No. 356, March 2018

No. 356-Egg Freezing for Age-Related Fertility Decline

This Clinical Practice Guideline has been prepared by the Canadian Fertility and Andrology Society (CFAS) Clinical Practice Guideline committee in collaboration with the SOGC Reproductive, Endocrinology and Infertility (REI) committee and reviewed by the SOGC Guideline Management and Oversight Committees and approved by the Boards of the SOGC and CFAS.

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Disclosure statements have been received from all authors.

Key Words: Oocyte vitrification, social egg freezing, elective egg freezing, fertility preservation, delayed child-bearing

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J Obstet Gynaecol Can 2018;40(3):356–368

https://doi.org/10.1016/j.jogc.2017.08.004

Abstract

Objective: To provide a comprehensive review and evidence based recommendations for Canadian fertility centres that offer social egg freezing.

Outcomes: In social egg freezing cycles we evaluated thawed oocyte survival rates, fertilization rates, embryo quality, pregnancy rates, and live birth rates. We also review how these outcomes are impacted by age, ovarian reserve, and the number of eggs cryopreserved. Finally, we discuss the risks of social egg freezing, the alternatives, the critical elements for counselling and informed consent, and future reporting of egg freezing outcome data.

Evidence: Published literature was reviewed through searches of MEDLINE and CINAHL using appropriate vocabulary and using key words ("oocyte cryopreservation," "egg freezing," "egg vitrification," "social egg freezing," and "elective egg freezing"). Results included systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. Expert opinion based on clinical experience, descriptive studies, or reports of expert committees was also included to discuss aspects of egg freezing not currently rigorously studied.

Values: The evidence obtained was reviewed and evaluated by the Clinical Practice Guideline (CPG) Committees of the Canadian Fertility and Andrology Society (CFAS) under the leadership of the principal authors.

Benefits, Harms, and Costs: Implementation of this guideline should assist the clinician to develop an optimal approach in providing counselling for egg freezing while minimizing harm and improving patient outcomes during treatment.

Validation: These guidelines have been reviewed and approved by the membership of the CFAS and by the CPG Committees of CFAS and The Society of Obstetricians and Gynaecologists of Canada (SOGC).

Sponsors: CFAS and SOGC.

Recommendations:

1. Patients should be advised that thawed oocyte survival rates vary, typically between 80% and 90% (Strong, High).
2. Thawed oocytes should be fertilized using intra cytoplasmic sperm injection and patients should be advised that fertilization rates vary, typically between 70% and 80% (Strong, High).
3. Patients should be advised that vitrified oocytes yield fewer blastocysts than fresh oocytes do (Weak, Moderate).
4. Patients should be advised that there are very limited data on live birth rates after social egg freezing, but that the existing data suggest similar clinical pregnancy rates after transfer of embryos obtained by either vitrified or fresh oocytes (Strong, Moderate).
5. Women considering social egg freezing should be advised that the age at which they freeze their eggs and the number of eggs that are frozen impact the probability that these eggs will enhance their fertility (Strong, Moderate).
6. Ovarian reserve testing should be offered to help predict the number of retrievable eggs from a controlled ovarian stimulation cycle and to properly counsel those women at risk of very low oocyte yield (Strong, High).
7. Women considering social egg freezing should be advised that more than one cycle may be required to obtain the number of mature eggs that is desired (Strong, High).
8. Patients considering social egg freezing should be informed about the risks of controlled ovarian stimulation, oocyte retrieval, and pregnancy at a more advanced maternal age (Strong, Moderate).
9. Patients considering social egg freezing should be advised that there is a chance they may not need to use their frozen eggs and that no guarantees can be made that their frozen eggs would produce a viable pregnancy (Strong, High).
10. Women considering social egg freezing should be counselled about the alternative options (Strong, Moderate).
11. Women undergoing social egg freezing should receive sufficient information to provide informed consent (Strong, High).
12. In vitro fertilization centres offering social egg freezing should provide their patients with an estimate of their chances of success. This estimate should not only consider the published medical literature but also should take into account national data regarding social egg freezing and clinic-specific data regarding cumulative live birth rates per oocyte retrieval (Strong, Low).

