REVIEW ARTICLE

Fertility preservation in young patients' with cancer

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ABSTRACT

Preservation of fertility is an important issue in the management of young cancer patients. Though embryo cryostorage is a well-established procedure, it can only be availed by couples. Recent studies have indicated increasing success rates with mature and immature oocyte cryopreservation. Cryostorage induces injuries on the human oocytes which can be minimized by slow freezing and vitrification. Selection of candiidates is crucial so that the most suitable technique can be offered without any delay in initiation of cancer therapy. Factors affecting suitability are age of patient, assessment of ovarian reserve, hormonal status and type and stage of neoplastic disease. Encouraging results have been obtained with oocyte *in vitro* maturation (IVM) followed by vitrification for cryostorage. Data on the use of vitrified eggs in routine *in vitro* fertilization (IVF) show that pregnancy rates can be comparable to those achieved with fresh oocytes.

Key Words: Cancer, oocyte cryopreservation, vitrification

INTRODUCTION

During the past three decades, fertility preservation has become an important issue in cancer patients' management. Survival rates have improved dramatically in childhood cancers and also in young women who undergo cancer treatment,[1] leading to long term cancer survivors who are affected by iatrogenic infertility and premature ovarian insuffiency.[2] Abdominal radiotherapy, total body irradiation, and chemotherapy regimens all lead to ovarian damage consequently leading to infertility.

Though disease remission is the first goal of cancer treatment, greater attention is being focused on the delayed effects of cancer treatment and towards safeguarding future fertility.[3]

Many approaches have been considered to preserve fertility. Embryo cryostorage is a well established technique but may be available only to couples. Survival rates per thawed embryo range between 35-90%, implantation rates between 8-30% and cumulative pregnancy rates >60%.[4]

Oocyte cryostorage is considered as an important tool for fertility preservation as no surgery is required and minimally invasive ovarian stimulation protocols are available.

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There are certain challenges faced in breast and endometrial cancer patients as conventional ovarian hyperstimulation regimens in *in vitro* fertilization (IVF) cycles result in estradiol levels which may be 10 fold higher than peak estradiol levels seen in natural cycles, and thus may not be recommended in breast cancer patients'.[5]

Even though tamoxifen results in peak estradiol levels, it can block the effect of supraphysiological level on breast tissue and inhibits the growth of breast tumors by competitive antagonism of estrogen at its receptor site.[6] Endometrial cancer patients' cannot be given tamoxifen for ovarian stimulation since it has a stimulatory effect on endometrium, for such patients' aromatase inhibitors can be used for ovarian stimulation, *in vitro* fertilization (IVF) and embryo cryopreservation.[7] Aromatase inhibitors have shown to benefit in ovulation induction alone or in combination with follicle stimulating hormone (FSH). They have also been suggested in the treatment of poor responders.[8]

Mature and immature oocyte cryopreservation: Since embryo cryopreservation may not be an option for single

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women, freezing of mature and immature oocytes can be considered instead. However, early results with oocyte cryopreservation have been disappointing with low survival, fertilization and pregnancy rates after IVF of thawed oocytes.[9] Recent studies have suggested increasing success rates.[10]

In earlier reports, survival and fertilization rates of frozen-thawed mature oocytes varied between 25-95%.[11] Review of recent data revealed a mean survival rate of 47%, mean fertilization rate of 52.5%, and a mean pregnancy rate per thawed oocyte of 1.52%. Cryostorage induced injuries on human oocytes include ice crystal formation, osmotic stress and toxicity of cryoprotectant agents, zona pellucida cracking, mitochondrial shrinkage and alterations in microfilaments.[12] The main consequences of freezing/thawing procedures involve organelle displacement, mitochondrial disruption, vacuolization of the cytoplasm, loss of spindle cell polarity with predisposition to an altered chromosomal alignment.[13] Cryobiology aims at minimizing these harmful effects and two well-established laboratory protocols have been proposed. The slow freezing protocol and the vitrification protocol.

Selection of candidates for fertility preservation is crucial in order to offer the best suitable technique for each patient. The procedure should be safe, having a good chance of oocyte retrieval and a minimal risk of growth of the preexisting neoplasm. It should also be quick so that there is no delay in initiation of cancer therapy.

