

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

**Comparison of the effect of immediate versus delayed transfer following a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed embryo transfer cycles: a study protocol for a randomised trial.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020507
Article Type:	Protocol
Date Submitted by the Author:	07-Nov-2017
Complete List of Authors:	LI, HE LI, LU; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China LU, XIANG; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China SUN, XIAOXI; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China; Key Laboratory of Female Reproductive Endocrine Related Diseases, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China Ng, Ernest; The University of Hong Kong, Department of Obstetrics and Gynecology
Keywords:	Reproductive medicine < GYNAECOLOGY, Assisted reproductive technology, Frozen embryo transfer

SCHOLARONE™  
Manuscripts

only

1  
2  
3 **Comparison of the effect of immediate versus delayed transfer following**  
4 **a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed**  
5 **embryo transfer cycles: a study protocol for a randomised trial.**  
6  
7

8  
9  
10 Authors and affiliations

11 He Li<sup>1</sup>, Lu Li<sup>1</sup>, Xiang Lu<sup>1</sup>, Xiaoxi Sun<sup>1,2\*</sup>, Ernest Hung Yu Ng<sup>3\*</sup>

- 12  
13 1. Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology  
14 Hospital, Fudan University, Shanghai, China  
15  
16 2. Key Laboratory of Female Reproductive Endocrine Related Diseases,  
17 Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China  
18  
19 3. Department of Obstetrics and Gynaecology, The University of Hong Kong,  
20 Hong Kong Special Administrative Region, Hong Kong, Hong Kong  
21  
22

23 \* Corresponding authors: Email: [nghye@hku.hk](mailto:nghye@hku.hk) (EHY Ng) or: Email:  
24 [xiaoxi\\_sun@aliyun.com](mailto:xiaoxi_sun@aliyun.com) (X Sun)  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**ABSTRACT**

Introduction: Frozen-thawed embryo transfer (FET) has become an increasingly important part of in vitro fertilization (IVF) treatment. Currently, there is still no good scientific evidence to support when to perform FET following a stimulated IVF cycle. Since all published studies are retrospective and the findings are contradictory, a randomized study is needed to provide Level 1 evidence to guide the clinical practice.

Methods/analysis: This is a randomized trial. A total of 724 women undergoing the first FET following ovarian stimulation in IVF will be enrolled and randomized according to a computer-generated randomization list to either (1) the immediate group in which FET will be performed in the first cycle following the stimulated IVF cycle or (2) the delayed group in which FET will be performed at least in the second cycle following the stimulated IVF cycle. The primary outcome is the ongoing pregnancy defined as a viable pregnancy beyond 12 weeks gestation.

Ethics/dissemination: An ethical approval has been granted from the ethics committee of assisted reproductive medicine in Shanghai JiAi Genetics and IVF institute (JIAI E2017-12). A written informed consent will be obtained from each woman before any study procedure is performed, according to good clinical practice. The results of this trial will be disseminated in a peer-reviewed journal.

Trial registration numbers: NCT03201783

### Strengths and limitations of this study

1. This is the first randomised controlled trial comparing the ongoing pregnancy rate of immediate versus delayed FET following a stimulated IVF cycle.
2. The researchers, doctors and the participants cannot be blinded to treatment allocation.

### BACKGROUND

Frozen-thawed embryo transfer (FET) has become an increasingly important part of in-vitro fertilisation (IVF) treatment.[1] When women fail to get pregnant after replacing embryos in the stimulated IVF cycle, many of those who have frozen embryos would like to proceed FET as soon as possible in order to get pregnant as soon as possible.

Ovarian stimulation exerts a detrimental effect on endometrial receptivity.[2] Ovarian stimulation leads to supraphysiological hormonal concentrations in blood which may exert negative influence on perinatal and neonatal outcomes.[3-5] The freeze-all strategy has drawn attention in recent literature with the advantages of increased maternal safety, improved pregnancy rates, lower ectopic pregnancy rates and better obstetric and neonatal outcomes.[6] The better outcomes after elective FET in the context of a freeze-all strategy may be at least partially attributed to the lack of endometrial impairment that is observed during ovarian stimulation.

Robust information regarding the optimal timing for FET following a stimulated IVF cycle is still lacking. One option is to perform FET in the first cycle following the stimulated IVF cycle i.e. immediate transfer. Another option is to postpone FET for at least one menstrual cycle i.e. delayed transfer. Delaying FET may add to the stress and anxiety accompanying the IVF treatment. Several retrospective studies showed similar clinical pregnancy rates or live birth rates between immediate and delayed FET performed following fresh embryo transfers or in a frozen-all policy.[7-9] Another retrospective analysis showed that significantly higher implantation, clinical pregnancy and live birth

1  
2  
3 rates were found in the delayed FET group than in the immediate group after  
4 failed fresh ET cycles.[10] Since these studies are all retrospective and the  
5 findings are contradictory, a randomized study is needed to provide Level 1  
6 evidence to guide the clinical practice.  
7  
8  
9

10  
11 We aim in this randomized trial to compare the ongoing pregnancy rate of  
12 immediate versus delayed FET following a stimulated IVF cycle. The  
13 hypothesis is that the ongoing pregnancy rates of immediate and delayed FET  
14 are comparable.  
15  
16  
17

## 18 19 **MATERIALS AND METHODS**

20  
21 Study design (figure 1)

22  
23 This is a single-center randomized study carried out in the Shanghai JiAi  
24 Genetics and IVF institute. The trial has been registered at ClinicalTrial.gov  
25 (NCT03201783)  
26  
27

### 28 29 **Participants**

30  
31 Eligible women will be recruited if they fulfil all of the inclusion criteria and do  
32 not meet any of the exclusion criteria. They will be included once for this study.  
33 Informed written consent will be obtained.  
34  
35  
36

37  
38 Inclusion criteria are:

- 39 • Women aged  $\leq 43$  years at the time of IVF treatment
  - 40 • Undergoing IVF with a standard stimulation
  - 41 • At least one frozen embryo or blastocyst
  - 42 • The first FET cycle following ovarian stimulation in IVF
- 43  
44  
45  
46

47  
48 Exclusion criteria include

- 49 • Use of mild stimulation or natural cycle for IVF treatment
  - 50 • Severe ovarian hyperstimulation syndrome during IVF treatment
  - 51 • Preimplantation genetic diagnosis treatment
  - 52 • Use of donor oocytes
- 53  
54  
55  
56  
57  
58  
59  
60

- Presence of hydrosalpinx which is not surgically treated or endometrial polyp on scanning during ovarian stimulation

#### Randomization

Women will be randomized according to a computer-generated randomization list prepared by a designated research staff into one of the following two groups:

- (1) the immediate group in which FET will be performed in the first cycle following the stimulated IVF cycle and
- (2) the delayed group in which FET will be performed at least in the second cycle following the stimulated IVF cycle.

#### Blinding

No blinding because of the nature of the intervention.

#### Interventions

Women will undergo IVF treatment in the centre as clinically indicated. Standard ovarian stimulation with gonadotrophins in either a GnRH antagonist protocol or long GnRH agonist will be employed. Oocyte retrieval will be performed under transvaginal ultrasound guidance 34–36h after triggering with hCG or an agonist. Oocytes will be fertilized using either conventional insemination or intracytoplasmic sperm injection depending the semen quality of the husbands in accordance with the standard protocol. Normal fertilization will be assessed and confirmed by the presence of two pronuclei and a second polar body at 16–18 h after insemination or intracytoplasmic sperm injection. On day 3 after egg retrieval, an embryo with at least seven blastomeres and Grades 1 and 2 is defined as good quality. Embryos with at least six blastomeres and fragments <50% will be frozen. All good embryos will be frozen or vitrified using the Crytop method as cleavage stage embryos on Day 3 or as full to expanded blastocysts on Day 5 or Day 6 of embryo culture according to the standard protocol.

1  
2  
3 Hormone replacement treatment (HRT) will be used for endometrial  
4 preparation. On Day 3 of the menstrual cycle, estradiol valerate (E2,  
5 Progynova, Schering AG, Berlin, Germany) will be commenced 4mg daily for  
6 10 days. When the thickness of the endometrial layer reaches at least 8 mm  
7 on pelvic scanning, vaginal progesterone 90 mg per day (Crinone,  
8 Merck-Serono, Switzerland) will be administered. For Day 3 embryos, FET is  
9 scheduled on the fourth day of starting vaginal progesterone. For blastocysts,  
10 FET is scheduled on the sixth day of starting vaginal progesterone. A  
11 maximum of 1–2 embryos or blastocysts with the best morphology will be  
12 transferred under ultrasound guidance using a soft embryo transfer catheter.  
13 Serum hCG level will be checked 14 days after FET. All hormone therapy will  
14 be stopped if the serum hCG level is negative. All pregnant women will  
15 continue the hormonal therapy until 12 weeks of gestation.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25

#### 26 Follow-up and data collection

27 If the serum hCG level is positive, transvaginal ultrasound will be performed  
28 two weeks later to locate the pregnancy and confirm foetal viability.  
29 Subsequent management will be the same as other women with early  
30 pregnancy. They will be referred for antenatal care when the ongoing  
31 pregnancy is 12 weeks.  
32  
33  
34  
35  
36  
37

38 Written consent regarding retrieval of pregnancy and delivery data will be  
39 sought from the patient at the time of study. The patient will be contacted after  
40 delivery by phone to retrieve the information of the pregnancy outcomes. The  
41 outcome of the pregnancy (delivery, miscarriage), number of babies born, birth  
42 weights and obstetrics complications will be recorded.  
43  
44  
45  
46  
47

#### 48 Outcome measurements

##### 49 Primary outcome

50 The primary outcome is an ongoing pregnancy defined as a viable pregnancy  
51 beyond gestation 12 weeks  
52  
53  
54  
55

##### 56 Secondary outcomes include

57  
58  
59  
60



- 1
- 2
- 3 - positive hCG level
- 4
- 5 - clinical pregnancy defined as presence of intrauterine gestational sac on
- 6 ultrasound
- 7
- 8 - implantation rate as the number of gestational sacs per embryo transferred
- 9
- 10 - multiple pregnancy, ectopic pregnancy and miscarriage rates
- 11
- 12 - live birth rate and
- 13 - birth weight of newborns
- 14
- 15

#### 16 Data entry and quality control of data

17 Participates information forms will be developed for data entry, and quality  
18 control of the data will be handled at two different levels. The investigators will  
19 be required to ensure the accuracy of the data as the first level of control, and  
20 the second level will include data monitoring and validation that will be carried  
21 out on a regular basis through out the study.  
22  
23  
24  
25  
26  
27

#### 28 Sample size calculations and statistical analysis

##### 29 **Sample size estimation**

30  
31 According to our data of the Centre, the ongoing pregnancy rate per FET was  
32 about 30%. We hypothesize that a difference in the ongoing pregnancy rate of  
33 10% between the immediate versus delayed groups as equivalence, the  
34 sample size required for a test of equivalence would be 329 in each arm to  
35 give a power of 0.8 and type I error of 0.05. Allowing 10% drop-out, 724  
36 subjects or 362 in each arm will be needed.  
37  
38  
39  
40  
41  
42

##### 43 **Data analysis**

44 Data will be analysed with an intention to treat and per protocol. Demographic  
45 features of the two groups will be compared. Comparison of quantitative  
46 variables will be performed using Student's t, while categorical variables will be  
47 compared using a Chi-square analysis. A multivariable logistic regression  
48 analysis will be used to compare the variables between two groups. All  
49 statistical analyses of the data will be performed using the SPSS program  
50 V.21.0 (SPSS Inc, Chicago, Illinois, USA), and a p value <0.05 will be  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 considered statistically significant.  
4  
5

