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)*

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Date: Oct 14, 2021
To: "Alina Pelikh" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1972

RE: Manuscript Number ONG-21-1972

The role of Medically Assisted Reproduction treatment types on birth outcomes: A between- and within-family analysis using birth certificate data

Dear Dr. Pelikh:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 28, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Manuscript # ONG-21-1972
Title: The Role of Medically Assisted Reproduction treatment types on birth outcomes: A between and within - family analysis using birth certificate data
The manuscript describes a retrospective analysis of birth comes by types of medically assisted reproduction treatments using birth certificates from Utah between 2009-2017. Given the nature of the incidence of large families in Utah, the investigators attempted to analyze the outcomes of siblings born during the years abstracted who were conceived naturally. A well performed study would be of modest interest to readers of Obstetrics and Gynecology. I will address the manuscript from the points of view, assignment, assessment, analysis, interpretation, and extrapolation.
Assignment:
1. The use of extensive inclusion/exclusion criteria introduces selection bias.
a. For example, the inclusion of "surgery for endometriosis" as an included infertility treatment differs significantly other endocrine causes of infertility. Pain is often the indication that leads to diagnosis not infertility (line 93).
b. The use of the 8-year database limits the in-family analysis. Many large families extend over more than 8 years.
c. Donor gametes and higher order multiple gestations are an integral part of IVF and should not be excluded from the primary analysis (104-8); a secondary analysis on singleton gestation might add information.
d. The exclusion of stillbirths is problematic (line 104-8). A pregnancy associated with selective feticide may be quite different than those without feticide. How did the investigators handle the rare occurrence of a death of a co-twin?
e. If the "sensitivity analysis" (line 106) confirmed no differences in results from the selected analysis, then why exclude these subjects
Assessment
1) The outcome variables need to be expanded to include perinatal mortality, gestational age at delivery, births less that 32 weeks and less than 37 weeks, and birthweight percentile for gestational age. These outcomes have much more meaning to the average obstetric practitioner.
2) There is little information in regard to maternal outcomes by group, mode of delivery, complications of pregnancy other than chronic hypertension. Rare outcomes such as maternal death, ICU admissions, multiple blood transfusions, etc.
3) In the in-family analysis, did you identify and control for remarriage or change in the father of the baby?
Analysis
1) The validity of birth certificate information is notoriously poor. Has the new birth certificate been validated with actual chart review?
2) How many of the cases used in the multivariate analysis had missing data points? How were these handled in the analysis?

3) The analysis apparently only looked at main effects of the independent variable on the dependent variables. Were interaction variables analyzed?
4) Linear regressions require a linear relationship within each variable. How was the data transformed to adjust for a no-linear distribution of variable data.
Interpretation
1) Poor definitions of outcome variable limit the real value of the results.
2) A clear statement of the validity of the birth certificate data is needed.
3) The exclusion/inclusion criteria limit interpretation and bias the results against finding a significant difference.
4) The in-family analysis interpretation is limited by the truncated database (2009-2017) and the failure to control for or identify the biologic father of the other children.
5) Selected subgroup analyses might address many of the weaknesses.
Extrapolation
1) Line 314 A different interpretation might be that Utah fertility practitioners are more likely to choose invasive MAR techniques at a younger maternal age than revealed in the literature from other populations.
2) The highly selected final data allow the authors to conclude MAR on limited poor outcomes is "more similar to naturally conceived (NC) pregnancies" (line317). This assertion overstates the data. This could allow a distorted patient educational process for the infertile patient.

Reviewer #2: ONG 21-1972

In the manuscript under review, we evaluate the results of a retrospective analysis evaluating the impact of assisted reproduction treatment on birth outcomes using a between family and a within-family analysis. Using birth certificate data from Utah, the authors concluded that more invasive treatments are associated with adverse birth outcomes

A few comments on the manuscript are as follows:

ABSTRACT
1. Line 2- - the abbreviation NC has not been defined for the reader.

INTRODUCTION
2. Line 76 - please add the references that make this statement true
3. A clear hypothesis is missing

METHODS
4. Line 101 - why was this timeline chose? The authors give a rationale for initiating in 2009 but why use 2017 as the upper boundary? Was a sample size calculated?
5. Line 111 - what is the primary outcome of this analysis? What was the rate of change the authors expected to discover? Why were these 4 outcomes chosen?
6. Line 112 - Why did the authors not use a standardized and validated BW curve?
7. Line 116-119 was gestational age considered as a variable? This is an extremely important variable since several of the outcomes of interest are dependent on this variable.
8. Was the research protocol submitted to the IRB?
9. How did the authors account for twins in the analysis? If twin A was SGA but twin B was AGA, how was that pregnancy counted?
10. Please add a line stating that the STROBE guidelines were followed for this manuscript.

RESULTS
11. To make it more user friendly, I would suggest splitting table 1 into 2 tables - one for baseline characteristics and the other for the outcomes of interest.
12. Since they have such a large and diverse database, did the authors consider running a propensity score analysis?
13. Table 2 - reporting odds ratio or relative risk with 95% CI for the dichotomous outcomes is more easily interpreted by the readership.

DISCUSSION
14. Line 311-313 - please add references that backs this claim.
15. One additional limitation that should be added is the risk of residual confounding still present in the analysis

STATISTICS EDITOR COMMENTS:

Lines 100-109: Need to include a flow diagram outlining the exclusions from the 469 k children to the analyzed sample of 248 k.

Tables 1 and 2: The "unknown" status for Hispanic ethnicity has a similar proportion to the proportion confirmed as having Hispanic ethnicity and the unknown fraction is significantly higher for the MAR subset. Therefore model 3 which includes ethnicity as an adjustor, is likely imprecise and possibly biased. Need to acknowledge that among the limitations and provide an alternate Model 3 analysis for between family samples.

Table 2: Given the size of the MAR samples, particularly for the within-family analyses, should round all the %s to nearest 0.1%, rather than citing to nearest 0.01%.

Table 2: Need to acknowledge that the within-family analyses are based on a subset of families that used MAR. Namely, overall there were 12,943 MAR for the between family analyses and 5,498 (~42%) MAR within families that had at least one additional NC for comparison (within family analyses). So, the two MAR family sets are not comparable, since the smaller subset had a history of NC and may not be similar in terms of perinatal risk as those who had no history of NC. What were the results of a between family analysis if the MAR subset only included those families without a NC?

Table 2: Was there any relationship between whether there was a prior NC among the MAR group and the type of MAR used?

Figs 1, 2: Should include indication of any statistical differences, either on the figure itself or in its legend.

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 clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
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* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

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5. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

6. 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.

7. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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

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* 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).
* 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]."

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In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

10. 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.

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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%").

13. Your manuscript contains a priority claim. 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. 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.

15. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

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* 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. Do not omit your responses to the Editorial Office or Editors' comments.