Oocyte cryopreservation is the best technique to preserve fertility of women without an established partner and may be preferable to ovarian tissue freezing since it obviates the need of surgery.[14] The age of the woman is the most important limiting factor for oocyte cryopreservation. Storage of oocytes in women above the age of 40 years results in a very poor chance to get a pregnancy in the future. Assessment of ovarian reserve is important. Besides age, factors such as antral follicle count, hormonal levels like follicle stimulating hormone (FSH) and anti-mullerian hormone (AMH) need to be considered. The procedure involves a controlled ovarian hyperstimulation with exogenous gonadotrophins that lead to supraphysiological and high levels of serum estradiol. Type and stage of neoplastic disease and patients' overall health status influence the feasibility and selection of protocols of ovarian stimulation.[15] This procedure may not be suitable for prepubertal girls since their hypothalamic, pituitary,ovarian axis is not fully developed. Ovarain cortex ablation and cryostorage with subsequent autografting is an option available to prepubertal girls, however it is still experimental with limited results.

The growing body of literature shows encouraging results of oocyte *in vitro* maturation (IVM) followed by vitrification for cryostorage. This option consists in the possibility of retrieving immature oocytes from unstimulated preantral follicles, which are arrested in the prophase of first meiotic division. The technique is safe and effective for all oncological patients' as no hormonal stimulation is needed and is not limited by any time restriction. The effectiveness of the procedure appears to be higher when immature oocytes are first matured *in vitro* and then frozen.[16,17] Some data also suggest that immature oocytes could be less sensitive to cryodamage than mature oocytes since their nuclear apparatus was not fully developed and after thawing could be matured *in vitro* to metaphase II.[18] Cryopreservation of immature oocytes should be considered in oncological patients' who cannot undergo hormonal stimulation with high peak estradiol concentrations.

Slow freezing and rapid thawing was the first cryostorage protocol adopted for oocytes in IVF laboratories and was originally introduced with the aim to preserve supernumerary embryos obtained from assisted reproduction procedures. It is considered the gold standard technique for oocyte cryopreservation for years with survival rates of 60-80%.[19,20] However, few authors have observed a detrimental effect of high sucrose concentration on oocyte cytoplasm organelles and have proposed alternate freezing techniques and timing schedules. Clinical reports on slow freezing show a pregnancy rate ranging between 13-20% (pregnancy/embryo transfer) and implantation rates still low in comparison to those in fresh cycles.[21] Grifo and Noyes compared slow freezing to vitrification on sibling oocytes showing similar results in terms of survival, but higher fertilization and blastocyst formation rates using the former.[20]

Vitrification method is a relatively recent phenomenon in human IVF. The scientific basis of vitrification consists in the ultrarapid freezing of cells, whose intra- and extracellular environment turns into a glassy like state. Vitrfication combines two different biophysical processes: A preliminary equilibration step, in which oocytes are exposed to low concentrations of cryoprotectants to allow water outflow, and a subsequent vitrification phase in which cells undergo a high osmotic gradient that completes cell dehydration. In this condition, the oocytes can be directly merged into liquid nitrogen and then subsequently stored. Oocytes must be warmed rapidly to avoid recrystallization of water. The cryoprotectants used during vitrification are the same as slow freezing such as ethylene glycol (EG), sucrose, 1,2 propanediol (PROH) and dimethyl sulphoxide (DMSO) but are more concentrated.

Successful vitrification occurs when samples are loaded in a minimal fluid volume and then frozen/thawed at an extremely fast rate (1500-2000°C).[22] Although no cross contamination between liquid nitrogen and stored oocytes have been reported to date, closed systems may provide a safer and more effective vitrification procedure. Oocyte survival after vitrification reaches 90% in several reports.[16,23] Oocyte spindle repolymerization occurs within an hour of warming suggesting that the ultrastructure of these gametes is better preserved by vitrification than slow freezing and metabolomic profiling of vitrified oocytes is comparable to fresh eggs.

Data on the clinical use of vitrified eggs in routine IVF show that pregnancy rates can be comparable to those achieved with fresh oocytes.[14] Studies which have compared vitrification and slow freezing have reported implantation and pregnancy rates higher with vitrification but the number of observed cases have been very low. Though significant improvements have been achieved in the clinical effectiveness of oocyte freezing and thawing techniques, further studies need to be done to establish an optimum protocol for oocyte storage so that maximum women can be benefitted.

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