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Planned Oocyte Cryopreservation in Women with Diminished Ovarian Reserve and Advanced Reproductive Age: an 11-Year Follow-up

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Planned Oocyte Cryopreservation in Women with Diminished Ovarian Reserve and Advanced Reproductive Age: an 11-Year Follow-up

Capsule summary

In this 11-year cohort of 1121 women with diminished ovarian reserve and/or advanced reproductive age, most froze too few oocytes to meet age-specific live birth benchmarks. After warming, live birth per woman was 30% when oocytes were frozen before age 38 years versus 5.1% at 38 years or older.

Abstract

Purpose: To assess patient and cycle characteristics, trends in OC, utilization, and reproductive outcomes after warming among women with diminished ovarian reserve (DOR) and/or advanced reproductive age (ARA) undergoing planned OC.

Methods: Single-center retrospective cohort study of 1121 women with DOR and/or ARA who underwent 1642 OC cycles at a private tertiary center between October 2014 and December 2025. Outcomes included annual trends, oocyte yield by age, achievement of age-specific oocyte benchmarks, and reproductive outcomes after warming, stratified by age at OC (<38 vs ≥38 years).

Results: The number of women undergoing OC and OC cycles more than doubled over 11 years, while mean age at OC declined by 0.3 years per year (P=0.001). Below age 38 years, oocyte yield and cycles per woman were stable; thereafter, each additional year was associated with 0.6 fewer

mature oocytes cryopreserved (P<0.001) without more cycles. Most women did not reach the oocyte number associated with an approximately 50% chance of live birth (LB); only 3.9% achieved these benchmarks. Sixty-three women (5.6%) returned for utilization; 27.0% did not reach embryo transfer. Among 15 clinical pregnancies, 46.7% miscarried, resulting in eight LBs; live birth per woman was 30% (6/20) at <38 versus 5.1% (2/39) at ≥38 years.

Conclusions: Women with DOR and/or ARA should receive individualized, transparent counseling on expected oocyte yield, cancellation rates, the need for multiple cycles, and age-specific live birth probabilities. Younger age at OC improves outcomes after warming, but recommended oocyte targets are difficult to reach in clinical practice.

Keywords

Planned oocyte cryopreservation, diminished ovarian reserve, egg freezing, fertility preservation, advanced reproductive age

Introduction

Total fertility rates have declined globally, from 4.84 in 1950 to 2.23 in 2021, and are projected to continue decreasing to 1.59 by 2100 [1]. Key drivers of this demographic shift include increased educational attainment and workforce participation among women, wider access to family planning, rising economic costs of childcare, and a broader societal trend toward delayed childbearing [2].

As more women postpone childbearing, they are likely to encounter age-related fertility decline, characterized by decrease in both oocyte quality and quantity, diminished fertility potential, and increased aneuploidy rates [3–5]. Another group at risk of reduced fertility potential includes women with diminished ovarian reserve (DOR), who may face premature ovarian insufficiency (POI) or early menopause at a younger age.

International guidelines recommend that women with risk factors for POI be identified and counselled regarding POI risk and fertility preservation [6]. In this context, fertility awareness has become increasingly important, given that age and ovarian reserve are among the most important predictors of live birth [3–5].

Planned oocyte cryopreservation (OC) is currently the most widely used form of fertility preservation and has increased steadily since the American Society of Reproductive Medicine (ASRM) removed the "experimental" label from OC in 2012 [7]. Despite this increase, the utilization rates remain low [2,8,9]. Counseling should include realistic expectations regarding the number of mature oocytes likely to be obtained, the number of cycles required, the probability of returning to use cryopreserved oocytes, and expected reproductive outcomes after warming.

Available data suggest that age at cryopreservation and the number of mature oocytes frozen are among the most important determinants of subsequent reproductive success [5,10]. Studies of women who returned to use their cryopreserved oocytes after planned OC suggest that, to obtain one euploid embryo or achieve an estimated 50-60% chance of live birth, women younger than 35 years require at least 12 mature oocytes. For comparable outcomes, women aged 35-37, 38-40, and older than 40 require more than 15, 20, and 25 mature oocytes, respectively [11,12]. Among women younger than 38 years with normal ovarian reserve, one or two OC cycles may often be sufficient to achieve these goals [2,13,14]. In contrast, women with DOR or advanced reproductive age frequently require multiple stimulation cycles and may still be unable to reach age specific oocyte thresholds [15,16].

Most published data on planned OC, including cycle characteristics, return rates, and reproductive outcomes, are derived predominantly from women with normal ovarian reserve, often single women in their late thirties with an average of 9 to 19 retrieved oocytes per woman [17,18]. However, not all women undergoing OC achieve these oocyte numbers, especially women with DOR or advanced reproductive age [9]. In a recent study using the SART database from 2014 to 2020, 13.5% of women undergoing planned OC had poor ovarian response (POR), defined as < 5 oocytes cryopreserved [9]. These women have lower chances of live birth and often require more stimulation cycles than similarly aged women with normal ovarian reserve [5]. Nevertheless, evidence regarding cycle characteristics, utilization, and reproductive outcomes after OC in this subgroup remains limited [9]. Approximately one in five women undergoing planned OC has been reported to be a low responder [19], and data on clinical outcomes after OC at advanced reproductive age remain scarce [20].

Türkiye has a uniquely restrictive regulatory framework that limits planned OC to specific indications, including DOR and risk of early menopause. Until 2014, OC was legal in Türkiye only for medical indications. Following new ART regulations introduced in November 2014, non-medical OC became legal for nulliparous women with DOR or a family history of early menopause. In clinical practice, women of advanced reproductive age who face age-related fertility decline may also benefit from OC under this framework. Of note, Turkish legislation permits in vitro fertilization (IVF) treatment only for married women.