INTRODUCTION

For the past four decades, industrialized countries have experienced an increase in child-bearing age. In Canada, the average age at which women have their first child increased from 23.7 in 1970 to 28.5 in 2011, and more than half of all births now occur in women age 30 and older.[1] The growing delay in parenting has been attributed to improved methods of contraception, as well as economic, professional, educational, and personal changes in modern society.[2–6] In consequence, postponement of parenthood has increased the probability that women will reach an age at which the quantity and quality of their remaining oocytes prevent spontaneous conception if such a conception is desired. It has been estimated that the risk of infertility is approximately 6% at age 20 to 24, 16% at age 30 to 34, and 64% at age 40 to 44.[7] The physiologic decrease in the chances of conception associated with ageing is called age-related fertility decline.

As a result, many women are consulting fertility centres to guard against age-related fertility decline or to optimize future conception. Options include trying to conceive at a younger age, donor sperm insemination, donor egg/embryos, or cryopreserving one's own oocytes for use in future attempts at genetic reproduction.

The first live births after oocyte cryopreservation (egg freezing) occurred over 30 years ago.[8,9] However, due to technical challenges, it was not until recently that the European Society for Human Reproduction and Embryology,[10] the ASRM,[11] and the Canadian Fertility and Andrology Society withdrew their experimental designations for oocyte cryopreservation. Although not intended as an endorsement of elective oocyte cryopreservation, these decisions facilitated consideration of egg freezing as a reproductive option for women who wish to guard against the natural age-related decline in their fertility—so-called "social egg freezing."

ABBREVIATIONS

AFC	antral follicle count
AMH	anti-Müllerian hormone
ART	assisted reproductive technology
ASRM	American Society for Reproductive Medicine
CARTR-BORN	Canadian Assisted Reproductive Technologies Register – Better Outcomes Registry & Network
CS	Caesarian section
FSH	follicle-stimulating hormone
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
LBR	Live Birth Rate
RCT	randomized controlled trial

In this guideline, we distinguish social egg freezing from other reasons for oocyte cryopreservation such as pre-gonadotoxic therapy, the unexpected absence of sperm on the day of oocyte retrieval, pre-gender confirmation treatment, or egg freezing performed at the time of IVF because of moral, religious, or legal constraints related to the creation or freezing of supernumerary embryos. Although some have criticized the use of the term "social egg freezing" and recommend instead the term "anticipated gamete exhaustion banking," social egg freezing remains the most commonly used term for this specific indication.[12]

A substantial number of IVF centres in Canada offer social egg freezing.[13] However, this service is not without controversy.[14] Therefore, the purpose of this guideline is to provide a comprehensive review and evidence-based recommendations for Canadian fertility centres that offer social egg freezing. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology framework, and the interpretation of strong and weak recommendations is described in Table 1 and Table 2.[15]

WHAT IS THE EFFICACY OF EGG FREEZING?

Oocyte cryopreservation has had to overcome numerous technical challenges related to large cell size, high water content, the delicate chromosomal spindle arrangement of the mature oocyte (an oocyte that has completed the first meiotic division, that has reached metaphase II, and that is capable of being fertilized),[16–19] and the hardening of the zona pellucida that impairs fertilization.[20,21] For many years, the standard procedure for oocyte cryopreservation was slow-freezing. This approach has now largely been replaced by vitrification which uses high initial concentrations of cryoprotectant and ultra-rapid cooling to solidify the cell into a glass-like state without formation of ice crystals.[22] Oocyte vitrification induces less damage to internal structures[23] than slow-freezing and results in superior post-thaw success rates.[24–28] Furthermore, subsequent use of ICSI overcomes fertilization issues related to hardening of the zona pellucida.[29–31]

There is considerable literature regarding the efficacy of oocyte cryopreservation for egg donation, but very limited information on social egg freezing. Indeed, most of the data on social egg freezing come from high-volume centres, and in some cases, the same data overlap different publications. It therefore remains unclear to what extent individual IVF programs can apply the existing data to accurately estimate individual success rates.

Table 1. Key to grading of recommendations, assessment, development, and evaluation (GRADE)[1]

Strength of the recommendation	Definition
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences; or undesirable consequences outweigh the desirable consequences).
Weak[a]	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	**Definition**
High|++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate|+++0	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low|++00	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low|+000	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Weak recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.

Examples:

Strong, Moderate|+++0: Strong Recommendation, Moderate Quality of Evidence.

Weak, Low|++00: Weak Recommendation, Low Quality of Evidence.

