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*In*dividual participant data meta-analysis of trials comparing *fro*zen versus f*r*esh e*m*bryo transfer strategy (INFORM): a protocol

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ABSTRACT

Introduction Existing randomised controlled trials (RCTs) comparing a freeze-all embryo transfer strategy and a fresh embryo transfer strategy have shown conflicting results. A freeze-all or a fresh transfer policy may be preferable for some couples undergoing in-vitro fertilisation (IVF), but it is unclear which couples would benefit most from each policy, how and under which protocols. Therefore, we plan a systematic review and individual participant data meta-analysis of RCTs comparing a freeze-all and a fresh transfer policy.

Methods and analysis We will search electronic databases (Medline, Embase, PsycINFO and CENTRAL) and trial registries (ClinicalTrials.gov and the International Clinical Trials Registry Platform) from their inception to present to identify eligible RCTs. We will also check reference lists of relevant papers. The search was performed on 23 September 2020 and will be updated. We will include RCTs comparing a freeze-all embryo transfer strategy and a fresh embryo transfer strategy in couples undergoing IVF. The primary outcome will be live birth resulting from the first embryo transfer. All outcomes listed in the core outcome set for infertility research will be reported. We will invite the lead investigators of eligible trials to join the *In*dividual participant data meta-analysis of trials comparing *fro*zen versus f*r*esh e*m*bryo transfer strategy (INFORM) collaboration and share the deidentified individual participant data (IPD) of their trials. We will harmonise the IPD and perform a two-stage meta-analysis and examine treatment–covariate interactions for important baseline characteristics.

Ethics and dissemination The study ethics have been granted by the Monash University Human Research Ethics Committee (Project ID: 30391). The findings will be disseminated via presentations at international conferences and publication in peer-reviewed journals.

PROSPERO registration number CRD42021296566.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This individual participant data meta-analysis (IPDMA) offers a unique opportunity evaluate outcomes that were impossible in existing aggregate data meta-analysis due to heterogeneous reporting and/or analysis strategies in the primary trials, including time to pregnancy leading to live birth and perinatal outcomes.
⇒ This IPDMA has the potential to identify individuals that would benefit most from a freeze-all policy or a fresh transfer policy, and thus provide guidance towards personalised in-vitro fertilisation treatment.
⇒ The coordination of international collaboration will promote research transparency and data sharing, making clinical trials more useful for their end-users.
⇒ Limitations include (un)availability of data on covariates of interest across trials.

INTRODUCTION

Infertility affects up to one in seven couples globally.[1 2] In-vitro fertilisation (IVF) is a treatment option for all couples with prolonged unresolved infertility. Over 10 million IVF children have been born since 1978, and over 2.5 million cycles are being performed every year.[3 4]

About a decade ago, a few small randomised controlled trials (RCTs) suggested that a freeze-all transfer policy may improve IVF success rates, while minimising the risk of ovarian hyperstimulation (OHSS).[5 6] The scientific rationale includes the avoidance of reduced endometrial receptivity in the fresh cycles, the prevention of late-onset OHSS and the reduction in early-onset OHSS if a gonadotropin-releasing hormone (GnRH) agonist trigger is used.[7] This has led to a global increase in the number of clinics adapting a freeze-all transfer policy for both elective and non-elective indications.[8]

Over the last decade, multiple large RCTs across different countries comparing a strategy of freeze-all versus a fresh embryo transfer have been published. Some RCTs suggested an improvement in live birth rates[5 9 10] while others either found insufficient evidence of a difference between the two options[6 11–14] or a decline in live birth rate.[15] Meanwhile, recent meta-analyses showed that a freeze-all embryo transfer strategy was associated with a lower risk of OHSS, preterm delivery and small for gestational age baby, but a higher risk of a large for gestational age baby and hypertensive disorders of pregnancy, and a higher birth weight.[16 17] These meta-analyses also showed moderate to severe unexplained heterogeneity,[16 17] suggesting study protocols features affected the results of comparisons. Although the precise reasons for findings on these perinatal outcomes are not known, they have profound implications for the long-term health of mothers undergoing IVF as well as their offspring.