## 6 **ETHICS AND DISSEMINATION**

7  
8 FET in HRT cycles is a standard procedure in IVF centers. The women who  
9 agree to participate in the study will sign a consent form after detailed  
10 counseling of the study and they are free to withdraw from the study at any  
11 time without giving any reasons and having any impact on the medical care  
12 they are receiving.  
13  
14  
15

16  
17  
18 Data will be entered electronically. All data will be stored in locked computer  
19 files that are accessible only to the investigators and research staffs involved  
20 in the study. Original study forms will be kept locked at the study site and  
21 maintained in storage for a period of 3 years after the completion of the study.  
22  
23 The principal investigator will be responsible for data management including  
24 data coding, monitoring and verification. The investigators have always  
25 maintained a strict privacy policy. The investigators permit trial-related  
26 monitoring, audits, IRB/IEC review and regulatory inspections, providing direct  
27 access to source data/documents. For questions about the study, the  
28 participants should contact their physician.  
29  
30  
31  
32  
33  
34  
35

36  
37 A data and safety monitoring committee will review and interpret the data  
38 generated from the study, and its primary objectives will be to ensure the  
39 safety of the study participants and the integrity of the research data. The  
40 committee consists of two independent researchers with experience in  
41 reproductive medicine.  
42  
43  
44  
45

46  
47 The results of this trial will be disseminated in peer-reviewed journals and  
48 presented at international meetings.  
49  
50

## 51 **DISCUSSION**

52  
53 FET has been a routine procedure in the IVF treatment,[11,12] but the optimal  
54 time for FET following ovarian stimulation is still unknown. This randomized  
55 study has been designed, therefore, to evaluate ongoing pregnancy rate of  
56  
57  
58  
59  
60

1  
2  
3 immediate versus delayed FET following a stimulated IVF cycle. It seeks to  
4 add significantly to the clinical evidence base and to allow conclusions to be  
5 made on the time interval in the FET following a stimulated IVF cycle. The  
6 present study is the first RCT to compare immediate versus delayed FET  
7 followed stimulated IVF cycle on ongoing pregnancy rate.  
8  
9  
10  
11  
12

13 In order to increase the generalizability of our results, we include both patients  
14 having the first FET cycle after a failed stimulated IVF cycle or undertaking the  
15 freeze all strategy.  
16  
17  
18

19 The study was designed in May 2017, and the first participant was randomised  
20 on 9 August 2017. At the time of the manuscript preparation, we have recruited  
21 200 women and the recruitment is ongoing.  
22  
23  
24  
25  
26

27 **Authors' contributions:** HL, XXS and EHYN conceived and designed the  
28 study. HL and EHYN drafted and critically revised the manuscript for important  
29 intellectual content. XXS sought ethical approval. LL and XL participated in the  
30 coordination of the study and recruitment of subjects. All the authors  
31 contributed to the further writing of the manuscript and approved the final  
32 manuscript.  
33  
34  
35  
36

37 **Funding statement:** This research received no specific grant from any  
38 funding agency in the public, commercial or not-for-profit sectors.  
39

40 **Competing interests :** None declared.  
41

42 **Patient consent:** Obtained.  
43

44 **Ethics approval:** Approval was obtained from the Ethics Committee of  
45 assisted reproductive medicine in Shanghai JiAi Genetics and IVF institute  
46 (JIAI E2017-12).  
47

48 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

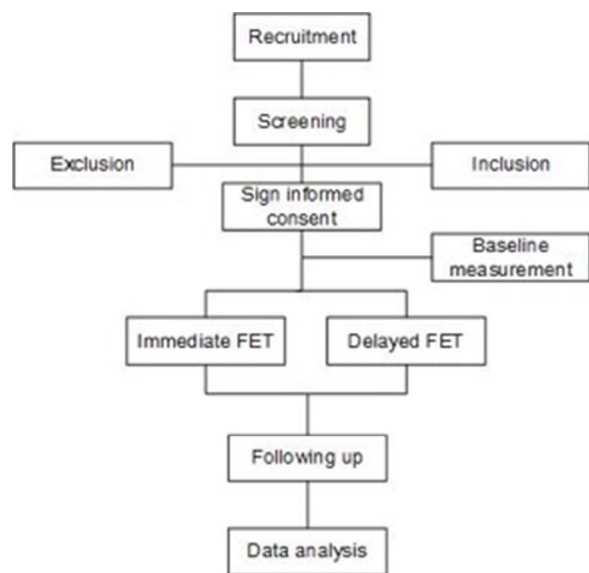
## **References:**

1. Doody KJ. Cryopreservation and delayed embryo transfer-assisted reproductive technology registry and reporting implications. *Fertil Steril* 2014;102(1):27-31.
2. Shapiro BS, Daneshmand ST, Garner FC, et al. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011;96(2):344-8.
3. Venetis CA, Kolibianakis EM, Bosdou JK, et al. Estimating the net effect of progesterone elevation on the day of hCG on live birth rates after IVF: a cohort analysis of 3296 IVF cycles. *Hum Reprod* 2015;30(3):684-91.
4. Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh embryos: the translational rationale. *Fertil Steril* 2014;102(1):10-8.
5. Roque M, Valle M, Guimaraes F, et al. Freeze-all policy: fresh vs. frozen-thawed embryo transfer. *Fertil Steril* 2015;103(5):1190-3.
6. Blockeel C, Drakopoulos P, Santos-Ribeiro S, et al. A fresh look at the freeze-all protocol: a SWOT analysis. *Hum Reprod* 2016;31(3):491-7.
7. Santos-Ribeiro S, Polyzos NP, Lan VT, et al. The effect of an immediate frozen embryo transfer following a freeze-all protocol: a retrospective analysis from two centres. *Hum Reprod* 2016;31(11):2541-48.
8. Santos-Ribeiro S, Siffain J, Polyzos NP, et al. To delay or not to delay a frozen embryo transfer after a failed fresh embryo transfer attempt? *Fertil Steril* 2016;105(5):1202-07 e1.
9. Lattes K, Checa MA, Vassena R, et al. There is no evidence that the time from egg retrieval to embryo transfer affects live birth rates in a freeze-all strategy. *Hum Reprod* 2017;32(2):368-74.
10. Volodarsky-Perel A, Eldar-Geva T, Holzer HE, et al. Cryopreserved embryo transfer: adjacent or non-adjacent to failed fresh long GnRH-agonist protocol IVF cycle. *Reprod Biomed Online* 2017;34(3):267-73.
11. Cedars MI. Fresh versus frozen: initial transfer or cumulative cycle results: how do we interpret results and design studies? *Fertil Steril* 2016;106(2):251-6.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

12. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. *Fertil Steril* 2014;102(1):19-26.

For peer review only



Study design (figure 1)

102x99mm (72 x 72 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title <b>P1</b>	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration <b>P2</b>	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding <b>P9</b>	4	Sources and types of financial, material, and other support
Roles and responsibilities <b>P9</b>	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale <b>P3-4</b>	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives <b>P4</b>	7	Specific objectives or hypotheses
Trial design <b>P4</b>	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

## Methods: Participants, interventions, and outcomes

Study setting	P4	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	P4-5	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	P5-6	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	P6-7	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	P4-6	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	P7	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment		15	Strategies for achieving adequate participant enrolment to reach target sample size

## Methods: Assignment of interventions (for controlled trials)

### Allocation:

Sequence generation	P5	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
---------------------	----	-----	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------



1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking) P5		participants, care providers, outcome assessors, data analysts), and
12			how
13			
14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial
17			

### 18 **Methods: Data collection, management, and analysis**

19			
20	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
21	methods P6-7		trial data, including any related processes to promote data quality (eg,
22			duplicate measurements, training of assessors) and a description of
23			study instruments (eg, questionnaires, laboratory tests) along with
24			their reliability and validity, if known. Reference to where data
25			collection forms can be found, if not in the protocol
26			
27			
28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols
31			
32	Data	19	Plans for data entry, coding, security, and storage, including any
33	management P7-		related processes to promote data quality (eg, double data entry;
34	8		range checks for data values). Reference to where details of data
35			management procedures can be found, if not in the protocol
36			
37	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
38	methods P7		Reference to where other details of the statistical analysis plan can be
39			found, if not in the protocol
40			
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses)
44			
45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation)
48			

### 49 **Methods: Monitoring**

50			
51	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
52	P8		and reporting structure; statement of whether it is independent from
53			the sponsor and competing interests; and reference to where further
54			details about its charter can be found, if not in the protocol.
55			Alternatively, an explanation of why a DMC is not needed
56			
57			
58			
59			
60			

1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
2			
3			
4			
5			
6	Harms P8	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
7			
8			
9			
10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
11			
12			
13			

### Ethics and dissemination

14			
15			
16	Research ethics approval P9	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
17			
18			
19	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
20			
21			
22			
23			
24	Consent or assent P8	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
25			
26			
27			
28		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
29			
30			
31	Confidentiality P8	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
32			
33			
34			
35	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
36			
37			
38	Access to data P8	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
39			
40			
41			
42	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
43			
44			
45	Dissemination policy P8	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
46			
47			
48			
49			
50			
51		31b	Authorship eligibility guidelines and any intended use of professional writers
52			
53			
54		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
55			
56			
57			
58			
59			
60			

**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

---

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

# BMJ Open

**Comparison of the effect of immediate versus delayed transfer following a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed embryo transfer cycles: a study protocol for a randomised controlled trial.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020507.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Jan-2018
Complete List of Authors:	LI, HE LI, LU; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China LU, XIANG; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China SUN, XIAOXI; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China; Key Laboratory of Female Reproductive Endocrine Related Diseases, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China Ng, Ernest; The University of Hong Kong, Department of Obstetrics and Gynecology
<b>Primary Subject Heading</b>:	Reproductive medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Subfertility < GYNAECOLOGY, IVF, FET, ART

SCHOLARONE™  
Manuscripts

1  
2  
3 **1 Comparison of the effect of immediate versus delayed transfer following**  
4 **2 a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed**  
5 **3 embryo transfer cycles: a study protocol for a randomised controlled**  
6 **4 trial.**  
7  
8  
9  
10

11 6 Authors and affiliations

12 7 He Li<sup>1</sup>, Lu Li<sup>1</sup>, Xiang Lu<sup>1</sup>, Xiaoxi Sun<sup>1,2\*</sup>, Ernest Hung Yu Ng<sup>3\*</sup>

13 8 1. Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology  
14 9 Hospital, Fudan University, Shanghai, China

15 10 2. Key Laboratory of Female Reproductive Endocrine Related Diseases,  
16 11 Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China

17 12 3. Department of Obstetrics and Gynaecology, The University of Hong Kong,  
18 13 Hong Kong Special Administrative Region, Hong Kong, Hong Kong

19 14 \* Corresponding authors: Email: [nghye@hku.hk](mailto:nghye@hku.hk) (EHY Ng) or: Email:  
20 15 [xiaoxi\\_sun@aliyun.com](mailto:xiaoxi_sun@aliyun.com) (X Sun)  
21 16

**ABSTRACT**

Introduction: Frozen-thawed embryo transfer (FET) has become an increasingly important part of in vitro fertilization (IVF) treatment. Currently, there is still no good scientific evidence to support when to perform FET following a stimulated IVF cycle. Since all published studies are retrospective and the findings are contradictory, a randomized controlled study is needed to provide Level 1 evidence to guide the clinical practice.

