OBSTETRICS & GYNECOLOGY

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

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

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: Apr 16, 2020
To: "Michal Kirshenbaum" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-333

RE: Manuscript Number ONG-20-333

Obstetric and perinatal outcome in pregnancies resulting from preimplantation genetic testing

Dear Dr. Kirshenbaum:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by May 16, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review your work.

Authors conducted a retrospective chart review on pregnancy outcomes of 3 cohorts: PGT, non-PGT IVF, and spont pregnancies in a single hospital in Israel.

General comments

1. As a benign gyn surgeon, PGD is not my area of expertise, but I do have to have frequent conversations with patients and their IVF providers about PGD in my practice when we make surgery-related fertility decisions so I try to keep with trends. I do think that we need more studies to help us clarify pros and cons of PGD so that we could do a better job of helping patients make complex decisions. Thank you for addressing this very important topic!

2. Aside from advantages listed in 2nd paragraph in into, how about its utility in increasing successful ET (embryo transfer) rates, decreasing failed ET transfer rates, and decreasing rates of miscarriage? These metrics are important to patients.

Intro:
3. Line 92-92. Prior studies you are referring to here were done for PGD patients without infertility or mix of infertility patients along with those who needed testing for familial disorders?

4. Please clarify what your aim (last sentence) to study effect of PGT for all comers (bread and butter infertility IVF cycle) or just for specific subset of patients with no known infertility (familial disorders)? Since intro gave pretty detailed review of use of PTD for different indications, it was a bit hard to follow.

5. Intro was a bit for me to follow as a non-IVF provider. I like the style and simplicity of the terms explained in reference below in case authors find it of use.

BMJ. 2012 Sep 18;345:e5908. doi: 10.1136/bmj.e5908.
Preimplantation genetic testing.
Brezina PR1, Brezina DS, Kearns WG.

Methods:
6. Authors chose 3 cohorts for comparison. PGT, non-PGT IVF, and spont.

7. They explain their rationale in discussion, lines 186-190. To better set the stage for why they when with this specific study design, they should move this discussion into intro.

Aside from this, stating that comparing PGT IVF pregnancies done for familiar reasons to spont pregnancies was bit difficult for me to conceptualize. How about comparing them to women with same familiar disorders who instead of PGT IVF opted for spont preg with prenatal invasive genetic testing? That would theoretically decrease risk of bias since there might be something high risk about those couples in general compared to women who are not affected.

8. Given that selection biases are a common challenge in this type of study, was there consideration given to adding another group which closely matches PGT, which is frozen IVF cycles that match ET (embryo transfer date) to PGT pregnancies? That would help to match in terms of frozen vs. fresh cycles, and to match in term of day of blastocyst life on which ET occurred. Matching of groups based on all relevant factors seems like would be of use in this study.

9. How was sample size determined? If it was a convenience sample, please state.

10. It seems to me that it would be of use to only include singleton pregnancies when you are trying to tease out influence of PTD on outcomes. What was the reason for not doing that in this study?

11. Please describe what the "usual" practice is for IVF in Israel. Do patients go to have fresh or frozen cycles? Is PGD use prevalent for aneuploidy screening? Do IVF centers report their outcomes to SARS type database? Is it common to do single embryo transfers? How prevalent are multiples in IVF pregnancies? Trying to understand if is similar to the US.

12. What % of PGT patients had confirmation via invasive prenatal and postnatal testing?

Results
13. Please add figure with flow chart of study subjects and inclusion/exclusion criteria.

14. Line 125-6. Please explain what "ovum pick up" and "embryo biopsies" were in this setting to audience that may not be familiar with this thermology. I assume "ovum pick up" was oocyte retrieval. What day were embryo biopsies done? Are there different techniques for embryos biopsies or one standard one?

15. Based on reference below, common techniques are trophectoderm biopsy and blastomere biopsy. Please address.

J Obstet Gynaecol Can. 2015 May;37(5):451-63.
Technical Update: Preimplantation Genetic Diagnosis and Screening.
Dahdouh EM1, Balayla J1, Audibert F1; Genetics Committee, Wilson RD2, Audibert F1, Brock JA3, Campagnolo C4, Carroll J5, Chong K5, Gagnon A6, Johnson JA2, MacDonald W7, Okun N5, Pastuck M8, Vallée-Pouliot K1.

16. Lines 143-145. Given that there were demographic differences between cohorts, how was risk adjusted for in terms of outcomes? For example, if IVF group was older, then maternal age would increase risk of IURG, so effect of PGD on IUGR risk would be amplified.

17. Lines 160-162. To address questions about incidence of aneuploidy in PGT group, please explain local practice in this regard. Is it no common to screen for aneuploidy at the time of PGT done for familial reasons? Same questions would be asked about Ashkenazi screening-were parents both tested for carrier status before IVF? If testing was done, what did it consist of?

Discussion
18. Line 194. What is ESTRE PGD consortium? General audience is not likely to know.

19. Lines 233-235. In my opinion, it would be better to say " termination of pregnancy carries procedure-specific risks" instead of getting into risk of infertility and Ashermans' which is very low for most terminations.

20. Lines 241-245. Mode of fertilization and fresh vs. frozen cycle was not avail in the data set. This seems like a common metric to report. Why was it not available? Also, authors state that they divide IVF and ICSI -can you pls expand on that practice? General OBGYN audience may not be familiar.

21. What would the next steps be? What do authors think would be a good follow up study on this topic?

Reviewer #2: This is a retrospective cohort study comparing risk of placental-related complications among pregnancies conceived spontaneously, through IVF and through preimplantation genetic testing (PGT). The authors found a higher rate of fetal growth restriction and hypertensive disorders of pregnancy in the PGT group compared to pregnancies conceived spontaneously or after IVF without PGT. Overall, this is a large well-written study.

Several items would need to addressed prior to consideration to publication.

1. The authors make the assumption that couples undergoing IVF with PGT are fertile. In the US, many couples undergoing IVF for infertility reasons choose to undergo PGT for aneuploidy testing, as another "component" to their IVF cycle. Can the authors discuss if this is an option in Israel. If so, then it would be important to know the number of couples undergoing "directed" PGT.

2. IVF protocols including the use ICSI should be expanded. The authors briefly address the use of ICSI in the Discussion. It would be important to know the number of ICSI pregnancies, as this has been shown to increase the risk of pregnancy complications, above IVF alone.

3. Do the authors have any information of definitions used for pregnancy outcomes such as FGR and gestational hypertensive disorders?

4. Overall, the statistical analysis is too simplistic. An adjusted analysis needs to be done to account for potential confounders, such as age, race, parity, prior history, gestational age.

Reviewer #3: The authors present obstetric and perinatal outcome data on pregnancies resulting from preimplantation genetic testing (PGT) as compared to pregnancies conceived spontaneously and after IVF without PGT. The authors found a higher risk of complications in the PGT group as compared to IVF without PGT and spontaneous pregnancies. Specifically, the risks of placenta related complications such as IUGR and hypertensive disorders were increased. They conclude that PGT may carry increased obstetric risks that should be discussed with patients prior to the procedure.

Specific comments:

1. The study is a large cohort study of patients at one university medical center.

2. The study covered 12 years of PGT patients from 2006 to 2018. The techniques for embryo biopsy included blastomere biopsy of day 3 embryos and trophectoderm biopsies of day 5-6 embryos. It would be important to differentiate these patient groups. Biopsy of blastomeres on day 3 embryos would leave behind totipotent blastomeres in the embryos ultimately transferred. However, trophectoderm biopsies of day 5-6 embryos remove cells that will later develop into the placenta after implantation. One could theorize that the placental related disorders noted in the PGT group would be increased in the trophectoderm biopsied embryos as compared to the blastomere biopsied embryos. If the authors cannot separate these 2 groups of PGT patients, they should address this concern in the discussion.

3. There is no information on the number of embryos transferred. It would be helpful to know what the average number of day 3 and day 5-6 embryos that were transferred.

