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Development of hypertensive complications in oocyte donation pregnancy: protocol for a systematic review and individual participant data meta-analysis (DONOR IPD)

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ABSTRACT

Introduction The assisted reproductive technique of oocyte donation (OD) is comparable to in vitro fertilisation (IVF), with the distinction of using a donated oocyte and thus involving two women. Compared with IVF and naturally conceived (NC) pregnancies, OD pregnancies have a higher risk for pregnancy complications as pregnancy-induced hypertension (PIH) and pre-eclampsia (PE). Various covariates among women pregnant by OD, however, also contribute to an increased risk for developing hypertensive complications. Therefore, we will conduct the DONation of Oocytes in Reproduction individual participant data (DONOR IPD) meta-analysis to determine the risk for the development of hypertensive complications in OD pregnancy, in comparison to autologous oocyte pregnancy (non-donor IVF/intracytoplasmic sperm injection (ICSI) and NC pregnancy). The DONOR IPD meta-analysis will provide an opportunity to adjust for confounders and perform subgroup analyses. Furthermore, IPD will be used to externally validate a prediction model for the development of PE in OD pregnancy.

Methods and analysis A systematic literature search will be performed to search for studies that included women pregnant by OD, and documented on hypertensive complications in OD pregnancy. The authors from each study will be asked to collaborate and share IPD. Using the pseudoanonymised combined IPD, we will perform statistical analyses with one-stage and two-stage approaches, subgroup analyses and possibly time-to-event analyses to investigate the risk of developing hypertensive complications in OD pregnancy. Furthermore, we will formally assess a prediction model on its performance in an external validation with the use of IPD.

Ethics and dissemination Ethical approval and individual patient consent will not be required in most cases since this IPD meta-analysis will use existing pseudoanonymised data from cohort studies. Results will be disseminated through peer-reviewed journals and international conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The DONation of Oocytes in Reproduction individual participant data (IPD) meta-analysis will provide a unique opportunity to confirm the risk of hypertensive complications in oocyte donation (OD) pregnancy.
⇒ IPD meta-analysis offers greater statistical power, the possibility to adjust for multiple confounding factors, performing subgroup analysis and many more advantages.
⇒ Using IPD as external dataset leads to a more stringent form of validating a prognostic prediction model, which could work as a support tool for the management of OD pregnancies in medical practice.
⇒ The synthesis of IPD may encounter several difficulties, such as poor quality of primary studies, unavailable IPD and heterogeneity in the recording and measurement of variables.

INTRODUCTION

Rationale

Oocyte donation (OD) is an assisted reproductive technique comparable to in vitro fertilisation (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. Since the first successful OD pregnancy in 1984,[1] thousands of OD procedures have been performed worldwide.[2] These numbers are rising, due to postponing pregnancy, leading to higher maternal age and concomitant reproductive problems.

In addition, over the years, the indications for OD have expanded from premature ovarian insufficiency to age-related diminished ovarian reserve, recurrent IVF failure, maternal inherited genetic abnormalities and surgical/chemical menopause.[3–7] Nowadays, more than 7% of all IVF cycles are performed with donated oocytes in Europe. Actual

numbers are probably even higher though, while not all countries provide their OD data for the yearly publication by the European Society of Human Reproduction and Embryology.[2]

Although the number of OD pregnancies are increasing, the method is accompanied with a high incidence of obstetrical complications.[7] Hypertensive complications, including pregnancy-induced hypertension (PIH) and pre-eclampsia (PE), are one of the most common complications in OD pregnancies. Indeed, numerous meta-analyses combing the evidence indicated an increased risk of hypertensive diseases of pregnancy in OD pregnancies compared with naturally conceived (NC) and non-donor IVF pregnancies.[8–12] These meta-analyses are, however, limited by the quality and heterogeneity of included studies. The OD participant population is represented by advanced maternal age, primiparous status, obesity, ensuing IVF procedure and multiple gestation. These inherent characteristics are important risk factors for the development of several pregnancy complications, such as PE.[13–17] Therefore, adjustment in design or analysis is of high importance to estimate a causal relation between OD pregnancy and the development of hypertensive complications. In most individual studies included in the meta-analyses however, a considerable amount of bias remains that could influence this association.