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 Oct 28, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD
Editor-in-Chief

2020 IMPACT FACTOR: 7.661
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Cover letter

We thank the reviewers and the editors for their helpful comments and suggestions that helped us improve the manuscript. In line with the comments, we made substantial changes to manuscript:

- **We have extended the range of outcomes analyzed in the paper by including additional analyses for gestational age at delivery (continuous in days), preterm births (<37 weeks of gestation) and very preterm births (<32 weeks of gestation). The results of the new analyses echoed our findings from the analyses on birth weight, LBW, SGA, and term-SGA. Differences between MAR and NC children were smaller in the unadjusted within-family analysis compared to the between-family analysis. The baseline associations were attenuated by 40 to 70% among all types of MAR treatment after adjustment for parental background and child's characteristics. Among siblings, the differences between MAR and NC children became substantively small and statistically insignificant for all types of treatments.**
- **We excluded Hispanic origin from the explanatory variables in Model 3 due to the disproportionally higher frequency of missing data among MAR mothers. The results for the MAR coefficients were almost identical.**
- **We revised the Results and Methods section to make the presentation of our findings more straightforward and intuitive:**
    - **we included Figure 1 with the study sample flow diagram;**
    - **we divided Table 1 into two tables – Table 1 for the descriptive statistics of birth outcomes and Table 2 describing the characteristics of women and children in the analytical sub-sample;**
    - **we included additional Appendix tables for the conventional odds ratios from between-family logistic regression models on main binary outcomes (LBW, preterm, SGA) (Appendix Table 1), moved the results of the Term-SGA and newly added very preterm analyses to the Appendix Table 2); included additional analyses on the subset of singleton births for the main outcomes (Appendix Table 3)**

In addition, we have revised the manuscript based on the reviewers' comments and suggestions of the reviewers. A detailed response to each comment with line numbers from the revised manuscript is presented in bold below. We also confirm that we have read the author instructions and complied to the best of our ability.

REVIEWER COMMENTS:

Reviewer #1: Manuscript # ONG-21-1972
Title: The Role of Medically Assisted Reproduction treatment types on birth outcomes: A between and within - family analysis using birth certificate data
The manuscript describes a retrospective analysis of birth comes by types of medically assisted reproduction treatments using birth certificates from Utah between 2009-2017. Given the nature of the incidence of large families in Utah, the investigators attempted to analyze the outcomes of siblings born during the years abstracted who were conceived naturally. A well performed study would be of modest interest to readers of Obstetrics and Gynecology. I will address the manuscript from the points of view, assignment, assessment, analysis, interpretation, and extrapolation.

Assignment:

1. The use of extensive inclusion/exclusion criteria introduces selection bias.

a. For example, the inclusion of "surgery for endometriosis" as an included infertility treatment differs significantly other endocrine causes of infertility. Pain is often the indication that leads to diagnosis not infertility (line 93).

RE: We do not consider surgery for endometriosis as Medically Assisted Reproduction unless it was used in combination with either FED, AI/IUI, or ART. We amended the text to make it clearer:

"From 2009 to the present, Utah birth certificates contain information related to infertility treatments used to achieve pregnancies. Through these questions we identified children conceived through specific MAR treatments – FED, AI or IUI, or ART. We considered women who reported other treatments such as progesterone, metformin, and surgery for endometriosis in the natural conception group (n=1,236), unless they reported undergoing these treatments together with one of the MAR treatments (n=3,338)" (lines 120-126)

b. The use of the 8-year database limits the in-family analysis. Many large families extend over more than 8 years.

RE: Information on the mode of conception has been collected on birth certificates in Utah only since 2009. The 9-year observation window gives us a comprehensive view of all births in the population (which is a strength of the study design) and hence we have representative (i.e., the population, not just a sample) data on all sets of births visible in the state. It is also important to acknowledge that the interpregnancy interval (IPI) in Utah in 2011 was around 25 months and over 30% did not wait the recommended 18 months to become pregnant again. Utah had also the lowest rate of long IPI (>60 months) in the US, at 12.5% (Copen et al. Natl Vital Stat Rep. 2015). This data suggests that a large proportion of families with two or more children would at least have the second child within our observation window and hence would be included in our within-family analysis as MAR children are most likely to be first- or second-born.

c. Donor gametes and higher order multiple gestations are an integral part of IVF and should not be excluded from the primary analysis (104-8); a secondary analysis on singleton gestation might add information.

RE: We agree that donor gametes are an integral part of IVF. Nonetheless, given the paper's aims, we excluded cases where conception involved donor gametes as it would not be possible to link biological parents' characteristics such as and demographic (e.g., biological mother's age) to the children's birth outcomes and amongst siblings. Because of this, for these cases we would not be able to separate the effect of MAR treatments from the confounding factors such as parental subfertility and other underlying health conditions. This is now mentioned in the text in line 131-133.

Birth of triplets was a rare event in both subsamples of NC and MAR children (51 NC (0.02%) 135 MAR (1.0%)). There were only 2 families with quadruplets and one family with quintuplets among MAR families and none among NC. Even though the sensitivity analysis confirmed that including these groups in the sample would not alter the main findings, comparing birth outcomes of the subgroups of triplets and

higher order gestations among MAR and NC children would not be accurate due to the small sample sizes.

As per reviewer's suggestion, in the revised manuscript we have included the analysis for the subset of singleton births in Appendix Table 1. The main results for all outcomes were very similar when we excluded multiple births(twins) from the analysis (see Table R1 below). There was some minor variation in the magnitude of the effects, however the 95% CI overlapped for all coefficients. Differences between MAR and NC children were smaller in the unadjusted within-family analysis of singletons compared to the between-family analysis. Among singleton siblings, the differences between MAR and NC children became substantively small and statistically insignificant for all types of treatments after adjustment for parental background and child's characteristics, confirming the findings from the main analysis. We added a sentence to the paper: "The results of the main analysis were highly similar if we excluded multiple births from the analytical sample (Appendix Table 3))." (lines 249-250)

Appendix Table 3 (extended to main results). Between- and within-family models of birth outcomes of children born in Utah in 2009-2017, MAR versus NC children: a) analytical sample with twins (main paper results); b) analytical sample of singletons.

	Between-family analysis		Within-family analysis	
	a) Model 3 (twins included; main analysis)	b) Model 3 (singletons only)	a) Model 3 (twins included; main analysis)	b) Model 3 (singletons only)
a) Birth weight (g). Linear models				
MAR as one category				
MAR	-77(-85 to -67)	-84(-93 to -74)	-25 (-41 to -10)	-29(-46 to -13)
By type of treatment				
FED	-68 (-80 to -57)	-75(-87 to -63)	-18(-36 to 1)	-23(-42 to -5)
AI or IUI	-94 (-117 to -70)	-98(-123 to -73)	-56(-84 to -1)	-68(-112 to -24)
ART	-85 (-103 to -67)	-102(-123 to -81)	-43(-84 to -1)	-31(-79 to 17)
b) Gestational age (days). Linear models				
MAR as one category				
MAR	-1.8(-2.0 to -1.5)	-1.9(-2.2 to -1.7)	0.2(-0.2 to 0.6)	0.1(-0.3 to 0.5)
By type of treatment				
FED	-1.2(-1.5 to -1.0)	-1.4(-1.7 to -1.2)	0.3(-0.1 to 0.8)	0.2(-0.3 to 0.6)
AI or IUI	-2.4(-2.9 to -1.8)	-2.5(-3.1 to -1.9)	0.2(-0.9 to 1.2)	-0.1(-1.2 to 1.0)
ART	-2.8(-3.2 to -2.3)	-3.1(-3.6 to -2.6)	-0.6(-1.7 to 0.5)	-0.3(-1.5 to 0.9)
c) LBW. Linear probability models (percentage change in the predicted probability)				
MAR as one category				
MAR	2.2(1.8 to 2.7)	2.6(2.1 to 3.0)	0.5(-0.4 to 1.4)	0.7(-0.1 to 1.6)
By type of treatment				
FED	1.9(1.4 to 2.5)	2.3(1.8 to 2.9)	0.6(-0.4 to 1.6)	0.9(0.0 to 1.8)
AI or IUI	1.9(0.8 to 3.0)	2.1(1.0 to 3.2)	-1.8(-4.2 to 0.6)	-0.7(-3.0 to 1.5)
ART	3.2(2.4 to 4.1)	3.6(2.6 to 4.5)	2.4(-0.1 to 4.8)	0.9(-1.6 to 3.4)
d) Preterm. Linear probability models (percentage change in the predicted probability)				
MAR as one category				
MAR	2.4(1.9 to 2.9)	2.7(2.2 to 3.2)	-0.5(-1.5 to 0.5)	-0.1(-1.1 to 0.9)
By type of treatment				
FED	1.4(0.8 to 2.0)	1.7(1.1 to 2.3)	-0.7(-1.8 to 0.4)	-0.2(-1.3 to 0.9)
AI or IUI	2.7(1.5 to 3.9)	3.5(2.3 to 4.8)	-0.7(-3.3 to 1.9)	0.5(-2.2 to 3.1)

