**PEER REVIEW HISTORY**

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**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | Development of hypertensive complications in oocyte donation pregnancy: protocol for a systematic review and individual participant data meta-analysis (DONOR IPD) |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | van Bentem, Kim; van der Hoorn, Marie-Louise; van Lith, Jan; le Cessie, S; Lashley, Eileen |

**VERSION 1 – REVIEW**

| REVIEWER       | Savasi, Valeria  |
|----------------|------------------|
|                | Universita degli Studi di Milano Facolta di Scienze e Tecnologie |
| REVIEW RETURNED| 28-Jan-2022      |

**GENERAL COMMENTS**

Concerning the study protocol from Van Bentem et al, I found it a very interesting project that may will help to elucidate some aspects about the association between oocyte donation and development of hypertensive disorders in pregnancy. I guess it will require a big effort to collect all studies participant data minimizing possible bias that can occur during this phase (authors say that different data formats will be accepted, moreover variables collected in initial studies may be different and contradictory). Furthermore, the choice to include old studies (since 1984) can be questioned, introducing a possible error depending on the evolution of the technique, the selection of patients and the introduction of screening for preeclampsia (PE) and the use of acetylsalicylic acid for PE prevention. About the manuscript itself, I would comment only the first line of the abstract and the introduction: I found imprecise the statement “oocyte donation is comparable to in vitro fertilization, with the distinction of using a donated oocyte”; I believe the authors can be more accurate in the definition of the technique and they should change it.

| REVIEWER       | Ho, Vu           |
|----------------|------------------|
|                | My Duc Hospital, Ho Chi Minh City, IVFMD |
| REVIEW RETURNED| 13-Feb-2022      |

**GENERAL COMMENTS**

This is a well-written study protocol for a meta-analysis investigating the development of hypertensive complications in oocyte donation pregnancies. There were some tiny issues to be clarified in this protocol: - Firstly, the authors addressed in the Abstract that “oocyte donation (OD) is comparable to in vitro fertilization (IVF)”. Please clarify the meaning of “comparable” in this section. - Secondly, for the eligibility criteria, it should be “pregnant women after 20 weeks of gestation”.

Finally, please explain more clearly the reason why the authors will include cycles with embryo donation into this study as the title of this study protocol mentioned on "oocyte" donation not "gamete" donation.

REVIEWER
Wang, Rui
Monash University, Department of Obstetrics and Gynaecology

REVIEW RETURNED
27-Feb-2022

GENERAL COMMENTS

Overall, this is a clearly reported protocol for an IPDMA on the association between oocyte donation pregnancy and hypertensive complications. The authors may wish to consider the following comments.

Major comments:
1. The findings of study screening (Figure 1) and detailed study characteristics (Appendix 2) belong to results. Therefore, these should be ideally presented in the final paper, instead of presenting them in the protocol. If the authors consider mentioning eligible studies important for this IPD protocol, a brief summary on the numbers/participants would be sufficient, instead of Appendix 2.
2. Two different control groups are planned (natural conception and IVF/ICSI without donation), but it is unclear how these two control groups will be handled in the synthesis. It would be useful to clarify whether these will be treated in two separate analyses and how. Similarly, it is unclear whether IVF and ICSI will be analysed together as they were reported separately in some studies.
3. Please prespecify covariates to be adjusted in the analysis. This would be applicable to both two-stage and one-stage models. If the authors plan to consider different control groups in different comparisons, it would also be important to prespecify whether covariates will be different when different control groups are used, as the natural conception group refer to a different study population (without infertility).
4. As some neonatal outcomes are planned in Appendix 3, do the authors plan to report neonatal outcomes in this IPDMA as well? If so, please provide further details; otherwise, please ignore this comment.
5. As the included studies are non-randomised studies of interventions, it would be ideally to use the ROBINS-I tool for the risk of bias assessment.
   https://www.bmj.com/content/355/bmj.i4919
6. Can the authors provide a citation for DONOR-2 as the section on "prediction model development and validation" is a bit vague? If not possible, it would be useful to provide some essential elements of model validation according to TRIPOD.
7. Ethical approval may not be required for the coordinating institute, but it may be needed in some data providing institutes. This is especially the case for some countries when the IPD is only pseudo anonymized (page 9). Rewording the description on ethical approval would be helpful.

