ORIGINAL ARTICLE: ASSISTED REPRODUCTION

How does closed system vitrification of human oocytes affect the clinical outcome? A prospective, observational, cohort, noninferiority trial in an oocyte donation program

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Objective: To evaluate whether is possible to vitrify oocytes in an aseptic (hermetically closed) fashion and maintain clinical results comparable with those of fresh oocytes.
Design: Prospective, observational, cohort, noninferiority trial.
Setting: Private in vitro fertilization center.
Patient(s): One hundred eighty-four recipients of donated vitrified oocytes.
Intervention(s): Closed system vitrification.
Main Outcome Measure(s): Pregnancy rate per cycle and clinical pregnancy rate per cycle.
Result(s): No statistically significant differences were observed between two groups regarding the pregnancy rate per cycle (63.1% vs. 60.9%) or the clinical pregnancy rate per cycle (55.4% vs. 58.7%). Biochemical pregnancy rate was statistically significantly higher in the fresh group (7.6% vs. 2.2%). The mean number of embryos transferred was similar (2.0 $\pm$ 0.0 vs. 1.97 $\pm$ 0.3). Concerning embryologic data, there were no statistically significant differences regarding the fertilization, cleavage, top quality day-3 embryo, or blastocyst rates, whereas the top quality blastocyst rate on day 5 was statistically significantly higher in the fresh oocyte group (31.7% vs. 26.1%).
Conclusion(s): Aseptically (in a closed system) vitrified oocytes show similar clinical efficiency compared with their sibling fresh oocytes. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Aseptic technique, closed system vitrification, egg donor bank, oocyte donation, oocyte vitrification

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For over 15 years vitrification as a cryopreservation technique has been successfully applied to human embryos. From the moment that vitrification was proven to be a promising alternative to cryopreserve oocytes, the popularity of the technique in the field of assisted reproduction technology (ART) has grown (1, 2). Many published studies have reported the superiority of vitrification over the slow freezing technique for oocyte cryopreservation, and the success rates using vitrified oocytes have been similar to those obtained with fresh oocytes (2–13). The birth of healthy infants resulting from vitrified oocytes (14–17) has established vitrification as

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the gold standard technique for oocyte cryopreservation and has widened the indications for use of this technique.

In the past, regardless the disappointing results, oocyte cryopreservation was the only option in specific circumstances, such as for women at risk of losing their ovarian reserve (from cancer, immunologic or genetic disorders, or aggressive medical treatments), for overcoming legal, ethical, and religious restrictions, or for addressing logistic situations such as an absent semen sample on the day of oocyte pickup. At present, due to the promising results and the safety of the technique, as demonstrated in healthy infants, vitrification is no longer considered an experimental method (18). With the introduction of efficient, harmless, and safe vitrification techniques, the indications for vitrifying oocytes could be widened and proposed to women who are seeking fertility preservation for social reasons or used to promote the development of egg donor banks.

Noticeable is the fact that a longer period of storage, ranging from months to several years, will be needed if the demand for egg freezing increases in the future (19). In such prolonged storage conditions, safety is another key issue because the biological sample must be aseptically isolated and not in direct contact with liquid nitrogen (20).

To guarantee aseptic vitrification and storage conditions, closed carrier systems have been introduced (21, 22). At present, few data using closed devices that ensure aseptic cooling and storage have been reported in cases of oocytes cryopreservation. Recent reviews (1, 23) have noted the obvious preference of scientists for using open systems for oocyte vitrification. This reluctance to vitrify using closed devices derives from a common belief (2, 23–25) that reduced cooling rates, such as those produced in closed systems due to thermo-isolation, could be harmful or lethal to the cells, increasing the probability of ice crystal formation during the cooling process (26). However, it has been reported that reduced cooling rates do not compromise survival rates in aseptically vitrified oocytes (27–30), zygotes (30, 31), or blastocysts (21, 32, 33) if very high warming rates are applied.

Such statements are reinforced by recent studies of Mazur et al. (34–37), who have shown that the primary cause for cell injury or cell death during vitrification procedure is not the ice crystal formation during cooling but the recrystallization during warming (devitrification). According to their studies, warming rates are as important as cooling rates; in fact, warming rates should be higher than cooling rates for a successful vitrification and warming cycle. Therefore, a closed system could be as sufficient as an open one so long as we keep the warming rates high.

So far, a few studies have described the competence of closed systems for oocyte vitrification (5, 27, 32, 38), but their clinical data are not enough to support the efficiency of these devices. Unlike the open systems, there are no prospective studies comparing fresh embryo transfers (ET) versus ET after oocyte vitrification in hermetically closed devices. To evaluate the efficiency of hermetically closed devices in oocyte vitrification we compared the clinical outcome after ET derived from sibling oocytes to recipients being synchronized (fresh oocytes) or not (aseptically vitrified oocytes) with their donor in our oocyte donation program.

MATERIALS AND METHODS

A prospective, observational, cohort study was performed at IAKENTRO Fertility Center from recruitment start date on January 19, 2014, to the completion date on December 15, 2014. All procedures were performed at the same laboratory. This clinical trial was a part of a doctoral study at the Medical School of University of Ioannina, Greece. The study was approved by the institutional review board of the Ioannina Medical School (Ref: 808a/8-3-2011). This trial was registered in ISRCTN registry (identification number ISRCTN56275481) and was approved by the IAKENTRO review board (reference number 1/2014, 19/1/2014). Informed consent was obtained from all women participating.

Noninferiority Test, Sample Size, and Study Design

Based on a positive hCG/transfer baseline rate of 61% among controls and 59% for study subjects, a sample size of 92 transfers per arm would be required to be able to reject the null hypothesis that the one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 20% with a statistical significance level of 5% and a power (1-β) of 80%. Power calculation was performed with Sealed Envelope Ltd 2012 (39).

Ninety-two oocyte donors participated in our study. A single stimulation cycle was included for each donor. Pairs of recipients, sharing sibling oocytes from the same donor, were included in the study. Each pair consisted of a recipient for whom fresh oocytes were used for their donation cycle and another recipient for whom the oocytes were vitrified and used after a short period of time. A single donation cycle was included for each recipient. One hundred and eighty-four couples who received sibling oocytes donated from the same donor were allocated to receive fresh (92 couples) or vitrified sibling oocytes (92 cases). Biological and clinical parameters were evaluated. Pregnancy rates were a secondary tracked outcome; the intervention did not depend on it, nor did it affect the execution of the study in any way.

The current study contains a randomization procedure. During the donor's oocyte pickup, two separate dishes for oocyte collection were used. The retrieved cumulus oocyte complexes were randomly and equally assigned into the two dishes during oocytes retrieval. Odd numbered oocytes were allocated to the fresh group (dish 1: group 1), and even numbered oocytes were allocated to the closed vitrified group (dish 2: group 2). This allocation method could potentially have the drawback of recruiting a higher number of oocytes to group 1 as in all odd-numbered cases group 1 would have more oocytes enrolled. However, according to our experience, the larger follicles are first retrieved in each procedure are more likely to contain higher quality (mature) oocytes, so it is likely that the last-retrieved odd oocytes would be of poor

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