

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Oct 24, 2019
To: "Jennifer L. Eaton" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1685

RE: Manuscript Number ONG-19-1685

Prevalence of a good perinatal outcome with cryopreserved versus fresh donor oocytes

Dear Dr. Eaton:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

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).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Results section, please clarify:

- ICSI and assisted hatching more common with frozen oocyte cycles (Lines 166-167). Can you discuss how this difference likely impacts good perinatal outcomes in discussion? Controlled for in analysis?

- Less likely to have two or more embryos transferred with cryopreserved oocytes (Line 168). Was this controlled for in analysis that showed increased multiple births with fresh oocytes? Can you discuss implications of this difference in discussion?

- Blastocyst-stage embryo transfer more common with fresh cycles (Line 167). Again, if discussion could comment on how difference likely impacts outcome and whether or not this variable was controlled for in analysis.

Novelty is questionable: Recently published using SART data base that fresh donor oocytes have significantly higher live birth rates per recipient cycle than cryopreserved oocytes.

- I agree that the outcome measure of "good perinatal outcome" is superior to live birth rate for clinical practice.

- Another strength, which is explained well in conclusion is the addition of total number of retrieved oocytes in fresh and frozen cycles

- Unsure if absolute percentages for good perinatal outcome from 22% with frozen oocytes to 24% with fresh oocytes is clinically significant, especially in setting of findings of increased rates of multiple birth, prematurity, and low birth weight in fresh oocytes.

Reviewer #2:

Specific comments:

1. Heading should probably mention - 'cryopreserved-thawed or cryopreserved-warmed oocytes'.

2. All sections are well structured.

3. Can the authors provide rationale for their findings (i.e. is it genetic changes, thaw rates, operator difference, ICSI, assisted hatching which is making frozen rates lower?)
4. Is there a way to know whether a particular batch of frozen oocytes were used for multiple recipients?
5. Is endometrial synchronization better than planning a HRT-FET for frozen thawed ET
6. Table 6 and 7 needs more clarity.
7. Also, its interesting to note that frozen oocytes are associated with reduced risk pf preterm labor and increased birth weight. Also, note that in cases of e-SET there is no statistical difference.

Add discussion part to justify the findings.

Reviewer #3: This is a retrospective study comparing reproductive outcomes for pregnancies from donor cryopreserved compared to fresh donor oocytes. Well-designed and conducted study!

Main issues:

Please include donor oocytes in the title! The inference that the results can be applied to non-donor cycles would need further validation!

Specific issues:

- 1- Title: Please include "donor" in the title
- 2- Methods:
 - a. Was the unit of analysis a patient or a cycle? Please clarify and correct figure 1 accordingly
 - b. Please consider changing the primary outcome to "good perinatal outcome" to "live birth", Way a baby that is healthy otherwise and weight 2450 grams or 4050 grams be a different outcome?
- 3- Results, tables and figures:
 - a. Figure 1: Please clarify the selection of the patients from the total patients included in the SART database!
 - b. Table 5: Was race is for the donor or the recipient?
 - c. Table 5: what do you mean by zero embryo transferred, transfer of nothing? If no transfer, then this should not be included and if transfer was done with nothing in it this should be reported!
- 4- Discussion:
 - a. How does the SART database reflect the US population? Please discuss!
 - b. How do the results of this study affect decision for women undergoing oocyte freezing for fertility preservation?

STATISTICAL EDITOR COMMENTS:

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

lines 61-66: Since the primary outcome was "good perinatal outcome", the results section, beginning with the sentence on line 62, should begin with the rates and aOR for the primary. The subsequent sentences should report the secondary outcomes.

For Tables 4-7: Should separately cite the primary outcome as unadjusted rates, aOR, then adjusted rates, so that the reader can easily see not only the relative, but the absolute difference in rates of "good perinatal outcome". This should be in a separate Table, clearly separate from the secondary outcomes.

Tables 5, 6, 7: The odds ratios cited all are multivariable, so they should be labelled in Table and text as aORs or adjusted ORs. Either in methods, footnote to Tables or as supplemental material, should list the variables included in the final models for each.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

For instance, the "Objective" section of the Abstract should be a simple "TO" statement without background.

- why did you not include the absence of identified fetal/neonatal anomalies?

- PRESENTATION OF STATS INFORMATION

P Values vs Effect Size and Confidence Intervals: While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript. Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.

- As "good perinatal outcome" is your primary outcome, it should be presented first--here and in manuscript results and discussed first in the discussion section.

