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Frozen autologous and donor oocytes are associated with differences in clinical and neonatal outcomes compared with fresh oocytes: a Society for Assisted Reproductive Technology Clinic Outcome Reporting System Analysis

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Objective: To study the clinical and neonatal outcomes of embryos derived from frozen oocytes relative to fresh oocytes in both autologous and donor oocyte cycles after fresh embryo transfer (ET).
Design: This is a retrospective cohort study using the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database between 2014 and 2015.
Setting: The Society for Assisted Reproductive Technology Clinic Outcome Reporting System database was used to identify autologous and donor oocyte cycles that resulted in a fresh ET during 2014 and 2015.
Patients: There were 154,706 total cycles identified that used embryos derived from fresh or frozen oocytes and resulted in a fresh ET, including 139,734 autologous oocyte cycles and 14,972 donor oocyte cycles.
Interventions: Generalized linear regression models were used to compare the clinical and neonatal outcomes of frozen oocytes relative to fresh oocytes. Models were adjusted for maternal age, body mass index, smoking status, parity, infertility diagnosis, number of embryos transferred, and preimplantation genetic testing. An additional sensitivity analysis was performed to examine singleton pregnancies separately.
Main Outcome Measures: The live birth (LB) rate was the primary outcome. Secondary outcomes include pregnancy and birthweight outcomes.
Results: Differences in clinical and neonatal outcomes between fresh and frozen-thawed oocytes after fresh ET were observed. Specifically, our study found a higher incidence of high-birthweight infants after the use of frozen oocytes relative to fresh oocytes in both autologous oocytes (12.5% [frozen] vs. 4.5% [fresh], adjusted risk ratio [aRR] 2.67, 95% confidence interval [CI] 1.65–4.3) and donor oocyte cycles (6.2% [frozen] vs. 4.6% [fresh], aRR 1.42, 95% CI 1.1–1.83). This finding remained true when the analysis was restricted to singleton gestations only for both groups: autologous (17.3% [frozen] vs. 7.1% [fresh], aRR 2.77, 95%

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CI 1.74–4.42) and donor oocytes (9.4% [frozen] vs. 7.8% [fresh], aRR 1.38, 95% CI 1.07–1.77). Additionally, we observed a decrease in LB (aRR 0.81, 95% CI 0.77–0.85); clinical pregnancy (aRR 0.83, 95% CI 0.8–0.87); and an increase in biochemical pregnancy loss (aRR 1.22, 95% CI 1.05–1.43) after the use of frozen oocytes in donors, but not autologous cycles.

Conclusions: Our findings of an increased incidence of high-birthweight infants after the transfer of embryos derived from frozen oocytes in both autologous and donor oocyte cycles raise questions about oocyte vitrification and deserve further study. Additionally, the finding of a decreased likelihood of LB with frozen-donor oocytes compared with fresh donor oocytes is an important finding, especially because more patients are seeking to use frozen oocytes in their donor egg cycles. Future research should be directed toward these findings to optimize the use of frozen oocytes in clinical practice. (Fertil Steril Rep® 2024;5:40–6. ©2023 by American Society for Reproductive Medicine.)

Key Words: Autologous, donor, frozen oocytes, fresh oocytes

The number of cycles completed with the strict intent to bank oocytes or embryos for future use has increased 20-fold in recent history, from approximately 5,000 to 105,000 cycles from 2005 to 2016 (1, 2). Additionally, almost 15% of assisted reproductive technology (ART) cycles that use embryos from donor oocytes are derived from frozen-donor oocytes (1). The increased utilization and success of oocyte freezing are primarily due to the widespread adoption of rapid vitrification as opposed to the older method of "slow freezing." This important technological adaptation has been shown to better protect the fragile oocyte by preventing ice crystal formation (3, 4). Consequently, the American Society of Reproductive Medicine recommended in 2013 that oocyte cryopreservation no longer be considered experimental (5).

