Current trends and progress in clinical applications of oocyte cryopreservation

Aylin P. Cil[a] *and Emre Seli*[b]

Purpose of review
To delineate the current trends in the clinical application of oocyte cryopreservation.

Recent findings
Although the first live birth from oocyte cryopreservation was reported approximately three decades ago, significant improvement in the clinical application of oocyte cryopreservation took place only over the past decade. On the basis of the available evidence suggesting that success rates with donor oocyte vitrification are similar to that of IVF with fresh donor oocytes, the American Society of Reproductive Medicine has recently stated that oocyte cryopreservation should no longer be considered experimental for medical indications, outlying elective oocyte cryopreservation. Meanwhile, a few surveys on the attitudes toward oocyte cryopreservation revealed that elective use for the postponement of fertility is currently the most common indication for oocyte cryopreservation. Most recently, a randomized controlled trial revealed important evidence on the safety of nondonor oocyte cryopreservation, and confirmed that the clinical success of vitrification is comparable to that of IVF with fresh oocytes.

Summary
The evidence suggesting similar IVF success rates with both donor and nondonor cryopreserved oocytes compared with fresh oocytes will increase the utilization of elective oocyte cryopreservation. Appropriate counseling of women for oocyte cryopreservation requires the establishment of age-based clinical success rates with cryopreserved oocytes for various indications.

Keywords
elective oocyte cryopreservation, fertility preservation, oocyte cryopreservation, slow freezing, vitrification

INTRODUCTION

Although embryo cryopreservation is the most established method of fertility preservation [1], oocyte cryopreservation now represents the most applicable option for single reproductive-age women in need of delaying childbearing for any reason. Due to challenges related to the structure of the oocyte and the optimization of the freezing methods, it took more than 20 years for oocyte cryopreservation to evolve into a technique with acceptable clinical success rates. This transition was made possible by three important achievements: utilization of intracytoplasmic sperm injection (ICSI), improvements in cryoprotectants, and introduction of vitrification [2–5].

Without any doubt, both the improvements in the technique and the recent removal of the 'experimental' label on oocyte cryopreservation by the American Society of Reproductive Medicine (ASRM) Practice Guideline Committee [6▪▪] have opened a new era for this technology. Oocyte cryopreservation is expected to take the lead in fertility preservation. In addition, oocyte cryopreservation is likely to become a useful adjunct to routine IVF in various clinical scenarios such as the unavailability of sperm at the time of egg retrival [7,8], in cases of ovarian hyperstimulation syndrome [9], in poor responders [10,11], in patients at risk of losing their fertility potential due to genetic abnormalities such as BRCA mutation carrier status [12], Turner syndrome [13], fragile X premutation, and deletions of the X chromosome

[a]Department of Obstetrics and Gynecology, Kirikkale University School of Medicine, Kirikkale, Turkey and [b]Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut, USA

Correspondence to Emre Seli, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, 310 Cedar Street, LSOG 304D, New Haven, CT 06520–8063, USA. Tel: +1 203 785 7873; fax: +1 203 785 7134; e-mail: emre.seli@yale.edu

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KEY POINTS

- Fertilization, in-vitro embryo development, and pregnancy rates using vitrified nondonor and donor oocytes are similar to those achieved with fresh oocytes; success rates with slow-freezing are lower compared with vitrification.
- As a result of significantly improved clinical outcomes reported for vitrified oocytes, oocyte cryopreservation now represents the most applicable option for single reproductive-age women in need of fertility preservation.
- In addition to fertility preservation, oocyte cryopreservations consititues a valuable adjunct to IVF in specific situations, such as the unavailability of sperm at the time of egg retrival, in cases of ovarian hyperstimulation syndrome, in poor responders, in patients at risk of losing their fertility potential due to genetic abnormalities, and for couples who do not wish to cryopreserve supernumerary embryos for ethical, legal, or religious concerns.
- EOC is the most common reason for utilization of oocyte cryopreservation.
- Outcomes using oocyte cryopreservation strongly correlate with female age at the time of oocyte retrieval.