ART	4.8(3.9 to 5.7)	5.1(4.1 to 6.2)	1.1(-1.5 to 3.8)	<0.1(-2.9 to 2.9)
e) SGA. Linear probability models (percentage change in the predicted probability)				
MAR as one category				
MAR	2.0(1.4 to 2.5)	2.1(1.4 to 2.7)	1.7(0.6 to 2.8)	1.6(0.5 to 2.6)
By type of treatment				
FED	2.2(1.5 to 3.0)	2.1(1.4 to 2.9)	1.8(0.6 to 3.0)	1.5(0.3 to 2.7)
AI or IUI	1.9(0.5 to 3.4)	1.9(0.3 to 3.4)	2.2(-0.7 to 5.1)	3.3(0.4 to 6.2)
ART	1.3(0.1 to 2.4)	1.9(0.6 to 3.2)	0.4(-2.5 to 3.3)	0.2(-2.9 to 3.4)

d. The exclusion of stillbirths is problematic (line 104-8). A pregnancy associated with selective feticide may be quite different than those without feticide. How did the investigators handle the rare occurrence of a death of a co-twin?

RE: We agree that stillbirth and perinatal mortality are important adverse birth outcomes; however, the reasons leading to the occurrence of these rare outcomes could be associated with confounders and processes which differ from those commonly associated with the birth outcomes analysed in this paper and thus go beyond the scope of this paper. Moreover, the sibling design wouldn't be applicable to these outcomes. For these reasons, we believe it is more appropriate to investigate these outcomes in a separate paper, which we plan to work on in the near future.

50 children in the sample had twins who were stillborn, out of them 21 were NC, 29 were MAR. We excluded the dead twin from the analysis but kept the surviving twin and accounted that this was a multiple pregnancy in the analysis. Further analysis were restricted by the small sample size.

e. If the "sensitivity analysis" (line 106) confirmed no differences in results from the selected analysis, then why exclude these subjects

RE: We explained this in the comment to the point "c" above

Assessment

1) The outcome variables need to be expanded to include perinatal mortality, gestational age at delivery, births less that 32 weeks and less than 37 weeks, and birthweight percentile for gestational age. These outcomes have much more meaning to the average obstetric practitioner.

RE: We thank the reviewer for the valuable suggestion. We included gestational age at delivery (continuous in days) and preterm births (<37 weeks of gestation) to the main outcomes of the paper. As the occurrence of a very preterm birth (<32 weeks of gestation) was quite rare in the within-family sample, it was not possible to conduct analyses even by mode of conception (MAR vs NC). We included the findings of the between-family analysis for very preterm births in Appendix Table 2.

As a result of the fact that we expanded on the outcomes presented in the paper, we moved the Term-SGA analysis to the Appendix material (Appendix Table 2). We updated the text and all tables to reflect the inclusion of the additional outcomes.

We explained in point "d" above the rationale for not including perinatal mortality among the outcomes for this paper.

We thank the reviewer for the suggestion to look at birth weight percentile for gestational age. We present below the results of the between-family analysis for birth weight percentile for gestational age. The findings are in line with the associations observed for other outcomes. Conducting the within-family analysis using birth weight percentiles calculated for the between-family sample would not be entirely accurate as there are differences in the birth weight distribution across two samples (reflected in Table R1) and hence the results would not be comparable. We therefore suggest extending the range of outcomes in the paper only by including additional analyses for gestational age at delivery, preterm births and very preterm birth.

However, if the reviewer felt that including the analyses by birth weight percentiles would strengthen the paper, we would be happy to include these additional analyses in the Appendix.

Table R1. Between-family models for birth weight in percentiles for gestational age of children born in Utah in 2009-2017, MAR versus NC children

	Between-family analysis		
	Model 1 (Baseline)	Model 2 (birth order + multiple birth + child's sex)	Model 3(Model 2 + maternal age, marital status, education, smoking, BMI, chronic hypertension)
	Birth weight in percentiles for gestational age		
MAR as one category			
MAR	-3.5(-4.0 to -3.0	-0.2(-0.8 to 0.3)	-2.4(-2.9 to -1.9)
By type of treatment			
FED	-2.4(-3.1 to -1.7)	-0.6(-1.2 to 0.1)	-3.0(-3.6 to -2.3)
AI/IUI	-3.5(-4.8 to -2.2)	-0.3(-1.6 to 1.0)	-2.3(-3.6 to -1.0)
ART	-5.9(-6.9 to -4.9)	0.6(-0.4 to 1.6)	-0.9(-1.9 to 0.1)

2) There is little information in regard to maternal outcomes by group, mode of delivery, complications of pregnancy other than chronic hypertension. Rare outcomes such as maternal death, ICU admissions, multiple blood transfusions, etc.

RE: The aim of this paper was to compare risks of adverse birth outcomes in children. We investigate differences in maternal outcomes by mode of conception in a separate paper. Chronic hypertension is measured pre-pregnancy and serves as an indicator of women's health pre-pregnancy that might affect the birth outcomes in children.

We amended a sentence in the introduction to make it clearer that the focus of the paper is on birth outcomes in children: "In this study, we aim to compare risks of adverse birth outcomes by mode of conception and type of MAR treatments and test whether and how specific type of MAR treatments is associated with health outcomes at birth in children after controlling for maternal health factors, parental socio-economic status, and children's characteristics" (line 91-95)

3) In the in-family analysis, did you identify and control for remarriage or change in the father of the baby?

RE: We thank the reviewer for this valuable comment. We do acknowledge that remarriage and having a different biological father might affect birth outcomes in families with MAR and NC children. However, conducting any further analysis was restricted by the low prevalence of this event. 24 children in our within-family sample had missing father ID. Out of the rest, 194 children had at least one sibling born to a different father (1.6% of the total sample with known fathers). The event was too rare to investigate any substantial changes in the outcomes by mode of conception or by type of MAR treatments. For example, only 15 children conceived through AI/IUI had siblings from different fathers. As we are restricted by the word limit, we included a short sentence to the main text: "194 children had at least one sibling born to a different father, however, the sample was too small to account for any differences in the outcomes by mode of conception and type of MAR treatment."(line 197-199)

Analysis

1) The validity of birth certificate information is notoriously poor. Has the new birth certificate been validated with actual chart review?

RE: One of the concerns about investigations that rely on administrative (birth certificate) data is their quality and validity relative to medical charts and records. Our analysis did not conduct a chart review primarily because the quality of the child outcome variables of interest – birth weight, gestational age, preterm births and demographic variables – from birth certificate data across a range of populations have been found to be exceptionally high – sensitivity and specificity exceed 85% and often approach 100% when compared to medical records (Andrade et al 2013; Buescher et al 1993; DiGuiseppe et al, 2002; Northam and Knapp, 2006; Reichman and Hade, 2001; Roohan et al, 2003; Zollinger et al, 2006). Other covariates used in the analysis such as a history of hypertension and smoking during pregnancy have lower sensitivity but still exceptionally high (>80%) specificity (Reichman and Hade, 2001; Roohan et al, 2003)*.

It is worth noting that data quality of birth certificates varies by hospitals. To the extent that measurement error clusters by place of delivery, our within-family analysis controls for hospital effects.

The validity of birth certificates with regards to reporting MAR treatments is discussed in the Discussion of the paper (lines 284-295).