Methods/analysis: This is a randomized controlled trial. A total of 724 women undergoing the first FET following ovarian stimulation in IVF will be enrolled and randomized according to a computer-generated randomization list to either (1) the immediate group in which FET will be performed in the first cycle following the stimulated IVF cycle or (2) the delayed group in which FET will be performed at least in the second cycle following the stimulated IVF cycle. The primary outcome is the ongoing pregnancy defined as a viable pregnancy beyond 12 weeks gestation.

Ethics/dissemination: An ethical approval has been granted from the ethics committee of assisted reproductive medicine in Shanghai JiAi Genetics and IVF institute (JIAI E2017-12). A written informed consent will be obtained from each woman before any study procedure is performed, according to good clinical practice. The results of this trial will be disseminated in a peer-reviewed journal.

Trial registration numbers: NCT03201783

### Strengths and limitations of this study

1. This is the first randomised controlled trial comparing the ongoing pregnancy rate of immediate versus delayed FET following a stimulated IVF cycle.
2. This is the first trial that seeks to add significantly to the clinical evidence base and to allow conclusions to be made on the time interval in the FET following a stimulated IVF cycle.
3. The study includes women aged 20–43 years undergoing the first FET after GnRH agonist and GnRH antagonist ovarian stimulation in IVF/ICSI; thus, results can be extrapolated to the majority of the infertile population.
4. The researchers, doctors and the participants cannot be blinded to treatment allocation.

### BACKGROUND

Frozen-thawed embryo transfer (FET) has become an increasingly important part of in-vitro fertilisation (IVF) treatment.[1] When women fail to get pregnant after replacing embryos in the stimulated IVF cycle, many of those who have frozen embryos would like to proceed FET as soon as possible in order to get pregnant as soon as possible.

Ovarian stimulation exerts a detrimental effect on endometrial receptivity.[2] Ovarian stimulation leads to supraphysiological hormonal concentrations in blood which may exert negative influence on perinatal and neonatal outcomes.[3-5] The freeze-all strategy has drawn attention in recent literature with the advantages of increased maternal safety, improved pregnancy rates, lower ectopic pregnancy rates and better obstetric and neonatal outcomes.[6] The better outcomes after elective FET in the context of a freeze-all strategy may be at least partially attributed to the lack of endometrial impairment that is observed during ovarian stimulation.

1  
2  
3 76 Robust information regarding the optimal timing for FET following a stimulated  
4 77 IVF cycle is still lacking. One option is to perform FET in the first cycle  
5  
6 78 following the stimulated IVF cycle i.e. immediate transfer. Another option is to  
7  
8 79 postpone FET for at least one menstrual cycle i.e. delayed transfer. Delaying  
9  
10 80 FET may add to the stress and anxiety accompanying the IVF treatment.  
11  
12 81 Several retrospective studies showed similar clinical pregnancy rates or live  
13 82 birth rates between immediate and delayed FET performed following fresh  
14 83 embryo transfers or in a frozen-all policy.[7-9] Another retrospective analysis  
15 84 showed that significantly higher implantation, clinical pregnancy and live birth  
16 85 rates were found in the delayed FET group than in the immediate group after  
17 86 failed fresh ET cycles.[10] Since these studies are all retrospective and the  
18 87 findings are contradictory, a randomized study is needed to provide Level 1  
19 88 evidence to guide the clinical practice.  
20  
21  
22  
23  
24  
25

26 90 We aim in this randomized trial to compare the ongoing pregnancy rate of  
27 91 immediate versus delayed FET following a stimulated IVF cycle. The  
28 92 hypothesis is that the ongoing pregnancy rates of immediate and delayed FET  
29 93 are comparable.  
30  
31  
32

33 94

## 34 95 **MATERIALS AND METHODS**

### 35 96 Study design

36  
37  
38 97 This is a multi-center randomized controlled study carried out in the Shanghai  
39 98 JiAi Genetics and IVF institute and Department of Obstetrics and Gynaecology,  
40 99 the University of Hong Kong. The trial has been registered at ClinicalTrials.gov  
41 100 (NCT03201783). The flow chart of this study is shown in figure 1 and the  
42 101 overview of the study visits is shown in table 1.  
43  
44  
45  
46

47 102

48 103

49 104

50 105

51 106

52 107



108 Table 1 Overview of study visits

	Screen and Baseline visit	Treatment visit	Pregnancy visit	Follow up visit
Physical examination (weight, height)	√			
Menstrual cycle	√			
Fasting blood samples for E2, P,		√		
Preconception counseling	√			
Questionnaire	√	√		
Transvaginal ultrasound	√	√	√	√
Pregnancy test			√	√
Pregnancy and neonatal records				√

109 E2, estradiol; P, progesterone.

110

111

112 Participants

113 The study participants will consist of women and their partners initiating ART

114 treatment at the Shanghai JiAi Genetics and IVF institute in China and

115 Department of Obstetrics and Gynaecology, the University of Hong Kong.

116 Recruitment will be carried out by the doctors at the fertility clinics. Eligible

117 women will be recruited if they fulfil all of the inclusion criteria and do not meet

118 any of the exclusion criteria. They will be included once for this study. Informed

119 written consent will be obtained.

120

121 Inclusion criteria are:

122 • Women aged  $\leq 43$  years at the time of IVF/ICSI treatment

123 • Undergoing IVF with a standard stimulation

124 • At least one frozen embryo or blastocyst

125 • The first FET cycle following ovarian stimulation in IVF

126 Exclusion criteria include

127 • Use of mild stimulation or natural cycle for IVF/ICSI treatment

128 • Severe ovarian hyperstimulation syndrome during IVF treatment

129 • Preimplantation genetic diagnosis treatment

- 1  
2  
3 130 • Use of donor oocytes  
4  
5 131 • Presence of hydrosalpinx which is not surgically treated or endometrial  
6  
7 132 polyp on scanning during ovarian stimulation

8 133 Standard and mild stimulation is defined according to the published  
9  
10 134 terminology for ovarian stimulation for IVF.[11] OHSS is diagnosed and  
11  
12 135 classified according to the RCOJ guideline.[12]

13  
14  
15 136

16  
17 137

### 138 Randomization

139 Women having the first FET cycle after a failed stimulated IVF cycle or  
140 undertaking the freeze all strategy will be randomized according to a  
141 computer-generated randomization list prepared by a study nurse who will not  
142 be involved in the recruitment into one of the following two groups. The exact  
143 timing of randomization is on the day of embryo freezing for patients taking the  
144 freeze all strategy and on the day of blood HCG test on 14 days after fresh-ET  
145 for the failed fresh-ET women. The randomization is carried out by a project  
146 nurse who is not involved in the recruitment and clinical management of  
147 patients using an online randomization program through the website  
148 www.randomization.com. Then the nurse will prepare the randomization arm  
149 and put it into opaque envelopes for use. On the randomization day, the  
150 recruited women will be randomized according to the opaque envelopes into  
151 one of the two groups

152 (1) the immediate group in which FET will be performed in the first cycle  
153 following the stimulated IVF cycle and

154 (2) the delayed group in which FET will be performed at least in the second  
155 cycle following the stimulated IVF cycle.

156

### 157 Blinding

158 Both the researchers and the participants cannot be blinded because the  
159 nature of the study. The embryologist performing the quality assessment is  
160 blinded to the allocated treatment.

161

### 162 Interventions

1  
2  
3 163 Women will undergo IVF treatment in the centre as clinically indicated.  
4 164 Standard ovarian stimulation with gonadotrophins in either a GnRH antagonist  
5 165 protocol or long GnRH agonist will be employed.  
6  
7  
8 166 Oocyte retrieval will be performed under transvaginal ultrasound guidance 34–  
9 167 36h after triggering with hCG or an agonist. Oocytes will be fertilized using  
10 168 either conventional insemination or intracytoplasmic sperm injection  
11 169 depending the semen quality of the husbands in accordance with the standard  
12 170 protocol. Normal fertilization will be assessed and confirmed by the presence  
13 171 of two pronuclei and a second polar body at 16–18 h after insemination or  
14 172 intracytoplasmic sperm injection. On day 3 after egg retrieval, an embryo with  
15 173 at least seven blastomeres and Grades 1 and 2 is defined as good quality.  
16 174 Embryos with at least six blastomeres and fragments <50% will be frozen. All  
17 175 good embryos will be frozen or vitrified using the Crytop method as cleavage  
18 176 stage embryos on Day 3 or as full to expanded blastocysts on Day 5 or Day 6  
19 177 of embryo culture according to the standard protocol. Patients ≥6 good quality  
20 178 embryos of on day 3 were eligible for a blastocyst culture and transfer.  
21 179 We will measure the stress and anxiety levels by the standard questionnaire  
22 180 before the randomization and at the time of starting FET. Chinese State-Trait  
23 181 Anxiety Inventory (C-STAI). The C-STAI was used to measure the patient's  
24 182 anxiety level.[13]  
25  
26 183 Hormone replacement treatment (HRT) will be used for endometrial  
27 184 preparation. On Day 3 of the menstrual cycle, estradiol valerate (E2,  
28 185 Progynova, Schering AG, Berlin, Germany) will be commenced 4mg daily for  
29 186 10 days. When the thickness of the endometrial layer reaches at least 8 mm  
30 187 on pelvic scanning, vaginal progesterone 90 mg per day (Crinone,  
31 188 Merck-Serono, Switzerland) will be administered. For Day 3 embryos, FET is  
32 189 scheduled on the fourth day of starting vaginal progesterone. For blastocysts,  
33 190 FET is scheduled on the sixth day of starting vaginal progesterone. A  
34 191 maximum of 1–2 embryos or blastocysts with the best morphology will be  
35 192 transferred under ultrasound guidance using a soft embryo transfer catheter.  
36 193 Serum hCG level will be checked 14 days after FET. All hormone therapy will  
37 194 be stopped if the serum hCG level is negative. All pregnant women will  
38 195 continue the hormonal therapy until 12 weeks of gestation.

1  
2  
3 196

4 197 Follow-up and data collection

5 198 If the serum hCG level is positive, transvaginal ultrasound will be performed

6 199 two weeks later to locate the pregnancy and confirm foetal viability.

7 200 Subsequent management will be the same as other women with early

8 201 pregnancy. They will be referred for antenatal care when the ongoing

9 202 pregnancy is 12 weeks.

10 203

11 204 Written consent regarding retrieval of pregnancy and delivery data will be

12 205 sought from the patient at the time of study. The patient will be contacted after

13 206 delivery by phone to retrieve the information of the pregnancy outcomes. The

14 207 outcome of the pregnancy (delivery, miscarriage), number of babies born, birth

15 208 weights and obstetrics complications will be recorded.

16 209

17 210 Outcome measurements

18 211 Primary outcome

19 212 The primary outcome is an ongoing pregnancy defined as a viable pregnancy

20 213 beyond gestation 12 weeks.

21 214

22 215 Secondary outcomes include

23 216 - positive hCG level: Conception is defined with the result of serum  $\beta$ -hCG  
24 217  $\geq 10$  mIU/mL.

25 218 - clinical pregnancy defined as presence of intrauterine gestational sac by  
26 219 transvaginal ultrasound at gestational week 6.

27 220 - implantation rate as the number of gestational sacs per embryo transferred.

