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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: Oocyte donation (OD) is comparable to in vitro fertilization (IVF), with the distinction of using a donated oocyte. Compared to IVF and naturally conceived (NC) pregnancies, OD pregnancies have a higher risk for pregnancy complications as pregnancy induced hypertension (PIH) and preeclampsia (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/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: We identified 20 relevant studies including 2,301 participants pregnant by OD or embryo donation out of a systematic review selecting cohort studies documenting on hypertensive complications in OD pregnancy. 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. The authors from each study will be asked to collaborate and share IPD. Using the anonymized combined IPD we will perform statistical analyses with one- 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 is not required since this IPD meta-analysis will utilize existing anonymized data from cohort studies. Results will be disseminated through peer-reviewed journals and international conferences.

PROSPERO registration number: CRD42021267908.

Keywords: individual participant data (IPD) meta-analysis; oocyte donation; pregnancy; hypertensive pregnancy complications; pregnancy induced hypertension; preeclampsia.

Strengths and limitations of this study

- The DONOR (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.
- Available IPD could lead to an evidence based statement for international guidelines in obstetrics and fertility.
- 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 (ART) comparable to *in vitro* fertilization (IVF), with the distinction of using a donated oocyte. 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 seven percent 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 (8).

Although the number of OD pregnancies are increasing, the method is accompanied with a high incidence of obstetrical complications (9). Hypertensive complications, including pregnancy induced hypertension (PIH) and preeclampsia (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 to naturally conceived (NC) and non-donor IVF pregnancies (10-14). 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 (15-19). 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 (20, 21). Moreover, IPD meta-analysis allows the inclusion of additional unpublished data, and consistent re-categorisation of definitions of outcomes and populations in order to answer the clinical questions of interest. This DONOR (DONation of Oocytes in Reproduction) IPD meta-analysis thus offers the generation of clinical relevant and robust level-1 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 (22-25). 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 generalizability, 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 to women pregnant using their autologous oocyte (NC or non-donor IVF/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 that apply to OD.

METHODS

Protocol development and registration

We will conduct the DONOR IPD meta-analysis with the specific requirements following the Preferred Reporting Items for Systematic Review and Meta-Analysis IPD (PRISMA-IPD) 2015 statement (26). This protocol was conducted using the PRISMA Protocol (PRISMA-P) 2015 statement (27), and has been registered in PROSPERO (CRD42021267908). To gain insight in the amount of IPD, an initial literature search has been conducted in September 2020 and is described below.

Eligibility criteria

We will include published and unpublished studies that describe cohorts of women pregnant after OD with a delivery after 24 weeks of gestation. Inclusion criteria for studies were verified according to the following PICOS criteria:

- *Participants*: pregnant women, not restricted to a certain age, ethnicity or singleton pregnancy;
- *Intervention*: conception through oocyte or embryo donation;
- *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*: retro- 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 International Society for the Study of Hypertension in Pregnancy (ISSHP) classification (24). Pregnancy induced hypertension (PIH) is defined as de novo development of high blood pressure detected after 20 weeks of gestation, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Preeclampsia (PE) is defined as hypertension and the coexistence of on 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 (e.g. renal insufficiency, liver involvement, neurological complications, hematological complications); or

3) Uteroplacental dysfunction manifesting in fetal growth restriction (24, 28). 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 mmHg systolic or ≥110 mmHg diastolic, or in the presence of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome (29). Early-onset PE is considered as that occurring before 34 weeks of gestation (29).

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 (MeSH) terms for OD, embryo disposition, pregnancy, pregnancy induced hypertension, in vitro fertilization and intracytoplasmic sperm injection. Appendix 1 contains the complete search term. The resulting articles were screened by title and abstract by two reviewers (KB 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. Figure 2 shows the flowchart of the study selection process which yielded 20 articles. Table 1 in Appendix 2 shows the characteristics of all included studies. We will update the described literature search at the beginning of the project and prior to completion of data in order to minimize 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

Risk of bias will be assessed according to the Newcastle-Ottowa Scale (NOS) for cohort studies (30). In addition, a validation checklist developed by Scholten *et al* (31) will be used to assess the risk of bias in the included studies, as 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, NOS score 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 main author. If initial emails fail to receive a response, another co-author 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 anonymized. The authors will be sent a data sharing 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-anonymized; (3) destroy or return the data after the mandatory storage period of fifteen 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 Appendix 3). 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 pseudo anonymized, 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 minimization, 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, univariate analyses, and multivariate analyses will be performed with the available IPD using SPSS Statistics (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. For all tests, a two-sided p<0.05 or 95% confidence interval 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 analyzed simultaneously, will be performed (32). 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 (33, 34).

One-stage approach

IPD will be pooled from all studies using a generalized 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 (33, 34).

