DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
THE UNIVERSITY OF HONG KONG

PATIENT INFORMATION AND CONSENT

PROTOCOL TITLE: A double blind randomized controlled trial of non-invasive preimplantation genetic testing for aneuploidy in in vitro fertilization
Version 1.0: Dated 8 March 2020

You are cordially invited to participate in the above named research study. You need to decide whether you want to participate or not. Please take your time to make up your mind. Carefully read the following and feel free to ask the study doctor any question which you may have.

Why is this study being done?
Couples with difficulty conceiving will require test-tube baby or in vitro fertilization (IVF). Despite advances in technology, the pregnancy rate of IVF remained around 35% per transfer. Chromosome aneuploidy is an error in cell division that results in the "daughter" cells having the wrong number of chromosomes. In some cases there is a missing chromosome, while in others an extra one. Chromosome aneuploidy is the major reason for failure of pregnancy and miscarriage.

The traditional preimplantation genetic testing for aneupoloidy (PGT-A) involves taking a few cells from a blastocyst, which requires skillful laboratory staff and laser equipment. Taking cells from a blastocyst is an invasive procedure and may lead to reduction in implantation potential. The demonstration of release of DNA from human embryos into the surrounding environment opens up the possibility of non-invasive PGT for aneuploidy (NIPGT-A). Collection of spent culture medium requires no specialized training and imposes negligible risk to the embryo. Spent culture medium may be more representative of the whole blastocyst.

The results of NIPGT-A will be able to prioritize the sequence of embryo transfer. There is still no good evidence to show the efficacy of NIPGT-A in IVF. The aim of this study is to compare with efficacy of embryo selection for replacement based on conventional method through embryo morphology versus morphology with additional input from result of NIPGT-A.

Who should be in this study?
You will be recruited if
1. You are aged less than 43 years at the time of ovarian stimulation, and
2. At least two blastocysts suitable for freezing on day 5 or 6 after oocyte retrieval

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You will not be included in this study if

1. Less than two blastocysts suitable for freezing on day 5 or 6 after oocyte retrieval;
2. Women undergoing PGT for monogenic diseases or structural rearrangement of chromosomes
3. Use of donor oocytes
4. Hydrosalpinx shown on pelvic scanning and not surgically treated

What will I be asked to do?

Recruited patients will undergo IVF as clinically indicated. Ovarian stimulation, ultrasound monitoring, and oocyte retrieval will follow the standard operating procedure of the unit.

Each blastocyst will be frozen individually and its spent culture medium (~8 µl) will be frozen at -80^{0}C separately and individually. The embryologist will prepare a sequence of blastocyst transfer based on the best morphology by Gardner's criteria.

On the day of blastocyst freezing, recruited women will then be randomly assigned into two groups using a randomization program.

1. the intervention group using morphology and NIPGT-A and
2. the control group based on morphology alone.

The women and doctors will be blinded to the treatment groups they are assigned. Only the laboratory staff in the PGT laboratory and the embryologists in the IVF laboratory will be aware of the group assignment.

In the intervention group, comprehensive chromosome screening using NGS will be performed. In the control group, the measurement will be done in the spent culture medium of the blastocyst that is replaced in the first transfer. The NIPGT-A report is used only to prioritize the sequence of embryo transfer. Blastocysts with non-euploid result in the NIPGT-A report will not be discarded.

Blastocysts can be replaced in the subsequent natural or hormonal replacement cycles, depending whether the women have regular menstrual cycles or not. Only one blastocyst will be transferred each time. In the control group, blastocysts with the best quality morphology will be replaced first and the sequence of blastocyst transfer is decided prior to randomization. In the intervention group, blastocysts with the best morphology and euploid result will be replaced first as the sequence of blastocyst transfer will be modified after the NIPGT-A reports are available.

Cheng HYH, *et al. BMJ Open* 2023; 13:e072557. doi: 10.1136/bmjopen-2023-072557

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How long will I be in the study?

1 IVF cycle

How many other people will be participating in the study?

We plan to recruit 500 women in this study.

Will I be paid?

No payment will be made to you for this study.

What adverse (bad) effects can happen to me by participating in the study?

There should be no major safety concern as all the embryos will be kept after prioritization regardless of the group recruited.

What benefit can I expect?

You may have a higher pregnancy rate per transfer, lower miscarriage rate and short time to pregnancy if you are randomized to the intervention group with NIPGT-A.

Can I refuse to be in the study?

Your participation in this study is voluntary. You can choose not to take part in the study, or you can quit at any time. You will not lose any benefit to which you are otherwise entitled. If you quit the study, you can receive the standard treatment as other patients in our Department.

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.

Subjects have the rights of access to personal data and known study results, if and when needed. Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486, 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 Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. For any query, you should consult the Privacy Commissioner for Privacy Data or his office (2827 2827) as to the proper monitoring or

supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

For questions about the study or reporting of adverse events, please call Dr Heidi Cheng at telephone no. 22553657. The phone number of the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong Wester cluster is 2255 4086.

If you consent to take part in the research, any of your medical records may be inspected by the research team for purposes of analysing the results. They may also be looked at by people from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

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PATIENT CONSENT FORM

PROTOCOL TITLE: A double blind randomized controlled trial of non-invasive preimplantation genetic testing for aneuploidy in in vitro fertilization

Name of Principal Investigator: **Dr. Heidi Cheng**

1. I confirm that I have read and understood the patient information sheet for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals who are relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree that the spent culture medium may be saved for future research.

5. I agree to take part in the above study.

I understand that I will be given a signed copy of this Patient Information and Consent Form.

_____	_____	_____
Subject's signature	Subject's name	Date
_____	_____	_____
Investigator's signature	Investigator's name	Date
_____	_____	_____
Witness' signature	Witness' name	Date