OOCYTE SURVIVAL RATES

Several studies have analyzed the survival rates of mature vitrified oocytes. The largest experience with egg freezing thus far is derived from egg donation cycles where published survival rates range from 86% to 97%.[32–35] Others have evaluated survival rates among infertile women, reporting values between 80% and 97%.[36–38] A meta-analysis that included all studies up to June 2013 reported a mean oocyte survival rate of 90% with donor eggs and 86% with non-donor eggs[39] (Table 3). Data on total failure of oocyte survival are sparse and insufficient to make a reliable estimate.[40]

To date, very few publications have evaluated oocyte survival rates, specifically in women undergoing social egg freezing. Cobo et al. described 120 women who returned for fertility treatment and reported a survival rate of 81% of 1080 frozen-thawed oocytes.[32] Doyle et al. described 128 thaw cycles, of which 52 were due to sperm unavailability, 44 for elective limited oocyte fertilization, and 32 for elective egg freezing as the original indications for oocyte freezing, and reported an oocyte survival rate of 86% (Table 3).[41] In comparison, vitrified embryo survival rates typically exceed 90%.[42–44]

Table 2. Judgement and interpretation of strong and conditional recommendations[15]

Judgement/ Interpretation	Strong recommendation "We recommend…"	Conditional recommendation "We suggest…"
Judgement by guideline panel	It is clear to the panel that the net desirable consequences of a strategy outweighed the consequences of the alternative strategy.	It is less clear to the panel whether the net desirable consequences of a strategy outweighed the alternative strategy.
Implications for patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Implications for clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual to arrive at a management decision consistent with his or her values and preferences.
Implications for policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

FERTILIZATION RATES

Fertilization rates of thawed vitrified oocytes after ICSI in different ART populations have ranged from 71% to 76% with donor eggs,[33,34,40] from 79% to 85% in infertile women,[36–38] and 70% in vitrified eggs from a mixed population of women[41] who underwent egg freezing for various indications (Table 3). In comparison, fertilization rates of fresh oocytes varied from 71% to 82% in donor oocytes cycles (an oocyte donated to a known or anonymous recipient for the purposes of achieving a pregnancy for the intended parent[s]),[33,34] and from 75% to 88% for infertile patients.[36–38]

Table 3. Oocyte performance after vitrification

	Number of eggs	Age	Survival rate	Fertilization rate	Implantation rate	Clinical pregnancy rate	Miscarriage rate	Live birth rate
Donor cycles								
Cobo et al. RCT[33]	n = 231	26.7 ± 3.6	97%	76%	41%	N/A	20%	N/A
Cobo et al. RCT[34]	n = 3286	26.7 ± 3.9	93%	74%	40%	55%	N/A	N/A
Solé et al. observational[35]	n = 98	26.1 ± 4.3	86%	78%	34%	54%	21%	43%[b]
Infertile autologous								
Rienzi et al. RCT[36]	n = 24	35.5 ± 4.8	97%	79%	20%	39%	20%	N/A
Parmegiani et al. RCT[37]	n = 168	35 ± 0.8	90%	85%	17%	36%	18%	23%[b]
Chang et al. RCT[38]	n = 86	35.4 ± 2.9	80%	84%	30%	45%	15%	50%
Doyle et al. observational[a,41]	n = 1283	34.9	86%	70%	41%	54%	29%	39%
Social egg freezing								
Cobo et al. observational[32]	n = 1080	37.2	81%	N/A	31%	41%	N/A	21%[b,c]

[a]Included a subset of elective fertility preservation.

[b]Live birth rate per cycle.

[c]Data based on LBR by the time of publication (24 live birth and 26 On-going pregnancy rate (OPR) of 102 transfers).

EMBRYO QUALITY

Some evidence suggests that the embryo quality from thawed vitrified oocytes does not differ from that of fresh oocytes. However, there is heterogeneity in the literature because some centres prefer to transfer at the cleavage stage whereas others do so at the blastocyst stage. A meta-analysis published in 2014 reported an embryo cleavage rate of 92% in fertilized thawed donor eggs and a rate of 84% in fertilized thawed non-donor eggs.[39] The effect of oocyte vitrification on embryo quality has also been evaluated in three RCTs involving patients undergoing treatment for infertility.[36–38] Again, no differences in the quality or percentage of cleavage stage embryos from fresh versus frozen oocytes were found.

