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SYMPOSIUM: OOCYTE CRYOPRESERVATION REVIEW

Oocyte cryopreservation for donor egg banking


Ana Cobo ^a, José Remohí ^a, Ching-Chien Chang ^b, Zsolt Peter Nagy ^{b,*}

^a IVI-Valencia, Plaza de la Policía Local 3, 46015 Valencia, Spain; ^b Reproductive Biology Associates, 1150 Lake Hearn Dr., Suite 600, Atlanta, GA 30342, USA

* Corresponding author. E-mail addresses: zsolt.peter.nagy@gmail.com, peter.nagy@rba-online.com (ZP Nagy).



Ana Cobo obtained her first degree at the University of Valle in Colombia in 1988. She obtained an MSc degree in the Biology of Reproduction at the University of Chile in 1994. After moving to Valencia, Spain in 1995, she joined Instituto Valenciano de Infertilidad (IVI) as part of the embryology staff. She obtained a Master's degree in Human Reproduction in 1998 and a PhD in 2003 at the University of Valencia, Spain. She is currently in charge of the cryobiology unit at IVI-Valencia. Her major areas of interest are oocyte and embryo cryopreservation and oocyte morphology linked to embryo development.

Abstract Oocyte donation is an efficient alternative to using own oocytes in IVF treatment for different indications. Unfortunately, 'traditional' (fresh) egg donations are challenged with inefficiency, difficulties of synchronization, very long waiting periods and lack of quarantine measures. Given the recent improvements in the efficiency of oocyte cryopreservation, it is reasonable to examine if egg donation through oocyte cryopreservation has merits. The objective of the current manuscript is to review existing literature on this topic and to report on the most recent outcomes from two established donor cryobank centres. Reports on egg donation using slow freezing are scarce and though results are encouraging, outcomes are not yet comparable to a fresh egg donation treatment. Vitrification on the other hand appears to provide high survival rates (90%) of donor oocytes and comparable fertilization, embryo development, implantation and pregnancy rates to traditional (fresh) egg donation. Besides the excellent outcomes, the ease of use for both donors and recipients, higher efficiency, lower cost and avoiding the problem of synchronization are all features associated with the benefit of a donor egg cryobank and makes it likely that this approach becomes the future standard of care. 

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KEYWORDS: cryobank, cryopreservation, oocyte, oocyte donation, vitrification

Introduction

Oocyte donation is nowadays a well-established practice, currently applied in cases of heritable maternal genetic disorders (Rosenwaks, 1987), early perimenopausal and/or menopausal women (Sauer et al., 1993), poor-responder patients (Remohi et al., 1993) and in cases of multiple unsuccessful IVF attempts (Burton et al., 1992). This strategy has consistently produced the highest pregnancy rates

reported for any assisted reproduction methods, basically because of the reduction of poor oocyte quality because of the selection of healthy young donors (Sauer and Kavic, 2006). This is all well and good, however, the successful clinical outcome of ovum donation programmes requires a receptive endometrium, usually prepared with exogenous steroids (Remohi et al., 1995, 1997), and a well-synchronized transfer of good-quality embryos. For synchronization, several strategies have been employed

with varying levels of success (Budak et al., 2007; Remohi et al., 1995, 1997; Soares et al., 2005), but certainly the most crucial factor is the availability of mature oocytes that can be fertilized to grow in synchrony with the receptivity of the recipient's uterus. Additionally, according to current regulations, donors must be tested to avoid possible infectious disease transmission (ASRM/SART, 2008). Although egg donors are tested in fresh donation treatment, the oocytes are not kept in proper quarantine conditions such as those used for sperm donation and semen banks. Additionally, in a fresh donation cycle, typically all oocytes from the donor are given to one recipient. This is mainly due to the difficulty in synchronizing multiple recipients, each having a receptive uterus within a defined window of implantation. When using egg banking, synchronization is not a problem. Indeed, all these limitations could be solved with an efficient egg-banking programme, which, in turn, obviously requires an efficient and reproducible oocyte cryopreservation methodology.