This regulatory setting has resulted in the accumulation of a large and distinctive cohort of women undergoing planned OC primarily because of DOR and/or advanced reproductive age-precisely the population for whom evidence remains limited and counseling is most challenging. Therefore, the present study aimed to assess patient and cycle characteristics, analyze trends in OC and warming, and evaluate utilization, and reproductive outcomes after oocyte warming in this underrepresented cohort.

Materials and methods

Study design and study population

This single-center retrospective cohort study included data from ------ Hospital. We retrospectively reviewed the electronic IVF database and patient records of those women who underwent oocyte retrieval for OC between October 2014 and December 2025. For women who had undergone OC at other centres before referral, these cycles (n=18) were recorded only to determine the total number of OC cycles per woman; oocyte yield data from these cycles were not available, and they were not included in the 1642 OC cycles analysed.

Due to the lack of standardized criteria for DOR in Turkish IVF legislation, and no clear consensus on the definition of DOR in the literature, the diagnosis of DOR relies on clinic or physician-specific parameters. Therefore, we included women who underwent OC for DOR with ≤10 retrieved mature oocytes and/or serum AMH levels ≤1.3 ng/mL regardless of their age, or who were aged ≥38 years regardless of their ovarian reserve. Young patients with a family history of early menopause who had normal or high ovarian reserve and cancer patients who had undergone OC were excluded.

Controlled ovarian stimulation protocols

Ovarian stimulation protocols and Gonadotropin doses were determined by the treating physician. The GnRH antagonist protocol was the most used protocol until 2020. Due to unavailability of GnRH antagonists in Turkiye during the COVID-19 pandemic, progestin primed ovarian stimulation became the standard for ovarian stimulation in IVF and OC cycles. In women with severe DOR or POI, mild ovarian stimulation with clomiphene or aromatase inhibitors, DuoStim or natural/modified natural cycle IVF were also used. Oocyte retrieval was performed by transvaginal ultrasound-guided follicular aspiration under intravenous sedation anesthesia.

OC, warming, in vitro fertilization and embryo transfer procedures

Cumulus oocyte complexes (COC) were denuded 2 – 4 hours after retrieval and metaphase II (MII) oocytes were vitrified, with a maximum of 3 oocytes per straw. For vitrification and warming our lab used Kitazato materials and tools. Cryotop vitrification method has been explained elsewhere [21–24].

In warming cycles, surviving oocytes were cultured for 2–3 hours under controlled conditions before intracytoplasmic sperm injection (ICSI). After ICSI, oocytes were placed in the Embryoscope (Vitrolife). Embryo transfers were done either on cleavage or blastocyst stage.

For transfer of embryos derived from cryopreserved oocytes, endometrial preparation was performed using either a programmed or a modified natural cycle at the discretion of the treating physician.

Data and Statistical analysis

Descriptive statistics were used to summarize patient demographics and cycle characteristics. For age-stratified analyses, women were grouped as <38 and ≥38 years.

Annual trends in new women undergoing OC, number of OC cycles, and mean age at first OC were presented graphically and assessed using linear regression, with year entered as a continuous independent variable.

Mean cumulative numbers of COCs retrieved, MII oocytes cryopreserved, and cryopreservation cycles per woman were plotted across age categories. Associations with age were assessed using separate univariable linear regression models, with age at first cryopreservation cycle entered as a continuous variable. Because inclusion criteria differed below and above age 38, analyses were performed in the overall cohort and separately for women aged <38 and ≥38 years.

Results are presented as unstandardized regression coefficients (B) with 95% confidence intervals (CI), R^2 values, and p-values. Statistical analyses were performed using IBM SPSS Statistics (Version 27, IBM Corp, Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

We also assessed whether women cryopreserved sufficient oocytes to achieve age-based OC goals to achieve 50% chance of live birth.

The distribution of women who returned for warming was analyzed according to age at cryopreservation and warming and presented as bar graphs. The interval between OC and warming was examined by age at OC. Reproductive outcomes were evaluated across all warming cycles. Reproductive outcomes after warming are presented descriptively for women aged <38 and ≥38 years at OC because of the small sample size.

Results

Sociodemographic and OC cycle characteristics of the study population

This study reviewed 1642 OC cycles in 1121 women. The mean age at OC was 37.6±5.0 years, and 60% of women were aged ≥38 years at the time of cryopreservation. The distribution of women and OC cycles by age group is presented in Fig. 1. The mean AMH level, mean numbers of total and mature oocytes per cycle and per women for the overall cohort and for women <38 and ≥38 years are presented in Table 1.