[6▪▪] and for couples who do not wish to cryopreserve supernumerary embryos for ethical, legal, or religious concerns [14]. The most applicable indication for oocyte cryopreservation that has now become a reality [15,16] is the establishment of donor oocyte banks. In the near future, IVF cycles using frozen-thawed donor oocytes will most probably outnumber those using fresh donor oocytes. In addition to all these indications, elective oocyte cryopreservation (EOC) for deferring child bearing remains the most debatable, however, surprisingly the most common indication for oocyte cryopreservation. Although the use of oocyte cryopreservation has been approved for medical indications by ASRM [6▪▪], two-thirds of programs currently performing oocyte cryopreservation in the United States do so for elective indications [17].

There are many factors that affect the efficiency of success with oocyte cryopreservation such as factors related to host (age, donor/nondonor oocyte, infertility factor), stimulation protocols and IVF techniques, cryopreservation methods (slow-freezing and vitrification), protocols, and devices (cryotop, cryoleaf, cryotip), as well as indications for oocyte cryopreservation (medical, nonmedical, or IVF-related reasons). Due to these variables, it is difficult to reliably estimate the success of oocyte cryopreservation from various studies. Only when the confounding variables are controlled for, can the specific impact of oocyte cryopreservation on clinical efficiency be assessed; this can most reliably be accomplished using a randomized controlled trial (RCT) study design. However, despite three decades of history, the majority of the studies on oocyte cryopreservation are observational, and only six RCTs with clinical outcomes have been published [15,18–20, 21▪▪,22] (Table 1). These RCTs will be detailed in the forthcoming subheadings of this review, with the aim of establishing a framework that can be used to counsel women who are considering oocyte cryopreservation for various reasons including EOC.

HISTORY OF CLINICAL SUCCESS WITH OOCYTE CRYOPRESERVATION

The first live birth with oocyte cryopreservation was reported in 1986 with slow freezing [23], but due to very low success rates, there were only five live births reported using this technique for over a decade [24]. In 1997, intracytoplasmic sperm injection (ICSI) was first used to fertilize frozen-thawed oocytes, circumventing zona hardening caused by the cryopreservation process [25]. Although ICSI helped improve fertilization of cryopreserved oocytes, further optimization of oocyte cryopreservation required another decade. In 1999, the first live birth with oocyte cryopreservation after vitrification was reported [26] followed by only a few case reports and clinical studies up until 2005 [24]. At that time, there were approximately 100 reported live births from oocyte cryopreservation; these were reviewed in a meta-analysis [24], which concluded that success rates with oocyte cryopreservation using slow freezing were lower than that of IVF with fresh oocytes. However, valid comparisons of vitrification with either slow freezing or fresh oocyte cycles could not be performed because of the limited number of reports with vitrification at the time of publication. Despite this limitation, the success rates of vitrification reports showed encouraging results compared with slow freezing [24].

Following the first RCT comparing slow freezing and vitrification, which showed that vitrification was more successful in terms of both embryological and clinical outcomes [18] (Table 1), multiple groups reported improved clinical outcomes using vitrification [14–16,19,27–31]. At the same time efficiency of slow-freezing protocols has also been improved [32–40]. However, the reported success rates remained lower for slow freezing compared with vitrification.

With the improvements in oocyte cryopreservation technology and associated clinical outcomes,

Table 1. Randomized controlled trials with clinical outcomes on oocyte cryopreservation

