible to the public in Israel an even provided by the government. People were tested not only due to symptoms but also after exposure to infected people, for isolation reduction, prior to vacations, etc. As a result, the majority of women included in this study had several COVID-19 tests in the months prior their birth. Accordingly, and for clarification, we added these indications to the Materials and Methods:

"Pregnant women over 24 weeks of their singleton gestation expected to give birth within three days, who were vaccinated with the third BNT162b2 (Pfizer/BioNTech) mRNA COVID-19 vaccination (booster group) at 17-30 weeks of pregnancy and were not known to be previously infected (negative results in all previous COVID-19 tests that were done due to symptoms, exposure to infected people, for isolation reduction, prior to vacations, etc.) with the virus, were enrolled and recruited consecutively upon admission to the delivery room." (lines 92-97)

However, there is possibility that some women had a naïve infection which could have influenced antibody levels in both groups since our lab antibody test can also recognize IgG to nucleocapsid protein of the virus itself. Therefore, we mentioned this as one of the limitations of the study:

"We assumed that women were not infected relying on previous tests that were done; however, some women may have asymptomatic or mild illness without confirmed diagnosis. Our laboratory uses an antibody test that also recognizes IgG to nucleocapsid

protein, thus an occult natural infection may have led to an increased immune response in some women." (lines 256-259)

Comment:

--line 118 - was the third dose due to timeline alone, or also because the patient may have been immunocompromised? Please clarify whether you included both groups of individuals, or only those who needed it due to the 6months elapsed, as combining women with differential indications for 3rd dose would not be appropriate

Response: We thank the reviewer for this comment. All of the women in the study received the third vaccine dose due to timeline alone and not for being immunocompromised. Accordingly, we added this clarification to the Materials and Methods:

"All women received the third mRNA COVID-19 Pfizer vaccine at least five months after their second mRNA COVID-19 Pfizer vaccination due to timeline alone and not for being immunocompromised." (lines 97-99)

Comment:

--how did you select the exposure time of 17-30 weeks for dose 3 ? was that a priori, or what the range was for this study ?

Response: The exposure time of 17-30 weeks was chosen a priori for two reasons. First, most of the women of the historical group received the second vaccine dose during this period of time and we intended to match the groups as much as possible. Second, we believe these are the weeks (around the second trimester) which have the most clinical relevance since showing that a possible protection is sustained until birth should strengthen the recommendation for vaccination relatively early in pregnancy.

Comment:

--line 141 - is the prior study published? if so please cite

Response: The prior study was published in JAMA Pediatrics. In the initial manuscript the the citation was omitted in accordance with the instructions for "Formatting for Double-

Blind Submissions" in the author guidelines. In the revised version we added that the study was published and conducted by our group with a citation:

"We used (some of the) data collected in a previous published study conducted by our group at the same medical center between May 2021 to July 2021 which evaluated maternal and neonatal antibody SARS-CoV-2 antibody levels at birth after receipt of two COVID-19 vaccine doses during the second trimester.[13]" (lines 121-125)

