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## Social egg freezing: for better, not for worse

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### Abstract

The possibility for healthy women to cryopreserve their oocytes in order to counter future infertility has gained momentum in recent years. However, women tend to cryopreserve oocytes at an age that is suboptimal from a clinical point of view - in their late thirties - when both oocyte quantity and quality have already considerably diminished and success rates for eventually establishing a pregnancy are thus limited. This also gives rise to ethical concerns, as the procedure is seen as giving false hope to (reproductively speaking) older women. We evaluate which measures can be taken to turn social freezing into a procedure that is both clinically and ethically better than the current practice. The main objective of these measures is to convince those women who are most likely to (want to) reproduce at an above average age to cryopreserve their oocytes at a time when this intervention is still likely to lead to a life birth and to discourage fertility clinics from specifically targeting women who have already surpassed the age at which good results can be expected.

### Keywords

fertility preservation; oocyte cryopreservation; social egg freezing;

## 1. Introduction

Women and their reproductive choices are always a welcome subject for ethical concern. Whether voluntary prostitution, surrogacy or oocyte donation are concerned, one of the recurring questions is always this: should women be allowed to engage in practices that may cause them physical or psychological harm, or should these practices be prohibited in the name of women's wellbeing and the moral high ground? The latest issue to feed the traditional standoff between respecting women's autonomous decisions and (paternalistically) protecting them from exploitation is the possibility for healthy women to cryopreserve their oocytes, just in case they have no (good) oocytes left by the time they are ready to reproduce. While the option for cancer patients to freeze oocytes in the face of treatments that may render them infertile is met with enthusiasm, offering the same option to healthy women is met with a lot more suspicion and reluctance, both by practitioners and policy-makers (ASRM, 2007; Jones, 2009; Martin, 2010; McCullough, 2004; Shkedi-Rafid and Hashiloni-Dolev, 2011). First, there are a number of 'fundamental' objections: oocyte cryopreservation is still experimental, it is unnatural, it represents an unwarranted medicalization of reproduction, risks for mother and child rise as the age of the mother rises, et cetera. A number of ethicists have done the exercise of addressing these objections and of weighing them against the benefits of social freezing: increased gender equality, increased control over reproductive destiny, time for women to find a suitable partner, complete their studies and achieve financial and psychological stability before embarking on parenthood, et cetera. (Dondorp and De Wert, 2009; Goold and Savulescu, 2009; Rybak and Lieman, 2009) We will not reiterate this discussion here.

Second, there are a number of more emotionally charged objections. Not only is the yuck-factor at play but there is also an ambiguous depiction of women who seek to store their oocytes for 'non-medical reasons'. They are either depicted as selfish career women (and thus undeserving of help) or as victims of a male-oriented society that neglects young mothers and of an unscrupulous fertility industry that is ready to cash in on their fear for infertility (and thus in need of protection). (Martin, 2010) But why should these women be either perpetrators or victims? Instead of casting a moral verdict, we start from the simple observation that more and more women postpone motherhood and we grant that those who consider to go through the burdensome procedure of cryopreserving oocytes, most likely have very good reasons for postponing motherhood.

While the success rates of IVF with oocytes that have been subjected to slow freezing are significantly lower than those with fresh oocytes (Borini et al., 2010; Magli et al., 2010), cryopreservation with the vitrification technique offers success rates similar to those with fresh

oocytes (Almodin et al., 2010; Grifo and Noyes, 2010; Kim et al., 2010; Rienzi et al., 2010; Trokoudes et al., 2011). However, just as for fresh oocytes, the outcomes of IVF with vitrified oocytes are – unsurprisingly – highly dependent on maternal age at the time of freezing (Rienzi and Ubaldi, 2011). According to the data of the ASRM of all the SART member clinics for 2009, for women younger than 35, 41,4% of regular (fresh embryo) IVF cycles result in a live birth, women aged between 35 and 37 can expect a live birth rate per cycle of 31,7%, women aged between 38 and 40 a rate of 22,3% and women aged 41-42 a rate of 12,6% (ASRM Office of Public Affairs, 2010). If only 40-year old women resort to social freezing in a desperate attempt to ‘save’ their fertility, it will hardly produce any positive results and we believe that it is this image that has sparked the narrative of social egg freezers as women vulnerable to exploitation (Martin, 2010). However, by banning social egg freezing, women who *would* stand to benefit from it and would not be exploited but helped by having a number of eggs in storage, will also lose out. If long term follow-up shows that vitrification is safe for the offspring and if correct information is supplied to candidate-freezers about the decline in their fertility, about pregnancy complications related to maternal age and about their individual chances of conceiving with their frozen eggs, a large part of the women who decide to cryopreserve their oocytes might actually be making a very rational and justified choice.