"There have been concerns about underreporting of ART treatments on birth certificates in some U.S. states as the data are self-reported.[31-33] Thoma et al [34] systematically compared data from the 2011 National ART Surveillance System (NASS) that collects data from fertility clinics around the country to birth certificates across the U.S. Reassuringly, the authors found no significant differences in the percentage of births resulting from ART procedures in Utah based on both sources, unlike some other states where underreporting reached 50% and higher. Second, we were able to distinguish between different types of MAR treatments both in the general population as well as in the within-family analysis which allowed us to investigate whether and how birth outcomes are associated with the type of treatments using two complementary perspectives. We found comparable prevalence of the specific type of MAR treatments on Utah birth certificates to the estimates published from the PRAMS.[22]"

***References mentioned earlier:**

1. **Andrade SE, Scott PE, Davis RL, Li DK, Getahun D, Cheetham TC, Raebel MA, Toh S, Dublin S, Pawloski PA, Hammad TA. Validity of health plan and birth certificate data for pregnancy research. Pharmacoepidemiology and drug safety. 2013 Jan;22(1):7-15.**
2. **Buescher PA, Taylor KP, Davis MH, Bowling JM. The quality of the new birth certificate data: a validation study in North Carolina. American journal of public health. 1993 Aug;83(8):1163-5.**
3. **DiGiuseppe DL, DC Aron, L Ranbom, DL Harper, GE Rosenthal. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J. 2002 Sep;6(3):169-79.**
4. **Northam S, Knapp TR. The reliability and validity of birth certificates. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2006 Jan 1;35(1):3-12.**
5. **Reichman NE, EM Hade, Validation of birth certificate data: a study of women in New Jersey's HealthStart program. Ann Epidemiol. 2001 Apr;11(3):186-93**
6. **Roohan PJ, Josberger RE, Acar J, Dabir P, Feder HM, Gagliano PJ. Validation of birth certificate data in New York State. Journal of community health. 2003 Oct;28(5):335-46.**
7. **Zollinger TW, Przybylski MJ, Gamache RE. Reliability of Indiana birth certificate data compared to medical records. Annals of epidemiology. 2006 Jan 1;16(1):1-0.**

2) How many of the cases used in the multivariate analysis had missing data points? How were these handled in the analysis?

RE: Missing data are presented in Table 2 and treated as separate categories in the analysis (Appendix Tables 4-8). The percentage of incomplete and missing data was exceedingly low (ranging between 0.1% and 1.6%) and thus unlikely to affect our results.

3) The analysis apparently only looked at main effects of the independent variable on the dependent variables. Were interaction variables analyzed?

RE: We looked at interaction effects between multiple births and MAR by type of treatment. We present separate analysis for singleton births in the revised manuscript as per reviewer's suggestion. We additionally looked at the interaction between birth order and MAR by type of treatment in the first two pregnancies among families who had both MAR and NC children (within-family sample). Having a prior NC was positively associated with birth weight of MAR children born afterwards (for all types of treatments) highlighting the importance of the birth order in families with MAR and NC children. Details of this additional analysis are presented in the response to the editor's comment later in this document (p.18-20).

While we acknowledge the importance of these additional findings, we would not be able to conduct similar analyses on all types of birth outcomes due to a significant reduction in the sample size after excluding higher order births from the subsample. We therefore decided not to include this additional modelling in the manuscript.

4) Linear regressions require a linear relationship within each variable. How was the data transformed to adjust for a no-linear distribution of variable data.

RE: We addressed the linearity assumption in two different ways. First, as some of the predictors are likely to have a non-linear marginal (main) effect on the outcomes, we allowed for non-linear relationships. In particular, maternal age and BMI are likely to operate in non-linear fashion. We therefore used categorized, not linear, operationalization of these variables, to flexibly allow for non-linear patterns between these predictors and the outcomes.

Second, we used linear regression models for dichotomous outcomes (LBW, preterm, very preterm, SGA and Term-SGA). The advantage of using linear regression for dichotomous outcomes is that the model interpretation is straightforward, as model coefficients can be interpreted as marginal (main) effects. The potential drawback is that in such linear probability regressions, the assumption of continuous outcome and normally distributed error term is violated. Strictly speaking this assumption never holds, and in applied work the question is to what extent deviations from the assumptions influence the results. We have checked that our results are robust to this assumption, as conventional logistic regression models for the between-family analysis provided similar results; we added a table with odds ratios to the online Appendix 1. The predicted probabilities from both linear probability models and logistic regression were very similar. Obtaining unconditional probabilities and marginal effects from the within-family fixed effects using logistic regression is not straightforward (e.g., Miller et al. 2019 National Bureau of Economic Research Working paper 26174), hence we presented the comparable results from linear probability models for both between- and within-family analyses. We included an explanation for our choice of modelling in line 170-176.

Interpretation

1) Poor definitions of outcome variable limit the real value of the results.
2) A clear statement of the validity of the birth certificate data is needed.
3) The exclusion/inclusion criteria limit interpretation and bias the results against finding a significant difference.
4) The in-family analysis interpretation is limited by the truncated database (2009-2017) and the failure to control for or identify the biologic father of the other children.
5) Selected subgroup analyses might address many of the weaknesses.

RE: We have addressed each of these comments above:

1) **We have extended the range of outcomes analyzed in the paper by including additional analyses for gestational age at delivery (continuous in days), preterm births (<37 weeks of gestation) and very preterm births (<32 weeks of gestation). The results of the new analyses echoed our findings from the analyses on birth weight, LBW, SGA, and term-SGA. Differences between MAR and NC children were smaller in the unadjusted within-family analysis compared to the between-family analysis. The baseline associations were attenuated by 40 to 70% among all types of MAR treatment after adjustment for parental background and child's characteristics. Among siblings, the differences between MAR and NC children became substantively small and statistically insignificant for all types of treatments.**

2) **We explained in our response to reviewer that the quality of the child outcome variables of interest and demographic variables from birth certificate data have been compared across a range of populations and were found reassuring. We do not include this statement in the main text we have approached the word limit of 5,500.**

The validity of birth certificates with regards to reporting MAR treatments is discussed in the Discussion of the paper (line 284-295).

3) **We explained the rationale for our inclusion/exclusion criteria in our response to the reviewer.**

4) **We acknowledge that having a different biological father might affect birth outcomes in families with MAR and NC children. However, conducting any further analysis was restricted by the low prevalence of this event (1.6% of children). We included a comment about it in the main text (line 197-199). We commented on the 9-year observation window in our response to the reviewer.**

5) **We included additional analyses on the subset of singleton births for the main outcomes (Appendix Table 3)**

Extrapolation

1) Line 314 A different interpretation might be that Utah fertility practitioners are more likely to choose invasive MAR techniques at a younger maternal age than revealed in the literature from other populations.

RE: We changed "seeking infertility treatments" to "undergoing infertility treatments" in that sentence to shift the focus from the choice of treatments. (line 324)

2) The highly selected final data allow the authors to conclude MAR on limited poor outcomes is "more similar to naturally conceived (NC) pregnancies" (line317). This assertion overstates the data. This could allow a distorted patient educational process for the infertile patient.

RE: We agree with the reviewer and in fact this is the message we meant to convey. The precis and the conclusions now more explicitly say that MAR are associated with adverse birth outcomes, but that there are differences between by type of treatments used. In comparison to more invasive MAR treatments (ART and AI/IUI) birth outcomes related to FED are more similar to those of NC children.

Reviewer #2: ONG 21-1972

In the manuscript under review, we evaluate the results of a retrospective analysis evaluating the impact of assisted reproduction treatment on birth outcomes using a between family and a within-family analysis. Using birth certificate data from Utah, the authors concluded that more invasive treatments are associated with adverse birth outcomes

A few comments on the manuscript are as follows:

ABSTRACT

1. Line 2- - the abbreviation NC has not been defined for the reader.

RE: We added definition of NC in line 53 in the abstract.

