Fifteen years of autologous oocyte thaw outcomes from a large university-based fertility center

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Objective: To review the outcomes of patients who underwent autologous oocyte thaw after planned oocyte cryopreservation.
Design: Retrospective cohort study.
Setting: Large urban university-affiliated fertility center.
Patient(s): All patients who underwent ≥1 autologous oocyte thaw before December 31, 2020.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome was the final live birth rate (FLBR) per patient, and only patients who had a live birth (LB) or consumed all remaining inventory (cryopreserved oocytes and resultant euploid/untested/no result embryos) were included. The secondary outcomes were laboratory outcomes and LB rates per transfer.
Result(s): A total of 543 patients underwent 800 oocyte cryopreservations, 605 thaws, and 436 transfers. The median age at the first cryopreservation was 38.3 years. The median time between the first cryopreservation and thaw was 4.2 years. The median numbers of oocytes and metaphase II oocytes (M2s) thawed per patient were 14 and 12, respectively. Overall survival of all thawed oocytes was 79%. Of all patients, 61% underwent ≥1 transfer. Among euploid (n = 262) and nonbiopsied (n = 158) transfers, the LB rates per transfer were 55% and 31%, respectively. The FLBR per patient was 39%. Age at cryopreservation and the number of M2s thawed were predictive of LB; the FLBR per patient was >50% for patients aged <38 years at cryopreservation or who thawed ≥20 M2s. A total of 173 patients (32%) have remaining inventory.
Conclusion(s): Autologous oocyte thaw resulted in a 39% FLBR per patient, which is comparable with age-matched in vitro fertilization outcomes. Studies with larger cohorts are necessary. (Fertil Steril® 2022;118:158-66. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Egg freezing, oocyte cryopreservation, oocyte thaw, fertility preservation, assisted reproductive technology

Several women in the industrialized world are now postponing childbearing. The mean age and rate of first birth in women aged ≥35 years are increasing in the United States (1). This trend toward motherhood at a later age is credited to educational, professional, financial, and personal reasons (2, 3). Unfortunately, the choice to delay procreation does not delay the inevitable age-related fertility decline (related to decreased oocyte quantity and quality) (4). Therefore, the choice to become a mother later in life is often accompanied by devastating costs—infertility, childlessness, inability to achieve one's desired family size, and adverse pregnancy outcomes (5, 6).

Oocyte cryopreservation (OC) is now accepted as a fertility preservation method for women facing age-related fertility decline. This technology allows women to postpone childbearing while maintaining the option of having a biologic child. Previous studies demonstrate that OC results in euploidy and pregnancy rates comparable with fresh in vitro fertilization (IVF) (7–11) and does not pose additional safety risks compared with IVF (7, 12). After the American Society for Reproductive Medicine lifted the experimental label from OC in 2012 (13), the use of this

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fertility preservation method increased dramatically (+880% in the United States from 2010 to 2016) (14).

Despite the growing demand for OC and the fact that patients reflect positively on OC (15–17), most patients who have cryopreserved oocytes have not yet returned for thaw (18, 19). Because most oocytes remain cryopreserved, there is a scarcity of thaw data. There are some reports of autologous oocyte thaws from national registries (12, 14, 20, 21) and individual fertility centers (18, 19, 22–27); however, most include patients with infertility and cancer. The inclusion of women with these medical diagnoses makes it difficult to extrapolate these outcomes to women cryopreserving oocytes solely because of age-related fertility decline.

This paucity of oocyte thaw data proves challenging when counseling patients about the pregnancy potential from cryopreserved oocytes. Physicians and patients often rely on predictive models that use data extrapolated from oocyte donors and IVF patients with normal ovarian reserve (28); however, the accuracy of these models remains unknown, and some fear that OC may provide women with false security rather than realistic expectations (29, 30). A better understanding of the live birth (LB) rate from OC for age-related fertility decline is necessary to inform patient decision-making. Furthermore, the American Society for Reproductive Medicine has called for up-to-date information on this topic (31). Therefore, we conducted a retrospective cohort study of all autologous oocyte thaws at our institution, with the aim of publishing up-to-date information.

MATERIALS AND METHODS

Design

With New York University Institutional Review Board approval (number S13-00389), we performed a retrospective cohort study of all patients who froze or vitrified autologous oocytes and then underwent ≥1 autologous oocyte thaw/warming ("thaw" will be used for consistency) cycle at the New York University Langone Prelude Fertility Center before December 31, 2020. Transfers from resultant embryos were included if they occurred before July 1, 2021. We included transfers that occurred up to 6 months after the last thaw to capture transfers for patients who thawed oocytes at the end of the study period.

Subjects

All patients who underwent ≥1 autologous oocyte thaw in the study period were reviewed. Patients were excluded if OC was performed for a medical indication, due to lack of sperm, due to a natural disaster, in combination with embryos, or as part of a research protocol where the intent was to thaw oocytes in the following month. Patients were also excluded if they had a cancer diagnosis or planned to use a gestational carrier.

Data Collection and Outcomes

Data regarding OC, oocyte thaw, and embryo transfer cycles were obtained from electronic medical records. Collected OC data included the following: date; patient age; and cryopreservation method (slow freezing vs. vitrification vs. both). Collected thaw data included the following: date; patient age; number of total oocytes, metaphase I oocytes (M1s), and metaphase II oocytes (M2s) thawed and surviving thaw; number of embryos with 2-pronuclear (2PN) fertilization and for preimplantation genetic testing (PGT), cryopreservation, or fresh transfer; and ploidy results. Collected transfer data included the following: date; patient age; number of embryos transferred; whether transferred embryos were fresh or cryopreserved; whether transferred embryos underwent PGT and ploidy result; and implantation and LB outcomes. Implantation was defined as ≥1 intrauterine gestational sac on ultrasound. We also ascertained whether patients had remaining inventory (cryopreserved oocytes or resultant euploid/untested/no result embryos in storage at our facility or that have been transported to another facility, donated, or discarded) as of July 1, 2021.