NUMBER OF BLASTOCYSTS AVAILABLE

The number of blastocysts available after oocyte thawing has been evaluated by several trials and has yielded conflicting results. In an RCT comparing fresh versus vitrified donor eggs, there were nearly double the number of blastocysts derived from fresh mature oocytes (42/219; 19%) compared to vitrified mature oocytes (24/231; 10%).[33] The same authors conducted another RCT that demonstrated a statistically significant difference in the number of blastocysts comparing fresh versus thawed vitrified donor oocytes (2.5 ± 2.3 vs. 2.0 ± 2.1).[34] In contrast, no differences in the number of day 3 embryos or blastocyst were observed in two RCTs involving infertile patients.[36,38] However, Doyle et al. reported a statistically significant difference in the number of blastocysts (fresh 66% vs. frozen 51%) in an observational cohort of social and medical egg freezing patients.[41]

PREGNANCY RATES

An RCT with more than 600 patients undergoing vitrified versus fresh egg donation cycles reported results after transfer of a mean of 1.7 embryos. The implantation rate (40%), clinical pregnancy rate (55%), and ongoing pregnancy rate (49%) from frozen eggs was not different compared to fresh donor eggs (Table 3).[34]

Similarly, studies in infertile women report non-significant differences between fresh and frozen eggs. Rienzi et al. randomized 80 women with a mean age of 35 who had at least six eggs at retrieval to either fresh embryo transfer or oocyte vitrification with subsequent thaw/ICSI/transfer.[36] They reported a clinical pregnancy rate of 38.5% and an ongoing pregnancy rate of 30.8% with vitrified eggs compared to 43.2% and 38.8%, respectively, with fresh eggs. A retrospective cohort study involving 1283 thawed vitrified oocytes from a mixed population of egg freezing patients was compared to 243 892 oocytes from fresh IVF.[41] The authors reported no statistical difference in implantation rates (43% vs. 35%) or clinical pregnancy rates (57% vs. 44%) with frozen versus fresh eggs, respectively. However, they also reported a higher pregnancy loss rate per clinical pregnancy with frozen (30%) versus fresh eggs (19%; $P = 0.048$) (Table 3).

LIVE BIRTH RATES

At present, the data regarding live birth rates from social egg freezing cycles are quite limited. Most of the evidence, instead, comes from a varied array of infertility and donor egg cycles, and some of these studies have developed predictive models for the estimation of live birth rate in regards of oocyte number and maternal age.

One of the largest egg donation programs reported 2102 live births from 32 460 thawed donor oocytes. In this program, a mean of 11 donor oocytes allocated per recipient resulted in a live birth rate of 39% per donation cycle. It is important to highlight that 70% of the original stimulated cycles resulted in supernumerary embryos for vitrification and that 632 of these births came from frozen embryos. In fact, the birth rates for the first, second, and third supernumerary frozen-thawed embryo transfers were 32%, 25%, and 24%, respectively. The authors found that the live birth rate per thawed oocyte was 6.5% and the mean number of mature frozen donor oocytes required to achieve a live birth was 15.[40]

Other authors have investigated the live birth rate probabilities in infertile women who underwent oocyte vitrification. One meta-analysis reported a live birth rate of 6% per thawed oocyte.[39] Another meta-analysis estimated that the most discriminatory age for success of oocyte cryopreservation (as measured by live birth) was 36 years (AUC 0.72).[45] In this meta-analysis, the reported live birth rate per transfer of 2.8 ± 1.3 cleavage stage embryos ranged from 12% to 26%. They estimate that thawing up to six oocytes would have a probability of live birth of 24% at 30, 17% at age 36, and 13% at age 40 year (Table 4).[45]

Data regarding live birth rates per frozen egg among women who underwent social egg freezing are quite preliminary. According to Doyle et al., to have a 70% chance of conceiving a child, a woman would need to freeze 14, 15, and 25 eggs at ages 30–34, 35–37, and 38–40, respectively.[41] In their model, it is estimated that the live birth rate per oocyte is 7.4%, 7%, 6.5%, and 5.2% at age <30, age 30–34, age 35–37, and age ≥38, respectively. However, the actual live birth rate was 38.6% per transfer cycle in patients with a mean age of 34.9 years. Another recent publication analyzing the outcomes exclusively from social egg freezing (137 women, 1182 thawed oocytes) concluded that there is a statistically significant difference in the live birth rate between women age ≤35 (50%, n = 32) and women older than 35 (22.9%, n = 105).[32] Using Kaplan-Meier curves, this group estimated that in social egg freezing patients ≤35 years, the cumulative live birth rate per 5, 8, and 10 frozen-thawed oocytes would be 15.4%, 40.8%, and 60.5%, respectively, whereas in women over age 35, it would be 5.1%, 19.9%, and 29.7%, respectively (Table 4).

