Fresh versus frozen single embryo transfer in Chinese women of advanced age undergoing IVF/ICSI: a study protocol for a randomized controlled trial

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Study protocol

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Posted Date: March 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18972/v1

Fresh versus frozen single embryo transfer in Chinese women of advanced age undergoing IVF/ICSI: a study protocol for a randomized controlled trial

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Abstract

Background: Elective frozen cleavage embryo transfer resulted in significantly higher live birth rate in patients with polycystic ovary syndrome but not in ovulatory women compared with fresh embryo transfer. Further, elective single frozen blastocyst transfer had significantly higher live birth rate in ovulatory women compared with single fresh blastocyst transfer. However, it is unknown whether single frozen cleavage embryo transfer results in higher cumulative live birth rate in women of advanced age undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). The aim of this study is to compare the effectiveness of frozen cleavage embryo transfer with fresh cleavage embryo transfer in Chinese women of advanced age.

Methods: This study is a double-blind randomized controlled clinical trial (1:1 treatment ratio of frozen embryo transfer vs. fresh embryo transfer). A total of 840 women of advanced age with normal ovarian reserve undergoing the first cycle of IVF or ICSI will be enrolled and randomized into two parallel groups. Participants in group A will undergo frozen single cleavage embryo transfer, and participants in group B will undergo fresh single cleavage embryo transfer. The primary outcome is the cumulative live birth rate of the trial IVF/ICSI cycle within 12 months after randomization. This study is powered to detect an absolute difference of 8% (23% vs 15%) at the significance level of 0.05 and 80% statistical power based on a two-sided test.

Discussion: The results of this study will provide evidence for the efficacy and safety of frozen cleavage embryo transfer compared with fresh cleavage embryo transfer in women of advanced age undergoing IVF/ICSI.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2000029330. Registered on 25 Jan 2020.

Keywords: Frozen embryo transfer, advanced age, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), live birth, randomized controlled trial.

Plain English summary

Previously, fresh embryo transfer was the common practice in most IVF centers, whereas surplus embryos were frozen by a slow-freezing method and thawed for later transfer when needed. The first case of live birth after frozen embryo transfer (FET) was reported in 1984. With the development of vitrification, the survival rates of thawed embryos were greatly improved as compared with slow-freezing. Moreover, there are some medical indications for elective FET such as genetic screening of embryos. Observational studies suggest that FET seems to have better obstetric and perinatal outcomes than fresh embryo transfer. Consequently, the clinical application of FET has increased in recent years. In theory, FET under physiological conditions may improve the chance of embryo implantation. Thus there were advocates proposing elective FET strategy. However, high-quality evidence comparing the live birth rate after elective FET versus fresh embryo transfer is limited. Recent meta-analyses of randomized controlled trials (RCT) show that elective FET is associated with decreased risks of small for gestational age, low birth weight and preterm birth but increased risks of large for gestational age, high birth weight and pre-eclampsia. Of notice, previous RCT studies were mainly conducted in young patients aged less than 35 years. It is unknown if elective FET can improve the live birth rate in women of advanced age than fresh embryo transfer. Therefore, we propose a RCT study to compare the cumulative live birth rate of elective FET versus fresh embryo transfer in Chinese women of advanced age.

Introduction

In the past 40 years, more than 7 million babies have been conceived by assisted reproductive technologies (ART) treatment, mainly through in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (1). Increasing evidence suggests that ART treatment is associated with adverse obstetric and perinatal outcomes, which may be related to the genetic factors of patients, multiple pregnancies and ART procedures per se (1, 2). To avoid multiple pregnancies, a single embryo transfer policy has been implemented in many IVF centers. In Shanghai of China, this policy was compulsary for all the women who are undergoing their first embryo transfer and no more than two embryos are allowed to be implanted after the first transfer since January 2019. However, even singletons conceived by ART are also at increased risk of adverse pregnancy outcomes such as low birth weight, preterm birth, small for gestational age, stillbirth, perinatal mortality and gestational diabetes compared with singletons conceived spontaneously (1, 2).