The primary outcome was the final LB rate (FLBR). This outcome was defined per patient, and only patients who had an LB or consumed all remaining inventory were included. The secondary outcomes were laboratory outcomes, implantation rate (IR) per number of embryos transferred, spontaneous abortion rate (SABR) per transfer, and LB rate (LBR) per transfer. Two LBs resulted from double embryo transfers with 1 embryo created from a thawed oocyte and 1 embryo created from a fresh oocyte retrieved during an IVF cycle; these LBs were excluded from transfer outcomes and FLBR.

Notably, some patients thawed oocytes from multiple retrievals in 1 thaw cycle, whereas others thawed oocytes from 1 retrieval in multiple thaw cycles. Therefore, to interpret the data and produce results helpful for patient counseling, several variables were summed and treated per patient.

OC, Thawing, and Embryo Transfer

Ovarian stimulation protocols were determined by the treating physician on the basis of age and ovarian reserve. Between 2004 and 2015, all retrieved M1s and M2s were cryopreserved; after 2015, M1s were only cryopreserved if <15 M2s were retrieved during the same OC cycle.

Oocytes were cryopreserved with slow freezing or vitrification using previously described techniques (10). During our laboratory's transition from slow freezing to vitrification, a combination of both technologies was often used to cryopreserve oocytes from a single retrieval. Therefore, some patients had a combination of slow-frozen and vitrified oocytes (from 1 OC cycle and/or different OC cycles). All OC cycles performed after July 2011 involved vitrification alone.

Oocytes were thawed using previously described techniques (10). Intracytoplasmic sperm injection was used to fertilize all oocytes. Embryos were cultured until transfer (days 3–7 on the basis of physician orders), trophectoderm biopsy for PGT, or cryopreservation at the blastocyst stage on days 5–7. Preimplantation genetic testing was performed with array comparative genomic hybridization or next-generation sequencing on the basis of what technology was standard at the time of thaw.

Our center routinely counsels all patients on the advantages and disadvantages of PGT. Advantages discussed include the ability to stratify embryos for selection and the knowledge of future reproductive potential. Disadvantages discussed include the financial cost, low but nonzero rates of technical error and "no result" embryos, and possibility of having no embryos to biopsy or no euploid embryos to transfer as well as the potential distress associated with these outcomes. The decision regarding whether or not to perform PGT is ultimately a shared decision between the treating physician and patient.

Before embryo transfer, saline infusion sonohysterography was performed to confirm that the uterine cavity was adequate for embryo transfer. Endometrial preparation for embryo transfer was determined by the treating physician. For fresh transfer of thawed autologous oocytes, a programmed or hormone-replaced protocol was used. For frozen transfer of thawed autologous oocytes, a programmed, natural cycle, or modified natural cycle (with letrozole, clomiphene citrate, or injectable gonadotropins) protocol was used as determined by the patients' physician. In programmed cycles, patients were given oral estradiol for $\geq$10 days or until the endometrium measured $\geq$7 mm in thickness. Then, progesterone in oil (50 mg daily) was administered, either alone or alternating with vaginal progesterone, and embryo transfer was planned for the appropriate day. Estrogen supplementation and progesterone supplementation were continued until a negative pregnancy test or 10 weeks of gestation. In natural cycles, follicular growth and hormones were monitored until both the endometrium was $\geq$7 mm in thickness and a dominant follicle measured $\geq$18 mm. Ovulation was then triggered with human chorionic gonadotropin or confirmed via a drop in serum estradiol levels and an increase in the progesterone level above 1 ng/m. After ovulation, progesterone was supplemented via vaginal suppository (Crinone 8% daily or Endometrin 100 mg 3 times daily), and embryo transfer was performed on day 6 of progesterone supplementation. Progesterone supplementation was continued until a negative pregnancy test or 8 weeks of gestation. Modified natural cycles used the same natural cycle criterion but with the addition of letrozole, clomiphene citrate, or injectable gonadotropins for added endometrial preparation.

Statistical Analysis

Continuous variables were assessed for normality using the Kolmogorov-Smirnoff test, found to be nonparametric, and compared with the Mann-Whitney *U* tests. Categorical variables were analyzed using the χ^2 tests. Logistic regression was used for modeling and adjustment of covariates to evaluate the outcome of LB. An alpha error of 0.05 was considered significant. The results are reported as medians with interquartile ranges (IQRs) or percentages.

RESULTS

A total of 543 patients met the inclusion criteria. These patients underwent 800 OCs, 605 oocyte thaws, and 436 embryo transfer cycles. The first OC was performed in 2005; 51% of patients first underwent OC in 2005–2012, and 49% of patients first underwent OC in 2013–2020. The first oocyte thaw was performed in 2006; a sharp increase in thaws occurred thereafter, with 70% occurring from 2016–2020.