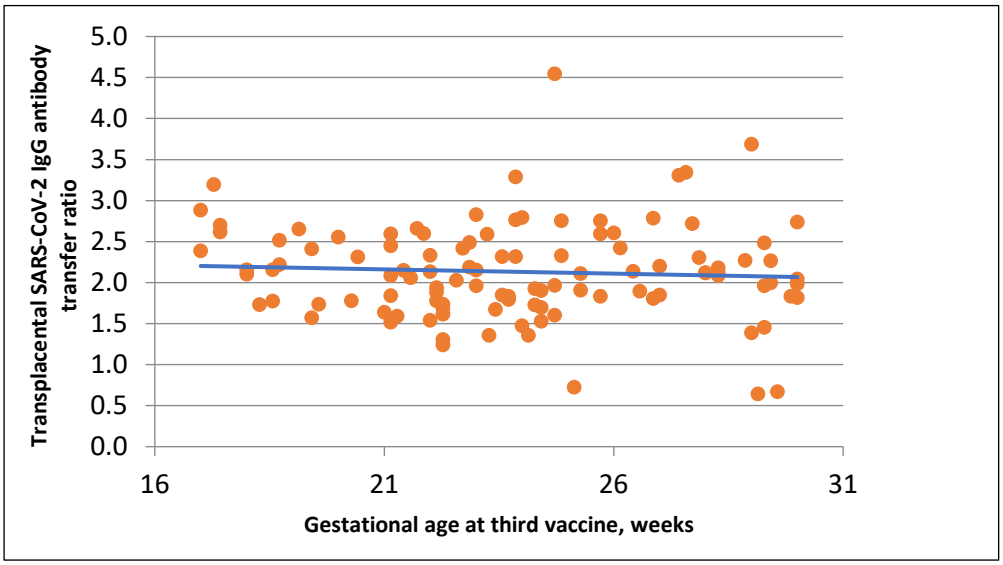
Results

Comment:

--are you able to show your placental transfer ratio by weeks of gestation of immunization for the booster? curious that the neonatal level is that much higher than the maternal on an aggregate level - would love to see if it varies by week of immunization.

Response: As requested by the reviewer Figure 2 was created to demonstrate the correlation between transplacental SARS-CoV-2 IgG antibody transfer ratio and gestational age at the 3rd COVID-19 vaccination:

Figure 2. Correlation between transplacental SARS-CoV-2 IgG antibody transfer ratio and gestational age at the 3rd COVID-19 vaccination; r=-0.04, 95% CI -0.22 to 0.14, P=0.657



Accordingly, we added to the Methods section:

"In addition, transplacental SARS-CoV-2 IgG antibody transfer ratios were calculated by dividing neonatal (umbilical cord blood) IgG levels, by the IgG antibody levels in paired maternal blood. Subsequently, correlation between transplacental SARS-CoV-2 IgG

antibody transfer ratios and gestational age at the 3rd COVID-19 vaccination were analyzed." (lines 116-119)

Also, we added to the statistical section:

"Correlations between the maternal and neonatal antibody levels, between transplacental antibody transfer ratio and gestational age at the 3rd COVID-19 vaccination, and between antibody levels and duration from last vaccine to birth were analyzed using the Spearman correlation." (lines 140-142)

These findings were also described in the Results section:

"We found a mean± SD transplacental SARS-CoV-2 IgG antibody transfer ratio of 2.1± 0.5. No correlation between transplacental SARS-CoV-2 IgG antibody transfer ratio and gestational age at the 3rd COVID-19 vaccination was found (r=-0.04, 95% CI -0.22 to 0.14, P=0.657) (Figure 2)." (lines 178-181)

In addition, we calculated and created a figure demonstrating the correlation between transplacental SARS-CoV-2 IgG antibody transfer ratio and the duration that passed from the 3rd COVID-19 vaccination to birth. (r=0.08, 95% CI -0.10 to 0.27, P=0.389)

We can add it if requested by the reviewer.

Comment:

--figures 2/3 - for each week that passed after the terminal vaccine dose - I feel this data is skewed as you did not have any women deliver immediately after the last dose of the vaccine, based on how I read your data. In reality if you had women deliver in every week after their terminal dose - you would first see an increase in antibody levels before you see the decrease. so to report that for every week that elapses since the last dose of vaccine, maternal and neonatal Ab levels drop by x%% does not completely capture the kinetics and will mislead some readers. can you rephrase to clearly explain this, and be clear that you are only talking about the ranges of xxx-yy weeks elapsed?

Response: We appreciate the reviewer's comment and to prevent misleading rephrased the sentence in the Results section for clarification:

“In the ranges of 5-23 weeks elapsed since the receipt of the 3rd vaccine dose, for each week that passed, maternal antibody levels dropped by -6.5% (95% CI -9.8% to -3.0%, *P*=0.001).” (lines 204-206)

Discussion

--the points above also merit discussion here.

Comment:

--figures 2/3 - for each week that passed after the terminal vaccine dose - I feel this data is skewed as you did not have any women deliver immediately after the last dose of the vaccine, based on how I read your data. In reality if you had women deliver in every week after their terminal dose - you would first see an increase in antibody levels before you see the decrease. so to report that for every week that elapses since the last dose of vaccine, maternal and neonatal Ab levels drop by x%% does not completely capture the kinetics and will mislead some readers. can you rephrase to clearly explain this, and be clear that you are only talking about the ranges of xxx-yy weeks elapsed?