STATISTICAL EDITOR COMMENTS:

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

General: What were the indications for PGT?

lines 79-80: If so, then why are the comparisons of PCT vs spontaneous cited? It seems that the more relevant control group for IVF would be matched IVF with vs. without PGF.

lines 120-121: Some of the counts in Tables 1, 2 are ≤ 5, so should use Fisher's test, not Chi-square, which changes some of the p-values. Need units for preterm birth categories (weeks). Need to define whether these were all the obstetric and neonatal complications that were evaluated in the initial design phase.

Table 2: For the neonatal outcomes, the individuals within a twin pair cannot be treated statistically as if they are independent events)eg., the n(%) for NICU admits are based on the total number of neonates, not twin pairs). Rather, BW, GA, NICU admit, hospitalization length of stay etc all would have some correlation within a twin pair. Need to account for that lack of independence, which effectively lowers the sample sizes to a number between the number of pregnancies and 2x the number of pregnancies. From the relationship of mean vs st dev, the length of hospitalization appears to be highly skewed. If the distributions were non-normal, then should cite as median (IQR or range) and test non-parametrically.

There are other variables that might have differed in the 3 groups which could have affected outcomes. What were the BMI of the 3 groups, did any have pre-existing HTN

EDITOR'S COMMENTS:

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 ad other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

Abbreviations need to be spelled out on first use, both in the abstract and in the manuscript.

Rather than intrauterine growth restriction, please use "fetal growth restriction". Abbreviations should not be used in the precis.

47. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given. Correct here and in manuscript.
Please state where Sheba Medical Center is.

50: For clarity, for inclusion did all of the patients have to deliver at your center, or only those who conceived spontaneously?

52: I'm really unclear as written which were IVF and which were spontaneous. Could you write something like. The IVF without PGT group included xx singletons and yy twins. The spontaneous conception group included aa singletons and bb twins."

54 and throughout your manuscript: 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, tables and figures.

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 relevant variables.

61: while certainly some preterm births are thought to be placentally mediated, all of them are not.

82: close—but it's premature rupture, not rapture!

84: Not sure what you mean by "invasive interventions"—it appears that you are writing specifically about interventions during the in vitro techniques. Are you equating ICSI w/ PGT? Please clarify.

86: might originate from….

87. Again, terms like "artificial interventions" and "external manipulations" are pretty vague. It would probably be best to make a statement about what you mean by "invasive interventions" "Artificial interventions" and "External manipulations".

88. Your reviewers were concerned about this blanket statement. Some women undergo PGT who are infertile. Please edit. Also relevant to statement made on line 96-97.
. Also one of your reviewers made some comments re: the different risks that may be associated with PGT at day 3 v day 5. Based on this comment it does seem reasonable to analyze these separately in a sensitivity analysis and you should comment on this issue here.

101: for clarity, no cases were included of women undergoing aneuploidy testing who may have been AMA or who just wanted that testing done at the time of IVF? (ie, otherwise uncomplicated?)

In the data, please make sure you indicate which of the IVF patients (with or without PGT) had ICSI or zona pellucida breaching.

107: Is this the complete definition of a biochemical pregnancy? I assume that these were + pregnancy tests by day 14 but no identified pregnancy on US.

113: This is not a random assignment. This is a selection of a control population but it's not random.

117: Hypertensive disorders of pregnancy is the current terminology.

Given that I am requesting some sensitivity analysis, your methods will need to be updated. How did you handle outcomes for couples who had > 1 pregnancy during the time period? As these are not independent events, likely it would have been best to include only the first pregnancy.

133: please provide the final number of including pregnancy.

Were these all truly "missed abortions"? That is, diagnosis of early pregnancy loss made by US in the absence of symptoms, such as bleeding?

140: It seems reasonable to exclude the triplet gestations altogether, as these are so few in number and these pregnancies are at such high risk of complications to begin with .

150. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.

I find Fig 1, Fig 2 very difficult to understand. First, Maternal age is not an obstetric or neonatal outcome and I would remove that. I would also remove the EGA and CS rates from the graphic and just describe them in the text. That way, your Y axis will only need to go to about 15-20% (the rate of GDM in the IVF group) and it will be easier to see values in groups. The arrows are a bit unusual. I will ask our graphics person help you make this a little clearer.

176: how did an embryo with Tri 18 get missed by PGT? Spelling of prematurity on line 177

192. This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMED, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

200: Do you have data on other risk factors for hypertensive disorders of pregnancy, such as weight, history of chronic hypertension, prior preeclampsia that can be controlled for in a logistic regression model?

204, 209: important to make it clear you are speculating about causation.

213: you have data re: why women had PGT at time of IVF. Can you control for maternal autosdomal disorders?

223: Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

233-234: The relationship between 2nd trimester D&C and future preterm birth and intrauterine adhesions is controversial. Probably best to delete this.

EDITORIAL OFFICE COMMENTS:

1. 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.

2. 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.

3. Please submit a completed STROBE checklist with your revision.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

4. 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.

5. 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.

6. 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).

7. 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.

8. 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.

9. 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.

10. 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%").

11. Line 192: 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.

12. 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.

13. Figures 1-2: Please cite the figures within the manuscript text and upload high res figure files to Editorial Manager.

14. 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/ifauth.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.

15. 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 30 days from the date of this letter. If we have not heard from you by May 16, 2020, 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

Editor-in-Chief

May 14, 2020

Dear Editor

RE: Manuscript Number ONG-20-333

“Obstetric and perinatal outcome in pregnancies resulting from preimplantation genetic testing”

We are very grateful for the reviewers and editors’ comments and thoughtful suggestions. We have carefully referred to all reviewers and editors’ comments and incorporated the required changes accordingly. The changes are also shown in the revised tract changes manuscript.

We confirm that we have read the journal’s instructions for authors.

We hope that following this revision, you will find our study suitable for publishing in “Obstetrics and Gynecology”.

Reviewer #1: Thank you for the opportunity to review your work.

Authors conducted a retrospective chart review on pregnancy outcomes of 3 cohorts: PGT, non-PGT IVF, and spont pregnancies in a single hospital in Israel.

General comments

1. As a benign gyn surgeon, PGD is not my area of expertise, but I do have to have frequent conversations with patients and their IVF providers about PGD in my practice when we make surgery-related fertility decisions so I try to keep with trends. I do think that we need more studies to help us clarify pros and cons of PGD so that we could do a better job of helping patients make complex decisions. Thank you for addressing this very important topic!

Reply: We would like to thank the reviewer for the ungrudging comments.

2. Aside from advantages listed in 2nd paragraph in into, how about its utility in increasing successful ET (embryo transfer) rates, decreasing failed ET transfer rates, and decreasing rates of miscarriage? These metrics are important to patients.

Reply: As mentioned in the introduction, our study group included patients who underwent IVF for PGT-M, i.e.- preimplantation diagnosis of monogenic diseases. These couples are generally fertile so that PGT-M enables conception with an unaffected embryo and serves as an alternative for antenatal diagnosis. The aforementioned advantages apply to PGT-A and not PGT for monogenic conditions. This was further clarified in the introduction.

Intro:

3. Line 92-92. Prior studies you are referring to here were done for PGD patients without infertility or mix of infertility patients along with those who needed testing for familial disorders?

Reply: references 9,11,13 and 14 studied fertile patients who underwent PGT-M for specific known inherited genetic diseases. Reference 12 does not specify the indication of PGT, and so, was omitted.

4. Please clarify what your aim (last sentence) to study effect of PGT for all comers (bread and butter infertility IVF cycle) or just for specific subset of patients with no known infertility (familial disorders)? Since intro gave pretty detailed review of use of PTD for different indications, it was a bit hard to follow.

Reply: In the present study, we concentrated on PGT-M patients which are generally fertile and not infertile patients who may use PGT-A. This is mentioned in the introduction: "Since couples undergoing ART treatment for PGT-M are fertile and can conceive spontaneously…… information regarding these outcomes is crucial for healthcare providers and patients who seek for ART-PGT-M treatment in the absence of infertility".