Author	Study design	Mean age at freezing	Target population	Method	Number of patients	Number of oocytes	Mean embryos	Day transfer	SR (%)	FR (%)	IR (%)	CP/T (%)	LB/T (%)
Nondonor – slow freezing versus vitrification													
Smith *et al.* United States [18]	Randomization appropriate for comparing both embryological and clinical outcome	31 ± 1	Infertile patients who failed in the fresh cycle and had >9 supernumerary oocytes	SF	30	238	3.2	3	67	67	11.5	21.1[b,c]	NA
		32 ± 1		VF	48	349	3.1	3	81	77	13.7	38.3[b,c]	NA
Nondonor – fresh versus vitrified oocytes													
Rienzi *et al.*[a] Italy [19]	Randomization appropriate for comparing embryological not for clinical outcome	35.5 ± 4.8	IVF patients <43 years old with >6 MII oocytes at retrieval	VF	40	124	2.3	2	96.8	79.2	20.4	38.5	30.8 (OPR)
				Fresh	40	120	2.5		NA	83.3	21.7	43.2	38.8 (OPR)
Parmegiani *et al.*[a] Italy [20]	Randomization appropriate for comparing embryological not for clinical outcome	35.0 ± 0.8	IVF patients <42 years old with >5 MII oocytes at retrieval	VF	31	168	2.5	2–3	89.9	84.9	17.1	35.5	22.6
				Fresh	31	NA	2.6		NA	88.3	NA	13.3	0
Forman *et al.* United States [21▪▪]	Randomization appropriate for comparing clinical outcome	29.9 ± 2.3	IVF patients <35 years old with >8 MII oocytes undergoing their first IVF cycle	VF	44 (26 paired transfers)	294	NA	5–6	81.6	77.9[b]	NA	NA	53.9 (OPR)
				Fresh	44 (26 paired transfers)	294	NA		NA	90.5[b]	NA	NA	57.7 (OPR)
Donor – fresh versus vitrified oocytes													
Cobo *et al.* Spain [22]	Randomization appropriate for comparing embryological not for clinical outcome because embryo recipients are not randomized in this study	26.7 ± 3.6	Oocyte donors	VF	30	231	3.8	3	96.7	76.3	40.8	65.2	47.8 (OPR)
				Fresh	30	219	3.9		NA	82.2	100	100	100 (OPR)
Cobo *et al.* Spain [15]	Randomization appropriate for comparing clinical outcome	26.7 ± 3.9	Oocyte donors	VF	295	3286	1.7	3	92.5	74.2	39.9	55.4	49.1
		26.6 ± 3.8		Fresh	289	3185	1.7		NA	73.3	40.9	55.6	48.3

CP/T, clinical pregnancy/transfer; FR, fertilization rate; IR, implantation rate; LB/T, live birth/transfer; SF, slow-freezing; SR, survival rate; VF, vitrification.
[a]sibling oocytes from the same patients were randomized.
[b]significantly different.
[c]CP/thaw cycle.

its clinical applications widened, resulting in more than a thousand live births reported to date [17,41]. Over the past 5 years, oocyte cryopreservation, especially with vitrification, has proven to be an efficient technique, resulting in pregnancy outcomes similar to that of IVF with fresh oocytes [15]. As a result of this progress, ASRM has stated that oocyte cryopreservation should no longer be considered 'experimental' for women who are unable to cryopreserve embryos and are facing infertility due to gonadotoxic therapies [6▪▪].

Most recently, a RCT has concluded that aneuploidy rates in embryos derived from vitrified oocytes were similar to those derived from fresh oocytes in young infertile women undergoing IVF with their own eggs [21▪▪]. This report suggests that oocyte cryopreservation does not have an adverse effect on chromosome segregation during meiotic division.

PROGRESS IN CLINICAL APPLICATION OF OOCYTE CRYOPRESERVATION

Almost all clinical studies reporting IVF outcome parameters using oocyte cryopreservation fall into one of two main categories: studies assessing donor oocyte cryopreservation/thaw cycles representing young fertile women, studies assessing infertile women with failed IVF attempts, who have supernumerary oocytes for cryopreservation. Studies on oocyte cryopreservation for poor responders [11] and for IVF cycles with failed sperm retrieval [8] constitute exceptions. Therefore, we will discuss the progress of oocyte cryopreservation by subgrouping it as nondonor (or autologus) oocyte cryopreservation representing infertile patients and donor oocyte cryopreservation. The results of success for other indications outlined in Table 2 are mostly based on case reports.

