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Social oocyte freezing

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Introduction

Reproductive aging has become an important social and medical development. The trend to delay childbearing in modern societies to a much less fecund age often confronts women with difficulties to conceive. The aging of the ovary resulting in a decline in the total number of oocytes and in their quality cannot be undone. However, it often engenders unrealistic expectations of what modern fertility treatment and particularly assisted conception can achieve.

Reversing the trend to having pregnancies at a younger age may be facilitated by social initiatives or reproductive health awareness campaigns (Nargund, 2009). Both preventive strategies aim to encourage more natural births. However, the factors that determine when women start having children such as lifestyle, educational opportunities, career choices and new unions are hard to change (Chen and Morgan, 1991; Gustafsson, 2001). In the developed world, these factors tend to postpone a first pregnancy and will eventually reduce the total number of children women have.

An emerging preventive solution for women is to freeze oocytes at a younger age for later use. The first human pregnancy after oocyte cryopreservation was reported by Chen in 1986. Oocyte cryopreservation had relatively low success rates in the past but with the introduction of the vitrification technique, pregnancy outcomes to date have been encouraging (Kuleshova *et al.*, 1999). Reportedly, oocytes preserved using vitrification have a more than 90% survival rate per oocyte after warming and a 75% fertilization rate (Oktay *et al.*, 2006; Gook and Edgar, 2007). Some IVF units report success rates with oocyte cryopreservation that approach those for fresh oocytes and frozen embryos (Nagy *et al.*, 2009).

This reported success of the use of oocyte vitrification should stimulate a renewed debate on oocyte storage for fertility preservation without a medical indication.

This article aims to critically evaluate the medical and societal aspects of social oocyte freezing. The potentials and the limits of this new phenomenon are reviewed as several fertility centers are currently offering oocyte cryopreservation to healthy women or plan so in the near future.

Current status of oocyte cryopreservation technologies

During vitrification, cryoprotectants are added at a high concentration while the oocyte is at room temperature. To further protect against ice-crystal formation, an extremely rapid rate of cooling is used. To achieve these rapid cooling rates, oocytes are placed in small volumes of cryoprotectants and exposed directly to liquid nitrogen.

Most of the peer reviewed literature reporting on the successful oocyte vitrification methods refer to 'open' vitrification systems. This system allows direct contact between the oocyte and the liquid nitrogen (LN2) allowing the hypothetical risk of disease transmission through the unsterile LN2. An alternative methods such as the 'closed' systems may possibly reduce the extremely rapid cooling rate necessary for vitrification due to an insulation barrier and therefore reduce the outcome after oocyte warming. Contamination risk during open system vitrification may be prevented by sterilization of the LN2 but storage will still require the carrier to be 'closed' (Parmegiani *et al.*, 2009). Other uncertainties regarding the vitrification technique such as the risk of spontaneous devitrification during long-term storage and the safety of transportation of vitrified oocytes still need to be clarified in the future.

More experimental strategies for fertility preservation and postponement such as cryopreservation of ovarian cortical tissue or of whole ovaries are

beyond the scope of this article (Bromer *et al*., 2008).

Medical and psychological aspects of social oocyte cryopreservation

What is the ideal age?

The ideal age for women to consider oocyte freezing is 31-35 years. Women in their late 20s still have time to find a partner or to have their oocytes frozen after the age of 30 years without a significant loss in reproductive potential. However, many requests for oocyte cryopreservation come from women aged 36-40 years (Gold *et al.*, 2006). Although cryopreserved oocytes from women in this age group will result in fewer pregnancies, these women may still benefit given the accelerated age-related decline in fertility after the age of 40 years. Moreover, the foreseen decline in pregnancy potential per oocyte can be compensated by additional cryopreservation cycles. Therefore, the expected reproductive gain from pre-emptive oocyte freezing will depend at least as much on the time interval between freezing and thawing of the oocytes than on the actual age at the time of cryopreservation. It is obvious that for health and social reasons, pregnancies may legally not be initiated beyond a certain maximum age.

What is the ideal number of oocytes?

There is currently no clear or reliable mathematical algorithm to advise a women how many oocytes should by cryopreserved. A meta-analysis by Oktay *et al.* concludes that the clinical pregnancy rate per warmed oocyte after vitrification is 4.5% in a population with an average age of 32.3 years old (Oktay *et al.*, 2006). The average number of oocytes needed for one clinical pregnancy would therefore be 22. The practice committee of the American Society for Reproductive medicine advices that informed consents should mention an approximate overall 4% live-birth rate per oocyte thawed using vitrification. (The practice committee of the SART and ASRM, 2008) Comparison of clinical outcomes between fresh and vitrified/warmed sibling oocytes obtained up to 39 years old showed that oocyte vitrification can offer effective fertility preservation options for women also of a more advanced reproductive age (Nagy *et al.*, 2009). However, as for fresh oocytes, a reduced clinical pregnancy rate per oocyte can be expected in this age group.

Maternal risks

Ovarian stimulation is a stressful procedure that has uncommon but potentially serious risks associated with it, including ovarian hyperstimulation syndrome (OHSS) and the surgical risks of oocyte retrieval such as infection or bleeding (De Sutter *et al.*, 2008). However, the most common complication of ovarian stimulation (OHSS) can effectively be prevented by replacing the hCG trigger by gonadotropin-releasing hormone agonist (DiLuigi *et al.*, 2010). Perioperative and post-operative complications of transvaginal ultrasound-guided oocyte retrieval are minimal. Therefore, the medical risks associated with social oocyte freezing cannot be viewed as an obstacle in view of general acceptance of oocyte donors undergoing ovarian stimulation and oocyte retrieval for many years. Ovarian stimulation can be prevented by harvesting immature oocytes for later in-vitro maturation (IVM) (Robertson *et al.*, 2000) Although this approach avoids hormone stimulation and reduces the cost, it is still considered experimental and currently available in only few fertility centers.