5. Intro was a bit for me to follow as a non-IVF provider. I like the style and simplicity of the terms explained in reference below in case authors find it of use.

BMJ. 2012 Sep 18;345:e5908. doi: 10.1136/bmj.e5908.

Preimplantation genetic testing.

Brezina PR1, Brezina DS, Kearns WG.

Reply: We thank the reviewer for the offer. We believe that the terms were clarified in the introduction. " Preimplantation genetic testing (PGT) for monogenic conditions (PGT-M), previously referred to as preimplantation genetic diagnosis or PGD,…... This specific terminology is in accordance to the new terminology established by the two most prominent societies responsible for the regulation of ART- The American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), 2019.

Methods:

6. Authors chose 3 cohorts for comparison. PGT, non-PGT IVF, and spont.

Reply: Please see reply to #7

7. They explain their rationale in discussion, lines 186-190. To better set the stage for why they when with this specific study design, they should move this discussion into intro.

Reply: Added accordingly to the introduction: ”Couples undergoing ART treatment for PGT-M are fertile and can conceive spontaneously, and their alternative to PGT is natural conception and prenatal genetic diagnosis. For these couples choosing PGT-M might add further risks inherent in the ART associated invasive manipulation such as IVF or ICSI procedures and embryo biopsy”.

Aside from this, stating that comparing PGT IVF pregnancies done for familiar reasons to spont pregnancies was bit difficult for me to conceptualize. How about comparing them to women with same familiar disorders who instead of PGT IVF opted for spont preg with prenatal invasive genetic testing? That would theoretically decrease risk of bias since there might be something high risk about those couples in general compared to women who are not affected.

Reply: Since our patients are fertile, undergoing PGT-ART due to their familial disorders, we chose two control groups: fertile (spontaneous conception) and infertile undergoing IVF without PGT, aiming to control for the embryo biopsy and the ART procedure, respectively. This clarification was added to the introduction.

A third control group of patients choosing to conceive naturally and undergo prenatal testing instead of PGT is of course valuable, but unfortunately, no such a registry/ cohort is available in our center, or in any previously published studies.

8. Given that selection biases are a common challenge in this type of study, was there consideration given to adding another group which closely matches PGT, which is frozen IVF cycles that match ET (embryo transfer date) to PGT pregnancies? That would help to match in terms of frozen vs. fresh cycles, and to match in term of day of blastocyst life on which ET occurred. Matching of groups based on all relevant factors seems like would be of use in this study.

Reply: Thank you for the important comment. As the reviewer mentioned, previous studies have found differences in obstetric outcome depending on ART procedures- IVF vs ICSI and fresh vs thawed embryo transfer (Pandey *et al.*, 2012)(Orvieto *et al.*, 2020). Therefore, we added a sub-analysis of our PGT cohort. We further examined the relationship between those covariates and the odds ratio of the obstetric complications that were found statistically significant in the initial analysis, using a multivariable regression model. This analysis revealed no in-between group differences. This was added to the methods and results (Suppl Table 1/2) sections.

9. How was sample size determined? If it was a convenience sample, please state.

Reply: As stated in the Material and Methods: "The study population included all pregnancies achieved following PGT-M treatment between January 2006 and August 2018, at the Sheba medical center".

10. It seems to me that it would be of use to only include singleton pregnancies when you are trying to tease out influence of PTD on outcomes. What was the reason for not doing that in this study?

Reply: As shown in the results and discussion, we analyzed separately the singleton and twin pregnancies.

11. Please describe what the "usual" practice is for IVF in Israel. Do patients go to have fresh or frozen cycles? Is PGD use prevalent for aneuploidy screening? Do IVF centers report their outcomes to SARS type database? Is it common to do single embryo transfers? How prevalent are multiples in IVF pregnancies? Trying to understand if is similar to the US.

Reply: Freeze for all and PGT-A are not commonly used in Israel. We do report to a national registry, described with the requested details in: https://www.ima.org.il//FilesUpload/Medicine/0/314/157412.pdf. The number of embryos transferred per cycle is determined by the Israel fertility association according to the patient's age and previous treatment outcome.

12. What % of PGT patients had confirmation via invasive prenatal and postnatal testing?

Reply: Prenatal genetic diagnosis is offered to all couples, as per our center policy. Outcomes of all pregnancy are pedantry retrieved. As already published by our group "No one- single case of misdiagnosis was encountered" (Feldman et al. J Assist 298 Reprod Genet. 2017;34(9):1179-1183). This was added to the Materials and methods.

Results

13. Please add figure with flow chart of study subjects and inclusion/exclusion criteria.

Reply: A figure of flow chart was added.

14. Line 125-6. Please explain what "ovum pick up" and "embryo biopsies" were in this setting to audience that may not be familiar with this thermology. I assume "ovum pick up" was oocyte retrieval. What day were embryo biopsies done? Are there different techniques for embryos biopsies or one standard one?

Reply: Corrected accordingly. Regarding the biopsy, it was done by a single technique on Day-3 blastomere, as mentioned in the M&M section:" zona pellucida laser breaching, balstomere biopsy, PCR technique and embryo culture were carried out as previously described"

15. Based on reference below, common techniques are trophectoderm biopsy and blastomere biopsy. Please address.

J Obstet Gynaecol Can. 2015 May;37(5):451-63.

Technical Update: Preimplantation Genetic Diagnosis and Screening.

Dahdouh EM1, Balayla J1, Audibert F1; Genetics Committee, Wilson RD2, Audibert F1, Brock JA3, Campagnolo C4, Carroll J5, Chong K5, Gagnon A6, Johnson JA2, MacDonald W7, Okun N5, Pastuck M8, Vallée-Pouliot K1.

Reply: As mentioned above, PGT-A cycles with trophectoderm biopsy were not included. Only PGT-M cycles with Day-3 blastomere biopsy were included.

16. Lines 143-145. Given that there were demographic differences between cohorts, how was risk adjusted for in terms of outcomes? For example, if IVF group was older, then maternal age would increase risk of IURG, so effect of PGD on IUGR risk would be amplified.

Reply: As mentioned in the M&M, “In order to randomly assign the control group, we included all women that gave birth at the Sheba medical center during the month of May, between 2006 and 2018 (the years of the study)”. We added a multivariable regression analysis to standardize the effect of covariates. Indeed, age was found to significantly affect the risk of hypertensive disease or FGR, as expected. Nonetheless, in spite of the more advanced maternal age among the IVF compared to the PGT group, the risk of those complications was higher among the latter.

17. Lines 160-162. To address questions about incidence of aneuploidy in PGT group, please explain local practice in this regard. Is it no common to screen for aneuploidy at the time of PGT done for familial reasons? Same questions would be asked about Ashkenazi screening-were parents both tested for carrier status before IVF? If testing was done, what did it consist of?

Reply: In our program/Israel, couples are screened pre-conception/treatment to the common inherited disorders related to their origin. No PGT-A is done to our patients. It is not a common practice to offer PGT-A in Israel, issue that is still worldwide debatable (Gleicher and Orvieto, 2017; Orvieto *et al.*, 2020).

Discussion

18. Line 194. What is ESTRE PGD consortium? General audience is not likely to know.

Reply: Explanation was added to the introduction: “The PGT Consortium of the ESHRE comprises a group of expert members in Preimplantation Genetic Testing and Screening whose activities take place under the auspices of the Reproductive Genetics Special Interest Group”.

19. Lines 233-235. In my opinion, it would be better to say "termination of pregnancy carries procedure-specific risks" instead of getting into risk of infertility and Ashermans' which is very low for most terminations.

Reply: Deleted according to reviewer #1 and associate-editor comments

20. Lines 241-245. Mode of fertilization and fresh vs. frozen cycle was not avail in the data set. This seems like a common metric to report. Why was it not available? Also, authors state that they divide IVF and ICSI -can you pls expand on that practice? General OBGYN audience may not be familiar.

Reply: PGT-M couple are undergoing IVF with Day-3 biopsy and fresh transfer. The extra plus healthy embryos are cryopreserved and transferred in subsequent cycle (if required).