The biggest challenge, however, is to assure that the procedure is used by those women who are most likely to benefit from it, namely women whose oocytes have not already considerably aged. In order to reach this goal, a double approach is needed. First, women need to be informed that they should store their oocytes before age 35 and second, the centres that offer elective oocyte cryopreservation should refrain from specifically targeting those women who are most desperate, namely those older than 35. In this way, social freezing is used for better, but not for worse.

## **2. The divergence between the best case scenario and the worst case scenario**

The best case scenario of elective freezing is the following. A woman in her late twenties or early thirties realizes that, although she has a strong desire to become a mother, she is unlikely to be in a good position to have children in the coming years (for example because she is single). She knows that by the time she will be ready to reproduce, her oocytes will have aged considerably (leading to low implantation rates and a higher risk of chromosomal abnormalities) or her ovarian reserve will be completely depleted so that she will remain childless or will have to use donor oocytes. This woman therefore proactively turns to an alternative option, namely to cryopreserve the young oocytes she has today, and use them to establish a pregnancy at a later point in her life.

At present, oocyte cryopreservation is still an experimental procedure, but this classification is increasingly contested (Noyes et al., 2010). Recent data are very encouraging, both concerning the health of the resulting offspring, (especially for vitrification) concerning oocyte survival after freezing and thawing and concerning the subsequent success rates which are comparable to those of fresh oocytes (Almodin et al., 2010; Grifo and Noyes, 2010; Kim et al., 2010; Rienzi et al., 2010; Trokoudes et al., 2011). Long term follow-up data on children born from vitrified oocytes are not yet available due to the novelty of the technique and thus the possibility remains that oocyte freezing may affect the long term health of the offspring. However, while it is currently uncertain if such risks are involved in oocyte cryopreservation, they are certain to exist in aged oocytes. This means that even in this experimental phase, freezing eggs for future use can reasonably be expected to increase the overall health of future offspring for those women who have already decided to postpone motherhood. One might argue that relying on young donor oocytes is still safer, but this is not a valid alternative option for many women as donor oocytes are in short supply and worries exist about the physical and psychological welfare of donors. Moreover, without wanting to over-estimate the importance of a genetic link between parents and children or the psychological damage suffered by donor-conceived children, we believe it is fair to say that, when given the option, parents strongly prefer to have a genetic link with their children (Ravin et al., 1997). Oocyte cryopreservation can therefore – in principle – be applauded as another step in offering women more reproductive freedom.

The worst case scenario, is that a woman only becomes aware of – or pays attention to – a decline in her fertility when she approaches or passes the symbolic age of 40 while lacking a stable relationship, then desperately seeks to hang on to whatever is left of her ovarian reserve and resorts to oocyte cryopreservation. In this scenario, a woman will either be irresponsive to ovarian stimulation all together or she will need multiple ovarian stimulation cycles to harvest a limited number of oocytes that are likely to give her a fairly small chance of conceiving when she is finally ready to reproduce. As Sage et al. (2008) have reported, “[t]he likelihood of retrieving an adequate number of mature oocytes decreases dramatically with age”. Moreover, the odds are considerable that a woman who is not ready to reproduce at 40 is no more ready a few years later and will thus never even return to use her frozen eggs. In this scenario, oocyte cryopreservation for healthy women appears to be a waste of medical resources and a source of unnecessary health risks.