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 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 subgroup analysis

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 versus twin or other multiplet);
- Maternal age (< 35yrs, 35-40yrs, 40-45 yrs, >45yrs);
- Ethnicity (Caucasian, Asian, Negroid, Hindu and Hispanic);
- Parity (nulliparous versus multiparous);
- Indication for OD (e.g. premature ovarian insufficiency, postmenopausal status, maternal inherited genetic abnormalities);
- Donor-recipient familiar relationship (yes or no);
- Use of salicylic acid during pregnancy (yes or no);
- Higher risk of preeclampsia 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 visualized 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 analysis

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.

Prediction model development and validation

In an earlier study protocol (DONOR-2), we suggested a prospective, national cohort study to investigate the prognostic effect of several factors on the development of hypertensive

complications in OD pregnancy. Within this national cohort, a prediction model will be conducted and internally validated. To formally assess the model on its performance in an external validation, the IPD is used. 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 (36, 37). The predictions of the initial model will be evaluated through calibration and discrimination. 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).

Participant and public involvement

This IPD meta-analyses uses existing data, hence design and conduct have already been determined in the past by the investigators of each study. Therefore, involving patients or the public in the design, conduct, reporting, or dissemination was not possible. The results will be disseminated as publications in open-access journals, and shared with patients in health care 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 generalizability, performing subgroup analyses, examining associations and interactions between prognostic factors, and externally 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 since the DONOR IPD meta-analysis will utilize existing anonymized data from cohort studies. Most of the included studies obtained consent from their local ethical review committee. Furthermore, 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 (e.g. 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 (26). The current stated authors of this protocol will be responsible for the preparation of 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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Authors' contributions

EL and MLH are the principal investigators in this project. They will supervise PhD student KB in setting up and conducting this IPD meta-analysis. KB and EL developed the initial study protocol. KB drafted the initial version of the manuscript. SC provided input for the statistical analysis part of the protocol. All authors critically revised the draft and approved the final manuscript as submitted.

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Competing interests

All authors declare that they have no competing interests.

Data availability statement

No additional data available.

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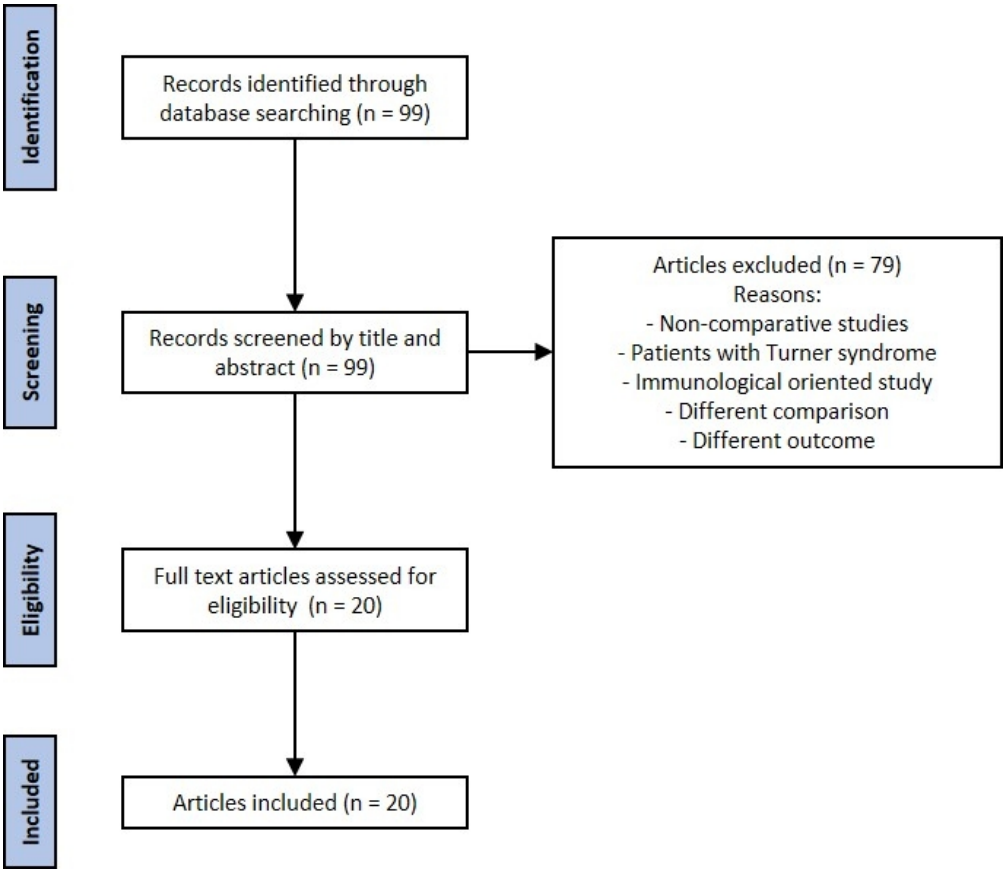

Figure 1. Flowchart of study selection process.