Regarding IVF and ICSI, in most centers, ICSI is applied to all PGT cycles, while in our center, as stated: “the common practice in our clinic is to divide equally the ovum fertilization to IVF or ICSI, unless there is a male factor dictating fertilization solely by ICSI”. We mentioned this point to explain why we use IVF and not ICSI for all. Justification for the use of IVF can be found in our previous study (Feldman *et al.*, 2017)and also in a recently published one (De Munck *et al.*, 2020)(De Munck et al. Hum Reprod 2020;35:317–327).

In the IVF without PGT group, information regarding the origin of the embryo transferred, whether from a fresh vs and thawed cycle or the method of insemination (ICSI/IVF) is incomplete and therefore was not presented. Nevertheless, we added a sub-analysis of the PGT group aiming to assess the effect of those covariates on obstetric outcome. A multivariable regression analysis revealed that the type of embryo transfer or the method of insemination did not affect the obstetric or neonatal outcome (suppl table 1/2).

21. What would the next steps be? What do authors think would be a good follow up study on this topic?

Reply: As concluded “we found an increased risk of hypertensive complications during pregnancy in PGT singleton and multiple pregnancies and increased risk of IUGR in PGT singleton pregnancies compared with spontaneous or IVF pregnancies”. Nowadays, except for improving the genetic platforms, the present study provides important information to both fertility and obstetrics specialists counseling and their patients. While determining the appropriate treatment choice for couples who require PGT, we should keep in mind the potential obstetric risk and the follow up should be adapted accordingly. Moreover, since Aspirin treatment has been proved to effectively reduce the risk of preeclampsia in high risk populations, more studies are needed to assess its utility in pregnant women who underwent PGT treatment. This was added to the discussion.

Reviewer #2: This is a retrospective cohort study comparing risk of placental-related complications among pregnancies conceived spontaneously, through IVF and through preimplantation genetic testing (PGT). The authors found a higher rate of fetal growth restriction and hypertensive disorders of pregnancy in the PGT group compared to pregnancies conceived spontaneously or after IVF without PGT. Overall, this is a large well-written study.

Several items would need to addressed prior to consideration to publication.

1. The authors make the assumption that couples undergoing IVF with PGT are fertile. In the US, many couples undergoing IVF for infertility reasons choose to undergo PGT for aneuploidy testing, as another "component" to their IVF cycle. Can the authors discuss if this is an option in Israel. If so, then it would be important to know the number of couples undergoing "directed" PGT.

Reply: Thank you for your comment.

As mentioned, and further clarified in the introduction section, the PGT group included only patients who underwent PGT for inherited monogenic diseases (PGT-M). PGT for aneuploidy (PGT-A) was not included. Considering worldwide debate on PGT-A efficiency (Orvieto and Gleicher, 2020)(Gleicher and Orvieto, 2017), in Israel, PGT-A is not routinely offered for patients undergoing ART for infertility problems, and so, the IVF group included only infertile patients who did not undergo PGT-A.

2. IVF protocols including the use ICSI should be expanded. The authors briefly address the use of ICSI in the Discussion. It would be important to know the number of ICSI pregnancies, as this has been shown to increase the risk of pregnancy complications, above IVF alone.

Reply: In most centers, ICSI is applied to all PGT cycles, while in our center, as stated: “the common practice in our clinic is to divide equally the ovum fertilization to IVF or ICSI, unless there is a male factor dictating fertilization solely by ICSI”. we mentioned this point to explain why we use IVF and not ICSI for all. Justification for the use of IVF can be found in our previous study (Feldman *et al.*, 2017)and also in a recently published one (De Munck *et al.*, 2020)(De Munck et al. Hum Reprod 2020;35:317–327).

In the IVF without PGT group, information regarding the method of insemination (ICSI/IVF) is incomplete and therefore was not presented. Nevertheless, this information is available for the PGT-M group. We added a sub-analysis of the PGT group aiming to assess the effect of those covariates on obstetric outcome. A multivariable regression analysis revealed that the type of embryo transfer or the method of insemination did not affect the obstetric or neonatal outcome (suppl table 1 and 2).

3. Do the authors have any information of definitions used for pregnancy outcomes such as FGR and gestational hypertensive disorders?

Reply: Gestational hypertensive diseases were defined as preeclampsia (new onset hypertension and proteinuria, or of hypertension and significant end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum) or as pregnancy induced hypertension (hypertension without proteinuria or other signs/symptoms of preeclampsia- related end-organ dysfunction that develops after 20 weeks of gestation)("ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia," 2019). FGR was defined as neonatal weight below the 10^{th} percentile according to gestational age using population- based growth curves for singleton and twins. The definitions were added to the method section.

4. Overall, the statistical analysis is too simplistic. An adjusted analysis needs to be done to account for potential confounders, such as age, race, parity, prior history, gestational age.

Reply: We thank the reviewer for this comment and the opportunity to improve the statistical analysis. We added a multivariable regression analysis to account for covariates.

Reviewer #3: The authors present obstetric and perinatal outcome data on pregnancies resulting from preimplantation genetic testing (PGT) as compared to pregnancies conceived spontaneously and after IVF without PGT. The authors found a higher risk of complications in the PGT group as compared to IVF without PGT and spontaneous pregnancies. Specifically, the risks of placenta related complications such as IUGR and hypertensive disorders were increased. They conclude that PGT may carry increased obstetric risks that should be discussed with patients prior to the procedure.

Specific comments:

1. The study is a large cohort study of patients at one university medical center.
2. The study covered 12 years of PGT patients from 2006 to 2018. The techniques for embryo biopsy included blastomere biopsy of day 3 embryos and trophectoderm biopsies of day 5-6 embryos. It would be important to differentiate these patient groups. Biopsy of blastomeres on day 3 embryos would leave behind totipotent blastomeres in the embryos ultimately transferred. However, trophectoderm biopsies of day 5-6 embryos remove cells that will later develop into the placenta after implantation. One could theorize that the placental related disorders noted in the PGT group would be increased in the trophectoderm biopsied embryos as compared to the blastomere biopsied embryos. If the authors cannot separate these 2 groups of PGT patients, they should address this concern in the discussion.

Reply: Thank you for your comment. As mentioned in the introduction section, **all** embryo biopsies were done by single technique on Day-3 blastomere. According to the European Society of Reproduction and Embryology (EHSRE) PGT consortium,

blastomere biopsy is the most common technique used for preimplantation monogenic disease testing(De Rycke *et al.*, 2017). Therefore, we can assume that the higher risk of placental related disorders is associated with the day 3 blastomere biopsy.

3. There is no information on the number of embryos transferred. It would be helpful to know what the average number of day 3 and day 5-6 embryos that were transferred.

Reply: PGT-M couple are undergoing IVF with Day-3 biopsy and fresh transfer. As mentioned in the M&M, "Embryos underwent biopsy on day 3 and transferred a day later. We transfer 1-2 embryos, depending on patients' characteristics, i.e. patient's age, rank of ART cycle (repeated IVF failures). Fresh embryo transfer was done in cases of available unaffected embryos. Surplus unaffected embryos were cryopreserved and transferred in a subsequent cycle, if required".

STATISTICAL EDITOR COMMENTS:

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

General: What were the indications for PGT?

Reply: As mentioned in the method section, "PGT was carried out for couples with monogenic diseases. Moreover, "380 of the 643 pregnancies underwent PGT-M due to maternal indications"

lines 79-80: If so, then why are the comparisons of PGT vs spontaneous cited? It seems that the more relevant control group for IVF would be matched IVF with vs. without PGF.

Reply: As mentioned in the method section, our study group included patients who underwent IVF for preimplantation diagnosis of monogenic disease. These couples

are usually fertile so that PGT-M enables conception with an unaffected embryo and serves as an alternative for antenatal diagnosis. Therefore, we chose two control groups: fertile (spontaneous conception) and infertile undergoing IVF, aiming to control for the ART procedure and the embryo biopsy, respectively.

lines 120-121: Some of the counts in Tables 1, 2 are ≤ 5, so should use Fisher's test, not Chi-square, which changes some of the p-values. Need units for preterm birth categories (weeks). Need to define whether these were all the obstetric and neonatal complications that were evaluated in the initial design phase.