The median age at the first OC was 38.3 (IQR, 36.8–39.7) years. At the first OC, 8% of patients were <35 years old (youngest, 27 years old), 80% were 35–40 years old, and 12% were $\geq$41 years old (oldest, 44 years old). Oocyte cryopreservation was performed at our facility for 89% of patients, an outside facility for 9% of patients, and both for 2% of patients. Moreover, 68%, 22%, and 9% of patients underwent 1, 2, and $\geq$3 OC cycles, respectively (median OC cycles, 1; maximum OC cycles, 8). The cryopreservation methods were vitrification for 72% of patients, slow freezing for 4% of patients, and both for 24% of patients (Supplemental Table 1, available online).

The median time between the first OC and thaw was 4.2 (IQR, 2.9–5.6) years. The longest time between the first OC and thaw was 12.6 years. The median age at the first thaw was 42.6 (IQR, 41.0–44.3) years. Moreover, 90%, 10%, and <1% of patients underwent 1, 2, and $\geq$3 thaws, respectively.

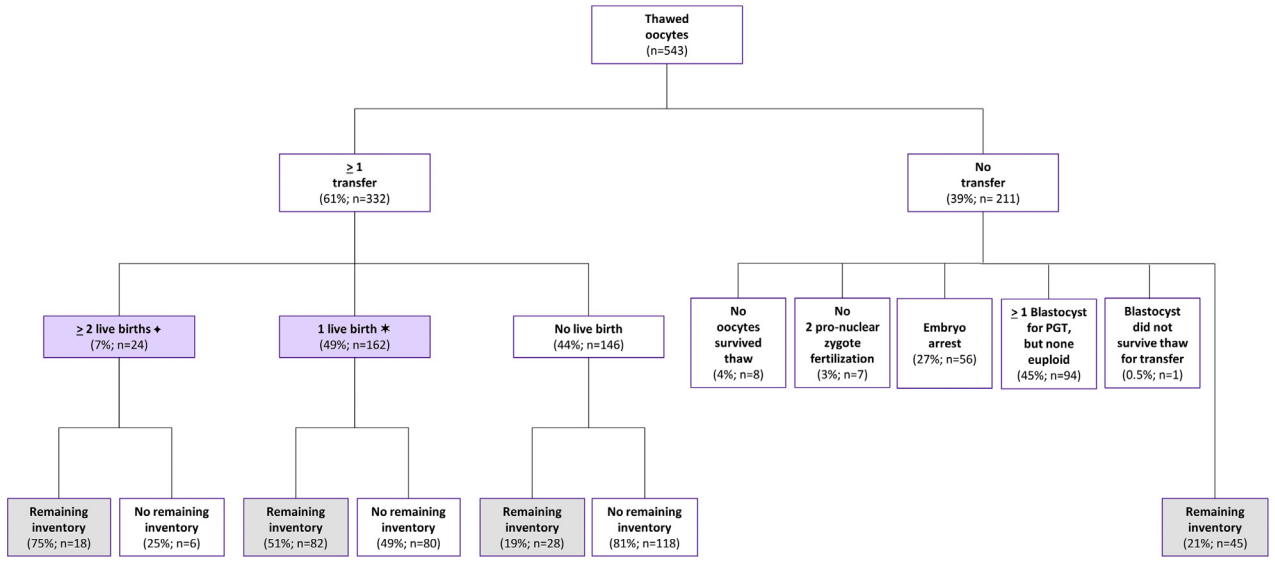
The median numbers of oocytes and M2s thawed per patient were 14 (IQR, 9–20) and 12 (IQR, 8–18), respectively. Overall cryopreserved oocyte survival was 79%; 24% of patients had 100% oocyte survival and 1% of patients had no oocyte survival. The 2PN zygote fertilization rate was 66% of surviving oocytes. Among patients with surviving oocytes, 8% had 100% 2PN fertilization and 2% had no 2PN fertilization. Among patients with all oocytes vitrified, the oocyte survival rate was 78%, and the 2PN fertilization rate was 65%; among patients with all oocytes slow-frozen, the oocyte survival rate was 78%, and the 2PN fertilization rate was 61%; and among patients with oocytes cryopreserved with both methods, the oocyte survival rate was 82%, and the 2PN fertilization rate was 69%. There were no significant differences in the oocyte survival (P=.83) or fertilization (P=.18) rates between the vitrification and slow freezing groups.

All patients thawed $\geq$1 M2, and 60% (n = 327) thawed $\geq$1 M1. Cryopreserved M2 survival was higher than cryopreserved M1 survival (80% vs. 68%, P<.0001). Among patients who thawed $\geq$1 M1, 9% (n = 30) had $\geq$1 M1 form a usable embryo (defined as an embryo for fresh transfer, PGT, or cryopreservation). In total, 25% of thawed M2s and 3% of thawed M1s led to usable embryos (P<.0001). Ultimately, there were 6 single embryo transfers of embryos from M1s, and 1 resulted in LB. There were also 6 embryo transfers with a combination of embryos from M1s and M2s, and 1 resulted in LB.

When patients returned for thaw, the plan was for fresh transfer of untested embryos for 26% of thaws, PGT for 73% of thaws, and embryo cryopreservation without PGT for 1% of thaws. When the plan was for fresh transfer of untested embryos, 91% of thaws led to $\geq$1 embryo for transfer. When the plan was for PGT, 54% of thaws led to $\geq$1 euploid embryo. Fifteen percent of thaws led to no usable embryos.

