

Social egg freezing: A viable option for fertility preservation

While cryopreservation of eggs is no longer considered experimental and is being offered as an employment benefit by some large organizations, it is important for women to understand that no number of stored eggs will guarantee a baby in the future.

ABSTRACT: Social egg freezing is now a viable option for women in our society who wish to preserve their fertility and delay childbearing. Over the past few years, substantial advancements have been made in the egg freezing technique. Evidence from randomized controlled trials has demonstrated that frozen eggs can work as well as fresh ones for in vitro fertilization. As a result, egg freezing is no longer considered experimental and the procedure has grown in popularity and gained mainstream attention. The use of this technology is driven by the fact that women are choosing to have children much later in life for a variety of reasons, the most common in one study being the lack of a partner. It is important for health care providers to educate women about the risks that come with delayed childbearing: infertility, aneuploidy, and miscarriage. Despite these and other concerns, including the false sense of security that social egg freezing can create, this technology is the best option when attempting to provide women with reproductive longevity more like that enjoyed by men.

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Egg freezing has come a long way since the first birth from a cryopreserved human oocyte was reported in the *Lancet* in 1986.¹ Initial attempts utilized a technique called slow-freezing that yielded eggs with poor survival and pregnancy rates of approximately 12% per embryo transferred.² As a result, egg freezing was generally reserved for women in countries where embryo storage was not permitted by law or in cases where a single woman undergoing potentially sterilizing treatments wished to preserve her fertility.^{3,4} An example of this would be a woman who banked her eggs before being treated for breast cancer with cyclophosphamide, a chemotherapeutic agent toxic to the ovaries.³ So even though the older techniques meant that 100 eggs might be needed to achieve one live birth, low success rates were acceptable given the bleak alternative of sterility for cancer patients.^{3,5} More recently, following substantial advancements in cryopreservation technique and evidence from randomized controlled trials, egg freezing has received mainstream attention.⁶⁻⁹ Pregnancy rates with frozen eggs now match those achieved with fresh eggs, and elective fertility

preservation is an exciting new frontier in reproductive medicine.

Social egg freezing refers to the cryopreservation of mature oocytes on an elective basis for the purpose of delayed childbearing. As of 2013, the American Society for Reproductive Medicine (ASRM) no longer considers egg freezing experimental, and large organizations such as Apple, Facebook, and the US military have started offering social egg freezing as an employee benefit.¹⁰⁻¹³

Why is egg freezing needed?

Over the past 30 years the industrialized world has seen a dramatic increase in the age of first birth.^{14,15} According to Statistics Canada, 2010

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marked the first time in our history that more women in their 30s were having children than women in their 20s.¹⁶ In 2011, there were 52.3 babies born per 1000 women age 35 to 39, compared with 45.7 per 1000 women age 20 to 24.¹⁷ In British Columbia, the percentage of live births to women age 35 and older rose from 11% in 1990 to 23% in 2011, while births in the 20 to 34 age category fell from 83% to 74% over the same period.¹⁸ In one study, the lack of a partner was by far the most common reason women gave for not pursuing childbearing earlier, followed distantly by professional and financial reasons.¹⁵ When researchers from the University of British Columbia surveyed 360 female undergraduate students about their childbearing intentions, they found that “although most women were aware that fertility declines with age, they significantly overestimated the chance of pregnancy at all ages and were not conscious of the steep rate of fertility decline.”¹⁹ It is therefore incumbent on health care providers to educate women about the risks of advancing reproductive age and to ensure that patients are not “sleepwalking” into unintended childlessness.²⁰ Women need to be made aware of the three main risks of delayed childbearing: infertility, aneuploidy, and miscarriage.

Egg freezing is currently the best way to provide females with reproductive potential more like that of males. The process of spermatogenesis takes approximately 70 days and continues throughout a man’s life, allowing most men to maintain fertility in perpetuity.²¹ A woman, in contrast, is born with a finite number of eggs that diminish over 5 or 6 decades until menopause is attained. In a unique study of 122 necropsy and surgical specimens from females age 0 to 51 years, Hansen and col-

leagues used stereology techniques to count the number of nongrowing follicles present in the ovary and establish each subject’s ovarian reserve.²² At 20 weeks’ gestation, we know a female fetus has her lifetime maximum of 6 to 7 million oogonia.²¹ Hansen and colleagues found that a newborn’s ovaries contained approximately 1 million eggs, and by puberty this number had fallen by half.²² The most clinically remarkable decline was seen between the 30 to 34 age group, where 200 000 eggs remained, and the 35 to 39 age group, where the average was less than 40 000. The menopause threshold was reached at approximately 51 years, when fewer than 1000 nongrowing follicles were seen. Importantly, menstruation is often erroneously equated with fertility, when in fact most women lose the ability to conceive 10 years or more before they cease menstruating.²³ As well, external gonadotoxic factors such as chemotherapy, pelvic radiation, ovarian surgery, and autoimmune disorders can have an impact on ovarian reserve by accelerating the normal age-related loss of eggs.²¹