Minor comments:
1. Page 3, Line 26, Please remove the numbers of eligible studies/participants as they belong to results.
2. Given that the planned IPD is pseudo anonymized, this would be differentiated from anonymized across the manuscript. For some institutions, this would result in different policy for data sharing.
3. Page 4, line 6: “lead to an …guideline” is an implication, but not a strength of the study per se. Suggest removing.

4. Page 4, line 41: “Therefore, adjustment in design or analysis is of high importance to estimate a causal relation...” The authors seem to consider the research question a causal question. If so, reporting detailed causal methods and including a DAG in the methods would be helpful. If not, this sentence would need to be rephrased.

5. Page 4, line 57: “robust level-1 evidence” Please rephrase this sentence as the robustness of evidence would be dependent on the quality of the data. In addition, all included studies will be observational studies, this will likely to be level-2.

6. Page 9, line 56: “univariate”, “multivariate” should be univariable and multivariable

7. Page 11, line 47: Please clarify the definition of “high risk of bias” as the output of NOS would be scores only.

8. Page 12, line 22: “Therefore, involving patients or the public in the design, conduct, reporting, or dissemination was not possible.” This is inaccurate as it is still possible to involve patients in this IPDMA as it is a different project from published trials. If the authors do not plan any patient or public involvement, please report so.

VERSION 1 – AUTHOR RESPONSE

Response to the comments of the first reviewer (Dr. Valeria Savasi, Universita degli Studi di Milano Facolta di Scienze e Tecnologie)

1. Concerning the study protocol from Van Bentem et al, I found it a very interesting project that may help to elucidate some aspects about the association between oocyte donation and development of hypertensive disorders in pregnancy. I guess it will require a big effort to collect all studies participant data minimizing possible bias that can occur during this phase (authors say that different data formats will be accepted, moreover variables collected in initial studies may be different and contradictory).

   We thank dr. Savasi for her interest in the project and her comments. Indeed, it will require a big effort to collect all the available data, but we are very motivated to execute this project and already got some enthusiastic responses from various authors. Regarding bias, we will address the data collection accurately, and minimize the possibility of bias. Nevertheless, we are indeed dealing with diversity in studies, because of, for example, varying methodological quality and different definitions of the outcome and other variables. We will deal with this critically in the methodology and interpretation of our results. As for the acceptance of different data formats (e.g. Word, Excel, SPSS, etc.), we intentionally opted for this option to accommodate the authors in sharing their data. Thereby, we ask for adequate labelling of variables. The received data will be collected in a data management system by us, in which definitions and units of variables are also accurately noted. If there is any uncertainty about the data, we will ask the corresponding authors for help. When IPD cannot be obtained from a study, aggregate data will be extracted from the publication, and combined with the IPD meta-analysis results in a sensitivity analysis (described in the section “Statistical analysis – Unavailable studies and missing data”).

2. Furthermore, the choice to include old studies (since 1984) can be questioned, introducing a possible error depending on the evolution of the technique, the selection of patients and the
introduction of screening for preeclampsia (PE) and the use of acetylsalicylic acid for PE prevention.

We understand that the inclusion of old studies can be questioned by the reviewer. We choose to include studies from 1984 onwards, since we want to have a complete overview of literature. Using the original individual participant data in the meta-analysis has the great advantage that we can improve the analysis than was done in the independent old studies. Nevertheless, we indeed need to deal with new developments over time, such as screening for PE, use of acetylsalicylic acid and the new definition for PE. In addition it is a possibility that data from old studies is not available anymore and cannot be supplied. However, when we do receive data from the old studies, it is possible to investigate whether publication year is related to the outcome by executing an additional meta-regression analysis. This has been added to the revised protocol in section "Statistical analysis – Planned sensitivity analysis".

Added text: Since studies from 1984 will be included, new developments over time (e.g. screening for PE, use of acetylsalicylic acid, new definition of PE) must be taken into account. To investigate whether publication year is related to the outcome, an additional meta-regression analysis will be performed.