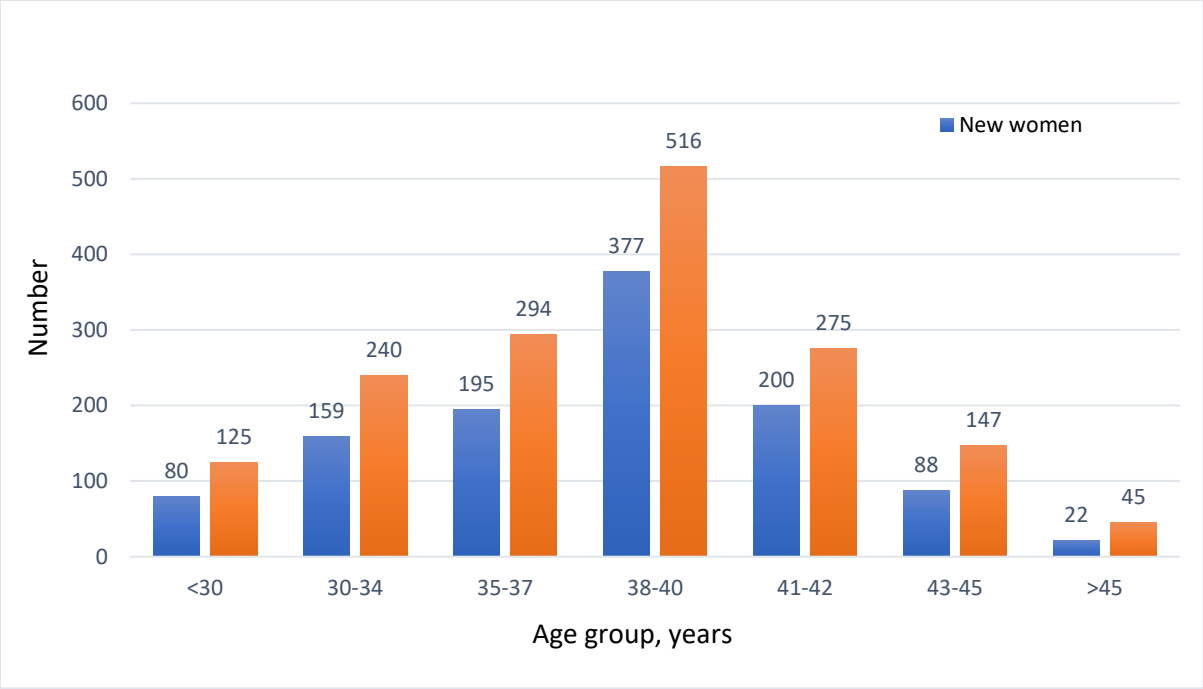


Fig. 1 Distribution of women and oocyte cryopreservation cycles by age group. The bars show the number of new women and the total number of oocyte cryopreservation cycles in each age group

Table 1 Demographics and cycle characteristics of the study population

	Overall cohort 1121 women/1642 cycles	**Women aged < 38 years with DOR 434 women/ 661 cycles**	**Women aged ≥38 years, regardless of ovarian reserve 687 women/981 cycles**
Age at first OC, years	37.7 ± 5.0	32.9 ± 4.1	40.8 ± 2.3
AMH, ng/ml	0.8 ± 0.8	0.6 ± 0.4	0.9 ± 1.0
Number of cycles per woman	1.5 ± 1.0	1.6 ± 1.0	1.4 ± 1.0
Retrieved oocytes per cycle	6.2 ± 4.9	5.8 ± 3.7	6.6 ± 5.4
Cryopreserved MII oocytes per cycle	4.6 ± 3.8	4.1 ± 2.8	4.8 ± 4.4
Total retrieved oocytes per woman	9.2 ± 6.2	9.2 ± 6.1	9.2 ± 6.4
Total cryopreserved MII oocytes per woman	6.7 ± 4.9	6.6 ± 4.8	6.8 ± 5.1

Values are presented as mean ± SD. AMH, anti-Müllerian hormone; DOR, diminished ovarian reserve; MII, metaphase II; OC, oocyte cryopreservation; SD, standard deviation.

Of the 1642 OC cycles, 236 (14.4%) were cancelled at oocyte retrieval. Cancellations were because no oocytes were retrieved in 61 cycles (3.7%) and no mature oocytes were obtained in 175 cycles (10.7%).

Trends in OC and return

Fig. 2 illustrates number of new women undergoing OC, annual OC cycles, and mean age at first OC. The low number in 2014 reflects inclusion of only 2 months of data and was therefore excluded from the trend analyses. The mean annual numbers of women and OC cycles followed similar trends up to 2021 and gradually increased afterwards. Linear regression analysis demonstrated a significant increase in both number of women (β=9.4 per year, R^2=0.65, p=0.003) and OC cycles (β=13.7 per year, R^2=0.71, p=0.001). Concurrently, mean age at first OC decreased significantly over the study period, with an average decline of 0.32 years per year (p=0.001) (Table 2).