- It seems that this last statement runs the risk of being a bit overstated. While you are correct about the statistical significance, the degree of difference in the two groups is not great. See article referenced below. The aOR of 0,88 is well within the zone of potential bias--very important in a retrospective study. Also on line 66 make sure you edit to aOR.

Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012; 120:920-7)

- are there risks, including to the donor?

- state why it was exempt

- What is meant by "intent for fresh embryo transfer". What is the alternative if its an IVF cycle?

- Thank you for this really excellent description of data base validation.

- Did you collect data for those with high order conception that may have undergone embryo reduction to twins or a singleton?

- missing data for perinatal outcome? why just "good" perinatal outcome?

- During the time frame, did anyone have >1 pregnancy? How did you control for them as they may not have independent outcomes.

- For the non REI reader, could you explain this a bit? Is it because in a frozen donor cycle, you thaw only a small number of available oocyte--may have alot more given that younger women tend to respond robustly to ovarian stimulation as noted with fresh cycles? So the lower number of frozen is iatrogenic--the doc selects a subset of available oocytes? Or is it something else? Mention in your discussion.

- Same sort of question as above. The majority of your readers will be general Ob GYN's and the decisions made by the REI doc and reasons for them may not be generally known. In the discussion section, please tell us why blastocyst embryo transfer is used at different rates in the 2 groups and why potentially important? Just a sentence or 2.

- give raw data

- (CDC) needs to be added here, since on line 212 you use the abbreviation.

2. The Editors of Obstetrics & Gynecology are seeking to increase 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:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

4. The cover page states that it was presented at ASRM in 2018. It appears that this was presented in 2017 (San Antonio, not Denver). See <https://doi.org/10.1016/j.fertnstert.2017.07.244>. Please correct this.

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 and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * 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).

8. The most common deficiency in revised manuscripts involves the abstract. Be 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 paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

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. 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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

12. Line 214: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

14. Figure 1: Please upload as a figure file on Editorial Manager.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

Please note that 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.

16. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter.

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


Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.



Nancy C. Chescheir, M.D.
Editor-in-Chief
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024

Dear Dr. Chescheir:

We have revised the manuscript, “Prevalence of a good perinatal outcome with cryopreserved versus fresh donor oocytes,” for publication in *Obstetrics & Gynecology*. The material contained in this manuscript has not been published and is not being submitted elsewhere for publication. This study was declared exempt by the Duke University Institutional Review Board. A waiver of informed consent was obtained. All authors fulfill all criteria for authorship, and the authors report no conflict of interest. We confirm that we have read the instructions for authors.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

We would like to thank the reviewers and editors for their helpful suggestions and comments. Our point-by-point responses are as follows:

Reviewer #1:

Results section, please clarify:

-ICSI and assisted hatching more common with frozen oocyte cycles (Lines 166-167). Can you discuss how this difference likely impacts good perinatal outcomes in discussion? Controlled for in analysis?

Thank you for this comment. These covariates were controlled for in the analysis (line 143), so should not have impacted good perinatal outcomes. We have added a sentence to the discussion reiterating that we adjusted for these covariates (lines 245-247).

- Less likely to have two or more embryos transferred with cryopreserved oocytes (Line 168). Was this controlled for in analysis that showed increased multiple births with fresh oocytes? Can you discuss implications of this difference in discussion?

Thank you for this comment. This was controlled for in the analysis (lines 145-147). We have now reiterated this in the discussion (lines 245-247).

- Blastocyst-stage embryo transfer more common with fresh cycles (Line 167). Again, if discussion could comment on how difference likely impacts outcome and whether or not this variable was controlled for in analysis.

Thank you for this comment. This was controlled for in the analysis (lines 145-147). We have now reiterated this in the discussion (lines 245-247).

Novelty is questionable: Recently published using SART data base that fresh donor oocytes have significantly higher live birth rates per recipient cycle than cryopreserved oocytes.

- I agree that the outcome measure of "good perinatal outcome" is superior to live birth rate for clinical practice.

Thank you for this comment. The previously published studies with SART data (Kushnir et al., JAMA 2015; Kushnir et al., J Ovarian Res 2018) did not use cycle-level data from SART CORS. Rather, they used the publically available data available on SART.org. This is a major limitation of those two studies, since data from SART.org is composite clinic-level data and the authors could not control for any confounders. Another recent study (Crawford et al., Fertil Steril 2017) used data from the CDC, not SART CORS. That analysis included only one year of data, and did not adjust for the number of available oocytes. This major limitation is mentioned in the discussion section of our manuscript.