At present, women who opt for elective cryopreservation tend to lean more towards the worst case scenario than to the best case scenario, as the average reported age of women freezing their eggs is

38 (Gold et al., 2006; Klein et al., 2006; Nekkebroeck et al., 2010; Sage et al., 2008). Moreover, the number of women who have so far actually frozen their oocytes might even represent the 'best' fraction of those who present themselves, as many women need to be turned down when preliminary tests indicate a diminished ovarian reserve. Of those women who do start the stimulation protocol, Klein et al. (2006) report a 24% cancellation rate due to suboptimal response and of those cycles that they completed, only 58% yielded more than 10 oocytes, while standard stimulation was employed.

There are several ways to deal with this situation: we can opt for a status quo, in which social freezing will bring about more heartache than happiness, we can 'pull the plug' on social freezing and label it 'unethical', whereby women will not be dragged into the worst case scenario, but only at the expense of those in the best case scenario or – preferably – we can try to promote oocyte cryopreservation for those women who are most likely to benefit from it and discourage or refuse those women who are the least likely to benefit from using the procedure. As female fertility starts to decline steeply from age 35 onwards, the optimal timing for elective freezing would be between 30 and 35. Freezing at a younger age would be more favourable from a clinical point of view, but it would result in low usage rates, as the chances are considerable that these women will find a partner and reproduce naturally before their ovarian reserve is depleted. Freezing at an older age would significantly reduce the success rates. Freezing above 43 years old is futile (with pregnancy rates per cycle of 2% and lower) and should not be offered at present (Hourvitz et al., 2009).

### **3. Public awareness**

As mentioned, the average reported age of non-medical patients freezing their oocytes is 38 years (Gold et al., 2006; Klein et al., 2006; Nekkebroeck et al., 2010; Sage et al., 2008). However, social freezers in Gold's study indicate that if they had been aware of the possibility to freeze earlier, they would have done so earlier. Creating more public awareness is therefore a key factor in lowering the average age of social freezers. What exactly should women know in order to make an informed decision regarding elective oocyte cryopreservation? Merely informing them about the technical possibility to freeze eggs is not enough. Public awareness should be created on several fronts:

- First, women need to be made aware that their fertility starts to decline long before the onset of menopause and that the age of 35 is a crucial turning point, rather than the age of 40.

- Second, they need to know that this means that not only their chances of conceiving naturally, but also their chances of conceiving through IVF (with their own – aged – oocytes) plummet at that point. This is important, as several studies have indicated that women not only underestimate the speed at which female fertility declines but also *overestimate* the possibilities of overturning age-related infertility through IVF (Bretherick et al., 2009; Lampic et al., 2006; Maheshwari et al., 2008).
- Next, women should be informed that if they want children, but can foresee that they will not be ready to reproduce at 35, they can increase their chances of establishing a pregnancy and of having a healthy baby after that age if they cryopreserve their eggs at a younger age.
- Finally, women above 35 need to understand that if they still want to cryopreserve oocytes, they are less likely to benefit from the procedure than their younger counterparts. Not only will the quality of their oocytes already have diminished, but they will also need to undergo more stimulation cycles to obtain the same number of oocytes. In other words: while they will need more oocytes, less will be harvested per stimulation cycle, rendering the whole procedure much more burdensome and less efficient.

The most straightforward way to create public awareness is by launching awareness campaigns as is done for example to stimulate breast cancer screening or to reduce smoking. In the past, several countries have organized campaigns to make women aware of a decline in fertility with age, but the objective was to stimulate women to have children at a younger age. If a similar effort was launched at present, we would expect the message to be at least twofold: women should have their children 'on time' or freeze their eggs on time (Dondorp and de Wert, 2009). Women have not always been very receptive towards the message of fertility decline and in fact, there is no significant difference in fertility awareness between women who intend to have their first child before or after their 30<sup>th</sup> birthday, which indicates that fertility awareness has little or no impact on the average planned age at first birth (Lampic et al., 2006). This does not mean, however, that women will be equally unreceptive to the message that oocyte cryopreservation is available for them, quite on the contrary. The fact that a better knowledge about fertility decline with age does not lead to women reproducing at a younger age can be attributed to the fact that family planning is very dependent on personal circumstances. Several studies have found that women find it increasingly important to first complete their education, have financial security, good housing and a stable relationship before taking on the responsibility of parenthood (Lampic et al., 2006; Maheshwari et al., 2008). Thus, a decline in fertility is only one of many factors that women take into account when balancing the pro's

and con's of reproducing earlier or later in life and only for those women who have a very strong child wish will it be a factor that outweighs the others. For other women, the message that they should reproduce at a young age will come across as intrusive and pedantic (Williams, 2005). By adding the possibility to cryopreserve oocytes to the message of fertility decline, women may feel helped rather than lectured.

