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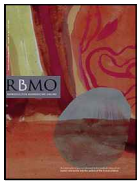

ARTICLE

Clinical outcomes and utilization from over a decade of planned oocyte cryopreservation

BIOGRAPHY

Angela Leung, MD, is a Reproductive Endocrinology and Infertility fellow at Beth Israel Deaconess Medical Center/Harvard Medical School and Boston IVF. She has a special interest in fertility preservation.

Angela Q. Leung[1,2,4,*], Katherine Baker[3,4], Denis Vaughan[1,2,4], Jaimin S. Shah[1,2,4], Ann Korkidakis[1,2,4], David A. Ryley[1,2], Denny Sakkas[1], Thomas L. Toth[1,2,4]

KEY MESSAGE

One-third of patients who used oocytes from planned oocyte cryopreservation cycles achieved an ongoing pregnancy or live birth. No patient who cryopreserved gametes at age 40 years or over was successful. Planned oocyte cryopreservation results in reasonable success at younger ages.

ABSTRACT

Research question: What is the clinical experience of patients who have undergone planned oocyte cryopreservation and oocyte thawing and warming?

Design: Retrospective observational cohort study. All women who completed planned oocyte cryopreservation at a single large university-affiliated fertility centre between June 2006 and October 2020 were identified, including the subset who returned to use their oocytes. Patients who underwent oocyte cryopreservation for medical reasons were excluded. Baseline demographics, oocyte cryopreservation and thawing–warming cycle parameters, and clinical outcomes, were extracted from the electronic medical record. The primary outcome was cumulative live birth rate (LBR), and secondary outcomes were cumulative clinical pregnancy rate (CPR), and CPR and LBR per transfer. Results were stratified by age at time of cryopreservation (<38 and ≥38 years).

Results: Of 921 patients who underwent planned oocyte cryopreservation, 68 (7.4%) returned to use their oocytes. Forty-six patients (67.6%) completed at least one embryo transfer. The CPR per transfer was 47.5% and LBR was 39.3%. The cumulative LBR per patient who initiated thawing–warming was 32.4%. Cycle outcomes were not significantly different in patients aged younger than 38 years and those aged 38 years or over. No patient aged 40 years or older (n = 6) was successful with their cryopreserved oocytes. Ten patients (14.7%) who were unsuccessful with their cryopreserved oocytes achieved a live birth using donor oocytes, with most (7/10) of these patients aged 38 years and older.

Conclusion: Only a small percentage of patients returned to use their oocytes, and 32% of those were able to achieve a live birth.

[1] Boston IVF, 130 2nd Avenue, Waltham Massachusetts 02451, USA
[2] Division of Reproductive Endocrinology and Infertility, Department of Ob/Gyn, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston Massachusetts 02215, USA
[3] Department of Ob/Gyn, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston Massachusetts 02215, USA
[4] Harvard Medical School, 25 Shattuck Street, Boston MA 02115, USA

*Corresponding author. E-mail address: angela.q.leung@gmail.com (A. Q. Leung). https://doi.org/10.1016/j.rbmo.2021.06.024 1472-6483/
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KEYWORDS

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Oocyte cryopreservation
Oocyte usage
Oocyte vitrification

INTRODUCTION

An age-related decline in fertility is a well-known physiologic effect related to decreases in oocyte quantity and quality (*ACOG and ASRM, 2014*). Older women who conceive naturally have an increased risk of fetal chromosomal abnormalities and pregnancy loss (*Spandorfer and Chung, 2004*). Despite this association, a global shift towards delayed childbearing has occurred (*OECD Family Database, OECD, 2019*). Age at first birth and the proportion of pregnancies in women over the age of 35 years have been increasing in the USA since 1980 (*Martin et al., 2*019). This trend is accompanied by rising numbers of people unable to achieve parenthood or desired family size (*Kneale and Joshi, 2008*; *Habbema et al., 2015*). Reasons for delaying childbearing include educational and professional pursuits, desire for financial security, lack of a partner and not feeling ready (*Goold and Savulescu, 2009*; *Lewis et al., 2016*). The effectiveness of assisted reproductive technology (ART) is also age-dependent, with older women having lower success rates (*Leridon, 2004*). Planned oocyte cryopreservation has risen as a means of preserving reproductive potential in the face of age-related fertility decline.

