Oocyte freezing: timely reproductive insurance?

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ABSTRACT

- Cryopreservation of unfertilised oocytes for later use in initiating pregnancy is now a viable technology, with acceptable pregnancy rates (over 20% per thaw cycle).
- Oocyte cryopreservation used as a form of insurance against "social" (age-related) infertility can improve the lifetime chance of pregnancy in women who defer pregnancy into their late 30s or early 40s.
- We report two pregnancies using oocytes that were frozen for social rather than medical reasons, as part of a larger series of nine pregnancies using cryopreserved oocytes.
- Use of oocytes harvested and frozen from women aged under 35 years may more than double the chance of pregnancy for a 41-year-old woman.
- The disadvantages of oocyte freezing for social infertility reasons include cost, the usual risks associated with in-vitro fertilisation, and the lack of a guarantee of eventual pregnancy.

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Reproductive ageing is an important social and medical development, and increased age is a very important factor in infertility (Box 1). The median age of all Australian women delivering babies (30 years in 2005) rose each year in the decade leading up to 2005, and 20.4% of all deliveries are now to mothers aged over 35 years. One in seven first-time mothers in 2005 (13.3%) were aged over 35 years, compared with only 7.6% in 1996.[1] In 2006, the average age of women seeking infertility treatment was 35.6 years, and 16% of all women accessing in-vitro fertilisation (IVF) were aged over 40 years.[2] However, all infertility treatments, including IVF, tend to work less well in women aged over 40 years (Box 2), and particularly poorly in women aged over 42 years.[2] Therefore, one in six IVF patients now has an age factor complicating and reducing the success rate of the procedure.

Pregnancy rates decrease exponentially after a maternal age of 37 years and enter an accelerated decline from 40 to 42 years.[3] This age-related decline is due to poorer oocyte quality, probably associated with genetic factors and DNA fragmentation or deterioration.

Reversing the trend back to having pregnancies at a younger age may be facilitated by early education of women about the span of their fertility or by changes to social and industrial policies, such as introducing woman-and-baby friendly workplace initiatives, paid maternity leave and tax-deductible child care. However, many women are currently unable to complete their reproduction by their mid 30s, and so run the risk of "social" (age-related) infertility. These women have no inherent medical reasons for being unable to conceive; rather, they lack a partner or want to delay motherhood for other reasons, such as career development. Some may have access to rare donor oocytes. Others may never achieve motherhood.

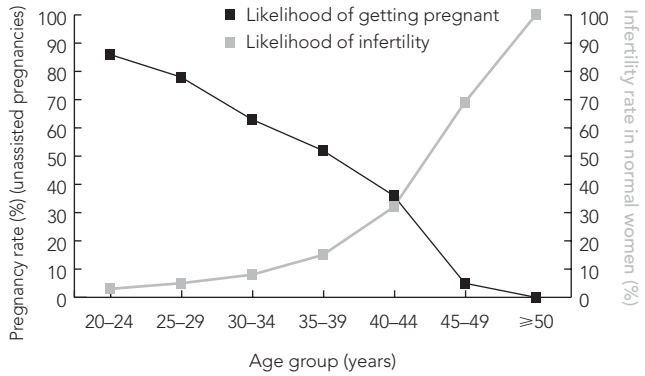
An emerging alternative is for a woman to freeze her oocytes at a younger age for later use, effectively creating a form of insurance against age-related fertility decline.

Oocyte cryopreservation

Successful oocyte cryopreservation is a relatively recent development in assisted reproduction. Patients undergo a standard IVF cycle with ovarian hyperstimulation and surgical oocyte retrieval. The oocytes are then cryopreserved without fertilisation. After thawing, they are inseminated using intracytoplasmic sperm injection (ICSI). Successful outcomes have increased in the past 7 years, from occasional pregnancies to pregnancy rates in excess of 20% per thaw cycle, particularly in Europe, where restrictive embryo freezing laws[4] have provided an impetus to focus on improving oocyte cryopreservation technology.

