NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
RE: Manuscript Number ONG-21-2392

In-Vitro Fertilization and Early Pregnancy Outcomes following Coronavirus Disease 19 Vaccination

Dear Dr. Aharon:

Thank you for your submission. The Editors have reviewed your manuscript. Given the importance and timeliness of the topic we are interested in fast tracking your submission for rapid online publication if you can adequately address the comments raised by the peer reviewers. If you chose to revise your manuscript we ask that you submit your revisions within 7 days to expedite review. If I can answer any questions, please feel free to contact me (jwright@greenjournal.org), otherwise we will expect your revision by January 11, 2022.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

REVIEWER COMMENTS:

Reviewer #1: This manuscript would be improved by attention to the following questions, comments, and/or suggestions:

* Precis Line 6 - You might consider making a more positive statement than "is not associated with". Maybe something along the lines of "Covid-19 mRNA vaccination did not have any detrimental effects on controlled ovarian stimulation or frozen embryo transfer outcomes".

* Abstract lines 9-10 - Similarly, you are not looking for an "association" of vaccination "with" but rather whether vaccination has any detrimental impacts.

* Lines 28-29 - Yet again, you are not looking for an "associate(ion) with stimulation or early pregnancy outcomes" but for the absence of any discernable detrimental impacts of Covid mRNA vaccination on stimulation or early pregnancy outcomes.

* Lines 70-72 - I'm confused by your exclusion language: "Oocyte cryopreservation cycles were not included. ... Fresh embryo transfers were not included in the analysis.". It appeared to me that you were looking at the oocyte and fertilization parameters of COH and pregnancy parameters of the FET cycles. How (and why) would you exclude cycles in which all embryos are cryopreserved?

* Lines 130-132 - Can you comment whether the statistically significant differences in stimulation protocols between control and vaccine groups in the COH arm may have obscured differences in outcomes between groups?

* Lines 147-148 - where there any differences between the groups of those patients who received BNT162b2 (n=119) or mRNA-1273 (n=103)?

Reviewer #2: This is a retrospective cohort study comparing the clinical, laboratory and early pregnancy outcomes of infertile women undergoing IVF/PGT-A with or without SARS-CoV-2 vaccination. Authors found no differences in outcomes following SARS-CoV-2 vaccination. The present findings should be reassuring to infertile women who are considering SARS-CoV-2 Vaccination prior to undergoing IVF/PGT-A.

Comments:
1. Authors should consider using the more appropriate term SARS-CoV-2 vaccination throughout the manuscript.

TITLE
2. See Comment #1

PRECIS
3. Page 1, line 6: Needs to be revised to "not associated with adverse..." Also, see Comment #1

ABSTRACT
4. See Comment #1
5. Page 2, line 28: See Comment #3

INTRODUCTION
6. Page 4, line 53: Change to "with adverse..."

METHODS
7. Authors need to include information about the clinical database used in this retrospective study. Per the Instructions for Authors" state who entered the data and how the accuracy of the database was validated".

8. How did Authors ascertain whether patients were SARS-CoV-2 negative immediately prior to oocyte retrieval and FET? This important information needs to be included in the Methods.

9. Page 5, lines 78-79: Authors start the sentence with "For cycles with preimplantation genetic testing for aneuploidy..." as if not all cycles underwent PGT-A. What percent of IVF patients did not undergo PGT-A? Later in the manuscript Authors give the readers the impression that ALL patients underwent PGT-A since only "a single euploid embryo was transferred in all cycles" (Page 5, line 88). This issue needs to be clarified for the readers, because in its current form is very confusing and vague!

10. Page 6, line 110: Correct with "embryo biopsy day".

RESULTS
11. Since the SARS-CoV-2 vaccine did not become readily available to non-healthcare workers until late January 2021, it would be interesting for the readers to know the patient vaccination uptake rate per month during the study period.

REFERENCES
12. Several references are either missing pagination (#1, 21) or the Journal acronyms lack capitalization (#4, 20).

TABLES
13. Page 16, line 295, Table 2: Correct to "single euploid frozen embryo transfer".
14. Page 18, line 300, Table 3: see Comment #13 above.

Reviewer #3: The authors described in vitro fertilization in early pregnancy outcomes following coronavirus disease 19 vaccination. To my knowledge this is the largest cohort study for addressing this issue. I have several concerns about this paper.