The purpose of this manuscript is to review current clinical experience using cryopreserved oocytes for donation.

The reported use of cryobanked oocytes for ovum donation programmes

Despite the wide diversity of the potential application of oocyte storage, donor-egg banking has not been a routine procedure until very recently; in fact, there are still very few centres worldwide that have included this practice in their clinical routine. The development of efficient cryopreservation techniques has represented a real challenge, as both freezing/vitrification and thawing/warming exposes cells to severe stress and can potentially cause cell death or decreased fertilization and impaired embryo development.

To date, the methodology most commonly used for embryo cryopreservation – slow freezing (Allan, 2004; Borini et al., 2006; Gook et al., 1994; Kazem et al., 1995; Levi Setti et al., 2006; Nawroth and Kissing, 1998; Notrica et al., 2004; Porcu et al., 1997; van Uem et al., 1987; Yang et al., 2002; Young et al., 1998) – has led to clinical application with limited success with oocytes (Oktay et al., 2006; Gook and Edgar, 2007). More recently, new or modified protocols for slow freezing have significantly improved the overall outcome (Borini et al., 2006; De Santis et al., 2007). Vitrification, on the other hand, although initially attempted in the late 1980s, has not been clinically applied until recently and represents an alternative technique. In particular, by means of methodologies that use a minimum volume, vitrification is currently producing very satisfactory outcomes (Vajta and Nagy, 2006).

Literature recording data on the donation of oocytes previously cryopreserved by the slow method are difficult to find, indicating the limitation in the clinical application of this technique. The literature does show that some countries had widely applied slow freezing for oocyte cryopreservation as dictated by law. Akin et al. (2007) published a case report after the use of slow frozen oocytes from a commercial donor-egg bank. Four patients received 19 cryopreserved oocytes (survival rate 76%) and two of them became pregnant. Other authors have also assessed the clinical

outcome after oocyte cryopreservation in an ovum donation programme (Barritt et al., 2007). A total of 68 out of 79 frozen oocytes (survival rate 86.1%) were donated to four recipients (mean of 17 oocytes per patient). Normal fertilization following intracytoplasmic sperm injection occurred in 89.7% of the surviving oocytes. Cleavage was observed in 91.8% of normally fertilized oocytes. A total of 23 embryos were transferred to the recipients (a mean of 5.75 embryos per recipient). Three pregnancies (clinical pregnancy rate of 75%) with an implantation rate of 26.1% were achieved.

The most widely used and clinically applied method of cryopreservation for ovum donation programmes has been vitrification. Kuleshova et al. (1999) reported a live birth after the transfer of one chromosomally normal embryo as assessed by fluorescence in situ hybridization, generated from a vitrified human oocyte using the open-pulled straw system. Yoon et al. (2003) reported their experience with the donation of vitrified oocytes using electron microscope grids. Thirty-two patients were included in the study (mean age 32.2 ± 5.8). Oocyte survival rate after warming was 325 out of 474 (68.6%) and 142 of those (43.7%) were fertilized normally. Pregnancy and implantation rates were 21.4% and 6.4%, respectively.

