AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS COMMENTARY

The dawn of a new ice age: social egg freezing

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Key words
Infertility, oocyte cryopreservation, vitrification, fertility preservation, social egg freezing

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article and they have not received or are due to receive any payment for writing this article.

Please cite this article as: Jones BP, Saso S, Mania A, Smith JR, Serhal P, Ben Nagi J. The dawn of a new ice age: social egg freezing. Acta Obstet Gynecol Scand 2018; 97:641–647.

Received: 11 December 2017
Accepted: 18 February 2018

DOI: 10.1111/aogs.13335

Abstract

Given the age-related decline in ovarian reserve and oocyte quality, it is unsurprising the global trend of deferring motherhood has resulted in increased levels of involuntary childlessness. The development of oocyte vitrification, with pregnancy and livebirth rates now comparable to using fresh oocytes, has provided an opportunity to cryopreserve oocytes electively for future use, empowering women with the capacity to delay their childbearing years. While it enhances reproductive autonomy, age-related obstetric complications, economic implications and the risk of unsuccessful future treatment make this a controversial therapeutic option. However, some women have no reasonable alternative, such as single women approaching their late thirties, in whom egg freezing, although not a guarantee against involuntary childlessness, offers hope by extending the window of opportunity to find a partner. Given the upward trend in women electively cryopreserving their eggs, it would appear that a new ice age, from a fertility perspective, is upon us.

Abbreviations: IVF, in vitro fertilization; SEF, social egg freezing.

Introduction

Over the last 50 years, the evolution of societal perceptions and norms has seen the advancement of gender equality and development of women's rights across the globe. Access to family planning, along with greater educational and professional opportunity has enhanced female economic independence and empowerment. Analogous with this societal advancement, the age of first-time mothers continues to rise, with more women over the age of 40 now giving birth than those under the age of 20 (1).

The ovarian reserve declines with age, from a peak of 6–7 million oogonia in utero to below 500 000 by the onset of puberty (2). There is an exponential decrease from the age of 37 years onwards (3), owing to increased follicle atresia, when just 25 000 oocytes remain. In tandem with a decrease in quantity, oocyte quality also

Key Message

Social egg freezing empowers women to overcome the irreversible physiological age-related decline in fertility. Although it provides an opportunity to defer childbearing and reduces the risk of involuntary childlessness, it does not guarantee success.

deteriorates with advancing maternal age, which subsequently increases the risk of aneuploidy (3). This manifests clinically with significantly reduced fecundity and, in those who do become pregnant, a dramatically increased risk of miscarriage, from approximately 11% in the third decade of life to 93% over the age of 45 (Figure 1) (4). The risk of chromosomal disorders such as Down's syndrome also increases with age from 1 in 1500 at age 20, to 1 in 35 at age 45 (5). When considering this irreversible age-related deterioration in ovarian reserve, it is unsurprising the trend of delaying motherhood has resulted in an increased proportion of women who remain childless involuntarily (6), and more women over the age of 45 using donor eggs rather than their own (7).

Since its introduction in 1978, an estimated 5 million babies have been born following in vitro fertilization (IVF) worldwide, and now accounts for 2% of childbirths in the UK (7). Although IVF can treat infertility secondary to numerous causes, it cannot overcome the irreversible decline in oocyte quality and quantity associated with advancing age. Oocyte cryopreservation was first reported three decades ago after successful pregnancies were reported following the use of a slow freeze and rapid thaw technique (8). However, low pregnancy rates and lack of understanding of key technical aspects prompted the development of a faster cryopreservation technique, oocyte vitrification. Not only has vitrification greatly improved oocyte survival and clinical pregnancy rates (9), but recent data have shown there is no difference in pregnancy, miscarriage or livebirth rates between fresh and frozen cycles (10). This has helped establish oocyte cryopreservation as a realistic fertility preservation option in women undergoing treatment for cancer or complex medical problems and has provided an opportunity for women to freeze oocytes electively at a younger age for "social" reasons.