The first successful human live birth from a cryopreserved oocyte occurred in 1986 (*Chen, 1986*). Despite this early success, limited progress was made in the infertility field owing to technical challenges (*Bernard and Fuller, 1996*). Legislative restrictions and ethical concerns surrounding the storage of embryos in countries such as Italy, however, propagated further research into oocyte cryopreservation (*Benagiano and Gianaroli, 2004*). Developments in cryopreservation methods, particularly with oocyte vitrification, have led to significant improvements in the efficacy of oocyte cryopreservation (*Smith et al., 2010*). As a result, the Human Fertilization and Embryology Authority in the UK approved the use of cryopreserved oocytes in 2000 (*Wise, 2000*). Similarly, in 2013, the American Society of Reproductive Medicine (ASRM) Ethics Committee removed the experimental label from oocyte cryopreservation after concluding that pregnancy rates were similar when using fresh oocytes compared with vitrified–warmed oocytes as part of IVF and intracytoplasmic sperm injection, making the procedure more widely available to women (*Mature oocyte cryopreservation: a guideline, 2013*). In 2018, ASRM further asserted that planned oocyte cryopreservation for non-medical indications was an ethically permissible treatment with the potential to enhance a women's reproductive autonomy (*Committee of the American Society for Reproductive Medicine et al., 2018*).

Oocyte cryopreservation is now considered an established technology that is offered in a large proportion of IVF centres worldwide. In the USA, Australia and New Zealand, a dramatic rise in the number of oocyte cryopreservation cycles has taken place, +880% between 2010 and 2016 and +311% between 2010 and 2015, respectively (*Johnston et al., 2020*). In the UK, this increase was about 460% between 2010 and 2016 (Egg freezing in fertility treatment, trends and figures: 2010–2016, *2018*). The rise in 'social' oocyte cryopreservation has garnered increased media attention and sparked significant debate about whether this option provides women with false security (*Lockwood, 2011*; *De Wiel, 2014*; *Baylis, 2015*). In recent years, many employers have started to offer coverage for planned oocyte cryopreservation as part of their benefits package, further accelerating the use of planned oocyte cryopreservation (*Miner et al., 2020*).

Data on the outcomes of planned oocyte cryopreservation, however, are lacking. Several cross-sectional surveys and interviews have investigated the experiences of women who have previously undergone planned oocyte cryopreservation; however, the scope of information is limited as only a small number of women have returned to use their cryopreserved gametes (*Hodes-Wertz et al., 2013*; *Baldwin et al., 2015*; *Stoop et al., 2015*; *Johnston et al., 2020*). Given the lack of available clinical outcome data, published reports limit their analyses to mathematical models designed to project the success of planned oocyte cryopreservation (*Doyle et al., 2016*; *Goldman et al., 2017*). A few retrospective studies from individual clinics or fertility groups have reported that live birth rates using planned cryopreserved oocytes have comparable outcomes to cycles using fresh oocytes and that live birth rates are age-dependent at the time of planned oocyte cryopreservation (*Cobo et al., 2016*, *2018*; *Doyle et al., 2016*; *Gürtin et al., 2019*; *Wennberg et al., 2019*).

The aim of the present study was to describe a cohort of women who returned to use their planned cryopreserved oocytes and to present their cycle outcomes.

MATERIALS AND METHODS

Study participants

A database search of the electronic medical record eIVF (PracticeHwy.com Inc, Irving TX, USA) was conducted at a single large university-affiliated fertility clinic to identify all patients who underwent a planned oocyte cryopreservation cycle for fertility preservation. The first case was carried out in June 2006 and patient data were collected up to October 2020. The subset of patients who returned to complete an oocyte thawing–warming cycle for an intended embryo transfer were also identified. Exclusion criteria included fertility preservation for medical indications, such as cancer diagnoses or no spermatozoa at the time of oocyte retrieval. Demographic and cycle outcome data were collected.

Oocyte cryopreservation, thawing–warming, and embryo transfer

The ovarian stimulation and embryo transfer protocols were determined by the treating physician. No specific policies recommended number of oocytes cryopreserved; initiation and conclusion of treatment was left to the discretion of the patient and provider. Slow cooling was used to cryopreserve the oocytes to 1 June 2010. After that time, the laboratory transitioned completely to vitrification using the Vit Kit (Irvine Scientific, Santa Ana, CA, USA) for both cryopreservation and warming. Embryologists trained specifically in oocyte cryopreservation and thawing–warming carried out all laboratory procedures. Intracytoplasmic sperm injection was used to fertilize thawed–warmed oocytes. Embryos were cultured to day 3 or 5 of development for transfer based on physician orders, or biopsied on day 5, 6 or 7 for preimplantation genetic testing with aneuploidy. Supernumerary embryos were cryopreserved if they met laboratory criteria of a blastocyst quality of 3BB or better, based on the Gardner scoring system (*Gardner, 1999*). Endometrial preparation for

frozen embryo transfer was carried out according to provider preference, using a natural cycle, a modified natural cycle with ovarian stimulation with clomiphene or letrozole, or programmed hormone replacement with oestradiol and progesterone. In the natural or modified natural cycles, the patient was monitored until a serum LH surge was detected, or an HCG trigger was administered for final follicular maturation. In the programmed cycles, oestrogen was given via oral or transdermal routes, and progesterone was administered intramuscularly, vaginally, or both. The success rates of both natural and programmed frozen embryo transfer cycles at this centre are equivalent, which is consistent with published research (*Ghobara et al., 2017*).