Another vitrification device, named Cryoloop, has been used for oocyte cryopreservation, which has assisted in achieving clinical pregnancies. Keskinetepe et al. (2009) attempted to establish the ideal conditions for vitrification through the selection of euploid oocytes after the first polar-body biopsy and by performing equilibrium at varying temperatures, then different incubation periods and various cryoprotectant-agent concentrations. The Cryoloop vitrification of first polar-body-biopsied metaphase-II human oocytes in the presence of 5.0 mol/l ethylene glycol plus 1.3 mol/l dimethylsulphoxide gave the best results in terms of fertilization (94%), embryo development (58%) and implantation rates (50%). A further publication by the same group reported the outcome of the vitrification of 111 euploid donor oocytes selected after first polar-body biopsy, using 20% ethylene glycol, 20% dimethylsulphoxide plus 1.0 mol/l sucrose and 0.1 mol/l Ficoll in modified human tubal fluid as the vitrification solution (Sher et al., 2008). Fertilization and blastocyst rates were 96% and 41%, respectively. After transferring an average of 1.6 ± 0.4 embryos, a 61% implantation rate was achieved. Twelve out of 19 (63%) recipients produced 17 healthy babies. This marked improvement in the implantation rate could be due to the selection of euploid oocytes after the first polar-body biopsy. Moreover, the outcome parameters for survival, fertilization and embryo development were higher for euploid oocytes than for aneuploid oocytes, indicating that the competence of mature oocytes is related to their ploidy.

Applying the Cryotop method to human oocytes, Kuwayama et al. (2005) have reported a 91% survival rate, 81% cleavage rate and a 50% blastocyst rate, with a 41% pregnancy rate per embryo transfer, resulting in 11 live births. Other groups have also published their experiences with the Cryotop method in humans. Katayama et al. (2003) reported excellent survival, fertilization and cleavage rates of 94%, 91% and 90%, respectively, and the first baby from vitrified oocytes in the USA. Other authors have assessed

the same methodology with donor's oocytes (Lucena et al., 2006), achieving a cleavage rate of 97% on day 2 and mean number of embryos transferred of 83.4% with a pregnancy rate per transfer of 60% (9/15).

Nagy et al. (2009) evaluated the suitability of oocyte vitrification by the same methodology in an oocyte donation programme. Their study included 153 oocytes from 10 donors assigned to 20 recipients. Fertilization, survival, day-3 cleavage and blastocyst rates were 87.6%, 87.3%, 98.4% and 68%, respectively. Forty-seven embryos were transferred to the 20 recipients (a mean of 2.4 per patient) and 26 (55.3%) successfully implanted. Fifteen patients became pregnant (75%) and two more became pregnant after a subsequent transfer of cryopreserved embryos from these oocytes (85% cumulative pregnancy rate; Chang et al., 2008). When the authors compared these results with those from the donors' previous fresh donation cycles, they observed a very similar outcome. These results support this study's assumption concerning the viability of employing the egg-banking model in ovum donation programmes. Such evidence provides an endorsement of the application of oocyte vitrification in infertile patients with different indications and leads to the recommendation of this approach in a routine IVF programme.

Cobo et al. (2008b) at Instituto Valenciano de Infertilidad (IVI) have also confirmed the potential of vitrification of oocytes using the Cryotop method through the simultaneous comparison of the outcome of both vitrified and fresh oocytes from the same ovarian-stimulated cycle. This model is extremely valuable to assess the possible effects of the vitrification procedure on oocytes' potential, since embryos could be simultaneously generated from vitrified and fresh oocytes from the same cohort and using the same semen sample.

In these series, embryo transfer was performed on day 3. Good-quality embryos derived from vitrified oocytes were transferred in preference to those derived from fresh oocytes. All embryos not transferred on day 3 were cultured until day 5–6. A survival rate of 96.7% was achieved and no significant difference in fertilization rates (76.3% and 82.2%), day-2 embryo cleavage rates (94.2% and 97.8%), day-3 embryo cleavage rates (77.6% and 84.6%), or blastocyst formation rates (48.7% and 47.5%) was detected for vitrified and fresh oocytes, respectively. The ratios of good-quality embryos on day 3 and at blastocyst stage were similar in vitrification and fresh groups. Pregnancy, implantation, miscarriage and ongoing pregnancy rates/transfer (65.2%, 40.8%, 20% and 47.8%, respectively) are comparable with results obtained in this oocyte donation programme conducted with fresh oocytes (Soares et al., 2005). In a subsequent publication (Cobo et al., 2008a), the potential benefits for oocyte banking in cancer patients were highlighted by the survival and clinical results obtained in this oocyte donation programme.