Reply:

The statistical tests were corrected in the method section and in the tables. Units were added for preterm birth categories. All the obstetric and neonatal complications that were evaluated in the initial design phase were assessed.

Table 2: For the neonatal outcomes, the individuals within a twin pair cannot be treated statistically as if they are independent events)eg., the n(%) for NICU admits are based on the total number of neonates, not twin pairs). Rather, BW, GA, NICU admit, hospitalization length of stay etc all would have some correlation within a twin pair. Need to account for that lack of independence, which effectively lowers the sample sizes to a number between the number of pregnancies and 2x the number of pregnancies. From the relationship of mean vs st dev, the length of hospitalization appears to be highly skewed. If the distributions were non-normal, then should cite as median (IQR or range) and test non-parametrically.

Reply:

- Since we separately analyzed twin pregnancies, and did not include nor compared to singleton pregnancies, the correlations only within twin pairs avoid the aforementioned skewed.

- Corrected as suggested, days of hospitalization were cited as median and IQR.

There are other variables that might have differed in the 3 groups which could have affected outcomes. What were the BMI of the 3 groups, did any have pre-existing HTN.

Reply: Thank you for your comment. We added a logistic regression analysis to examine the relationship between the three groups and obstetric outcome. Adjustment was conducted for maternal age, parity, BMI, smoking status, parity, methods of ART and PGT indication. Unfortunately, data regarding maternal background diseases was not available.

EDITOR'S COMMENTS:

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 relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

Abbreviations need to be spelled out on first use, both in the abstract and in the manuscript.

Reply:

Thank you, it was corrected

Rather than intrauterine growth restriction, please use “fetal growth restriction”.

Abbreviations should not be used in the precis.

Reply:

- IUGR was converted to FGR.

- We corrected the precis.

47. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given. Correct here and in manuscript.

Please state where Sheba Medical Center is.

Reply: Thank you. The study duration was corrected. We added the location of Sheba Medical Center.

50: For clarity, for inclusion did all of the patients have to deliver at your center, or only those who conceived spontaneously?

Reply: All patients in the control groups delivered in our center. "compared to pregnancies of women conceived by IVF with no PGT or spontaneously and *delivered at the Sheba medical center*"

52: I’m really unclear as written which were IVF and which were spontaneous. Could you write something like. The IVF without PGT group included xx singletons and yy twins. The spontaneous conception group included aa singletons and bb twins.”

Reply: Thank you for the suggestion, this paragraph was revised accordingly.

54 and throughout your manuscript: 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, tables and figures.
Please provide absolute values for variables, in addition to assessment of statistical significance.

Reply: Thank you for your comment. We added multivariable analysis for the relevant clinical outcome that were found significantly different between the PGT study group and the control IVF and spontaneous pregnancies groups. These analyses, presented in the results section as well as by additional tables (table 3 and 4), details of the Odds ratio and the CI in addition to the p value, were added as requested.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

Reply: Please refer to the previous comment.

61: while certainly some preterm births are thought to be placentally mediated, all of them are not.

Reply: Corrected accordingly

82: close—but it's premature rupture, not rapture!

Reply: Thank you, typo was corrected.

84: Not sure what you mean by "invasive interventions"—it appears that you are writing specifically about interventions during the in vitro techniques. Are you equating ICSI w/ PGT? Please clarify.

Reply: "Invasive manipulation" was related to the gamete manipulation done in ICSI procedure. It was further clarified.

86: might originate from….

Reply: Corrected

87. Again, terms like "artificial interventions" and "external manipulations" are pretty vague. It would probably be best to make a statement about what you mean by "invasive interventions" "Artificial interventions" and "External manipulations".

Reply: The ART treatment components which might affect the risk of obstetric complications were detailed.

88. Your reviewers were concerned about this blanket statement. Some women undergo PGT who are infertile. Please edit. Also relevant to statement made on line

Reply: As mentioned in the introduction "PGT was carried out for couples with monogenic diseases." our study group included patients who underwent IVF for preimplantation diagnosis of monogenic disease. These couples are usually fertile so

that PGT-M enables conception with an unaffected embryo and serves as an alternative for antenatal diagnosis. This was added to the introduction.

96-97. Also one of your reviewers made some comments re: the different risks that may be associated with PGT at day 3 v day 5. Based on this comment it does seem reasonable to analyze these separately in a sensitivity analysis and you should comment on this issue here.

Reply: According to the ESHRE PGD Consortium data collection XIV-XV (3) on PGT cycles for monogenic diseases, day 3 cleavage-stage embryo biopsy was still the most frequently used (93% of cycles) (De Rycke *et al.*, 2017). As tated in the method section we conducted a blastomere biopsy for all PGT-M tretment. Details regarding the PGT-M procedure were added to the method section for further clarification.

101: for clarity, no cases were included of women undergoing aneuploidy testing who may have been AMA or who just wanted that testing done at the time of IVF? (ie, otherwise uncomplicated?)

Reply: Correct. In Israel, PGT-A is not routinely offered for infertile patients undergoing IVF, and so, the IVF control group included only IVF without PGT treatments.

In the data, please make sure you indicate which of the IVF patients (with or without PGT) had ICSI or zona pellucida breaching.

Reply: We added the treatment characteristics of the PGT-M group to the results. Per PGT procedure, all embryos underwent zona pellucida breaching for the purpose of blastomere biopsy. Unfortunately, in the IVF without PGT group, information regarding the method of insemination (ICSI/IVF) is incomplete and therefore was not

presented. Nevertheless, we added a sub-analysis of the PGT group aiming to assess the effect of those covariates on obstetric outcome. A multivariable regression analysis revealed that the type of embryo transfer or the method of insemination did not affect the obstetric or neonatal outcome (supp table 1 and 2).

107: Is this the complete definition of a biochemical pregnancy? I assume that these were + pregnancy tests by day 14 but no identified pregnancy on US.

Reply: Thank you, corrected.

113: This is not a random assignment. This is a selection of a control population but it's not random.

Reply: Thank you, corrected.

117: Hypertensive disorders of pregnancy is the current terminology.

Reply: Terminology was changed.

Given that I am requesting some sensitivity analysis, your methods will need to be updated. How did you handle outcomes for couples who had > 1 pregnancy during the time period? As these are not independent events, likely it would have been best to include only the first pregnancy.

Reply:Methods were updated and the requested analysis was delivered.

133: please provide the final number of including pregnancy.

Were these all truly "missed abortions"? That is, diagnosis of early pregnancy loss made by US in the absence of symptoms, such as bleeding?

Reply: The final number of included pregnancies is mentioned in the results,: "Overall, the study group included 345 singleton pregnancies, 76 twin pregnancies and two triplet pregnancies that ended in live births. The control groups included 5290 singleton pregnancies and 92 twin pregnancies spontaneously conceived and 422 singleton pregnancies and 101 twin pregnancies conceived following IVF without PGT".

- Thank you for your comment, "missed abortions" was changed to "spontaneous abortions".

140: It seems reasonable to exclude the triplet gestations altogether, as these are so few in number and these pregnancies are at such high risk of complications to begin with.

Reply: We agree with the editor's suggestion. We did not do a separate analysis of triplet pregnancies. Rather, we included triplet pregnancies that resulted in twins or singleton pregnancies due to reduction or spontaneous abortion (5 cases overall). We decided to include those cases in light of a recent meta-analysis that suggested that fetal reduction of triplet pregnancies to twins is associated with comparable perinatal outcomes to that of non-reduced twins (Zipori *et al.*, 2017).

150. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.

Reply: Corrected and only statistical significant differences were mentioned.