Electively freezing eggs prior to the physiological decline in oocyte quality and quantity nullifies future age-related increased risk of miscarriage and congenital abnormality, optimizing the chances of a successful live birth. Referred herein as social egg freezing (SEF), it empowers women with the opportunity to defer their childbearing years, while potentially reducing, but not eliminating, the risk of unintentional permanent childlessness. Cobo et al. recently reported the outcomes of 1382 women who underwent SEF at a mean age of 37.7 years (11). Despite a short follow-up period of 2.2 years, 120 (8.7%) women returned to use their cryopreserved eggs with an oocyte survival rate of 85% and a clinical pregnancy rate of 39% (11). This pregnancy rate is comparable to that achieved by women between the ages of 35 and 37 using fresh embryo transfers (38.7%) (7), despite the mean age of 39.2 at embryo transfer. This exemplifies the potential clinical significance of SEF. Despite these promising results, utilizing SEF as reproductive insurance is a potentially costly reproductive gamble associated with significant risk. We discuss herein the key multidisciplinary components that underpin SEF, including the obstetric, psychosocial, economic, legal and ethical issues that require consideration.

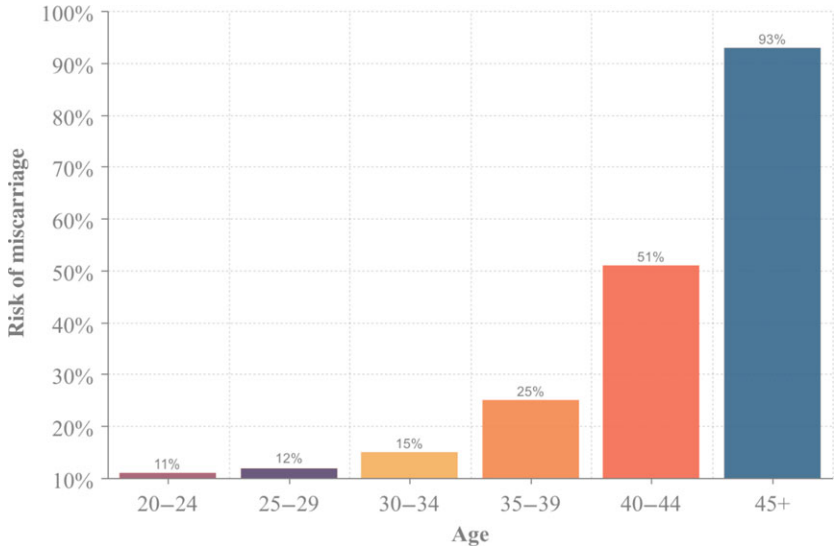

Figure 1. Relation between miscarriage and advancing age. Graph based on the data from Nybo Anderson et al. (4) (page 1710, paragraph 4, lines 4–6). [Color figure can be viewed at wileyonlinelibrary.com].

Obstetric considerations

Although pregnancy rates are superior using eggs frozen at an earlier age, the increased maternal morbidity and mortality associated with advanced maternal age remain. Mortality is increased threefold in women over the age of 40 when compared with women aged 20–24 (12). Not only is there a higher prevalence of chronic medical conditions in women of advanced maternal age (13), but there is also an increased likelihood of maternal and obstetric complications. Women over the age of 40 are at increased risk of hypertensive disorders of pregnancy, with almost twice the risk of developing preeclampsia (14). However, given the use of donor oocytes is itself an independent risk factor for preeclampsia (15), SEF may be associated with less risk than using donor eggs. Advanced maternal age is also a risk factor for fetal growth restriction (16), stillbirth (17), gestational diabetes, preterm birth and operative delivery (13).

Regarding neonatal outcomes, although higher neonatal morbidity has previously been implicated in older women, others report that in the context of high-risk antenatal care, similar neonatal outcomes to those of younger mothers can be expected (18). This is applicable even to women at the extremes of reproductive age and, although not advisable, appropriately screened women in their fifties can even expect successful neonatal outcomes (19). Although it is too early to assess the long-term impact to children born following vitrification, it is reassuring that congenital abnormality rates are similar to those born following natural conception (20) and development, at least for the first 3 years, is normal (21).

Social factors

The risk of permanent involuntary childlessness is 6% if childbearing is deferred until the age of 30 years but this increases almost sixfold to 35% if postponed another 10 years (22). The most common indication for SEF is not having a partner (7), which accounts for up to 88% of women undergoing elective oocyte cryopreservation (23). Moreover, in the aforementioned study by Cobo et al. (11), of the 79% who were single at the time of cryopreservation, 47% had found a partner by the time they returned to use their eggs, highlighting the potential significance of SEF in single women (11).