- Another strength, which is explained well in conclusion is the addition of total number of retrieved oocytes in fresh and frozen cycles

Thank you for this comment.

- Unsure if absolute percentages for good perinatal outcome from 22% with frozen oocytes to 24% with fresh oocytes is clinically significant, especially in setting of findings of increased rates of multiple birth, prematurity, and low birth weight in fresh oocytes.

Thank you for this comment. We agree that the difference between absolute percentages is small. We have added this to our discussion section (lines 274-276).

Reviewer #2:

Specific comments:

1. Heading should probably mention - 'cryopreserved-thawed or cryopreserved-warmed oocytes'.

Thank you for this comment. We have made this revision (line 29).

2. All sections are well structured.

Thank you for this comment.

3. Can the authors provide rationale for their findings (i.e. is it genetic changes, thaw rates, operator difference, ICSI, assisted hatching which is making frozen rates lower?)

Thank you for this comment. We have added rationale to the discussion (lines 248-253).

4. Is there a way to know whether a particular batch of frozen oocytes were used for multiple recipients?

Thank you for this comment. We agree that this would be interesting to examine; unfortunately, these data are not available.

5. Is endometrial synchronization better than planning a HRT-FET for frozen thawed ET

Thank you for this comment. We did not include frozen embryo transfers (FETs) in our analysis. With regard to endometrial preparation for fresh embryo transfer from cryopreserved oocytes, we are not aware of any benefit of HRT vs. natural cycle. For the present analysis, we did not have data on the method of endometrial preparation.

6. Table 6 and 7 needs more clarity.

Thank you for this comment. Based on the feedback of the reviewers and Editor, we have deleted Tables 6 and 7. We created a new table (new Table 4) combining the data previously presented in Tables 5-7.

7. Also, its interesting to note that frozen oocytes are associated with reduced risk pf preterm labor and increased birth weight. Also, note that in cases of e-SET there is no statistical difference.

Add discussion part to justify the findings.

Thank you for this comment. We have added this to the discussion (lines 265-270).

Reviewer #3: This is a retrospective study comparing reproductive outcomes for pregnancies from donor cryopreserved compared to fresh donor oocytes. Well-designed and conducted study!

Thank you for this kind comment.

Main issues:

Please include donor oocytes in the title! The inference that the results can be applied to non-donor cycles would need further validation!

Thank you for this comment. The long and short titles both specify donor oocytes. Please let us know if further clarification is needed.

Specific issues:

1- Title: Please include "donor" in the title

Thank you for this comment; the word “donor” is in the title. Please let us know if we can provide further clarification.

2- Methods:

a. Was the unit of analysis a patient or a cycle? Please clarify and correct figure 1 accordingly

Thank you for this comment. The unit of analysis was a cycle, as reflected in Figure 1. Please let us know if we can provide more clarification.

b. Please consider changing the primary outcome to "good perinatal outcome" to "live birth", Way a baby that is healthy otherwise and weight 2450 grams or 4050 grams be a different outcome?

Thank you for this comment. We agree that live birth is an important outcome and have included it in our results. The use of “good perinatal outcome” as the primary outcome, however, is a strength rather than a limitation. The use of live birth as the primary outcome underestimates the impact of multiple birth on maternal and neonatal morbidity and mortality. For that reason, a good perinatal outcome has been advocated as the most relevant fertility treatment outcome (lines 254-272).

3- Results, tables and figures:

a. Figure 1: Please clarify the selection of the patients from the total patients included in the SART database!

Thank you for this comment. When data are requested from SART CORS, only the relevant data for the study are provided. Therefore, there is no way to know the total number of patients in the SART database. We have provided numbers for the data that we received.

b. Table 5: Was race is for the donor or the recipient?

Thank you for this comment. Race is for the recipient (line 143). We have clarified this in Table 2.

c. Table 5: what do you mean by zero embryo transferred, transfer of nothing? If no transfer, then this should not be included and if transfer was done with nothing in it this should be reported!

Thank you for this comment. Table 5 has now been deleted. To explain why it previously said “zero embryo transferred,” the analysis included all cycles, including those that were cancelled (no retrieval was performed) or those that did not proceed to transfer due to no available embryos. It is important to include these cycles in the analysis, as they represent different types

of a failed (negative) cycle. In the old Table 5 and Table 6, the number of embryos transferred was set to 0 in order to include these cycles in the analysis. This methodology is explained in lines 148-149 of the Methods. We also performed a sensitivity analysis based on complete cases in which at least one embryo was transferred (lines 154-155).

