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Closed versus open vitrification for human blastocyst cryopreservation: A meta-analysis

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ABSTRACT

Closed vitrification can minimize the risk of microbiological transmission through liquid nitrogen during the cooling, storage, and warming procedures. As cooling rates may reduce when closed vitrification is applied, clinical outcomes should be compared between closed and open vitrification in order to justify the use of closed vitrification. This study was conducted to investigate the differences in survival, implantation, clinical pregnancy, and live birth rates between closed and open vitrification for human blastocyst cryopreservation. This systematic review and meta-analysis included 7 studies that reported survival, implantation, clinical pregnancy, or live birth rates following closed or open vitrification. There were no statistically significant differences in survival rates (risk ratio [RR]: 1.00, 95% confidence interval [CI]: 0.98–1.02), implantation rates (RR: 1.02, 95% CI: 0.93–1.11), clinical pregnancy rates (RR: 0.99, 95% CI: 0.89–1.10), and live birth rates (RR: 0.77, 95% CI: 0.58–1.03) between closed and open vitrification. Although there was no statistical significance, the tendency of lower live birth rates with closed vitrification than with open vitrification could be clearly identified. Therefore, it is not yet possible to conclude that closed vitrification clearly provides an aseptic alternative to open vitrification in human blastocyst cryopreservation.

1. Introduction

Vitrification is the solidification of liquid through an extreme elevation in viscosity during cooling and not through crystallization [6]. It is currently the most widely used method for cryopreservation of human oocytes and embryos. As high cooling and/or warming rates should be ensured for effective vitrification, a carrier device has been designed to allow direct contact of biological samples with liquid nitrogen. However, in this open vitrification system, the risk of microbiological transmission through liquid nitrogen may increase theoretically [1,21]. With this background, the concept of closed vitrification was introduced. The key point of the closed vitrification system is the physical separation of biological samples from liquid nitrogen throughout the cooling, storage, and warming procedures [19,22]. This may reduce the risk of microbiological transmission; however, the cooling rates might decrease. It is possible to assume that effective vitrification may not be achieved with this approach. Considering these points, it is important to determine whether closed vitrification could be used as an alternative method to open vitrification for cryopreservation of human oocytes and embryos. Additionally, for closed vitrification, it should be determined whether protocol modification is necessary to compensate for the reduction in the cooling rates, which is inevitable with this approach [22].

In the present study, we conducted a systematic review and meta-analysis to investigate the differences in survival, implantation, clinical pregnancy, and live birth rates between closed and open vitrification for human blastocyst cryopreservation.

2. Materials and methods

The protocol of this study was designed according to the PRISMA-P statement [15], and the detailed process of this study followed the PRISMA statement [14].

2.1. Data sources and search

A literature search was performed using the MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases. A combination of the following search terms was used: closed

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vitrification, aseptic vitrification, open vitrification, and blastocyst.

2.2. Study selection

A 2-step process was used to select the studies that were appropriate for our analysis. First, we checked for the presence of duplicate articles in the databases and excluded all duplicate articles. Next, 2 authors (H.S.Y. and J.C.) conducted literature selection independently for the remaining articles. Studies comparing survival, implantation, clinical pregnancy, or live birth rates between closed and open vitrification were selected. No language restriction was applied.

2.3. Data extraction

The basic form was created on a spreadsheet. The number of corresponding outcomes and the number of total cases of survival, implantation, clinical pregnancy, and live birth were recorded for each group (closed and open vitrification).

2.4. Risk of bias assessment

Two assessment tools were used individually to assess the risk of bias. Cochrane Collaboration's tool for assessing risk of bias (RoB) was used for prospective studies and the risk of bias assessment tool for nonrandomized studies (RoBANS) was used for retrospective studies. The risk of bias assessment was performed by 2 authors (H.S.Y. and J.C.) [8,11].

2.5. Statistical analysis

A random effects model (DerSimonian and Laird estimator) was used, and the results were expressed as risk ratio (RR) with 95% confidence interval (CI). I^2 statistics were used to assess the heterogeneity among studies. Analysis of the publication bias was not conducted because the number of studies included was less than 10 [20].