Other reasons to defer childbearing include seeking high level education, career prioritization or economic uncertainty (Figure 2). There are also potential advantages to postponing parenthood such as greater family stability, higher household income, better quality of living and superior parenting practices (24). It has also been shown to result in better long-term outcomes in offspring, including higher self-sufficiency in adulthood (25), as well as better educational and psychosocial outcomes (26).

Even in populations that have a good understanding of age-related infertility, women continue to defer childbearing (23). In a survey of over 1000 women in the UK and Denmark, 89% considered reproductive planning to be an acceptable indication for SEF (27). These positive attitudes towards SEF are reflected by an almost threefold increase in the number of eggs frozen in the UK, from 2476 in 2008 to 7047 in 2013 (28). Moreover, the number of women freezing eggs for future personal use continues to rise by 25–30% each year (Figure 3) and the number

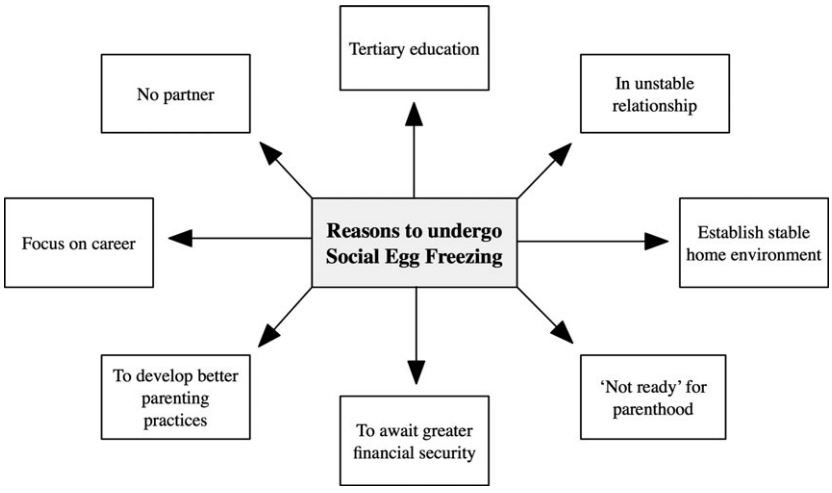

Figure 2. Reasons women defer childbearing.