Fresh embryo transfer is the common practice in most IVF centres, while surplus embryos are cryopreserved and thawed for later transfer when needed. The first successful pregnancy and the first case of live birth after frozen embryo transfer (FET) was reported in 1983 and 1984 respectively (3, 4). In recent years, with the development of vitrification, the survival rates of thawed embryos was greatly improved as compared with slow-freezing (5). There are some medical indications for elective frozen embryo transfer (eFET) or 'freeze-all' approach, including hydrosalpinx, increased risk of ovarian hyperstimulation syndrome (OHSS), elevated progesterone levels, genetic

screening, low responders, inadequate uterine cavity, high blood pressure and Zika virus (6). Women undergo progestin-primed ovarian stimulation (PPOS) protocol or luteal phase stimulation protocol also require eFET. Consequently, the clinical application of FET has increased in recent years. For instance, the data from the USA showed that the number of FET cycles increased by 82.5% from 2006 to 2012, compared to a 3.1% increase in fresh embryo transfer cycles during the same period (7). Globally, the data showed that the number of FET cycles increased by 27.6% from 2008 to 2010 (8).

A systematic review of eleven observational studies suggests that the transfer of frozen thawed IVF embryos seem to have better obstetric and perinatal outcomes than the fresh embryo transfer (9). The mechanism may be related to the improvement of endometrial receptivity and the synchronization of embryos and endometrium under physiological estradio levels during the frozen transfer cycle. For example, a large retrospective cohort study in the US included 4071 normal responder patients with live singleton births and found supraphysiologic estradiol was an independent predictor of low birth weight in singletons born after fresh embryo transfer cycles (10). Thus, there were advocates proposing eFET strategy (11, 12).

Although FET has been widely used, there are few high-quality studies comparing the live birth rate after eFET versus fresh embryo transfer. Shapiro et al. performed two small randomized controlled trials (RCTs) and showed that the clinical pregnancy rate of the elective frozen blastocyst transfer group increased by about 15% in high responders and 30% in the normal responders respectively, compared with the fresh blastocyst transfer group (13, 14). A large RCT study in 2016 showed that frozen cleavage embryo

transfer resulted in a higher rate of live birth, a lower risk of the OHSS, and a higher risk of preeclampsia after the first transfer compared with fresh cleavage embryo transfer in patients with polycystic ovary syndrome (PCOS) (15). In contrast, two large RCT studies in 2018 showed no significant difference in live birth rate after elective frozen or fresh cleavage embryo transfer in ovulatory women (16, 17), but FET was associated with a lower risk of the OHSS (17). A recent large RCT study found a higher singleton livebirth rate but increased risk of pre-eclampsia in ovulatory women with good prognosis undergoing frozen single blastocyst transfer versus fresh single blastocyst transfer (18). Compared with fresh embryo transfer, recent meta-analyses show that frozen embryo transfer is associated with decreased risks of small for gestational age, low birth weight and preterm birth but increased risks of large for gestational age, high birth weight and pre-eclampsia (19, 20). Noteably, previous studies were mainly conducted in young patients aged less than 35 years. It is unknown if eFET can improve the live birth rate in women of advanced age than fresh embryo transfer. Therefore, we propose a randomized controlled clinical trial to compare the cumulative live birth rate of eFET versus fresh embryo transfer in women of advanced age.

The results of this study will provide the data for clinicians and infertile couples whether eFET is beneficial for women of advanced age.

Methods/Design

Study design and setting

This study is a single centre, parallel, double-blind, superiority randomized controlled clinical trial (1:1 treatment ratio). Participants will be recruited at Shanghai First Maternity and Infant Hospital. This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). The trial design is summarized in Figure 1, whereas the schedule of enrolment, interventions and assessments during the study period is shown in table 1.

Inclusion criteria

- Women aged 35-44 years
- Women who have normal ovarian reserve (AFC>6 follicles, or AMH$\geqslant$1.2 ng/ml)
- Infertile couples scheduled for their first IVF/ICSI cycle.
- Women who will receive either gonadotrophin-releasing hormone agonist protocol or gonadotrophin-releasing hormone antagonist protocol as their COH treatment.
- Informed consent.

Exclusion criteria

- Women with congenital or secondary uterine abnormalities, such as uterine malformations including single-horned uterus, septate uterus or double uterus, adenomyosis, uterine submucosal fibroids, intrauterine adhesions
- Couples undergoing preimplantation genetic testing (PGT)
- Women with hydrosalpinx
- Women with recurrent miscarriage

- Women with polycystic ovarian syndrome (PCOS)
- Women with endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney)
- Women undergoing blastocyst transfer
- Natural cycles or IVM cycles
- Sperm donation or egg donation cycles

Recruitment

Infertile couples who come to the outpatient clinic to receive IVF/ICSI will be screened by trained clinical team who are very familiar with the eligible criteria. Eligible patients will then be approached by a member of the research team and explained the trial details before the start of IVF/ICSI treatment. Couples will be offered time for consideration to decide to participate the trial. If the couple agrees to participate, they will make an appointment to sign the consent form in their next visit of clinic. Couples who refuse to participate will be treated according to the conventional protocols at the centre. The decision to refuse or withdraw will not affect their conventional clinical treatments and the relationship with clinical practitioners.