28 221 - multiple pregnancy, ectopic pregnancy and miscarriage rates. Miscarriage  
29 222 rate is defined as a clinically recognized pregnancy loss before the 22  
30 223 weeks of pregnancy. The denominator is the clinical pregnancy.

31 224 - live birth rate and: A live birth is defined as the delivery of any number of  
32 225 newborns  $\geq 22$  weeks' gestation with heartbeat and breath.

33 226 - birth weight of newborns.

34 227

35 228 Data entry and quality control of data

1  
2  
3 229 Treatment-related data including baseline information and COH data are  
4 230 collected at the day of embryo frozen. Data on FET cycle are collected at  
5 231 frozen embryo transfer day. Follow-up data on all pregnancies resulting from  
6 232 FET according to the study protocol will be followed from study inclusion and 1  
7 233 year onwards. Participants information forms will be developed for data entry,  
8 234 and quality control of the data will be handled at two different levels. The  
9 235 investigators will be required to ensure the accuracy of the data as the first  
10 236 level of control, and the second level will include data monitoring and validation  
11 237 that will be carried out on a regular basis through out the study. Data are  
12 238 backed up daily to another computer in the same physical location as the  
13 239 server.

14  
15  
16  
17  
18  
19  
20  
21  
22  
23 240

24 241 Sample size calculations and statistical analysis

25 242 **Sample size estimation**

26 243 According to our data of the Centre, the ongoing pregnancy rate per FET was  
27 244 about 30%. We hypothesize that a difference in the ongoing pregnancy rate of  
28 245 10% between the immediate versus delayed groups as equivalence, the  
29 246 sample size required for a test of equivalence would be 329 in each arm to  
30 247 give a power of 0.8 and type I error of 0.05. Allowing 10% drop-out, 724  
31 248 subjects or 362 in each arm will be needed.

32  
33  
34  
35  
36  
37  
38 249

39 250 **Data analysis**

40 251 Data will be analysed with an intention to treat and per protocol. Demographic  
41 252 features of the two groups will be compared. Comparison of quantitative  
42 253 variables will be performed using Student's t, while categorical variables will be  
43 254 compared using a Chi-square analysis. A multivariable logistic regression  
44 255 analysis will be used to compare the variables between two groups. We use  
45 256 the multivariable logistic regression to adjust for potentially confounding  
46 257 factors and results, namely female age (as a continuous variable), retrieved  
47 258 oocytes, COH protocol, ovulation trigger, number of good quality embryos  
48 259 produced (as a continuous variable) and number of embryos transferred (one  
49 260 versus two), developmental stage (cleavage versus blastocyst stage) and  
50 261 quality of the embryos transferred (quality of the embryo transferred). All

1  
2  
3 262 statistical analyses of the data will be performed using the SPSS program  
4 263 V.21.0 (SPSS Inc, Chicago, Illinois, USA), and a p value <0.05 will be  
5  
6 264 considered statistically significant.  
7

8 265

## 9 266 **ETHICS AND DISSEMINATION**

10  
11 267 Since FET in HRT cycles is a standard procedure in IVF centers, and there is  
12 268 no agreement regarding the time interval between the stimulated IVF and the  
13 269 subsequent FET in the literature, there are not predefined criteria for  
14  
15 270 premature termination of the study. There is no interim analysis during the  
16  
17 271 study.

18  
19 272 The women who agree to participate in the study will sign a consent form (see  
20 273 online supplementary appendix 1) after detailed counseling of the study and  
21 274 they are free to withdraw from the study at any time without giving any reasons  
22  
23 275 and having any impact on the medical care they are receiving.  
24  
25 276

26  
27  
28 277 Data will be entered electronically. All data will be stored in locked computer  
29 278 files that are accessible only to the investigators and research staffs involved  
30 279 in the study. Original study forms will be kept locked at the study site and  
31 280 maintained in storage for a period of 3 years after the completion of the study.

32  
33 281 The principal investigator will be responsible for data management including  
34 282 data coding, monitoring and verification. The investigators have always  
35 283 maintained a strict privacy policy. The investigators permit trial-related  
36 284 monitoring, audits, IRB/IEC review and regulatory inspections, providing direct  
37 285 access to source data/documents. For questions about the study, the  
38 286 participants should contact their physician.  
39  
40 287

41  
42 288 A data and safety monitoring committee will review and interpret the data  
43 289 generated from the study, and its primary objectives will be to ensure the  
44 290 safety of the study participants and the integrity of the research data. The  
45 291 committee consists of two independent researchers with experience in  
46 292 reproductive medicine.  
47  
48 293

49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 294 An audit trail will be designed as another security measure.  
4  
5 295 Computer-generated and time-stamped audit trails will be implemented for  
6  
7 296 tracking changes in the electronic source documentation. Internal safeguards  
8  
9 297 will be built into the computerised system. Records will be regularly backed up,  
10  
11 298 and record logs will be maintained to prevent data loss and to ensure the  
12  
13 299 data's quality and integrity.

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

300  
301 Amendments of the protocol will be agreed on by the IRB/IEC, data and safety  
302 monitoring committee and will be approved by the ethics committee prior to  
303 implementation.

304

305 The results of this trial will be disseminated in peer-reviewed journals and  
306 presented at international meetings.

307

## 308 **DISCUSSION**

309 FET has been a routine procedure in the IVF treatment,[14,15] but the optimal  
310 time for FET following ovarian stimulation is still unknown. This randomized  
311 study has been designed, therefore, to evaluate ongoing pregnancy rate of  
312 immediate versus delayed FET following a stimulated IVF cycle. It seeks to  
313 add significantly to the clinical evidence base and to allow conclusions to be  
314 made on the time interval in the FET following a stimulated IVF cycle. The  
315 present study is the first RCT to compare immediate versus delayed FET  
316 followed stimulated IVF cycle on ongoing pregnancy rate.

317

318 In order to increase the generalizability of our results, we include both patients  
319 having the first FET cycle after a failed stimulated IVF cycle or undertaking the  
320 freeze all strategy.

321

322 The study was designed in May 2017, and the first participant was randomised  
323 on 9 August 2017. At the time of the manuscript preparation, we have recruited  
324 200 women and the recruitment is ongoing.

325

1  
2  
3 326 **Authors' contributions:** HL, XXS and EHYN conceived and designed the  
4 327 study. HL and EHYN drafted and critically revised the manuscript for important  
5 328 intellectual content. XXS sought ethical approval. LL and XL participated in the  
6 329 coordination of the study and recruitment of subjects. All the authors  
7 330 contributed to the further writing of the manuscript and approved the final  
8 331 manuscript.

9 332 **Funding statement:** This research received no specific grant from any  
10 333 funding agency in the public, commercial or not-for-profit sectors.

11 334 **Competing interests :** None declared.

12 335 **Patient consent:** Obtained.

13 336 **Ethics approval:** Approval was obtained from the Ethics Committee of  
14 337 assisted reproductive medicine in Shanghai JiAi Genetics and IVF institute  
15 338 (JIAI E2017-12).

16 339 **Provenance and peer review:** Not commissioned; externally peer reviewed.

17 340

18 341

19 342

20 343

21 344

22 345

23 346

24 347

25 348

26 349

27 350

28 351

29 352

30 353

31 354

32 355

33 356

34 357

35 358



1  
2  
3 359 **References:**

- 4 360 1. Doody KJ. Cryopreservation and delayed embryo transfer-assisted  
5 361 reproductive technology registry and reporting implications. *Fertil Steril*  
6 362 2014;102(1):27-31.  
7  
8 363 2. Shapiro BS, Daneshmand ST, Garner FC, et al. Evidence of impaired  
9 364 endometrial receptivity after ovarian stimulation for in vitro fertilization: a  
10 365 prospective randomized trial comparing fresh and frozen-thawed embryo  
11 366 transfer in normal responders. *Fertil Steril* 2011;96(2):344-8.  
12  
13 367 3. Venetis CA, Kolibianakis EM, Bosdou JK, et al. Estimating the net effect of  
14 368 progesterone elevation on the day of hCG on live birth rates after IVF: a cohort  
15 369 analysis of 3296 IVF cycles. *Hum Reprod* 2015;30(3):684-91.  
16  
17 370 4. Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh  
18 371 embryos: the translational rationale. *Fertil Steril* 2014;102(1):10-8.  
19  
20 372 5. Roque M, Valle M, Guimaraes F, et al. Freeze-all policy: fresh vs.  
21 373 frozen-thawed embryo transfer. *Fertil Steril* 2015;103(5):1190-3.  
22  
23 374 6. Blockeel C, Drakopoulos P, Santos-Ribeiro S, et al. A fresh look at the  
24 375 freeze-all protocol: a SWOT analysis. *Hum Reprod* 2016;31(3):491-7.  
25  
26 376 7. Santos-Ribeiro S, Polyzos NP, Lan VT, et al. The effect of an immediate  
27 377 frozen embryo transfer following a freeze-all protocol: a retrospective analysis  
28 378 from two centres. *Hum Reprod* 2016;31(11):2541-48.  
29  
30 379 8. Santos-Ribeiro S, Siffain J, Polyzos NP, et al. To delay or not to delay a  
31 380 frozen embryo transfer after a failed fresh embryo transfer attempt? *Fertil Steril*  
32 381 2016;105(5):1202-07 e1.  
33  
34 382 9. Lattes K, Checa MA, Vassena R, et al. There is no evidence that the time  
35 383 from egg retrieval to embryo transfer affects live birth rates in a freeze-all  
36 384 strategy. *Hum Reprod* 2017;32(2):368-74.  
37  
38 385 10. Volodarsky-Perel A, Eldar-Geva T, Holzer HE, et al. Cryopreserved  
39 386 embryo transfer: adjacent or non-adjacent to failed fresh long GnRH-agonist  
40 387 protocol IVF cycle. *Reprod Biomed Online* 2017;34(3):267-73.  
41  
42 388 11. Nargund G, Fauser BC, Macklon NS, et al. The ISMAAR proposal on  
43 389 terminology for ovarian stimulation for IVF. *Hum Reprod* 2007;22(11):2801-4.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59

