

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A randomised double blind controlled trial of non-invasive preimplantation genetic testing for aneuploidy in in vitro fertilisation: a protocol paper
<b>AUTHORS</b>	Cheng, Hiu Yee Heidi; Chow, Judy F.C.; Lam, Kevin K.W.; Lai, Shui Fan; Yeung, William Shu Biu; Ng, Ernest

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Ge Lin Central South University
<b>REVIEW RETURNED</b>	03-Mar-2023

<b>GENERAL COMMENTS</b>	<p>1、 In the method section, the insemination method was not clearly stated. Was it conventional IVF or ICSI ?The method of sample collection is also not clarified, such as when the medium is collected, whether there is additional processing, etc.Lines 50-51 on page 6 of the article describe "Each blastocyst will be cryopreserved on day 6 by vitrification", whether blastocysts that meet the freezing criteria on day5 will continue to be cultured until day6 and then freeze, and whether blastocysts that do not meet the freezing criteria on day6 will continue to be cultured until day7.</p> <p>2、 The calculated sample size is 500 subjects, and the random number of subjects in the "consort 2010 flow diagram" is 828. What is the reason for this inconsistency?</p> <p>3、 The description of statistical methods is too simple. The article involves pregnancy time comparison, sensitivity analysis, OR calculation, etc. What are these analysis methods?</p>
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<b>REVIEWER</b>	Maja Tomic University Medical Centre Ljubljana, obstetrics and gynecology
<b>REVIEW RETURNED</b>	09-Mar-2023

<b>GENERAL COMMENTS</b>	<p>Page 3, line 50: quotation no. 6 should be placed at the end of a sentence. (same rules apply throughout the paper)</p> <p>Page 4, line 5: do not use future tense in the introduction. There is no "will be" when you are giving us an overview of literature and of what is already known.</p> <p>Page 4, lines 36-41, lines 59-60, and page 5, lines 1-6 : there are no references</p> <p>Inclusion criteria: be more specific (previous live birth information, previous IVF, endometriosis/PCOS/ other disease inclusion/exclusion). Add age stratification.</p> <p>Includle inclusion/exclusion criteria for men and at least male age.</p> <p>Overall, a well written study protocol. There could be more current references, including about niPGT-A. Please make sure to correct the</p>
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	inclusion/exclusion criteria. There could also be age stratification added
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Ge Lin, Central South University

Comments to the Author:

1、 In the method section, the insemination method was not clearly stated. Was it conventional IVF or ICSI ? The method of sample collection is also not clarified, such as when the medium is collected, whether there is additional processing, etc. Lines 50-51 on page 6 of the article describe "Each blastocyst will be cryopreserved on day 6 by vitrification", whether blastocysts that meet the freezing criteria on day5 will continue to be cultured until day6 and then freeze, and whether blastocysts that do not meet the freezing criteria on day6 will continue to be cultured until day7.

Reply: Both conventional insemination and intracytoplasmic sperm injection (ICSI) will be employed depending on the semen parameters in line with our standard operating procedures of the Centre. Previous studies (1) have confirmed conventional IVF have comparable performance with ICSI in niPGT-A using spent culture medium.

About 8µl of SCM will be saved and frozen on day 6 after collection of transferrable blastocyst for vitrification and no further additional processing of SCM is performed.

In our standard operating procedures, all embryos will be cultured up to day 6 only and those blastocysts which do not meet the criteria for vitrification on day 6 will be discarded. These were added in the manuscript as highlighted.

2、 The calculated sample size is 500 subjects, and the random number of subjects in the "consort 2010 flow diagram" is 828. What is the reason for this inconsistency?

Reply: This is a typo and the consort 2010 flow diagram was revised with 500 subjects highlighted.

3、 The description of statistical methods is too simple. The article involves pregnancy time comparison, sensitivity analysis, OR calculation, etc. What are these analysis methods?

Reply: A detailed statistical analysis plan will be prepared later prior to the completion of the recruitment. Quantitative variables will be compared by T-test or Mann-Whitney U-test where appropriate. Categorical variables will be compared using Chi-square analysis, multivariable logistic regression or one-way ANOVA test depending on the number of categories compared.

Reviewer: 2

Dr. Maja Tomic, University Medical Centre Ljubljana

Comments to the Author:

Page 3, line 50: quotation no. 6 should be placed at the end of a sentence. (same rules apply throughout the paper) Page 4, line 5: do not use future tense in the introduction. There is no "will be" when you are giving us an overview of literature and of what is already known.

Reply: Updated

Page 4, lines 36-41, lines 59-60, and page 5, lines 1-6 : there are no references

Reply: Reference list updated. P.5 describes the possible reason accountable for the difference in ploidy status between niPGT and PGT technically.

Inclusion criteria: be more specific (previous live birth information, previous IVF, endometriosis/PCOS/ other disease inclusion/exclusion). Add age stratification.

Include inclusion/exclusion criteria for men and at least male age.

Reply: Thanks for the suggestion. As we have now recruited a major proportion of cases already, the selection criteria cannot be further modified at this stage.