Data analysis

Patient and cycle details were stratified by age younger than 38 and age 38 years or over at the time of cryopreservation and reported using descriptive statistics. Additional subgroup analysis was carried out using the Society for Assisted Reproductive Technology (SART) age categories. Outcome data resulting from the oocyte thawing–warming cycles were reported and compared across age categories. Pregnancy rate was defined as a positive serum pregnancy test. Clinical pregnancy rate (CPR) was defined as presence of a fetal sac on ultrasound. Live birth rate (LBR) was defined as a delivery of a live born baby after 34 weeks. Chi-square test was used for categorical variables, and student's t-test was used for continuous variables, with $P < 0.05$ determining significance.

Ethical approval

This study was exempt from Institutional Review Board approval by Beth Israel Deaconess Medical Center on 3 December 2019 (Reference number: 2019P000254).

RESULTS

Patient characteristics

Between June 2006 and October 2020, 1079 patients underwent oocyte cryopreservation for a total of 1441 cycles. Of these patients, 921 underwent planned oocyte cryopreservation for fertility preservation and completed a total of 1265 cycles. Sixty-eight patients from this cohort (7.4%) returned to use their cryopreserved oocytes to create embryos for transfer (FIGURE 1).

A larger proportion of patients who cryopreserved oocytes at an older age used them ($P = 0.0009$) (TABLE 1). Most of the patients' oocytes (58/68 [85.3%]) were cryopreserved using vitrification. A large increase in the number of planned oocyte cryopreservation cycles has taken place each year since 2006, with the fastest growth in the past 5 years (FIGURE 2). The mean age of patients who completed oocyte cryopreservation over the past 14 years was 36.6 years. Age, however, has declined over time (between 2006 and 2020), with a mean (calculated by performing a rolling average) of 37.1 years in the early years of the technology, compared with a mean age of 35.7 years most recently ($P = 0.001$).

Baseline characteristics of the patients who used their cryopreserved oocytes are presented in TABLE 1. Most of these patients were aged between 35 and 40 years (88.2%) at the time of planned oocyte cryopreservation, with a mean (± SD) age of 38.1 ± 1.8 years at time of cryopreservation. This mean has stayed relatively constant over time, with a mean age of 38.0 years before 2015 compared with 38.2 years since 2015. Only two patients were aged younger than 35 years (youngest age 34 years) and six patients were aged older than 40 years (oldest aged 42 years). On average, patients waited 3.7 ± 1.7 years before returning to use their cryopreserved oocytes, with a mean age at oocyte thawing–warming of 41.8 ± 2.1 years. Patients who cryopreserved oocytes at a younger age waited a mean of 4.1 ± 1.7 years to use them compared with 3.2 ± 1.5 years in those aged 38 years or older. Most of these patients (70.6%) thawed–warmed their oocytes after a diagnosis of infertility based on clinical workup or history, or after other unsuccessful ART treatments. The remaining 29.4% of patients elected to conceive by directly using their cryopreserved oocytes, even without a diagnosis of infertility or other treatment attempts. Most patients had male partners who provided the sperm source (64.7%), although 42.4% of women aged 38 years or over used donor spermatozoa compared with 30.6% of women aged younger than 38 years. Baseline characteristics of ovarian reserve, such as anti-Müllerian hormone (AMH), FSH and antral follicle count (AFC) were similar among the age groups ($P = 0.49$, $P = 0.46$ and $P = 0.41$, respectively).

Oocyte cryopreservation and thawing–warming

A mean of 17.1 ± 8.6 oocytes was cryopreserved from 1.4 ± 0.6 planned oocyte cryopreservation cycles per patient and 14.4 ± 7.9 thawed–warmed over 1.1 ± 0.4 thawing–warming cycles per patient (TABLE 1). The number of oocytes cryopreserved and thawed–warmed were similar between those aged younger than 38 years and those aged 38 years or older ($P = 0.39$ and $P = 0.46$, respectively). When the data were further stratified by SART age categories (<35, 35–37, 38–40 and >40 years), patients aged over 40 years had the fewest mean oocytes cryopreserved and thawed–warmed (Supplementary Table 1); however, this was not significantly different from the group aged 35–37 years, which was used as the reference group ($P = 0.31$ and $P = 0.38$). The oocyte survival rate was 84.9% for vitrified oocytes and 57.1% for slow-cooled oocytes. The fertilization rate was 74% and about one-half of the embryos progressed to the blastocyst stage (TABLE 1). The fertilization rate, blastulation rate and number of embryos transferred were similar between ages 38 years or younger and 38 years or over ($P = 0.42$, $P = 0.44$ and $P = 0.48$, respectively). Patients aged 38 years or older had 1.9 ± 2.4 supernumerary embryos for cryopreservation compared with 3.3 ± 3.7 in those aged younger than 38 years.