Nondonor or autologus oocyte cryopreservation

Most of the reports on cryopreservation of nondonor oocytes are observational studies, with only a few RCTs (Table 1) performed in infertile women undergoing IVF who prefer cryopreservation of their surplus oocytes, as they decline embryo cryopreservation due to ethical or legal concerns. In addition, there are also studies that compare the efficacy of oocyte cryopreservation by temporarily cryopreserving oocytes under an institutional review board approval [21▪▪]. Importantly, only a single study to date assessed the efficiency of nondonor oocyte cryopreservation when applied to young fertile women [42].

Nondonor oocyte cryopreservation: randomized controlled trials

There are four published RCTs on nondonor oocyte crypreservation; all four report the outcomes of IVF using vitrified/warmed nondonor oocytes from infertile patients [18–20,21▪▪] (Table 1). At present, there are no RCTs evaluating IVF outcomes of slow frozen oocytes compared with fresh oocytes.

Of the four RCTs investigating the use of vitrified/warmed nondonor oocytes from infertile patients, only one study compared slow freezing

Table 2. Indications of oocyte cryopreservation

A. Nondonor oocyte cryopreservation	
Medical indications	Cancer patients receiving gonadotoxic therapies or undergoing surgery
	Noncancer patients receiving gonadotoxic therapies for various reasons
	Sickle-cell anemia
	Rheumatologic diseases
	Myelodysplastic syndrome
	Patients at risk of losing their fertility potential because of genetic abnormalities
	BRCA mutation carriers
	Turner syndrome
	Fragile X premutation
	Deletions of the X chromosome
	Twins of patients with premature ovarian failure
IVF related	Oocyte cryopreservation for those unable to cryopreserve embryos
	Poor responder patients
	Ovarian hyperstimulation syndrome (OHSS)
	Failure to obtain sperm for IVF
Elective oocyte cryopreservation	Deferring child bearing
B. Donor oocyte cryopreservation	

and vitrification, reaching the conclusion that vitrification is superior to slow-freezing in terms of oocyte survival, fertilization, implantation, and clinical pregnancy rates. This remains the only RCT comparing the two techniques [18] (Table 1).

Two RCTs were conducted in infertile couples with supernumerary oocytes available to vitrify and warm only if pregnancy was not achieved in the fresh cycle [19,20]. In other words, fresh sibling oocytes were transferred in the first cycle and if pregnancy failed to occur, than the cryopreserved sibling oocytes were thawed, fertilized, and transferred to the same patient in a subsequent cycle. With this design, the authors were able to compare the fertilization and embryo developmental rates of vitrified and fresh sibling oocytes but not clinical pregnancy outcomes. Both studies concluded that similar fertilization and embryo development rates were achieved with fresh and vitrified oocytes [19,20] (Table 1).

In the most recently published RCT, Forman *et al.* [21▪▪] adopted a unique and innovative design, which allowed the comparison of clinical outcomes with nondonor vitrified and fresh oocytes. In this study, the authors divided retrieved oocytes from infertile patients less than 35 years of age. One group of oocytes underwent temporary vitrification while their counterparts remained in culture. Subsequently, vitrified oocytes were thawed, vitrified and nonvitrified oocytes were fertilized with ICSI, and resulting embryos were cultured to the blastocyst stage. Embryos of sufficient quality to transfer or cryopreserve underwent trophectoderm biopsy for genotyping and a karyotype was assigned to each embryo. Blastocysts obtained from vitrified and fresh oocytes were then transferred in pairs and embryonic aneuploidy was assessed in each one. To determine the identity of the implanted embryos, DNA fingerprinting was performed on cell-free fetal DNA enriched from maternal serum specimens drawn at 9 weeks of gestation or on newborn DNA taken from a buccal swab. The authors detected no differences between the two groups regarding aneuploidy. In addition, the ongoing pregnancy rate per transferred embryo was similar for vitrified and fresh oocytes. However, it is noteworthy that the fertilization and embryo development rates were lower in vitrified compared with fresh oocytes. This finding is in contrast with the previous trials reporting similar fertilization and embryo develoment rates for both nondonor [19,20] and donor cryopreserved oocytes [15,22] compared with fresh oocytes. Importantly, the findings of Forman *et al.* suggest that oocyte vitrification does not increase the rate of aneuploidy or diminish the implantation potential of viable blastocysts. The authors demonstrate that clinical success rates with nondonor vitrified oocytes from young infertile women are similar to their sibling fresh oocytes.