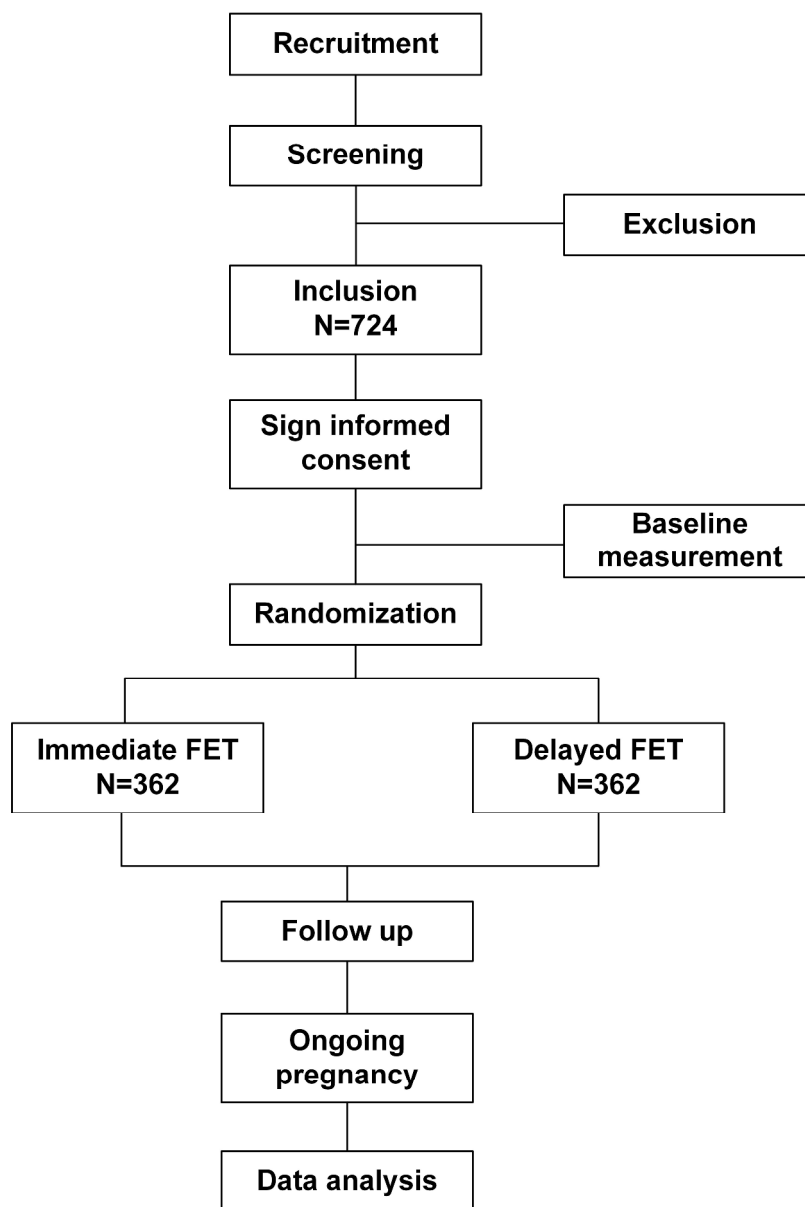
- 1  
2  
3 390 12. Green-top guideline No.5: Ovarian Hyperstimulation Syndrome,  
4 391 <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg5/>. (26  
5 392 February 2015, date last accessed).  
6  
7  
8 393 13. Shek DTL. The Factorial Structure of the Chinese Version of the  
9 394 State-Trait Anxiety Inventory: A Confirmatory Factor Analysis. *Educational &*  
10 395 *Psychological Measurement* 1991;51(4):985-97.  
11  
12 396 14. Cedars MI. Fresh versus frozen: initial transfer or cumulative cycle results:  
13 397 how do we interpret results and design studies? *Fertil Steril*  
14 398 2016;106(2):251-6.  
15  
16 399 15. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human  
17 400 embryos and its contribution to in vitro fertilization success rates. *Fertil Steril*  
18 401 2014;102(1):19-26.  
19  
20 402  
21 403  
22 404  
23 405  
24 406  
25 407  
26 408  
27 409  
28 410  
29 411  
30 412  
31 413  
32 414  
33 415  
34 416  
35 417  
36 418  
37 419  
38 420  
39 421  
40 422

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

423 **Figure 1**

424 The study flow chart. FET, frozen-thawed embryo transfer.

For peer review only



Flow chart of study

178x266mm (600 x 600 DPI)

**Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

**PATIENT INFORMATION AND CONSENT**

**STUDY TITLE:** A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

You are being invited to participate in the above named research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the purpose of the study?**

Information regarding the optimal timing for frozen-thawed embryo transfer (FET) following a stimulated in vitro fertilization (IVF) is lacking. One option is to perform FET in the first cycle following the stimulated IVF cycle, i.e. immediate transfer. Another option is to postpone FET for at least one menstrual cycle, i.e. delayed transfer.

Several retrospective studies showed similar success for these two options. Another retrospective analysis showed higher clinical pregnancy and live birth rates in the delayed group. Since these studies are all retrospective and the findings are contradictory, a randomized study is needed to provide good evidence to guide the clinical practice.

This randomized study aims to compare the ongoing pregnancy rate of immediate versus delayed FET following a stimulated IVF cycle.

**Why have I been chosen?**

You are chosen because

- You are  $\leq 43$  years of age at the time of IVF treatment.
- You underwent IVF with a standard stimulation.
- You have at least one frozen embryo or blastocyst.
- You are undergoing the first FET following ovarian stimulation in IVF.

You will not be included in this study if

- You are using mild stimulation or natural cycle in the IVF treatment.
- You had severe ovarian hyperstimulation syndrome during IVF treatment.
- You had pre-implantation genetic diagnosis treatment.
- You are using donor oocytes.

## **Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

- Presence of hydrosalpinx which is not surgically treated or endometrial polyp on scanning during ovarian stimulation.

### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you do not join or if you quit the study, you will still receive the standard treatment as other patients in our Department.

### **What will happen to me if I take part?**

If you agree to participate in the study, you will be randomized by a computer-generated list into one of the two groups:

(1) **Immediate group:** Your thawed embryos will be transferred into your womb in the first cycle following the stimulated IVF cycle.

(2) **Delayed group:** Your thawed embryos will be transferred into your womb at least in the second cycle following the stimulated IVF cycle.

The groups are selected by a computer that has no information about the individual, i.e. by chance. We will compare the outcomes between the two groups at the end of the study.

### **How many other people will be participating in the study?**

We plan to recruit 724 women in this study.

### **What are the disadvantages and risks of taking part?**

There should be no safety concern. No specific risk is expected. No extra charge or visit is required for participating in the study.

### **What are the benefits of taking part?**

No payment will be made to you for this study.

### **What will happen to the results of the research?**

The results of the study will be presented in international meetings and published in a medical journal. You will not be identified in any report or publication.

## **Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

### **Confidentiality and privacy**

The investigators have always maintained a strict privacy policy. We never sell, trade or otherwise share your details with any sources. All correspondence to the department is held confidentially; furthermore, at no time will your personal and/or identifying information be shared outside of our organization, for any reason.

You have the rights of access to personal data and publicly available study results, if and when needed. Under the laws of China, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of China, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study.

By consenting to participate in this study, you expressly authorize:

- the principal investigator, the research team and the Institutional Review Board responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process; and
- the relevant government agencies (e.g. the Shanghai Municipal Commission of Health and Family Planning) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

### **Contact for further information**

For questions about the study or reporting of adverse events, you may contact the Principal Investigator, Dr Li He at telephone no.13817223099. The phone number of Shanghai JIAI Genetics & IVF is 021-63459977.

Thank you for your time to read this information sheet and for taking part in the study.

**Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

**PATIENT CONSENT FORM**

**Patient Identification Number for this trial:** \_\_\_\_\_

**Title of Project: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle**

1. We confirm that we have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. We understand that our participation is voluntary and that we are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected.
3. We understand that sections of any of our medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to our taking part in research. We give permission for these individuals to have access to our records.
4. We agree to take part in the above study.
5. We give permission to the investigators to retrieve pregnancy and delivery data.

\_\_\_\_\_  
Patient's signature

\_\_\_\_\_  
Patient's name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Patient's husband signature

\_\_\_\_\_  
Patient's husband name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator's signature

\_\_\_\_\_  
Investigator's name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness's signature

\_\_\_\_\_  
Witness's name

\_\_\_\_\_  
Date





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description
<b>Administrative information</b>		
Title	1 P1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a P4	Trial identifier and registry name. If not yet registered, name of intended registry
	2b n/a	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 n/a	Date and version identifier
Funding	4 P12	Sources and types of financial, material, and other support
Roles and responsibilities	5a P12	Names, affiliations, and roles of protocol contributors
	5b n/a	Name and contact information for the trial sponsor
	5c n/a	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d P12	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	6a P3-4	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b P3-4	Explanation for choice of comparators
Objectives	7 P4	Specific objectives or hypotheses

1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

Trial design	8 P4	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
<b>Methods: Participants, interventions, and outcomes</b>		
Study setting	9 P4	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10 P5-6	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a P6-7	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b P10	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c P6-8	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d P6-8	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 P8	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13 P4	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 P9	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 P5	Strategies for achieving adequate participant enrolment to reach target sample size

### Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a P6	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
3	generation		
4			
5			
6			
7			
8			
9	Allocation	16b P6	
10	concealment		
11	mechanism		
12			
13			
14	Implementation	16c P6	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
15			
16			
17	Blinding	17a P6	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
18	(masking)		
19			
20			
21			
22		17b n/a	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
23			
24			
25			

### Methods: Data collection, management, and analysis

26			
27			
28	Data collection	18a P9-11	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
29	methods		
30			
31			
32			
33			
34			
35			
36			
37		18 P9-11	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
38			
39			
40			
41	Data	19 P9-11	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
42	management		
43			
44			
45			
46			
47	Statistical	20a P9-10	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
48	methods		
49			
50			
51			
52		20b P9-10	Methods for any additional analyses (eg, subgroup and adjusted analyses)
53			
54			
55			
56			
57			
58			
59			
60			

1		20c n/a	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1			
2	Ancillary and	30 n/a	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a P11	Plans for investigators and sponsor to communicate trial results
6	policy		to participants, healthcare professionals, the public, and other
7			relevant groups (eg, via publication, reporting in results
8			databases, or other data sharing arrangements), including any
9			publication restrictions
10			
11		31b n/a	Authorship eligibility guidelines and any intended use of
12			professional writers
13			
14		31c	Plans, if any, for granting public access to the full protocol,
15			participant-level dataset, and statistical code
16			Please see the data sharing plan in <a href="http://www.ClinicalTrials.gov">www.ClinicalTrials.gov</a>
17			(NCT03201783)
18			
19			
20	<b>Appendices</b>		
21			
22	Informed consent	32 P10	Model consent form and other related documentation given to
23	materials		participants and authorised surrogates
24			
25	Biological	33 n/a	Plans for collection, laboratory evaluation, and storage of
26	specimens		biological specimens for genetic or molecular analysis in the
27			current trial and for future use in ancillary studies, if applicable
28			

---

29 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
 30 Explanation & Elaboration for important clarification on the items. Amendments to the  
 31 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
 32 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"  
 33 license.  
 34  
 35  
 36  
 37  
 38  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46  
 47  
 48  
 49  
 50  
 51  
 52  
 53  
 54  
 55  
 56  
 57  
 58  
 59  
 60

# BMJ Open

**Comparison of the effect of immediate versus delayed transfer following a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed embryo transfer cycles: a study protocol for a randomised controlled trial.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020507.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Mar-2018
Complete List of Authors:	LI, HE LI, LU; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China LU, XIANG; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China SUN, XIAOXI; Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China; Key Laboratory of Female Reproductive Endocrine Related Diseases, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China Ng, Ernest; The University of Hong Kong, Department of Obstetrics and Gynecology
<b>Primary Subject Heading</b>:	Reproductive medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Subfertility < GYNAECOLOGY, IVF, FET, ART

SCHOLARONE™  
Manuscripts

1  
2  
3 **1 Comparison of the effect of immediate versus delayed transfer following**  
4 **2 a stimulated IVF cycle on the ongoing pregnancy rate of frozen-thawed**  
5 **3 embryo transfer cycles: a study protocol for a randomised controlled**  
6 **4 trial.**  
7  
8  
9  
10

11 6 Authors and affiliations

12 7 He Li<sup>1</sup>, Lu Li<sup>1</sup>, Xiang Lu<sup>1</sup>, Xiaoxi Sun<sup>1,2\*</sup>, Ernest Hung Yu Ng<sup>3\*</sup>

13 8 1. Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology  
14 9 Hospital, Fudan University, Shanghai, China

15 10 2. Key Laboratory of Female Reproductive Endocrine Related Diseases,  
16 11 Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China

17 12 3. Department of Obstetrics and Gynaecology, The University of Hong Kong,  
18 13 Hong Kong Special Administrative Region, Hong Kong, Hong Kong

19 14 \* Corresponding authors: Email: [nghye@hku.hk](mailto:nghye@hku.hk) (EHY Ng) or: Email:  
20 15 [xiaoxi\\_sun@aliyun.com](mailto:xiaoxi_sun@aliyun.com) (X Sun)  
21 16

**ABSTRACT**

Introduction: Frozen-thawed embryo transfer (FET) has become an increasingly important part of in vitro fertilization (IVF) treatment. Currently, there is still no good scientific evidence to support when to perform FET following a stimulated IVF cycle. Since all published studies are retrospective and the findings are contradictory, a randomized controlled study is needed to provide Level 1 evidence to guide the clinical practice.