Among patients who have thawed all oocytes, 1.7% had no oocytes that survived thaw, 15% had no usable embryos, and 36% had no euploid/untested embryos to transfer (Supplemental Table 2, available online). Patients aged $\geq$41 years were more likely to have no usable embryos (P<.02)

FIGURE 1



Overview of oocyte thaw outcomes. ✦ includes 10 patients who had 1 pregnancy from thawed oocytes (9 with twins and 1 with triplets), 13 patients who had 2 separate pregnancies from thawed oocytes, and 1 patient who had 3 singleton live births from thawed oocytes. * includes 1 patient with an unknown birth outcome (ongoing at last contact) and 2 patients who had singleton pregnancies from double embryo transfers involving 1 embryo created from a thawed oocyte and 1 embryo created from a fresh oocyte retrieved during an in vitro fertilization cycle. Remaining inventory is defined as cryopreserved oocytes or resultant euploid/untested/no result embryos that are currently stored at our facility or that have been transported to other facilities, donated, or discarded. n = number of patients; PGT = preimplantation genetic testing.

Cascante. Fifteen years of oocyte thaw outcomes. Fertil Steril 2022.

and no euploid/untested embryos to transfer ($P<.003$) than patients aged ≤38 and 38–40 years.

Among patients who thawed all oocytes and planned PGT for all thaws, 17% had no embryos to biopsy, 46% had no euploid embryos, and 54% had ≥1 euploid embryo (Supplemental Table 3, available online)). Older patients were more likely to have no embryos for biopsy ($P\leq.04$) and less likely to have ≥1 euploid embryo ($P\leq.006$).

A total of 332 patients (61% of those who thawed oocytes) underwent ≥1 transfer at our center before July 1, 2021 (Fig. 1). The median time between the first OC and transfer was 4.6 (IQR, 3.4–6.0) years. The median age at the first transfer was 42.8 (IQR, 41.2–44.5) years. Thirty-six percent of transfers were fresh, with 2% using rush PGT, and 64% of transfers were frozen, with 98% using PGT. Most patients (79%) underwent single embryo transfer. Ninety percent of transfers involved day 5 or 6 embryos; there were 25 day 3, 1 day 4, and 15 day 7 transfers. Eighty-seven percent of transfers involved blastocysts. Across all ages and transfer types, the IR, SABR, and LBR were 46%, 14%, and 46%, respectively. Among day 3 transfers, the IR, SABR, and LBR were 12%, 40%, and 12%, respectively. Among patients who thawed oocytes but did not undergo transfer, the most common reasons were no euploid embryos after PGT (45%) and embryo arrest (27%).

Table 1 displays the thaw and transfer outcomes by age at the first OC. Patients aged <38 years at the first OC thawed more oocytes and M2s than patients aged 38–40 and ≥41 years ($P\leq.003$); the numbers of oocytes ($P=.42$) and M2s ($P=.11$) thawed did not differ between patients aged 38–40 and ≥41 years. The oocyte and M2 survival rates were higher in patients aged 38–40 years than in patients aged <38 and >41 years ($P\leq.001$). Patients aged <38 years had more usable embryos ($P\leq.02$) and more euploid embryos among biopsied embryos ($P\leq.0001$) than patients aged 38–40 and ≥41 years. Patients aged 38–40 years had more euploid embryos among biopsied embryos than patients aged ≥41 years ($P\leq.0001$). Patients aged ≥41 years were less likely to undergo transfer than patients aged <38 years ($P\leq.02$) and transferred more embryos per transfer than patients aged <38 years (median, 1.5 vs. 1.0; $P\leq.008$). Patients aged <38 years were more likely to transfer a euploid than patients aged 38–40 and ≥41 years ($P\leq.0002$), and patients aged 38–40 years were more likely to transfer a euploid than patients aged ≥41 years ($P\leq.001$). The IR was higher in patients aged <38 years than in patients aged 38–40 and ≥41 years ($P\leq.004$). The SABR and LBR were not different between age groups.

Supplemental Figure 1(available online) displays the euploid and nonbiopsied embryo transfer outcomes. Among euploid transfers (n = 262), the IR, SABR, and LBR were 65%, 12%, and 55%, respectively. Among nonbiopsied transfers (n = 158), the IR, SABR, and LBR were 29%, 19%, and 31%.

There were 2 transfers of aneuploid embryos and 10 transfers of mosaic embryos. The aneuploid transfers did not result in pregnancy. Among mosaic transfers, 6 involved low levels, and 4 involved high levels; 5 resulted in LB (4 from

TABLE 1

Oocyte thaw and transfer outcomes by age at the first cryopreservation.

Age at the first cryopreservation	Median oocytes thawed per patient	Median M2s thawed per patient	Oocytes that survived/oocytes thawed	M2s that survived/M2s thawed	Usable embryos/2PNs	Euploid embryos/embryos biopsied for PGT	Patients with ≥1 transfer	Euploid embryo transfers/all embryo transfers	Median number of embryos per transfer	Implantation rate per number of embryos transferred	Spontaneous abortion rate per transfer	Live birth rate per transfer
All ages (n = 543)	14	12	79% (6,729/8,526)	80% (6,022/7,492)	43% (1,901/4,460)	31% (4,77/1,535)	61%	60% (262/434)	1	46% (257/556)	14% (32/232)	46% (200/434)
<38 y (n = 236)	15	14	77% (3,122/4,048)	79% (2,821/3,587)	45% (939/2084)	37% (298/806)	65%	72% (153/213)	1	55% (132/242)	14% (17/122)	49% (105/213)
38–40 y (n = 243)	13[a]	11[a]	82%[d] (2,932/3,593)	83%[d] (2,624/3,164)	41%[a] (805/1,954)	27%[a] (170/628)	60%	54%[a] (100/185)	1	42%[a] (102/245)	12% (11/91)	43% (80/185)
≥41 y (n = 64)	12.5[a]	9[a]	76% (675/885)	79% (577/741)	37%[a] (157/422)	9%[b] (9/101)	48%[a]	25%[b] (9/36)	1.5[c]	33%[a] (23/69)	21% (4/19)	42% (15/36)

Notes: A usable embryo was defined as an embryo that underwent fresh transfer, PGT, or cryopreservation. Transfer outcomes include 1 pregnancy with an unknown outcome (ongoing at last contact) as a live birth. 2PNs = embryos with 2-pronuclear fertilization; M2s = metaphase II oocytes; n = number of patients; PGT = preimplantation genetic testing.