The application of this recent technology to oocyte freezing has provided women with the ability to preserve their reproductive potential, even in the absence of a partner, for both elective and medical reasons. It has also led to new options for oocyte donation, including the development of donor oocyte banks. In vitro fertilization laboratories that have extensive experience in vitrifying oocytes have reported postthaw survival rates as high as 80%–90% (6–10). Although we have seen increased success with oocyte vitrification and thawing and more cycles are being performed with the intent to bank frozen oocytes, questions remain about the potential impact of vitrification on the egg because it pertains to pregnancy and neonatal outcomes compared with fresh oocytes.

Although little data exists regarding neonatal outcomes in fresh oocytes compared with frozen oocytes, more data exists regarding the outcomes of fresh compared with frozen embryo transfer (ET). Both observational studies and randomized controlled clinical trials have shown an increased risk of preeclampsia as well as large for gestational age infants and/or macrosomia after frozen ET compared with fresh ET (11–15). Meanwhile, fresh ET has been reported to be associated with increased rates of preterm birth and low-birthweight infants (11, 16, 17). Although these observed outcomes may in part be due to differences in the endometrial environment after frozen ET compared with fresh ET, the impact of vitrification itself on either the embryo or the egg is unclear (18–20). A large population-based study observed no differences in neonatal outcomes between fresh and frozen-donor oocytes, including premature birth, low birthweight, and birth defects (21). However, the currently available literature is limited to donor oocytes only and excludes autologous cycles (7, 10, 21, 22).

Therefore, questions remain surrounding oocyte freezing: does oocyte freezing impact clinical and neonatal outcomes, and are these outcomes similar in donor and autologous frozen oocyte cycles? Our objective was to systematically answer these questions by utilizing a large national database with two separate analyses of fresh ETs: outcomes from fresh compared with frozen autologous oocytes and outcomes from fresh compared with frozen-donor oocytes. Examining both analyses allows for the evaluation of the impact of oocyte freezing on clinical and neonatal outcomes in the general population (autologous oocytes), where the endometrial preparation is expected to be different between the two groups, as well as in a good-prognosis population (donor oocytes) with consistent uterine preparation in the recipients of both groups. Our hypothesis was that oocyte cryopreservation impacts the clinical and neonatal outcomes of embryos derived from frozen, thawed oocytes in both autologous and donor oocytes after fresh ET.

MATERIALS AND METHODS

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database from 2014 until 2015 was used to identify all cycles that resulted in a fresh ET during this timeframe. Data were collected through voluntary submission, verified by the Society for Assisted Reproductive Technology (SART), and reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The Society for Assisted Reproductive Technology maintains Health Insurance Portability and Accountability Act-compliant business associate agreements with reporting clinics. In 2004, after a contract change with the Centers for Disease Control and Prevention, SART gained access to the SART CORS data system for the purposes of conducting research. In 2015, 93% (464/499) of all ART clinics in the United States submitted data to SART (23).

Of note, 2014 was the first year that data was available in SART CORS on thawed oocytes linked with their subsequent fresh ET. Fresh ETs resulting from embryos created from both fresh and frozen autologous and donor oocytes were included. Cycles involving frozen ETs and donor embryo cycles were all excluded. Demographic data collected included maternal age, body mass index (BMI), smoking status, parity, infertility diagnosis, prior in vitro fertilization attempt, use of intracytoplasmic sperm injection (ICSI), use of assisted hatching, and

TABLE 1

Demographics of frozen and fresh oocyte cycles, autologous, and donor.