Response: In addition to rephrasing of the results we also rephrased the first paragraph of the Discussion:

“Beginning from 5 weeks since the receipt of the booster vaccine, both maternal and neonatal antibody titers decreased with longer time interval between vaccine administration and time of birth.” (lines 220-222)

Comment:

--conclusion of the abstract - it is important to qualify the findings that we don't know the immune correlates of protection - especially for the neonate. Ie - is more better?

Response: We appreciate the comment and revised the conclusion of the main manuscript as suggested:

“Maternal and neonatal SARS-CoV-2 IgG antibody titers following second trimester maternal BNT162b2 mRNA COVID-19 vaccination, were significantly higher after the booster (third) vaccine, compared to the two-dose vaccination. While there is uncertainty if antibody levels correlate with protection, this data may support the importance of mRNA

COVID-19 booster vaccination during the second trimester in order to restore and enhance maternal and neonatal protection against the ongoing COVID-19 pandemic. Future studies will need to evaluate the best vaccination protocol against COVID-19, before and during pregnancy, to ensure ideal coverage and protection for both the mother and her neonate."(lines 268-275)

Comment:

--line 119 - how exactly did you know the patient was SARS-CoV-2 naive? Please clarify. a clinical history of symptomatic COVID19 infection is not adequate.

Response: We appreciate the reviewer's important comment. During the period of the omicron variant COVID-19 tests (PCR or antigen) were very accessible to the public in Israel an even provided by the government. People were tested not only due to symptoms but also after exposure to infected people, for isolation reduction, prior to vacations, etc. As a result, the majority of women included in this study had several COVID-19 tests in the months prior their birth. Accordingly, and for clarification, we added these indications to the Materials and Methods (pasted in the response above).

However, there is possibility that some women had a naïve infection which could have influenced antibody levels in both groups since our lab antibody test can also recognize IgG to nucleocapsid protein of the virus itself. Therefore, we mentioned this as one of the limitations of the study:

"We assumed that women were not infected relying on previous tests that were done; however, some women may have asymptomatic or mild illness without confirmed diagnosis. Our laboratory uses an antibody test that also recognizes IgG to nucleocapsid protein, thus an occult natural infection may have led to an increased immune response in some women." (lines 256-259)

Reviewer #3:

Comment:

Title, lines 81-82: Vaccine efficacy calculation depends on comparison of proportion with infection, serious infection, hospitalization or some other definition of infection with SARS. This study provides no clinical information re: infections, but rather, only titers. Should change the title to reflect change in immunogenicity, not direct evidence of change in infections. Could also compare titers to hypothetical levels of required for viral neutralization, but again that is not direct evidence of efficacy.

Response: We appreciate the reviewer's important comment. Accordingly, the title was revised to:

"Maternal and Neonatal SARS-CoV-2 Immunoglobulin G Levels Following the Third (Booster) BNT162b2 Messenger RNA COVID-19 Vaccination During the Second Trimester of Pregnancy" (lines 1-2)

Comment:

lines 4-6: In order to corroborate this statement, need to adhere to the comments re: Figs 2 and 3, to ensure that like times since last vaccine, BMI and maternal age are each equivalent.

Response: In the comparison of characteristics between the two groups (Table 1), no statistically significant differences were found in any parameter including BMI and maternal age (lines 369-371):

	Received three vaccines n=121	**Received two vaccines n=121**	**p-value**
Maternal age, mean (SD), years	32.5 ± 4.2	32.1 ± 4.8	0.426
Body mass index, median (SD), kg/ m^2	28.6 ± 4.6	27.9±5.4	0.301

Comment:

Table 1: Since the comparison of titers vs virus or spike protein neutralizing frequently is shown vs titer on a log scale, should include Table or figure based on log scale of titer.