3. About the manuscript itself, I would comment only the first line of the abstract and the introduction: I found imprecise the statement “oocyte donation is comparable to in vitro fertilization, with the distinction of using a donated oocyte”; I believe the authors can be more accurate in the definition of the technique and they should change it.

We thank the reviewer for notifying the imprecision in the definition of the technique of OD, and added some extra explanatory information.

Revised text: Oocyte donation (OD) is an assisted reproductive technique (ART) comparable to in vitro fertilization (IVF), with the distinction of using a donated oocyte and thus involving two women. Thereby, the oocyte donor receives hormonal treatment followed by an oocyte retrieval procedure, and the oocyte recipient undergoes hormonal treatment to prepare the endometrium for embryo transfer.

Response to the comments of the second reviewer (Dr. Vu Ho, My Duc Hospital, Ho Chi Minh City)

1. This is a well-written study protocol for a meta-analysis investigating the development of hypertensive complications in oocyte donation pregnancies. There were some tiny issues to be clarified in this protocol: Firstly, the authors addressed in the Abstract that "oocyte donation (OD) is comparable to in vitro fertilization (IVF)". Please clarify the meaning of "comparable" in this section.

We thank Dr. Vu Ho for notifying us on some issues that need clarification. As his first comment was also stated by another reviewer, we added some extra explanatory information that clarifies that the technique used for OD is comparable to IVF, but involves two women.

Revised text: Oocyte donation (OD) is an assisted reproductive technique (ART) comparable to in vitro fertilization (IVF), with the distinction of using a donated oocyte and thus involving two women. Thereby, the oocyte donor receives hormonal treatment followed by an oocyte retrieval procedure, and the oocyte recipient undergoes hormonal treatment to prepare the endometrium for embryo transfer.

2. Secondly, for the eligibility criteria, it should be "pregnant women after 20 weeks of gestation". This comment is corrected in the eligibility criteria.
Revised text: We will include published and unpublished studies that describe cohorts of women pregnant after OD and beyond 20 weeks of gestation. Inclusion criteria for studies were verified according to the following PICOS criteria:

- **Participants**: pregnant women beyond 20 weeks of gestation, not restricted to a certain age, ethnicity or singleton pregnancy;

3. **Finally, please explain more clearly the reason why the authors will include cycles with embryo donation into this study as the title of this study protocol mentioned on “oocyte” donation not “gamete” donation.**

We agree with the reviewer that this can cause confusion. In this DONOR IPD meta-analysis, the main focus and most important outcome will be the development of hypertensive complications in oocyte donation pregnancy. We considered to include embryo donation pregnancies from an immunological perspective, as double gamete donation does not seem to affect the development of hypertensive complications (Preaubert et al., Eur J Obstet Gynecol Reprod Biol 2018). However, investigating the development of hypertensive complications in embryo donation pregnancies might seem to be a different research question with a different population. Therefore, we decided to leave out embryo donation in the revised protocol.

Response to the comments of reviewer 3 (Dr. Rui Wang, Monash University)

Overall, this is a clearly reported protocol for an IPDMA on the association between oocyte donation pregnancy and hypertensive complications. The authors may wish to consider the following comments.

We thank Dr. Rui Wang for his incisive commentary, and explain our changes in response below.

**Major comments:**

1. **The findings of study screening (Figure 1) and detailed study characteristics (Appendix 2) belong to results. Therefore, these should be ideally presented in the final paper, instead of presenting them in the protocol. If the authors consider mentioning eligible studies important for this IPD protocol, a brief summary on the numbers/participants would be sufficient, instead of Appendix 2.**

We decided to report the study screening and characteristics of our initial PubMed literature search to give an idea of the amount of IPD that could potentially be collected. As we were in doubt about whether or not to report this, this comment convinced us to leave it for the final paper. Figure 1 and Appendix 2 are therefore removed from the protocol. The protocol does now only briefly mention the number of eligible studies from the initial PubMed search in the section “Systematic search”.

Revised text: This initial PubMed literature search yielded 20 eligible studies, including 2,301 OD pregnancies and over one million autologous pregnancies. The literature search will be updated at the beginning of the project and prior to completion of data in order to minimize the potential missing of relevant studies.