I find Fig 1, Fig 2 very difficult to understand. First, Maternal age is not an obstetric or neonatal outcome and I would remove that. I would also remove the EGA and CS rates from the graphic and just describe them in the text. That way, your Y axis willonly need to go to about 15-20% (the rate of GDM in the IVF group) and it will be easier to see values in groups. The arrows are a bit unusual. I will ask our graphics person help you make this a little clearer.

Reply: We changes the figures according to the editor's suggestions.

176: how did an embryo with Tri 18 get missed by PGT? Spelling of prematurity on line 177

Reply: As mentioned above, the indication for PGT in our study group was monogenic diseases. In those couples, we check for the specific mutation and not a comprehensive analyses of all 46 chromosomes (as in PGT-A). Nonetheless, we do encourage all couple undergoing PGT-M to perform antenatal genetic tests during pregnancy.

192. This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMED, Google Scholar, EMBASE for example) and the search terms used. IF not done,please edit it out of the paper.

Reply: Corrected accordingly

200: Do you have data on other risk factors for hypertensive disorders of pregnancy, such as weight, history of chronic hypertension, prior preeclampsia that can be controlled for in a logistic regression model?

Reply: To examine the association between covariates and the obstetric and neonatal outcome, we added a multivariate logistic regression model accounted for the following variables: age, BMI, current smoking habits, parity, mode of conception and ART treatment. Data regarding complications in prior pregnancy was not available, and so was not included as a covariate.

204, 209: important to make it clear you are speculating about causation.

Reply: We clarified and discriminate association from causation

213: you have data re: why women had PGT at time of IVF. Can you control for maternal autosomal disorders?

Reply: This data was added to the results. Moreover, multivariable analysis was conducted in order to assess the effect of ART methods and the indication for PGT-M on obstetric outcomes (Suppl table 1 and 2).

223: Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

Reply: Thank you for your comment, corrected accordingly.

233-234: The relationship between 2nd trimester D&C and future preterm birth and intrauterine adhesions is controversial. Probably best to delete this.

Reply:Deleted.

EDITORIAL OFFICE COMMENTS:

1. 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.

Reply: Yes, please publish my point-by-point response letter.

2. 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.

Reply: Coauthors were informed.

3. Please submit a completed STROBE checklist with your revision.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluationsof health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

Reply: Thank you. STROBE form was added to the submission.

4. Standard obstetrics 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.

5. 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.

Reply: The revised manuscript adheres to those restrictions.

6. 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).

7. 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.

Reply: We have changed the abstract according to the revised manuscript.

8. 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.

Reply: Corrected accordingly throughout the manuscript.

9. 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.

Reply: Corrected accordingly throughout the manuscript.

10. 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%").
Reply: Thank you for the comment. Details of the Odds ratio and the CI in addition to the p value, were added where relevant as requested.

11. Line 192: 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.
Reply: Thank you, corrected

12. 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.

13. Figures 1-2: Please cite the figures within the manuscript text and upload high res figure files to Editorial Manager.

Reply: figures citations were added.

14. 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/ifauth.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.

15. 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.

Reply: Thank you, added above.

Date: May 27, 2020
To: "Michal Kirshenbaum" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-333R1

RE: Manuscript Number ONG-20-333R1

[SENT ON THE BEHALF OF DR. CHESCHEIR]

Dear Dr. Feldman:

Thank you for your revision of ONG 20-333 regarding outcomes of pregnancies conceived following prenatal genetic testing. We have made many suggestions for editing your manuscript. One very important one that I wish to emphasize here, as well as in the edited file being return to you, is the use of group names for your 3 groups. Please label them PGT-M, spontaneous conception, and IVF. However, when you are discussing prenatal genetic testing and not using it in reference to the group name, it needs to be spelled out completely. We've worked with this some, and made some of these substitutions in our document as examples, but you need to go through and make sure this is consistently done. Both the introduction and discussion need to be edited to be more concise and focused. I've given you substantial suggestions for these edits.

The latest version of your manuscript is uploaded to your Author account in Editorial Manager (5-27-20v2). Please contact me by email if you cannot locate this file.

Please track your changes and leave the ones made by the Editorial Office. Your next version should be uploaded to Editorial Manager with a point-by-point reply letter to the comments below.

Your next version will be due by June 10.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Line 7: Please correct use of capitals throughout as needed. This should like be "Sackler School of Medicine", for instance.

3. Precis: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.

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6. Line 51-52: Please write in complete sentences throughout the submission.

7. Abstract-Methods: Please describe your statistical techniques here and in the body text.

8. Line 59: Deliveries or pregnancies? Line 196 indicates "pregnancies."

9. Abstract-Results: 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 relevant variables.

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that appear in the Abstract must also appear in the body text for consistency.

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15. Line 69:For space reasons in the abstract, I would omit the data on twins and include that in the manuscript only. The way you've worded the data on Twins is more concise than the similar data presentation you did for singletons and you may wish to adopt that in the abstract and likely the manuscript as well

16. Line 69: Please be sure these data (p=0.03) are stated in the body of your paper, tables, or figures. The "15.7" here appears to be an error.

17. Lines 72-75: This last sentence does not really add anything. The reader can figure out that the information should be included in counseling patients

18. Introduction: The introduction should be approximately 1 page in length (250 words); your's is twice that. Please edit. I will give you some suggestions for editing for conciseness. For instance, your first and second sentences here are essentially saying the same thing, pick one of them and delete the other. Overall, when reading your introduction, you have a lot of extraneous information here. You can consider an outline of about 4 paragraphs: 1. What is preimplantation genetic testing for monogenic disorders, when and how is it done. Please provide 1 example of a monogenic disease typically tested for at your institution. 2. A brief description of the increased risks associated with ART and the manipulations done during it. 3. A brief description of the generally low risk profile for women undergoing testing for monogenic disease and set that up as an important distinction to women undergoing IVF, ICSI for AMA, infertility, etc such that the additional risks of IVF and blastomere biopsy need to be examined. 4. Last paragraph describes your reasons for doing this study.

19. Line 96: Are you referencing a specific committee? "Preimplantation Genetic Genetic Diagnosis Consortium" ? If so, it should be capitalized. This would also be clearer if written "According to the Preimplantation Genetic Diagnosis ConsortiumXIV-XV of the European Society of Human Reproduction and Embryology, on preimplantation

20. Line 101: Why is this important to the topic of your paper?

21. Line 124 and elsewhere: ACOG is moving toward discontinuing the use of “provider.” Please replace “provider” throughout your paper with either a specific term that defines the group to which are referring (for example, “physicians,” “nurses,” etc.), or use “health care professional” if a specific term is not applicable

22. Line 144: Please clarify this sentence. Do you mean they are offered prenatal genetic testing for confirmatin of the preimplantation genetic testing results or for aneuploidy

23. Line 143: Please clarify that this deletion is correct.

24. Line 156: This sentence should be rewritten as something like "All women with spontaneous conceptions who delivered in May, from 2006 to 2018 were included as one control group. Women who underwent IVF at our center without prenatal genetic testing from...to.... were selected as the other control group

25. Line 162: Please use this current terminology throughout

26. Line 163: This is not fetal growth restriction, this would be small for gestational age (SGA). Please update throughout inclding abstract, manuscript and all tables. FGR is the prenatal identification of estimated fetal weight or AC < 10% percentile

27. Line 174 and elsewhere: Please introduce the naming convention (PGT-M) for your groups above where you define your groups. . I'm asking you to refer to your 3 groups by names "PGT-M, Spontaneous Conception, and IVF" . When you refer to "preimplantation genetic test for monogenic diseases" other than as a name for their study group, you need to spell it out

28. Line 185: Now I'm really confused. You say elsewhere that you had 643 pregnancies who under went day 3 blastomere biopsies. Here you say only 380 of them underwent preimplantation genetic testing. What bout the other 263? Why did they have blastomere biopsies

29. Was it ever due to paternal monogenic aberrations? If so, then this should be "parental monogenic disorders". Let's avoid calling them aberrations.