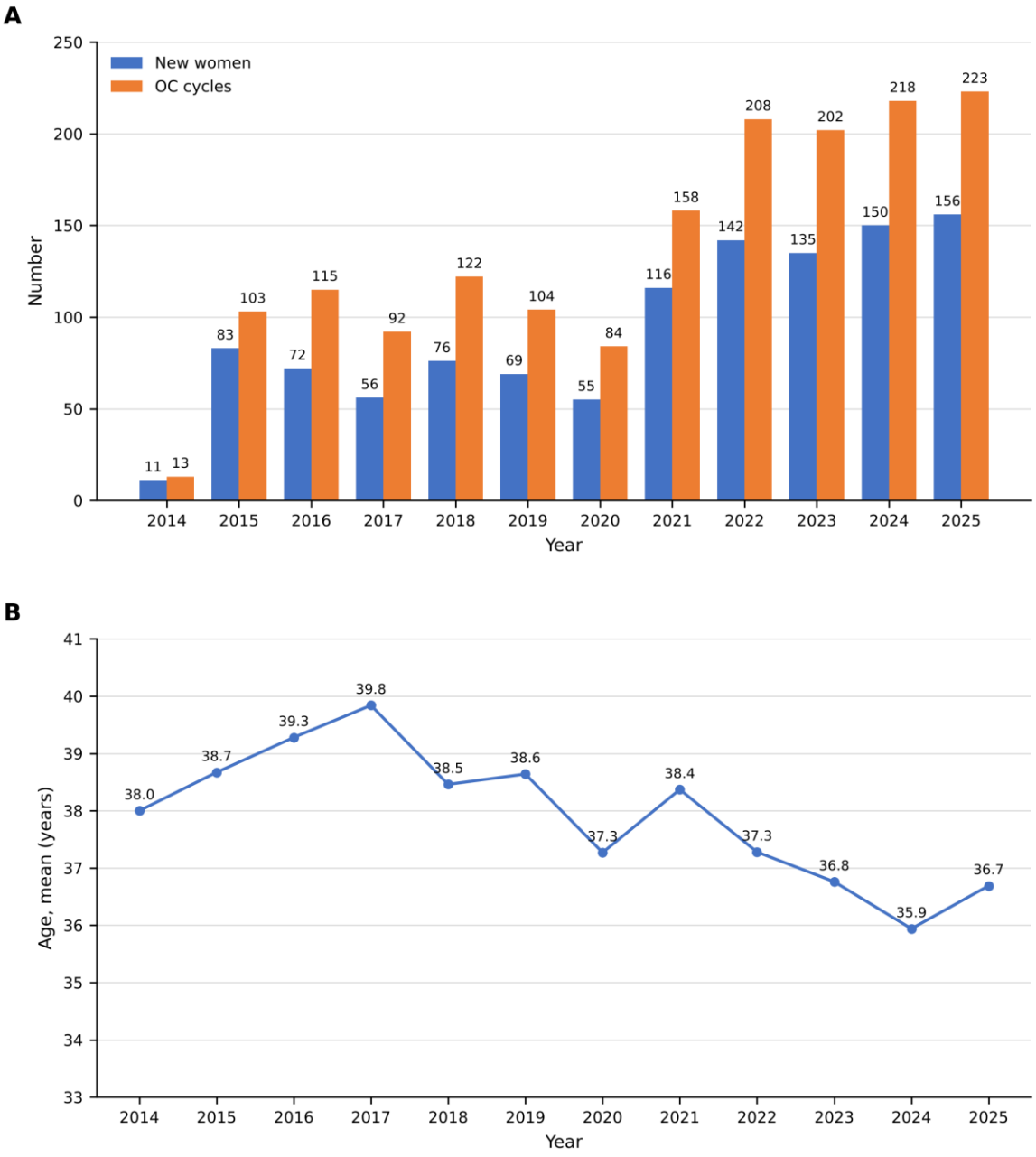


Fig. 2 Annual trends in oocyte cryopreservation. (A) Annual number of new women presenting for oocyte cryopreservation and total number of oocyte cryopreservation cycles. (B) Mean age of new women at their first oocyte cryopreservation cycle in each year. OC, oocyte cryopreservation

Table 2 Linear regression analysis of annual trends for age, number of new women and oocyte cryopreservation cycles

Outcome	B per year	95% CI	P value	R^2

New women	9.436	4.171 to 14.702	0.003	0.646
OC cycle	13.664	7.018 to 20.309	0.001	0.706
Mean age at first OC	−0.316	−0.453 to −0.179	0.001	0.752

Values represent unstandardized coefficients from linear regression models with calendar year entered as a continuous independent variable. New women count was assigned according to the year of each woman's first OC cycle. Mean age was calculated using age at first OC. Annual OC cycle count was calculated from cycle-level data, other outcomes were calculated from patient level data. CI, confidence interval; OC, oocyte cryopreservation; R^2, coefficient of determination.

Fig. 3 shows retrieved and cryopreserved mature oocytes, and OC cycles attempted by age category. Cumulative COC and mature oocyte yields were relatively stable below age 38, peaked at ages 38-40, and declined thereafter, whereas the number of cycles per woman remained stable across age categories (β=-0.011, R^2=0.003, p=0.074). In the overall cohort, increasing age was associated with small reductions in cumulative COCs (β=-0.11, R^2=0.007, p=0.006) and mature oocytes cryopreserved (β=-0.070, R^2=0.005, p=0.022)., but not with the number of cryopreservation cycles per woman (β=-0.01, R^2=0.003, p=0.074). Among women aged <38 years, age was not associated with any outcome. In contrast, among women aged ≥38, each additional year of age was associated with 0.76 fewer COCs and 0.57 fewer mature oocytes cryopreserved per woman (p<0.001) (Table 3).