Aneuploidy, or chromosomal error, is more common in embryos derived from older eggs. This is believed to result from the age-related deterioration in cellular mechanisms required for meiotic spindle function.²¹ When meiosis is reinitiated by the luteinizing hormone (LH) surge or fertilizing sperm, chromosome or sister chromatid segregation can occur unevenly between the egg and its resulting polar bodies.²¹ Newly developed techniques permit the analysis of embryos created through in vitro fertilization (IVF) and the selection and transfer of only those embryos that are euploid in a process termed preimplantation genetic screening (PGS) or comprehensive chromosome screening (CCS). The embryo’s

trophectoderm (the outer layer destined to form the placenta) is biopsied on day 5 or 6 after fertilization and the chromosomal complement of those cells is assessed. In a large series of 15 169 trophoctoderm biopsies from 2701 patients, only 20.7% of embryos from women age 29 were abnormal, compared with 34.5% of embryos from women age 35 and 58.2% from women age 40. By age 43, only 16.6% of embryos were chromosomally normal.²⁴

Knowing that a substantial majority of conceptions in women over 40 are aneuploid helps us understand why there is an increase in the time needed to achieve pregnancy and in pregnancy losses, both clinical and biochemical, as women age. Miscarriage rates in natural pregnancies for women younger than 30 are 7% to 15% and become marginally higher for women 30 to 34 at 8% to 21%. In the 35 to 39 age group the rate is 17% to 28% and in the over 40 age group 34% to 52% of pregnancies end in miscarriage.²¹

In short, women in our society are waiting longer to start families but their ovaries remain programmed for reproduction at a younger age. As women continue to strive for equality, they are finding it increasingly difficult to reconcile their professional and political goals with the rigid biology of reproduction. In the words of one researcher, egg freezing may be able to “bridge the gap between reproductive prime and when a woman is realistically ‘ready’ to have children.”¹⁵

What does egg freezing involve?

Women seeking social egg freezing at a fertility clinic begin by having their ovarian reserve assessed. This is done with blood tests for early follicular phase (day 3) follicle-stimulating hormone (FSH) and antimüllerian

hormone (AMH) levels, and then an antral follicle count (AFC) performed by transvaginal ultrasound. Findings from these investigations provide an estimate of the patient's remaining eggs compared with other women her age. They also help the fertility doctor determine how many eggs can safely and/or realistically be obtained in one cycle of controlled ovarian stimulation.

In vitro fertilization involves an average of 10 days of gonadotropin injections (FSH and LH) before the eggs are prompted to undergo maturation by triggering an endogenous LH surge, or by the administration of human chorionic gonadotropin (hCG). Egg retrieval is an outpatient surgical procedure that takes approximately 10 minutes under conscious sedation. A transvaginal ultrasound-guided needle is used to aspirate the fluid from each ovarian follicle, which an embryologist then examines to isolate eggs. After that, mature eggs are counted and prepared for freezing.

As the largest cells in the human body, eggs are very difficult to freeze. Their spherical shape, high water content, and low surface area to volume ratio make eggs especially difficult to permeate with cryoprotectants and prone to intracellular ice crystal formation.²⁵ Eggs are susceptible to meiotic spindle and lipid membrane damage, hardening of the zona pellucida, and depolymerization of microtubules.²⁵ For years the slow-freezing technique used for embryos was used for eggs, but with little success. In 2004, when changes to Italian reproduction laws made it illegal to freeze embryos, the need to cryopreserve supernumerary eggs⁴ sparked the development of a new, more efficient flash-freezing method called vitrification.^{25,26} This technique uses ultrarapid cooling rates and high concentrations of cryoprotectants. There

is now a growing body of evidence that IVF outcomes with vitrified eggs are the same as those with fresh eggs.^{6,27-29}

How well does egg freezing work?

Most of the evidence on egg freezing comes from research in countries where remuneration for human gametes is legal, such as the US and Spain.⁵ In order to ease the logistical burden of anonymous egg donation in synchronous IVF cycles, fertility clinics will often bank frozen eggs from donors and subsequently distribute them to recipients for warming and fertilization at a more convenient time. In a review of 3610 donor egg warming procedures, the vitrified egg survival rate was 90.4% and the oocyte-to-baby rate was 6.5%.³⁰ Since these eggs came from donors who were typically in their 20s and selected for a good prognosis, it may be too optimistic to extrapolate these findings to social egg freezing. Given that the widespread utilization of vitrification and the nonexperimental use of egg freezing have increased only recently, long-term outcome data from large trials of social egg freezing are still forthcoming.