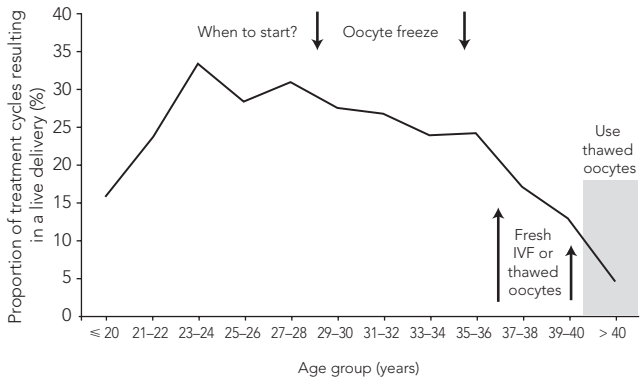
We have previously reported pregnancies from frozen/thawed oocytes in Australian women.[5] These women were already undergoing IVF treatment and either had religious objections to embryo

1 Pregnancy rates (unassisted pregnancies) and infertility rates in normal women, by age group, Australia and New Zealand*



* Source: Queensland Fertility Group brochure. ◆

2 Proportion of non-donor fresh ART treatment cycles with oocyte retrieval that resulted in a live delivery, by maternal age group, Australia and New Zealand, 2004[2]*†



ART = assisted reproductive technology. IVF = in-vitro fertilisation. * Owing to small numbers, values for women aged ≤ 20 years were combined, and values for women aged > 40 years were combined. † Figure reproduced with permission from the Australian Institute of Health and Welfare. ◆

freezing or had problems obtaining sperm from their partners on the day of IVF. Other medical reasons to freeze oocytes include the need for a woman to undergo cytotoxic cancer treatment and the assessment that a woman is at high risk of premature menopause.

Our Queensland Fertility Group has produced Australia's largest case series so far: nine pregnancies from frozen/thawed oocytes. Five women have delivered six healthy children (including a set of twins), there was one ectopic pregnancy, and three pregnancies are ongoing beyond 34 weeks. In two of these pregnancies, the oocytes were frozen to mitigate the risk of age-related fertility decline (Box 3). As far as we are aware, this is the first report of pregnancies in Australia using oocytes frozen for social rather than medical reasons.

Pregnancy rates in women using cryopreserved oocytes

It is difficult to assess the efficacy of frozen/thawed oocytes.[6] The technology is new, and many units have only small pregnancy numbers. Although oocyte freezing is becoming more common, thaw cycles are rare. Pregnancy rates are dependent on the woman's age at oocyte harvesting and freezing and on the technical expertise of the freeze/thaw process.

There is an initial attrition of oocytes after collection. Immature oocytes are discarded and only mature ones are frozen. It is common in a thaw cycle to use only 3–6 oocytes each time, whereas in a fresh IVF cycle, all the oocytes are exposed to sperm (with a fertilisation rate of 60%–70%) and the best embryos are selected for transfer. It is thus difficult to compare the outcome of a restricted oocyte thaw cycle with that of a single completed fresh IVF cycle.

Experienced IVF units are achieving success rates with oocyte cryopreservation that approach those for fresh oocytes and frozen embryos.[7-10] Survival rates of cryopreserved oocytes are 65%–80%, similar to those of frozen embryos, and fertilisation rates after insemination are 60%–80%, similar to those of fresh oocytes. Current data suggest there is one clinical pregnancy arising from every 17–25 thawed, surviving and inseminated oocytes,[8] which is comparable to the figure of one pregnancy for every 15–20 usable, inseminated oocytes in a fresh IVF program.

In unpublished data from our own program over the period 2005–2007, the survival rate of thawed oocytes frozen when the women were under 36 years of age has been 72%, the fertilisation rate has been 69%, and one pregnancy has been achieved from every 20 thawed oocytes and every 15 usable and inseminated oocytes. In comparison, from 2005 to 2007 in our IVF program, 1297 ICSI cycles in patients aged under 36 years yielded 12 353 fresh oocytes that were microinjected with sperm. A pregnancy occurred from one in every 17 microinjected oocytes in this group. In similar patients aged 41 years, the rate was only one pregnancy for every 38 usable fresh oocytes. This dramatic difference becomes even more significant when the average oocyte number retrieved is compared. Patients aged under 36 years averaged 12 oocytes per IVF cycle, whereas 41-year-olds averaged seven per cycle. This means 41-year-old patients need nearly twice the number of IVF treatment cycles to achieve the same total egg numbers as the younger group. These fewer oocytes then work only half as well.