115x100mm (150 x 150 DPI)

APPENDIX 1: Search term

("Oocyte Donation"[Mesh] OR "Oocyte Donation"[tw] OR "Oocyte Donations"[tw] OR "Ovum Donation"[tw] OR "Ovum Donations"[tw] OR "Egg Donation"[tw] OR "Egg Donations"[tw] OR "Embryo Disposition"[Mesh] OR "Embryo Disposition"[tw] OR "Embryo Abandonment"[tw] OR "Embryo Donation"[tw] OR "Embryo Donations"[tw]) AND ("Hypertension, Pregnancy-Induced"[Mesh] OR "Pregnancy-Induced Hypertension"[tw] OR "Pregnancy Induced Hypertension"[tw] OR "Gestational Hypertension"[tw] OR "Pregnancy Transient Hypertension"[tw] OR "Eclampsia"[tw] OR "Eclampsias"[tw] OR "HELLP Syndrome"[tw] OR "Pre-Eclampsia"[tw] OR "Pre Eclampsia"[tw] OR "Preeclampsia"[tw] OR "Pregnancy Toxemia"[tw] OR "Pregnancy Toxemias"[tw] OR "Edema-Proteinuria-Hypertension Gestosis"[tw] OR "Edema Proteinuria Hypertension Gestosis"[tw] OR "Toxemia of Pregnancy"[tw] OR "Toxemia Of Pregnancies"[tw] OR "EPH Complex"[tw] OR "EPH Gestosis"[tw]) AND (("Pregnancy"[Mesh] OR "Pregnancy"[tw] OR "Pregnancies" OR "Gestation"[tw] OR "Gestations"[tw]) OR ("Fertilization in Vitro"[Mesh] OR "Fertilization in Vitro"[tw] OR "Fertilizations in Vitro"[tw] OR "In Vitro Fertilization"[tw] OR "In Vitro Fertilizations"[tw] OR "Test-Tube Fertilization"[tw] OR "Test Tube Fertilization"[tw]) OR ("Sperm Injections, Intracytoplasmic"[Mesh] OR "Intracytoplasmic Sperm Injection"[tw] OR "Intracytoplasmic Sperm Injections"[tw] OR "ICSI"[tw]) OR ("Insemination, Artificial"[Mesh] OR "Artificial Insemination"[tw] OR "Artificial Inseminations"[tw]))

APPENDIX 2: Table 1. Study characteristics

Study	Journal	Country	De-sign	Study period	Inclusion criteria	Exclusion criteria	Control group	Participants (n)	Mean maternal age (years)	Primary outcome
Elenis 2015	BMC Pregnancy and Childbirth	Sweden	RC	2005-2008	Singleton OD pregnancies	Women who did not speak or read Swedish	1. Age-matched nulliparae with singleton NC pregnancies and a history of subfertility 2. Heterosexual w with singleton autologous IVF pregnancies	76 OD 150 NC 63 IVF	OD: 35.0 (25-43) NC: 34.0 (19-36) IVF: 33.0 (25-39)	PIH, PE, HELLP, eclampsia
Henne 2007	The Journal of Reproductive Medicine	USA	RC	1997 – 2002	Conception through OD at any IVF center and delivery at Lucille Packard Children's Hospital	-	Women >38 years w conceived with autologous oocytes and delivered at the same hospital in the same period	69 OD 681 controls	OD: 45.28 ±3.63 (36.77-55.78) Controls: 41.60 ±1.37 (38.03-48.55)	PE, HELLP
Jeve 2016	International Journal of Gynecology and Obstetrics	UK	RC	2007-2014	OD pregnancy and delivery of a live neonate after 24 weeks at a teaching hospital in Leicester in the period	Pregnancies after preimplantation genetic diagnosis, after surgical sperm retrieval or use of donor sperm	Age-matched IVF and NC pregnancies	45 OD 45 IVF 45 NC	OD: 40.23 ±5.64 IVF: 39.23 ±1.71 NC: 39.69 ±0.71	PIH, PE
Keegan 2007	Fertility and Sterility	USA	RC	1999-2003	OD pregnancies of patients <35 years and ≥40 years of age	Triplet pregnancies, frozen embryo transfer, cycles monitored at program satellite offices	Age-matched conventional IVF pregnancies	19 OD <35 296 IVF <35 171 OD ≥40 192 IVF ≥40	OD<35: 31.7±0.4 IVF<35: 31.0±0.2 OD≥40: 43.9±0.2 IVF≥40:41.4±0.1	PIH
Klatsky 2010	Obstetrics & Gynecology	USA	RC	1998-2005	Singleton and twin OD pregnancies resulting in live birth, both fresh and cryopreserved cycles	Monozygotic twins and if outcome data were not reported	Age- and plurality-matched IVF pregnancies	77 OD 81 IVF	OD: 40.2 ±3.5 IVF: 39.8 ±4.1	PIH, PE
Krieg 2008	Fertility and Sterility	USA	RC	2001-2005	OD treatment at Stanford Infertility Center and delivery at Lucille Packard Children's Hospital	-	Women >38 years old with autologous IVF in the same center and delivery at the same hospital	71 OD 108 IVF	OD: 42.7 ±4.40 (30.7-53.0) IVF: 41.3 ±1.84 (38.0-47.2)	PE