Recommendations

1. Patients should be advised that thawed oocyte survival rates vary, typically between 80% and 90% (Strong, High).
2. Thawed oocytes should be fertilized using intra cytoplasmic sperm injection, and patients should be advised that fertilization rates vary, typically between 70% and 80% (Strong, High).
3. Patients should be advised that vitrified oocytes yield fewer blastocysts than fresh oocytes do (Weak, Moderate).
4. Patients should be advised that there are very limited data on live birth rates after social egg freezing, but that the existing data suggest similar clinical pregnancy rates after transfer of embryos obtained by either vitrified or fresh oocytes (Strong, Moderate).

WHAT FACTORS SHOULD BE ADDRESSED BEFORE CONSIDERING EGG FREEZING? IS THERE A RECOMMENDED AGE?

The highest probability of live birth in egg freezing programs has been obtained when oocyte cryopreservation is performed before the age of 36.[32,41,45] It is well known that natural fecundity rates decrease after the age of 30, with a steeper decline after the age of 35.[6,7] However, in cost-effectiveness modeling scenarios, the highest live birth rates are attained by egg freezing before the age of 30, but the greatest cost benefit is seen later—that is, for women who freeze their eggs at age 35–37.[46–49] This is not unexpected because women in their 20s or early 30s have relatively stable fertility rates, and the marginal benefit of freezing eggs becomes magnified for these women only if the time between the age of freezing and the age of thawing is significant. Indeed, in the largest social egg freezing series published to date, more than 50% of cases were done at ages 36–39.[32] Despite this late age, only 10% of patients had returned to use their eggs over the time period studied, and the mean storage time was 2.2 years.

OVARIAN RESERVE

Ovarian reserve refers to the number of follicles that may respond to gonadotropin stimulation. Ovarian reserve testing is used to tailor ovarian stimulation in IVF, but it does not necessarily predict conception. Although both the American College of Obstetrics and Gynecology (ACOG)[50] and ASRM[51] have conceptualized ovarian reserve as an indicator of both oocyte number and quality—ovarian reserve

Table 4. Vitrified oocytes live birth rate

	Age	Oocyte number (estimated LBR)	Actual LBR per series
Donor cycles Cobo et al.[40]	21–35	10 (40%[b])	37% per warming cycle n = 3467 cycles Age = 25.9
		12 (54%[b])	
		15 (68%[b])	
		20 (81%[b])	
Infertile autologous Pelin Cil et al.[45]	30	2 (21%)	12% to 37% per transfer n = 303 cycles Age = 34.1 ± 4.7
		4 (23%)	
		6 (24%)	
	35	2 (16%)	
		4 (17%)	
		6 (18%)	
	40	2 (12%)	
		4 (13%)	
		6 (13%)	
Chang et al.[38]	30–36	1 (8%)	50% per cycle n = 22 cycles Age = 35.4 ± 2.9
	37–39	1 (3%)	
Doyle et al.[a,41]	30–34	1 (8%)	39% per transfer cycle n = 128 cycles Age = 34.9
		5 (30%)	
		10 (55%)	
	35–37	1 (7%)	
		5 (30%)	
		10 (50%)	
	38–40	1 (5%)	
		5 (20%)	
		10 (35%)	
Social egg freezing Cobo et al.[32]	≤35	5 (15%)	20% per cycle, plus 11 ongoing pregnancies at the time of publication n = 148 cycles Age = 37.2
		10 (61%)	
		15 (85%)	
	≥36	5 (5%)	
		10 (30%)	
		11 (36%)	

[a]Included a subset of elective fertility preservation.

[b]Cumulative live birth rate.

testing is only able to directly measure oocyte quantity.[52–56] Several markers are available, and because no single marker is 100% sensitive or specific to determine ovarian reserve, they are often assessed together to give an overall estimate of the number of oocytes that may be retrieved per stimulated cycle.

A basal FSH and estradiol level measured at day 2 to 5 of the menstrual cycle has traditionally been used as a marker of ovarian reserve and to confirm menopause. The main limiting factor of FSH as an ovarian reserve marker is that it varies from cycle to cycle. However, if basal FSH values are consistently elevated, a poor reproductive prognosis is expected.[57,58]

The AFC is a better prognostic indicator of ovarian stimulation than the basal FSH.[59–62] AFCs decline with age,[63] and lower than expected numbers of antral follicles are a sign of ovarian aging[64] and predict fewer retrievable eggs.[65,66] Although traditionally measured around menstrual cycle day 3, studies show that AFCs remain relatively stable and retain predictive value no matter when they are measured in the cycle.[67,68] A limiting factor is the possibility of inter-observer measurement variability.