Some studies have found that pregnant women aged 35 years or older carry an increased risk for perinatal mortality, low birth weight infants and preterm delivery (Jolly *et al.*, 2000; Cleary-Goldman *et al.*, 2005). However other studies challenge these findings (Berkowitz G 1990; Newburn-Cook C 2005). Older women undergoing IVF face the same risks, and it is currently accepted that these risks are not so high that women should be prevented from taking them on, as long as they are fully informed. Moreover, the age related risk increase for fetal chromosomal abnormalities are halted by cryopreserving the oocytes.

Risks to the child

A recent systematic review collected 22 papers presenting information on neonatal health of children born after slow freezing of oocytes (Wennerholm *et al.*, 2009). They found limited data on birthweight or karyotype examinations and in most studies the only information given about children was 'healthy'. One large study has been published on the neonatal outcome of 200 children born after oocyte vitrification (Chian *et al.*, 2008). However preliminary, the authors conclude that these findings provide reassuring evidence that pregnancies and infants conceived following oocyte vitrification are not associated with increased risk or adverse obstetric and perinatal outcomes. As the vitrification technique is fairly recent, there is no data available on the long-term child follow-up. It is also worth noting that differences in concentrations of potentially toxic cryoprotectants result in a theoretically different risk profile after vitrification as compared to the conventional slow-freezing technique.

Psychological impact

Women must be properly informed about the present uncertainties concerning the efficiency and safety of future reproductive use of their oocytes. They need to be fully aware that the technique cannot guarantee success, whatever the number of oocytes that have been stored.

Information on the consequences of late parenthood for the psychological development of the child are scarce (McMahon *et al.*, 2007). It therefore seems wise to maintain the age-limit for IVF using donor oocytes which is currently set at 45 years in The Netherlands and 47 years in Belgium. Preliminary data collected from questionnaires among our candidate social freezers show that few envisage pregnancies beyond the age of 45.

Societal aspects of social oocyte cryopreservation

Gender-equality in reproduction

Women face a relatively early loss of fecundity, particularly in view of the ever extending life expectancy of modern humans. Moreover, men already cryopreserve their sperm for medical (e.g. working in toxic environments or before chemotherapy) and non medical reasons (before vasectomy) for many years (Homburg *et al.*, 2008; Dondorp and De Wert, 2009). A feminist argument in favor could be that social oocyte freezing widens the window of opportunity to exercise women's right to establish a family. However, feminists could also argue that it will become more likely for women to be pushed into undergoing a burdensome and costly medical procedures because her partners' desire to postpone children or lack of commitment.

Motherhood at advanced age

Critics may argue that a further increase in the maternal age at the time of childbirth may be expected as oocyte cryopreservation facilitates motherhood at an age of reduced background fertility. Using this assumption as an argument against social freezing ignores the fact that women already have that opportunity through oocyte donation. The law that dictates the age limit up to which an ET may be performed after oocyte donation that exist in many countries will obviously also apply for an ET after fertilization of previously vitrified oocytes. Hence, if we continue to allow women in their 40s to have IVF or to undergo oocyte donation treatments, then concerns about maternal risks cannot support a prohibition on social egg freezing.

Countering declining birth rates in developed countries

Many western countries are facing serious demographic changes resulting from declining birth rates and increases in longevity (Maccheroni, 2008). Birth rates have declined steadily since the latter half of the 20th century to levels well below the replacement rate to stabilize the population size in the absence of immigration (Commission of the European Communities, 2006). In some countries, assisted reproductive technologies (ART) already constitutes an integrated part of the tools to address these demographic challenges as a more curative measure (Ziebe *et al.*, 2008).

The decline in fertility go together with a trend to delaying motherhood until later in life which can be explained by the fact that births are now more strictly planned. Postponing a child after the age of 37 confronts women with dramatically decreased pregnancy rates, which are even more pronounced if they postpone until the age of 40 years. Therefore, many women run the risk of "social" (age related) infertility and some women will never get pregnant, at least not with their own oocytes.

Financial costs

Ten clinics in the UK are currently offering egg-freezing services at a cost of around £2.000-£3.000 per cycle for retrieval not including the subsequent cost of ICSI treatment (Goold and Savulescu, 2009). Coverage or reimbursement for fertility preservation for non-medical reasons should not be expected in the near future. However, it would be illogic not to reimburse these women when using their vitrified oocytes once they are faced with infertility while women of the same age get fresh IVF treatments fully covered. Women that did not need to use their vitrified oocytes may eventually receive financial compensation if they are prepared and eligible to donate the oocytes. As research evidence accumulates with regard to the safety and efficiency of oocyte vitrification, the general opinion on social freezing may shift from 'luxury medicine' towards 'preventive medicine'.

Conclusion

Although embryo preservation is considered standard practice for fertility preservation, oocyte cryopreservation holds the major advantage that it avoids the necessity for sperm at the time of oocyte retrieval (Lee *et al.*, 2006). Therefore, oocyte cryopreservation has become a tool for medical fertility preservation (e.g. before gonadotoxic

treatment), especially in adolescents and single women. There is much debate about oocyte cryopreservation for fertility preservation for social indications. As the oocyte cryopreservation techniques are still considered experimental, the main professional bodies consider the non medical use premature (The Practice committee of SART and ASRM, 2008). It remains difficult to properly counsel patients who consider oocyte cryopreservation on the expected outcome after thawing and on the limited follow-up data of children born from vitrified oocytes.

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