TurnitinTheUtilizationofOocyte Cryopreservation

by Edi Wibowo

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THE UTILIZATION OF OOCYTE CRYOPRESERVATION AMONG INDONESIAN WOMEN

Batara Sirait[1*], Nining Handayani[2], Ayu Mulia Sundari[2], Tri Aprilliana Wulandari[2], Ivan Sini[2], Arie A. Polim[3], Muhammad Rizal[4], Arief Boediono[5]

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia

[2]IRSI Research and Training Centre, Jakarta, Indonesia

[3]Department of Obstetrics and Gynecology, School of Medicine and Health Sciences, Atmajaya Catholic University of Indonesia, Jakarta, Indonesia

[4]Morula IVF Jakarta Clinic, Jakarta, Indonesia

[5]Department of Anatomy, Physiology and Pharmacology, IPB University, Bogor, Indonesia

*Correspondence email: batarasirait@gmail.com

ABSTRACT

Our study aims to assess the utilization of oocyte cryopreservation (OC) in Indonesian women. Data from 122 women who had undergone OC were retrospectively analyzed from medical records. The baseline profile, clinical characteristics, and main outcomes comprising intentions for oocyte vitrification and outcomes following oocyte warming were examined. Out of 122 women who underwent OC, 49 patients returned and used their cryopreserved oocytes, with a median duration of storage was two months. Arranged from the greatest to the least, participants had undergone the cycle of OC due to sperm factor [51 (41.80%)], increased embryo availability [6 (12.1%)], postponement of marriage [6 (12.1%)], social reasons [10 (8.19%)], and other reasons [8 (6.55%)]. Meanwhile, treatment due to advanced maternal age [6 (4.91%)], poor ovarian reserve [6 (4.91%)], cancer [5 (4.09%)], PCOS [2 (1.63%)], and endometriosis [2 (1.63%)] was reported among remaining subjects. Clinical pregnancy was reported in 12 (40.0%) patients constituting of each 6 (50.0%) subjects of day-3 and day-5 embryo transfer, respectively. Our study demonstrated that sperm factor, increased embryo availability, and postponement of marriage is the main reason for women undergoing OC in Indonesia.

Keywords: Fertility preservation; Oocyte cryopreservation; Oocyte vitrification

INTRODUCTION

Along with the advancement in science and technology, fertility preservation has become an integral element of the practice of reproductive medicine. One of the most reliable methods for this purpose is vitrification. Vitrification is a cryopreservation technique to preserve living cells and tissues by cooling the samples to an extremely low temperature.[1,2] Allows the solidification of the cells and the surrounding environment into an amorphous, glass-like state without the formation of ice crystals, and vitrification appears to be reliable for storage as it minimizes the probability of cell injury.

Among all types of reproductive cells, embryo cryopreservation is the most well-established technique in which more than 50% of embryos are cryopreserved.[2–4] Nevertheless, an increase in oocyte vitrification has been observed in recent years. A tri-national retrospective cohort study showed that in the last five years, a dramatic rise in the number of oocyte cryopreservation (OC) cycles was observed for 880% in the USA and 311% in Australia/New Zealand, respectively.[5] A doubling number of cycles was also reported in other regions worldwide.[1]

OC was initially intended to overcome ethical issues of embryo storage and to provide women with medical indications which are likely to render them infertile, a chance to preserve their reproductive

potential.[6] This strategy is foremostly a good opportunity for women diagnosed with cancer as treatment often results in a reproductive loss. A high dose of alkylating agents and ionizing radiation utilized in chemotherapy and radiation therapy are known to be gonadotoxic for inducing DNA damage and apoptosis in the oocytes and the surrounding cells of the ovary leading to early ovarian follicle depletion, premature menopause, and subsequent infertility.[7–9] OC is also a feasible strategy for unexpected sperm retrieval failure on the day of ovum pick up (OPU) in women undergoing in vitro fertilization cycle. This failure is unusual but frequently in patients with severe oligospermia or non-obstructive azoospermia (NOA), and that oocyte-freezing is the only means of ovarian stimulation has been cycled.[10] Along with the growing trend of delayed marriage and childbearing in modern female society, participation in the cycle due to non-medical reasons, termed elective oocyte freezing, is emerging in women populations worldwide.[11,12]

Conditions such as couples with advanced maternal age or women who plan to have children in the future but lack of partner are underlying decisions to undergo this procedure as it allows a woman to freeze her younger and healthier oocytes for later use when she is unable to conceive.[12–14] This is based on increasing awareness and knowledge amongst women of reproductive age regarding the decline in fertility with age. Reports have shown that elective freezing is increasing in popularity in which its proportion is comparable to those for medical reasons.[15,16] However, there is no report regarding the utilization of OC among Indonesian women. Therefore, this present study aims to assess patients' demographic profiles as well as the utilization of OC among Indonesian women.