1. The main problem is sample size. The cohort comparison was based on a power analysis of clinical pregnancies outcome difference of 15%. In fact, my crude analysis shows that your sample size would find an 11% difference in clinical pregnancy outcome (Vaccinated vs unvaccinated, COH 222 vs 983, FET 214 vs 733). Thus differences up to 11% would have been missed only in clinical pregnancy. It is difficult to estimate the differences in any of the other variables that were studied, i.e. Ongoing pregnancies biochemical loss a clinical pregnancy loss, estradiol at trigger, eggs retrieved, MII ratios, etc. However, in the clinical sense: quality, quantity, oocytes and embryos are not as important as pregnancy outcomes. The true answer to your clinical question requires multiple institution data. I feel that pregnancy outcome differences (birth rate, anomalies, abortions) are a more appropriate and the differences need to be more on the 3% level (back ground anomaly rate). Please comment

2. How was it determined that the patients were vaccinated? Why were patients not tested for COVID or antibodies? Please comment how you feel this affected your study.

3. One of the most important co variants that needs to be controlled for in any fertility study is diagnosis of infertility (PCOS, male factor, tubal factor, etc)? Why was this not included your study? Please comment

4. In the unlabeled graph, although there was not any statistical difference as denoted by the error bars, coincidentally
vaccinated individuals had lower percentage in pregnancy, clinical pregnancy, and ongoing pregnancy. Furthermore, unvaccinated individuals had lower percentage of biochemical loss and clinical pregnancy loss. I found this to be interesting since ALL the parameters appear to favor unvaccinated individuals, granted although not statistically significant at current sample size. It would be interesting if in a larger sample size these differences did not become significant.

5. Your discussion needs to be more accurate and forthcoming as to the weaknesses of this study. Please include statements that discuss the limitations of your sample size, the limited ability to note differences in oocyte/embryo quality and the lack of the important clinical question such as pregnancy outcomes (birth rate, anomalies, abortions, etc).

6. The results section needs to be limited. Describing long list of non-significant clinical difference in data is not appropriate. Either included in the tables or in the text, not in both. Please use text only to highlight important differences not every difference.

7. Although adjusted for stimulation protocol, I was surprised to see the difference in those that underwent a flare? Is there certain patients that in your practice undergo a flare stimulation protocol? Could there be a difference in the cause of infertility that resulted in different stimulation protocols? Please comment.

8. Since there was so little difference in vaccinated/unvaccinated variables, I doubt the adjusted odds ratio with this sample size would make any difference. In fact, once you control for multiple measurements the only difference that stands out is the flare stimulation protocol. Please comment.

Ln 25: It is unnecessary to include odds ratio is the cross 1 especially in the abstract. Please leave this for results section. I think it is important to include sample size/power analysis discussion in abstract.

Ln 60: You stated that only euploid FET were studied (only 80% of FET underwent PGA-T). Was there any difference in PGT-A findings vaccinated/unvaccinated?

Ln 71: Although you excluded cancel cycles, did you note any difference between vaccinated/unvaccinated rate of cancellations?

LN 77: Were all oocytes fertilized by ICSI? Is this what occurs normally in your practice? I see the rate of PGT-A was 80%. How to use PGT-A in your practice? It appears almost to be Universal.

Ln 94: Why was the primary outcome selected for COH cycle as fertilization, would not clinical pregnancy outcomes be a more appropriate primary outcome?

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 14-15, Abstract, Results and Tables: The two primary outcomes need to be clearly separated from all secondary outcomes and shown more prominently in Results etc than the various secondary ones.

lines 113-118: While the sample size calculations for the two primary outcomes are mathematically correct, there are two issues in their formatting. First, since there were two primaries, the alpha should have been = 0.025, not 0.05. Second, the ratio of unvac to vac was ~ 4:1, while the calculations were based on an assumption of 1:1 ratio. The first would increase the sample sizes, while the second would decrease them. The net effect is that the sample sizes in the study were more than adequate to discern the differences posited. However, how was an absolute difference of 15% (relative differences of ~ 19% and ~ 23% for fertilization and clinical pregnancy rates, respectively) chosen? Seems like a wide clinical margin. A smaller margin e.g., 10% absolute difference, would have required larger samples and made the clinical pregnancy evaluation underpowered. Also, need to make clear for the reader that the calculations on lines 113-118 are based on absolute differences of 15%, not relative differences based on the proposed referent rates.

Tables 1, 2: Gravidity and Parity can only have integer values. Should format as median (range or IQR) or as categories, not as mean ± SD.

Table 2: Need to include CIs for pregnancy rate row and the 4 rows following it, similar to Table 1 format.

Table 2, 3: Need to include column of crude ORs to contrast with aORs. The column of p-values is redundant and should be removed, since CIs are included.

Table 3: There are 10 adjustors cited in the aOR model. While technically this should be sufficient for the adjusted modeling, Authors should corroborate their results (for the two primary outcomes) with propensity matching on the various
baseline characteristics. Given the ~ 4:1 ratio of unvac to vac, that should be doable.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

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   * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byl ine authors).
   * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
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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.

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14. Figures 1 and 2 may be resubmitted as-is with the revision.

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Sincerely,

Jason D. Wright, MD
Editor-in-Chief

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