In contrast to conventional meta-analysis, individual participant data (IPD) meta-analysis uses the IPD of the original studies and permits synthesis at an individual level, which enables checking the reliability of the data and examine causes for heterogeneity by investigating the effect in different subgroups.[18 19] Moreover, IPD meta-analysis allows the inclusion of additional unpublished data, and consistent recategorisation of definitions of outcomes and populations in order to answer the clinical questions of interest. This DONation of Oocytes in Reproduction (DONOR) IPD meta-analysis thus offers the generation of clinical relevant and robust evidence regarding the development of hypertensive complications in OD pregnancy.

Background

Currently, none of the widely used guidelines of the National Institute for Health and Clinical Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG), the International Society for the Study of Hypertension in Pregnancy (ISSHP) or the International Federation of Gynecology and Obstetrics (FIGO) indicate OD as a risk factor for hypertensive complications.[20–23] This IPD meta-analysis is important to increase the knowledge and alertness of patients and health professionals towards the risk profile for developing hypertensive complications in OD pregnancy. An IPD meta-analysis will give us the opportunity to increase statistical power, be able to adjust for multiple confounding factors, enhance generalisability and perform subgroup analyses. By investigating the development of hypertensive complications in diverse subgroups of women that underwent OD, new insights in treatment or preventive options may be provided. Moreover, one of the main principles in clinical research and practice is to distinguish individuals who have a high risk of developing an adverse outcome, so that preventative strategies could be applied. Based on underlying characteristics, a statistical prediction model could be used to assess the individual risk for adverse outcome. In addition, to formally asses a prognostic prediction model on its performance, IPD could be used for external validation. Applying a prediction model, that predicts the development of hypertensive complications in patients that apply to OD, in advance of the reproduction method, will certainly improve obstetric and financial outcome as well as the clinical management of OD pregnancies.

Objectives

Our primary objective is to assess, using IPD meta-analysis, the risk for developing hypertensive complications, such as PE and PIH, in women pregnant after OD compared with women pregnant using their autologous oocyte (NC or non-donor IVF/intracytoplasmic sperm injection (ICSI)).

The secondary objective is to assess the risk for severe PE, and time to development of hypertensive complications using IPD meta-analysis. Furthermore, IPD will be used in the external validation of a model to predict the risk for the development of hypertensive complications in women who apply to OD.

METHODS

Protocol development and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis IPD (PRISMA-IPD) 2015 statement will be used to improve the reporting of this systematic review and IPD meta-analysis.[24] To improve the reporting of this protocol, the PRISMA Protocol 2015 statement was used,[25] and the protocol has been registered in PROSPERO. We already started with the DONOR IPD project (start date: 1 September 2020) and we plan to conclude in the second half of 2023. Currently, we completed the systematic literature search, study quality assessment and have already received some IPD.

Eligibility criteria

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.
- Intervention: conception through OD.
- Comparison: conception with autologous oocyte (non-donor IVF/ICSI, NC).
- Outcomes: studies to be included must report on hypertensive complications during pregnancy,

including PIH and/or PE according to international definition (see below).
- Time: studies since 1984.
- Study design: retrospective or prospective cohort studies.

Studies that included only patients with Turner syndrome, non-comparative studies, immunological-oriented studies and studies that not reported the primary outcome will be excluded. Selection is not restricted to English language or year of publication.

Definition of outcome

The outcome, hypertensive complications in pregnancy, is defined according to the ISSHP classification.[22] PIH is defined as de novo development of high blood pressure detected after 20 weeks of gestation, with systolic blood pressure≥140 mm Hg and/or diastolic blood pressure≥90 mm Hg. Pre-eclampsia (PE) is defined as hypertension and the coexistence of one or more of the following: (1) proteinuria (>300 mg/L on dipstick testing, spot urine protein/creatinine>30 mg/mmol or a urine protein excretion of >300 mg in 24 hours); or (2) other maternal organ dysfunction (eg, renal insufficiency, liver involvement, neurological complications, haematological complications); or (3) uteroplacental dysfunction manifesting in fetal growth restriction.[22 26] Since this definition is renewed in 2014, most of the included studies will maintain the definition of PE as hypertension with proteinuria. Severe PE is defined if blood pressure was ≥160 mm Hg systolic or ≥110 mm Hg diastolic, or in the presence of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.[27] Early-onset PE is considered as that occurring before 34 weeks of gestation.[27]

Systematic search

An initial PubMed literature search was performed in September 2020. The search term was conducted in collaboration with a trained librarian using medical subject headings terms for OD, embryo disposition, pregnancy, PIH, IVF and ICSI. Online supplemental appendix 1 contains the complete search term. The resulting articles were screened by title and abstract by two reviewers (KvB and EL). When titles and abstracts met the inclusion criteria, the full-text articles were assessed for eligibility independently by the two reviewers. Disagreement was resolved by discussion and consensus. In addition to the search, reference lists of the selected articles were scanned to identify other studies. This initial PubMed literature search yielded 20 eligible studies, including 2301 OD pregnancies and over 1 million autologous pregnancies. The literature search will be updated at the beginning of the project and prior to completion of data in order to minimise the potential missing of relevant studies. Furthermore, we will expand our search in other electronic databases including Embase, Google Scholar and Cochrane. Experts in the field will be asked if they can identify unpublished cohorts of women with OD pregnancies.