Methods/analysis: This is a randomized controlled trial. A total of 724 women undergoing the first FET following ovarian stimulation in IVF will be enrolled and randomized according to a computer-generated randomization list to either (1) the immediate group in which FET will be performed in the first cycle following the stimulated IVF cycle or (2) the delayed group in which FET will be performed at least in the second cycle following the stimulated IVF cycle. The primary outcome is the ongoing pregnancy defined as a viable pregnancy beyond 12 weeks gestation.

Ethics/dissemination: Ethical approval has been granted from the ethics committee of assisted reproductive medicine in Shanghai JiAi Genetics and IVF institute (JIAI E2017-12) and from Institutional Review Board of the University of Hong Kong Hospital Authority Hong Kong West Cluster (UW 17-371). A written informed consent will be obtained from each woman before any study procedure is performed, according to good clinical practice. The results of this trial will be disseminated in a peer-reviewed journal.

Trial registration number: NCT03201783



### Strengths and limitations of this study

1. This is the first randomised controlled trial comparing the ongoing pregnancy rate of immediate versus delayed FET following a stimulated IVF cycle.
2. This is the first trial that seeks to add significantly to the clinical evidence base and to allow conclusions to be made on the time interval in the FET following a stimulated IVF cycle.
3. The study includes women aged 20–43 years undergoing the first FET after GnRH agonist and GnRH antagonist ovarian stimulation in IVF/ICSI; thus, results can be extrapolated to the majority of the infertile population.
4. The researchers, doctors and the participants cannot be blinded to treatment allocation.
5. The sample size calculation is based on a difference in the ongoing pregnancy rate of 10% between the immediate versus delayed groups as equivalence and may not be able to detect a smaller difference in the ongoing pregnancy rate.

### BACKGROUND

Frozen-thawed embryo transfer (FET) has become an increasingly important part of in-vitro fertilisation (IVF) treatment.[1] When women fail to get pregnant after replacing embryos in the stimulated IVF cycle, many of those who have frozen embryos would like to proceed FET as soon as possible in order to get pregnant as soon as possible.

Ovarian stimulation exerts a detrimental effect on endometrial receptivity.[2] Ovarian stimulation leads to supraphysiological hormonal concentrations in blood which may exert negative influence on perinatal and neonatal outcomes.[3-5] The freeze-all strategy has drawn attention in recent literature with the advantages of increased maternal safety, improved pregnancy rates, lower ectopic pregnancy rates and better obstetric and neonatal outcomes.[6] The better outcomes after elective FET in the context of a freeze-all strategy

1  
2  
3 76 may be at least partially attributed to the lack of endometrial impairment that is  
4 77 observed during ovarian stimulation.  
5  
6  
7

8 78

9 79 Robust information regarding the optimal timing for FET following a stimulated  
10 80 IVF cycle is still lacking. One option is to perform FET in the first cycle  
11 81 following the stimulated IVF cycle i.e. immediate transfer. Another option is to  
12 82 postpone FET for at least one menstrual cycle i.e. delayed transfer. Delaying  
13 83 FET may add to the stress and anxiety accompanying the IVF treatment.

14 84 Several retrospective studies showed similar clinical pregnancy rates or live  
15 85 birth rates between immediate and delayed FET performed following fresh  
16 86 embryo transfers or in a frozen-all policy.[7-9] Another retrospective analysis  
17 87 showed that significantly higher implantation, clinical pregnancy and live birth  
18 88 rates were found in the delayed FET group than in the immediate group after  
19 89 failed fresh ET cycles.[10] Since these studies are all retrospective and the  
20 90 findings are contradictory, a randomized study is needed to provide Level 1  
21 91 evidence to guide the clinical practice.  
22  
23  
24  
25  
26  
27  
28  
29  
30

31 92

32 93 We aim in this randomized trial to compare the ongoing pregnancy rate of  
33 94 immediate versus delayed FET following a stimulated IVF cycle. The  
34 95 hypothesis is that the ongoing pregnancy rates of immediate and delayed FET  
35 96 are comparable.  
36  
37

38 97

## 39 98 **MATERIALS AND METHODS**

### 40 99 **Study design**

41 100 This is a two center randomized controlled study carried out in the Shanghai  
42 101 JiAi Genetics and IVF institute and Department of Obstetrics and Gynaecology,  
43 102 the University of Hong Kong. The trial has been registered at ClinicalTrials.gov  
44 103 (NCT03201783). The flow chart of this study is shown in figure 1 and the  
45 104 overview of the study visits is shown in table 1.  
46  
47  
48  
49  
50

51 105  
52  
53  
54  
55  
56  
57  
58  
59  
60

106

Table 1 Overview of study visits

	Screen and Baseline visit	Treatment visit	Pregnancy visit	Follow up visit
Physical examination (weight, height)	√			
Menstrual cycle	√			
Fasting blood samples for E2, P,		√		
Preconception counseling	√			
Questionnaire	√	√		
Transvaginal ultrasound	√	√	√	√
Pregnancy test			√	√
Pregnancy and neonatal records				√

107 E2, estradiol; P, progesterone.

108

109

110 Participants

111 The study participants will consist of women and their partners initiating IVF or  
 112 intracytoplasmic sperm injection (ICSI) treatment at the Shanghai JiAi  
 113 Genetics and IVF institute in China and Department of Obstetrics and  
 114 Gynaecology, the University of Hong Kong. Recruitment will be carried out by  
 115 the doctors at the fertility clinics. Eligible women will be recruited if they fulfil all  
 116 of the inclusion criteria and do not meet any of the exclusion criteria. They will  
 117 be included once for this study. After detailed explanation, counselling and  
 118 signing the informed consent form, the eligible participants will be randomly  
 119 allocated to either the immediate group or the delayed group.

120

121 Inclusion criteria

- 122 • Women aged  $\leq 43$  years at the time of IVF/ICSI treatment
- 123 • Undergoing IVF with a standard stimulation
- 124 • At least one frozen embryo or blastocyst
- 125 • The first FET cycle following ovarian stimulation in IVF/ICSI

126 Exclusion criteria

- 127 • Use of mild stimulation or natural cycle for IVF/ICSI treatment

- 1  
2  
3 128 • Severe ovarian hyperstimulation syndrome during IVF/ICSI treatment  
4  
5 129 • Preimplantation genetic diagnosis treatment  
6  
7 130 • Use of donor oocytes  
8  
9 131 • Presence of hydrosalpinx which is not surgically treated or endometrial  
10 132 polyp on scanning during ovarian stimulation

11 Standard and mild stimulation is defined according to the published  
12 terminology for ovarian stimulation for IVF.[11] OHSS is diagnosed and  
13 134 classified according to the RCOG guideline.[12]  
14  
15 135

16 136

### 17 137 Randomization

18  
19 138 Women having the first FET cycle after a failed stimulated IVF cycle or  
20 139 undertaking the freeze all strategy will be randomized according to a  
21 140 computer-generated randomization list into one of the following two groups.  
22  
23 141 The exact timing of randomization is on the day of embryo freezing for patients  
24 142 taking the freeze all strategy and on the day of blood HCG test on 14 days  
25 143 after fresh-ET for the failed fresh-ET women. The randomization is carried out  
26 144 by a project nurse who is not involved in the recruitment and clinical  
27 145 management of patients using an online randomization program through the  
28 146 website [www.randomization.com](http://www.randomization.com). Then the nurse will prepare the  
29 147 randomization arm and put it into opaque envelopes for use. On the  
30 148 randomization day, the recruited women will be randomized according to the  
31 149 opaque envelopes into one of the two groups  
32  
33 150 (1) the immediate group in which FET will be performed in the first cycle  
34 151 following the stimulated IVF cycle and  
35 152 (2) the delayed group in which FET will be performed at least in the second  
36 153 cycle following the stimulated IVF cycle.

37 154

### 38 155 Blinding

39 156 Both the researchers and the participants cannot be blinded because the  
40 157 nature of the study. The embryologist performing the quality assessment is  
41 158 blinded to the allocated treatment.

### 42 159 Interventions

1  
2  
3 160 Women will undergo IVF/ICSI treatment in the centre as clinically indicated.  
4 161 Standard ovarian stimulation with gonadotrophins in either a GnRH antagonist  
5 162 protocol or long GnRH agonist protocol will be employed. Oocyte retrieval will  
6 163 be performed under transvaginal ultrasound guidance 34–36h after triggering  
7 164 with hCG or an agonist. Oocytes will be fertilized using either conventional  
8 165 insemination or intracytoplasmic sperm injection depending the semen quality  
9 166 of the husbands in accordance with the standard protocol. Normal fertilization  
10 167 will be assessed and confirmed by the presence of two pronuclei and a second  
11 168 polar body at 16–18 h after insemination or intracytoplasmic sperm injection.  
12 169 On day 3 after oocyte retrieval, an embryo with at least seven blastomeres and  
13 170 Grades 1 and 2 is defined as good quality. Embryos with at least six  
14 171 blastomeres and fragments <50% will be frozen. All good embryos will be  
15 172 frozen or vitrified using the Crytop method as cleavage stage embryos on Day  
16 173 3 or as full to expanded blastocysts on Day 5 or Day 6 of embryo culture  
17 174 according to the standard protocol. Patients who have  $\geq 6$  good quality  
18 175 embryos on day 3 will be counseled for extended culture and blastocyst  
19 176 transfer.  
20 177  
21 178 We will measure the stress and anxiety levels by the standard questionnaire  
22 179 before the randomization and at the time of starting FET. The Chinese  
23 180 State-Trait Anxiety Inventory (C-STAI) was used to measure the patient's  
24 181 anxiety level.[13]  
25 182  
26 183 Hormone replacement treatment (HRT) will be used for endometrial  
27 184 preparation. On Day 3 of the menstrual cycle, estradiol valerate (E2,  
28 185 Progynova, Schering AG, Berlin, Germany) will be commenced 4mg daily for  
29 186 10 days. When the thickness of the endometrial layer reaches at least 8 mm  
30 187 on pelvic scanning, vaginal progesterone 90 mg per day (Crinone,  
31 188 Merck-Serono, Switzerland) will be administered. For Day 3 embryos, FET is  
32 189 scheduled on the fourth day of starting vaginal progesterone. For blastocysts,  
33 190 FET is scheduled on the sixth day of starting vaginal progesterone. A  
34 191 maximum of 1–2 embryos or blastocysts with the best morphology will be  
35 192 transferred under ultrasound guidance using a soft embryo transfer catheter.