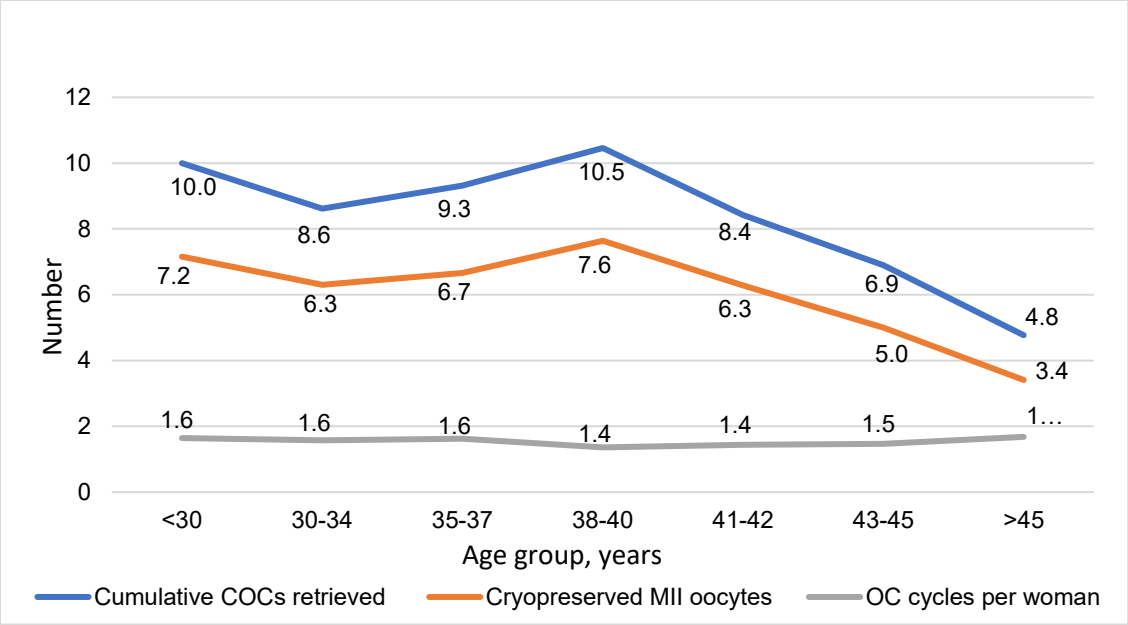


Fig. 3 Oocyte cryopreservation cycle outcome per woman by age group. Mean cumulative numbers of COCs retrieved, mature oocytes cryopreserved, and cryopreservation cycles per woman according to age categories. Cumulative oocyte yield peaked at ages 38-40 and declined thereafter, while cycle number remained stable. COC, cumulus-oocyte complex; MII, metaphase II, OC, oocyte cryopreservation

Table 3 Linear regression analyses of age in relation to cumulative oocyte yield and number of cryopreservation cycles per woman

Outcome	Age	B per 1-year increase in age	95% CI	Standardized β	P value	R^2
Cumulative COCs retrieved per woman	Overall cohort	−0.108	−0.184 to −0.032	−0.083	0.006	0.007
	<38 years	−0.055	−0.196 to 0.087	−0.037	0.446	0.001
	≥38 years	−0.764	−0.976 to −0.551	−0.260	<0.001	0.068
Cumulative mature oocytes cryopreserved per woman	Overall cohort	−0.070	−0.130 to −0.010	−0.068	0.022	0.005
	<38 years	−0.040	−0.150 to 0.070	−0.034	0.474	0.001
	≥38 years	−0.567	−0.736 to −0.397	−0.244	<0.001	0.059
Cryopreservation cycles per woman	Overall cohort	−0.011	−0.023 to 0.001	−0.053	0.074	0.003
	<38 years	<0.001	−0.023 to 0.024	0.002	0.974	<0.001
	≥38 years	0.033	−0.002 to 0.067	0.071	0.062	0.005

Values were derived from separate univariable linear regression models with age at the first OC cycle entered as a continuous predictor. B represents the mean change in the outcome associated with a 1-year increase in age. Analyses were performed in the overall cohort and separately in women aged <38 and ≥38 years. CI, confidence interval; COC, cumulus-oocyte complex; OC, oocyte cryopreservation.

Return for utilization of cryopreserved oocytes was 5.6%. The age distribution of these women at the time of OC and at the time of warming is given in Fig. 4. Only four women were aged <38 years at warming. The mean interval between OC and utilization was 3.8±2.1 years. This interval decreased with advancing age at cryopreservation, from a mean of 5.2 years in women aged <35 years to 2.0 years in those aged >45 years (Fig. 4).

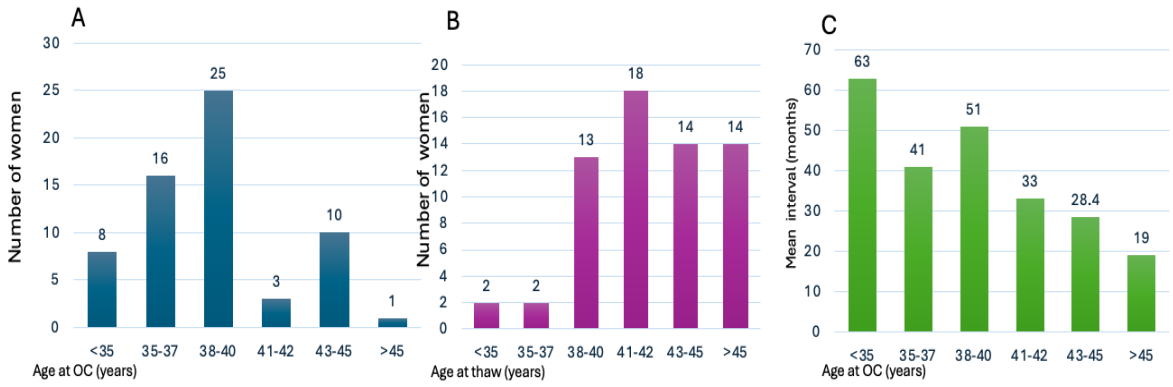


Fig. 4 Age distribution and thaw interval among women returning for oocyte thawing. (A) Age at oocyte cryopreservation. (B) Age at thaw. (C) Mean interval between oocyte cryopreservation and thaw, in months, by age at oocyte cryopreservation. OC, oocyte cryopreservation

Number of OC cycles undertaken, average number of oocytes frozen per cycle and per patient

Among the 1121 women, 71%, 18%, 6%, and 5% underwent 1, 2, 3, and >3 OC cycles, respectively, including cycles performed at other centres before referral. Age at first OC cycle, mean number of mature oocytes frozen per cycle and patient based on the number of OC cycles are presented in Table 4.