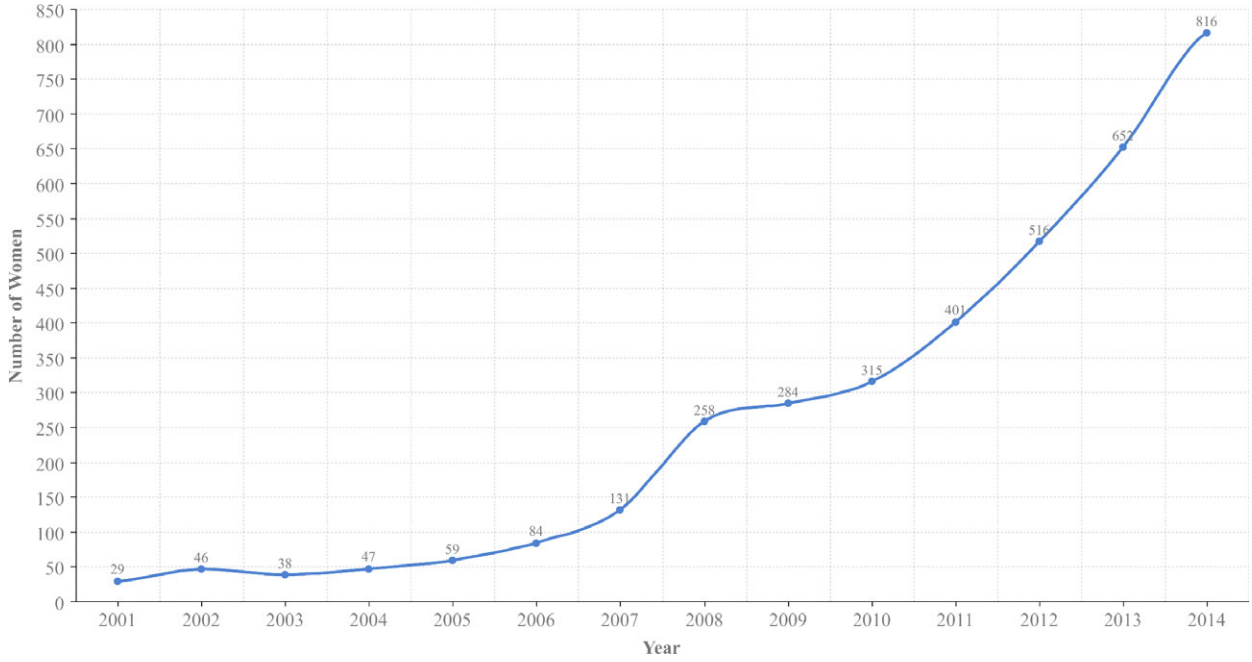

Figure 3. Number of women undergoing elective oocyte cryopreservation in the UK in 2014. Based on data reported in the HFEA trends and figures 2014 data sheet on egg freezing (7). [Color figure can be viewed at wileyonlinelibrary.com].

of clinics offering egg storage cycles also continues to increase (Figure 4) (7). Although these figures include medical reasons in addition to social factors, the majority of cases over the age of 38 cited no partner as the reason for storage, indicating an increasing awareness and demand for SEF.

Economic and legal implications

The highest chance of successful live birth following SEF is when it is performed before the age of 34 years (29). However, owing to the additional expenditure of storing eggs and significant chance of spontaneous conception during these fertile years, the most cost-effective time to achieve a live birth is prior to the age of 38. In women who plan to defer childbearing until over the age of 40, SEF prior to the age of 38 actually reduces the cost of a live birth (30). This figure is based on the US economy but similar cost-effectiveness would be expected in the context of other developed healthcare systems.

From a legal perspective in the UK, Human Fertilisation & Embryology Authority (HFEA) regulations allow the storage of gametes for a standard 10-year period (31). Although this can be extended in circumstances where the individual has or is likely to become prematurely infertile, it may be counterproductive in SEF, particularly in women who cryopreserve at an earlier age to optimize future success. Women who experience physiological age-related fertility decline would therefore be prohibited from extending longer than the current 10-year storage limit, culminating in the destruction of the stored eggs if they are not used. The fact that these women could subsequently use donor eggs, instead of their own, exemplifies the perverse nature of this regulation, which may need updating once the practical implications it has on SEF are exposed.

If the primary role of a storage limit is to safeguard against the potential for women to become pregnant outside of their natural reproductive years, it may be logical instead to implement legislation limiting the age at which future utilization of stored oocytes can be undertaken. This may prevent the significant adverse social implications, legal ramifications and financial repercussions associated with raising children at retirement age, particularly when there is the future risk of personal ill-health.

Ethical reflection

Social egg freezing empowers women and allows greater reproductive autonomy. By allowing women to extend their reproductive potential into their forties, when men traditionally remain fertile, it helps facilitate gender reproductive equality. However, it has been argued that technological solutions to societal problems repress, as oppose to liberate, those women involved (32). As such, SEF may actually augment the societal issues for which it