The recruitment in the study centre will start in March 2020 and continue until the needed number of participants is included, anticipated until February 2022.

Randomization and blinding

Eligible women will be randomized to single frozen embryo transfer or single fresh embryo transfer. Randomization and allocation of patients to study arms will be

199 performed on the day of the oocyte retrieval if 4～15 oocytes are retrieved. Permuted
200 block randomization is controlled by collaborative investigators who are not involved in
201 the consulting and treatment procedure. When there is an eligible participant to be
202 enrolled into the study, Investigators will login the trial system (REDCap) to get
203 allocation of patients according to a computer-generated randomization list in a 1:1
204 ratio, with a variable block size of 2, 4 or 6.
205 This study will be blinded to embryologists and laboratory technicians until the
206 completion of statistical analysis of this study. However, participants, clinicians,
207 investigators and nurses who conduct follow-up will not be blinded.
208

209 **Interventions**

210 All participants will receive controlled ovarian hyperstimulation (COH) treatment, which
211 is performed by standard routines at the study centre. The selection of protocol will be
212 done by physicians, who are blinded for group allocation. In the gonadotrophin-
213 releasing hormone antagonist (GnRH-ant) protocol, all participants will be injected
214 gonadotropin (Gonal-F or Puregon or HMG) daily from day 2 or day 3 of menstrual cycle.
215 When at least one follicle has reached a diameter of 12mm or on day 6 of ovarian
216 stimulation, GnRH antagonist (Cetrotide or Ganirelix) 0.25mg daily will be administered
217 subcutaneously until the trigger day (include the trigger day). For long GnRH-a protocol,
218 pituitary down-regulation will be initiated 7-10 days before the menstrual cycle with
219 GnRH agonist (subcutaneous Triptorelin 0.1mg/d or intramuscular Triptorelin 1.25-
220 1.88mg one-time). After 10-14 days or on day 2 of menstrual cycle, gonadotropin
221 treatment will start.

For all the protocols, menstrual cycle of patient includes spontaneous menstrual cycle, and irregular menstrual cycle by the use of oral contraceptives (OC) or progestins. Before COH treatment, baseline pelvic ultrasound, as well as baseline serum hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH), estradial (E2), progesterone (P) and β-hCG) will be measured. The starting dose of gonadotrophins is 150–300IU/day for the first 4 days based on the characteristics of each patient. Transvaginal ultrasound scanning and hormonal measurement will be repeated every 2–3 days to monitor follicle growth. The subsequent dose of gonadotrophin will be adjusted according to the individual response. After two or more follicles reach a diameter ≥18 mm, 250ug of hCG will be once injected on trigger day. In women with hyper-response (≥15 follicles ≥12 mm), 0.2 mg Triptorelin or 4000 IU of hCG will be administered.

Oocyte retrieval is scheduled for 36h (±2) after hCG injection. Fresh ejaculate semen samples will be obtained on the day of oocyte retrieval, and are prepared by swim-up protocol according to routines (21). For couple who take IVF, the procedure has been previously described (21). All the oocytes will be inseminated with 2-5×10^6 per oocyte motile spermatozoa approximately 39-42h after hCG injection. Gametes are then co-incubated overnight at 37℃ under 5% O_2 and 6% CO_2 in the conventional incubators. Assessment of fertilization are carried out about 16-18h (day 1) after fertilization. Then zygotes are left in conventional incubators for a further 48 hours. For couple who take ICSI, the oocytes will be denuded by hyaluronidase before micromanipulation. Only the mature, metaphase-II (MII) oocytes with an extruded first polar body are microinjected.

The procedure of ICSI has been previously described (22). After injection, oocytes are transferred to the standard culture dishes in conventional incubators. Assessments of fertilization and embryo quality after ICSI for the conventional incubators group are identical with IVF. The cleavage embryo quality for both groups will be observed at 48 (day 2) or 72 (day 3) hours after oocyte retrieval. The embryos are scored according to the quality, numbers, size of the blastomeres and the amount of anucleate fragmentation.