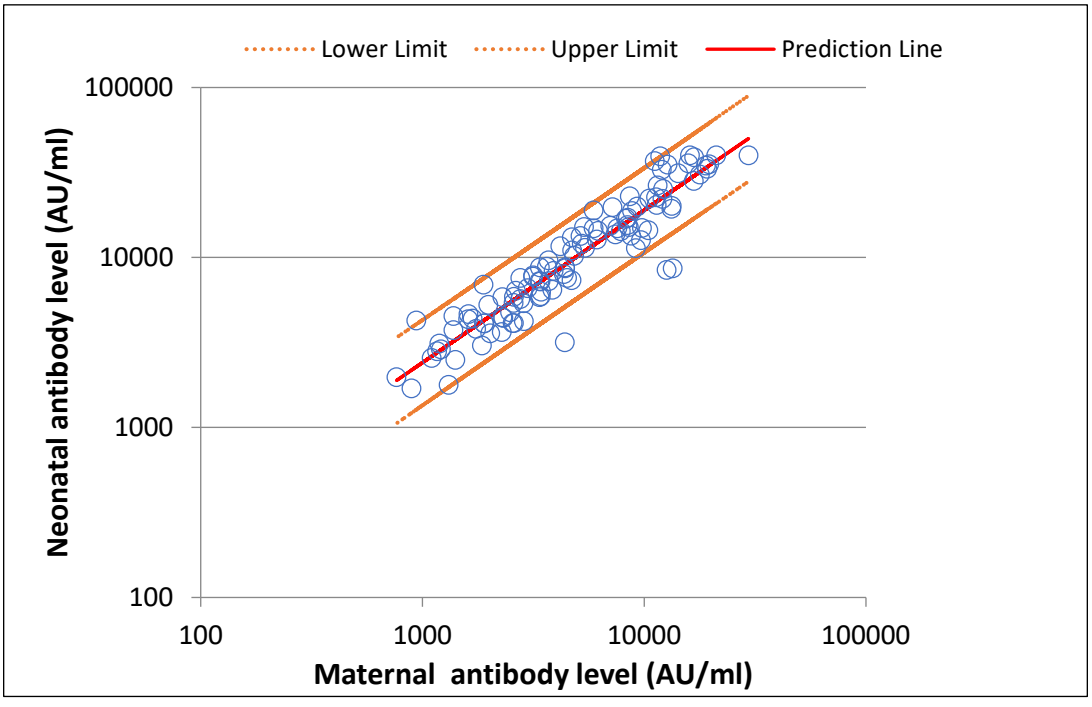
Response: As requested, Figure 1, Figure 2 (Figure 3 in the revised manuscript) and Figure 3 (Figure 4 in the revised manuscript) were all revised now based on the log scale of the antibody titer.

Comment:

Figure 1: There are both fewer data points and more dispersion of them as maternal and neonatal AB levels increase. Should include the slope of the regression line (with CIs) and should include prediction intervals (not CIs) for the regression line. This would both quantify the 2x relationship of neonatal: maternal titers and provide the variation on that average relationship.

Response: The slope the regression line with CIs and the predication intervals were calculated and added to both Figure 1 and to the Results section:

Figure 1. Correlation between maternal SARS-CoV-2 IgG antibodies and neonatal SARS-CoV-2 IgG antibodies after the 3rd COVID-19 vaccination; Slope=0.9, 95% CI 0.83-0.96, *P*<0.001, Prediction line mean (lower limit, upper limit): 9701 (5586, 17,154) AU/ml. (lines 426-428)



Comment:

Fig 2: As can be seen from the figure, there are no data points prior to ~10 weeks duration for the 2nd dose cohort and few from ~ 6-10 weeks for the 3rd dose cohort. The comparison of slopes (i.e., rates of decline) should compare like with like in terms of duration, e.g., from 10 to 20 weeks duration.

Fig 3: Similarly to Fig 2, need to provide more information re: the respective slopes of the two regression lines (which appear to be statistically indistinguishable).

Also, there is scant data available for 3rd vaccine < 10 weeks duration and essentially none for 2nd vaccine < 10 weeks. Again, should compare similar duration times for regression analysis of neonatal 2nd vs 3rd doses.