Not everyone will agree that information campaigns to inform women about the possibility to cryopreserve oocytes are warranted, either because the problem (infertility due to age) is not grave enough, or simply because one can expect an automatic increase in awareness as private cryobanks will start to offer social freezing and will advertise their services. Private cryobanks have a financial benefit in informing women about a decline in their fertility with age and about the option of oocyte cryopreservation as more 'customers' will generate more revenue. Many fertility clinic websites offer correct information and are upfront about what their potential customers can expect. However, in some cases commercial interests can also taint the information that is conveyed and lead to an overly optimistic representation of social freezing. Women browsing the internet in search for information on egg freezing will find claims such as "Egg freezing effectively suspends the ever-present ticking of the reproductive biological clock" ([http://uscfertility.org/fertility\\_options/egg\\_freezing/](http://uscfertility.org/fertility_options/egg_freezing/)) and "There are now safe, successful techniques to preserve a woman's fertility indefinitely" (<http://www.infertile.com/infertility-treatments/preserving-your-fertility.htm>). Even the use of terms such as 'fertility preservation' may create the impression that by freezing oocytes, a status quo is offered as far as a woman's reproductive options are concerned. However, this is far from true. Every preserved oocyte represents one single *chance* to conceive, not a conception, let alone a baby. For example, Rienzi reports an ongoing implantation rate per warmed oocyte of 12,9% in women with a mean age of 35,5 (Rienzi et al., 2010). In this perspective, a lottery ticket would be a better metaphor for a cryopreserved oocyte than an insurance policy, especially for women freezing in their late thirties or later. A minimum requirement for websites that seek to inform women honestly is that success rates are stratified by age. A study by Abusief et al. (2007) shows that in the US, only 52% of private fertility clinics and 33% of academic fertility clinics publish success rates based on age on their websites. Moreover, only 35% of the former and 22% of the latter clarify their definition of success rates.

A crucial question is to what extent women will be equally receptive to information offering them little hope as to information offering them much more hope of a successful pregnancy. Chances are



that they will deem the centres that present the highest success rates and the most optimistic message to be the most competent ones. As Cutting et al. (2009) have previously mentioned, “the request for treatment [...] and the circumstances around it carry emotional and life issues which can impede the ability of patients to hear and process the information around oocyte cryopreservation”.

All things considered, cryobanks will play a large part in creating public awareness in the years to come, but to make sure that women have easy access to unbiased information, it is preferable that independent health care workers such as general physicians and especially gynaecologists who are not connected to centres that offer oocyte cryopreservation either actively inform their patients around age 30 when they come for check-ups and/or place flyers in their waiting rooms. If gynaecologists discuss the issue of declining fertility and the option of elective freezing with their patients before they start to browse the internet for answers, women’s expectations are more likely to be realistic and they can be guided in the interpretation of success rates that they will find.

#### **4. Specific data to be offered to candidate-freezers**

After handing them the necessary unbiased information about the procedure, physicians or gynaecologists can refer women who express interest in social freezing to specialized fertility centres. It is crucial that these centres present some specific information to candidate-freezers and provide individual and independent counselling. In line with the suggestions of Cutting et al. (2009), subjects that need to be discussed include the following.

First, rather than ‘overall’ success rates, success rates should be given for the specific age of the candidate (at the time of freezing), especially when she is over 35. Hourvitz et al. (2009) report clinical pregnancy rates (for regular IVF) of 7,7%, 5,4%, 1,9% and 0% and delivery rates of 4,2%, 3,3%, 0,6% and 0% per cycle for women aged 42, 43, 44 and 45, respectively. This means that presenting a 44 year old woman with statistics from 42 year old women – which seems like a minor age difference – gives her a *fourfold* overestimation of her chances to achieve a clinical pregnancy and an even greater overestimation of her chances of a live birth, which illustrates the importance of precision in this area.