Oocyte thawing–warming cycle outcomes

The final outcomes of all patients who completed an oocyte thawing–warming cycle are presented in FIGURE 1. A total of 46 patients (67.6%) underwent 61 embryo transfers. The cycle outcomes per transfer and per patient are presented in TABLE 2 and TABLE 3. If a patient was able to achieve at least one transfer, the CPR per transfer was 47.5% and LBR was 39.3%. Cycle outcomes per transfer and per patient were not significantly different between the two age groups.

Twenty-two patients (32.4%) did not achieve an embryo transfer. Of these, 19 patients had planned preimplantation genetic testing with aneuploidy cycles and 13 patients had no embryos to biopsy or no euploid embryos. The remaining six patients had euploid embryos cryopreserved but have not yet completed a transfer. One patient had untested blastocysts cryopreserved and has not yet initiated a transfer. Two

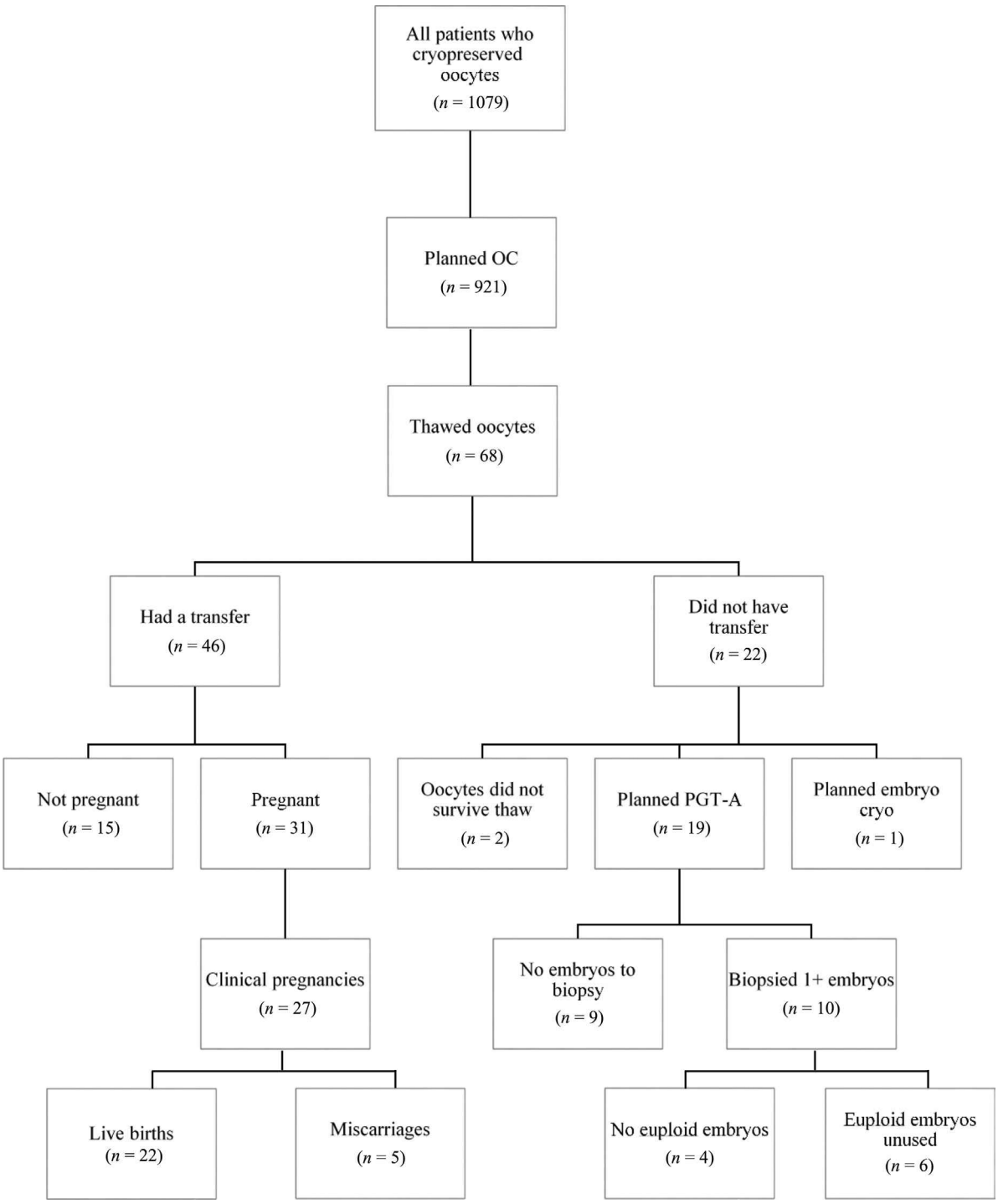

FIGURE 1 Patients who completed an oocyte cryopreservation cycle, those who returned to use cryopreserved oocytes and their subsequent thawing–warming cycle outcomes.

patients had oocytes that did not survive thawing–warming.

When cumulative outcomes were analysed based on patients who initiated oocyte thawing–warming, 32.4% (22/68) of these patients were able to achieve a live birth with their cryopreserved oocytes (TABLE 3). Almost 40% of patients who were aged younger than 38 years at the time of planned oocyte cryopreservation achieved a live birth from their cryopreserved oocytes, compared with 25% of those aged 38 years or over; however, these rates were not statistically significantly different. No patient over the age of 40 years at the time of planned oocyte cryopreservation was successful (Supplementary Table 2). A total of 14.7% (10/68) of patients underwent donor oocyte cycles when their autologous cryopreserved oocytes were unsuccessful, and all achieved a live birth. Most of these patients were aged 38 years or older (21.9 versus 8.3% of patients aged ≥38 years versus those aged <38 years). Seven of these