Hence, the optimal strategy for each couple is not yet known, and there is an urgent need to provide clear evidence on which couples would benefit most from each policy.[8 18] None of the individual trials is large enough to provide definitive conclusions with any degree of precision especially when it comes to obstetric and perinatal outcomes. The effectiveness of a freeze-all embryo transfer strategy may vary by maternal age, number of oocytes retrieved, stage at which embryos are frozen, endometrial preparation, luteal support protocol, embryo selection/assessment before and after cryopreservation and the stage at which embryos are replaced (cleavage stage or blastocyst), but existing meta-analyses based on published aggregated data are unable to conduct meaningful subgroup analyses due to different reporting strategies of subgroup data in primary trial reports.[17 19] Moreover, time to pregnancy leading to live birth is an important patient-centred outcome but could not be analysed in aggregated data due to the heterogeneous reporting approaches in the primary trials.[17]

We propose to undertake a systematic review and individual participant data meta-analysis (IPDMA) of eligible RCTs to evaluate the effectiveness and safety of a freeze-all transfer strategy versus a fresh embryo transfer strategy in couples undergoing IVF. Our research questions include:

Does a freeze-all embryo transfer strategy differ from a fresh embryo transfer strategy in

- Live birth rate after the first transfer and in whom?
- Cumulative live birth rate and shorten time-to-pregnancy leading to live birth?
- Maternal safety during IVF treatment?
- Obstetric and perinatal complications?

METHODS AND ANALYSIS

Search strategy

Comprehensive literature searches using an appropriate combination of index terms and free words will be conducted to identify published, ongoing and unpublished randomised trials assessing the clinical effectiveness of freezing all embryos followed by thawed frozen embryo transfer compared with fresh embryo transfer for couples undergoing IVF.

Various electronic databases will be searched from their date of inception to the present day, these include: Medline (1946 to present), Embase (1980 to present) and PsycINFO (1806 to present) (Ovid platform), CENTRAL via The Cochrane Register of Studies Online (inception to present, Web platform) and The Cochrane Gynaecology and Fertility Group Specialised Register (inception to present, ProCite platform). Key clinical trial registries including ClinicalTrials.gov and the WHO International Clinical Trials Registry portal will also be searched (web platforms). The comprehensive strategy for this IPDMA is based on the search strategy of the latest Cochrane systematic review on this topic,[14] which was run from the date of inception of the databases to 23 September 2020. Therefore, we will run our database searches from 23 September 2020 to present. In this way we will ensure that we include all RCTs from inception to present.

The reference lists of relevant trails will be examined. Recent conference proceedings of key professional organisations and trial registers from all continents will also be scrutinised. Trial investigators who have agreed to share their data and take part in the IPDMA will be asked for information on any additional trial reports. No language or publication date restrictions will be applied to the searches. The detailed search strategy is listed in online supplemental appendix 1.

Eligibility criteria

Only RCTs (published or unpublished) comparing the clinical effectiveness of a freeze-all versus a fresh embryo transfer strategy in couples undergoing IVF will be eligible for inclusion. RCTs on preimplantation genetic testing (PGT) will be excluded. For multiarm RCTs involving both PGT and non-PGT, the non-PGT arms will be included. The following eligibility criteria will be followed:

- Population: women undergoing IVF, using their own oocytes; for trials including both couples with both autologous oocytes and oocyte donations, couples with oocytes donation will be excluded.
- Intervention: elective freezing of all suitable embryos followed by thawed frozen embryo transfer.
- Comparison group: fresh embryo transfer followed by thawed frozen embryo transfer.
- Outcome measures: the core outcome set for infertility research and consensus definitions of these outcomes[20 21] will be used (indicated with * below), with additional outcomes of interest listed below. All outcomes will be measured based on the first embryo transfer, except for cumulative live birth and time to pregnancy leading to live birth, where multiple episodes of embryo transfers resulting from the same oocyte retrieval cycle in same couple will be included.