Rationale for oocyte cryopreservation for social reasons

Oocyte freezing for social reasons is now being offered nationally and internationally. Oocyte freezing is being used to hold donor eggs in banks, similar to donor sperm banks. If a woman needs treatment for infertility after the age of 40 years for any reason, the above data suggest that her thawed oocytes collected and frozen before the age of 35 years will produce a higher pregnancy rate than her own fresh older oocytes.

The ideal age for women to consider oocyte freezing is 31–35 years. Women in their late 20s still have time to find a partner or to have their oocytes frozen after the age of 30 years with little age penalty. However, many requests for oocyte freezing come from women aged 36–40 years, as illustrated by the two case studies described in Box 3. Although oocytes from patients in this age group will produce fewer pregnancies than those from women under 35 years, these patients may still benefit from pre-emptive oocyte freezing, given that the age-related decline in fertility after 42 years is so severe. An oocyte collected and frozen from a woman at 38 years may still work better than a fresh one collected at 43 years. Little benefit would be derived from freezing oocytes collected after the age of 40–41 years. The maximal mathematical benefit of cryopreservation for reproductive insurance is derived from oocytes harvested and frozen when a woman is under 35 years and used after the age of 40 years. Ideally, for health and social reasons, pregnancies should not be initiated in women older than 55 years.

3 Case reports of two pregnancies from oocytes cryopreserved for social reasons

Case 1

"Mary" was a busy career woman with a high-level management position in a major Australian company. She was financially independent, but because of heavy work demands and long hours spent at work, she had been unable to develop a long-term relationship. At 37 years of age, she had seven of her oocytes frozen. At the age of 40 years, she decided she was now in a position to have a baby, and chose to use her stored oocytes with donor sperm. Two embryos were transferred, and a subsequent ultrasound scan showed a live twin pregnancy, which has now progressed beyond 34 weeks.

Case 2

"Angela" was concerned about her lack of a partner and had 13 of her oocytes frozen when she was 36 years of age. At the age of 39 years, she decided that her financial and social situation was suitable for her to become pregnant. She elected to use the stored oocytes rather than undergo the surgical rigours of a fresh in-vitro fertilisation cycle. Eight oocytes were thawed, of which four fertilised. Two embryos were transferred, and the two excess embryos were frozen. A singleton pregnancy ensued and has now progressed beyond 34 weeks. ◆

Potential problems with oocyte cryopreservation for social reasons

Oocyte cryopreservation is an emerging and improving technology which, when used for social reasons, does not yet have universal support.[11] Freezing methods are improving. The potential for using vitrification (ultra-rapid freezing that reduces the risk of damage to the oocyte) rather than standard slow-freeze technology is still to be realised, although the use of vitrification is becoming more common.[12,13] If oocyte freezing for social reasons is likened to insurance, it is an expensive policy ($7000–$10 000 per cycle, and $300 per year to store the eggs) that may never be used if the woman becomes pregnant spontaneously or decides never to

conceive. IVF is a stressful procedure that has uncommon but potentially serious risks associated with it, including ovarian hyperstimulation syndrome and the surgical risks of oocyte retrieval (such as infection or bleeding).

There is currently no clear or reliable mathematical algorithm to advise a woman how many oocytes should be frozen to give the best chance of pregnancy. It is the nature of IVF that some batches of oocytes may produce several pregnancies and others may produce none. If a woman has relied solely on frozen oocytes to achieve a pregnancy and is unsuccessful, especially in her late 40s, she may be devastated by the total loss of the chance of having a child. Extensive counselling and consent is obviously required for women who wish to access this service. It is important to discuss the woman's long-term reproductive plans and give a realistic assessment of the potential failures of oocyte freezing. Some women may have unrealistic expectations of the likely success rate of the procedure. For some women with medical or psychiatric illnesses, oocyte freezing may be unsuitable. General practitioners considering referrals for this service should use age as the primary screening criterion, with under 35 years being the preferred standard.

To date, the public health message in relation to deferring childbearing has been to inform patients of the risks, educate women about reproduction, and cautiously encourage conception at a younger age. The availability of oocyte freezing for social reasons does blur this message and will no doubt influence some women, perhaps detrimentally, to delay their reproduction.

Conclusion

The technology of oocyte preservation to insure against social infertility is not without controversy, but if developed to its full potential, in which a woman could choose her reproductive timing, the social and industrial impacts of oocyte freezing may be as profound as the invention of the oral contraceptive pill.

Competing interests

None identified.

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