As opposed to FSH and AFC, AMH has little inter-cycle variability and may be a better marker for assessing the age-related decline of the ovarian follicular pool and the potential for a poor response to ovarian stimulation.[53,69–76] As the number of ovarian follicles decreases with age, a concomitant decrease in AMH level occurs, which reflects this age-related oocyte depletion.[77] Low AMH levels strongly predict poor response in controlled ovarian stimulation and may be used to help adjust the dose of gonadotropin medication.[78,79]

AMH can be measured at any time throughout the menstrual cycle, as there is only slight inter- and intra-cycle variation in its levels.[80,81] One limitation of AMH testing is the variability of results between the available assays and the inability to compare AMH levels when different assays are used.[82] Another challenge specific to the egg freezing population is the potential for oral contraceptives to suppress by as much as 20% AFCs and AMH levels.[83–85]

NUMBER OF CYCLES NEEDED

According to the two groups with the largest experience on social egg freezing, the risk of cycle cancellation due to lack of eggs for vitrification or no transferable embryos range from 1.5% to 4.7%.[32,41] However, another group reported that as many as 21% of women undergoing social egg freezing had ≤3 oocytes at retrieval or had their cycle cancelled because of lack of response to conventional ovarian stimulation.[86] It has been suggested that at least 8–10 vitrified eggs are required to have a reasonable chance of pregnancy and that most women require more than one stimulation cycle to achieve this objective.[32] A more recent model suggested that women age 34 would need to freeze 10 eggs to have a 75% likelihood of having at least one live birth, but that women age 37 would need to freeze 20 eggs and women age 42 would need to freeze 61 eggs to achieve this same probability.[87]

Recommendations

5. Women considering social egg freezing should be advised that the age at which they freeze their eggs and the number of eggs that are frozen impact the probability that these eggs will enhance their fertility (Strong, Moderate).
6. Ovarian reserve testing should be offered to help predict the number of retrievable eggs from a controlled ovarian stimulation cycle and to properly counsel those women at risk of very low oocyte yield (Strong, High).
7. Women considering social egg freezing should be advised that more than one cycle may be required to obtain the number of mature eggs that is desired (Strong, High).

WHAT ARE THE RISKS OF SOCIAL EGG FREEZING?

Ovarian hyperstimulation syndrome is a potential consequence of ovarian stimulation. The mild form (bloating, abdominal discomfort) is seen in 20% to 30% of women undergoing controlled ovarian stimulation for IVF, while the most severe form occurs in 1%. Several strategies may be used to prevent ovarian hyperstimulation syndrome in women undergoing social egg freezing, including identifying those patients at highest risk, individualizing gonadotropin dosing, utilizing an antagonist protocol with agonist trigger, and using dopamine agonists.[88–90] The risks related to the procedure of egg retrieval itself include bleeding, infection, injury to intra-peritoneal structures, and conscious sedation/anaesthesia. There is also a potential risk of ovarian torsion from enlarged ovaries, but this risk is extremely rare.[91–93]

The risks of delaying child-bearing via social egg freezing include the risks of pregnancy at a more advanced maternal age.[94,95] Studies in pregnant women age 35 and older demonstrate increased risk for hypertension, gestational diabetes, placenta previa, intrauterine growth restriction, preterm birth, and CS.[96–101] Conversely, the risk of chromosomal abnormalities in the embryo are directly related to the age of the eggs at the time of cryopreservation, and thus, may be reduced in women using their own "younger" eggs. Thus far, there does not appear to be any increased risk of congenital abnormalities related to oocyte vitrification.[102] However, it is important to highlight that long-term data concerning child health and well-being are not yet available.

Other concerns with social egg freezing are related to never having to use the frozen oocytes, which would confer unnecessary financial cost. This is more likely when the women are younger; for example, less than 32 years of age.[103] Indeed, in the largest series reported to date, only 9% of women who underwent social egg freezing had actually returned to use their eggs (mean age of women who returned 39.2; mean storage time 2.1 years).[32] There is also the possibility of basing future decisions/behaviour on the assumption that one's frozen eggs will ensure future fertility. Clearly, those eggs may or may not survive the thaw, they may or may not fertilize, and they may or may not produce viable embryos.