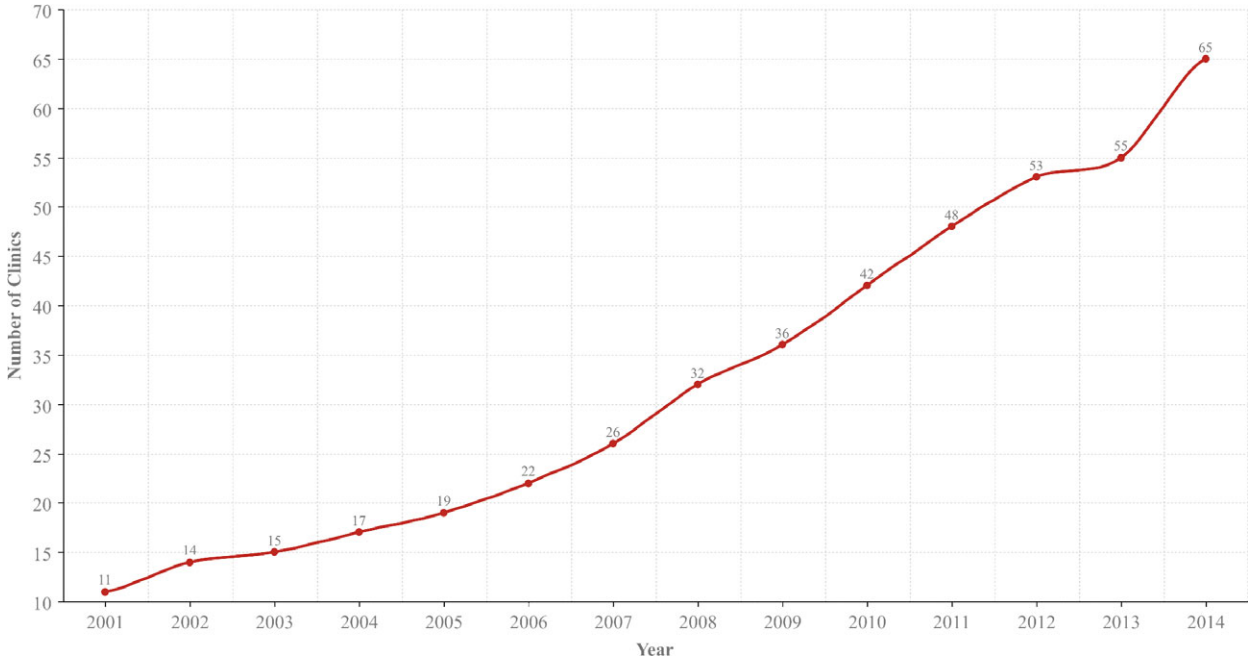

Figure 4. Number of fertility clinics offering elective oocyte cryopreservation in the UK in 2014. Based on data reported in the HFEA trends and figures 2014 data sheet on egg freezing (7). [Color figure can be viewed at wileyonlinelibrary.com].

is being considered, with women instead relying upon it as "reproductive insurance." This may also be reinforced by women feeling pressured by their employers to delay motherhood (33). This may be intensified further by reports of companies such as Facebook and Apple offering to fund SEF as an employment benefit. In women who have the option to procreate earlier, utilizsing SEF as "reproductive insurance" is risky, as the number of eggs in storage is finite (34). Although this risk can be reduced by freezing more eggs at younger ages (11), this will have significant economic implications and there is still no guarantee of success.

"*Primum non nocere*" (first, do no harm) deserves particular attention in this context. Not only is IVF associated with risks such as drug reactions, surgical complications and ovarian hyperstimulation syndrome (OHSS), it is physically and psychologically demanding. Although SEF in a woman in her early twenties may optimize the future chances of successful live birth, the likelihood of spontaneous conception in her remaining reproductive years is significant, potentially resulting in cryopreserved eggs that are subsequently not used. Not only would this have entailed unnecessary treatment with physical risk and financial burden, it raises important questions about the disposition of stored oocytes. Although morally more neutral than fertilized embryos, the disposition of cells that have the potential to create life is never straightforward. However, considering the widespread shortage of donor eggs, and the ongoing need for innovation in the field, unused eggs could be used by women who require egg donation or for research. Given the favorable patient acceptability of egg donation of between 74 and 88%, donation of unused oocytes could be a viable solution (23,35).

Conclusion

Spontaneous conception during a woman's most fertile reproductive years is undoubtedly the safest and most efficacious way to acquire motherhood. However, in the context of a society where the age of motherhood and rates of involuntary childlessness continue to increase, SEF offers the opportunity for women to preserve their reproductive potential if spontaneous conception is not possible.

Women with absolute indications to freeze their eggs, such as those approaching their late thirties who are not in a relationship and want future biologically related children, should consider SEF before their ovarian reserve deteriorates irreversibly. SEF extends the window of opportunity for single women to find a partner, but retains the option to use a sperm donor in the future if they remain single. SEF in women with relative indications to delay childbearing, such as those who decide to focus on their career or prioritize their education, is without question a reproductive gamble. Extensive counseling is paramount to ensure the women are fully informed,

including the possibility of unsuccessful treatment in the future with a finite number of stored eggs, as well as the pregnancy-related risks associated with advanced maternal age. Ultimately, each case should be individualized, with consideration of physiological, legal and economic aspects, to optimize timing of oocyte vitrification and determine how many oocytes to store.

The creation of official guidelines and recommendations is necessary to help regulate SEF. The development of impartial and widely available patient information and support groups is essential to encourage appropriate education, to facilitate autonomous decision making and prevent commercial exploitation. SEF shows promise in a select group of fully informed women in certain scenarios, but it should not be advertised as a commercialized reproductive insurance policy that encourages young women to freeze their eggs on the off-chance they need to use them in the future.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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