Very recently, Cobo et al. (2010) failed to demonstrate any superiority of using fresh donor's oocytes over the vitrified cryo-stored ones in a randomized controlled clinical trial. Six-hundred oocyte recipients were randomized into two groups that received either vitrified oocytes from IVI's oocyte bank ($n = 300$) or fresh oocytes ($n = 300$). The primary end-point of the study was the ongoing pregnancy

rate per randomized recipients. The secondary end-points were clinical pregnancy rate, implantation rate, fertilization rate and embryo quality. A total of 3039 vitrified oocytes (a survival rate 92.5%) and 3158 fresh metaphase-II oocytes were donated. There was no difference between patients receiving vitrified cryobanked oocytes versus those receiving fresh oocytes with respect to fertilization (74.2% versus 73.3%) or embryo cleavage on day 3 (87.3% versus 88.2%). The proportion of top-quality embryos resulting from inseminated vitrified oocytes (36.1%) was similar to that achieved after the insemination of fresh oocytes (37.7%). The superiority of fresh oocytes, in terms of ongoing pregnancy rate per intention-to-treat population achieved in the group of patients receiving oocytes (41.7%), was not proven (ongoing pregnancy rate 43.7% for vitrified oocytes). Instead, the non-inferiority of the vitrification groups could be assumed. These remarkable findings underline the clinical efficiency of oocyte vitrification and demonstrate that the use of stored vitrified oocytes is currently feasible and yields a successful clinical outcome, absolutely comparable with fresh oocytes.

The study by Cobo et al. (2010) has also enabled the impact of oocyte storage to be assessed in the dynamic of the ovum donation programme. One of the most relevant aspects related to the use of cryo-stored oocytes is the availability of these gametes once the endometrial preparation for the recipient is finished. In the above-mentioned study, endometrial preparation for women receiving fresh and vitrified oocytes was performed according to IVI's current protocol. Women with normal ovarian function were first down-regulated in the luteal phase with a single dose of gonadotrophin-releasing hormone agonist depot. After menses, all subjects received oral oestradiol valerate, starting with a daily dose of 2 mg that increased to 6 mg. Approximately 10–15 days after initiation of oestradiol valerate, serum oestradiol concentrations and endometrial thickness were determined. At this point, patients receiving fresh donor oocytes were placed on a waiting list until an appropriate donor was available and donations of vitrified oocytes were carried out immediately.

The mean number of days of endometrial preparation was 15.5 ± 4.6 and 22.4 ± 5.4 for recipients receiving vitrified and fresh oocytes, respectively (not significantly different). Moreover, 11 patients were cancelled because of endometrial bleeding or oestrogen replacement for longer than 50 days in recipients of fresh oocytes. No patients were cancelled in the vitrification group due to these causes. These findings clearly show one of the most relevant advantages of oocyte cryobanking. In fact, with the establishment of IVI's egg-banking programme, there has been a significant drop in the cancellation rate of recipients in the oocyte donation programme (data not shown).

Current experience and results from the routine use of cryobanked oocytes for ovum donation programmes

Based on these studies and encouraging preliminary experience (Cobo et al., 2008a,b 2010; Nagy et al., 2009), IVI and Reproductive Biology Associates have established the

Table 1 2008–2009 (24 month) outcome data using vitrified donor oocytes in IVF treatment for recipients in two IVF centres.