In 2016, reports were published for two studies that examined large numbers of elective egg freezing cycles. The first study, by Cobo and colleagues,²⁷ included 1468 women who underwent social egg freezing. The researchers found that 137 of these subjects (9.3%) had returned to use their eggs, that the average age of those returning was 37.7 years, and that the overall egg survival rate was 85.2%. For women who were 35 or younger at the time of egg freezing and who banked 10 eggs, the average live birth rate when 10 eggs were used was an impressive 60.5% (95% CI, 34.5-89.5%). In the group of women

36 or older, the same 10 eggs yielded a significantly lower live birth rate of 29.7% (95% CI, 15.2%-34.2%).²⁷ The second study, by Doyle and colleagues,²⁸ reported on 1283 vitrified eggs from 128 autologous IVF cycles. The researchers found an egg-to-live-birth efficiency rate of 6.4% for these autologous cycles, which was very similar to the rate of 6.5% reported previously for donor cycles.³⁰ When they compared the performance of autologous frozen eggs to fresh eggs in IVF cycles, the overall live birth rate was reassuringly similar (39% versus 35%).²⁸ To put these figures in perspective, it helps to consider what success rate a woman of a given age could expect if she were to pursue an IVF pregnancy today rather than freezing her eggs. Aggregate data from 31 IVF clinics across Canada in 2014 found the following average clinical pregnancy rates for each age group: younger than 35 years = 48.7%, 35 to 37 = 43.5%, 38 to 40 = 34.3%, 41 to 42 = 20.5%, 43 or older = 14.4%.³¹ This means that for women younger than 36, social egg freezing appears to be at least as good as the national IVF averages. Given that social egg freezing is relatively new, the vast majority of eggs retrieved for elective freezing so far are presently in cryostorage. At our centre, two patients have returned to use their eggs, both of whom have ongoing pregnancies at the time of publication.

Egg vitrification is gaining acceptance with the improving efficiency of our freezing techniques.^{5,9} The best chance for a future pregnancy appears to result from freezing at least 8 to 10 eggs before age 36.²⁷ In Canada, the average cost of an egg freezing cycle, including procedures and medication, ranges from \$7000 to \$10000 and annual storage fees range from \$200 to \$400. To determine the most cost-effective approach, a

US study developed a decision-tree model that looked at the cost of egg freezing compared with taking no action between age 25 and 40 and assuming an attempt at procreation was made 3, 5, or 7 years after the initial decision.¹⁴ The researchers weighed the chances of spontaneous pregnancy against the chances of success with IVF using frozen eggs in various age groups. They concluded that although the highest probability of live birth was achieved when egg freezing was performed before age 34 (greater than 74%), egg freezing was most cost effective at age 37.¹⁴

What are some concerns about egg freezing?

Egg freezing does not appear to increase the likelihood of fetal malformations or pregnancy complications. Initial reports from the Italian experience up until 2007 and a case series of 900 infants published in 2009 both showed no increase in congenital anomalies among children resulting from egg freezing.^{32,33} A more recent study compared 804 pregnancies from vitrified eggs with 996 pregnancies from fresh eggs and found no difference in adverse obstetrical outcomes, including gestational diabetes, hypertension, preterm birth, cholestasis, and anemia.³⁴ There were also no differences in perinatal outcomes, including gestational age at delivery, preterm birth, APGAR scores, birth defects, neonatal ICU admission, and perinatal mortality.³⁴

Vitrified eggs can likely remain in cryostorage indefinitely, although many clinics impose an upper patient age limit of 50 years for embryo transfer. Evidence from donor egg IVF cycles has demonstrated that the uterus is capable of sustaining a pregnancy well beyond menopause with the administration of exogenous estrogen and progesterone.³⁵ The

cardiovascular and other physical demands of pregnancy present more substantial challenges, as do the ethical implications of postmenopausal motherhood.^{36,37} Despite the encouraging statistics, media attention, and corporate support for egg freezing, the practice has generated much controversy. Some of the more frequently cited concerns are the financial barriers and the lack of access for all women, along with the false sense of security that the technology may provide. Women face societal pressures to achieve their education and professional goals, to meet the right partner, and to start a family within a relatively short 10- or 15-year period. Egg freezing may be seen by some of these women as a way to “have it all” or for employers to “expect it all.”^{25,37} Ethicists have stated that health care providers should “frame discussions” about egg freezing “within the broader context of reproductive health and family-making to assist women in making informed choices.”³⁷

Conclusions

Social egg freezing is a safe and viable option for women in our society. It does not provide women with the same reproductive longevity that men enjoy, but it can allow women to delay childbearing for 2 to 10 years and may be a reasonable choice for women wishing to do this. Egg freezing appears to be most effective when at least 8 to 10 eggs are banked before age 36 and most cost-effective when undertaken at age 37. Women may regard social egg freezing as a reproductive insurance policy or simply as a backup plan. However, it is important for women to understand that no number of stored eggs will guarantee a baby in the future.

Women are already choosing to have children later in life. Whether egg freezing increases or decreases

the pressure on women to make choices about their partners, professional goals, and fertility lies in the eye of the beholder. It is important for health care providers to educate women about the risks of infertility, aneuploidy, and miscarriage that come with delaying the creation of a family. Women have the right to shift priorities as they adapt to their evolving roles in society, and social egg freezing may help them do this.

Competing interests

None declared.

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