For participants receive fresh embryo transfer, embryo transfer will be performed on Day 3 after oocyte retrieval under ultrasound guidance. Surplus embryos will be frozen according to the routines at the study centre. Luteal support is administered in the form of vaginal progesterone (Crinone) 90 mg/d until the confirmation of biochemical pregnancy, and will be maintained to 10 weeks of gestation. The progesterone will be used until the menses when the biochemical pregnancy is not observed. Oral progesterone (20mg b.i.d.; Duphaston) will be offered for women who appear vaginal bleeding in case.

For participants undergo frozen thawed embryo transfer, patients with irregular menses will receive oral E2 valerate (Progynova) 4-6mg/d on 2-3 days of subsequent artificial menstrual cycle (by the use of oral contraceptives (OC) or progestins) within 6 months after oocyte aspiration. Oral progesterone will be added if the endometrial thickness is ≥8 mm. Patients with regular menses will have ovulation monitoring by transvaginal ultrasound from day 12 of menstrual cycle. Oral progesterone will be added on the day of ovulation. Frozen-thawed embryos will be transferred on Day 3 after progesterone

initiation. The transfer procedure will be the same as that used for the fresh embryo transfer. Oral medications will be continued at an unchanged dose until the confirmation of biochemical pregnancy, and will be maintained to 10 weeks of gestation, and it will be used until the menses when the biochemical pregnancy is not observed.

Follow-up

Urine and blood hCG will be measured 14 days after embryo transfer, and positive results indicate biochemical pregnancy. If the gestational sac is observed with ultrasonography on 7 weeks after transfer, clinical pregnancy will be confirmed. Ongoing pregnancy is defined by the presence of a gestational sac with fetal heartbeat after 12 weeks of gestation.

For women who are confirmed as ongoing pregnancy, they will be required to notify researchers of the time of delivery. In 2 weeks after delivery, the information of pregnancy (pregnancy complications, and fetus information), delivery information (gestational age, delivery mode, placenta abnormality and/or delivery complications), infant information (such as sex, birth weight, birth defect) will be collected by completing forms.

Outcome measures

The primary outcome will be cumulative live birth of the trial IVF/ICSI cycle within 12 months of randomization. Live birth will be defined as a delivery of one or more living infants (≥22 week's gestation or birth weight more than 500g).

For the effectiveness of the treatment, we will record these secondary outcomes in terms of effectiveness:

- Fertilisation: defined as number of zygotes with 2PN (per woman randomised and per oocyte retrieved).
- Available embryo: defined as number of embryos ≥4 cells and ≤30% fragmentation on day 3 observation.
- Good quality embryo: defined as number of embryos with ≥6 cells and ≤30% fragmentation developed from 2PN embryos on day 3 observation.
- Biochemical pregnancy: defined as blood hCG≥10 U/L at 14 days after embryo transfer.
- Implantation: defined as the number of gestational sacs observed per embryo transferred.
- Clinical pregnancy: defined as one or more observed gestational sac or definitive clinical signs of pregnancy under ultrasonography at 7 weeks after embryo transfer (including clinically documented ectopic pregnancy).
- Multiple pregnancy: defined as a pregnancy with two or more gestational sacs or positive heart beats at 7 weeks of gestation.
- Ongoing pregnancy: defined as the presence of a gestational sac and fetal heartbeat after 12 weeks of gestation.

For the safety of the treatment, we will record the following treatment complications as secondary outcomes:

- Ovarian hyperstimulation syndrome (OHSS): defined as exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate, or severe according to the degree of abdominal distention, ovarian enlargement, and respiratory, hemodynamic, and metabolic complications.
- Miscarriage: defined as the spontaneous loss of an intra-uterine pregnancy prior to 22 completed weeks of gestational age.
- Ectopic pregnancy: defined as the implantation takes place outside the uterine cavity, confirmed by sonography or laparoscopy.

