Elective egg freezing

State of the ART

CPD

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Background
Women are having children later in life, and the risk and prevalence of involuntary childlessness is thus increasing. Oocyte storage is widely available and increasingly used for elective (non-medical) indications by women trying to safeguard future fertility. There is controversy, however, regarding who should consider oocyte freezing, at what age and how many oocytes should be frozen.

Objective
The aim of this article is to provide an update on the practical management of non-medical oocyte freezing, including patient counselling and selection.

Discussion
The latest studies indicate that younger women are less likely to return to use their frozen oocytes, while a live birth is far less likely to result from oocytes frozen at an older age. While not guaranteeing a future pregnancy, oocyte cryopreservation is also associated with a substantial financial burden and uncommon but serious complications. Therefore, patient selection, appropriate counselling and maintenance of realistic expectations are crucial for this new technology to be used with the greatest positive impact.

FERTILITY DECLINE in women is age related as a result of a finite supply of eggs (oocytes). Furthermore, the best-quality oocytes are released early in reproductive life; as a woman ages, the quantity and quality of oocytes decrease. This decline is gradual but becomes exponential at approximately the age of 35 years, with a significant decrease in the chances of spontaneous conception every year. Despite widespread belief that contemporary artificial reproductive technologies (ART) can alleviate such fertility decline, they cannot.[1] In particular, in vitro fertilisation (IVF) is ill-suited for this purpose, and the chance of its success declines in line with the chance of spontaneous conception. Complete oocyte exhaustion and inability to achieve either spontaneous or IVF-conceived pregnancy occurs in the mid-40s.

As a result of a variety of societal changes, the average age at first motherhood has been gradually increasing; from 2010 to 2020 there was an increase from 28.3 to 29.6 years.[2] Concurrently, the proportion of mothers giving birth later in life has also increased, where 36% of all mothers are aged between 30 and 34 years at the time of giving birth. Interestingly, 37% of women in this age group are childless, while their fertility is at its peak.[3] These trends show an increased prevalence of postponing motherhood in Australia. This, together with suboptimal awareness surrounding fertility, has led to an unfortunate consequence of increasing prevalence of involuntary childlessness, the extent of which is difficult to quantify (estimated to be approximately 5%[4]) but has significant negative health and emotional consequences.[5] Furthermore, a significant proportion of women and couples do not achieve their desired family size.

Oocyte cryopreservation is a relatively new technique that became possible because of advances in cryopreservation techniques, in particular vitrification or snap freezing. The oocyte is the largest cell in the human body and, as such, is difficult to freeze by conventional means while avoiding ice crystal formation that creates irreparable damage. Vitrification addresses this problem,[6] with thawed oocyte survival of up to 97%.[7] Latest reports indicate that the reproductive potential of oocytes is minimally altered by vitrification and is comparable to fresh oocytes.[8,9] The obstetric and neonatal outcomes of children born from vitrified oocytes also appear to be comparable to children conceived via conventional IVF.[10,11] These reassuring developments prompted the American Society for Reproductive Medicine to remove the 'experimental' designation from oocyte vitrification[7] and

to consider oocyte vitrification to preserve future fertility 'ethically permissible'.[12] This sentiment is echoed in the Australian guidelines.[13]

Oocyte cryopreservation pros and cons

The process of oocyte cryopreservation is identical to the egg maturation/collection process in conventional IVF. An oocyte freezing cycle involves daily self-administered hormone injections for 10–16 days, ultrasonography to monitor ovarian response, a 'trigger' injection to achieve final oocyte maturation and an oocyte collection, which is usually performed with light sedation under ultrasound guidance.[14] Despite its simplicity and demonstrated utility, there are three broad areas of concern that have been expressed in relation to widespread adoption of this technology: possible complications, cost and the rate of future use of stored oocytes. It must be stressed that oocyte cryopreservation, and IVF in general, does not adversely affect future fertility potential. These interventions do not reduce the overall oocyte pool available for spontaneous conception or fertility treatments in the future.

Complications

Medical complications are related to ovarian stimulation and the procedure of oocyte retrieval. The most common clinically significant complication of ovarian stimulation is ovarian hyperstimulation syndrome.[15] It can result in significant morbidity; however, with current stimulation protocols it has become very uncommon in the elective oocyte cryopreservation setting.[16,17] Surgical morbidity related to oocyte retrieval – such as infections, bleeding, pain and anaesthetic complications – is estimated to occur in 0.4% of oocyte retrievals, with a 0.1% risk of requiring further surgical interventions.[18]

Costs

The cost associated with oocyte cryopreservation is a significant barrier to its widespread use. To attract a Medicare Benefits Schedule rebate and medication subsidy in the setting of oocyte cryopreservation, a patient is required to be medically infertile or at a significant risk of imminent fertility decline (eg prior to chemotherapy). Most oocyte freezing cycles are done without medical indications, and therefore the full cost of the cycle is usually billed to a patient directly. This includes cycle fees, medication costs, day procedure costs and anaesthetic fees. The current total price of an oocyte vitrification cycle ranges between $5,000 and $10,000, depending on the fertility clinic and the types of medications that are used for ovarian stimulation. There are suggestions that elective oocyte freezing should be publicly funded, and there appears to be some support for this from the broader public.[19] An innovative solution was proposed by these authors' group, where people who were electively freezing oocytes would be reimbursed if they were to donate their oocytes should they decide not to use them.[20] Other options for disposal of unused oocytes include altruistic donation to either known or anonymous recipients and oocyte donation for research. Should these be widely taken up, it would not only improve the cost-effectiveness of oocyte cryopreservation, but is also likely to increase its overall societal acceptance and may enhance enthusiasm for its public funding.

