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Review Article

Clinical Perspective to Oocyte Cryopreservation

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Abstract

Oocyte cryopreservation has achieved a benchmark in infertility treatment. It is increasingly being used for various medical, legal and social reasons. A major role of which is providing options for fertility preservation in women at risk of compromising fertility due to oncological treatment or chronic diseases, also in oocyte donation, delaying childbirth, thereby eliminating several religious, ethical, and legal concerns of embryo freezing. The introduction of this new 'vitrification' technique has made the success rates for actual conception more reliable than the earlier method of slow freezing. Due to improvements in this techniques and clinical outcomes related with oocyte cryopreservation, American Society of Reproductive Medicine (ASRM) has rightly declared that this technique of oocyte freezing should no longer be considered experimental. Following which, oocyte freezing and egg banking have been proposed for various newer indications.

Keywords: Oocyte Cryopreservation; Fertility; Vitrification; Oocyte Freezing

Introduction

Advances in reproductive technologies continue to offer the infertile couple the opportunity to embrace parenthood despite the limitation of infertility. Cryopreservation is one of these advancements in the field of assisted reproduction. It is being rightly described as 'women's emancipation set in stone [1]. It also serves as a backup method or 'insurance' to women who want to postpone their pregnancy. Cryopreservation of oocyte technique yielded successful pregnancies decades ago in Australia, Europe and the United States.

However, it took a long time to evolve as a routine procedure. As live birth following oocyte freezing was first reported in 1986 [2], this technique has expanded its role encompassing various medical, legal and social indications. Further, developments in the form of Vitrification has provided more reliability compared to an earlier method of slow freezing in terms of actual conception rate. Lilavati Hospital and Research Centre is a pioneer Institute in India for Oocyte cryopreservation, which started in 2007. In this centre, we have performed freezing on more than 1000 oocytes yielding successful pregnancy outcomes. For women with various indications.

Indications

There are several areas where an efficient oocyte cryopreservation program could prove beneficial. Firstly, it can be useful for fertility preservation in females harbouring malignant or premalignant conditions, with promising survival chances post chemo or radiotherapy. Also in certain cases, such as breast cancer, where it is not advisable to wait for the next menstrual period to start a stimulation protocol, considering the urgency of cancer therapy. In such case, the random-start ovarian stimulation protocol has been proposed. Further, oocyte freezing is a very good option for these women as embryos can be created at a later stage when they find a suitable partner, or are in remission period. Apart from malignant cases, it is also useful in fertility preservation for women with several genetic conditions, such as BRCA1 and BRCA 2 mutation.

These women require prophylactic salpingo opherectomy at an early age considering their high risk for acquiring ovarian cancer. In addition, other genetic conditions which have been associated with premature ovarian failure, such as Turner's syndrome, fragile X permutation and deletion of X chromosome. Oocyte freezing is a viable option. This technology further has a role in women whose cytotoxic cancer treatment threatens their ovarian reserve, or

whose medical pathology presents a similar danger. For example, conditions such as severe endometriosis and severe Crohn's disease.

Successful oocyte freezing/thawing technique has led to the creation of a donor oocyte bank which circumvents the need to match recipient's and donor's cycles. Another group of women who may benefit from oocyte cryopreservation are women who wish to delay the childbirth. Social oocyte freezing provides a good option to women who freeze their eggs at the peak of fertility and creating embryos at a later stage. Oocyte cryopreservation also provides a reasonable option in situations where a husband is unable to give a semen sample, due to an unexpected problem or a failure in yielding sperms during testicular biopsy on the day of oocyte retrieval. A novel indication for oocyte cryopreservation is for women with poor ovarian response. Oocyte pooling and egg banking is a practical option in these women, wherein multiple stimulation cycles are done. All the collected oocytes are thawed together and ICSI is performed creating embryos, hence mimicking a similar situation to a normal responder. It also facilitates performing PGS as there are large a number of embryos. A recent indication is being developed for transgender people, who wish to undergo a sex change from female to male. There are some legal/ethical reasons as well for oocyte freezing. For example, in countries like Italy, as embryo freezing is not yet permitted. Oocyte freezing provides a good option and can be used later.