[a] Significantly lower than in the <38 years age group ($P<.05$).
[b] Significantly lower than in the <38 and 38–40 years age groups ($P<.05$).
[c] Significantly higher than in the <38 years age group ($P<.05$).
[d] Significantly higher than in the <38 and ≥41 years age groups ($P<.05$).

Cascante. Fifteen years of oocyte thaw outcomes. Fertil Steril 2022.

low levels, 1 from a high level). Thus, among mosaic transfers, the IR, SABR, and LBR were 55%, 0, and 50%, respectively.

In our cohort, the FLBR per patient was 39%. The FLBR was not different on the basis of OC location (40% for patients who cryopreserved at our facility vs. 27% for patients who cryopreserved elsewhere, $P=.10$). Patients aged <38 years at the first OC had an FLBR of 51%, which was higher than those of patients aged 38–40 and ≥41 years at the first OC ($P\leq.009$) (Fig. 2). Patients who underwent 1 OC cycle thawed fewer M2s (11 vs. 14, $P\leq.00001$) and had a lower FLBR (37% vs. 49%, $P\leq.04$) than patients who underwent 2 OC cycles (Supplemental Table 4, available online)). Ultimately, 95 (40%), 75 (31%), and 14 (22%) patients aged <38, 38–40, and ≥41 years, respectively, at the first OC achieved LB. These percentages differ from the FLBRs because they include patients with remaining inventory. Two patients aged 43 years at OC had LBs from thawed oocytes, but OC at ≥44 years did not result any LBs (n = 0/5 patients).

When patients were stratified by number of M2s thawed (Table 2 and Supplemental Fig. 2, available online), those who thawed 0–9 M2s had a lower FLBR than those who thawed 10–14, 15–19, and ≥20 M2s ($P\leq.002$). Across all age groups, patients who thawed ≥20 M2s had a 58% FLBR. Patients aged <38 years who thawed ≥20 M2s had a 70% FLBR.

In a multiple logistic regression model controlling for age at the first OC, cryopreservation duration, and number of M2s thawed, age at the first OC (B = −0.120; adjusted odds ratio [aOR], 0.89; 95% confidence interval [CI], 0.82–0.96; $P\leq.004$) and the number of M2s thawed (B = 0.039; aOR, 1.04; 95% CI, 1.02–1.06; $P\leq.001$) were predictive of LB, but cryopreservation duration (B = −0.001; aOR, 1.00; 95% CI, 0.99–1.01; $P=.76$) was not. The Hosmer and Lemeshow test was nonsignificant for all analyses.

Our patients have 211 children (including 11 sets of twins and 1 set of triplets) from thawed oocytes. A total of 183 patients had ≥1 LB, and 24 patients had ≥2 LBs. One additional patient had an unknown birth outcome (pregnancy was ongoing at last contact).

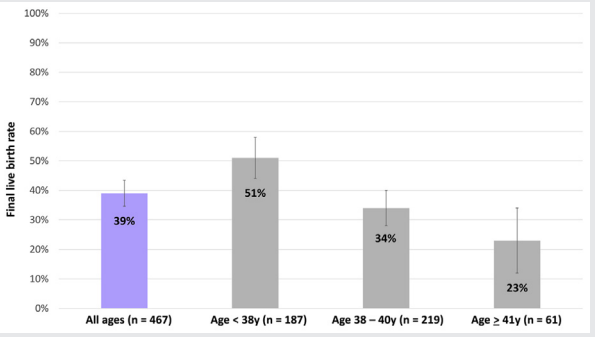
The numbers of patients with multiple LBs were 20 with 2 children (9 with twins and 11 with 2 singletons) and 4 with 3 children (1 with triplets, 2 with twins followed by a singleton, and 1 with 3 singletons).

As of July 1, 2021, 173 patients (32%) have remaining inventory. Thirty-eight patients have remaining oocytes, 108 patients have remaining embryos, and 27 patients have a combination of both. Among patients with remaining embryos, 118 have euploid embryos, and 17 have embryos with unknown ploidy. Moreover, 42% of patients with remaining inventory do not have an LB from OC owing to a transfer at our center.

DISCUSSION

As OC utilization increases, outcome data should be published so patients can make informed decisions about the value of OC in securing their reproductive futures. To our

FIGURE 2



Final live birth rate per patient by age at the first cryopreservation; 95% confidence intervals are shown. Live births include 1 pregnancy with an unknown outcome (ongoing at last contact). The median number of oocyte cryopreservation cycles for each group was 1. n = number of patients.

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knowledge, this is the largest US report of thaw outcomes from OC performed for age-related fertility decline. Our patients underwent a median of 1 OC cycle, which yielded a 39% FLBR per patient. This FLBR is comparable with the LBR of women aged 38 years (median age at the first OC in this cohort) who underwent fresh IVF (32) and LBRs from OC at other high-volume centers (19, 24).