Even if ages are specified, success rates in IVF treatment in general are all but unambiguous. Statistics can be given on fertilization rates, cleavage rates, implantation rates, clinical pregnancy rates, biochemical pregnancy rates, live birth rates, (term) singleton live birth rates, per patient, per stimulation cycle, per retrieved oocyte, per fresh embryo, per embryo surviving thawing, per embryo

transferred or per transfer cycle. For a woman to be well informed, she should not be drowned in irrelevant information obscuring the rates that actually matter to her personally. A broad discussion on this topic has already taken place. For regular IVF, a good standard appears to be the term singleton live birth rate per initiated ART cycle (Min et al., 2004) or alternatively the live birth rate per ovarian stimulation started (Griesinger et al., 2004), whereby the percentage of multiple pregnancies is specified.

In the specific context of elective oocyte cryopreservation, however, it may be better to focus on cumulative birth rates. Unlike 'standard' IVF-patients, a social freezer cannot take it 'one cycle at a time'. What a social freezer wants to know is this: "If I freeze 10 (or 15, 20, 25,...) oocytes, what are my chances of eventually having a child/children?" Once this question is answered, she can move on to the next question: "How many stimulation cycles will I (likely) need to obtain the number of oocytes that I want?" The minimal acceptable chance of a live birth and the maximum number of cycles should essentially be defined by the woman herself. The fact that not all IVF patients complete the maximum number of covered cycles even when they remain childless, while others take out loans to finance extra cycles, illustrates that not all people go to the same lengths to fulfil their child wish. However, this does not mean that reproductive clinics do not have the right to refuse treatment for those women whose chances of success are minimal. The exclusion of women above a certain age limit can be justified even when women are not deceived about their chances of success, as assisting these women would represent a waste of medical resources. A study by Rudick et al. (2009) shows that from those centres in the USA that offer elective oocyte cryopreservation, all programs accept women under the age of 35, half of them accept women aged 40 and about a third of them is willing to go beyond 40.

### **5. Specific tests to be offered to candidate-freezers**

In estimating ovarian response and thus the successful aspiration of oocytes and the number of cycles needed, predictive tests such as antral follicle count and/or antimullerian hormone (AMH) measurements should be offered (Jayaprakasan et al., 2010). It has been suggested that such tests can also be used to inform women about their chances of conceiving – either naturally or by IVF – and about the expected time of onset of infertility and menopause. If they were indeed able to do so, this would be an important tool in counselling women who want to cryopreserve their oocytes about how long they can 'wait and see' and when they should start considering freezing. However, at

present, data on this subject are inconclusive and further research needs to be conducted to determine under which circumstances these tests can be useful. Relying on the currently available data, it appears that while they are good indicators of ovarian reserve, these tests offer less – if any – insight into the quality of the remaining oocytes (Broer et al., 2009; Guerif, 2009; La Marca, 2010). For women under 35, they are therefore poor predictors of pregnancy rates. That being said, at least one study indicates that AMH testing is indicative of pregnancy rates in women of advanced age, which is of course of particular importance for social freezers (Lee et al., 2009). At present, the best way to counsel candidate freezers about their reproductive options is probably to take into consideration a number of variables such as age, family history of premature ovarian failure and ovarian reserve as measured by antral follicle count or AMH testing.

## **6. Conclusion**

Given the increased efficiency of oocyte freezing by vitrification and given the reassuring data on the health of resulting offspring, the possibility for women to store their oocytes theoretically expands their reproductive options and allows them to overcome the increasing gap between the optimal age to reproduce from a gynaecological point of view and the optimal age to reproduce from a socio-economic point of view. However, the average age of women who are currently opting to cryopreserve their oocytes (38 years) is too high to achieve a good balance between costs and benefits. If these women believe that they are insured against childlessness, they are more often wrong than right. Ideally, women in their early thirties who plan to postpone childbearing until their late thirties or forties should be informed about the possibility to freeze their eggs. Women whose oocytes have already significantly aged and are thus unlikely to benefit from elective oocyte cryopreservation should be honestly informed about their success rates and should not be specifically targeted.

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