Future use

Rate of future use of frozen oocytes is inversely related to the age at which oocyte cryopreservation is undertaken. Younger patients are less likely to use their frozen oocytes in the future[21] but are more likely to achieve a live birth using their frozen oocytes,[22] compared with older patients. This raises the central question: what is the optimal age at which elective oocyte cryopreservation should be considered? This is a difficult question to answer and involves complex cost-effectiveness modelling,[23,24] which has inherent limitations related to its underlying assumptions. It appears that the optimal age to consider elective oocyte vitrification is somewhere between 35 and 37 years.[25] Freezing oocytes at a significantly younger age (ie <30 years of age) is not cost-effective as it is unlikely that those oocytes will ever be used. By the same token, undergoing the procedure later in one's reproductive life (ie >40 years of age) is also unlikely to be cost-effective since the chance of a successful pregnancy resulting from these oocytes is very low.[26] Oocytes that are no longer required by a gamete provider can be discarded, donated to known or anonymous recipients or donated to research. Comprehensive discussion of disposal intentions should be a part of pre-procedure counselling.

When to freeze and how many?

Oocyte cryopreservation for non-medical indications must not be considered a definitive path to biological motherhood. Every step of the IVF process is associated with some degree of attrition: some collected oocytes are immature and are unsuitable for freezing; some will not survive the warming process; some will not fertilise; some fertilised embryos will experience developmental arrest and will not progress to be viable, good-quality embryos; and some embryos that are transferred will not produce a viable pregnancy and live birth.[27] Therefore, oocyte cryopreservation can only be considered a 'plan B' or an insurance policy, with no guarantee of a live birth at the end of the process. This concept of attrition also raises the very important and often-asked question regarding how many oocytes should be frozen to have a reasonable chance of producing a baby. The answer depends on the age at which oocytes are frozen and the number of oocytes stored. The quality of oocytes cannot be assessed prior to fertilisation being attempted. Table 1 provides an approximate guide to how many mature oocytes need to be cryopreserved at different ages to achieve at least one live birth. This allows for individualised counselling, treatment planning and expectations management in a patient-centred fashion. The precision of this modelling is not absolute and is based on

Table 1. Chance of live birth (%) based on a patient's age at the time of oocyte collection and the number of oocytes cryopreserved[26]

	Number of oocytes cryopreserved				
Age (years)	5	10	15	20	25
30	64%	87%	95%	98%	99%
32	55%	80%	91%	96%	98%
34	47%	72%	85%	92%	96%
36	40%	64%	78%	87%	92%
38	26%	44%	59%	69%	77%
40	17%	31%	42%	52%	60%
42	10%	19%	28%	35%	42%

various assumptions,[27] which themselves are open to criticism. Nevertheless, it provides an approximate guide to the possible outcomes of the procedure.

Patients commonly enquire as to how many oocytes can be collected and stored in one IVF cycle. While a comprehensive discussion of ovarian reserve testing in a population with untested natural fertility is beyond the scope of this article, it is sufficient to state that anti-Müllerian hormone (AMH) and antral follicle count (AFC) may play a part in assessing probable response in the setting of elective oocyte freezing. As a rough guide, both AMH levels and AFC provide an approximation of the number of oocytes that can be retrieved from one stimulated cycle. For example, an AMH level of 15 pmol/L would predict a yield of between 12 and 18 oocytes. Similarly, a numerical value of AFC is directly correlated with the number of oocytes that can be collected in one cycle, also at a ratio of 1:1.[28]

Conclusion

Natural fertility and the probability of artificial conception via IVF gradually decline in line with female age. This decline accelerates around the age of 35 years, and by mid-40s the possibility of either spontaneous conception or IVF success approaches zero. Societal changes over the past few decades have resulted in women delaying motherhood, which may increase the number of women who remain involuntarily childless by the end of their reproductive lives. Elective oocyte freezing offers a potential technological solution to this societal problem. Women can now freeze their oocytes when they are at the peak of their reproductive potential to be used later in life. This approach is not without controversy, and questions remain regarding the timing of oocyte freezing as well as the required number of oocytes to be frozen to ensure a birth of genetically connected progeny. While freezing oocytes at a younger age (ie before 30 years of age) gives the highest chance of eventually achieving pregnancy and live birth, the utilisation rate in this age group appears to be very low. Conversely, freezing at a more advanced age (ie over 40 years of age) is unlikely to be successful. A balanced approach appears to be to consider oocyte freezing somewhere in the mid-30s, with women between 32 and 38 years of age being the best candidates. Both the potential number of oocytes frozen per ovarian stimulation cycle and the chance of a live birth per oocyte frozen can be approximated with some degree of accuracy based on previously published models and the individual clinic's outcomes. A discussion of future reproductive intentions should become part of routine preventive health arsenal, with timely referral to a fertility specialist should an extensive delay of conception be contemplated.

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