INTRODUCTION

2. Line 76 - please add the references that make this statement true

RE: This sentence is no longer part of the manuscript as we had to shorten some parts of the text to meet the word limit of 5,500 words.

3. A clear hypothesis is missing

RE: We have added the following sentence to the introduction: "In this study, we aim to compare risks of adverse birth outcomes by mode of conception and type of MAR treatments and test whether and how specific type of MAR treatments is associated with health outcomes at birth after controlling for maternal health factors, parental socio-economic status, and children's characteristics. Based on previous evidence,[7,20,21] we expect that more invasive treatments are likely to be associated with worse outcomes. In the siblings comparisons, we expect the association between MAR and birth outcomes to attenuate, however, it is unclear whether there are any differences by type of treatments." (line 91-98)

METHODS

4. Line 101 - why was this timeline chose? The authors give a rationale for initiating in 2009 but why use 2017 as the upper boundary? Was a sample size calculated?

RE: Figure 1 shows the study sample flow diagram. At the time the study started, UPDB had received the birth certificate data up to 2017 and these data were linked to the database.

5. Line 111 - what is the primary outcome of this analysis? What was the rate of change the authors expected to discover? Why were these 4 outcomes chosen?

RE: Following reviewer's 1 suggestion, the revised paper includes five main birth outcomes: birth weight (in grams, continuous); gestational age (in days, calculated from available data on full weeks of gestation) (continuous); low birth weight (<2500 grams; LBW); preterm (<37 weeks of gestation), and small for gestational age (birth weight < 10th percentile of all children born in Utah 2009-2017 for the appropriate gestation week; SGA). All outcomes are important for assessing infant's health and identifying the needs for closer monitoring during the neonatal period. We aimed to test whether and how specific type of MAR treatments is associated with health outcomes at birth in children after controlling for maternal health factors, parental socio-economic status, and children's characteristics. Due to the limited availability of large-scale data providing details on different MAR treatments, only a few studies were able to investigate how perinatal outcomes differ by types of treatment (Poon and Lian, 2013 (Journal of paediatrics and child health 2013;49: 733-740., Stanford et al., 2016 (BJOG: An International Journal of Obstetrics & Gynaecology 2016;123: 718-729), Doty et al., 2021 (Fertility and Sterility 2021:115(6):1503-1510)). These studies have found substantial differences between the treatment types, but due to differences in research questions and variety in identification of treatments (e.g., treating ovulation induction drugs together with AI/IUI, or only focusing on IVF among the ART procedures), we could not quantify the prediction in the differences we expected to discover.

6. Line 112 - Why did the authors not use a standardized and validated BW curve?

RE: The definition of being small for gestational age is dependent on the characteristic of the population used to calculate the 10th birth weight percentile thresholds. It has been shown applying standardized charts might lead to an overestimation or underestimation of the proportion of SGA if the population of interest differs from those used to produce these thresholds (i.e., in terms of ethnicity composition or environmental factors (for example, Norris et al., 2015: BMJ Open 2015;5:e006743). To avoid the risk of this bias, we calculated gender-specific percentiles for each gestational age based on all children born in Utah 2009-2017.

We conducted sensitivity analysis using birth weight charts produced by Talge et al. (2014) for the whole population of the U.S. for the period of 2009-2010 and corrected for implausible gestational age estimates (Pediatrics 2014: 133(5):844-53). The results showing the associations between mode of conception and risk of being SGA were fully consistent with the main paper results. The results of the between-family analysis produced slightly smaller differences between MAR and NC children, reflecting, on average, higher birth weight in the 10th percentile of the distribution by gestational age among children born in Utah compared to the whole of the U.S. In the within-family models, the differences between MAR and NC children by all types of treatments were insignificant in the adjusted models, confirming our previous findings. We therefore present the results based on the charts we produced for children born in Utah 2009-2017.

7. Line 116-119 was gestational age considered as a variable? This is an extremely important variable since several of the outcomes of interest are dependent on this variable.

RE: We have now included gestational age and preterm analyses as additional outcomes to the paper.

8. Was the research protocol submitted to the IRB?

RE: This study was approved by the Institutional Review Boards of the University of Utah and by the Utah Resource for Genetic and Epidemiologic Research, an administrated board that oversees access to the Utah Population Database (UPDB) which holds data derived from all Utah birth certificates. We had to exclude this information from the manuscript according to the double-blind peer review requirements. We have now included this information in the main body of the manuscript (line 115-118).

9. How did the authors account for twins in the analysis? If twin A was SGA but twin B was AGA, how was that pregnancy counted?

RE: We analysed outcomes separately for each twin in the twin pair, i.e. if twin A was SGA then its outcome would be SGA, but twin B (AGA) would not be contributing to the SGA group. In the between-family analysis, we had 1924 pairs of twins who were both AGA (n=3848; 2840 NC and 1368 MAR), 530 pairs of twins who were both SGA (n=1060; 670 NC and 390 MAR), and 386 pairs where one twin was AGA and another was SGA (n=772; 446 NC and 306 MAR).

10. Please add a line stating that the STROBE guidelines were followed for this manuscript.

RE: We added a statement about following the STROBE guidelines in line 119-120:

"The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies were followed."

RESULTS

11. To make it more user friendly, I would suggest splitting table 1 into 2 tables - one for baseline characteristics and the other for the outcomes of interest.

RE: Following the reviewer's suggestion, we divided Table 1 into two tables.

12. Since they have such a large and diverse database, did the authors consider running a propensity score analysis?

RE: We believe that using propensity score matching (PSM) is unlikely to make an additional contribution to our analyses. First, it would not be straightforward to match women conceiving through MAR (and especially by type of treatment) with those conceiving naturally since the data we use in this paper does not provide us with comprehensive information on some of the characteristics leading to the mode of conception. For example, we lack information on the time to conception (i.e. degree of sub-fertility which can also affect couples who conceive naturally) which could affect both the mode of conception and subsequent birth outcomes. It would be more suitable to use PSM on survey type data which provides richer information on individual characteristics which distinguish MAR women from NC women, but lower sample size resulting in the inability to look at different treatment types separately and wouldn't allow to compare siblings. In contrast, the administrative data we use in the paper provides large sample size, information on different treatment types and information to compare siblings – data strengths we rely and build on in this paper using a sibling design and fixed effects models. Second, more generally, relying on PSM could lead to an increase in confounder imbalance and greater bias in the estimates of the outcomes of interest as was shown by King and Nielsen 2019: Political Analysis 27:435-454.

13. Table 2 - reporting odds ratio or relative risk with 95% CI for the dichotomous outcomes is more easily interpreted by the readership.

RE: We chose to present the results of linear probability models for the dichotomous outcomes (LBW, preterm, very preterm, SGA and Term-SGA) as model coefficients can be interpreted as marginal (main) effects. Conventional logistic regression models for the between-family analysis provided similar results; we added a table with odds ratios to the online Appendix 1. Obtaining unconditional probabilities and marginal effects from the within-family fixed effects using logistic regression is not straightforward[30], hence we presented the comparable results from linear probability models for both between- and within-family analyses. We included an explanation for our choice of modelling in line 170-176.