2. **Two different control groups are planned (natural conception and IVF/ICSI without donation), but it is unclear how these two control groups will be handled in the synthesis. It would be useful to clarify whether these will be treated in two separate analyses and how. Similarly, it is unclear whether IVF and ICSI will be analysed together as they were reported separately in some studies.**

In the DONOR IPD meta-analysis, NC and IVF/ICSI pregnancies will be analysed as two separate control groups. In the OD group, both cycles with IVF and ICSI will have been performed, so there is no reason to analyse IVF and ICSI separately. Hence, IVF and ICSI pregnancies will be analysed...
together as one control group using network meta-analysis. In addition, a network meta-analysis of autologous pregnancies as control group, consisting of both NC and IVF/ICSI pregnancies, will be executed. This is reported in section “Statistical analysis”.

**Added text:** In the DONOR IPD meta-analysis, NC and IVF/ICSI pregnancies will be analysed as two separate control groups. As both cycles with IVF and ICSI will have been performed in the OD group, IVF and ICSI pregnancies will be analysed together as one control group using network meta-analysis. In addition, a network meta-analysis of autologous pregnancies as control group, consisting of both NC and IVF/ICSI pregnancies, will be executed.

3. **Please prespecify covariates to be adjusted in the analysis. This would be applicable to both two-stage and one-stage models. If the authors plan to consider different control groups in different comparisons, it would also be important to prespecify whether covariates will be different when different control groups are used, as the natural conception group refer to a different study population (without infertility).**

The covariates to be adjusted for in the analysis are prespecified in section “Statistical analysis – Planned adjustment for confounders”. A directed acyclic graph to clarify the causal path and associated confounders has already been published in the DONOR protocol in the BMJ open, so a citation to this protocol is added in the revised protocol.

4. **As some neonatal outcomes are planned in Appendix 3, do the authors plan to report neonatal outcomes in this IPDMA as well? If so, please provide further details; otherwise, please ignore this comment.**

The DONOR IPD meta-analysis investigates the development of hypertensive complications in OD pregnancy compared to autologous pregnancies. Hence, studies that report on this outcome in these groups are searched, and studies that only report on neonatal outcomes are excluded. However, from the studies that report hypertensive complications, neonatal variables will also be requested when noted. These neonatal variables may be related to the severity of hypertensive complications in OD pregnancy. Following this comment, no adjustments have been made in the revised protocol.

5. **As the included studies are non-randomised studies of interventions, it would be ideally to use the ROBINS-I tool for the risk of bias assessment.**

Thanks to the reviewer, we will use the ROBINS-I tool for the risk of bias assessment, as the NOS is not well validated. This has been adjusted in the section “Quality assessment and risk of bias”.

**Revised text:** Currently, there is a lack of a single obvious candidate tool for assessing quality of observational epidemiological studies. The frequently used ‘one size fits all’ approach for assessing quality of these studies is therefore probably misleading, considering the large heterogeneity in observational research. It has been recommended to develop a set of criteria for each observational systematic review and meta-analysis, and to assess risk of bias in a qualitative manner (30). In this IPD meta-analysis, the risk of bias is assessed according to the ROBINS-I tool (Risk Of Bias In Non-randomised Studies – of Interventions) (31), as well as according to a validation checklist developed by Scholten et al (32). The ROBINS-I tool is a widely used instrument, and its validity and interobserver variability have been well established. The validation checklist developed by Scholten et al (32) is recommended by Cochrane Netherlands. In this checklist, three relevant domains of risk of bias are distinguished: bias due to confounding, information bias and selection bias (including bias due to loss of follow-up or missing data). Risk of bias will be assessed by two reviewers (KB and EL). For each individual study, the ROBINS-I risk of bias judgement (ranging from low to critical risk of bias) and risk of bias within and across domains will be assessed and described. Disagreement will be resolved by consensus.
6. Can the authors provide a citation for DONOR-2 as the section on “prediction model development and validation” is a bit vague? If not possible, it would be useful to provide some essential elements of model validation according to TRIPOD.