Primary outcome

*Live birth resulting from the first embryo transfer. Live birth resulting from spontaneous pregnancy after randomisation before the first embryo transfer will also be included.[20]

Secondary outcomes (refer to the first pregnancy unless specified)

Pregnancy outcomes

- *Clinical pregnancy (a pregnancy diagnosed by ultrasonographic examination of at least one fetus with a discernible heartbeat)[20];
- Pregnancy (defined as positive pregnancy test at 11–17 days after embryo transfer);
- *Pregnancy loss (including ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy)[20];
- *Multiple pregnancy[20];
- *Gestational age at delivery (weeks of gestation);
- Healthy baby (defined as term (>37 weeks) singleton live birth with appropriate weight for gestation. Appropriate weight will be determined by plotting weight against the gestational age on the standardised ethnicity-based growth charts).

Obstetric outcomes

- Gestational diabetes.
- Hypertensive disorders of pregnancy (comprising pregnancy induced hypertension; pre-eclampsia and eclampsia) as reported by individual investigators.
- Antepartum haemorrhage (placenta praevia, placenta accrete and other antepartum haemorrhage).
- Postpartum haemorrhage.

Other maternal safety outcomes

- Moderate or severe OHSS.

Neonatal outcomes

- *Birth weight
  Small for gestational age
  Large for gestational age
- *Neonatal mortality
- * Major congenital anomaly

Cumulative outcomes

- Cumulative live birth (only the first live birth resulting from the same oocyte retrieval cycle after randomisation will be included);
- Time to pregnancy leading to live birth (resulting from the same oocyte retrieval cycle after randomisation). The time of randomisation will be the starting time point. For RCTs where randomisation occurs before oocytes retrieval, the start time of this outcome will be truncated at a comparable time to other RCTs.

Study selection

Two members of the team will independently assess eligibility of studies identified through the search. Disagreements will be resolved by involving a third member of the team. Investigators of included trials will not be involved in the assessments of their own trials. Study selection will be performed and managed in an online platform, Covidence.[22]

Establishment of the INFORM collaboration

We have already established contacts with the principal investigators of these trials and invited them to participate in this study and form an international collaboration: the *In*dividual participant data meta-analysis of trials comparing *fr*ozen versus fresh e*m*bryo transfer strategy (INFORM) collaboration. Table 1 lists the trial groups

Table 1 Trial groups in the *In*dividual participant data meta-analysis of trials comparing *fr*ozen versus fresh e*m*bryo transfer strategy (INFORM) collaboration up to February 2022

Trial	Location	Status	Sample size
31	Italy	Published	125
NCT00963625[5]	USA	Published	137
NCT00963079[6]	USA	Published	122
NCT01841528[9]	China	Published	1508
NCT02471573[12]	Vietnam	Published	782
ChiCTR-IOR-14005406[11]	China	Published	2157
NCT01954758[32]	Spain	Published	458
ChiCTR-IOR-14005405[10]	China	Published	1650
NCT02148393[33]	Belgium	Published	212
34	China	Published	100
NCT02746562[13]	Denmark	Published	460
NTR3187[15]	Netherlands	Published	205
ISCTRN-61225414[14]	UK	Published	619
ACTRN 12616000643471	Australia	Ongoing	400

identified during the pilot search that have joined the collaboration.

Data collection, acquisition and cleaning

We will seek to collect data from all participants included in eligible RCTs. All primary investigators will be asked to share their deidentified trial IPD electronically using encrypted or protected data transfer procedures (FileShare via Monash Secure Data Enclaves platform) after signing a data usage agreement. Data from individual datasets will remain the property of the primary trial investigators who have provided them. The core team of researchers at Monash University will be responsible for the collection, handling, checking and analysis of IPD. A data variable list is presented in online supplemental appendix 2.

Data will be accepted in an electronic format, with variables and categories either adequately labelled within the dataset or accompanied by a separate dictionary. Comprehensive details of units or coding used will be requested, including how missing or not applicable values were dealt with. If any parts of the data are unclear, clarification will be sought from the relevant trials' investigators. Trial protocols will also be requested.