MATERIAL AND METHODS

This retrospective observational cohort study was conducted at Morula IVF Jakarta clinic, Indonesia. 122 women were recruited to the study according to inclusion criteria: underwent ovarian stimulation and oocyte freezing between January 1, 2015, and December 31, 2021. Subjects who cryopreserved oocytes but had incomplete datasets were excluded from the study. Baseline characteristics and study outcomes are presented as means ± standard deviations, median (Q1-Q3), or the number of subjects (percentage) according to data distribution. Ethical approval was obtained from the Faculty of Medicine, Universitas Indonesia Ethics Committee (KET-986/UN2.F1/ETIK/PPM.00.02/2022).

RESULT

Subject characteristics

At the time of undergoing OC, the median age of women and men participants was 38 and 41, respectively (Table 1). Among all participants, 99 subjects (81.1%) were identified to have primary infertility. Meanwhile, 23 subjects (18.9%) had secondary infertility with an overall median infertility duration and BMI of five years and 22.66 (Table 1). At the end of the cycle, the median number of retrieved oocytes and the median number of oocytes being cryopreserved was six and five (Table 1).

Procedure intentions

The purposes of the participants are presented in Table 1. According to the frequency, 51 participants had undergone the cycle of OC due to sperm factor, representing almost half of the total subjects (41.80%). Postponement of marriage [6 (12.1%) and increased embryo availability [6 (12.1%) is the second biggest reason for patients to store their oocyte. In the 3rd and 4th positions, ten participants (8.19%) and eight participants (6.55%) had engaged due to social reasons and other reasons such as partner with HIV, COVID-19 positive, and so on. Advanced maternal age [6 (4.91%)], poor ovarian reserve [6 (4.91%)], cancer [5 (4.09%)], PCOS [2 (1.63%)], and endometriosis [2 (1.63%)] were reported in the rest of the study population.

Table 1. Baseline and clinical characteristics

	Median (Q1-Q3) **N (%)**
Number of total patients	122
Age (year)	
Female	38 (33–42)
Male	42 (37–48)
Type of infertility	
Primary	99 (81.1%)
Secondary	23 (18.9%)
Infertility duration (year)	5 (2–10)
Body Mass Index (Kg/m^2)	22.66 (20.66–24.61)
Number of retrieved oocytes	6 (3–11)
Number of vitrified oocytes	5 (2–9)
Main outcomes	
Reason for oocyte vitrification	
Advanced maternal age	6 (4.91%)
Attempt to increase the number of embryo availability	16 (12.11%)
Cancer (male or female)	5 (4.09%)
Postponement of marriage	16 (12.11%)
Sperm factor	51 (41.80%)
Poor ovarian reserve	6 (4.91%)
PCOS	2 (1.63%)
Endometriosis	2 (1.63%)
Social reason	10 (8.19%)
Others (i.e., partner with HIV, COVID-19 positive, etc)	8 (6.55%)

Oocyte thawing–warming cycle outcomes

Out of 122 participants, 49 patients returned to the clinic and underwent oocyte warming after a median duration of vitrification of 2 months (Table 2). Following treatment, 46 (93.9%) patients obtained survived oocytes after injection, while 3 (6.1%) patients had a total oocyte post-warming survival failure. Successful fertilization was reported among 39 (84.8%) patients, with 7 (15.2%) total fertilization failures. 38 (97.4%) participants subsequently achieved cleavage stage embryo with a median cleavage embryo was 2.

Following culture, 17 (56.7%) patients transferred their embryos on the third day, while 21 (55.3%) patients extended their culture to day 5. Following prolonged culture, 18 (85.7%) participants achieved blastocysts stage embryo with a median of two. A total of 13 (43.3%) patients were subsequently undergoing day-5 embryo transfer. Clinical pregnancy was reported in 12 (40.0%) patients resulting from 6 (50.0%) subjects of day three embryo transfer and 6 (50.0%) subjects of day five embryo transfer, respectively.

Table 2. Patients with oocytes warming

	Distribution
Number of patients (n)	49
Duration of oocyte vitrification (months)	2 (1-3)
Warming oocytes	
Number of patient with survived oocytes following injection (n(%))	46 (93.9%)
Number of patients with total oocyte post-warming failure (n(%))	3 (6.1%)
Fertilization	
Number of patients with fertilization	39 (84.8%)
Number of patients with total fertilization failure (n(%))	7 (15.2%)
Number of patients achieved cleavage (n(%))	38 (97.4%)
Number of achieved cleavage	2 (1-3)
Number of patient Day 3 embryo transfer (n(%))	17 (56.7%)
Number of patients following extended culture to day 5	21 (55.3%)
Number of patients who achieved blastocysts (n(%))	18 (85.7%)
Number of achieved blastocysts	2 (1-3)
Number of patient Day 5 embryo transfer (n(%))	13 (43.3%)
Clinical pregnancy (n(%))	12 (40.0%)
Clinical pregnancy Day 3 embryo transfer (n(%))	6 (50.0%)
Clinical pregnancy Day 5 embryo transfer (n(%))	6 (50.0%)

Data are presented as median (Q1-Q3) and the number of subjects (percentage) [n (%)].

