Fertility Preserving Options for Women (Egg Freezing)

Introduction

Statistics show a consistent increase in the proportion of women choosing to delay child bearing until later in their reproductive years. This trend has largely been attributed to the increase in women pursuing postgraduate education and higher levels of professional achievement. Because the ability to conceive is strongly linked to a woman's age, many are therefore facing a decrease in fertility by the time they wish to conceive. Infertility increases significantly after 35 to 37 years. By 40 years, 50% of women are physiologically incapable of having children and by 45 years this is almost 100% although there will always be sporadic instances of women conceiving after this time.

Socially, the awareness of age related fertility decline is increasing and so interest in technologies to preserve fertility has grown enormously. Traditionally these procedures and technology were considered for women undergoing potentially sterilising treatment such as chemotherapy, radiation therapy, or removal of ovaries. Increasingly, elective use of these technologies to preserve fertility and therefore to prolong reproductive life is being used. However many aspects of this approach remain controversial.

Age related decline infertility - an important concept

This decline has been established by a number of observational studies, which consistently demonstrate a decline in pregnancy and birth rates. Furthermore as the ability to fall pregnant every month *(fecundability)* decreases, so too the ability to deliver a live baby *(fecundity)* decreases. The decrease in fertility is not simply due to a decrease in number of oocytes (eggs). The oocyte pool peaks when the female fetus is in utero, reaching approximately 6 to 7 million at 20 weeks gestation. There is progressive loss of oocytes (atresia) so that the number of remaining oocytes is in the order of 1 to 2 million at birth and 200,000 at the onset of puberty.

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There is continued atresia during reproductive years, leading to the average age of menopause, which is 52 years. At this age there are approximately 1,000 viable oocytes remaining. However these oocytes may not be responsive to the hormone fluctuations of the cycle and may not ovulate, or indeed the chance of a pregnancy.

As the number of oocytes declines over time, the quality of oocytes declines eventually reaching a critical threshold below which a pregnancy is unlikely.

This decrease in quality primarily reflects an increased prevalence of oocytes, which have abnormal chromosomes (aneuploid). It is estimated that the prevalence of aneuploid oocytes reaches around 100% after the age of 45. Extensive experience with assisted reproductive technology (ART) through egg donation shows that reproductive ageing is primarily due to the age of the oocyte and there is very little if any influence by the age of the uterus or the recipient. The ability of the uterus to successfully host a pregnancy is maintained despite maternal age. This is of course, dependent on other medical or surgical factors, which may also increase in prevalence with age. *As a result the probability of a pregnancy when using donor eggs is determined by the age of the donor rather than the age of the recipient.*

Advancing paternal age

The age of the sperm donor is also important, but not as important as the age of the prospective mother. Furthermore "young" oocytes are able to correct abnormal sperm and so often an ageing male will readily be able to conceive with a younger female. However as the male age increases, so too does generally the age of his partner.

Options for fertility preservation

There have been several strategies for preserving fertility. Briefly these are embryo freezing, egg freezing and ovarian cortex freezing.

1. Embryo Freezing (cryopreservation)

This is the technology with which we have the most experience and success to date. The world's first frozen embryo pregnancies were conducted by Monash IVF in the 1990's. Cryopreservation has now reached a level, where the vast majority of embryos survive freezing and thawing and may go on to provide perfectly healthy pregnancies. In this setting cryopreservation may be relevant in delaying transfer of embryos already created during an IVF cycle, or creating embryos, without a transfer, for elective freeze and delayed transfer. This obviously depends on the availability of a suitable sperm donor, either partner or donor.

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Again *live birth rates from frozen-thawed embryos depend on the age of the woman at the time that the egg was retrieved*. Obstetric outcomes in pregnancy resulting from frozen embryos are generally slightly better than those from freshly transferred embryos.

2. Cryopreservation of oocytes

The success of freezing of mature eggs has improved dramatically over the last ten years, and is no longer considered experimental. In women who do not have a male partner and who are not currently interested in donor insemination, oocyte preservation is generally the preferred option. It is worth remembering that neither large studies nor long follow up on children born of cryopreserved oocytes exist.

As with embryo freezing, ovarian hyper stimulation followed by egg retrieval is necessary. The mature eggs (those which result, after normal ovulation, whether it is spontaneous or induced by an IVF cycle) are frozen shortly after retrieval. Although the first pregnancy from egg freezing was reported in 1986 the overall success rate remained low for many years. This situation is now improving; however results still lag slightly behind embryo freezing.