DISCUSSION

14. Line 311-313 - please add references that backs this claim.

RE: We added a reference

15. One additional limitation that should be added is the risk of residual confounding still present in the analysis

RE: We added a sentence to the discussion (line 306-308):

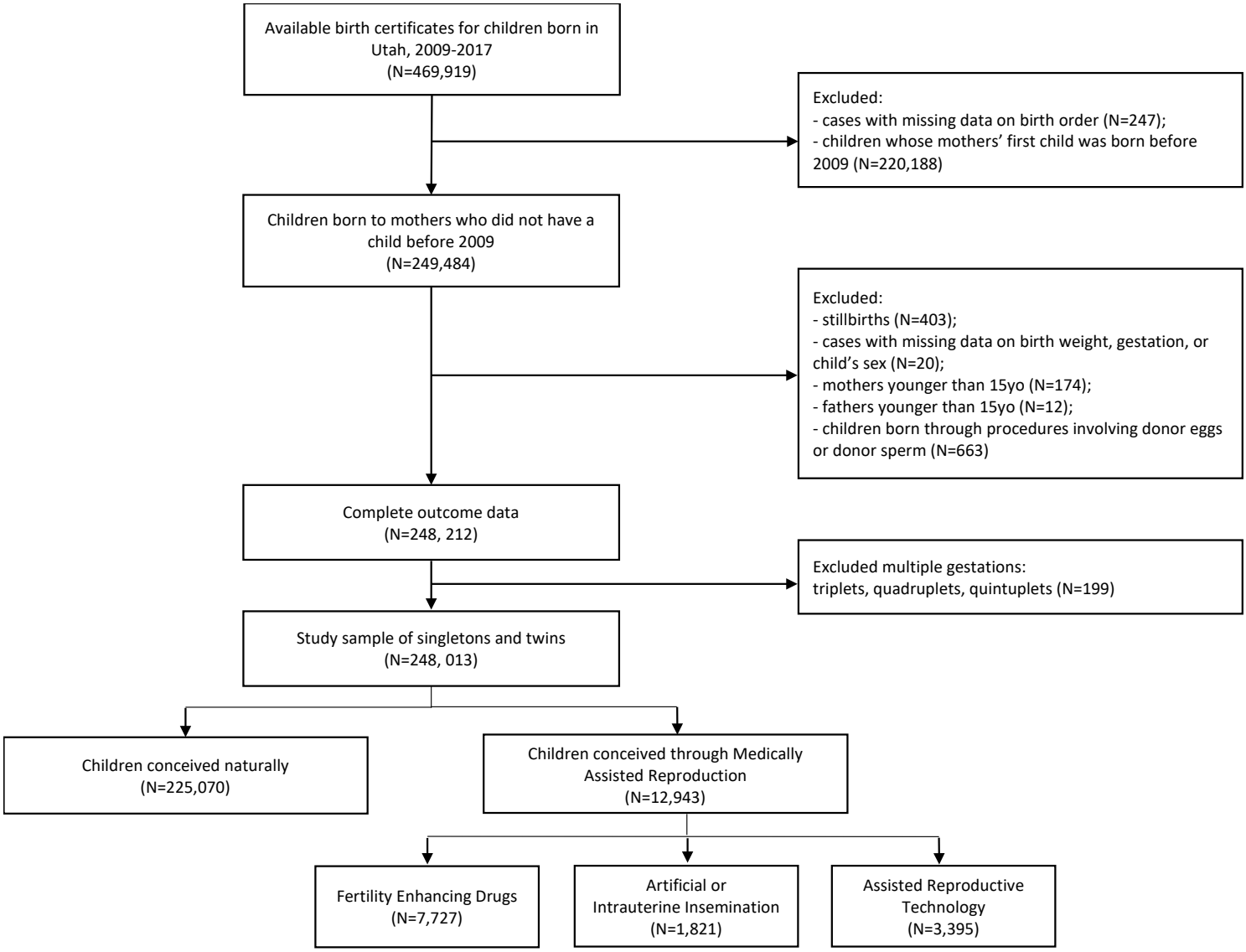
“We acknowledge that our analyses are limited by the availability of data on potential confounders and the risk of residual confounding is still present in the analysis.”

STATISTICS EDITOR COMMENTS:

Lines 100-109: Need to include a flow diagram outlining the exclusions from the 469 k children to the analyzed sample of 248 k.

RE: We included a study sample flow diagram as Figure 1 (See below).

Figure 1. Study sample flow diagram



Tables 1 and 2: The "unknown" status for Hispanic ethnicity has a similar proportion to the proportion confirmed as having Hispanic ethnicity and the unknown fraction is significantly higher for the MAR subset. Therefore model 3 which includes ethnicity as an adjustor, is likely imprecise and possibly biased. Need to acknowledge that among the limitations and provide an alternate Model 3 analysis for between family samples.

RE: We thank the editor for pointing out the issue with the Hispanic ethnicity variable. We acknowledge that the "unknown" group has a higher prevalence among MAR group. Table R2 below presents the descriptive statistics for all outcomes by Hispanic origin, including the "unknown" category. The "unknown" group tends to have better birth outcomes for both NC and MAR groups – on average, higher birth weight and gestational age, lower prevalence of LBW, preterm, SGA, Term-SGA, and very preterm. By type of MAR treatment, the pattern is similar for FED and ART groups.

Table R2. Descriptive statistics of birth outcomes by Hispanic origin and mode of conception

	NC			MAR			FED			AI or IUI			ART		
Outcomes	Hispanic (n=44,103)	Non Hispanic (n=155,836)	Unknown (n=33,131)	Hispanic (n=1,332)	Non Hispanic (n=9,269)	Unknown (n=2,342)	Hispanic (n=886)	Non Hispanic (n=5,560)	Unknown (n=1,281)	Hispanic (n=173)	Non Hispanic (n=1,329)	Unknown (n=319)	Hispanic (n=273)	Non Hispanic (n=2,380)	Unknown (n=742)
Birth weight (g), mean (sd)	3220(518)	3284(529)	3306(507)	3078(670)	3091(649)	3126(625)	3123(641)	3172(605)	3219(565)	3187(593)	3090(657)	3088(607)	2863(760)	2903(702)	2981(698)
Gestational age (days), mean (sd)	270(13)	270(13)	271(11)	265(18)	266(17)	266(15)	266(17)	268(16)	269(13)	268(15)	266(18)	266(15)	258(22)	261(20)	262(19)
LBW, (%)	6.9	6.2	5.2	15.8	15.6	14.6	13.3	11.5	9.3	11.6	14.2	13.8	26.7	25.8	24.0
Preterm, (%)	8.2	8.0	7.0	18.6	18.1	16.7	15.0	13.3	10.2	11.0	17.5	16.6	35.2	29.8	27.9
Very preterm , (%)	1.0	1.1	0.7	3.5	2.7	1.6	2.6	2.1	0.9	NA	NA	NA	7.7	4.0	2.7
SGA, (%)	13.8	10.9	10.3	13.8	14.9	14.1	14.1	13.7	12.6	11.6	14.9	16.0	14.3	17.8	16.0
Term-SGA, (%)	14.0	10.9	10.1	13.8	14.3	13.8	14.3	13.2	12.2	11.0	14.2	16.5	14.1	17.5	16.1

Note: NA cells for very preterm in AI or IUI groups correspond to values less than <10 people per group for some categories and could not be reported due to the data provider's restrictions.

We conducted additional analysis to test if the results are sensitive to the missing category for the Hispanic variable. The results are presented in Table R3 below: Model 3 (original specification), Model 4 (which retains the Hispanic variable in the model but excludes the cases with missing information on Hispanic origin) and Model 5 (which excludes the Hispanic variable all together). The results of Model 4 show that by excluding cases with missing information on Hispanic origin the difference between MAR and NC group become more pronounced – which is consistent with the descriptive statistics in R3, i.e. we are excluding a higher proportion of MAR children than NC children with more favourable birth outcomes. Nonetheless, compared to Model 3, the differences in the size of the MAR coefficients are small and the story remains unchanged. The results shown in Models 3 and Model 5 are almost identical. Based on these results and on the fact that race doesn't play a crucial role in explaining differences in the birth outcomes between MAR and NC children, we decided to exclude this variable from the analyses and acknowledge this limitation in the methods section: "We did not adjust for maternal race or ethnicity in the analyses due to the very low proportion of non-White women who conceived through MAR in Utah (i.e. <10 women per some race groups by treatment type) and a high prevalence of missing Hispanic origin among MAR mothers (18% vs 10% with confirmed Hispanic origin).(line XX). Excluding the Hispanic origin variable had little effect on the magnitude of other covariates.