Table 4 Cycle outcomes based on the number of OC cycles per woman

Number of OC cycles completed per woman[a]	Women, n (%)	Age at first OC cycle, years	Mean MII oocytes cryopreserved per cycle	Mean MII oocytes cryopreserved per woman
1	793 (70.7)	37.9 ± 4.6	6.0 ± 4.4	6.0 ± 4.4
2	214 (19.1)	36.7 ± 5.3	3.9 ± 2.7	7.8 ± 5.0
3	65 (5.8)	37.5 ± 4.7	3.1 ± 2.3	9.4 ± 5.9
4	24 (2.1)	35.9 ± 5.1	2.1 ± 1.6	7.8 ± 4.8
5	14 (1.2)	36.4 ± 6.4	1.6 ± 1.3	8.4 ± 4.9
6	7 (0.6)	39.6 ± 5.2	1.6 ± 1.7	10 ± 4.0
7	3 (0.3)	40 ± 6.1	3.4 ± 4.0	24.3 ± 29.2
15	1 (0.1)	38	1	14

Values are presented as mean ± SD unless otherwise indicated. Age refers to the first OC cycle. Mean MII oocytes cryopreserved per cycle represents the average number of MII oocytes cryopreserved per stimulation cycle among women in each cycle-number category. Mean MII oocytes cryopreserved per woman represents the cumulative number of MII oocytes cryopreserved across all cycles. MII, metaphase II; OC, oocyte cryopreservation; SD, standard deviation.

[a]Includes 18 OC cycles performed at other centres before referral. These cycles were counted only in the number of OC cycles per woman; oocyte and MII counts from these cycles were not available and are not included.

Number of patients who achieved age- based recommended number of oocytes to freeze to obtain one euploid embryo or 50% chance of live birth

Among women aged <35 years (n=211), 21 (8.8%) cryopreserved ≥12 oocytes. Among women aged 35–37 years (n=197), 13 (6.6%) cryopreserved ≥15 oocytes. Among women aged 38–40 years (n=374), 10 (2.7%) cryopreserved ≥20 oocytes. Among women aged >40 years (n=308), only three cryopreserved 20- 25 oocytes, and none cryopreserved >25 oocytes. Overall, 44 of 1121 women (3.9%) achieved the age-based recommended number of oocytes for cryopreservation.

Pregnancy Outcome

Of the 1121 women, 63 (5.6%) returned to use their cryopreserved oocytes. Women underwent a mean of 1.6±1.0 OC cycles, accumulating 6.4±4.1 mature oocytes. Mean age was 38.5±3.6 years at cryopreservation and 42.2±3.6 years at warming. Oocyte survival rate was 80.5%, yielding a mean of 5.2±3.3 surviving MII oocytes per warming cycle. Return rates were similar in women aged <38 and ≥38 years at OC (24/434, 5.5% vs 39/687, 5.7%).

Embryo transfer was cancelled in 17 of 63 women (27.0%), mainly because of embryo arrest or failure to reach the blastocyst stage. Four women who returned for thawing subsequently cryopreserved embryos for later use and were excluded from patient-based reproductive outcome calculations. A total of 46 embryo transfers were performed in 42 women, resulting in 21 pregnancies. Fifteen were clinical pregnancies, 46.7% of which miscarried, resulting in eight live births. Mean age of the women at OC who had miscarriage and live birth were significantly different (39.2±3.7 vs 36±2.7, $p<0.05$). Details of reproductive outcomes after thaw is given in Table 5.

Table 5 Outcomes after oocyte thawing

	N=63	<38 (n=24)	≥38 (n=39)
Age at OC, years	38.5 ± 3.6	35.2 ± 2.1	40.7 ± 2.5
Age at thaw, years	42.2 ± 3.6	39.2 ± 2.8	44.0 ± 2.7
Return rate	63/1121 (5.6 %)	24/434 (5.5 %)	39/687 (5.7 %)
Number of OC cycles per woman	1.6 ± 1.0	1.7 ± 0.8	1.6 ± 1.1
Cryopreserved MII oocytes per woman	6.4 ± 4.1	6.43 ± 4.6	6.5 ± 3.7
Survived MII oocytes per patient	5.2 ± 3.3	5.2 ± 3.8	5.2 ± 3.0
Embryo transfer cancellations	17/63 (27.0%)	4/24 (16.7%)	13/39 (33.3%)

Pregnancy rate per embryo transfer	21/46 (45.7%)	10/17 (58.8%)	11/29 (37.9%)
Clinical pregnancy rate per embryo transfer	15/46 (32.6%)	7/17 (41.2%)	8/29 (27.6%)
Miscarriage rate per clinical pregnancy	7/15 (46.7%)	1/7 (14.3%)	6/8 (75.0%)
Live birth rate per embryo transfer	8/46 (17.4%)	6/17 (35.3%)	2/29 (6.9%)
Live birth rate per woman	8/59[a] (13.6%)	6/20[a] (30.0%)	2/39 (5.1%)
Live birth rate per warmed oocyte	8/386 (2.1%)	6/129 (4.7%)	2/257 (0.8%)

Values are presented as mean ± standard deviation or n/N (%). MII, metaphase II; OC, oocyte cryopreservation. Return rate was calculated among women with stored oocytes. Pregnancy and live birth outcomes were calculated among patients who underwent embryo transfer, unless otherwise specified. [a]Four women who returned for thawing subsequently cryopreserved embryos for later use and were excluded from patient-based reproductive outcome calculations.