TABLE 1 PATIENT AND CYCLE CHARACTERISTICS OF THOSE WHO THAWED–WARMED OOCYTES FROM PLANNED OOCYTE CRYOPRESERVATION CYCLES BETWEEN 2006 AND 2020

	Age <38 years	Age ≥38 years	Total	*P*-value
Patient characteristics				
Patients, *n*	36	33	68[a]	–
Age at time of oocyte cryopreservation, years	36.6 (0.9)	39.6 (1.2)	38.1 (1.8)	0.02
Age at time of thawing–warming, years	40.8 (1.7)	42.9 (1.9)	41.8 (2.1)	0.20
Time between oocyte cryopreservation and thawing–warming, years	4.1 (1.7)	3.2 (1.5)	3.7 (1.7)	0.34
Utilization rate, %	5.6	11.9	7.4	0.0009
Reason for thawing–warming (elective/infertility), %	36.1 / 63.9	16.7 / 83.3	29.4 / 70.6	0.86
BMI	25.6 (5.3)	24.5 (3.3)	25.1 (4.5)	0.44
AMH, ng/ml	2.2 (2.1)	2.2 (2.4)	2.2 (2.3)	0.49
FSH, mIU/ml	7.7 (2.5)	7.3 (2.6)	7.5 (2.6)	0.46
AFC, *n*	14.4 (7.6)	12.6 (4.2)	13.6 (6.3)	0.41
Age of male partner at time of thawing–warming, years	41.8 (9.2)	42.6 (11.8)	42.2 (10.5)	0.48
Sperm source (partner/donor), %	69.4/30.6	57.6/42.4	64.7/35.3	0.15
Cycle characteristics				
Thawing–warming cycles, *n*	42	35	77	–
Oocyte cryopreservation cycles per patient	1.6 (0.7)	1.2 (0.4)	1.4 (0.6)	0.34
Oocytes cryopreserved per patient	18.4 (9.2)	15.2 (7.7)	17.1 (8.6)	0.39
Oocyte thawing–warming cycles per patient	1.2 (0.4)	1.1 (0.4)	1.1 (0.4)	0.46
Oocytes thawed–warmed per patient	14.5 (7.9)	14.2 (7.9)	14.4 (7.9)	0.49
Fertilization rate	0.78 (0.20)	0.70 (0.28)	0.74 (0.25)	0.42
Blastulation rate	0.51 (0.25)	0.46 (0.27)	0.48 (0.26)	0.44
Embryos transferred, *n*	1.45 (0.61)	1.40 (0.70)	1.43 (0.64)	0.48
Supernumerary embryos cryopreserved, *n*	3.3 (3.7)	1.9 (2.4)	2.6 (3.2)	0.38

Values are presented as means (SD) unless otherwise stated.

[a] One patient completed an oocyte cryopreservation cycle at age 37 years then again at age 41 years, and is counted separately in the age categories but as a single patient in the total category.

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index.