In terms of study design, prospective studies can be considered to have fewer potential sources of bias and confounding than retrospective studies. It is necessary to clarify this distinction in the analysis. Therefore, the studies were divided into prospective and retrospective studies, and subgroup analysis was performed with a focus on the effect size.

All statistical analyses were carried out using the “meta” package in the R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) framework.

3. Results

3.1. Study selection

A flow diagram of the study selection process is presented in Fig. 1. The literature search identified 145 articles from the databases and 7 from other sources. After excluding duplicate articles and reading titles and abstracts, we selected 15 articles for full-text assessment. After full-text assessment, 8 articles were excluded. Therefore, 7 studies were finally selected for systematic review and meta-analysis [4,5,7,9,10,12,13].

3.2. Study characteristics

The characteristics of the included studies are shown in Table 1. The studies were divided into prospective (n = 3) and retrospective (n = 4) groups according to the study design.

3.3. Risk of bias

The risk of bias was assessed with an individual assessment tool according to the study design (Table 2). RoB was employed for prospective studies and RoBANS was employed for retrospective studies. The RoB result for prospective studies was “unclear” in terms of the selection bias and revealed a weak plan for random sequence generation. The RoBANS result for retrospective studies revealed a weak consideration and plan for the selection of participants and the confounding variables in terms of selection bias. Both the RoB and RoBANS results were “low” for other biases.

3.4. Meta-analysis

3.4.1. Survival rates

Six studies were analyzed. The RR of closed vitrification to open vitrification was 1.00 (95% CI: 0.98–1.02, I^2: 49%). There was no statistically significant difference in survival rates between closed and open vitrification.

The RR was 0.98 (95% CI: 0.94–1.03, I^2: 27%) in 2 prospective studies and was 1.01 (95% CI: 0.98–1.03, I^2: 61%) in 4 retrospective studies.

3.4.2. Implantation rates

Six studies were analyzed. The RR of closed vitrification to open vitrification was 1.02 (95% CI: 0.93–1.11, I^2: 8%). There was no statistically significant difference in implantation rates between closed and open vitrification.

The RR was 1.02 (95% CI: 0.81–1.28, I^2: 0%) in 2 prospective studies and was 1.02 (95% CI: 0.90–1.15, I^2: 43%) in 4 retrospective studies.

3.4.3. Clinical pregnancy rates

Six studies were analyzed. The RR of closed vitrification to open vitrification was 0.99 (95% CI: 0.89–1.10, I^2: 24%). There was no statistically significant difference in clinical pregnancy rates between closed and open vitrification.

The RR was 0.84 (95% CI: 0.65–1.08, I^2: 2%) in 2 prospective studies and was 1.03 (95% CI: 0.93–1.13, I^2: 5%) in 4 retrospective studies.

3.4.4. Live birth rates

Five studies were analyzed. The RR of closed vitrification to open vitrification was 0.77 (95% CI: 0.58–1.03, I^2: 81%). There was no statistically significant difference in live birth rates between closed and open vitrification.

The RR was 0.93 (95% CI: 0.72–1.21, I^2: not applicable) in 1 prospective study and was 0.73 (95% CI: 0.50–1.07, I^2: 85%) in 4 retrospective studies.

A summary of the results is shown in Table 3 and Figs. 2–5 as forest plots.

4. Discussion

This meta-analysis showed that there is no statistically significant difference between closed and open vitrification with regard to survival, implantation, clinical pregnancy, and live birth rates. However, we noted that the live birth rates were lower with closed vitrification than with open vitrification, although the difference was not statistically significant, and this was more pronounced for retrospective studies. In the subgroup analysis of live birth rates, a borderline trend of the 95% CI and effect size deviation of the RR from 1.0 were observed in the results for the retrospective studies and overall studies, respectively. From the perspective of sensitivity analysis, we found that the RR of closed vitrification to open