Le Ray 2012	Human Reproduction	France	RC	2008-2010	Women >43 years old giving birth after OD	-	Autologous IVF and NC pregnancies	104 OD 236 NC 40 IVF	NC: 44.1 ±1.4 IVF: 44.0 ±1.4 OD: 46.2 ±2.9	PE
Letur 2016	Fertility and Sterility	France	RC	2005-2012	Singleton OD pregnancies	Multiple pregnancies, OD abroad	Singleton autologous IVF/ICSI pregnancies at the same center	217 OD 363 controls	OD: 34.4 ±9.4 Controls: 34.2 ±4.5	PIH, PE, eclampsia
Levron 2014	American Journal of Obstetrics and Gynecology	Israel	RC	2005-2011	Singleton OD pregnancies	Congenital or chromosomal abnormalities	Women >38 years, autologous IVF pregnancy in same period, delivery at the same center	139 OD 126 IVF	OD: 45 (23-57) IVF: 41 (38-46)	PIH, PE
Malchau 2013	Fertility and Sterility	Denmark	RC	1995-2010	Singleton OD pregnancies	OD abroad	Age- and year-of-IVF matched IVF, ICSI and NC pregnancies	251 OD 11.060 IVF 5.866 ICSI 33.852 NC	OD: 36.8 ±5.2 IVF: 34.0 ±4.0 ICSI: 33.2 ±4.0 NC: 30.2 ±4.8	PIH, PE
Nejdet 2016	Acta Obstetrica et Gynecologica Scandinavica	Sweden	RC	2003-2012	Singleton OD pregnancies after fresh and thawed cycles	-	Singleton IVF, ICSI and NC pregnancies	388 OD 26.696 IVF/ICSI 999.804 NC	Split categories: OD 16.5% ≥40 years; IVF/ICSI 7.9% ≥40 years	PE
Salha 1999	Human Reproduction	England	RC	1992-1997	Conception through donated gametes	Patients with pre-existing medical condition that might predispose to the development of PE	Conception with autologous gametes, matched for age, parity and demographic background	22 OD 33 IUI with donor sperm 12 embryo donation 27 controls	OD: 38.1 (27-42) Controls: 37.6	PIH, PE
Simeon 2016	Minerva Ginecologica	Italy	RC	2009-2011	Women >35 years with OD conception	First trimester miscarriage or termination, ectopic pregnancy, lack of data	Women >35 years with autologous IVF conception	65 OD 71 IVF	OD: 43.4 ±3.8 IVF: 38.9 ±3.21	PE, HELLP
Söderström-Anttila 1998	Human Reproduction	Finland	RC	1992-1996	Women with OD conception, who delivered a liveborn or stillborn infant at ≥24 weeks or ≥500 g	-	Autologous IVF pregnancies, delivered at ≥24 weeks	51 OD 97 IVF	OD: 33.5 ±4.7 IVF 33.4 ±3.7	PIH, PE
Stoop 2012	Reproductive Biology and Endocrinology	Belgium	RC	1999-2008	Singleton OD pregnancies resulting in offspring after more than 20 weeks of gestation	Preimplantation genetic diagnosis, testicular sperm extraction or use of donor sperm	Matched autologous IVF pregnancies, conceived in the same period	148 OD 148 IVF	OD: 36.3 ±4.5 IVF: 36.2 ±4.5	PIH, PE

