Oocyte Cryopreservation: An Update

Melanie E. Ochalski, MD, FACOG and
Robert B. Filer, MD, FACOG
The Fertility Center

Since October 2012, oocyte cryopreservation has no longer been classified as an "experimental" procedure by the American Society for Reproductive Endocrinology (ASRM), and egg freezing has become available to clinicians. This article describes this recent addition to advanced reproductive technologies, and its role in clinical practice.

INTRODUCTION

Since the birth of In-vitro Fertilization (IVF) into clinical practice in 1978,[1] several additional technologies have become available to the couple faced with infertility. Among them are Intracytoplasmic Sperm Injection (ICSI) for the treatment of severe male factor infertility; Pre-implantation Genetic Diagnosis (PGD) for patients carrying a known genetic mutation that they wish to avoid passing to their offspring; and embryo cryopreservation, which allows couples to freeze excess embryos that are not immediately transferred during an IVF cycle. Most recently, another technology that has generated considerable attention in both the scientific literature and the lay press is oocyte cryopreservation, or "egg freezing."[2]

OOCYTE CRYOPRESERVATION TECHNOLOGY

Oocyte cryopreservation refers to the freezing of a mature metaphase-II (M-II) oocyte, one that has completed the first meiotic division and is capable of being fertilized. When this procedure was made available for clinical practice in October 2012, it had been almost 6 decades since the first human birth from frozen sperm,[3] and almost 3 decades since the first human birth from a frozen embryo.[4] The delay in development of successful oocyte cryopreservation was due to the unique make-up of the human oocyte. The mature M-II oocyte is one of the largest cells in the human body.[5] It has a high water content and a unique chromosomal arrangement in which the metaphase chromosomes are lined up by the meiotic spindle along the equatorial plate. Initial attempts to freeze oocytes were thwarted by the formation of ice crystals and damage to the meiotic spindle apparatus.[2] Successful freezing of oocytes could only be accomplished after cryopreservation technology advanced with a new process of freezing, called vitrification.[6] By utilizing higher concentrations of cryoprotectants, and decreasing the interval to reach freezing temperatures, vitrification decreases the formation of ice crystals.

As in a typical IVF cycle, oocyte cryopreservation often involves stimulating the ovaries with gonadotropins and surgically retrieving mature oocytes. As with most superovulation techniques, gonadotropins are started at a specific time in the patient's menstrual cycle, and continued for approximately 9 days. Oocytes are then retrieved via ultrasound-guided transvaginal aspiration. The retrieved oocytes are then cryopreserved within several hours of retrieval, in their unfertilized state.

INDICATIONS

a. For the reproductive-age female who is faced with an immediate threat to her fertility, such as treatment with chemotherapy, or need for oophorectomy for benign or malignant disease, cryopreservation of mature oocytes is an option for preservation of fertility. In postpubertal females without a committed male partner, who do not wish to use donor sperm, it represents a previously unavailable option. In contrast with cryopreservation of embryos, freezing oocytes gives the female patient greater control of how she uses her gametes in the future.[7]

b. For couples in the U.S. who choose not to cryopreserve embryos because of religious or ethical concerns about storage and disposal of embryos, freezing of oocytes rather than embryos provides an alternative.

c. Delaying childbearing by the elective cryopreservation of oocytes can be an attractive, albeit controversial use of this new technology.[2] Females who wish to electively preserve their fertility because of career commitments or because they have not met a male partner during their most fertile years, have also begun to utilize oocyte cryopreservation. Oocyte quantity and quality steadily decline throughout a female's

life, up until the age of 35, after which this decline rapidly accelerates. Oocyte cryopreservation may allow women to have biological children later in life.

d. Another possible use of oocyte cryopreservation may be its ability to simplify oocyte donation. Currently, oocyte donation cycles require coordination of fresh cycles between the donor and recipient. Using cryopreserved oocytes may provide patients with more choices, more flexibility in timing their pregnancy, and possibly reduced cost.[2]