We will also collect the following obstetric and perinatal complications:

- Gestational diabetes mellitus (GDM)
- Hypertensive disorders of pregnancy (comprising pregnancy induced hypertension (PIH); pre-eclampsia and eclampsia)
- Antepartum haemorrhage, including placenta previa, placenta accreta and unexplained
- Preterm birth: defined as birth of a fetus delivered after 22 and before 37 completed weeks of gestational age in participants confirmed ongoing pregnancy.
- Birth weight, including low birth weight (defined as weight < 2500 gm at birth), very low birth weight (defined as < 1500 gm at birth), high birth weight (defined as >4000 gm at birth) and very high birth weight (defined as >4500 gm at birth)
- Large for gestational age (defined as birth weight >90th centile for gestation, based on standardized ethnicity based charts) and small for gestational age (defined as less

than 10th centile for gestational age at delivery based on standardized ethnicity based charts)

- Congenital anomaly (any congenital anomaly will be included)
- Perinatal mortality: defined as fetal or neonatal death occurring during late pregnancy (at 22 completed weeks of gestational age and later), during childbirth, or up to seven completed days after birth.

Data management and monitoring

The data collected for the trial will be a mixture of routinely clinical data (such as demographic data, fertility history, ART records), which are verifiable from the medical record and questionnaire data. All researchers and physicians are required to receive training classes and pass the test. Each participant will be assigned an appropriate code number that is consistent with the allocated intervention, which will appear on all report forms to maintain confidentiality.

All data are collected at baseline and follow-up through a standard clinical electronic data collection system (EDC). Initially, all of the researchers and physicians will be required to keep accurate and verifiable source notes in the medical record relevant to each participant's eligible criteria of this trial. After recruitment of eligible participants, trained assessors will take charge of the data input: they can log on to a secure data portal with the individual ID, and upload the data from medical record to eCRF with the personal trail ID of each participant. When the trial is close-out, all participant-

identifiable data, such as consent forms, screening and identification logs will be stored in the investigator site files, accessible only to delegated members of the study team.

Sample size calculation

According to the data of our centre, live birth rate among women aged ≥35 years in the control arm were around 15.0%. Based on other studies within fertility care as well as the discussion by gynaecologist and epidemiologists, we assumed that the minimal clinical important difference to make frozen embryo transfer preferable over fresh embryo transfer would be 8.0%. To demonstrate this difference with two-sided test, 5.0% alpha-error, 80% statistical power, and taking consideration of dropout as 10%, the lowest numbers of participants we need to enrol for the study are 840. The ratio between test and control group will be 1:1.

Statistical analysis

Baseline characteristics will be described by descriptive analysis, and the balance between the two arms will be assessed. For continues variables, the normality test will be estimated using frequency histograms and the Shapiro test initially. If the parameters are normally distributed then they will be presented as mean with standard deviation (SD). If the parameters are non-normally distributed, their medians and inter-quantile ranges (IRQs) will be reported. For categorical variables, we will present the proportions of the two arms. In addition, we will also report the numbers of recruitment, participants lost to follow-up, protocols violation, and other relevant descriptive data.

Data analysis of this trial will follow the intention-to-treat principle, which includes all randomized women in the primary comparison between the two arms. Per-protocol analysis may be conducted as a secondary analysis. The primary outcome, cumulative live birth rate, will be compared between the two arms using Pearson's chi-square test or Fisher's exact test for the purpose of unadjusted analysis. We will also compute unadjusted risk ratio (RR) and its 95% confidence interval (95% CI). In the event of prominent imbalance of potential confounders between the two arms, we will perform multivariable Poisson Regression or Log-Binomial model to compute adjusted RR and its 95% CI. Secondary outcomes will be compared between the two arms using the similar approach described for the primary outcome.

For missing values regarding baseline characteristics, we will first perform analysis by excluding missing values, we will then perform multiple imputation to impute missing values and conduct subsequent analysis to estimate the robustness of the findings. For loss to follow-up and protocol violation, we will attempt sensitive analyses to explore the effect of these factors on the trial findings.

Primary and secondary outcomes will be compared between the two arms within subgroups of different COH protocols in which the effects on outcomes might be modified. Due to the concern over multiplicity of sub-group analysis, we will place limited importance on subgroup findings.

All tests will be two-tailed, and differences with p value <0.05 will be considered statistically significant.

Safety

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to intervention, will be recorded and reported to an independent Data and Safety Monitoring Board (DSMB).

The investigator will inform subjects and the reviewing accredited medical research ethics committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited medical research ethics committee, unless suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

Interim analysis

The DSMB will perform an interim analysis within 3 months after the first 365 randomised participants have completed embryo transfer. They will do so using the endpoint ongoing pregnancy, as data on live birth will not be available. The interim analysis will be conducted using a two-sided significant test with the Haybittle–Petospending function and a Type I error rate of 5% with stopping criteria of $P < 0.001$ (Z alpha = 3.29). The study could be stopped prematurely based on the advice of the DSMB.