At this moment, the DONOR-2 protocol is not yet published. Therefore, some essential elements from the TRIPOD statement for model validation are highlighted in section “Statistical analysis – Prediction model development and validation”.

Revised text: Recently, we suggested a prospective, national cohort study to investigate the prognostic effect of several factors on the development of hypertensive complications in OD pregnancy (DONOR-2 study, in progress). Within this national cohort, a prediction model will be conducted and internally validated. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement will be used to report the development and validation of this prognostic prediction model (38). The TRIPOD statement strongly recommends to use new participant data to externally validate the performance of the model. In this external validation, outcome predictions for each individual in the new data set are calculated using the initial model, and compared with the observed outcomes. The performance of the initial model will be evaluated through calibration and discrimination. Participant data collected by other researchers in another hospital or country, even using different definitions and measurements, may be used. Therefore, the DONOR IPD could serve as a data set for external validation. The advantage of using IPD as external dataset is that a more stringent form of validation is used, with patients from other geographical areas and from other time periods, improving the predictive accuracy (39). In case of poor performance, the model can be updated or adjusted on the basis of the validation data set. Updating methods could consist of the adjustment of predictors weights, re-estimating predictor weights, and adding or removing predictors (40).

7. Ethical approval may not be required for the coordinating institute, but it may be needed in some data providing institutes. This is especially the case for some countries when the IPD is only pseudo anonymized (page 9). Rewording the description on ethical approval would be helpful.

The description of ethical approval is rephrased in the revised protocol. We already drafted a data transfer agreement in which a possible additional ethical approval will be mentioned.

Revised text: Ethical approval and individual patient consent will not be required in most cases, since the DONOR IPD meta-analysis will utilize existing pseudo anonymized data from cohort studies. Most of the included studies obtained consent from their local ethical review committee to execute the research. For some institutions, an additional approval for data transfer of pseudo anonymized data is needed and will be drafted. This will also be mentioned in the already drafted data transfer agreement.

Minor comments:
1. Page 3, Line 26, Please remove the numbers of eligible studies/participants as they belong to results.

The number of eligible studies/participants has been removed on this page, but is still briefly mentioned in the section “Systematic search”, as previously described in response to “Major comments - comment 1”.

2. Given that the planned IPD is pseudo anonymized, this would be differentiated from anonymized across the manuscript. For some institutions, this would result in different policy for data sharing.

We corrected this throughout the manuscript, and adjusted the description of ethical approval as stated in “Major comments – comment 7”.

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3. Page 4, line 6: “lead to an ...guideline” is an implication, but not a strength of the study per se. Suggest removing.
We agree with the reviewer, so this implication is removed from strengths in the revised protocol.

4. Page 4, line 41: “Therefore, adjustment in design or analysis is of high importance to estimate a causal relation...” The authors seem to consider the research question a causal question. If so, reporting detailed causal methods and including a DAG in the methods would be helpful. If not, this sentence would need to be rephrased.
Indeed, we consider the research question as a causal question. A directed acyclic graph to clarify the causal path and associated confounders has already been published in the DONOR protocol in BMJ open, so a citation to this protocol is added in the revised protocol. This is described in section “Statistical analysis – Planned adjustment for confounders”.

Added text: Planned adjustment for confounders
To estimate a causal relation between OD pregnancy and the development of hypertensive complications using observational studies, adjustment the analyses is of high importance. Possible associated covariates are visualized in a directed acyclic graph previously published in the protocol for the DONOR study (38), highlighting the confounding factors that need to be adjusted.
These confounding factors include maternal age, ethnicity, and plurality. Adjustment will be done by multivariable analyses. Furthermore, subgroup analyses are planned to demonstrate potential modifiers in the causal path.

5. Page 4, line 57: “robust level-1 evidence” Please rephrase this sentence as the robustness of evidence would be dependent on the quality of the data. In addition, all included studies will be observational studies, this will likely to be level-2.
As our primary objective is to assess the risk for developing hypertensive complications in women pregnant after OD compared to women pregnant using their autologous oocyte, we believe that this IPD meta-analysis is indeed likely to offer robust evidence. Since our research question is dependent on observational studies (with additional disadvantages), one can debate whether this IPD meta-analysis does not lead to level-1 evidence after all. However, we agree with the fact that the robustness of evidence is dependent on the quality of the data, so “level-1” has been removed from the revised protocol.