Quality assessment and risk of bias

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 misguiding, 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.[28] In this IPD meta-analysis, the risk of bias is assessed according to the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool,[29] as well as according to a validation checklist developed by Scholten *et al*.[30] 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*[30] 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 to follow-up or missing data). Risk of bias will be assessed by two reviewers (KvB 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.

Study records

Data collection process

Corresponding authors of each included study will be contacted to inform them about the DONOR IPD project and invited to collaborate. We will identify contact information from the published studies. An initial email will be sent to the corresponding author. If initial emails fail to receive a response, another coauthor from the study will be contacted. If an author considers to participate, the research protocol will be sent and the original dataset is requested. Any data format is accepted, provided that variables are adequately labelled and pseudoanonymised. The authors will be sent a data transfer agreement in advance, in which is stated that we commit to (1) use the data only for research purposes and not to identify any individual participant; (2) secure the data using appropriate computer technology in case the data are non-anonymised; (3) destroy or return the data after the mandatory storage period of 15 years. All authors will be invited to inspect the list of included studies to identify any additional studies or unpublished cohorts of women with OD pregnancies. If IPD are unavailable from a selected study, it will be included in the IPD meta-analysis using aggregate data where possible.

Development of database

We will develop a set of prespecified and defined variables for IPD meta-analysis at both the study, participant and outcome level (see online supplemental appendix 2). These variables, which may be related to the development of hypertensive complications in OD pregnancy, will be

requested and possibly considered as covariates to establish the risk and prediction model.

Data management

We are aware that the received IPD is pseudoanonymised, and therefore treated with integrity: the data will be sent securely via a save file sender, and stored in a data safe of the Leiden University Medical Center with access minimisation, managed by the principal investigators. Each dataset will be converted to a common format and variables will be renamed in a consistent manner. If the variables are compatible, the original data will be merged in a master dataset for analysis, using the data management system Castor EDC (https://www.castoredc.com/).

Statistical analysis

Descriptive statistics, univariable analyses and multivariable analyses will be performed with the available IPD using SPSS Statistics V.28 (IBM SPSS Software), R and/or Stata. Descriptive statistics will be executed to compare differences for the most important baseline characteristics between the groups, stratified by study. 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. For all tests, a two-sided $p<0.05$ or 95% CI not including the null value is considered as statistically significant.

IPD meta-analysis models

Both a two-stage approach, where effect estimates are calculated for each study separately and subsequently pooled in a meta-analysis, and a one-stage approach, where all IPD from all studies are analysed simultaneously, will be performed.[31] To determine whether pooling is justified, heterogeneity between studies will be assessed using the between-study effect variation τ and the I^2 statistic. We will use a random effects model to account for between-study heterogeneity in the estimated effect.

Two-stage approach

Effect estimates will be computed for every study separately to produce study-specific estimates of exposure effect. Afterwards, the combined estimate is calculated using random effects meta-analysis. These analyses will result in forest plots allowing to compare results across studies visually.[32 33]

One-stage approach

IPD will be pooled from all studies using a generalised linear mixed model framework, taking potential heterogeneity across studies into account. With this model, the overall meta-analytic effect from all IPD will be estimated simultaneously while accounting for clustering of participants within studies. For the dichotomous outcome, logistic mixed-effect models will be used to calculate odds ratios.[32 33]

Unavailable studies and missing data

When IPD cannot be obtained from a study, aggregate data will be extracted from the publication where possible, and combined with the IPD meta-analysis results in a sensitivity analysis. If covariate data are missing for some participants, reasons for missing of this data will be explored. When missing completely at random is likely, a complete case analysis will be used in the first instance. If patterns of missingness are being observed or if the number of missing values is substantial, we will assume missing at random and use multiple imputation to impute missing covariates, taking study effect into account. Sensitivity analyses based on best and worst case scenarios will be used to assess the impact of missing outcome data.