Overall, RCTs investigating the use of cryopreserved nondonor oocytes from infertile patients suggest that vitrification is more successful compared with slow freezing [18]; fertilization and embryo development rates of vitrified oocytes are comparable to fresh oocytes [19,20]; at least for women less than 35 years, pregnancy rates and embryo aneuploidy rates of vitrified oocytes are similar to fresh oocytes [21▪▪].

Nondonor oocyte cryopreservation: observational studies

As there are no RCTs comparing slow-frozen oocytes to fresh oocytes in women undergoing IVF, a brief review of recent, large observational studies is warranted.

Many observational studies on the efficacy of oocyte cryopreservation have been reported and most of these studies (almost 90% of slow freezing and 50% of vitrification studies to date) were conducted in centers located in Italy. This is because the earlier Italian legislation prohibited insemination of more than three oocytes and banned embryo cryopreservation, which inevitably forced oocyte cryopreservation into routine clinical practice.

In the largest of these studies, supernumerary oocytes from infertile women were cryopreserved using slow freezing, and 940 thaw cycles were performed in eight centers [38]. The overall survival rate of thawed oocytes was 55.8%. The fertilization rate (72.5 versus 78.3%), implantation rate (10.1 versus 15.4%), pregnancy rate per transfer (17 versus 27.9%), and delivery rate per transfer (11.6 versus 21.6%) were all significantly lower for cryopreserved oocyte cycles compared with fresh cycles. Despite the reported lower success rates the latter protocol is still evolving [39]. Recently, Azambuja *et al.* [40] using a Na-depleted media and Bianchi *et al.* [39] using a modified slow-freezing protocol reported higher encouraging success rates with slow freezing.

Nondonor oocyte cryopreservation: studies on novel indications

Although the proposed application of oocyte cryopreservation is for preserving fertility in women with cancer, the data on clinical success of oocyte cryopreservation in cancer patients are limited. Consequently, for the purposes of counseling, success rates might be extrapolated from other populations.

Cancer patients are treated with the assumption that their reproductive potential is similar to that of age-matched healthy individuals. However, studies

evaluating oocyte yield in cancer patients report conflicting results, some suggesting comparable results with nondonor patients [43–46], whereas others suggesting diminished oocyte yield [47–50]. If further studies with larger sample size confirm that women with cancer have diminished ovarian reserve, appropriate counseling of these women will be crucial as women with diminished ovarian reserve are expected to be more susceptible to gonadotoxic agents.

More recently, oocyte cryopreservation is used in poor responders [11], and in situations when sperm cannot be obtained for IVF [7,8]. Recently, Cobo *et al.* [11] reported a new strategy with vitrification for managing poor responder patients. They suggest that for poor responders, accumulation of oocytes by vitrification and simultaneous insemination yields live birth rates comparable to those in normoresponders.

Donor oocyte cryopreservation

There are two RCTs with vitrified donor oocytes [15,22] (Table 1). The largest RCT including 600 recipients of donor oocytes demonstrated the noninferiority of ongoing pregnancy rates with vitrified donor oocytes compared with fresh donor oocytes [15]. This study reported implantation and clinical pregnancy per embryo transfer rates of 39.9 versus 40.9% and 55.4 versus 55.6% for vitrified donor and fresh donor oocytes, respectively. Oocyte donors are women under the age of 35; therefore, the results of these studies may be extrapolated to young patients seeking fertility preservation.

With the current reported success with cryopreserved donor oocytes, it is now possible to justify and establish oocyte cryobanking. This strategy will also allow quarantine of oocytes, although donors are tested and retested to establish absence of sexually transmitted diseases.