Reproductive outcomes differed markedly by age at OC (Table 5). Among the 63 women who returned, 24 (38%) were aged <38 years and 39 (62%) were aged ≥38 years at OC; mean age at warming was 39.2±2.8 and 44.0±2.7 years, respectively. The number of OC cycles (1.7±0.8 vs 1.6±1.1), cryopreserved MII oocytes (6.4±4.6 vs 6.5±3.7), and surviving MII oocytes (5.2±3.8 vs 5.2±3.0) per woman were similar between groups. Embryo transfer was cancelled in 4 of 24 women (16.7%) aged <38 years and 13 of 39 women (33.3%) aged ≥38 years. Among women aged <38 years, 17 transfers resulted in 10 pregnancies (58.8%) and 7 clinical pregnancies (41.2%), of which one (14.3%) miscarried, yielding six live births (35.3% per transfer; 30% per woman). In women aged ≥38 years, 29 transfers resulted in 11 pregnancies (37.9%) and 8 clinical pregnancies (27.6%), of which six (75%) miscarried, yielding two live births (6.9% per transfer; 5.1% per woman). Live birth per warmed oocyte was 4.7% (6/129) in women aged <38 years and 0.8% (2/257) in those aged ≥38 years. Of note, 46 transfers were performed in 42 women, so per-transfer rates include repeated transfers in the same woman.

Additionally, 31 women also underwent fresh IVF cycles with or without warming of cryopreserved oocytes, resulting in 11 pregnancies and two live births. Live births were from women aged 40 and 42.

Discussion

This is the largest single-center cohort study to date with the longest follow-up, evaluating patient and cycle characteristics, trends in OC and warming, and reproductive outcomes in women with DOR and age-related fertility decline. Unlike most prior studies, which largely include younger women with normal ovarian reserve (Cobo et al., 2016; Blakemore et al., 2021; Bakkensen et al., 2022; Boedeker et al., 2025), our cohort represents an underrepresented and clinically challenging group.

The main findings of our study reflect the implications of Turkish IVF legislation, which restricts non-medical OC to women with DOR, while highlighting the characteristics of a previously underrepresented population. Most women in our cohort who returned to use their cryopreserved oocytes were of advanced reproductive age, with nearly 61% having cryopreserved their oocytes at 38 years or older. Both the number of women undergoing OC and total OC cycles increased significantly, while mean age at OC declined over time. This trend may reflect increasing awareness of age-related fertility decline, broader patient counseling, and greater acceptance of OC among younger women. However, because this cohort was shaped by the Turkish regulatory framework, in which OC is primarily offered to women with DOR and/or advanced reproductive age, the observed decrease in age may more likely reflect earlier identification, counseling and referral of women at risk for diminished reproductive potential.

The average number of frozen MII oocytes and OC cycles per woman remained stable below age 38 years, were highest among women aged 38-40 years, and both declined thereafter. Among women aged 38 years or older each additional year of age was associated with approximately 0.8 fewer COCs retrieved, and 0.6 mature oocytes cryopreserved per woman. In contrast, the number of cryopreservation cycles did not increase significantly with age. Although women aged ≥38 years generally require more cryopreserved oocytes to achieve a comparable chance of live birth compared to younger women, they accumulated fewer rather than more mature oocytes. Overall, most women were unable to cryopreserve the number of mature oocytes considered necessary to obtain at least one euploid embryo or to achieve an approximately 50% chance of live birth, based on age-specific benchmarks [11,12]. The eleven-year crude return rate for oocyte utilization was low (5.6%), with those who returned being older at the time of OC and when they returned, and older women returning sooner for warming.

A central finding of this study is that, across all age groups, most women underwent an insufficient number of OC cycles to reach age-specific oocyte numbers associated with a meaningful probability of live birth. Only 3.9% achieved the proposed age-specific benchmarks. The mean number of cryopreserved mature oocytes per woman ranged from 7.2 among women younger than 30 years to 3.4 among women older than 45 years (Fig. 3), all below recommended thresholds [11,12]. Despite the increasing oocyte requirements with advancing age, the average number of OC cycles remained low and relatively stable across age groups, ranging from 1.4 to 1.7 cycles per woman. These findings suggest that, in real world practice, the cumulative oocyte numbers required for a reasonable chance of success are rarely achieved in woman with DOR and/or advanced reproductive age. Our findings are consistent with a recent study comparing women with and without POR undergoing OC, which showed that women with POR were less likely to

achieve age-based OC goals and required more cycles to do so [16]. In that study, 7% to 25% of women with POR achieved the recommended age-based oocyte number, depending on their POSEIDON category, compared with 3.9% in our cohort.

The reasons for the lower proportion of women reaching age-specific oocyte targets in our cohort compared with the POR study are unclear. Differences in study population, ovarian reserve, age distribution, financial constraints, treatment burden, counseling practices, or patient expectations may have contributed. Together, these findings underscore the difficulty of achieving recommended oocyte numbers in women with DOR and/or advanced reproductive age in real-world practice.

The return rate for oocyte utilization was low (5.6%). The utilization rate of cryopreserved oocytes varies across studies, depending on the length of follow-up and patient populations [9,14,17,18,25–27]. Although in the longest follow-up study to date, 38% of the women returned after 10-15 years [26], two recent meta-analyses reported 11% return rate among studies of planned OC [17,18]. In a study including SART data examining the association between POR and the rate of patients returning to use cryopreserved oocytes, the return rate at 6-year follow-up was 4% in the POR group, higher than the 2.3% in the normal ovarian response group [9]. The authors hypothesized that a newly diagnosed POR might serve as a stressor prompting earlier attempts at conception, compared with those exhibiting a normal ovarian response. The low return rate in our cohort should be interpreted in the context of relatively short follow-up for some women and the possibility that many patients may still use their oocytes in the future.