Outcome	IVI	RBA
Donation cycles	1051	168
Recipient cycles	919	322
Age (years)	41.2 ± 4.3	41.1 ± 4.9
Total oocytes warmed (per recipient)	12,786 (12.9 ± 4.0)	2001 (6.2 ± 1.9)
Total oocytes for ICSI	11,949 (11.4 ± 3.4)	1750 (5.4 ± 1.7)
Two-pronuclei ICSI fertilization rate	8920 (74.7)	1494 (85.4)
Good-quality embryos on day 3 (per inseminated oocyte) ^a	5366/11,949 (44.9)	979/1750 (55.9)
Good-quality embryos on day 5 (per embryo subjected to extended culture) ^a	1427/3568 (40.0)	582/1185 (49.1)
Implantation rate	655/1655 (39.6)	255/577 (44.2)
Embryos cryopreserved	1915 (1.8 ± 2.0)	414 (1.3 ± 1.5)
Clinical pregnancies (per transfer) ^b	502 (55.4)	182 (56.5)
Infants born ^c	343 (180 female; 163 male)	146 (64 female; 82 male)

Values are *n*, mean ± standard deviation, *n* (mean ± standard deviation), *n* (%) or *n*/total (%). ICSI = intracytoplasmic sperm injection, IVI = Instituto Valenciano de Infertilidad; RBA = Reproductive Biology Associates.

^aIVI and RBA embryo scoring systems are different, thus it may not be possible to directly compare these numbers.

^bAdditionally, 25 (IVI) and 21 (RBA) more clinical pregnancies from subsequent embryo cryotransfer were obtained.

^cAdditionally, 10 infants born from subsequent embryo cryotransfer at IVI (six female and four male) and 17 infants at RBA (nine female and eight male). There is no data on all infants born during this period. Four newborns at RBA had birth defects.

routine use of cryopreserved donor oocytes for IVF treatment. Outcomes of ongoing routine clinical use of vitrified donor oocytes have confirmed that these procedures are efficient, reliable and safe and consistent (data from the last 2 years of consecutively performed donor egg cryo-cycles from these two centres are shown in **Table 1**). When looking at the outcome data regarding survival and fertilization as well as pregnancy and implantation rates, it is striking to see the similar efficiencies of these two programmes (located in two different continents and managed completely independently from each other), which demonstrates that this vitrification approach to cryopreserve eggs can be easily established and implemented throughout the globe. There is only one principle difference between these two programmes: this is how to manage the distribution of the donated oocytes. At IVI, all oocytes vitrified from one donor are warmed and provided to one recipient. At Reproductive Biology Associates, on the other hand, oocytes from one donor are divided among several recipients (typically three recipients obtain oocytes from one donor, limiting the number of warmed oocytes to an average of six per recipient). Despite the lower number of oocytes per recipient in this programme, pregnancy rates are maintained at the same level as for fresh oocyte donation (Nagy et al., 2009). One reason for this difference is the 'economy' of egg donation; in Spain, the donor cost is much lower than in the USA, thus an important reduction in the cost of this treatment in the USA could be achieved by distributing oocytes from one donor to several recipients, which would make it more accessible to patients who need this service. Another difference between the two programmes is that at Reproductive Biology Associates all patients using cryopreserved oocytes have to review, agree and sign an Institutional Review Board document according to ASRM guidelines (Practice Committee of the American Society for Reproduc-

tive Medicine, Practice Committee of the Society for Assisted Reproductive Technology, 2008a,b), a restraint that is currently debated by many professionals (Noyes et al., 2010).

Discussion

There are a number of other practical benefits to using the donor egg cryobank, such as recipients can make their own choice from a large donor pool without waiting long for an appropriate match. Also, donors can programme their donation cycle to easily fit their schedule and not be dependent on the recipient. Cryobanking eggs also provides the possibility to quarantine oocytes for 6 months or longer to retest donors for safer donation, as is the criteria established for semen banks.

The study centres' experience with the storage of oocytes for donation shows a positive impact on the management of an oocyte donation programme, becoming easier and much more efficient at achieving excellent clinical results, in fact as high as obtained with fresh donor oocytes. Additionally, egg cryobanking provides the possibility of distributing oocytes among two or more recipients, without facing any difficulties of endometrial synchronization, which can also make the treatment more economical and so more affordable.

Oocyte donation as a form of IVF treatment should and will be performed only through egg cryobanking, as it provides a more efficient, safer and more affordable alternative to fresh oocyte donation.

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