DISCUSSION

To the best of our knowledge, our study is the first report to present the utilization of OC among Indonesian women by which, according to our analysis, sperm factor, increased embryo availability, and postponement of marriage are the main underlying purpose of the procedure. These findings demonstrate that, except for embryo freezing, a trend for oocyte freezing has existed in Indonesian women reflecting that fertility preservation awareness has emerged in the population.

In this present study, the age of the female participants who underwent treatment ranged from 33 to 42 years, with a median of 38. This is in line with previous reports in which, according to Johnston et al. (2021), women undergoing OC were usually in their late 30s with an average age between 37 and 39.2 years.[5,17] This also meets recent recommendations, which suggest that OC provides the highest benefit when performed at an earlier age, where the age of 37 is the optimum age and is the most cost-effective.[18] On the other hand, participants in the present research had both retrieved and cryopreserved oocyte numbers of 3-11 and 2-9, respectively. A study found that the live birth rate (LBR) after embryo transfer plateaued between 15 and 20 oocytes and steadily declined beyond 20, suggesting that 15 oocytes, at minimum, are needed to optimize LBR during IVF.[19] As such, we assumed that some of the participants in our population might be unsuccessful in attaining a live birth from their stored oocytes, particularly those who took the cycle at an older age.

In terms of the reason for cryopreservation, almost half of the participants in this study were undergoing OC due to sperm factor. Okohue et al. (2011) estimated that 1 – 200 male partners had an unexpected inability to produce semen at the time of oocyte retrieval resulting in ejaculation failure[20]. Causes such as spinal cord injuries, degenerative disease, and drugs are reported to be related to the phenomenon, but anxiety is known to play a more significant role in these reported cases.[20,21]

Considering studies found no detrimental effect on LBR when frozen sperm are injected into the post-warming oocytes compared with fresh, OC serves as a salvage method for this unexpected event, especially in severe oligospermia or non-obstructive azoospermia that, according to our opinion, is the explanation of the finding of our study.[22,23] Our findings corroborate the previous result that ejaculation failure could be the major reason for OC as an emergency strategy to solve the issue. As such, sperm cryopreservation needs to be considered.

Following sperm factors, we found that increased embryo availability and postponement of marriage are the second biggest concern for women seeking OC. Cobo et al. (2016) suggest that at least 8-10 mature oocytes are required to achieve reasonable IVF success.[24] Consequently, considering not all fertilized oocytes can develop into a viable blastocyst and some immature oocytes are commonly retrieved during ovum pick up, multiple cycles of retrieval are sometimes needed to obtain a sufficient number of metaphase II oocytes for freezing.[25] As reported by Diekkebroeck et al. (2010), some women are willing to undergo several cycles of oocyte freezing by an average of 2 times.[26] On the other hand, with an emerging trend of delayed childbearing, women across the world encounter increased risk of age-related infertility. Hodes-Wertz et al. (2013) reported that a total of 478 women had completed ≥1 OC cycle at their fertility clinic, with the majority is to defer reproduction.[27] Therefore, our findings demonstrate that Indonesian women were relatively knowledgeable that there is no guarantee of pregnancy post-IVF, which underlies the decision of OC to increase prospective embryos and also illuminates that awareness about fertility preservation already exists in Indonesia. Most women in the present study had not yet returned to use their cryopreserved oocytes after storage. This is in line with the current trend in other countries where a low return for thaw cycles is reported in the USA and Australia[5]. Similarly, Jones et al. (2018) reported that it was only 8.7% of women returned to use their cryopreserved oocytes.[28] Baldwin et al. (2015) revealed that an intention to try to conceive naturally before using their stored oocytes is identified among women post-OC, especially among younger women. In addition, several participants conveyed that they would try to conceive through a fresh IVF cycle instead of using their cryopreserved oocytes, which may also appear among our study population.[11] In terms of clinical pregnancy, our finding is in agreement with previous reports. It was demonstrated that the clinical pregnancy rate after OC per transfer was 50.7%.[29]

CONCLUSION

Most participants in this study were undergoing OC due to sperm factor, increased embryo availability, and postponement of marriage.

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