10 patients were aged 38 years or older, with five between the ages of 38 and 40 years and two aged 40 years or older. In contrast, 19.4% of younger patients who initiated a thawing–warming cycle (7/36) had a successful live birth with other autologous ART treatment compared with 9.4% of older patients (3/32).

DISCUSSION

To the best of our knowledge, the present study represents one of the larger reports of clinical outcomes from patients who used planned cryopreserved oocytes. Almost one-third of patients successfully achieved a live birth from their cryopreserved gametes, with age 39 years as the upper limit of success. Although not statistically significant, a trend towards lower clinical pregnancy and live birth rates was observed with older age of planned oocyte cryopreservation, which is consistent with the known effect of age on fertility (*ACOG and ASRM, 2014*). Furthermore, despite the fact that planned oocyte cryopreservation patients do not have a diagnosis of infertility at time of oocyte cryopreservation, the rate of success in these patients is on par with IVF success rates for infertile patients in these age groups (*SART National Summary Report for 2017*).

The mean age of all patients who completed planned oocyte cryopreservation was 36.6 years; however, those who used their cryopreserved oocytes were on average older (38.1 years) (TABLE 1). A recent report of SART data showed that the average age of oocyte cryopreservation in 2010 was 36.7 years and dropped to 34.7 years in 2016 (*Johnston et al., 2020*). A similar trend was also seen in this study: since the inception of planned oocyte cryopreservation, the mean age of patients has declined from 37.1 to 35.7 years between 2006 and 2020. This contrasts with the mean age at time of oocyte cryopreservation of patients who used their oocytes, which has stayed constant over the past decade. This indicates that, although patients are increasingly undergoing fertility preservation at a younger age, individuals who use their cryopreserved eggs have consistently been those who cryopreserved at an older age.

One explanation for the observed higher mean age at oocyte cryopreservation in the study patients who used their cryopreserved oocytes compared with the mean age of all patients who completed planned oocyte cryopreservation may be that patients who complete fertility preservation at a later age (and thus likely start family building even later) are the individuals who most likely need to use their

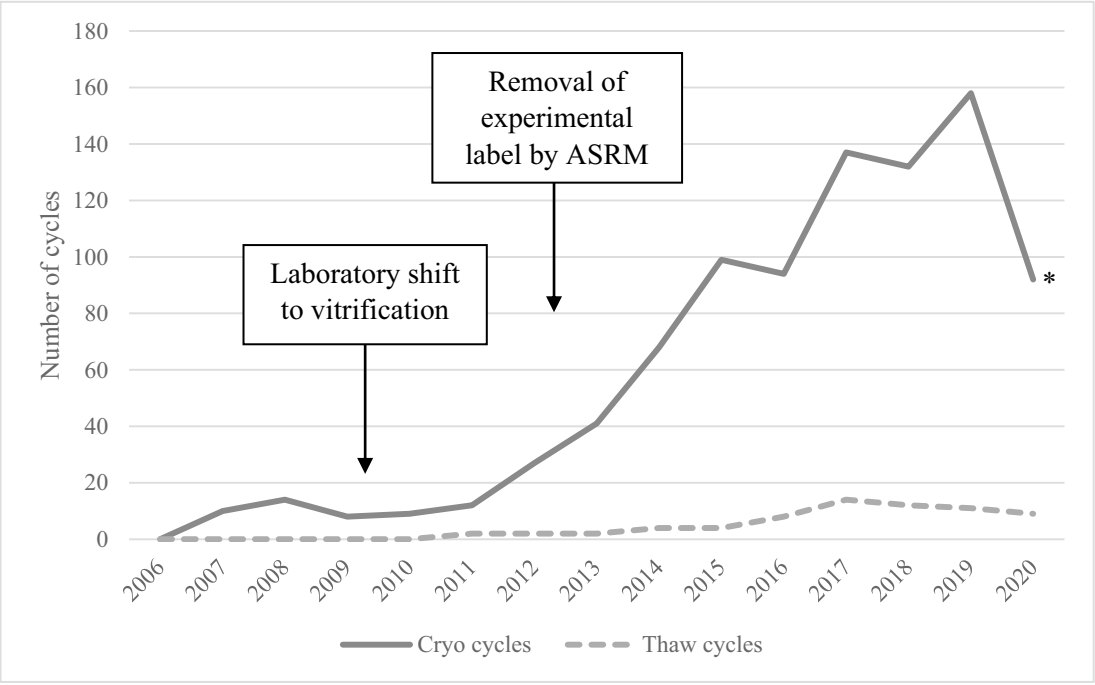

FIGURE 2 Planned oocyte cryopreservation and thawing–warming cycle trends over a 14-year period. Number of planned oocyte cryopreservation and thawing–warming cycles between 2006 and 2020, with notations of the transition from slow-freezing to vitrification and the removal of the experimental label on oocyte cryopreservation by the American Society of Reproductive Medicine (ASRM). *The numbers for 2020 are low because of the closure of the clinic for part of the year because of COVID-19.