Tarlatzi 2016	Reproductive Biomedicine Online	Belgium	RC	1991-2013	Singleton OD pregnancies, delivery after more than 22 weeks of gestation	Multiple pregnancies, testicular sperm extraction, cycles with preimplantation genetic diagnosis, cryopreserved embryos, women with Turner's syndrome	Singleton IVF/ICSI pregnancies, delivery after more than 22 weeks of gestation at the same hospital during the same period	144 OD 144 IVF/ICSI	Both groups: 35.64 ±4.54 (22-43)	PIH, PE
Tranquilli 2013	Journal of Maternal-Fetal & Neonatal Medicine	Italy	RC	-	ICSI pregnancies using heterologous oocytes	-	Homologous ICSI or NC pregnancies in women >40 years	26 OD 52 ICSI 52 NC	OD: 42.7 (28-52) ICSI: 37.5 (29-47) NC: 41.5 (40-45)	PIH, PE
Van Dorp 2014	European Journal of Obstetrics & Gynecology and Reproductive Biology	Nether-lands	RC	1992-2009	All women who underwent OD treatment in the Erasmus MC Medical Centre	-	Matched autologous IVF subjects	110 OD 311 IVF	OD: 36.8 (32.5-39.2) IVF 37.2 (33.5-39.1)	PIH, PE
Wiggins 2005	American Journal of Obstetrics and Gynecology	USA	RC	1999-2004	OD pregnancies	-	Autologous IVF pregnancies	50 OD 50 IVF	OD: 37.7 ±3.6 (31-50) IVF: 41.9 ±5.1 (30-45)	PIH, PE
Wolff 1997	Obstetrics and Gynecology	USA	RC	1988-1996	OD pregnancies	-	NC pregnancies of women ≥38 years	46 OD 49 NC	OD 41.5 ±1.8 NC 42.7 ±2.2	PIH

Abbreviations: n = number; RC = retrospective cohort; OD = oocyte donation; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; NC = naturally conceived; PIH = pregnancy induced hypertension; PE = preeclampsia; HELLP = hemolysis, elevated liver enzymes and low platelets.

APPENDIX 3: Variables for IPD meta-analysis

Study level information

- In- and exclusion criteria
- Country
- Setting ((non-)academic hospital)
- Dates of start and end of study
- Number of participants included
- Informed consent procedure
- Adjustment for confounding
- Outcomes collected (primary and secondary)

Participant level information

- Maternal demographic details including: age, ethnicity, and socio-economic status at study entry
- Maternal BMI
- Maternal smoking status, alcohol consumption and drug usage before and during the pregnancy
- Maternal medical and obstetric history, including medication use
- Donor age, country of origin, donor-recipient relation
- Indication and method of OD treatment (IVF or ICSI)
- Use of medication during pregnancy
- Gestational age at delivery
- Mode of delivery
- Complications during delivery
- Live birth
- Neonatal birthweight, gender, APGAR scores, congenital abnormalities
- Single/multiple (if multiple: order of birth)
- Admission to neonatal intensive care unit (NICU)

Outcome level information

- Highest diastolic and systolic blood pressure during pregnancy
- Amount of proteinuria
- Development and time of onset of PIH, PE and/or HELLP

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page where item is reported in DONOR-IPD protocol_final
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n.a.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7, Appendix 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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

Authors

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ABSTRACT

Introduction: The assisted reproductive technique of oocyte donation (OD) is comparable to in vitro fertilization (IVF), with the distinction of using a donated oocyte and thus involving two women. Compared to IVF and naturally conceived (NC) pregnancies, OD pregnancies have a higher risk for pregnancy complications as pregnancy induced hypertension (PIH) and preeclampsia (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/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 pseudo anonymized combined IPD, we will perform statistical analyses with one- 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 utilize existing pseudo anonymized data from cohort studies. Results will be disseminated through peer-reviewed journals and international conferences.

PROSPERO registration number: CRD42021267908.

Keywords: individual participant data (IPD) meta-analysis; oocyte donation; pregnancy; hypertensive pregnancy complications; pregnancy induced hypertension; preeclampsia.

Strengths and limitations of this study

- The DONOR (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 (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. 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 seven percent 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 (8).

Although the number of OD pregnancies are increasing, the method is accompanied with a high incidence of obstetrical complications (9). Hypertensive complications, including pregnancy induced hypertension (PIH) and preeclampsia (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 to naturally conceived (NC) and non-donor IVF pregnancies (10-14). 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 (15-19). 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 (20, 21). Moreover, IPD meta-analysis allows the inclusion of additional unpublished data, and consistent re-categorisation of definitions of outcomes and populations in

order to answer the clinical questions of interest. This DONOR (DONation of Oocytes in Reproduction) 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 (22-25). 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 generalizability, 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 to women pregnant using their autologous oocyte (NC or non-donor IVF/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 that 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 (26). To improve the reporting of this protocol, the PRISMA Protocol (PRISMA-P) 2015 statement was used (27), and the protocol has been registered in PROSPERO (CRD42021267908).