4- Discussion:

a. How does the SART database reflect the US population? Please discuss!

Thank you for this comment. The Methods section specifies that the SART CORS database contains data from >90% of US clinics (lines 102-103). We have added a section describing the external validity of the analysis to our Discussion (lines 243-245).

b. How do the results of this study affect decision for women undergoing oocyte freezing for fertility preservation?

Thank you for this comment. The findings do not support any conclusions about women undergoing oocyte cryopreservation for fertility preservation.

STATISTICAL EDITOR COMMENTS:

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

lines 61-66: Since the primary outcome was "good perinatal outcome", the results section, beginning with the sentence on line 62, should begin with the rates and aOR for the primary. The subsequent sentences should report the secondary outcomes.

Thank you for this comment. We have made this change.

For Tables 4-7: Should separately cite the primary outcome as unadjusted rates, aOR, then adjusted rates, so that the reader can easily see not only the relative, but the absolute difference in rates of "good perinatal outcome". This should be in a separate Table, clearly separate from the secondary outcomes.

Thank you for this comment. We have created a new table (new Table 4) and deleted Tables 5-7. This allows us to present both the unadjusted and adjusted rates in the same table.

Tables 5, 6, 7: The odds ratios cited all are multivariable, so they should be labelled in Table and text as aORs or adjusted ORs. Either in methods, footnote to Tables or as supplemental material, should list the variables included in the final models for each.

Thank you for this comment. We have made the recommended changes to the new Table 4.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

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For instance, the "Objective" section of the Abstract should be a simple "TO" statement without background.

Thank you for this comment. We have edited the abstract as requested and confirmed that the rest of the manuscript is consistent with Green Journal formatting requirements.

- why did you not include the absence of identified fetal/neonatal anomalies?

Thank you for this comment. Unfortunately, these data are not available in SART CORS.

- PRESENTATION OF STATS INFORMATION

P Values vs Effect Size and Confidence Intervals: While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript. Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.

Thank you for this comment. We have provided ORs as requested.

- As "good perinatal outcome" is your primary outcome, it should be presented first--here and in manuscript results and discussed first in the discussion section.

Thank you for this comment. We have made the requested edits.

- It seems that this last statement runs the risk of being a bit overstated. While you are correct about the statistical significance, the degree of difference in the two groups is not great. See article referenced below. The aOR of 0,88 is well within the zone of potential bias--very important in a retrospective study. Also on line 66 make sure you edit to aOR.

Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)

Thank you for this comment. We have edited the discussion to reflect the small effect size.

- are there risks, including to the donor?

Thank you for this comment. There are no additional risks. Risks to the donor are the same with cryopreserved or fresh oocytes.

- state why it was exempt

Thank you for this comment. The study was exempt because the data were de-identified. We have added this to our methods section (lines 98-99).

- What is meant by "intent for fresh embryo transfer". What is the alternative if its an IVF cycle?

Thank you for this comment. All included cycles were started with intent to transfer a fresh embryo. We excluded frozen embryo transfer cycles (cycles in which cryopreserved embryos were thawed for transfer).

- Thank you for this really excellent description of data base validation.

Thank you for this comment.

- Did you collect data for those with high order conception that may have undergone embryo reduction to twins or a singleton?

Thank you for this comment. We did not collect data to examine spontaneous or selective reduction. We agree that this is an interesting question.

- missing data for perinatal outcome? why just "good" perinatal outcome?
Figure 1, 190 cycles were excluded due to missing good perinatal outcome.

Thank you for this comment. Good perinatal outcome was our primary outcome. Any cycles missing any component of "good" perinatal outcome (live birth, birth weight, or gestational age) were excluded. Please let us know if we can provide further clarification.

- During the time frame, did anyone have >1 pregnancy? How did you control for them as they may not have independent outcomes.

Thank you for this comment. Table 1 shows the frequencies of women who had one, two, or more pregnancies. Since women undergoing multiple IVF cycles are correlated, we accounted for this correlation in our analysis with the use of the generalized estimating equations modeling technique as detailed in the Methods section (lines 136-138).

- For the non REI reader, could you explain this a bit? Is it because in a frozen donor cycle, you thaw only a small number of available oocyte--may have alot more given that younger women tend to respond robustly to ovarian stimulation as noted with fresh cycles? So the lower number of frozen is iatrogenic--the doc selects a subset of available oocytes? Or is it something else? Mention in your discussion.