30. Line 187: Not sure why you are using 400 here. You note earlier that only 380 underwent PGT-M. I would think your PGT-M group would have only 380 pregnancies in it, only some of which would be singletons. Please make a clear statement in the first paragraph of your results how many patients are in the PGT-M group

31. Line 189: Were these genetic abnormalities that were false negatives on PGT? or something else?

32. Line 193: How were the 15 with loss of 1 twin counted? As twins or as singletons? Since.you included twins reduced from triplets as twins, did you count these as singletons. ? I think a flow chart of your PGT-M patients might be helpful so we know how you allocated different of them to different groups for your subanalysis

33. Line 198: This is 423 pregnancies. Please state something like: Thus, the PGT-M group included 423 pregnancies that ended in live births: 345 singletons, 76 twins and 2 triplets." Do you have group names for these? If so, please use them."

34. Line 200: Please cite Figure 1 somewhere in the existing text. It should appear before Figure 2, or else you will need to renumber your figures

35. Line 210: In places where you state that something is different from one group to the other, please do as you have here by providing the absolute numbers, but please provide 95% CI's. and OR's. In places where you report results of the multivariable regression analysis, please indicate that you are presenting adjusted OR's (aOR)

36. Line 215: You don't need to tell us the purpose of a multivariable analysis. Are you saying in the the following: "Multivariable analysis results show that the hypertensive disorders of pregnancy were more common in the PGT-M vs Spontaneous Conception group (aOR 14.8, 95% CI 7.4-29..9) and slightly associated with maternal age (aOR...; Hypertensive disorders of pregnancies were less common in parous women (aOR...))

37. Line 216: Please use the naming convention throughout

38. Line 226: Please locate the information of prematurity adjacent to each other

39. Line 228: Please add an in-text citation for supplemental table 2 called "Appendix 2."

40. Discussion: Your discussion has a good deal of redundant or tangential information in it. Here is your stated objective: " Our aim was to asses and compare the obstetric and neonatal outcomes of pregnancies conceived following preimplantation genetic testing for monogenic diseases to those conceived after IVF with no preimplantation testing or spontaneously, aiming to control for the embryo biopsy and the ART procedure.
The discussion should focus on that. Some of these lines should now be captured in the introduction as I suggested it to you., so you do not need to repeat it. Please start your introduction by stating that you found several obstetrical and neonatal adverse outcomes that were worsened among pregnancies following prenatal genetic testing for monogenic disorders compared to spontaneously conceived and IVF pregnancies without prenatal genetic testing. Make a brief statement about why you chose these 2 control groups and how that differs from other studies that have been published. Then give us a paragraph on the SGA, and hypertensive disorders of pregnancy without repeating all the data, linking these as possibly placentally mediated, identifying where you are speculating. next paragraph with other + findings and - findings. Next paragraph: strengths and weakness or limitations of your work; last a conclusion as to how to use the data. This should be about 2 pages in length

41. Line 274-277: These linea do not relate to your stated objectives and should be deleted. Please be sure to edit your reference numbering if needed

42. Line 308: Elsewhere you said 345 singletons. please clarify

43. Line 324: Okay to change to "preimplantation genetic testing"?

44. Table 1: please change cesarean section to cesarean delivery throughout including in tables. ; change IUGR to SGA; please substitute 95% CI's for all P values throughout the tables. Use the group names in the columns (PGT-M, Spontaneous Conception, IVF) and describe those nin the footnote to the table

45. Table 3: Captialize; substitute SGA for FGR

46. Appendix: Your appendix file is being returned to you in case you need to update it.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief

_____

Dear editor,

We thank the editors for the thorough revision of our manuscript.

Hereinafter is a point-by-point reply to the editor's comments.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Line 7: Please correct use of capitals throughout as needed. This should like be "Sackler School of Medicine", for instance.

Reply: We made the required changes.

3. Precis: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.

Reply: Corrected accordingly.

4. Abstract: Your abstract is 351 words and needs to be cut to 300, per the Instructions For Authors. Please re-read the Instructions and comply throughout the revision.

Reply: Abstract was shortened.

5. Line 48: Please review the edits throughout regarding this abbreviation. "PGT-M" was expanded according to the way it was described in the abstract, "preimplantation genetic testing for monogenic diseases." There are some instances where spelling it out may make the sentence wordy and you may want to rewrite. We can use the abbreviation only when you discuss your study group.

Reply: As the editor suggested, we used "PGT-M" when referring to the study group and "preimplantation genetic testing (+/- for monogenic diseases)" when referring to the method.

6. Line 51-52: Please write in complete sentences throughout the submission.

Reply: Thank you. These sentences were rephrased.

7. Abstract-Methods: Please describe your statistical techniques here and in the body text.

Reply: Statistical techniques were added.

8. Line 59: Deliveries or pregnancies? Line 196 indicates "pregnancies."

Reply: Final analysis included pregnancies resulted in deliveries.

9. Abstract-Results: 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 relevant variables.

Reply: We added the absolute values and the crude OR and adjusted OR as requested.

10. Line 62: Line 210 says "14.8; 95% CI 7.4-29.9." Which is correct?

Reply: Thank you for the correction. 14.8; 95% CI 7.4-29.8 is the correct value.

11. Line 62: These would be adjusted OR's, so please indicate that as such

Reply: Thank you. Corrected as requested.

12. Line 65-66: Please be sure these data are stated in the body of your paper, tables, or figures. Statements and data that appear in the Abstract must also appear in the body text for consistency.

Reply: Thank you. This data is detailed in the results: "A multivariable regression analysis revealed that the statistically significant factors associated with SGA were preimplantation genetic testing for monogenic diseases treatment (PGT-M vs Spontaneous Conception: adjusted OR 2.3; 95% CI 1.5-3.4. PGT-M vs IVF: adjusted OR 2.5; 95% CI 1.2-5)…."

13. Line 68: Please be sure these data (p=0.02) are stated in the body of your paper, tables, or figures

Reply: These data is presented in table 4. Nonetheless, we decided not to mention the p value in the abstract, as the significance may be interpreted from the aOR and 95% CI..

14. Line 69: Line 245 says "3.9." Which is correct?

Reply: 3.7 is the correct value, it was changed accordingly in the text.

15. Line 69: For space reasons in the abstract, I would omit the data on twins and include that in the manuscript only. The way you've worded the data on Twins is more concise than the similar data presentation you did for singletons and you may wish to adopt that in the abstract and likely the manuscript as well.

Reply: Thank you for the suggestion. If accepted by the editors, we would prefer to mention the twin pregnancies outcome as well, as it emphasizes the potential effect of preimplantation genetic testing for monogenic diseases. As suggested, we rephrased the singleton outcome in the abstract.

16. Line 69: Please be sure these data (p=0.03) are stated in the body of your paper, tables, or figures. The "15.7" here appears to be an error.

Reply: Please refer to comment number 13. "15.7" typo was erased.

17. Lines 72-75: This last sentence does not really add anything. The reader can figure out that the information should be included in counselling patients

Reply: We gratefully accept this change.

18. Introduction: The introduction should be approximately 1 page in length (250 words); your's is twice that. Please edit. I will give you some suggestions for editing for conciseness. For instance, your first and second sentences here are essentially saying the same thing, pick one of them and delete the other. Overall, when reading your introduction, you have a lot of extraneous information here. You can consider an outline of about 4 paragraphs: 1. What is preimplantation genetic testing for monogenic disorders, when and how is it done. Please provide 1 example of a monogenic disease typically tested for at your

institution. 2. A brief description of the increased risks associated with ART and the manipulations done during it. 3. A brief description of the generally low risk profile for women undergoing testing for monogenic disease and set that up as an important distinction to women undergoing IVF, ICSI for AMA, infertility, etc such that the additional risks of IVF and blastomere biopsy need to be examined. 4. Last paragraph describes your reasons for doing this study.

Reply: The introduction was revised and shortened.