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 oocyte donation;
- *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*: retro- 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 International Society for the Study of Hypertension in Pregnancy (ISSHP) classification (24). Pregnancy induced hypertension (PIH) is defined as de novo development of high blood pressure detected after 20 weeks of gestation, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Preeclampsia (PE) is defined as hypertension and the coexistence of on 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 (e.g. renal insufficiency, liver involvement, neurological complications, hematological complications); or 3) Uteroplacental dysfunction manifesting in fetal growth restriction (24, 28). 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 mmHg systolic or ≥110 mmHg diastolic, or in the presence of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome (29). Early-onset PE is considered as that occurring before 34 weeks of gestation (29).

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 (MeSH) terms for OD, embryo disposition, pregnancy, pregnancy induced hypertension, in vitro fertilization and intracytoplasmic sperm injection. Appendix 1 contains the complete search term. The resulting articles were screened by title and abstract by two reviewers (KB 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 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. 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 (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.

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 main author. If initial emails fail to receive a response, another co-author 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 pseudo anonymized. 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-anonymized; (3) destroy or return the data after the mandatory storage period of fifteen 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 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 pseudo anonymized, 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 minimization, 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 (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 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. For all tests, a two-sided $p<0.05$ or 95% confidence interval 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 analyzed simultaneously, will be performed (33). 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 (34, 35).

One-stage approach

IPD will be pooled from all studies using a generalized 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 (34, 35).

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 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 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 (36), 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 versus twin or other multiplet);
- Maternal age (< 35yrs, 35-40yrs, 40-45 yrs, >45yrs);
- Ethnicity (Caucasian, Asian, Negroid, Hindu and Hispanic);
- Parity (nulliparous versus multiparous);
- Indication for OD (e.g. premature ovarian insufficiency, postmenopausal status, maternal inherited genetic abnormalities);
- Donor-recipient familiar relationship (yes or no);
- Use of salicylic acid during pregnancy (yes or no);
- Higher risk of preeclampsia 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 visualized by Kaplan-Meier survival curves separately for each study, subsequently the Kaplan-Meier curves will be pooled together (37). 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 (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.

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 (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).

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 health care 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 generalizability, performing subgroup analyses, examining associations and interactions between prognostic factors, and externally 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 (41).

Ethics and dissemination

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. 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 (e.g. 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 (26). The current stated authors of this protocol will be responsible for the preparation of 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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Authors' contributions

EL and MLH are the principal investigators in this project. They will supervise PhD student KB in setting up and conducting this IPD meta-analysis. KB and EL developed the initial study protocol. KB drafted the initial version of the manuscript. SC provided input for the statistical analysis part of the protocol. All authors critically revised the draft and approved the final manuscript as submitted.

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Competing interests

All authors declare that they have no competing interests.

Data availability statement

No additional data available.

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APPENDIX 1: Search term

("Oocyte Donation"[Mesh] OR "Oocyte Donation"[tw] OR "Oocyte Donations"[tw] OR "Ovum Donation"[tw] OR "Ovum Donations"[tw] OR "Egg Donation"[tw] OR "Egg Donations"[tw] OR "Embryo Disposition"[Mesh] OR "Embryo Disposition"[tw] OR "Embryo Abandonment"[tw] OR "Embryo Donation"[tw] OR "Embryo Donations"[tw]) AND ("Hypertension, Pregnancy-Induced"[Mesh] OR "Pregnancy-Induced Hypertension"[tw] OR "Pregnancy Induced Hypertension"[tw] OR "Gestational Hypertension"[tw] OR "Pregnancy Transient Hypertension"[tw] OR "Eclampsia"[tw] OR "Eclampsias"[tw] OR “HELLP Syndrome"[tw] OR "Pre-Eclampsia"[tw] OR "Pre Eclampsia"[tw] OR "Preeclampsia"[tw] OR "Pregnancy Toxemia"[tw] OR "Pregnancy Toxemias"[tw] OR "Edema-Proteinuria-Hypertension Gestosis"[tw] OR "Edema Proteinuria Hypertension Gestosis"[tw] OR "Toxemia of Pregnancy"[tw] OR "Toxemia Of Pregnancies"[tw] OR "EPH Complex"[tw] OR "EPH Gestosis"[tw]) AND (("Pregnancy"[Mesh] OR "Pregnancy"[tw] OR "Pregnancies" OR "Gestation"[tw] OR "Gestations"[tw]) OR ("Fertilization in Vitro"[Mesh] OR "Fertilization in Vitro"[tw] OR "Fertilizations in Vitro"[tw] OR "In Vitro Fertilization"[tw] OR "In Vitro Fertilizations"[tw] OR "Test-Tube Fertilization"[tw] OR "Test Tube Fertilization"[tw]) OR ("Sperm Injections, Intracytoplasmic"[Mesh] OR "Intracytoplasmic Sperm Injection"[tw] OR "Intracytoplasmic Sperm Injections"[tw] OR "ICSI"[tw]) OR ("Insemination, Artificial"[Mesh] OR "Artificial Insemination"[tw] OR "Artificial Inseminations"[tw]))