The median age at thaw was 42.6 years, an age at which in vivo oocytes rarely result in pregnancy. Most patients aged <38 years at OC or who thawed ≥20 M2s had ≥1 LB from OC. Unsurprisingly, multiple logistic regression demonstrated that age at OC and the number of M2s thawed were predictive of LB. Importantly, cryopreservation duration was not predictive of LB.

The median age at the first OC in this cohort (38 years) was older than the optimal age for OC. Most physicians now recommend OC at ≤35 years. Most patients in this cohort cryopreserved oocytes between 2005 and 2012. During this time, OC was experimental and was not covered by insurance or employers. Thus, several patients who underwent OC during this period were concerned about their current, rather than their future, reproductive potential. In 2020, the median age of OC patients at our center was 35 years, and 44% of OC patients were <35 years old. Because age at OC is predictive of LB, the FLBR among patients aged <35 years is likely higher than our reported FLBR. Our cohort did not contain enough patients aged <35 years to meaningfully examine the FLBR in this subgroup. Future studies should determine the optimal age for OC.

In contrast to previous studies (19), we report 14 LBs from patients who underwent OC at the age of 41–43 years. LB from OC at this age is unlikely, but still possible. Importantly, we do not report any LBs from OC at ≥44 years.

Patients who underwent 1 OC cycle had a lower FLBR than patients who underwent 2 OC cycles, suggesting that a second OC cycle improves the likelihood of LB. The number of patients with ≥3 OC cycles was small (n = 34), making it difficult to interpret outcomes in this subgroup; however, the FLBR in this subgroup was not higher than the FLBR in the 1 or 2 OC cycle subgroups. Patients who underwent ≥3 OC cycles were older but did not thaw more M2s, than patients who underwent 2 OC cycles. Furthermore, patients who underwent ≥3 OC cycles had fewer M2s retrieved per OC cycle than patients who underwent 1 or 2 OC cycles. Thus, we believe that patients in our cohort who underwent ≥3 OC cycles have poor prognostic factors. If these patients had similar demographics to patients in other subgroups, we expect that a third OC cycle would have increased FLBR.

Importantly, 73 patients in our cohort without LB from OC have remaining inventory. Our FLBR may be an underestimate because it does not include these patients. For example, if we assume that these patients each have 1 euploid embryo and 55% achieve LB after transferring that embryo, our FLBR would increase to 43%. Further research should explore why several patients have remaining inventory, despite not achieving LB and ≥6 months elapsing since thaw.

Twenty-four patients had ≥2 LBs from OC, and 14 patients had ≥2 transfers, which resulted in LB. Thus, OC can help patients achieve their ideal family size, even if ≥1 child. Interestingly, most patients (55%) with ≥1 LB from OC have remaining inventory. Future studies should determine how many of these patients will return to expand their families and how many will be successful. Forthcoming research should also examine the rate of discarded/unused reproductive tissue after oocyte thaw.

TABLE 2

Final live birth rate per patient by age at the first cryopreservation and number of M2s thawed.

Age at the first cryopreservation	0–9 M2s thawed	10–14 M2s thawed	15–19 M2s thawed	≥20 M2s thawed
All ages (n = 467)	24% (43/176)	45%[a] (54/120)	44%[a] (38/87)	58%[a] (49/84)
<38 y (n = 187)	36% (16/45)	54% (32/59)	41% (16/39)	70%[b] (31/44)
38–40 y (n = 219)	23% (23/100)	37%[a] (18/49)	49%[a] (19/39)	48%[a] (15/31)
≥41 y (n = 61)	13%[c] (4/31)	33% (4/12)	33% (3/9)	33%[c] (3/9)

Notes: Live births include 1 pregnancy with an unknown outcome (ongoing at last contact). M2s = metaphase II oocytes; n = number of patients.
[a] Significantly higher than in the 0–9 M2s thawed group ($P < .05$).
[b] Significantly higher than in the 0–9 and 15–19 M2s thawed groups ($P < .05$).
[c] Significantly lower than in the ≤38 years age group ($P < .05$).

Cascante. Fifteen years of oocyte thaw outcomes. Fertil Steril 2022.

Cryopreserved M1s are less likely to survive or form usable embryos than cryopreserved M2s; however, 1 LB resulted from a thawed M1. Thus, M1 cryopreservation may be a viable option for patients with a low M2 yield. Further discussion of M1 cryopreservation is beyond the scope of this study but is being researched at our center. To our knowledge, this is the first report of an LB from a cryopreserved M1.

This study's major strength is that it reports real clinical outcomes, rather than modeled data, which are most of what has been published on OC outcomes. We provided an FLBR per patient—the most helpful parameter when counseling patients pursuing OC. In Table 2, we stratified the FLBR by age at the first OC and the number of M2s thawed; these real clinical outcomes can help physicians provide personalized patient counseling. These outcomes not only provide patients with realistic expectations but can also assist them in deciding whether to pursue additional OC cycles to obtain more oocytes.

Our FLBR for patients who thawed 0–14 M2s was comparable Brigham and Women's Hospital's model (33), but our FLBRs for patients who thawed more M2s were lower than the model's. The model predicted LBRs were above the 95% CIs of our FLBRs for patients with a median age of 38 years who thawed 15–19 or ≥20 M2s. Therefore, OC models should be used cautiously because they likely overestimate the LBRs for certain patients. We suggest that actual clinical outcomes be used for patient counseling.