Techniques of Oocyte Freezing

Cryopreservation refers to the cooling of cells and tissues in live condition at such low temperature, that the entire cell metabolism comes to a standstill. Two techniques commonly used for cryopreservation are slow freezing and vitrification. Slow freezing method (equilibrium method) is freezing method, where extracellular ice formation drives cellular dehydration through an equilibrium process. Vitrification (non-equilibrium method) on the other hand, is a form of rapid cooling which utilises very high concentrations of cryoprotectant that solidify without forming ice crystals.

The main problem related to slow freezing method noted was its low oocyte survival rate. Evidence showed that meiotic spindle apparatus may be damaged by intracellular ice formation during the freezing or thawing process [3]. However, modifications in the combination and composition of cryoprotectants in slow freeze protocols have improved the survival rate of frozen MII oocytes. The technique of vitrification as a method to cryopreserve oocytes has achieved remarkable success due to its multiple advantages like being rapid, simple, inexpensive, and higher oocyte survival and pregnancy rates. In humans, most studies suggest that post-thaw survival rates of vitrified oocytes are superior to those that have undergone slow-freeze protocols [4].

A recent Cochrane review has also reported that Vitrification was associated with an increased clinical pregnancy rate compared to slow freezing (RR 3.86, 95% CI 1.63 to 9.11, P = 0.002). The authors concluded that Oocyte vitrification compared to slow freezing probably increases clinical pregnancy rates in women undergoing assisted reproduction [5].

Factors Affecting Success Rate of Oocyte Cryopreservation

Several factors have been attributed to the success of oocyte cryopreservation. Factors, such as age, cause of infertility, stimulation protocols, number of oocytes, cryopreservation methods (slow-freezing and vitrification), and devices (cryotop, cryoleaf, cryotip) [6]. Age remains one of the most important determination factor of all the causes mentioned above. A recent meta-analysis reported live-birth success rates with cryopreserved oocytes show an age-related decline regardless of the freezing technique used, and an aged-based probability of live birth may be calculated for cryopreserved oocytes [7]. Another factor affecting the success is the available number of oocytes for freezing. Study by Rienzi., *et al*. concluded that more than eight vitrified oocytes are required to improve the outcome and delivery rates [8].

Advantages of Oocyte Freezing

Several advantages related to this technique can be described as follows. It simplifies the oocyte donation program as it avoids the need of donor and recipient synchronisation and thus avoids the inconvenience and cost. It also helps in avoiding loss of surplus oocytes in countries, where embryo freezing is not permitted. Most importantly it empowers women by giving them a way to preserve oocytes against the threat of age or disease and provides a better option for cancer patients than the still experimental ovarian tissue cryopreservation as it is not associated with the risk of reimplantation of malignant cells.

Problems Related with Oocyte Freezing

Despite its advantages, several concerns have been expressed with oocyte freezing. There is a concern related to damage of the meiotic spindle as well as cellular and subcellular alterations that may lead to chromosomal or other cellular anomalies. However,

studies are reassuring in this regard. Cobo., *et al*. [9] showed no increase in numerical chromosomal abnormalities in embryos derived from oocytes slow-frozen compared with non-frozen controls.

As stated in the ASRM-SART guideline, "there is not yet sufficient statistics to recommend oocyte cryopreservation for the solitary purpose of circumventing reproductive aging in women because there is no data to support the efficacy, safety, ethics, emotional risks, and cost-effectiveness associated with oocyte cryopreservation for this indication" [10]. There is a need for long-term studies on congenital anomalies and health risk associated with egg freezing.

There is also a theoretical concern related to infectious disease due to the use of open vitrification methods. However, infectious transmission has never been observed in reproductive tissues from this technique [11].

Conclusion

Women putting their 'eggs on ice' have made several headlines. A recent review in 2016 summarised the history, indications, techniques, and outcome of this technique. It stresses on 'the real need to monitor what is being done,and the success rates achieved [12]. It also points out that there is still a need to obtain quantitative as well as qualitative information.

Oocyte cryopreservation has provided high pregnancy and implantation rates, and thus can be considered as an efficient treatment procedure in ART. It has expanded its role from fertility preservation in cancer patients to several non-medical indications including women with risk of reduced reproductive capacity owing to age-related fertility decline. Further improvements in the form of vitrification technique with successful clinical outcomes are likely to result in an increased utilisation of oocyte cryopreservation in clinical practice.

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Volume 1 Issue 1 June 2017