6. Page 9, line 56: “univariate”, “multivariate” should be univariable and multivariable.
These errors are adjusted in the revised protocol.

7. Page 11, line 47: Please clarify the definition of “high risk of bias” as the output of NOS would be scores only.
For assessing quality of the observational epidemiological studies, it has been recommended to develop a set of criteria for each observational systematic review and meta-analysis and to assess risk of bias in a qualitative manner (Dekkers et al., PLoS Med 2019). In this IPD meta-analysis, we will assess the risk of bias according to three relevant domains of risk of bias, as recommended by Cochrane Netherlands (Scholten et al., Bohn Staffleu Van Loghum). Furthermore, we decided to use the ROBINS-I tool instead of the NOS to assess the risk of bias in non-randomised studies. The judgements of the ROBINS-I tool range from low to critical risk of bias, so no score is used.

8. Page 12, line 22 “Therefore, involving patients or the public in the design, conduct, reporting, or dissemination was not possible.” This is inaccurate as it is still possible to involve patients in this IPDMA as it is a different project from published trials. If the authors do not plan any patient or public involvement, please report so.
We do not plan any patient or public involvement, so this is adjusted in the revised protocol.
Revised text: For this IPD meta-analysis, patients or public are not being involved in the design, conduct, reporting, or dissemination. The results will be disseminated as publications in open-access journals, and shared with patients in health care settings related to OD.

VERSION 2 – REVIEW

| REVIEWER | Ho, Vu |
|----------|--------|
|          | My Duc Hospital, Ho Chi Minh City, IVFMD |
| REVIEW RETURNED | 17-May-2022 |

GENERAL COMMENTS
Thank you so much for your great efforts.

| REVIEWER | Wang, Rui |
|----------|-----------|
|          | Monash University, Department of Obstetrics and Gynaecology |
| REVIEW RETURNED | 27-May-2022 |

GENERAL COMMENTS
I would like to congratulate the authors for their excellent response. My concerns have been adequately addressed.

I have only one additional minor comment based on this R1. The authors added a network meta-analysis in this revision to compare OD, IVF/ICSI and natural conception, which seems unnecessary. As the aim of this IPDMA does not include comparing IVF/ICSI and natural conception and studies only comparing these two groups are not included. Therefore, the adding value of a network meta-analysis seems limited. In addition, network meta-analysis would require valid transitivity assumptions across groups. In this case, all included studies are observational by nature, which will likely to violate the assumption. Consequently, adding a network meta-analysis is likely introducing unnecessary complications. The authors may wish to reconsider the decision to add a network meta-analysis. I leave it to the authors to make a final call.

All the best with the DONOR IPD and I look forward to read the findings.

VERSION 2 – AUTHOR RESPONSE

Response to the comments of reviewer 3 (Dr. Rui Wang, Monash University)

I would like to congratulate the authors for their excellent response. My concerns have been adequately addressed. I have only one additional minor comment based on this R1. The authors added a network meta-analysis in this revision to compare OD, IVF/ICSI and natural conception, which seems unnecessary. As the aim of this IPDMA does not include comparing IVF/ICSI and natural conception and studies only comparing these two groups are not included. Therefore, the adding value of a network meta-analysis seems limited. In addition, network meta-analysis would require valid transitivity assumptions across groups. In this case, all included studies are observational by nature, which will likely to violate the assumption. Consequently, adding a network meta-analysis is likely introducing unnecessary complications. The authors may wish to reconsider the decision to add a network meta-analysis. I leave it to the authors to make a final call.
We thank dr. Rui Wang for his detailed review, and are pleased that his concerns have been adequately addressed. Regarding his final comment on the added network meta-analysis, we agree that this is unnecessary. Indeed, the aim of the DONOR IPD meta-analysis is not to compare IVF/ICSI and natural conception. To avoid the introduction of unnecessary complications due to the observational nature of the included studies, we decided to leave out the network meta-analysis. We thank the reviewer for his critical and accurate review.