1  
2  
3 193 Serum hCG level will be checked 14 days after FET. All hormone therapy will  
4 194 be stopped if the serum hCG level is negative. All pregnant women will  
5 195 continue the hormonal therapy until 12 weeks of gestation.  
6  
7

8 196

9  
10 197 Follow-up and data collection

11 198 If the serum hCG level is positive, transvaginal ultrasound will be performed  
12 199 two weeks later to locate the pregnancy and confirm foetal viability.

13 200 Subsequent management will be the same as other women with early  
14 201 pregnancy. They will be referred for antenatal care when the ongoing  
15 202 pregnancy is 12 weeks.  
16  
17  
18  
19

20 203

21 204 Written consent regarding retrieval of pregnancy and delivery data will be  
22 205 sought from the patient at the time of study. The patient will be contacted after  
23 206 delivery by phone to retrieve the information of the pregnancy outcomes. The  
24 207 outcomes of the pregnancy (delivery, miscarriage), number of babies born,  
25 208 birth weights and obstetrics complications will be recorded.  
26  
27  
28  
29

30 209

31 210 Outcome measurements

32 211 Primary outcome

33 212 The primary outcome is an ongoing pregnancy defined as a viable pregnancy  
34 213 beyond gestation 12 weeks.  
35  
36  
37

38 214

39 215 Secondary outcomes

- 40  
41 216 - positive hCG level: Conception is defined with the result of serum  $\beta$ -hCG  
42 217  $\geq 10$  mIU/mL.  
43  
44 218 - clinical pregnancy defined as presence of intrauterine gestational sac by  
45 219 transvaginal ultrasound at 6 gestational weeks.  
46  
47 220 - implantation rate as the number of gestational sacs per embryo transferred.  
48  
49 221 - multiple pregnancy, ectopic pregnancy and miscarriage rates. Miscarriage  
50 222 rate is defined as a clinically recognized pregnancy loss before the 22  
51 223 weeks of pregnancy. The denominator is the clinical pregnancy.  
52  
53 224 - live birth rate and: A live birth is defined as the delivery of any number of  
54 225 newborns  $\geq 22$  weeks gestation with heartbeat and breath.  
55  
56  
57  
58  
59  
60

1  
2  
3 226 - birth weight of newborns.  
4  
5 227

6 228 Data entry and quality control of data  
7

8 229 Treatment-related data including baseline information and COH data are  
9  
10 230 collected at the day of embryo frozen. Data on FET cycle are collected at  
11  
12 231 frozen embryo transfer day. Follow-up data on all pregnancies resulting from  
13  
14 232 FET according to the study protocol will be followed from study inclusion and 1  
15  
16 233 year onwards. Participants information forms will be developed for data entry,  
17  
18 234 and quality control of the data will be handled at two different levels. The  
19  
20 235 investigators will be required to ensure the accuracy of the data as the first  
21  
22 236 level of control, and the second level will include data monitoring and validation  
23  
24 237 that will be carried out on a regular basis throughout the study. Data are  
25  
26 238 backed up daily to another computer in the same physical location as the  
27  
28 239 server.

29 240  
30 241 Sample size calculations and statistical analysis

### 31 242 **Sample size estimation**

32 243 According to our data of the Centre, the ongoing pregnancy rate per FET was  
33  
34 244 about 30%. We hypothesize that a difference in the ongoing pregnancy rate of  
35  
36 245 10% between the immediate versus delayed groups as equivalence, the  
37  
38 246 sample size required for a test of equivalence would be 329 in each arm to  
39  
40 247 give a power of 0.8 and type I error of 0.05. Allowing 10% drop-out, 724  
41  
42 248 subjects or 362 in each arm will be needed.

### 43 249 **Data analysis**

44 250  
45 251 Data will be analysed with an intention to treat and per protocol. Demographic  
46  
47 252 features of the two groups will be compared. Comparison of quantitative  
48  
49 253 variables will be performed using Student's t, while categorical variables will be  
50  
51 254 compared using a Chi-square analysis. If randomisation fails to achieve two  
52  
53 255 balanced groups, we will use the multivariable logistic regression to adjust for  
54  
55 256 potentially confounding factors and results, namely female age (as a  
56  
57 257 continuous variable), failed fresh ET or freeze-all, retrieved oocytes, COH  
58  
59 258 protocol, ovulation trigger, number of good quality embryos produced (as a

1  
2  
3 259 continuous variable) and number of embryos transferred (one versus two),  
4 260 developmental stage (cleavage versus blastocyst stage) and quality of the  
5 261 embryos transferred (quality of the embryo transferred). If the primary  
6  
7 262 unadjusted analysis and secondary adjusted analysis are discordant, we will  
8  
9 263 give greater weighting to the primary analysis in the interpretation of trial  
10  
11 264 findings.

12  
13 265

14 266 All statistical analyses of the data will be performed using the SPSS program  
15 267 V.21.0 (SPSS Inc, Chicago, Illinois, USA), and a p value <0.05 will be  
16  
17 268 considered statistically significant.

18  
19 269

### 20 270 **Patient and public involvement**

21 271 The research question about the optimal timing for FET following a stimulated  
22 272 IVF cycle was first proposed by patients who failed fresh ET or in freeze-all  
23 273 policy. Patients were not involved in the recruitment and conduct of the study.

24 274 The study was designed as a randomised trial with participants from the  
25 275 infertility patients attending the clinic. The results will be disseminated to study  
26 276 participants by their physician.

27  
28 277

### 29 278 **ETHICS AND DISSEMINATION**

30 279

31 280 Since FET in HRT cycles is a standard procedure in IVF centers, and there is  
32 281 no agreement regarding the time interval between the stimulated IVF and the  
33 282 subsequent FET in the literature, there are not predefined criteria for  
34 283 premature termination of the study. There is no interim analysis during the  
35 284 study.

36 285 The women who agree to participate in the study will sign a consent form (see  
37 286 online supplementary appendix 1) after detailed counseling of the study and  
38 287 they are free to withdraw from the study at any time without giving any reason  
39 288 and having any impact on the medical care they are receiving.

40  
41 289

42 290 Data will be entered electronically and all data will be stored in locked  
43 291 computer files that are accessible only to the investigators and research staffs



1  
2  
3 292 involved in the study. Original study forms will be kept locked at the study site  
4 293 and maintained in storage for a period of 3 years after the completion of the  
5 294 study. The principal investigator will be responsible for data management  
6 295 including data coding, monitoring and verification. The investigators have  
7 296 always maintained a strict privacy policy. The investigators permit trial-related  
8 297 monitoring, audits, IRB/IEC review and regulatory inspections, providing direct  
9 298 access to source data/documents. For questions about the study, the  
10 299 participants should contact their physician.

11 300  
12 301 A data and safety monitoring committee will review and interpret the data  
13 302 generated from the study, and its primary objectives will be to ensure the  
14 303 safety of the study participants and the integrity of the research data. The  
15 304 committee consists of two independent researchers with experience in  
16 305 reproductive medicine.

17 306  
18 307 An audit trail will be designed as another security measure to preserve the  
19 308 integrity of the trial. Computer-generated and time-stamped audit trails will be  
20 309 implemented for tracking changes in the electronic source documentation.  
21 310 Internal safeguards will be built into the computerised system. Records will be  
22 311 regularly backed up, and record logs will be maintained to prevent data loss  
23 312 and to ensure the data's quality and integrity.

24 313  
25 314 Amendments of the protocol will be agreed on by the IRB/IEC, data and safety  
26 315 monitoring committee and will be approved by the ethics committee prior to  
27 316 implementation.

28 317  
29 318 The study has been approved by the Ethics Committee of assisted  
30 319 reproductive medicine in Shanghai JiAi Genetics and IVF institute (JIAI  
31 320 E2017-12) and by the Institutional Review Board of the University of Hong  
32 321 Kong Hospital Authority Hong Kong West Cluster (UW 17-371). The results of  
33 322 this trial will be disseminated through peer-reviewed publications and  
34 323 presentations at international scientific meetings.

35 324

1  
2  
3 325 **Trial status**

4 326 The study was designed in May 2017, and the first participant was randomised  
5 327 on 9 August 2017. At the time of the manuscript preparation, we have recruited  
6 328 200 women and the recruitment is ongoing.  
7  
8  
9  
10 329

11 330 **Authors' contributions:** HL, XXS and EHYN conceived and designed the  
12 331 study. HL and EHYN drafted and critically revised the manuscript for important  
13 332 intellectual content. XXS sought ethical approval. LL and XL participated in the  
14 333 coordination of the study and recruitment of subjects. All the authors  
15 334 contributed to the further writing of the manuscript and approved the final  
16 335 manuscript.  
17  
18  
19  
20

21 336 **Funding statement:** This research received no specific grant from any  
22 337 funding agency in the public, commercial or not-for-profit sectors.  
23  
24

25 338 **Competing interests :** None declared.

26 339 **Patient consent:** Obtained.

27  
28 340 **Provenance and peer review:** Not commissioned; externally peer reviewed.  
29  
30 341

1  
2  
3 342 **References:**

- 4 343 1. Doody KJ. Cryopreservation and delayed embryo transfer-assisted  
5 344 reproductive technology registry and reporting implications. *Fertil Steril*  
6 345 2014;102(1):27-31.
- 7  
8 346 2. Shapiro BS, Daneshmand ST, Garner FC, et al. Evidence of impaired  
9 347 endometrial receptivity after ovarian stimulation for in vitro fertilization: a  
10 348 prospective randomized trial comparing fresh and frozen-thawed embryo  
11 349 transfer in normal responders. *Fertil Steril* 2011;96(2):344-8.
- 12  
13 350 3. Venetis CA, Kolibianakis EM, Bosdou JK, et al. Estimating the net effect of  
14 351 progesterone elevation on the day of hCG on live birth rates after IVF: a cohort  
15 352 analysis of 3296 IVF cycles. *Hum Reprod* 2015;30(3):684-91.
- 16  
17 353 4. Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh  
18 354 embryos: the translational rationale. *Fertil Steril* 2014;102(1):10-8.
- 19  
20 355 5. Roque M, Valle M, Guimaraes F, et al. Freeze-all policy: fresh vs.  
21 356 frozen-thawed embryo transfer. *Fertil Steril* 2015;103(5):1190-3.
- 22  
23 357 6. Blockeel C, Drakopoulos P, Santos-Ribeiro S, et al. A fresh look at the  
24 358 freeze-all protocol: a SWOT analysis. *Hum Reprod* 2016;31(3):491-7.
- 25  
26 359 7. Santos-Ribeiro S, Polyzos NP, Lan VT, et al. The effect of an immediate  
27 360 frozen embryo transfer following a freeze-all protocol: a retrospective analysis  
28 361 from two centres. *Hum Reprod* 2016;31(11):2541-48.
- 29  
30 362 8. Santos-Ribeiro S, Siffain J, Polyzos NP, et al. To delay or not to delay a  
31 363 frozen embryo transfer after a failed fresh embryo transfer attempt? *Fertil Steril*  
32 364 2016;105(5):1202-07 e1.
- 33  
34 365 9. Lattes K, Checa MA, Vassena R, et al. There is no evidence that the time  
35 366 from egg retrieval to embryo transfer affects live birth rates in a freeze-all  
36 367 strategy. *Hum Reprod* 2017;32(2):368-74.
- 37  
38 368 10. Volodarsky-Perel A, Eldar-Geva T, Holzer HE, et al. Cryopreserved  
39 369 embryo transfer: adjacent or non-adjacent to failed fresh long GnRH-agonist  
40 370 protocol IVF cycle. *Reprod Biomed Online* 2017;34(3):267-73.
- 41  
42 371 11. Nargund G, Fauser BC, Macklon NS, et al. The ISMAAR proposal on  
43 372 terminology for ovarian stimulation for IVF. *Hum Reprod* 2007;22(11):2801-4.
- 44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 373 12. Green-top guideline No.5: Ovarian Hyperstimulation Syndrome,  
4 374 <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg5/>. (26  
5  
6 375 February 2015, date last accessed).  
7  
8 376 13. Shek DTL. The Factorial Structure of the Chinese Version of the  
9  
10 377 State-Trait Anxiety Inventory: A Confirmatory Factor Analysis. *Educational &*  
11 378 *Psychological Measurement* 1991;51(4):985-97.  
12  
13 379