CLINICAL OUTCOME

As cryopreservation and thawing have improved, oocyte cryopreservation in young healthy women has been associated with steadily improving pregnancy rates.[8,9] Four randomized controlled trials in Europe of fresh vs. vitrified/warmed oocytes indicate that implantation and clinical pregnancy rates are similar.[10-13] Two were conducted in egg donor/recipient cycles, and 2 were conducted in infertile couples with excess oocytes available to freeze/thaw only if pregnancy was not achieved in the fresh cycle. Overall, oocyte survival after freeze/thaw was 90%–97%, fertilization rates were between 71%–79%, implantation rates were 17%–41%, and clinical pregnancy rates per transfer ranged from 36%–61%. The clinical pregnancy rate (CPR) per thawed oocyte ranged from 4.5%–12%.

The generalizability of these studies is limited by the ideal circumstances under which oocytes were cryopreserved. These subjects were young (<30), healthy, and did not have a cancer diagnosis. For that reason, attention has been paid to larger observational studies, which indicate that implantation and pregnancy rates may be lower when frozen oocytes are used compared with fresh or frozen embryos.[14] Many of these observational studies have been conducted in Italy, where Italian law limits the number of oocytes that may be fertilized as part of IVF. Because of this restriction, programs in Italy have been offering oocyte cryopreservation to couples with additional oocytes available at retrieval for many years. Italian national register data from 193 IVF centers and over 120,000 IVF cycles from 2005 to 2007 that compared fresh to frozen oocyte cycles demonstrated higher fresh oocyte implantation rates (13.5% vs. 6.9%; odds ratio [OR] 2.12; 95% confidence interval [CI], 1.99–2.26) and pregnancy rates per transfer (24.9% vs. 12.5%; OR 2.32; 95% CI, 2.16–2.49).[14]

Recent observational data in the U.S., although limited by smaller sample sizes, have shown favorable success rates in the young, healthy population.[2] A retrospective cohort study of cryopreserved oocytes from 19 women less than 37 years of age reported an oocyte survival rate of 89%, a fertilization rate of 78%, an implantation rate of 45%, and a live-birth rate per transfer of 58%.[15] Importantly, the clinical pregnancy rate per thawed oocyte ranged between 4- 5%,[15-17] which was lower than the 4.5-12% reported in the European RCTs[10-13] and significantly lower than pregnancy rates from frozen embryos, which exceed 20%.[18]

As with embryo cryopreservation, pregnancy rates following oocyte cryopreservation decline with advancing age of the woman.[19] Data from retrospective cohort studies show significantly lower ongoing pregnancy rates in women over 40 years of age.[16] In one study, age-stratified CPR per transfer were: 48.6% in 34 year-olds, 24.1% in 35–37 year-olds, 23.3% in 38–40 year-olds, and 22.2% in 41–43 year-olds.[16]

Perinatal outcome data on children born from previously frozen oocytes are reassuring. Despite concerns regarding spindle abnormalities, the incidence of chromosomal abnormalities in human embryos obtained from cryopreserved oocytes is no different from that of control embryos.[17] A review of over 900 live births from cryopreserved oocytes showed that there is no increased risk of congenital anomalies compared to the general US population.[20]

Despite the increasing success with oocyte cryopreservation, embryo cryopreservation remains the superior option for postpubertal females that have a committed male partner and wish to preserve their fertility, due to the increased chance for livebirth with cyropreserved embryos. National data derived from the Society for Assisted Reproductive Technology (SART) indicates that the live birth rate per embryo transfer for embryos thawed from infertile women under 35 years of age was 38.7%, and 34.8% for thawed oocyte donor cycles.

