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Editorial

Female Fertility Preservation: Current Challenges and Future Prospects

A Shirazi[1,2]*

[1]Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Shahid Beheshti University, Iran
[2]Research Institute of Animal Embryo Technology, Shahrekord University, Iran

There are several fertility preservation options that would be of use in those females at the risk of fertility loss. The young women suffering from premature ovarian insufficiency after being exposed to gonadotoxic treatment or galactosemic patients, and those suffering from premature ovarian failure due to hereditaryissues or age-related infertility are the main candidates for fertility preservation. Apart from third-party assistance through gamete donation, gestational carriers, and adoption, fertility preservation is highly important from an ethical standpoint where the restoration of autonomy is concerned especially in those who wish to have their own child and might, in the future, become unable to conceive, due to treatment's side effects.

Currently, among different options, embryo and oocyte cryopreservation are the established fertility preservation techniques that can be offered widely to the women at the risk of fertility loss. Apart from restricted number of resulting oocytes or embryos and the impossibility of doing so in prepubertal women, both of these approaches involve hormonal medication that lead to delay in commencing treatment for the patients who are in need of urgent treatments.

To resolve this problem, *in vitro* maturation of oocytes as an attractive alternative for fertility preservation in cancerous patients does not require ovarian stimulation and can be performed at any time of the menstrual cycle which avoids delay in commencing treatment. Additionally, this technique can be combined with ovarian tissue cryobanking.

On the other hand in pre-pubertal girls, cryopreservation of ovarian tissue with subsequent re-transplantation after cessation of treatment is the only feasible approach. There are however various fertility preservation strategies for reduction the treatment's side effects in cancerous patients such as medical therapy before chemotherapy, ovarian transposition and pelvic shielding. Apart from established fertility preservation options there are, however, a few approaches though experimental which may be applicable in the future such as *in vitro* maturation of nonantral follicles, application of artificial ovary, and oogonial stem cells therapy.

Besides fertility preservation options and as adjunctive therapy, tissue- or cell-based hormone therapy in particular the artificial ovary is one of the most promising developments in fertility medicine that can provide a more natural form of hormone replacement therapy (HRT)

The engineering of bioartificial ovaries is an alternative way of restoring fertility in patients who cannot benefit from transplantation of cryopreserved ovarian tissue due to the threat of reintroducing malignant cells. Moreover, using this approach the ovarian cells in a capsule would stop the artificial ovary from being rejected by the patient immune system and allow the function of donatives ovarian tissue for women whose ovaries aren't functioning.

By using artificial ovary by coaxing three primary ovary cells (oocyte, granulose, and theca cells) into a 3-D structure resembling an ovary, immature eggs can be retrieved and then matured outside of the body. Therefore, women would not have to go through hormones of ovarian stimulation. Additionally, immature eggs may be better able to withstand freezing than mature eggs and accompanied ovarian somatic cells offers hope to replace natural ovarian hormones in women with premature ovarian failure or in women going through menopause. It would also allow body's feedback mechanisms to control the release of ovarian hormones. Transplantable artificial ovary is now wholly conceivable as an alternative method of HRT, opening up new perspectives to restore endocrine activity and fertility in women at a risk of ovarian insufficiency.

There are two main approaches to produce artificial ovary including: I) encapsulating ovarian cells (theca, granulose and oocytes) in multilayered alginate microcapsules and II) production of 3D artificial organ by growing hormone-producing cells onto the decellularized ovarian scaffold so that all ovarian cells are removed from tissue pieces, leaving a decellularized scaffold of extracellular matrix on which the patient ovarian cells are then seeded for transplantation. In biodegradable artificial ovary the isolated follicles and ovarian cells are able to survive and grow.

As an artificial ovary, autografting of isolated preantral follicles (PFs) and ovarian cells encapsulated in two fibrin matrices containing low concentrations of fibrinogen and thrombin has shown the survival and growth of isolated murine ovarian follicles 1 week after autotransplantation. The results are indicated that fibrin as an alternative for alginate is a promising candidate as a matrix for the construction of an artificial ovary.

The multi-step culture system of ovarian follicles is another approach for fertility preservation in which the primordial follicles in small ovarian cortical strips are cultured to the preantral stage. The pre-antral follicles are then dissected out and cultured, through 3-dimentional system, in activin-supplemented media. Once the follicles reach the antral stage, the oocyte–cumulus complexes are removed and cultured for a final period of development (in vitro maturation). The multi-step culture system is often applied to secondary and not to primordial and primary follicles whereby the *in vitro* culture (IVC) of isolated PFs need a more sophisticated IVC system, and may be affected by the isolation procedure.

It has been shown that medium supplementation with GDF-9 can maintain the survival of PFs and promote the activation of primordial follicles. Furthermore, GDF-9 can stimulate the transition from primary to secondary follicles and maintain the follicles' ultrastructural integrity. In this context, IVC of isolated caprine PFs has had promising

***Corresponding author:** A Shirazi, Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Shahid Beheshti University, P.O. Box: 19615-1177, Tehran, Iran, Tel: 0098 21 22404144; Fax: 0098 21 22432021; E-mail: shiraziabbas@yahoo.com

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results such as maintenance of follicular survival, follicle and oocyte growth, antrum formation, meiosis resumption and development of embryos following IVC of resulting oocytes.

The recent findings indicating the presence of ovarian stem cells (OSCs) in mice, which can presumably lead to a replenishment of follicles, has challenged the central doctrine of age-dependent follicle depletion in women. Accordingly, this has opened the door to a novel fertility preservation approach that would be of use in those female patients who, for reasons of age or urgency for treatment, the routine fertility preservation approaches are not applicable.

The presence of OSCs not only demonstrate the ability of adult human ovarian tissue to support folliculogenesis, but also provide the evidence that the ovarian follicle pool in women may, similar to that in mice, be amenable to renewal as natural precursor cells of oocytes.

Hypothetically, if human OSCs can be transplanted into human ovarian cortex and the ensuing primordial follicles are cultured in vitro in a serum-free multi-step system, any resultant mature competent oocytes can be used in IVF procedure.

Another possible strategy is the injection of isolated OSCs into a patient's ovaries, where they, theoretically, could undergo neo oogenesis in vivo and generate an entire population of hormone-secreting follicles that can provide a more physiological condition for oocyte development. This approach may have an additional benefit on general health consequences associated with the menopause state. To date, human OSCs have only been grown to early follicle-like structures in a xenotransplantation model, which is not acceptable in clinical use.

In case of realization of this approach, apart from its application in prepubertal girls, doing socanpreventthedelayin commencing lifesaving treatment and employs a method to prevent transplanting cancer cells back into a patient. This is also encouraging from a fertility preservation point-of-view, as it means that ovarian cortical tissues removed from girls or women can be safely stored until OSCs are required.

In conclusion, there is a very long way to go before the new topics discussed here, (artificial ovary, in vitro folliculogenesis, and ovary stem cells) be clinically applicable in human fertility preservation. Nonetheless, despite the limitations and distant prospect, it seems the novel approaches can provide promising results following strenuous studies in the future.

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