TRENDS IN CLINICAL APPLICATIONS OF NON-DONOR OOCYTE CRYOPRESERVATION

There are numerous nonrandomized studies investigating IVF outcome parameters associated with oocyte cryopreservation. As there are differences between these studies in design, cryopreservation protocols, indications for cryopreservation, age of the patients, number of oocytes thawed and embryos transferred, it is not appropriate to compare the success between different studies. However, these studies show that while the clinical success rates with slow freezing have an increasing trend with time, vitrification has been more successful than slow freezing and stable since the introduction of this technique irrespective of confounding variables. Since 2006, implantation and live birth rates increased from 2 to14% and 2 to 27% [39,40,51] for slow freezing, whereas they were ranging from 13 to 20% and 23 to 35%, respectively, following a more closer trend for vitrification [19,20,29,52].

Age trends in clinical application of nondonor oocyte cryopreservation

Most of the studies published to date reported results according to the mean ages of the patients, which range from 29.9 ± 2.3 [21▪▪] and 35.7 ± 5.7 [36]. However, it is not appropriate to use the reported success rates when counseling patients individually, as the success of IVF using cryopreserved oocytes is likely to be affected by the patient's age. According to an individual patient data meta-analysis, live-birth success rates with cryopreserved oocytes show an age-related decline regardless of the freezing technique used, and an aged-based probability of live birth may be calculated for cryopreserved oocytes [53].

Estimated age-based success rates may also change according to the indication for oocyte cryopreservation, such as elective oocyte cryopreservation or oocyte cryopreservation in poor responders. For example, in poor responders, accumulating cryopreserved oocytes in consecutive cycles followed by thaw, ICSI, and embryo transfer is reported to yield comparable success rates to those observed in normoresponders [10,11]. In addition, when this strategy was applied to poor responders over 40, live-birth/patient success rates were higher (15.8%) for the vitrified oocyte group compared with the fresh oocyte group (7.1%) [11].

Recently Melzer *et al.* [54] reported a similar approach for patients undergoing EOC. In that study of 132 patients undergoing multiple cycles of EOC with an average age of 38.4 at first and 39 at subsequent cycles, when more than one cycle was applied, subsequent cycles resulted in greater oocyte yield, albeit with the implementation of a higher dose. Although it seems reasonable to accumulate more oocytes for women over the age of 38, the ethical implications of the application of higher cumulative dose of gonadotropins without establishing whether these oocytes will be used, remains debatable.

Age trends in elective oocyte cryopreservation

According to a study reporting on the status of oocyte cryopreservation in the United States up

until mid-2009, among the programs offering EOC, half accepted women aged 38–40 years, and about one-third accepted women above 40 years [17]. Supporting this observation, a recent study analyzing 491 women reported that mean age of the patients undergoing EOC was 38 [55] in accordance with two other studies [56,57]. Importantly, more than 80% of women undergoing EOC were over 35 years old (range: 36–41) [56]. Despite the reported interest of older reproductive-age women toward oocyte cryorpeservation [55–57], one of these studies found that the mean age of women inquiring about this procedure was 35.2 ± 5.4 years [57]. The same study reported that the age for the application of EOC decreased from $39 + 1.4$ years in 2005 to $37.4 + 2.3$ years in 2011.

The above-mentioned findings show that EOC is primarily utilized by older reproductive-age women, although women inquire about the procedure earlier. However, to achieve higher success rates with IVF, both the age of inquiry and application of EOC should be at an age younger than 35 years.

CONCLUSION

Following the first live birth with cryopreserved oocytes in 1986, and a very slow progress for 20 years, clinical outcomes using cryopreserved oocytes showed significant improvement during the past decade. Recent RCTs suggest that fertilization, embryo development, and pregnancy rates with vitrified nondonor and donor oocytes are similar to fresh oocytes, whereas the overall success rates with slow freezing remain lower compared with vitrification.

The improvements in the cryopreservation technique and clinical outcomes are likely to result in an increased utilization of oocyte cryopreservation in clinical practice. In order to provide appropriate counseling to women considering oocyte cryopreservation for fertility preservation, as an adjunct to IVF, or as an elective procedure for deferring child bearing, it is necessary to delineate age-specific and indication-specific success rates for this promising technology.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 262–263).

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