Recommendations

8. Patients considering social egg freezing should be informed about the risks of controlled ovarian stimulation, oocyte retrieval, and pregnancy at a more advanced maternal age (Strong, Moderate).
9. Patients considering social egg freezing should be advised that there is a chance they may not need to use their frozen eggs and that no guarantees can be made that their frozen eggs would produce a viable pregnancy (Strong, High).

WHAT ARE THE ALTERNATIVES TO SOCIAL EGG FREEZING?

Alternatives to oocyte cryopreservation may involve delayed attempts at pregnancy with or without the use of assisted reproduction, child-bearing at an earlier reproductive age, the pursuit of social non-biological parenthood (through adoption, foster parenting, egg donation), and not having children.

Some women may choose to cryopreserve embryos for future use. Advantages of embryo cryopreservation include fertility centres' longstanding experience freezing and thawing embryos and that the creation of embryos provides insight into the reproductive potential of what is being cryopreserved. This may be a desirable option for women who wish to reproduce with a male partner with whom they are in a stable relationship. Others may choose to use sperm donation for the creation of embryos which they will freeze for their own personal use. Some individuals may feel moral discomfort or have religious opposition to the cryopreservation of embryos, and the fate of stored embryos may lead to legal disputes in cases of divorce or separation.[16,104]

Women may also choose not to cryopreserve their oocytes and to simply wait until they are ready to start a family. Of those, some will conceive naturally while others may require reproductive assistance. Those who require reproductive assistance may undergo IVF using their own fresh oocytes, donor oocytes, or a donor embryo. For most individuals, the use of one's own oocytes is desirable but the chances

of a live birth decrease with age. The use of donor oocytes or donor embryos can increase the chances of a live birth, but does not provide genetic connection.

Another option is to attempt pregnancy at an earlier reproductive age. Women should be advised about lifestyle practices and certain medical conditions that may impact fertility.[105] In many cases, conceiving at a younger age would eliminate the need for assisted reproduction. This option may not be ideal given certain personal, social, and financial circumstances.

Social parenthood—for example, domestic or international adoption, fostering, or parenting their (future) partner's children—can also be a meaningful family-building option. However, there may be legal, financial, and practical barriers to creating families in these ways.

Finally, some women may choose not to have children or refrain from having additional children in the future if they are already a parent. Not all women who inquire about social egg freezing will be certain that they want children, so for some, the choice to remain childless (or have fewer children) will allow them to pursue other things that they value.

Recommendations

10. Women considering social egg freezing should be counselled about the alternative options for future conception (Strong, Moderate).

WHAT ELEMENTS ARE IMPORTANT FOR COUNSELLING AND INFORMED CONSENT?

Prior to treatment, women considering social egg freezing should be counselled about the medical, physical, psychological, and financial aspects, and social risks/benefits of this technique and the alternatives listed above. Adequate counselling is essential for supporting the process of informed choice (consent or refusal) for social egg freezing. In 2008, the ASRM outlined the essential elements of informed consent for elective oocyte cryopreservation.[106] These elements have been incorporated into and expanded upon in Table 5.

The demographics of women who undergo social egg freezing have been well described. The majority of these women

Table 5. Essential elements for informed consent for social egg freezing

1. **Ovarian stimulation and oocyte retrieval**
   a) The side effects and risks associated with required medications.
   b) The requirements for blood sampling, transvaginal ultrasound, and oocyte retrieval.
   c) The potential risks of oocyte retrieval.
   d) A reasonable estimate of the number of oocytes that may be retrieved.
2. **Cryopreservation and storage**
   a) The cryopreservation method to be used.
   b) The location where the oocytes will be stored.
   c) The possibility that their cryopreserved oocytes will have to be transferred to a different location if the storage facility moves or ceases operation.
   d) The possibility that cryopreserved oocytes may be lost or damaged.
   e) The expected thaw-survival rate for cryopreserved oocytes including the possibility that none survive.
   f) The fact that cryopreservation does not guarantee live birth.
3. **IVF**
   a) The requirement for IVF-ICSI and the associated risks for the woman and resulting offspring.
   b) The expected success rates per thawed oocyte for fertilization, embryo development, pregnancy, and live birth (including clinic-specific data if available).
   c) Age-specific expected outcomes for IVF using cryopreserved vs. fresh oocytes.
   d) Any applicable requirements for single embryo transfer.
4. **Finances**
   a) The cost of oocyte cryopreservation (including medications).
   b) Annual storage fees for cryopreserved oocytes.
   c) The estimated cost of later IVF-ICSI with embryo transfer and possible embryo cryopreservation.
   d) Applicable exclusions or limitations on public funding for IVF.
5. **Advanced maternal age**
   a) The maternal and fetal risks associated with childbearing at an advanced age with natural or ART conceived pregnancies, and
   b) The potential challenges and benefits of parenting at a more advanced reproductive age.
6. **Use or disposition of cryopreserved oocytes**
   a) That cryopreserved oocytes may be destroyed if storage fees are not paid or if they exceed any clinic-specific time limits for the use of stored materials or access to IVF, or in the event of their death.
   b) That cryopreserved oocytes that are not used for the patient's reproduction may be disposed of (at the patient's request).
   c) That with prior consent, the cryopreserved oocytes may be donated to another couple or individual for the purposes of reproduction; they may be used for research aimed at improving reproductive techniques or training; or they may be used for other research purposes.
   d) That Canada currently prohibits the sale of gametes (including oocytes); and
   e) That there may be moral/ethical implications concerning the future disposition or use of unused cryopreserved oocytes.