The most effective way to freeze eggs is by vitrification as practiced by Monash IVF. This results in less "freeze injury" to the oocytes. Difficulty with egg freezing and fertilisation relate to hardening of the shell around the egg (zona pellucida), which is a consequence of freezing, membrane permeability ("leakiness"), sensitivity of the egg to low temperatures and susceptibility of the egg to toxicity from the freezing medium. These difficulties have been partly overcome by ICSI (intracytoplasmic sperm injection) where a viable sperm is injected through the shell of an egg. Freeze damage has been reduced by use of cryo protectants which permeate the cell membrane, such as propylene glycol and protect the egg from ice crystal formation. *Vitrification* is the best approach to oocyte freezing. It is based on the principal that metabolically active cells can be cooled so rapidly that ice does not have time to form. The first birth from vitrified human eggs was reported in 1999. Analysis of a total of five reports at the time of writing, on vitrification estimate that fertilization rate are around 75%, clinical pregnancy rates around 45% per transfer and live birth rates around 36% per transfer. These rates are probably close to those achieved using frozen-thawed embryos.

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Freezing of ovarian tissue

Ovarian tissue freezing is currently investigational. The theoretical advantage is that it has the potential to preserve a large number of eggs within primordial follicles (developing blisters) in the ovarian cortex without the need for ovarian stimulation. Theoretically the ovarian tissue can be reimplanted into the pelvis or elsewhere, where they will establish a blood supply and go on to produce viable mature oocytes. As at 2013, only 24 live births had been reported from this technology, in the world. This procedure is generally reserved for women at high risk of ovarian failure from cytotoxic drugs (for treating cancer) or radiation. It is still considered to be an investigational procedure in women considering fertility preservation for delayed child bearing.

Maximum age of for egg cryopreservation

Theoretically the maximum age for attempted egg freezing may be as high as 45 years, however in view of the above data, it is likely that most of these eggs would not have correct chromosome and are unlikely to result in a pregnancy. The best age to freeze oocytes, in terms of yield would be in the mid to late 20's however, many women in this situation will go on to find partners or undertake a spontaneous pregnancy prior to using these oocytes. *Recent studies suggest that the most cost effective age to freeze oocytes is at around 37 years*. This means that there is the best balance of chance of using the oocytes, oocyte yield and oocyte age. I would very rarely recommend that women freeze oocytes at the age of 45 years, unless they were fully aware of the low chance of a resultant pregnancy and therefore poor cost effectiveness.

Age of child bearing: until what age can I retain my oocytes?

Theoretically, once oocytes are frozen, they remain the property of the woman and may be used up to the age of natural menopause (average age 52 years). I consider this a socially responsible policy. If a woman wishes to undertake a pregnancy at this age, she must be aware of potential medical co morbidities that may affect her health during and after the pregnancy. I would also recommend extensive screening for concomitant medical problems, which would generally involve a cardiac stress echo, mammography, gastroscopy and colonoscopy. The issue here is not so much age of child bearing rather the number of healthy years a woman can expect in order to spend time raising her child.

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Are there any risks to the offspring?

Preliminary outcomes from egg preservation pregnancies are encouraging however numbers worldwide remain low and studies involving prolonged follow up are infrequent. Therefore, although we strongly suspect that children enjoy a healthy life afterwards, robust data is still lacking. There have been no reports of an increase in congenital anomalies from oocyte freezing.

Logistics and the cost including Medicare rebates

At the moment, Medicare does not cover elective oocyte freezing, for social reasons. Social reasons may loosely be defined as pure patient choice. Medically indicated freezing would apply to women who have pre-existing conditions which we know from experience will greatly impact on their fertility, with a chance of rapid evolution over the next several years, resulting in decreased fertility. You will need to undergo tests before we can decide if this applies to you. These will simply involve ultrasound and blood tests. If your ovarian reserve is estimated to be much less than usual, then this may qualify you for Medicare rebated therapy on the grounds of incipient ovarian failure.

It might be considered that freezing eggs at this stage is actually cost effective, as it would avoid subsequent multiple IVF cycles at cost to the community.

It is worth reiterating, that success rate is most clearly linked to oocyte age i.e. the age of the female at the time of the freezing. You will need to enquire at the time of consultation regarding current out of pockets for oocyte freezing.

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