Response: As suggested, Figure 2 (Figure 3 in the revised manuscript) and Figure 3 (Figure 4 in the revised manuscript) were revised to describe the time interval of 10-20 weeks from the last vaccination to compare the duration period in which data was available for both groups. This was first described in the Methods section:

"Furthermore, the correlation between maternal and neonatal SARS-CoV-2 IgG antibody levels and the duration from the last vaccine at the time interval of 10-20 weeks from the 2^{nd} or 3^{rd} COVID-19 vaccination were analyzed and compared between the groups. This time interval was chosen for comparison as most of the data for both groups was within this time frame." (lines 125-128)

Then we presented the data received including information regarding the respective slopes of the two regression lines with a comparison between them:

in the Results section:

"Furthermore, the negative correlation between the time interval of 10-20 weeks from the 2^{nd} or 3^{rd} COVID-19 vaccination and maternal SARS-CoV-2 IgG antibodies is shown in Figure 3; 2^{nd} vaccine: Slope=-0.24, 95% CI -0.18 to -0.09, P<0.001; 3^{rd} vaccine: Slope=-0.07, 95% CI -0.13 to -0.01, P=0.019. The decrease rate of maternal SARS-CoV-2 IgG antibodies was slower following in the booster group with statistical significance (Slope difference: 0.07, 95% CI 0.02 to 0.14, P= 0.045). (lines 192-196)

“The negative correlation between the time interval of 10-20 weeks from the 2nd or 3rd COVID-19 vaccination and neonatal SARS-CoV-2 IgG antibodies is shown in Figure 4; 2nd vaccine Slope=-0.14, 95% CI -0.19 to -0.08, P<0.001; 3rd vaccine: Slope=-0.09, 95% CI -0.15 to -0.03, P=0.004. The decrease rate of maternal SARS-CoV-2 IgG antibodies was slower following in the booster group, nevertheless no statistical significance was demonstrated (Slope difference: 0.05, 95% CI -0.03 to 0.13, P= 0.238).”(lines 197-201)

We appreciate this comment since it added results that reinforce our conclusion and the message of our manuscript. Accordingly, we added this information to the Discussion section:

“However, the decrease rate of maternal antibodies was slower in the booster group.” (lines 222-223)

“**Also, the decrease rate of maternal antibodies was slower in the booster group.** These results suggests that a booster vaccination during pregnancy may provide better and longer COVID-19 protection up to labor and postpartum for the mother and neonate.” (lines 241-244)

Comment:

Also, for that subset of 2nd and 3rd dose cohorts, were the BMI and maternal age ages comparable, or is there a need for adjustment or matching to make them more equivalent?

Response: In the comparison of characteristics between the two groups (Table 1), no differences were found in any parameter including BMI and maternal age: (lines 369-371)

	Received three vaccines n=121	**Received two vaccines n=121**	**p-value**
Maternal age, mean (SD), years	32.5 ± 4.2	32.1 ± 4.8	0.426
Body mass index, median (SD), kg/ m^2	28.6 ± 4.6	27.9±5.4	0.301

Comment:

Also (lines 177-179, 184-189), it appears that these rates of decline were statistically indistinguishable, with the 3rd dose cohort starting at higher value.

Response: In accordance with a previous comment of Reviewer 1, we omitted the description of the univariable analysis and revised this section of the Results (lines 182-210):

"The present study group was compared to the 2-dose group which included 121 women and 107 neonates with SARS-CoV-2 IgG levels measured at a mean± standard deviation of 14.6±2.6 weeks after the second vaccine. No significant differences were found between demographic and clinical characteristics (Table 1). Furthermore, maternal and neonatal outcomes were similar between the groups (Table 2). Median (IQR) maternal SARS-CoV-2 IgG antibody titers were significantly higher in the booster group (4485 (2569, 9702) AU/ml) compared to the 2-dose group (1122 (735, 1872) AU/ml) (P<0.001). Furthermore, neonatal SARS-CoV-2 IgG antibody titers were significantly higher in the booster group (8773 (5143, 18830) AU/ml) compared to the 2-dose group (3280 (2087, 5754) AU/ml) (P<0.001). The comparison of SARS-CoV-2 IgG antibody levels between the groups is demonstrated in Figure 3 and Figure 4.

Multivariable analysis revealed an inverse correlation between maternal titers at birth with the time interval from the third vaccination. In the ranges of 5-23 weeks elapsed since the receipt of the 3rd vaccine dose, for each week that passed, maternal antibody levels dropped by -6.5% (95% CI -9.8% to -3.0%, *P*=0.001).