Discussion

Age is an important factor that affects woman's fertility. Compared with younger women, older women have low ovarian reserve and a sharp decline in fertility.

Increased maternal age is also associated with higher risk of pregnancy loss, obstetric and perinatal complications, and chromosomal abnormalities of infants. Generally, women aged at 35 years or older are considered as women of advanced age. With the development of society, the reproductive age is gradually delayed, and the number of ART cycles in women of advanced age has significantly increased. Live birth rate of ART cycles decreases with age, due to poor response to controlled ovarian stimulation, poor oocyte and embryo quality, and increased pregnancy loss. Women of advanced age are classified as poor responders or a population of poor prognosis in ART cycles (23, 24).

It is unclear that whether frozen embryo transfer can improve the live birth rate of women with advanced age as high-quality evidence is lacked. A retrospective cohort study analyzed 1455 fresh blastocyst transfer cycles and 1455 frozen blastocyst transfer cycles from 12 reproductive centers in the US conducted from 2009 to 2015. The data showed the FET group had significantly higher ongoing pregnancy rate than the fresh transfer group (52% vs 45.3%, odds ratio (OR) :1.31 ,95% CI:1.13-1.51). The sensitivity analysis suggested that FET may have a beneficial effect with increasing maternal age, independently of progesterone levels before transfer (25). The data from the American Association for Assisted Reproductive showed that between 2006 and 2012, the live birth rate of women over 41 years old was higher after FET compared with fresh embryo transfer, whereas in women aged 35-40 years the live birth rate of frozen embryo transfer increased gradually and was higher than that of fresh embryo transfer in 2012 (7). These data suggest that FET may improve the outcome of ART therapy in women of

advanced age. Taken together, randomized controlled trials are needed to provide the efficacy and safety of frozen embryo transfer in women of advanced age.

Strengths of this trial include its randomized, controlled design and relatively large sample size, which should minimize bias and increase validity and reliability of data. The results of this study will provide evidence for the efficacy and safety of single frozen cleavage embryo transfer compared with single fresh cleavage embryo transfer in women of advanced age undergoing IVF/ICSI.

Abbreviations

AFC: antral follicle count; AMH: Anti-Mullerian hormone; ART: assisted reproductive technology; CI: confidence interval; COC: cumulus oocyte complexes; COH: controlled ovarian hyperstimulation; CRF: case report form; DSMB: Data Safety and Monitoring Board; E2: estradiol; EDC: electronic data collection; FET: frozen embryo transfer; FSH: follicle stimulating hormone; GDM: gestational diabetes mellitus; GnRH: gonadotrophin-releasing hormone; hCG: human chorionic gonadotrophin; HMG: human menopausal gonadotropin; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; ITT: Intent-to-treat; LH: luteinizing hormone; IVM: in vitro maturation; OHSS: ovarian hyperstimulation syndrome; OC: oral contraceptives; P: progesterone; PCOS: polycystic ovarian syndrome; PGT: preimplantation genetic testing; PIH: pregnancy induced hypertension; PN: pronuclei; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SPIRIT: Recommendations for Interventional Trials.

Declarations

Ethics approval and consent to participate

This trial was approved by the institutional ethical committee of Shanghai First Maternity and Infant Hospital on 20 January 2020 (Reference No.: KS2009). All participants in the trial will provide written informed consent. The study was registered on Chinese Clinical Trial Registry on 25 January 2020 (ChiCTR2000029330, http://www.chictr.org.cn/showproj.aspx?proj=48725) and will be conducted according to the principles outlined in the Declaration of Helsinki and its amendments, in accordance with the Medical Research Involving Human Subjects Act, and using Good Clinical Practice.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the public access repository ResMan of Chinese Clinical Trial Registry within six months after completion of the study. The principle investigator will publish the results of the study as soon as appropriate.

Competing interests

The authors have no conflicts of interest to declare.

Funding

The trial is supported by a grant from the Chinese Medical Association (18010030732). The funding bodies had no rule in the study design, implementation, analysis, manuscript, preparation or decision to submit this article for publication.