Table R3. Between-family analysis by mode of conception: Model3 (original model); Model 4 (sample excludes persons with missing Hispanic origin); Model 5(Model 3 without controlling for Hispanic origin), MAR vs NC

	Model 3 (birth order, child's sex, multiple births, maternal age, marital status, education, Hispanic origin, smoking, BMI, chronic hypertension)	Model 4 (Model 3, sample excludes persons with missing Hispanic origin)	Model 5 (Model 3 without controlling for Hispanic origin)
Birth weight (g). Linear models			
MAR	-77***	-80***	-76***
By type of MAR treatment			
FED	-69***	-74***	-68***
AI or IUI	-95***	-91***	-94***
ART	-86***	-89***	-85***
Gestational age (days). Linear models			

MAR	-2***	-2***	-2***
By type of MAR treatment			
FED	-1***	-1***	-1***
AI or IUI	-2***	-2***	-2***
ART	-3***	-3***	-3***
LBW. Linear probability models (percentage change in predicted probabilities)			
MAR	2.2***	2.2***	2.2***
By type of MAR treatment			
FED	1.9***	2.2***	1.9***
AI or IUI	1.9***	1.9***	1.9***
ART	3.3***	2.7***	3.2***
Preterm. Linear probability models (percentage change in predicted probabilities)			
MAR	2.4***	2.6***	2.4***
By type of MAR treatment			
FED	1.4***	1.8***	1.4***
AI or IUI	2.7***	2.7***	2.7***
ART	4.8***	4.4***	4.8***
SGA. Linear probability models (percentage change in predicted probabilities)			
MAR	2.0***	2.0***	2.0***
By type of MAR treatment			
FED	2.3***	2.3***	2.2***
AI or IUI	2.0**	1.6	1.9*
ART	1.3*	1.4*	1.3*
Very preterm. Linear probability models (percentage change in predicted probabilities)			
MAR	0.6***	0.7***	0.6***
By type of MAR treatment			
FED	0.4**	0.5***	0.4**
AI or IUI	0.6*	0.7*	0.6*
ART	1.0***	1.0***	1.0***
Term-SGA. Linear probability models (percentage change in predicted probabilities)			
MAR	2.0***	2.0***	2.0***
By type of MAR treatment			
FED	2.1***	2.2***	2.1***
AI or IUI	1.9*	1.4	1.8*
ART	1.7**	1.6*	1.7*

Table 2: Given the size of the MAR samples, particularly for the within-family analyses, should round all the %s to nearest 0.1%, rather than citing to nearest 0.01%.

RE: We rounded all %s to the nearest 0.1% in all tables.

Table 2: Need to acknowledge that the within-family analyses are based on a subset of families that used MAR. Namely, overall there were 12,943 MAR for the between family analyses and 5,498 (~42%) MAR within families that had at least one additional NC for comparison (within family analyses). So, the two MAR family sets are not comparable, since the smaller subset had a history of NC and may not be similar in terms of perinatal risk as those who had no history of NC. What were the results of a between family analysis if the MAR subset only included those families without a NC?

RE: We thank the editor for this valuable comment. We agree that the two subsamples present some differences. We comment on this aspect in the first two paragraphs of the Results section (lines 202-214) and in the limitation section (lines 312-318).

We recognise that results from the within-family analyses are based on a subset of MAR families with NC children which may differ from families without NC children. By excluding MAR families with NC children from the between-family sample we would increase the proportion of first-births among MAR in the remaining sample (80% vs 69% before the exclusion). The distribution by type of treatments would also shift towards more invasive treatments:

Table R4. Distribution of births by type of MAR treatments among MAR-conceived children in the between-family sample and sample excluding MAR families with NC children

	Between-family sample	Between-family sample excluding MAR families with NC siblings
FED	59.7%	50.0%
AI or IUI	14.1%	15.5%
ART	26.2%	35.5%

These exclusions would also result in a higher proportion of twins in the MAR group from 16% to 18.2%, mostly due to the increase in the proportion of ART children among MAR group.

These changes result in an increase in the magnitude of the MAR coefficients for most outcomes as we would be excluding a subset of MAR children conceived through less invasive treatments and of higher birth order (see Table R5 below) – which are both associated with more favourable birth outcomes. Whilst we acknowledge these changes compared to the results presented in the manuscript, we also observe considerable overlap in the 95%CI of the MAR coefficients of these analyses and the analyses presented in Model 3 in the paper and that the changes in the coefficients tend to be small in magnitude (i.e. increase in risk of SGA for MAR group increases from 2.0 (95%CI 1.4 to 2.5) to 2.2 (95%CI 1.4 to 3.0). Quite distinctively, the results for the ART group were quite similar across all outcomes. Whilst it is important to acknowledge the differences between the subsamples analysed, the analyses suggest that the link between MAR (type) and birth outcomes is not substantively different in MAR families who do not conceive naturally. We did not incorporate these sensitivity analyses in the manuscript, but we comment on them in the limitation section: "The results from the within-family analyses are based on a subset of MAR families with NC children which, as shown by the descriptive analyses, differ from families without NC children. Additional between-family analysis on a sample of MAR families without NC children (available upon request) confirmed similar associations between the type of MAR treatment and birth outcomes. This suggests that our within-family results are unlikely to be entirely driven by the selected characteristics of the MAR subsample with NC children". (line 312-318)

Table R5. Between-family analysis on a subset of MAR families without NC siblings vs. all MAR families, MAR vs. NC

	Model 3 (original between-family sample)	Model 3 (sample excludes MAR families with NC children)
MAR as one category		
MAR	-77(-85 to -67)	-91(-103 to -79)
By type of treatment		
FED	-68 (-80 to -57)	-88(-104 to -71)
AI or IUI	-94 (-117 to -70)	-116(-145 to -87)
ART	-85 (-103 to -67)	-85(-104 to -71)
MAR as one category		
MAR	-1.8(-2.0 to -1.5)	-2.2(-2.5 to -1.9)
By type of treatment		
FED	-1.2(-1.5 to -1.0)	-1.5(-3.7 to -2.3)
AI or IUI	-2.4(-2.9 to -1.8)	-3.0(-3.7 to -2.3)
ART	-2.8(-3.2 to -2.3)	-2.9(-3.4 to -2.4)
MAR as one category		
MAR	2.2(1.8 to 2.7)	2.9(2.4 to 3.5)
By type of treatment		
FED	1.9(1.4 to 2.5)	2.5(1.8 to 3.3)
AI or IUI	1.9(0.8 to 3.0)	3.5(2.1 to 4.9)
ART	3.2(2.4 to 4.1)	3.3(2.3 to 4.2)
MAR as one category		
MAR	2.4(1.9 to 2.9)	3.0(2.4 to 3.6)
By type of treatment		
FED	1.4(0.8 to 2.0)	1.8(1.0 to 2.7)
AI or IUI	2.7(1.5 to 3.9)	3.7(2.2 to 5.2)
ART	4.8(3.9 to 5.7)	4.5(3.4 to 5.5)
MAR as one category		
MAR	2.0(1.4 to 2.5)	2.2(1.4 to 3.0)
By type of treatment		
FED	2.2(1.5 to 3.0)	2.5(1.4 to 3.5)
AI or IUI	1.9(0.5 to 3.4)	2.8(0.9 to 4.6)
ART	1.3(0.1 to 2.4)	1.5(0.2 to 2.8)

Table 2: Was there any relationship between whether there was a prior NC among the MAR group and the type of MAR used?