This study is limited by the relatively small number of patients available for inclusion. This reflects the time lag between OC and thaw and the low utilization rate of cryopreserved oocytes (18, 19). Consequently, finding significance when stratifying patients by age, number of oocytes thawed, or other parameters is difficult. Our 95% CIs for the FLBR at various ages and numbers of M2s thawed were wide, reflecting the small sample size in each subgroup. Larger studies are necessary to more accurately detect differences in the FLBR on the basis of age and the number of oocytes thawed.

Thaw approaches varied widely among our patients. Some split oocytes from 1 OC into multiple thaws, whereas others combined oocytes from multiple OCs into 1 thaw. Some planned for fresh transfer, whereas others pursued PGT. Identifying an ideal approach to thawing is difficult given the diverse strategies in this small cohort. This topic should be explored as more women return to use their oocytes.

There have been several studies and trials evaluating the utility and efficacy of PGT for transfer success and cumulative LBR (34–39); however, all studies to date have focused on fresh oocytes that have not undergone freezing. There are not any trials exploring the use of PGT with embryos created from thawed oocytes. Thus, it is unknown whether PGT improves the LBR in our unique population of patients using embryos created from thawed oocytes. Further studies are needed to answer this question.

Our data are from a single high-volume urban university-affiliated institution and may not be generalizable to other centers. Additional studies from a variety of geographic locations and center types are necessary.

In conclusion, autologous OC is a viable fertility preservation method that results in LB for 39% of patients. Most patients who were <38 years at OC or who thawed ≥20 M2s had a child from oocyte thaw. This study is the largest US report of thaw outcomes from OC performed for age-related fertility decline and provides important insight into OC outcomes. Our results provide realistic expectations for those considering OC and demonstrate that OC empowers women with reproductive autonomy.

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REFERENCES

1. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: final data for 2019. Natl Vital Stat Rep 2021;70:1–51.
2. Goold I, Savulescu J. In favour of freezing eggs for non-medical reasons. Bioethics 2009;23:47–58.
3. Lewis EI, Missmer SA, Farland LV, Ginsburg ES. Public support in the United States for elective oocyte cryopreservation. Fertil Steril 2016;106:1183–9.
4. American College Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. Committee Opinion No. 589. Fertil Steril 2014;101:633–4.
5. Habbema JD, Eijkemans MJ, Leridon H, te Velde ER. Realizing a desired family size: when should couples start? Hum Reprod 2015;30:2215–21.
6. te Velde E, Habbema D, Leridon H, Eijkemans M. The effect of postponement of first motherhood on permanent involuntary childlessness and total fertility rate in six European countries since the 1970s. Hum Reprod 2012;27:1179–83.
7. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online 2009;18:769–76.
8. Grifo JA, Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. Fertil Steril 2010;93:391–6.
9. Hodes-Wertz B, Noyes N, Mullin C, McCaffrey C, Grifo JA. Retrospective analysis of outcomes following transfer of previously cryopreserved oocytes, pronuclear zygotes and supernumerary blastocysts. Reprod Biomed Online 2011;23:118–23.
10. Goldman KN, Noyes NL, Knopman JM, McCaffrey C, Grifo JA. Oocyte efficiency: does live birth rate differ when analyzing cryopreserved and fresh oocytes on a per-oocyte basis? Fertil Steril 2013;100:712–7.
11. Goldman KN, Kramer Y, Hodes-Wertz B, Noyes N, McCaffrey C, Grifo JA. Long-term cryopreservation of human oocytes does not increase embryonic aneuploidy. Fertil Steril 2015;103:662–8.
12. Levi-Setti PE, Borini A, Patrizio P, Bolli S, Vigiliano V, De Luca R, et al. ART results with frozen oocytes: data from the Italian ART registry (2005-2013). J Assist Reprod Genet 2016;33:123–8.
13. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril 2013;99:37–43.
14. Johnston M, Richings NM, Leung A, Sakkas D, Catt S. A major increase in oocyte cryopreservation cycles in the USA, Australia and New Zealand since