Authors' contributions

Study concept and design: MC, W-TL and B.W.M. Acquisition of data: MC, YW, XH, W-QL, CS and ZM. Analysis and interpretation of data: MC, YW, XH, W-TL, W-QL and B.W.M. Drafting of the manuscript: MC, W-TL and B.W.M. Critical revision of the manuscript for important intellectual content: YW, XH, W-QL CS, ZM and XT. Statistical analysis: MC, YW, XH, W-TL, W-QL and B.W.M. Study supervision: B.W.M and XT.

Acknowledgements

Not applicable.

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Figures

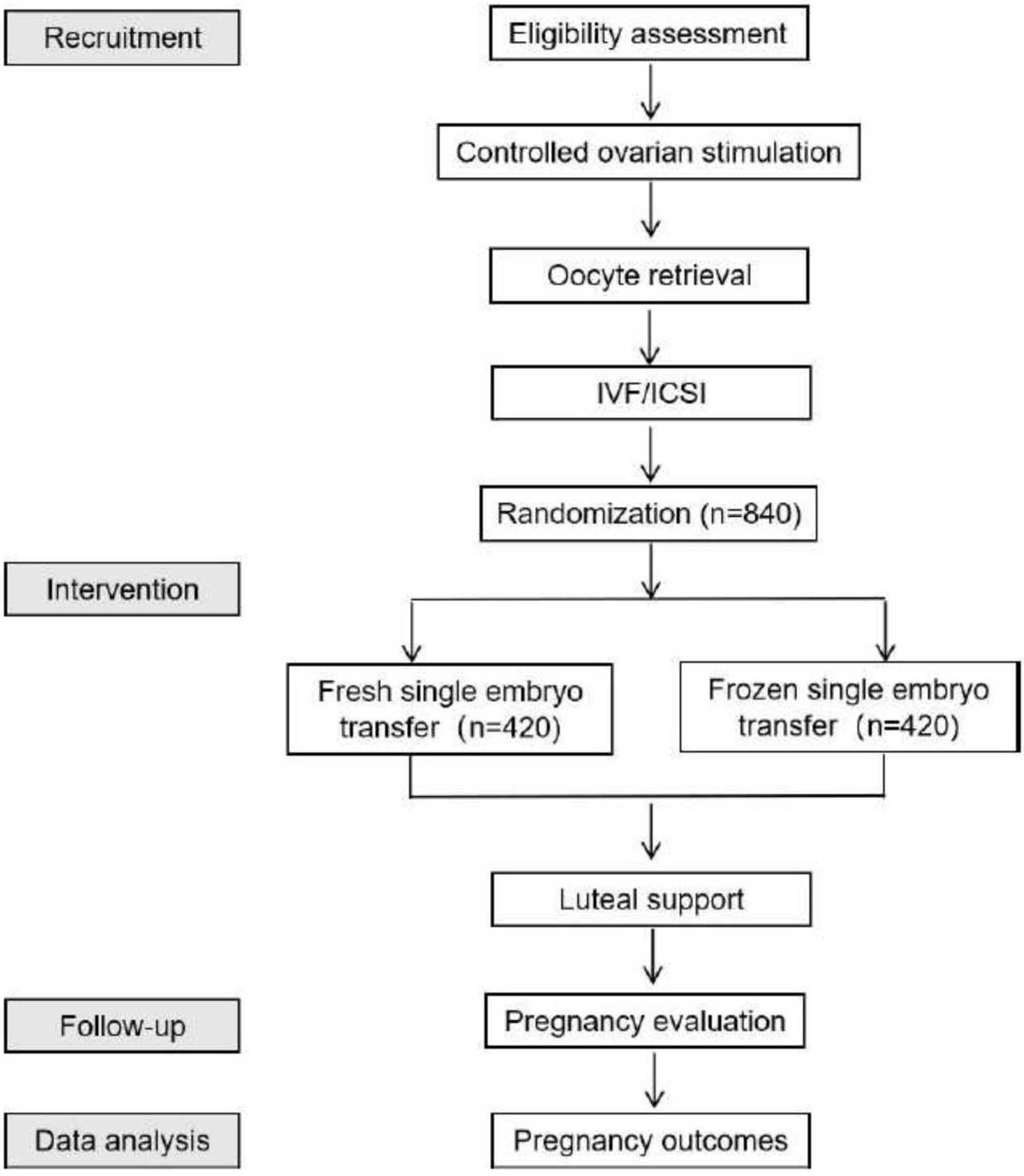

Figure 1

Flowchart followed the checklist of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) showing patient enrolment, allocation, treatment and follow-up of participants.

Supplementary Files

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- Table1Scheduleofenrolment.pdf