Planned adjustment for confounders

To estimate a causal relation between OD pregnancy and the development of hypertensive complications using observational studies, adjustment in the analyses is of high importance. Possible associated covariates are visualised in a directed acyclic graph previously published in the protocol for the DONOR study,[34] 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.

Planned subgroup analyses

The subgroups to be considered as causes of heterogeneity and potential modifiers on the effect of OD on the development of hypertensive complications include:

- Multiple pregnancy (singleton vs twin or other multiplet).
- Maternal age (<35 years, 35–40 years, 40–45 years, >45 years).
- Ethnicity (Caucasian, Asian, Negroid, Hindu and Hispanic).
- Parity (nulliparous vs multiparous).
- Indication for OD (eg, premature ovarian insufficiency, postmenopausal status, maternal inherited genetic abnormalities).
- Donor–recipient familiar relationship (yes or no).
- Use of acetylsalicylic acid during pregnancy (yes or no).
- Higher risk of PE based on medical history (including chronic hypertension, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, diabetes mellitus type 1 and 2) (yes or no).

We are aware that the possibility to perform these subgroup analyses depends on the amount of IPD received.

Planned time-to-event analysis

If the collected IPD allows, the relation between the mode of conception (OD, IVF/ICSI, NC) and the time until development of hypertensive complications will be visualised by Kaplan-Meier survival curves separately for

each study, subsequently the Kaplan-Meier curves will be pooled together.[35] The effect adjusted for confounders will be assessed within each study by fitting a Cox proportional hazards model. Hazard ratios will be pooled using random effects meta-analysis.

Planned sensitivity analyses

We will perform sensitivity analyses to assess whether the results are robust according to the methodological quality of the study by excluding studies assessed as high risk of bias. Where IPD cannot be retrieved, we will assess the robustness of the inclusion or exclusion of these trials by combining their aggregate data with the IPD. Finally, as already described, sensitivity analyses based on best and worst case scenarios will be used to assess the impact of missing outcome data. Since studies from 1984 will be included, new developments over time (eg, 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.

Prediction model development and validation

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.[36] 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.[37] 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.[38]

Participant and public involvement

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 healthcare settings related to OD.

DISCUSSION

The DONOR IPD meta-analysis will provide a unique opportunity to assess the risk of hypertensive complications in OD pregnancy, and to externally validate for a model to predict the development of PE in the pregnancies. Available IPD will lead to an evidence-based statement for international guidelines in obstetrics. Moreover, a validated prediction model could work as a support tool for the management of OD pregnancies in medical practice.

Strengths and limitations

IPD meta-analysis offers numerous potential advantages, including the increase of statistical power, possibility to adjust for multiple confounding factors, enhancement of generalisability, performing subgroup analyses, examining associations and interactions between prognostic factors and external validation of a prediction model. However, despite these potential advantages, the synthesis of IPD may also encounter several difficulties. For example, availability of IPD does not overcome poor quality of primary studies, IPD may not be available from every study desired, and studies may differ in the set of confounders recorded and their method of measurement. An IPD meta-analysis may be biased if the provision of IPD is associated with the study results. In such a situation, it is important to examine any differences between studies that provided IPD and studies that did not.[39]

Ethics and dissemination

Ethical approval and individual patient consent will not be required in most cases, since the DONOR IPD meta-analysis will use existing pseudoanonymised 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 pseudoanonymised data is needed and will be drafted. This will also be mentioned in the already drafted data transfer agreement. The objectives of the IPD meta-analysis are consistent with the objectives of the original studies, and no direct risks or benefits are associated with this analysis. To ensure patient confidentiality, any identifying information (eg, names and contact details) will be erased from the data before they are supplied. The results of the IPD meta-analysis will be reported in accordance with the PRISMA-IPD statement.[24] The current stated authors of this protocol will be responsible for the preparation of the manuscript, which will be circulated to each author that provided IPD for further discussion prior to submission. All authors providing IPD from their studies are offered authorship of the final publication. Results will be disseminated in peer-reviewed journals and presented at international conferences.

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Contributors EL and M-LvdH were the principal investigators in this project. They supervised PhD student KvB in setting up and conducting this IPD meta-analysis. KvB and EL developed the initial study protocol. KvB drafted the initial version of the manuscript. SIC provided input for the statistical analysis part of the protocol. KvB, M-LvdH, JvL, SIC and EL critically revised the draft and approved the final manuscript as submitted. KvB submitted the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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