2010 is highlighted by younger women but a need for standardized data collection. Hum Reprod 2021;36:624–35.
15. Hodes-Wertz B, Druckenmiller S, Smith M, Noyes N. What do reproductive-age women who undergo oocyte cryopreservation think about the process as a means to preserve fertility? Fertil Steril 2013;100:1343–9.
16. Hammarberg K, Kirkman M, Pritchard N, Hickey M, Peate M, McBain J, et al. Reproductive experiences of women who cryopreserved oocytes for non-medical reasons. Hum Reprod 2017;32:575–81.
17. Greenwood EA, Pasch LA, Hastie J, Cedars MI, Huddleston HG. To freeze or not to freeze: decision regret and satisfaction following elective oocyte cryopreservation. Fertil Steril 2018;109:1097–10104.e1.
18. Blakemore JK, Grifo JA, DeVore SM, Hodes-Wertz B, Berkeley AS. Planned oocyte cryopreservation-10-15-year follow-up: return rates and cycle outcomes. Fertil Steril 2021;115:1511–20.
19. Leung AQ, Baker K, Vaughan D, Shah JS, Korkidakis A, Ryley DA, et al. Clinical outcomes and utilization from over a decade of planned oocyte cryopreservation. Reprod Biomed Online 2021;43:671–9.
20. Human Fertilisation and Embryology Authority. Egg freezing in fertility treatment: trends and figures: 2010-2016. London, 2018.
21. Kawwass JF, Crawford S, Hipp HS. Frozen eggs: national autologous oocyte thaw outcomes. Fertil Steril 2021;116:1077–84.
22. Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. Fertil Steril 2016;105:459–66.e2.
23. Cobo A, Garcia-Velasco JA, Coello A, Domingo J, Pellicer A, Remohi J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril 2016;105:755–64.e8.
24. Cobo A, García-Velasco JA, Remohí J, Pellicer A. Oocyte vitrification for fertility preservation for both medical and nonmedical reasons. Fertil Steril 2021;115:1091–101.
25. Gurtin ZB, Morgan L, O'Rourke D, Wang J, Ahuja K. For whom the egg thaws: insights from an analysis of 10 years of frozen egg thaw data from two UK clinics, 2008-2017. J Assist Reprod Genet 2019;36:1069–80.
26. Wennberg AL, Schildauer K, Brannstrom M. Elective oocyte freezing for nonmedical reasons: a 6-year report on utilization and in vitro fertilization results from a Swedish center. Acta Obstet Gynecol Scand 2019;98:1429–34.
27. Garcia-Velasco JA, Domingo J, Cobo A, Martinez M, Carmona L, Pellicer A. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. Fertil Steril 2013;99:1994–9.
28. Goldman RH, Racowsky C, Farland LV, Munne S, Ribustello L, Fox JH. Predicting the likelihood of live birth for elective oocyte cryopreservation: a counseling tool for physicians and patients. Hum Reprod 2017;32:853–9.
29. Lockwood GM. Social egg freezing: the prospect of reproductive "immortality" or a dangerous delusion? Reprod Biomed Online 2011;23:334–40.
30. Baylis F. Left out in the cold: arguments against non-medical oocyte cryopreservation. J Obstet Gynaecol Can 2015;37:64–7.
31. Ethics Committee of the American Society for Reproductive Medicine. Planned oocyte cryopreservation for women seeking to preserve future reproductive potential: an Ethics Committee opinion. Fertil Steril 2018;110:1022–8.
32. Society for assisted reproductive technology. Final national summary report for 2018. Available at: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2018. Accessed May 2, 2022.
33. Goldman RH, Fox JH. BWH egg freezing counseling tool (EFCT) - MDCalc. Available at: https://www.mdcalc.com/bwh-egg-freezing-counseling-tool-efct. Accessed May 2, 2022.
34. Yan J, Qin Y, Zhao H, Sun Y, Gong F, Li R, et al. Live birth with or without preimplantation genetic testing for aneuploidy. N Engl J Med 2021;385:2047–58.
35. Munné S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril 2019;112:1071–9.e7.
36. Cornelisse S, Zagers M, Kostova E, Fleischer K, van Wely M, Mastenbroek S. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. Cochrane Database Syst Rev 2020;9:1–77, Cd005291.
37. Scott RT Jr, Upham KM, Forman EJ, Hong KH, Scott KL, Taylor D, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril 2013;100:697–703.
38. Forman EJ, Tao X, Ferry KM, Taylor D, Treff NR, Scott RT Jr. Single embryo transfer with comprehensive chromosome screening results in improved ongoing pregnancy rates and decreased miscarriage rates. Hum Reprod 2012;27:1217–22.
39. Yang Z, Liu J, Collins GS, Salem SA, Liu X, Lyle SS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet 2012;5:1–8.

Quince años de resultados de descongelación de ovocitos autólogos de un gran centro de fertilidad con sede universitaria.

Objetivo: Revisar los resultados de las pacientes que se sometieron a descongelación autóloga de ovocitos después de la criopreservación planificada de ovocitos.

Diseño: Estudio de cohorte retrospectivo.

Lugar: Gran centro de fertilidad afiliado a una universidad urbana.

Paciente(s): Todos los pacientes que se sometieron al menos 1 ciclo de descongelación autóloga de ovocitos antes del 31 de diciembre de 2020.

Intervención(es): Ninguna.

Principales medidas de resultados: el resultado primario fue la tasa final de nacido vivo (FLBR) por paciente, y solo fueron incluidos los pacientes que tuvieron un nacido vivo (LB) o consumieron todo el inventario restante (ovocitos criopreservados y embriones euploides/no probados/sin resultado resultantes). Los resultados secundarios fueron los resultados de laboratorio y las tasas de LB por transferencia.

Resultado(s): Un total de 543 pacientes se sometieron a 800 criopreservaciones de ovocitos, 605 descongelaciones y 436 transferencias. La mediana de edad en la primera criopreservación fue de 38,3 años. La mediana de tiempo entre la primera criopreservación y la descongelación fue de 4,2 años. La mediana del número de ovocitos y ovocitos en metafase II (M2) descongelados por paciente fue de 14 y 12, respectivamente. La supervivencia global de todos los ovocitos descongelados fue del 79%. De todos los pacientes, el 61% tuvo al menos una transferencia. Entre las transferencias euploides (n = 262) y no biopsiadas (n = 158), las tasas de LB por transferencia fueron del 55% y el 31%, respectivamente. El FLBR por paciente fue del 39%. La edad en la crioconservación y el número de ovocitos MII descongelados fueron predictivos de LB; el FLBR por paciente fue >50% para pacientes de <38 años en la crioconservación o que descongelaron al menos 20 ovocitos M II. Un total de 173 pacientes (32%) tienen todavía ovocitos criopreservados.

Conclusión(es): La descongelación de ovocitos autólogos dio como resultado un FLBR del 39% por paciente, que es comparable con los resultados de la fertilización in vitro de la misma edad. Son necesarios estudios con cohortes de mayor tamaño.