Reproductive outcomes were modest as expected in women with DOR and of advanced reproductive age. More than one-quarter of women who returned for warming (27.0%) did not

reach embryo transfer, mostly because of embryo arrest or failure to achieve blastocyst development; cancellation was twice as frequent in women aged ≥38 years (33.3% vs 16.7%). High cancellation rate is a critical and often underappreciated contributor to low live birth rate per woman. Expressing outcomes per woman rather than per transfer is clinically more meaningful and provides more accurate estimation of live birth success. Among those who underwent embryo transfer, clinical pregnancy rates were reasonable; however, the high miscarriage rate (47%) substantially reduced the live birth rate. Women who achieved live birth were significantly younger at the time of OC than those who miscarried, confirming that age at OC is the main predictor of live birth [15,17]. Outcomes were especially poor among women aged ≥38 years at OC, in whom only two live births occurred despite 11 pregnancies. A recent study of 731women returning for oocyte warming reported age-specific probabilities of live birth based on the number of cryopreserved oocytes. For 283 women in their cohort aged 38-40 at first OC, thawing 1-9 MII oocytes, the given cumulative live birth rate per patient was 21% [11], higher than in our ≥38-year group, which was older (mean age at OC 40.7±2.5 years). However, comparing outcomes across different cohorts and clinics has limitations. Counseling is best informed by real OC outcome data from each individual clinic. Therefore, each clinic should aim to follow and publish their outcome data, so that patients can make informed decisions for the cumulative number of oocytes they cryopreserve.

Stratification by age at OC highlights the importance of timing. Women who cryopreserved oocytes before 38 years achieved a live birth rate of 30% per woman and 35.3% per transfer, compared with 5.1% and 6.9%, respectively, in women aged ≥38 years, despite comparable numbers of cryopreserved and surviving oocytes in the two groups. Pregnancy rates per transfer were 58.8% and 37.9%, whereas miscarriage was five times more frequent in the older group (75%

vs 14.3%). This pattern is consistent with the known age-related increase in oocyte aneuploidy [3–5], although embryo ploidy was not assessed in our study. Our findings suggest that, once oocytes are successfully warmed, age at cryopreservation rather than oocyte number alone determines the probability of live birth. Notably, women aged <38 years in our cohort all had DOR, yet achieved clinically meaningful live birth rates, supporting earlier referral and cryopreservation in this group. Return rates were similar in both age groups, indicating that the higher proportion of women aged ≥38 years among those who returned reflects the composition of the cohort rather than greater utilization at older ages.

This study has several strengths and limitations. Its main strengths include a large single-center cohort of a unique patient population, more than a decade of follow-up, and availability of cycle-level data enabling longitudinal analysis and providing real-world evidence in an understudied population.

The main limitations include the retrospective single-center design, selected cohort, and regulatory restrictions on ART procedures, which limit generalizability. Reasons for non-utilization, including partnership status or natural conception, were not systemically available. Women who cryopreserved oocytes more recently, particularly after 2020, had shorter follow-up, and utilization rates may increase over time. In addition, natural conceptions and ART treatments performed at other centers were not available, which may have let to underestimation of the cohort's true cumulative success rate. Finally, demographic reasons for not pursuing additional cycles were unavailable. In addition, the age-stratified analyses of reproductive outcomes were based on small numbers (24 vs 39 women; 17 vs 29 transfers), per-transfer rates did not account for multiple transfers in the same woman, and the two groups differed in their inclusion criteria (ovarian reserve

was a requirement only in women aged <38 years). The age-stratified findings are therefore descriptive and should be confirmed in larger cohorts.

In conclusion, this study provides a comprehensive, long-term analysis of OC trends, utilization, and reproductive outcomes in women with DOR and advanced reproductive age, within a restrictive regulatory framework. Although the number of women seeking OC increased substantially, most were unable to cryopreserve enough mature oocytes to achieve age-based targets associated with a meaningful chance of a live birth. Utilization rates were low, and reproductive outcomes among women who returned to use their oocytes were modest, reflecting the biological constraints of DOR and advanced reproductive age. Outcomes differed markedly by age at cryopreservation: live birth per woman was 30% when oocytes were frozen before 38 years and 5.1% at 38 years or older.

These findings have important counseling implications. Women with DOR and/or advanced reproductive age should be informed about high cancellation rates during retrieval and after warming, and the likely need for multiple cycles to reach expected oocyte yield based on their age. Counseling should be individualized, evidence-based, and transparent, emphasizing that younger age at OC and more mature oocytes improve cumulative live birth rates, but that reaching recommended oocyte targets may be difficult in real-world practice. Women considering OC at ≥38 years should be specifically informed that live birth after warming was uncommon and miscarriage frequent, whereas women with DOR who cryopreserve oocytes before 38 years may have substantially better outcomes.

Although evaluating the regulatory framework is beyond the scope of this manuscript, our findings suggest that restricting planned OC primarily to women with DOR and/or advanced reproductive

age may limit its effectiveness. Earlier identification of younger women with DOR and timely counseling remain important. However, broader access to planned OC before substantial decline in ovarian reserve would likely yield better reproductive outcomes and a more favorable cost-effectiveness profile within the same healthcare infrastructure. The considerably better outcomes in women who cryopreserved oocytes before 38 years further support timely referral and earlier access to planned OC.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Claude and Grammarly to improve grammar, language clarity, and English editing. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

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