Fertility on Ice

Preserving Fertility with cryopreservation

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Oocyte Cryopreservation is an emerging field in Assisted Reproductive Technology (ART), owing largely to the advancement in cryopreservation techniques in recent years. Since a successful life birth from oocyte freezing over three decades ago, oocyte cryopreservation is no longer considered experimental and in fact is an integral part of ART.

Techniques

Cryopreservation implies cooling of cells and tissues to sub-zero temperature in order to halt all biological activities and keep them for future use. Successful pregnancies from frozen oocytes were first achieved in late 1980s, using slow freeze and rapid thaw cryopreservation techniques (Chen 1986, 1988; Van Uem 1987). However, the progress was slow due to low success rates and technical concerns. Over the past decade, Vitrification a.k.a. ultra-rapid cooling has become the preferred technique over slow freezing which was favoured in early protocols. Slow freezing results in liquid changing to a solid state whereas vitrification results in solidification of cell into glass -like state without formation of ice.

Trend towards Vitrification

Studies in the past few years have demonstrated the superiority of vitrification over slow freeze protocols. Vitrification has demonstrated better survival, fertilisation and pregnancy rates (Cao 2009; Fadini 2009; Smith 2010) although only Fadini (2009) reported significant higher pregnancy rates. There is also increasing evidence on the efficacy of IVF with vitrified oocytes suggesting similar outcomes to IVF with fresh oocytes, with oocyte survival rates over 84% (Nagy 2009; Almodin 2010; Ubaldi 2010; Rienzi 2012).

Outcome of Oocyte Cryopreservation

Data from several studies with regards to the efficacy and safety of oocyte freezing has been reassuring. The mean birthweight, incidence of congenital abnormalities (2.5%) were similar in infants born following oocyte vitrification to those born from spontaneous conception or through regular IVF (Chian 2008). Long term follow- up of these children has yet to be published.

Clinical Applications

Although oocyte preservation was initially conceived as a method of fertility preservation for medical indications in clinical practice, the most noticeable growth has been its elective use as means to circumvent age related decline in women's fertility in recent years.

Fertility Preservation in Cancer Patients

Cancer treatment regimes can have detrimental effect on women's fertility. The extent of damage depends on the ovarian reserve, age of patient, type and dose of treatment. The demand of fertility preservation amongst women in the reproductive age group has increased with improving cancer survival rates (Fleischer 2011; Noyes 2011).

Oocyte cryopreservation can now be offered to cancer patients who require fertility preservation. Initially, the disadvantage of cryopreserving mature oocytes in cancer patients is the need for ovarian stimulation. This can delay cancer treatment and carry particular risk for those with hormone sensitive cancer (Kim 2011a). However, newer protocols with

shorter duration of ovarian stimulation (under 2 weeks) and duo-stimulation (two cycles of controlled ovarian stimulation in succession within one menstrual cycle) allows more oocytes to be harvested and cryopreserved. Additionally, random start ovarian stimulation protocol allows flexibility in starting of ovarian stimulation. These have enabled more flexibility in terms of controlled ovarian stimulation without undue delay in cancer treatment.

Ovarian tissue banking which does not delay cancer treatment serves as an alternative to oocyte cryopreservation, especially in the paediatric population. Partial or total oophorectomy is performed surgically typically as day case. This can be done independent of the menstrual cycle. The disadvantages are that patients need to be fit for surgery, and the tissue must subsequently be re-grafted, with potential risk of reintroducing malignant cells (Hoekman 2015). A combination of oocyte cryopreservation with ovarian tissue banking may be the most effective fertility preservation technique in cancer patients (Donnez and Dolmans 2013).

It is crucial that women are referred quickly to fertility specialists in order to discuss their options and initiate treatment (Kim 2011a) since oocyte cryopreservation is available for cancer patients. The overall accessibility to fertility counselling for fertility preservation amongst oncological patients needs to be improved (Lee 2011).

Fertility Preservation in Non-Cancer Patients

Oocyte cryopreservation can be an important fertility option for women with range of medical conditions other than cancer (Donnez and Dolmans 2013). Women with endometriosis who may experience reduced ovarian reserve after surgery (Elizur 2009), women with autoimmune diseases requiring gonadotoxic drugs, and women with genetic conditions with risk of premature menopause, ie Turner's syndrome, Fragile X premutation and deletions of X chromosome. Early diagnosis of these conditions may raise the possibility of fertility preservations in the population (Borgstrom B 2009). The efficacy and risk of chromosomal abnormalities in offspring however remained to be elucidated.

Elective Oocyte Cryopreservation

There is an increasing trend to delay motherhood among women worldwide. Age related decline in fertility among women, which accelerates after 35 is a well-known phenomenon (Dunson2004; Sozou and Hartshorne 2012). This has resulted in the rising number of women experiencing unintended childlessness as many women are unaware of the effect of age on fertility (Lampic 2006; Hashiloni-Dolev 2011; Daniluk 2012). Amongst the infertile couples, age related diminished ovarian reserve, aneuploidies and fetal losses are significant contributory factors, which cannot be overcome by ART. Official recognition of infertility as a disease entity by the World Health Organisation, American Society for Reproductive Medicine and most recently American Medical Association implicitly suggest a role for prevention.

Oocytes cryopreservation, more commonly known as 'social egg freezing' in the media has become a popular subject after its use as a preventive measure for women to circumvent age-related fertility decline. There has been an increasing demand as well as a growing debate surrounding its use.

Oocyte cryopreservation has been regarded as a 'breakthrough for reproductive autonomy' (Harwood 2009), it gives women the ability to make reproductive choices, to decide when and with whom they wish to have children, just like oral contraceptives which give women control over the timing and circumstances of their pregnancy.

There have been several reports from large centres showing comparable live birth rates with the use of cryopreserved oocytes in IVF compared to fresh oocytes. In addition, there are economic savings considering that older women often undergo multiple cycles when using their own eggs (Leridon 2004) before considering different options such as gamete donation which can be psychologically and emotionally challenging. The use of cryopreserved autologous oocytes on the other hand allows the mother to have her own genetic child.

Success with oocytes cryopreservation is determined by a number of critical variables, including age at time of cryopreservation, number of oocytes cryopreserved and technical consideration at time of cryopreservation among others. Despite reassuring data on its outcome, women should be given the correct information about its success rates as even in optimal circumstances a patient pursuing IVF with cryopreserved oocytes may fail to conceive. While well understood by the clinicians, this truth may be at odds with patient's expectations of it being preventive.

Amongst others there are also concerns with the risks of the process of controlled ovarian stimulation and oocyte retrieval. If the women eventually conceives at an older age, there are risks of pregnancy complications such as pre-eclampsia, gestational diabetes and caesarean sections (Ziadeh and Yahaya 2001; Joseph 2005).

Women may also bank their oocytes for various reasons such as a lack of partner, career aspirations or

unreadiness. They consider this as a risk management strategy because they want to reduce their risk of childlessness in the future. It is prudent that women are well informed about their age-related probability of success and technology's limitations.

In summary oocyte cryopreservation is a reasonable strategy to reduce the possible burden of infertility, provided women receive the correct information in order to reduce regret if the initial treatment fails. It is now an established technology with a wide range of indications. Besides similar fertilisation and pregnancy rates of vitrified oocytes when compared to fresh oocytes, there is no increase in chromosomal abnormalities, birth defects or developmental delay amongst children born from cryopreserved oocytes. Indeed, fertility on ice is a new buzzword for ART!

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