Once all the data are collected, the definition and coding of variables will be assessed for compatibility. The original data from all trials will be stored into a single database for analysis. A unique trial identification variable will be created to identify individual trials within the pooled dataset. The data will be checked with respect to range, internal consistency, missing or extreme values, errors and consistency with the published reports. Trial details, such as randomisation methods, characteristics of intervention, outcome measures and missing data will be crosschecked against published reports, trial protocols and data collection schedules. Inconsistencies or missing data will be discussed with the individual investigators and attempts will be made to resolve any problems by consensus. Completeness of the data will be checked and where data are found to have missing values, the relevant trial's investigators will be asked to provide reasons and check whether the actual values are available.

All anonymised data received from the investigators of included trials will be treated as sensitive data and stored securely in Monash Secure Data Enclaves platform, which is a software-defined, secure and centralised private cloud infrastructure managed by Monash University. Identifiable information sent by the trial's investigators (eg, names and addresses of participants) will not be accepted. All data will be subject to the Data Protection regulations and laws. The data will only be used for the purpose set out in the research protocol for this project and stored for 5 years beyond the life of this project.

The planned timeline for data transfer is February 2023. For ongoing studies that cannot provide data by then, they will be included in future update.

Risk of bias and overall certainty of evidence assessment

The risk of bias of each trial will be assessed using the revised risk of bias tool for RCTs (ROB 2), including the following individual five domains and an overall assessment: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result.[23] Two reviewers will independently assess the risk of bias of included trials. Any disagreement between reviewers will be resolved by discussion or through consultation with a third member of the project team. If necessary, additional information from the trials' investigators will be sought to improve the accuracy of risk of bias assessment.

The overall certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach consisting of five domains consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

Statistical analysis

All analyses will be based on IPD from all included RCTs. The primary analysis for all primary and secondary outcomes will be by intention to treat (ITT), that is, per woman randomised. Secondary analyses will be performed to include the clinically relevant denominators such as: per total number of women with a pregnancy after embryo transfer, for miscarriage; and per total number of babies born, for birth weight and congenital anomalies. For neonatal outcomes, the unit of analysis in the ITT analysis will also be the mother in the primary analysis and in cases of multiple pregnancy where the infants' outcomes differed, the worst outcome will be used. This reflects the negative impacts of any neonatal complication among multiple pregnancies on the families from a patient's perspective. In secondary analyses of neonatal outcomes, the unit of analysis will be the infant.

To estimate the effect of freeze-all compared with fresh embryo transfer, a two-stage IPD meta-analysis will be performed.[24] The first stage will involve analysing the IPD separately in each study in order to obtain aggregate data (ie, the treatment effect in each study). Binary outcomes (eg, live birth) will be analysed using Poisson regression models in order to estimate risk ratios. Continuous outcomes (eg, birth weight) will be analysed using linear regression models. The overall estimated mean and SD by treatment group will be presented along with the mean difference in treatment effect and accompanying 95% CI. All models will be adjusted for participant level predictors (eg, female age and body mass index). The second stage will involve using random effects meta-analysis with restricted maximum likelihood methods to estimate the average treatment effect across trials, followed by the Hartung-Knapp-Sidik-Jonkman approach to estimate the confidence intervals.[25] The study-specific risk ratio and overall risk ratio with 95% CIs will be presented graphically using a forest plot. For time-to-event outcomes, Cox Proportional Hazards regression will be used but if not

applicable, other appropriate methods will be used.[26] The heterogeneity statistics I^2 and tau^2 will be reported.

A two-stage IPD meta-analysis will be the preferred approach. But in circumstances where there are RCTs with very small numbers of events or zero event for some outcomes, a one-stage approach will be used. Nevertheless, we intend to repeat the meta-analysis of the primary outcome using a one-stage approach as a sensitivity analysis to check for robustness. If data do not meet the assumptions of the model, transformations or alternative models will be considered. Publication bias across trials will be visualised using a contour-enhanced funnel plot. In the case of participants with some missing data for variables within trials, multiple imputation methods will be used as appropriate. Participants with non-compliant group allocation will be considered as per the group randomised in ITT analysis and will be excluded from the per protocol analysis. To evaluate IPD availability bias, we will compare summary estimates from studies providing IPD and those not providing or providing only incomplete IPD. A detailed statistical analysis plan will be developed by the project team and agreed on by the collaboration before statistical analysis. Statistical analysis will be performed in Stata V.16.1 (StataCorp, USA) or later versions, and IPDMA will be performed using 'ipdmetan'[27] and 'ipdforest'[28] suites.