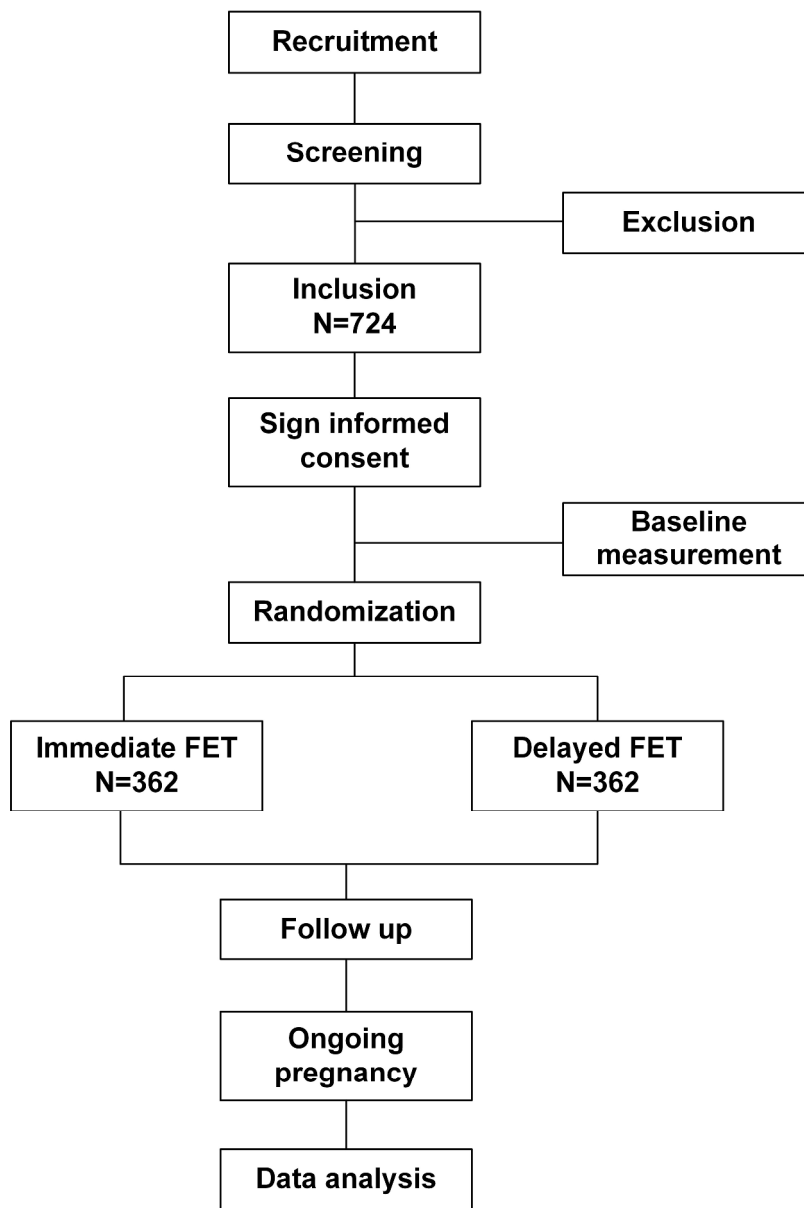
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

380 **Figure 1**  
381 The study flow chart. FET, frozen-thawed embryo transfer.

For peer review only



Flow chart of study

178x266mm (600 x 600 DPI)

**Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

**PATIENT INFORMATION AND CONSENT**

**STUDY TITLE:** A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

You are being invited to participate in the above named research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the purpose of the study?**

Information regarding the optimal timing for frozen-thawed embryo transfer (FET) following a stimulated in vitro fertilization (IVF) is lacking. One option is to perform FET in the first cycle following the stimulated IVF cycle, i.e. immediate transfer. Another option is to postpone FET for at least one menstrual cycle, i.e. delayed transfer.

Several retrospective studies showed similar success for these two options. Another retrospective analysis showed higher clinical pregnancy and live birth rates in the delayed group. Since these studies are all retrospective and the findings are contradictory, a randomized study is needed to provide good evidence to guide the clinical practice.

This randomized study aims to compare the ongoing pregnancy rate of immediate versus delayed FET following a stimulated IVF cycle.

**Why have I been chosen?**

You are chosen because

- You are  $\leq 43$  years of age at the time of IVF treatment.
- You underwent IVF with a standard stimulation.
- You have at least one frozen embryo or blastocyst.
- You are undergoing the first FET following ovarian stimulation in IVF.

You will not be included in this study if

- You are using mild stimulation or natural cycle in the IVF treatment.
- You had severe ovarian hyperstimulation syndrome during IVF treatment.
- You had pre-implantation genetic diagnosis treatment.
- You are using donor oocytes.

## **Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

- Presence of hydrosalpinx which is not surgically treated or endometrial polyp on scanning during ovarian stimulation.

### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you do not join or if you quit the study, you will still receive the standard treatment as other patients in our Department.

### **What will happen to me if I take part?**

If you agree to participate in the study, you will be randomized by a computer-generated list into one of the two groups:

(1) **Immediate group:** Your thawed embryos will be transferred into your womb in the first cycle following the stimulated IVF cycle.

(2) **Delayed group:** Your thawed embryos will be transferred into your womb at least in the second cycle following the stimulated IVF cycle.

The groups are selected by a computer that has no information about the individual, i.e. by chance. We will compare the outcomes between the two groups at the end of the study.

### **How many other people will be participating in the study?**

We plan to recruit 724 women in this study.

### **What are the disadvantages and risks of taking part?**

There should be no safety concern. No specific risk is expected. No extra charge or visit is required for participating in the study.

### **What are the benefits of taking part?**

No payment will be made to you for this study.

### **What will happen to the results of the research?**

The results of the study will be presented in international meetings and published in a medical journal. You will not be identified in any report or publication.



## **Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

### **Confidentiality and privacy**

The investigators have always maintained a strict privacy policy. We never sell, trade or otherwise share your details with any sources. All correspondence to the department is held confidentially; furthermore, at no time will your personal and/or identifying information be shared outside of our organization, for any reason.

You have the rights of access to personal data and publicly available study results, if and when needed. Under the laws of China, you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of China, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study.

By consenting to participate in this study, you expressly authorize:

- the principal investigator, the research team and the Institutional Review Board responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process; and
- the relevant government agencies (e.g. the Shanghai Municipal Commission of Health and Family Planning) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

### **Contact for further information**

For questions about the study or reporting of adverse events, you may contact the Principal Investigator, Dr Li He at telephone no.13817223099. The phone number of Shanghai JIAI Genetics & IVF is 021-63459977.

Thank you for your time to read this information sheet and for taking part in the study.

**Shanghai JiAi Genetics & IVF Institute**

Study: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle

**PATIENT CONSENT FORM**

**Patient Identification Number for this trial:** \_\_\_\_\_

**Title of Project: A randomized trial comparing the effect of immediate versus delayed frozen-thawed embryo transfer following a stimulated IVF cycle**

1. We confirm that we have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. We understand that our participation is voluntary and that we are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected.
3. We understand that sections of any of our medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to our taking part in research. We give permission for these individuals to have access to our records.
4. We agree to take part in the above study.
5. We give permission to the investigators to retrieve pregnancy and delivery data.

\_\_\_\_\_  
Patient's signature

\_\_\_\_\_  
Patient's name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Patient's husband signature

\_\_\_\_\_  
Patient's husband name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator's signature

\_\_\_\_\_  
Investigator's name

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness's signature

\_\_\_\_\_  
Witness's name

\_\_\_\_\_  
Date



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description
<b>Administrative information</b>		
Title	1 P1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a P4	Trial identifier and registry name. If not yet registered, name of intended registry
	2b n/a	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 n/a	Date and version identifier
Funding	4 P12	Sources and types of financial, material, and other support
Roles and responsibilities	5a P11-12	Names, affiliations, and roles of protocol contributors
	5b n/a	Name and contact information for the trial sponsor
	5c n/a	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d P11-12	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	6a P3-4	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b P3-4	Explanation for choice of comparators
Objectives	7 P4	Specific objectives or hypotheses

1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

Trial design 8 P4 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

### Methods: Participants, interventions, and outcomes

Study setting 9 P4 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria 10 P5-6 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions 11a P6-7 Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b P10 Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

11c P6-8 Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d P6-8 Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes 12 P8-9 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline 13 P4 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size 14 P9 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 P5 Strategies for achieving adequate participant enrolment to reach target sample size

### Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a P6	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
3	generation		
4			
5			
6			
7			
8			
9	Allocation	16b P6	
10	concealment		
11	mechanism		
12			
13			
14	Implementation	16c P6	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
15			
16			
17	Blinding	17a P6	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
18	(masking)		
19			
20			
21			
22		17b n/a	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
23			
24			
25			

### Methods: Data collection, management, and analysis

26			
27			
28	Data collection	18a P9-11	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
29	methods		
30			
31			
32			
33			
34			
35			
36			
37		18 P9-11	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
38			
39			
40			
41	Data	19 P9-11	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
42	management		
43			
44			
45			
46			
47	Statistical	20a P9-10	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
48	methods		
49			
50			
51			
52		20b P9-10	Methods for any additional analyses (eg, subgroup and adjusted analyses)
53			
54			
55			
56			
57			
58			
59			
60			

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

20c n/a Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

### Methods: Monitoring

Data monitoring 21a P10-11 Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b P10-11 Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 P10 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 P11 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

### Ethics and dissemination

Research ethics approval 24 P11 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25 P11 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a P10 Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b n/a Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 P9-11 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28 P12 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 P10-11 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

1	Ancillary and	30 n/a	Provisions, if any, for ancillary and post-trial care, and for
2	post-trial care		compensation to those who suffer harm from trial participation
3			
4	Dissemination	31a P11	Plans for investigators and sponsor to communicate trial results
5	policy		to participants, healthcare professionals, the public, and other
6			relevant groups (eg, via publication, reporting in results
7			databases, or other data sharing arrangements), including any
8			publication restrictions
9			
10			
11		31b n/a	Authorship eligibility guidelines and any intended use of
12			professional writers
13			
14		31c	Plans, if any, for granting public access to the full protocol,
15			participant-level dataset, and statistical code
16			Please see the data sharing plan in <a href="http://www.ClinicalTrials.gov">www.ClinicalTrials.gov</a>
17			(NCT03201783)
18			
19			
20	<b>Appendices</b>		
21	Informed consent	32 P10	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates
23			
24			
25	Biological	33 n/a	Plans for collection, laboratory evaluation, and storage of
26	specimens		biological specimens for genetic or molecular analysis in the
27			current trial and for future use in ancillary studies, if applicable
28			

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.