In the multivariable analysis maternal antibody titers and maternal age remained significantly correlated with neonatal antibody titers. For each one percent increase in maternal antibody level, neonatal antibody levels increased by 0.9% (95% 0.8-1.0, P<0.001). Furthermore, for each 1-year increase in maternal age, neonatal antibody levels changed by -1.8% (95% CI -3.1% to -0.5%, P=0.008)."

Comment:

Also, should clarify for the reader that the decline only has occurred after a number of weeks, and the Authors are not suggesting a weekly decline in titers immediately following the 3rd dose, which would not make biological sense. Rather there would be an immune response, a peak value, then a decline, not an instantaneous peak coincident with the 3rd dose.

Response: We embraced this comment which was also given by Reviewer #2. To prevent misleading rephrased the sentence in the Results section for clarification:

"In the ranges of 5-23 weeks elapsed since the receipt of the 3rd vaccine dose, for each week that passed, maternal antibody levels dropped by -6.5% (95% CI -9.8% to -3.0%, *P*=0.001)." (lines 204-206)

In addition to rephrasing of the results we also rephrased in the first paragraph of the Discussion:

"Beginning 5 weeks after receipt of the last vaccine, both maternal and neonatal antibody titers decreased with longer time interval between vaccine administration and time of birth." (lines 220-222)

Comment:

Also, should clarify for the reader that the rate of weekly decline does not begin at the time of the dose, but rather the only data allows for that estimate beginning weeks after the dose, thus avoiding confusion that the max titer coincides with the inoculation.

Response: We agree with this comment and made the necessary changes as detailed in the responses to the comments above.

Editorial Office Comments:

1. I agree for the publication the revision letter and the point-by-point responses.
2. We disclosed in both the title page and at the end of the abstract that our study had no funding. Our study is not a clinical trial and there for no registration numbers are applicable. The IRB (Carmel Medical Center institutional review Board) with the approval number and date are provided in the Methods section. We mentioned in the Methods section that the study was conducted in the delivery ward of Carmel Medical Center, Haifa, Israel.
3. All coauthors were asked and reminded to complete the authorship form sent to them.
4. Person first language was used and accordingly a few changes were done in the revised manuscript.
5. The revitalize definitions were used and a few changes were done accordingly in the revised manuscript such as: “delivery” was replaced by “birth”; “vacuum delivery” was replaced by “vacuum assistance”; “cesarean section” was replaced to “cesarean birth”.
6. The revised manuscript meets the word limit of 3000 words for the body text.
7. We disclosed in both the title page and at the end of the abstract that our study had no funding. There are no acknowledgments to be disclosed and no payment was given for preparation assistance. This study was not presented in scientifical meetings. The manuscript was not uploaded to a preprint server prior to submission to Obstetrics and Gynecology.
8. All statements in the abstract also appear in the body text and there are no inconsistencies between them. The abstract has a clear conclusion statement based on the results found in the manuscript. Manuscript and Abstract word counts are provided in the manuscript file:

   Manuscript word count: 2388 words (within the word limit of 3000 words)

   Abstract word count: 300 words (within the word limit of 300 words)

In addition, The Introduction section was also shortened to 250 words (within the word limit of 250 words). Also, the Discussion section's word count is 745 words (within the word limit of 750 words).

9. Only standard abbreviations and acronyms are used. However, they are not used in the title or precis (changes were made in the revised title page and manuscript). Abbreviations and acronyms are spelled out the first time they are used in the abstract and in the body of the manuscript.
10. The virgule symbol is not used in sentences with words in the revised manuscript.
11. P values are put it the right context. P values do not exceed three decimal places and all percentages are expressed to one decimal place.
12. The tables conform to the journal style and Table Checklist.
13. References were adapted to the journal style including the addition of DOI.
14. The revised manuscript has been developed in consultation with all co-authors and they gave approval to the final form of the version.

Sincerely,

Kugelman Nir, M.D

Obstetrics and Gynecology Department,

Carmel Medical Center, 7 Michal St., Haifa, Israel,

[redacted]

[redacted]