Subgroup analysis or treatment covariate interaction

We will follow the current recommendations for examining the interactions between treatment effect and participant-level covariates in IPDMA, including nonlinear relationships between continuous covariates and treatment effects.[29 30] The following treatment–covariate interactions (subgroup effects) will be assessed for the primary.[8] All continuous variables will be considered as continuous variables without categorisation and non-linear interactions will also be considered.

Participant-level covariates

- Maternal age
- Serum antimullerian hormone levels
- Antral follicle count
- Stage embryo transfer (cleavage/blastocyst)*
- Quality of embryo(s) transferred
- Number of embryos transferred
- Number of oocytes retrieved
- Number of good quality embryos available on day 3
- Progesterone level on the day of human chorionic gonadotropin (hCG) trigger
- Polycystic ovary syndrome (PCOS/WHO group II-anovulation (cause of infertility)
- Previous IVF failure.

*These could be a postrandomisation variable in some studies.

We will also consider the following treatment-level covariates. As these covariates either occur after randomisation or are relevant to the intervention group (freeze-all) only, the findings will be considered exploratory only. If the variables are not available at participant level, they will be treated as centre-level or trial-level covariate in the analysis.

- Stage of embryo cryopreservation
- Method of embryo cryopreservation
- Endometrial preparation protocol for FET (natural vs artificial)
- Luteal support protocol (progesterone type, dose, duration).

Sensitivity analysis

A sensitivity analysis will be performed, excluding trials judged to be at high risk of bias. To assess the impact of non-adherence to the randomised treatment allocation (ie, women who were randomised to receive thawed frozen embryo transfer, receiving fresh embryo transfer—non-compliers), a per protocol analysis will be performed. To test the robustness of the findings, a one-stage IPDMA will also be performed. All sensitivity analyses will be performed for the primary outcome.

Patient and public involvement (PPI)

We have patient and public representatives involved in this IPDMA. This has been integral to the design of the proposed IPDMA with input from Kate Brian (previous Women's Voices Lead at the Royal College of Obstetrics and Gynaecology), Gwenda Burns (CEO of Fertility Network UK) and Karin Hammarberg (The Victorian Assisted Reproductive Treatment Authority). PPI representatives were involved in the inception of the idea and development of the research protocol. Patient representatives have (a) confirmed the critical importance of the proposed IPDMA in generating results which will improve clinical care for couples undergoing IVF and (b) helped to prioritise our clinical outcomes and key subgroups. Ongoing PPI will be integrated into our research and aim to provide value via the following: (a) continuing involvement of all PPI collaborators throughout the course of the project, including interpretation of results and report preparation as well as (b) involvement in the dissemination of research findings.

DISCUSSION

This IPDMA offers a unique opportunity evaluate both effectiveness and safety outcomes based on individual patient characteristics, some of which were impossible in existing aggregate data meta-analysis due to heterogeneous reporting and/or analysis strategies in the primary reports. These outcomes include time to pregnancy leading to live birth and perinatal outcomes. This project will be timely due to the growing relevance of a major unanswered clinical question with exponentially increasing demand at a time when multiple RCTs have either been published recently or are due to be completed soon. In addition, this IPDMA will help us identify individuals that would benefit most from a freeze-all policy or a fresh transfer policy, and thus provide guidance towards

personalised IVF treatment. The coordination of international collaboration will also promote research transparency and data sharing in our research area, making clinical trials more useful for their end-users.

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Contributors Study conception and design: RW, DJM, MGS, BWM, SB and AM. Acquisition of data: SL, Z-JC, DW, RSL, ZW, YS, KW, LNV, PH, AP, SS, XS, CS, NT, CB, FM, APF, BSS, FCG, RL, CAV. Analysis: RW, DJM, SL, and AM. Drafting of the manuscript: RW and AM. Interpretation and critical revision of the article: DJM, MGS, SL, Z-JC, DW, RSL, ZW, YS, KW, LNV, PH, AP, SS, XS, CS, NT, CB, FM, APF, BSS, FCG, RL, CAV, BWM and SB.

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