Variable	Fresh autologous oocyte cycles	Frozen autologous oocyte cycles	*P* value	Fresh donor oocyte cycles	Frozen donor oocyte cycles	*P* value
Cycle type, n (%)	139,181 (99.6)	553 (0.4)		11,482 (76.7)	3,490 (23.3)	
Intended parent age (y), mean ± SD	35 ± 4.7	38.6 ± 5.2	<.0001	41.2 ± 5.6	41.9 ± 4.8	<.0001
Intended parent age (y), n (%)						
<35	65,176 (46.8)	133 (24.1)	<.0001	1,505 (13.1)	298 (8.5)	<.0001
35–37	30,223 (21.7)	68 (12.3)		1,062 (9.2)	259 (7.4)	
38–40	25,283 (18.2)	107 (19.3)		1,779 (15.5)	504 (14.4)	
41–42	11,366 (8.2)	104 (18.8)		1,770 (15.4)	595 (17)	
>42	7,133 (5.1)	141 (25.5)		5,366 (46.7)	1,834 (52.6)	
Donor age (y), mean ± SD	N/A	N/A		26.4 ± 3.7	26 ± 3.2	<.0001
Race/ethnicity, n (%)						
Nonhispanic White	56,082 (40.3)	243 (43.9)	<.0001	4,266 (37.2)	1,199 (34.4)	<.0001
Nonhispanic Black	6,634 (4.8)	17 (3.1)		582 (5.1)	230 (6.6)	
Asian	13,598 (9.8)	25 (4.5)		1,050 (9.1)	183 (5.2)	
Hispanic	6,986 (5)	15 (2.7)		552 (4.8)	168 (4.8)	
Other	1,832 (1.3)	5 (0.9)		300 (2.6)	23 (0.7)	
Unknown	54,049 (38.8)	248 (44.8)		4,732 (41.2)	1,687 (48.3)	
BMI of an intended parent, mean± SD	25.6 ± 5.7	23.9 ± 4.9	<.0001	25.6 ± 5.4	26 ± 5.6	.0001
Smoking status, n (%)						
Smoker	4,944 (3.6)	11 (2)	<.0001	272 (2.4)	139 (4)	<.0001
Nonsmoker	120,756 (86.8)	403 (72.9)		9,357 (81.5)	2,932 (84)	
Unknown	13,481 (9.7)	139 (25.1)		1,853 (16.1)	419 (12)	
Reproductive history, mean ± SD						
Prior gravidity	1 ± 1.4	0.7 ± 1.2	<.0001	1.3 ± 1.7	1.4 ± 1.7	.1064
Prior full-term birth	0.7 ± 0.9	0.6 ± 0.8	.1064	0.7 ± 1	0.7 ± 1	.5068
Prior preterm birth	0.1 ± 0.3	0.1 ± 0.3	.1083	0.1 ± 0.3	0.1 ± 0.3	.4328
Prior spontaneous abortion	0.9 ± 1.1	0.6 ± 0.9	.0004	1.1 ± 1.3	1.1 ± 1.2	.267
No. of prior ART cycles	1 ± 0.7	1.2 ± 0.6	<.0001	1.1 ± 0.7	1.1 ± 0.4	.0094
Infertility diagnosis, n (%)						
Male factor	49,323 (35.4)	163 (29.5)	.0033	1,641 (14.3)	527 (15.1)	.2376
Tubal factor	19,141 (13.8)	25 (4.5)	<.0001	657 (5.7)	240 (6.9)	.013
Endometriosis	11,885 (8.5)	18 (3.3)	<.0001	534 (4.7)	147 (4.2)	.2863
Uterine factor	7,517 (5.4)	27 (4.9)	.7055	595 (5.2)	227 (6.5)	.0034
Polycystic ovary syndrome	21,272 (15.3)	47 (8.5)	<.0001	366 (3.2)	100 (2.9)	.3731
Diminished ovarian reserve	34,624 (24.9)	194 (35.1)	<.0001	8,706 (75.8)	2,921 (83.7)	<.0001
Unexplained	20,310 (14.6)	38 (6.9)	<.0001	435 (3.8)	159 (4.6)	.0475
Other	22,533 (16.2)	205 (37.1)	<.0001	2,426 (21.1)	495 (14.2)	<.0001
ART factors used, n (%)						
Assisted hatching	8,943 (8.7)	59 (17.5)	<.0001	660 (7.2)	351 (19.9)	<.0001
ICSI	10,8892 (78.2)	533 (96.6)	<.0001	9,502 (82.8)	3,447 (98.8)	<.0001
PGS/PGT	27,186 (19.5)	96 (17.4)	.2162	2,260 (19.7)	86 (2.5)	<.0001
No. embryos transferred, mean ± SD	1.8 ± 0.8	1.9 ± 0.9	.0534	1.6 ± 0.5	1.5 ± 0.5	<.0001
Elective single embryo transfer	22,051 (73.7)	70 (53.8)	<.0001	3,243 (91.2)	1,228 (79.7)	<.0001