Thank you for this comment. Our introduction explains that cryopreserved oocytes are purchased in small batches (lines 88-91). We have added additional explanation to the discussion (lines 221-226).

- Same sort of question as above. The majority of your readers will be general Ob GYN's and the decisions made by the REI doc and reasons for them may not be generally known. In the discussion section, please tell us why blastocyst embryo transfer is used at different rates in the 2 groups and why potentially important? Just a sentence or 2.

Thank you for this comment. The explanation regarding blastocyst transfer is now contained within the discussion (lines 221-226).

- give raw data

Thank you for this comment. We have added the raw data in the new Table 4.

- (CDC) needs to be added here, since on line 212 you use the abbreviation.

Thank you for this comment. We have made this change.

2. The Editors of Obstetrics & Gynecology are seeking to increase 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:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

Thank you for this comment. We plan to opt in if the manuscript is accepted.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic

Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

Thank you for this comment. I have confirmed with the coauthors.

4. The cover page states that it was presented at ASRM in 2018. It appears that this was presented in 2017 (San Antonio, not Denver). See https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.1016_j.fertnstert.2017.07.244&d=DwIGaQ&c=imBPVzF25OnBgGmVOLcsiEgHoG1i6YHLR0Sj_gZ4adc&r=ZQwd0-s_vm9TEeKWKxeyeLXU-s4T9kWa8F7pUgFgM48&m=vb8m8q32juGweFbsPE3c_9-GS9k9qaMwVTrgo7zfNrM&s=YX2Pd2lQ6nqRHiY-pWsQ3lckq_WEnhtODhep1WUeL8k&e=. Please correct this.

Thank you for this comment. The requested edit was made.

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 and gynecology data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG-2DDepartments_Patient-2DSafety-2Dand-2DQuality-2DImprovement_reVITALize&d=DwIGaQ&c=imBPVzF25OnBgGmVOLcsiEgHoG1i6YHLR0Sj_gZ4adc&r=ZQwd0-s_vm9TEeKWKxeyeLXU-s4T9kWa8F7pUgFgM48&m=vb8m8q32juGweFbsPE3c_9-GS9k9qaMwVTrgo7zfNrM&s=CxUry41RSWCfzEF431-m80_HApl_58TDMjZnlWYA_ec&e=. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Thank you for this comment. We have used the reVITALize definitions.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

Thank you for this comment. We have adhered to the restrictions.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * 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).

Thank you for this comment. We have adhered to these rules.

8. The most common deficiency in revised manuscripts involves the abstract. Be 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 paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

Thank you for this comment. Our abstract contains 271 words.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A_edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=ZQwd0-s_vm9TEeKWKxeyeLXU-s4T9kWa8F7pUgFgM48&m=vb8m8q32juGweFbsPE3c_9-GS9k9qaMwVTrgo7zfNrM&s=KdZt4Sxi21FdugB12cwKHunZfmfb-mh5B49cXddigM4&e=. 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.

Thank you for this comment. We have used standard abbreviations.

10. The journal does not use the virgule symbol (/) in sentences with words. 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.

Thank you for this comment. We have avoided using the virgule symbol.

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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

Thank you for this comment. We have added ORs where appropriate. We have adhered to the other guidelines listed above.

12. Line 214: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Thank you for this comment. We have removed this claim.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:
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Thank you for this comment. Our tables conform to journal style.

14. Figure 1: Please upload as a figure file on Editorial Manager.

Thank you for this comment. We have uploaded the figure file.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_LWW-2DES_A48&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=ZQwd0-s_vm9TEeKWKxeyeLXU-s4T9kWa8F7pUgFgM48&m=vb8m8q32juGweFbsPE3c_9-GS9k9qaMwVTrgo7zfNrM&s=PutYICDFF52rZqj9gl5mWATho9kQhWvmsA03I-buPgs&e= . The cost for publishing an article as open access can be found at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_acd_accounts_ifauth.htm&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=ZQwd0-s_vm9TEeKWKxeyeLXU-s4T9kWa8F7pUgFgM48&m=vb8m8q32juGweFbsPE3c_9-GS9k9qaMwVTrgo7zfNrM&s=j_NUQVWJEC4w0YCzHvHzG0rGfb8RCsRjaaECSyOE1ho&e= .

Please note that 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.

Thank you for this comment.

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- * A point-by-point response to each of the received comments in this letter.

Thank you for this comment.

[REDACTED]

Sincerely,

Jennifer L. Eaton, M.D., M.S.C.I.

Jennifer L. Eaton, M.D., M.S.C.I.