19. Line 96: Are you referencing a specific committee? "Preimplantation Genetic Genetic Diagnosis Consortium" ? If so, it should be capitalized. This would also be clearer if written "According to the Preimplantation Genetic Diagnosis ConsortiumXIV-XV of the European Society of Human Reproduction and Embryology, on preimplantation

20. Line 101: Why is this important to the topic of your paper?

Reply: This paragraph was omitted.

21. Line 124 and elsewhere: ACOG is moving toward discontinuing the use of “provider.” Please replace “provider” throughout your paper with either a specific term that defines the group to which are referring (for example, “physicians,” “nurses,” etc.), or use “health care professional” if a specific term is not applicable.

Reply: The term was changed to healthcare professionals.

22. Line 144: Please clarify this sentence. Do you mean they are offered prenatal genetic testing for confirmation of the preimplantation genetic testing results or for aneuploidy

Reply: We routinely recommend a prenatal genetic test for confirmation of the preimplantation genetic test. Of course, couples can elect to do other screening genetic tests. This was clarified in the text.

23. Line 143: Please clarify that this deletion is correct.

Reply: Thank you. This is correct.

24. Line 156: This sentence should be rewritten as something like "All women with spontaneous conceptions who delivered in May, from 2006 to 2018 were included as one control group. Women who underwent IVF at our center without prenatal genetic testing from...to.... were selected as the other control group.

Reply: Patients in the IVF group gave birth at Sheba Medical Center. They did not necessarily undergo fertility treatment in our center. Data regarding the medical obstetric and fertility history of control groups was meticulously collected and restored in the patient’s clinical file.

25. Line 162: Please use this current terminology throughout

Reply: Thank you for the correction. We used the updated terminology.

26. Line 163: This is not fetal growth restriction; this would be small for gestational age (SGA). Please update throughout inclding abstract, manuscript and all tables. FGR is the prenatal identification of estimated fetal weight or AC < 10% percentile

Reply: Thank you, we changed the definition to SGA.

27. Line 174 and elsewhere: Please introduce the naming convention (PGT-M) for your groups above where you define your groups. . I'm asking you to refer to your 3 groups by names "PGT-M, Spontaneous Conception, and IVF" . When you refer to "preimplantation genetic test for monogenic diseases" other than as a name for their study group, you need to spell it out

Reply: Thank you for the suggestion. We renamed the study and control groups. We used the full term of “preimplantation genetic test for monogenic diseases” when not referring to that group.

28. Line 185: Now I'm really confused. You say elsewhere that you had 643 pregnancies who under went day 3 blastomere biopsies. Here you say only 380 of them underwent preimplantation genetic testing. What bout the other 263? Why did they have blastomere biopsies

Reply: We are sorry for the misunderstanding. All pregnancies (643) in the PGT-M gtoup underwent day 3 blasomere biopsy and PCR analysis. 380 of them were due to maternal genetic disease, the others (263) were due to paternal genetic disease.

29. Was it ever due to paternal monogenic aberrations? If so, then this should be "parental monogenic disorders". Let's avoid calling them aberrations.

Reply: Thank you, disorder was used instead of aberrations. Please refer to comment #28.

30. Line 187: Not sure why you are using 400 here. You note earlier that only 380 underwent PGT-M. I would think your PGT-M group would have only 380 pregnancies in it, only some of which would be singletons. Please make a clear statement in the first paragraph of your results how many patients are in the PGT-M group

Reply: As clarified in comment 28- PGT-M treatment resulted in 643 pregnancies, of whom 507 continued to clinical pregnancy (400 singleton, 100 twins, 7 triplets). This is also written in the text and presented in Figure 1 (flow chart of PGT-M pregnancies): “. These treatment cycles resulted in 643 pregnancies, of which 129 (20%) were biochemical pregnancies, 7 (1%) were ectopic pregnancies and 507 (79%) were ongoing clinical pregnancies-400 singleton, 100 twin and 7 triplet pregnancies (fig 1).”

31. Line 189: Were these genetic abnormalities that were false negatives on PGT? or something else?

Reply: These genetic abnormalities were not related to the specific tested abnormalities. It was clarified in the text.

32. Line 193: How were the 15 with loss of 1 twin counted? As twins or as singletons? Since.you included twins reduced from triplets as twins, did you count these as singletons. ? I think a flow chart of your PGT-M patients might be helpful so we know how you allocated different of them to different groups for your subanalysis

Reply: These pregnancies were counted as singleton pregnancies. As mentioned in the materials and methods: “Pregnancies in which a loss of fetus occurred or reduction of fetus was done were categorized according to the number of fetuses in the ongoing pregnancy. “

We added a flow chart of the PGT-M pregnancies (Figure 1), as was requested in the initial revision.

33. Line 198: This is 423 pregnancies. Please state something like: Thus, the PGT-M group included 423 pregnancies that ended in live births: 345 singletons, 76 twins and 2 triplets." Do you have group names for these? If so, please use them."

Reply: Changed as suggested.

34. Line 200: Please cite Figure 1 somewhere in the existing text. It should appear before Figure 2, or else you will need to renumber your figures

Reply: Thank you. Figure 1 is cited in the text.

35. Line 210: In places where you state that something is different from one group to the other, please do as you have here by providing the absolute numbers, but please provide 95% CI's. and OR's. In places where you report results of the multivariable regression analysis, please indicate that you are presenting adjusted OR's (aOR)

Reply: Thank you for the correction. Analysis was changed and presented accordingly.

36. Line 215: You don't need to tell us the purpose of a multivariable analysis. Are you saying in the the following: "Multivariable analysis results show that the hypertensive disorders of pregnancy were more common in the PGT-M vs Spontaneous Conception group (aOR 14.8, 95% CI 7.4-29..9) and slightly associated with maternal age (aOR...; Hypertensive disorders of pregnancies were less common in parous women (aOR...))

Reply: Corrected

37. Line 216: Please use the naming convention throughout

Reply: Naming was changes and used appropriately.

38. Line 226: Please locate the information of prematurity adjacent to each other

Reply: Thank you. Corrected

39. Line 228: Please add an in-text citation for supplemental table 2 called "Appendix 2."

Reply: Added.

40. Discussion: Your discussion has a good deal of redundant or tangential information in it. Here is your stated objective: " Our aim was to asses and compare the obstetric and neonatal outcomes of pregnancies conceived following preimplantation genetic testing for monogenic diseases to those conceived after IVF with no preimplantation testing or spontaneously, aiming to control for the embryo biopsy and the ART procedure.
The discussion should focus on that. Some of these lines should now be captured in the introduction as I suggested it to you., so you do not need to repeat it. Please start your introduction by stating that you found several obstetrical and neonatal adverse outcomes that were worsened among pregnancies following prenatal genetic testing for monogenic disorders compared to spontaneously conceived and IVF pregnancies without prenatal genetic testing. Make a brief statement about why you chose these 2 control groups and how that differs from other studies that have been published. Then give us a paragraph on the SGA, and hypertensive disorders of pregnancy without repeating all the data, linking these as possibly placentally mediated, identifying where you are speculating. next paragraph with other + findings and - findings. Next paragraph: strengths and weakness or

limitations of your work; last a conclusion as to how to use the data. This should be about 2 pages in length

Reply: Thank you. We changed and shortened the discussion as much as possible, as suggested.

41. Line 274-277: These linea do not relate to your stated objectives and should be deleted. Please be sure to edit your reference numbering if needed

Reply: Deleted.

42. Line 308: Elsewhere you said 345 singletons. please clarify

Reply: 345 deliveries. 400 ongoing pregnancies.

43. Line 324: Okay to change to "preimplantation genetic testing"?

Reply: Yes, thank you.

44. Table 1: please change cesarean section to cesarean delivery throughout including in tables. ; change IUGR to SGA; please substitute 95% CI's for all P values throughout the tables. Use the group names in the columns (PGT-M, Spontaneous Conception, IVF) and describe those nin the footnote to the table

Reply: Tables were changed as requested.

45. Table 3: Captialize; substitute SGA for FGR

Reply: Please refer to the previous comment.

46. Appendix: Your appendix file is being returned to you in case you need to update it.