ART = assisted reproductive technology; BMI = body mass index; ICSI = intracytoplasmic sperm injection; N/A = not applicable; No. = number; PGS/PGT = preimplantation genetic screening/preimplantation genetic testing; SD = standard deviation.

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number of embryos transferred. This retrospective cohort study was considered exempt by the University Hospitals Cleveland Medical Center Institutional Review Board.

Study outcomes

The primary outcome of the study was live birth would recommend we write out livebirth throughout document vs abbreviating as LB. Live birth was defined as a live-born infant who was delivered at 20 weeks of gestation or greater. Secondary outcomes included pregnancy and birthweight outcomes. Additional pregnancy outcomes included: clinical pregnancy, clinical miscarriage, biochemical pregnancy loss, and multiple gestations. Clinical miscarriage was defined as pregnancy loss after the presence of a gestational sac on viability ultrasound. Biochemical pregnancy loss was defined as a pregnancy loss that occurred after a positive pregnancy test but before a viability ultrasound. Birthweight outcomes included low birthweight infants (<2,500 g), normal birthweight infants (≥2,500 g and ≤3,999 g), and high-birthweight infants (>4,000 g).

Statistical analysis

Demographic and cycle characteristics were compared between groups using Fisher's exact tests and chi-square tests for categorical variables and the Student's *t* test for continuous variables, as appropriate (Table 1). We then assessed the likelihood of pregnancy and neonatal outcomes according

to the transfer of fresh embryos derived from frozen compared with fresh autologous oocytes and the fresh transfer of embryos derived from frozen compared with fresh donor oocytes into intended parent recipients. Generalized linear regression models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) to evaluate associations between frozen oocytes and clinical and neonatal outcomes relative to fresh oocytes. Models were adjusted for maternal age, BMI, smoking status, parity, infertility diagnosis, number of embryos transferred, and preimplantation genetic testing. These factors were controlled for in both Tables 2 and 3. The model was not adjusted for ICSI because this was considered an inherent characteristic of frozen oocyte cycles. For women who had multiple cycles and transfers between 2014 and 2015, only their first ET was included. The study sample was limited to singleton pregnancies in an additional sensitivity analysis.

RESULTS

There were 154,706 total cycles identified in the SART CORS database that used embryos derived from fresh or frozen oocytes and resulted in a fresh ET between 2014 and 2015. This included 139,734 autologous oocyte cycles and 14,972 donor oocyte cycles to intended parent recipients, as shown in Table 1.

Autologous oocyte cycles

Although >99% (139,181) of autologous oocyte cycles used fresh oocytes, there were 553 cycles that used embryos derived from frozen-thawed oocytes (Table 1). Women using frozen autologous oocytes tended to be older and have a lower BMI than women using fresh autologous oocytes (age: 38.6 ± 5.2 years [frozen] vs. 35 ± 4.7 years [fresh], BMI: 23.9 ± 4.9 kg/m^2 [frozen] vs. 25.6 ± 5.7 kg/m^2 [fresh]). The most common infertility diagnosis for women who underwent a transfer derived from frozen-thawed autologous oocytes was diminished (35.1%) ovarian reserve and other (37.1%), whereas for women who underwent a transfer derived from fresh autologous oocytes the most common diagnosis was male factor (35.4%). The mean number of embryos transferred was 1.9 ± 0.9 [frozen] vs. 1.8 ± 0.8 [fresh]. There was a lower proportion of elective single ET cycles in patients using frozen autologous oocytes compared with fresh oocytes (53.8% vs.73.7%).