ALTERNATIVES

Embryo and oocyte cryopreservation represent the most efficacious strategies for preservation of fertility in the female patient.[7] Experimental alternatives include ovarian tissue cryopreservation, immature oocyte cryopreservation with in-vitro maturation (IVM), and ovarian suppression with GnRH analogs. These techniques may have benefit for prepubertal females and for those who cannot delay cancer treatment in order to undergo ovarian stimulation and oocyte retrieval, but their efficacy and safety remain unclear.[7]

CONCLUSIONS

Fertility-preservation technologies are rapidly evolving, and for adult female patients, oocyte freezing represents an important addition to the advanced reproductive technologies that currently exist. More data are needed to determine which populations can benefit most from this technology. In the meantime, the first step in fertility-preservation for our patients will be increasing their awareness of the natural age-related decline in fertility, as well as the significant risks of infertility with cancer and other gonadotoxic therapies.

REFERENCES

1. Wade, M.J. and S.M. Shuster, Bateman (1948): pioneer in the measurement of sexual selection. Heredity (Edinb), 2010; 105(6): 507-8.
2. Mature oocyte cryopreservation: a guideline. Fertil Steril, 2013; 99(1): 37-43.
3. Sherman, J.K., Synopsis of the use of frozen human semen since 1964: state of the art of human semen banking. Fertil Steril, 1973; 24(5): 397-412.
4. First baby born of frozen embryo. New York Times, 1984. Level III.
5. Mandelbaum, J., Oocytes. Hum Reprod, 2000; 15 Suppl 4: 11-8.
6. Cobo, A. and C. Diaz, Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril, 2011; 96(2): 277-85.
7. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril, 2013; 100(5): 1214-23.
8. Cobo, A., et al., Vitrification: an effective new approach to oocyte banking and preserving fertility in cancer patients. Clin Transl Oncol, 2008. 10(5): p. 268-73.
9. Noyes, N., et al., Oocyte cryopreservation: a feasible fertility preservation option for reproductive age cancer survivors. J Assist Reprod Genet, 2010. 27(8): p. 495-9.
10. Cobo, A., et al., Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod, 2010. 25(9): p. 2239-46.
11. Parmegiani, L., et al., Efficiency of aseptic open vitrification and hermetical cryostorage of human oocytes. Reprod Biomed Online, 2011. 23(4): p. 505-12.
12. Rienzi, L., et al., Embryo development of fresh 'versus' vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. Hum Reprod, 2010. 25(1): p. 66-73.
13. Cobo, A., et al., Comparison of concomitant outcome achieved with fresh and cryopreserved donor oocytes vitrified by the Cryotop method. Fertil Steril, 2008. 89(6): p. 1657-64.
14. Scaravelli, G., et al., Analysis of oocyte cryopreservation in assisted reproduction: the Italian National Register data from 2005 to 2007. Reprod Biomed Online, 2010. 21(4): p. 496-500.
15. Hodes-Wertz, B., et al., Retrospective analysis of outcomes following transfer of previously cryopreserved oocytes, pronuclear zygotes and supernumerary blastocysts. Reprod Biomed Online, 2011. 23(1): p. 118-23.
16. Ubaldi, F., et al., Cumulative ongoing pregnancy rate achieved with oocyte vitrification and cleavage stage transfer without embryo selection in a standard infertility program. Hum Reprod, 2010. 25(5): p. 1199-205.
17. Cobo, A., et al., Use of fluorescence in situ hybridization to assess the chromosomal status of embryos obtained from cryopreserved oocytes. Fertil Steril, 2001. 75(2): p. 354-60.
18. https://www.sartcorsonline.com/rptCSR_PublicMultYear. . 2014.
19. Borini, A., et al., Multicenter observational study on slow-cooling oocyte cryopreservation: clinical outcome. Fertil Steril, 2010. 94(5): p. 1662-8.
20. Noyes, N., E. Porcu, and A. Borini, Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online, 2009. 18(6): p. 769-76.

Melanie E. Ochalski, MD, FACOG and
Robert B. Filer, MD, FACOG
Lancaster General Health Campus
Medical Office Building, Suite 300
2108 Harrisburg Pike
Lancaster, PA 17604

130 Leader Heights Rd,
York, PA 17403
fertilitycenter@thefertilitycenter.com