APPENDIX 2: Variables for IPD meta-analysis

Study level information

- In- and exclusion criteria
- Country
- Setting ((non-)academic hospital)
- Dates of start and end of study
- Number of participants included
- Informed consent procedure
- Adjustment for confounding
- Outcomes collected (primary and secondary)

Participant level information

- Maternal demographic details including: age, ethnicity, and socio-economic status at study entry
- Maternal BMI
- Maternal smoking status, alcohol consumption and drug usage before and during the pregnancy
- Maternal medical and obstetric history, including medication use
- Donor age, country of origin, donor-recipient relation
- Indication and method of OD treatment (IVF or ICSI)
- Use of medication during pregnancy
- Gestational age at delivery
- Mode of delivery
- Complications during delivery
- Live birth
- Neonatal birthweight, gender, APGAR scores, congenital abnormalities
- Single/multiple (if multiple: order of birth)
- Admission to neonatal intensive care unit (NICU)

Outcome level information

- Highest diastolic and systolic blood pressure during pregnancy
- Amount of proteinuria
- Development and time of onset of PIH, PE and/or HELLP

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page where item is reported in DONOR-IPD protocol_final
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n.a.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7, Appendix 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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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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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 fertilization (IVF), with the distinction of using a donated oocyte and thus involving two women. Compared to IVF and naturally conceived (NC) pregnancies, OD pregnancies have a higher risk for pregnancy complications as pregnancy induced hypertension (PIH) and preeclampsia (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/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 pseudo anonymized combined IPD, we will perform statistical analyses with one- 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 utilize existing pseudo anonymized data from cohort studies. Results will be disseminated through peer-reviewed journals and international conferences.

PROSPERO registration number: CRD42021267908.

Keywords: individual participant data (IPD) meta-analysis; oocyte donation; pregnancy; hypertensive pregnancy complications; pregnancy induced hypertension; preeclampsia.

Strengths and limitations of this study

- The DONOR (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 (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. 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 seven percent 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 (8).

Although the number of OD pregnancies are increasing, the method is accompanied with a high incidence of obstetrical complications (9). Hypertensive complications, including pregnancy induced hypertension (PIH) and preeclampsia (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 to naturally conceived (NC) and non-donor IVF pregnancies (10-14). 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 (15-19). 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 (20, 21). Moreover, IPD meta-analysis allows the inclusion of additional unpublished data, and consistent re-categorisation of definitions of outcomes and populations in

order to answer the clinical questions of interest. This DONOR (DONation of Oocytes in Reproduction) 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 (22-25). 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 generalizability, 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 to women pregnant using their autologous oocyte (NC or non-donor IVF/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 that 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 (26). To improve the reporting of this protocol, the PRISMA Protocol (PRISMA-P) 2015 statement was used (27), and the protocol has been registered in PROSPERO (CRD42021267908). We already started with the DONOR IPD project (start date: September 1, 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 oocyte donation;
- *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*: retro- 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 International Society for the Study of Hypertension in Pregnancy (ISSHP) classification (24). Pregnancy induced hypertension (PIH) is defined as de novo development of high blood pressure detected after 20 weeks of gestation, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Preeclampsia (PE) is defined as hypertension and the coexistence of on 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 (e.g. renal insufficiency, liver involvement, neurological complications, hematological complications); or 3) Uteroplacental dysfunction manifesting in fetal growth restriction (24, 28). 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 mmHg systolic or ≥110 mmHg diastolic, or in the presence of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome (29). Early-onset PE is considered as that occurring before 34 weeks of gestation (29).

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 (MeSH) terms for OD, embryo disposition, pregnancy, pregnancy induced hypertension, in vitro fertilization and intracytoplasmic sperm injection. Appendix 1 contains the complete search term. The resulting articles were screened by title and abstract by two reviewers (KB 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 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. 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 (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.

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 main author. If initial emails fail to receive a response, another co-author 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 pseudo anonymized. 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-anonymized; (3) destroy or return the data after the mandatory storage period of fifteen 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 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 pseudo anonymized, 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 minimization, 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 (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% confidence interval 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 analyzed simultaneously, will be performed (33). 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 (34, 35).

One-stage approach

IPD will be pooled from all studies using a generalized 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 (34, 35).