RE: To be able to comment on the association between a prior NC among the MAR group and the type of MAR used, we focused on the first two pregnancies in the within-family sample. Families who were able to conceive naturally first had a slightly higher proportion of MAR children conceived through FED and lower proportion conceived through ART. This is likely to be explained through more severe types of infertility among couples who were not able to conceive at all without MAR.

Table R6. Distribution of births by type of MAR treatments among MAR-conceived children in the within-family sample of first two pregnancies, by birth order

	NC first, followed by MAR (N=2,904)	MAR first, followed by NC (N=4,451)
FED	**76%**	**71%**
AI or IUI	**15%**	**15%**
ART	**9%**	**14%**

We present an additional analysis for birth weight using these subsamples. The results for birth weight differed depending on whether MAR were first- or second-born. Thus, in families where first-born children were NC, the birth weight of MAR children did not differ from their siblings regardless of the type of treatments after adjusting for parental and child's characteristics. On the contrary, in families where MAR children were born first, the birth weight of MAR children was significantly lower than of their NC siblings for all types of treatment. These results highlight the importance of the birth order in families with MAR and NC children. Having a prior NC is positively associated with the outcomes of MAR children born afterwards, for all types of treatments. Our findings are fully in line with the previous evidence on the effects of being born first among NC and MAR children in the sibling analyses (as a group, without distinguishing by type of treatment) published by Goisis et al. 2019: Lancet 2019; 393: 1225–32.

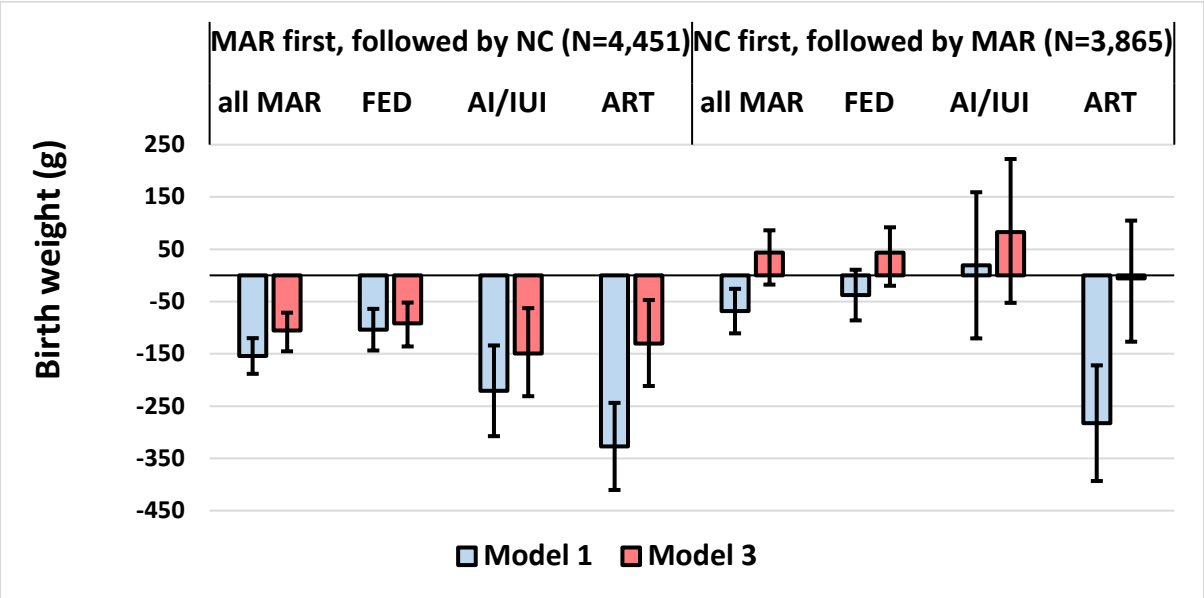
While we acknowledge the importance of these additional findings, the main contribution of our paper is to analyse differences in birth outcomes by type of treatment. We would not be able to conduct similar analyses on all types of birth outcomes due to a significant reduction in the sample size from dividing the sub-sample into two groups (NC following MAR vs. MAR following NC) and because of the exclusion of higher order births from the sample. In addition, in order to accommodate the additional outcomes, we would need to go beyond the word limit of 5,500. We therefore decided not to include this additional modelling in the manuscript. However, if the editor felt that including them would strengthen the paper, we would be happy to include these additional results in the manuscript.

Table R7. Within-family analysis for birth weight, by birth order and type of treatments, MAR vs NC

Within-family analysis for birth weight		
	Model 1 (Baseline)	**Model 3 (Model 1 + multiple birth, child's sex, maternal age, BMI)**
MAR first, followed by NC (N=4,451)		
MAR as one category		
MAR (NC-ref.)	-154(-188 to -120)	-105(-145 to -66)
By type of treatment		
FED	-104(-144 to -64)	-92(-136 to -48)
AI/IUI	-221(-308 to -134)	-149(-231 to -68)
ART	-327(-410 to -244)	-130(-212 to -49)
NC first, followed by MAR (N=2,904)		
MAR as one category		
MAR (NC-ref.)	-68(-111 to -26)	44(-18 to 105)

By type of treatment		
FED	-104(-86 to 11)	43(-20 to 107)
AI/IUI	-221(-121 to 159)	83(-53 to 218)
ART	-327(-393 to -172)	-6(-127 to 115)

Figure R1. Difference in mean birth weight (95% CI) of MAR children (reference – NC) by type of treatment from within-family models, by birth order



Figs 1, 2: Should include indication of any statistical differences, either on the figure itself or in its legend.

RE: We revised the figure legends as follows:

Figure 1. Study sample flow diagram

Figure 2. Difference in mean birth weight and gestational age (95% CI) of MAR children (reference – NC) by type of treatment from between- and within-family models

Figure 3. Percentage change in the probability (95% CI) of LBW and preterm for MAR children (reference – NC) by type of treatment from between- and within-family model

Footnotes under both figures additionally specify that error bars on the graphs show the 95% CI.

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RE: YES

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* 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.

RE: All details were included back to the manuscript.

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RE: The coauthors have confirmed their disclosures are displayed correctly and will complete the eCTA if not already done.

4. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

RE: The data was obtained from the Utah Population Database (UPDB) which holds data derived from all Utah birth certificates.

5. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

RE: We did not include maternal race or ethnicity in the analyses due to the very low proportion of non-White women who conceived through MAR in Utah (i.e. <10 women per some race groups by treatment type) and a high prevalence of missing Hispanic origin among MAR mothers (18% vs 10% of Hispanic origin).

6. 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://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=04%7C01%7Ca.pelikh%40ucl.ac.uk%7C8334dec09ebf4662920508d98f556c47%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C637698420514933720%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=BSE39kGhp%2BwBBYXGRFifvyDdTXKNPwBKe%2F7xz4im0GQ%3D&reserved=0 and the gynecology data definitions at https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=04%7C01%7Ca.pelikh%40ucl.ac.uk%7C8334dec09ebf4662920508d98f556c47%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C637698420514933720%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=6joBSfb%2F49wmyDHqTV90j0Y3OFymKF9x2aLXnBlu3aQ%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

RE: We believe the paper is line with reVITALize definitions.

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RE: The manuscript is in compliance with space length limitations. The word count is 5,497 including figure captions.

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nown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=Yn0o%2F3BiHa8rwuVhGrhakX9ZWK1X8aumWi8qLuPw%2Fj4%3D&reserved=0.

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* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments. **RE: Included**