TABLE 2 CYCLE OUTCOMES PER TRANSFER

	Age <38 years	Age ≥38 year	Total
Embryo transfers, *n*	33	28	61
Pregnancy rate	60.1 (43.9 to 77.3)	50.0 (31.5 to 68.5)	55.7 (43.3 to 68.2)
Clinical pregnancy rate	54.5 (37.6 to 71.5)	39.3 (21.2 to 57.4)	47.5 (35.0 to 60.1)
Live birth rate	48.5 (31.4 to 65.5)	28.6 (11.8 to 45.3)	39.3 (27.1 to 51.6)
Miscarriage rate	11.1 (0 to 25.6)	27.3 (1.0 to 53.6)	17.2 (3.5 to 31.0)

Values are presented as % (95% CI).

No significant difference was found between the age groups for any outcome.

TABLE 3 CUMULATIVE CYCLE OUTCOMES PER PATIENT WHO ACHIEVED TRANSFER AND LIVE BIRTH RATE PER INITIATED THAWING–WARMING

	Age <38 years	Age ≥38 years	Total
Per patient who achieved transfer, *n*	25	21	46
Pregnancy rate	72.0 (54.4 to 89.6)	61.9 (41.1 to 82.7)	67.4 (53.8 to 80.9)
Clinical pregnancy rate	64.0 (45.2 to 82.8)	52.4 (31.0 to 73.7)	58.7 (44.5 to 72.9)
Live birth rate	56.0 (36.5 to 75.5)	38.1 (17.3 to 58.9)	47.8 (33.4 to 62.3)
Miscarriage rate	12.5 (0 to 28.7)	27.3 (1.0 to 54.6)	18.5 (3.9 to 33.2)
Per patient who initiated thawing–warming, *n*	36	32	68
Live birth rate	38.9 (23.0 to 54.8)	25.0 (10.0 to 40.0)	32.4 (21.2 to 43.5)

Values are presented as % (95% CI).

No significant difference was found between the age groups for any outcome.

cryopreserved gametes. Younger patients who preserve their fertility may never have issues conceiving and, therefore, will not need their cryopreserved oocytes. An additional consideration is the effect of insurance coverage on the age of patients who access planned oocyte cryopreservation and, consequently, thawing–warming. This study was conducted in an insurance-mandated state, in which many patients have insurance coverage for fertility treatments once a diagnosis of infertility is established. Fertility preservation cycles, however, are generally not covered by insurance, except for some employer-based fertility-specific plans. Because patients in this region may know that necessary future treatment is covered, it is possible they do not seek out fertility preservation to mitigate future infertility with as much urgency. Furthermore, younger patients may simply not be able to afford oocyte cryopreservation, which can affect the age of the cohort that accesses this treatment. An increase in fertility awareness as well as increasing employer-based fertility benefits (which include fertility preservation) (*2021 Survey on Fertility Benefits, 2021*), however, may be contributing to the declining age of patients undergoing planned oocyte cryopreservation.

In addition, the higher average age of patients at the time of planned oocyte cryopreservation in the present study who used their oocytes, compared with all patients who cryopreserved gametes, may have led to lower success rates. Furthermore, seven patients never underwent a transfer, but still have unused embryos cryopreserved. Therefore, the reported cumulative outcomes may be underestimating true potential for live birth.

The use of planned cryopreserved oocytes in this study was about 7%; however, this low value is likely to be an underestimation as patients who completed planned oocyte cryopreservation within the last few years may not have yet had the opportunity to return for a thawing–warming cycle. As the number of patients undergoing planned oocyte cryopreservation at this centre has dramatically increased in the past 5 years, use may change going forward. Notably, the average time between planned oocyte cryopreservation and thawing–warming was 3.7 years. If it is assumed that all patients who plan to use their cryopreserved oocytes will do so within 4 years, and the use calculation is restricted to those who completed oocyte cryopreservation by the end of 2016, the utilization rate would be 16.5%. In general, utilization rate of oocytes has not been clearly defined as there is an inherent time delay in the process of planned oocyte cryopreservation and oocyte thawing–warming. A report of SART data found a utilization rate of 4.5% (*Johnston et al., 2020*); however, this includes oocyte cryopreservation cycles that were carried out for medical indications. Previously published studies, however, have shown that planned oocyte cryopreservation is cost-effective only if 49–61% of patients return to use their oocytes (*van Loendersloot et al., 2011*; *Devine et al., 2015*; *Ben-Rafael, 2018*), and if planned oocyte cryopreservation is completed before the ages of 37–38 years (*Devine et al., 2015*; *Mesen et al., 2015*). It remains uncertain whether around 50% is a reasonable expected utilization rate. Certain geographic areas (and hence, demographic differences) may predispose to higher usage. A recent report from a high volume planned oocyte cryopreservation centre reported a 38% utilization rate (*Blakemore et al., 2020*). Our study population, even when restricting to only oocyte cryopreservation cycles completed 4 years ago, does not reach such a high utilization rate. Future studies describing use of planned cryopreserved oocytes from different centres is needed.