Table 6. Cumulative live birth rate per batch of oocytes retrieved (from CARTR-BORN Jan 1, 2013–Dec 31, 2014, after all resulting embryos, fresh and frozen, have been transferred or discarded)

Number of mature eggs retrieved	Age of oocyte provider				
	Less than 30	30–34	35–37	38–40	41–42
<5 eggs	20.3%	21.3%	17.0%	11.7%	5.9%
5–9 eggs	35.6%	38.3%	31.4%	23.8%	13.4%
10–14 eggs	46.8%	45.3%	41.9%	31.8%	21.8%
15–19 eggs	46.8%	51.1%	45.5%	33.2%	30.3%
20–24 eggs	47.6%	53.1%	50.3%	45.9%	26.7%
25+ eggs	43.7%	48.9%	53.1%	54.0%	40.9%
Total	38.5%	38.3%	30.9%	21.8%	12.5%

tend to be older than 35, single, childless, heterosexual, and with higher education.[3,32,107] A survey of women post-oocyte cryopreservation showed that almost 100% still desired a pregnancy, around 50% were in a relationship, and one-third were trying to conceive. Of these patients, 17% had tried to conceive naturally in the past 12 months without success and 29% reported a pregnancy/delivery since freezing their eggs. Despite changes in relationship and/or parenting status, when women were asked about regrets from social egg freezing, the overwhelming majority stated that they would do it again but at a younger age.[107]

Recommendations

11. Women undergoing social egg freezing should receive sufficient information to provide informed consent (Strong, High).

HOW DO WE REPORT OUTCOME DATA WHEN SO LITTLE DATA ARE AVAILABLE?

Ideally, all clinics that offer social egg freezing would be able to report their clinic-specific outcome data. However, because the number of women undergoing social egg freezing is relatively small and because the number of women who have thus far returned to use their frozen eggs is even smaller, it will take many years, if not decades, for most clinics to have reliable, representative, age-specific data. As a result, many clinics refer to the medical literature and imply that these data represent the chance for success. Unfortunately, the data reported from large international centres may, or may not, have external validity.

An alternative may be to report national data for social egg freezing from the CARTR-BORN registry. Although not centre-specific, this should reflect the scope and diversity of centres that offer social egg freezing in Canada. However, these data have only recently come into the CARTR-BORN registry, and we do not yet have live birth data to report.

Another alternative, or supplement, may be to report cumulative live birth rates per oocyte retrieval. This, too, is a recent addition to CARTR-BORN and provides the option of both national and centre-specific, age-specific data (Table 6). Clearly, one cannot assume that the results with social egg freezing would be equivalent to autologous, newly completed IVF cycles, but this could provide a way of estimating the upper limit for the success rate of this technique.

Recommendations

12. In vitro fertilization centres offering social egg freezing should provide their patients with an estimate of their chances of success. This estimate not only should consider the published medical literature but also should take into account national data regarding social egg freezing and, if available, clinic-specific data regarding cumulative live birth rates per oocyte retrieval (Strong, Low).

CONCLUSION

Social egg freezing is an increasingly common method for women to attempt to guard against the natural age-related fertility decline. Although existing data are limited, they demonstrate an acceptable pregnancy rate, as well as some psychosocial benefit. Nevertheless, caution is required when counselling women about their chances of success. As with all medical interventions, a thoughtful discussion about the risks, benefits, and alternatives to social egg freezing is paramount.

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