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 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 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 (36), 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 versus twin or other multiplet);
- Maternal age (< 35yrs, 35-40yrs, 40-45 yrs, >45yrs);
- Ethnicity (Caucasian, Asian, Negroid, Hindu and Hispanic);
- Parity (nulliparous versus multiparous);
- Indication for OD (e.g. premature ovarian insufficiency, postmenopausal status, maternal inherited genetic abnormalities);
- Donor-recipient familiar relationship (yes or no);
- Use of salicylic acid during pregnancy (yes or no);
- Higher risk of preeclampsia 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 visualized by Kaplan-Meier survival curves separately for each study, subsequently the Kaplan-Meier curves will be pooled together (37). 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 (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.

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 (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).

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 health care 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 generalizability, performing subgroup analyses, examining associations and interactions between prognostic factors, and externally 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 (41).

Ethics and dissemination

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. 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 (e.g. 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 (26). The current stated authors of this protocol will be responsible for the preparation of 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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Authors' contributions

EL and MLH are the principal investigators in this project. They will supervise PhD student KB in setting up and conducting this IPD meta-analysis. KB and EL developed the initial study protocol. KB drafted the initial version of the manuscript. SC provided input for the statistical analysis part of the protocol. KB, MLH, JL, SC, and EL critically revised the draft and approved the final manuscript as submitted. KB submitted the protocol.

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Competing interests

All authors declare that they have no competing interests.

Data availability statement

No additional data available.

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APPENDIX 1: Search term

("Oocyte Donation"[Mesh] OR "Oocyte Donation"[tw] OR "Oocyte Donations"[tw] OR "Ovum Donation"[tw] OR "Ovum Donations"[tw] OR "Egg Donation"[tw] OR "Egg Donations"[tw] OR "Embryo Disposition"[Mesh] OR "Embryo Disposition"[tw] OR "Embryo Abandonment"[tw] OR "Embryo Donation"[tw] OR "Embryo Donations"[tw]) AND ("Hypertension, Pregnancy-Induced"[Mesh] OR "Pregnancy-Induced Hypertension"[tw] OR "Pregnancy Induced Hypertension"[tw] OR "Gestational Hypertension"[tw] OR "Pregnancy Transient Hypertension"[tw] OR "Eclampsia"[tw] OR "Eclampsias"[tw] OR “HELLP Syndrome"[tw] OR "Pre-Eclampsia"[tw] OR "Pre Eclampsia"[tw] OR "Preeclampsia"[tw] OR "Pregnancy Toxemia"[tw] OR "Pregnancy Toxemias"[tw] OR "Edema-Proteinuria-Hypertension Gestosis"[tw] OR "Edema Proteinuria Hypertension Gestosis"[tw] OR "Toxemia of Pregnancy"[tw] OR "Toxemia Of Pregnancies"[tw] OR "EPH Complex"[tw] OR "EPH Gestosis"[tw]) AND (("Pregnancy"[Mesh] OR "Pregnancy"[tw] OR "Pregnancies" OR "Gestation"[tw] OR "Gestations"[tw]) OR ("Fertilization in Vitro"[Mesh] OR "Fertilization in Vitro"[tw] OR "Fertilizations in Vitro"[tw] OR "In Vitro Fertilization"[tw] OR "In Vitro Fertilizations"[tw] OR "Test-Tube Fertilization"[tw] OR "Test Tube Fertilization"[tw]) OR ("Sperm Injections, Intracytoplasmic"[Mesh] OR "Intracytoplasmic Sperm Injection"[tw] OR "Intracytoplasmic Sperm Injections"[tw] OR "ICSI"[tw]) OR ("Insemination, Artificial"[Mesh] OR "Artificial Insemination"[tw] OR "Artificial Inseminations"[tw]))

APPENDIX 2: Variables for IPD meta-analysis

Study level information

- In- and exclusion criteria
- Country
- Setting ((non-)academic hospital)
- Dates of start and end of study
- Number of participants included
- Informed consent procedure
- Adjustment for confounding
- Outcomes collected (primary and secondary)

Participant level information

- Maternal demographic details including: age, ethnicity, and socio-economic status at study entry
- Maternal BMI
- Maternal smoking status, alcohol consumption and drug usage before and during the pregnancy
- Maternal medical and obstetric history, including medication use
- Donor age, country of origin, donor-recipient relation
- Indication and method of OD treatment (IVF or ICSI)
- Use of medication during pregnancy
- Gestational age at delivery
- Mode of delivery
- Complications during delivery
- Live birth
- Neonatal birthweight, gender, APGAR scores, congenital abnormalities
- Single/multiple (if multiple: order of birth)
- Admission to neonatal intensive care unit (NICU)

Outcome level information

- Highest diastolic and systolic blood pressure during pregnancy
- Amount of proteinuria
- Development and time of onset of PIH, PE and/or HELLP

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page where item is reported in DONOR-IPD protocol_final
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n.a.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7, Appendix 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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