A concern of women seeking to preserve fertility through planned oocyte cryopreservation is the likelihood of success based on number of oocytes obtained. This is commonly understood as the 'oocyte efficiency' or 'oocyte to baby' ratio; however, no universal definition exists for how this rate is calculated (*Patrizio and Sakkas, 2009*; *Doyle et al., 2016*; *Goldman et al., 2017*; *Cobo et al., 2018*). In general, it typically involves a theoretical calculation of live birth outcomes based on observed live births plus projected live births from unused oocytes or embryos. Because of the retrospective observational nature of the present study, we have not included a theoretical 'oocyte efficiency' calculation, as the small numbers in this study would make such a conjecture prone to high error. Furthermore, our intention was to report our centre's experience with planned oocyte cryopreservation and thawing–warming, and not make predictions based on limited numbers. Future large prospective studies will be better suited to address this question.

Strengths of this study include the reporting of clinical outcome data of used cryopreserved oocytes, in contrast to mostly theoretical data that has been published so far. The outcomes were also described on a per cycle basis, as well as cumulatively per patient. The cumulative live birth rate is the best parameter that assists in counselling patients on their overall chance of success. The study comprises 14 years of data at a single large institution that provides a large percentage of the IVF services in the region. Therefore, it is a comprehensive report of the experiences of patients in this area over more than a decade.

A significant limitation to this study is the small number of patients available for inclusion in the analysis. This reflects the low utilization rate that was discussed previously. Consequently, it is not surprising that no statistical significance was found between the age groups for any clinical outcome. Confidence intervals for these outcomes were also wide, again reflective of the low number of patients. Therefore, the results reported here should be interpreted conservatively. A larger study would allow better power to adequately detect differences between age groups; to detect a difference in LBR of 15% with a power of 80%, 152 patients would be required in each age category. Given that the utilization of cryopreserved oocytes is low, and the inherent time delay from cryopreservation until thawing–warming, it may take many years for such numbers to be accumulated. Considering the current paucity of published clinical data in this patient population, it is beneficial to examine available data closely. Despite the limitation of sample size, the present study is still one of the larger reports to date to describe outcomes from thawing–warming of planned cryopreserved oocytes. When stratified by SART age groups, the number of patients in each category is further reduced, leading to an inability to find statistically significant differences between the groups. The trend that pregnancy and live birth rates decline with increasing age at oocyte cryopreservation, however, is supported by other studies (*Doyle et al., 2016*; *Goldman et al., 2017*; *Johnston et al., 2020*).

Other limitations are that results may be less generalizable to other regions. The influence of an insurance mandate for fertility coverage on the patient population is discussed previously. Furthermore, the inclusion of oocytes cryopreserved by slow cooling may have skewed towards worse outcomes. Notably, only one patient who used oocytes that were slow cooled was successful in achieving a live birth. Another confounder that may have affected success rates is the possibility that patients had undiagnosed subfertility at the time of planned oocyte cryopreservation, which is also related to increasing age. Although age specific mean AMH, FSH and AFC values were within expected ranges, several patients completed other fertility treatments before electing to proceed with planned oocyte cryopreservation. Given the limitations of the electronic medical record and variability in documentation, it is difficult to fully ascertain truly 'elective' fertility preservation cases. Future larger studies from a variety of different geographic locations and practice types will be useful to further elucidate clinical outcomes after planned oocyte cryopreservation and thawing–warming.

In conclusion, a small number of patients have returned to use their planned cryopreserved oocytes. One-third of patients were able to achieve a live birth from these oocytes. Rates of success seemed to decline with increasing age at planned oocyte cryopreservation, although not significantly, and planned oocyte cryopreservation at age 40 years or older did not lead to any live births. Although the total number of patients included in this study is small, it is one of the larger reports of this patient cohort and provides valuable insight into the profile of women pursuing planned oocyte cryopreservation and thawing–warming. Results should be interpreted cautiously as this is primarily an observational study but may still serve as a useful counselling tool to set appropriate expectations for women contemplating fertility preservation.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2021.06.024.

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