Clinical outcomes: autologous Oocytes

There was no difference in the likelihood of LB after fresh ET of embryos derived from frozen-thawed oocytes compared with fresh oocytes in autologous cycles (23.9% [frozen] vs. 25.7% [fresh], adjusted RR [aRR] 0.93, 95% CI 0.79–1.09) (Table 2). No differences were observed in other pregnancy outcomes between embryos derived from frozen-thawed oocytes compared with fresh in autologous cycles, including the percentage of clinical pregnancy (28.2% [frozen] vs. 31% [fresh], aRR 0.91, 95% CI 0.79–1.04), clinical miscarriage (11.2% [frozen] vs. 10.9% [fresh], aRR 1.03, 95% CI 0.81–1.31), and biochemical pregnancy loss (6.9% [frozen] vs. 5.8% [fresh], aRR 1.28, 95% CI 0.93–1.76) (Table 2).

There was, however, a higher percentage of high-birthweight infants (birthweight >4,000 g) observed in embryos derived from frozen-thawed autologous oocytes compared with fresh autologous oocytes (12.5% [frozen] vs. 4.5% [fresh], aRR 2.67, 95% CI 1.65–4.3). This remained true when the sample was limited to singleton pregnancies (17.3% [frozen] vs. 7.1% [fresh], aRR 2.77, 95% CI 1.74–4.42). No difference was observed in the percentage of low birthweight infants between frozen-thawed and fresh autologous oocytes, both overall (20.4% [frozen] vs. 28.4% [fresh], aRR 0.92, 95% CI 0.65–1.31) and when restricted to singleton gestations (10% [frozen] vs. 9.9% [fresh], aRR 1.13, 95% CI 0.56–2.27).

Donor oocyte and intended recipient cycles

Our second analysis examined frozen compared with fresh donor oocytes with fresh ETs into intended parent recipients. Of the 14,972 donor oocyte cycles that were analyzed, 11,482 (77%) used embryos derived from fresh donor oocytes, and 3,490 (23%) cycles used embryos derived from frozen-thawed donor oocytes (Table 1). The average age of oocyte donors was similar in both groups (26 ± 3.2 [frozen] vs. 26.4 ± 3.7 [fresh]). The mean intended parent recipient age was also similar between the two groups (41.9 ± 4.8 [frozen] vs. 41.2 ± 5.6 [fresh]). The mean BMI of intended parent recipients was slightly higher in those utilizing frozen oocytes (26.9 ± 5.6 kg/m^2 [frozen] vs. 25.6 ± 5.4 kg/m^2 [fresh]). As expected, the most common infertility diagnosis for intended parent recipients in both groups was diminished ovarian reserve (83.7% [frozen] vs. 75.8% [fresh]). The mean number of embryos transferred was 1.5 ± 0.5 [frozen] vs. 1.6 ± 0.5 [fresh]. A lower proportion of frozen-donor oocyte cycles used elective single ET (79.7% [frozen] vs. 91.2% [fresh]).

Clinical outcomes: donor oocytes

In unadjusted models, no difference in the likelihood of LB was noted with frozen-thawed donor oocytes compared with fresh donor oocytes (RR 1.02, 95% CI 0.98–1.07) (Table 3). However, after the model was adjusted for maternal age, BMI, smoking status, parity, infertility diagnosis, number of embryos transferred, and preimplantation genetic testing, a decrease in the likelihood of LB was observed with frozen-donor oocytes in all pregnancies (aRR 0.81, 95% CI 0.77–0.85), compared with fresh donor oocytes.

Similarly, a decrease was observed in the percentage of clinical pregnancy after fresh transfer of embryos using frozen-thawed donor oocytes relative to fresh donor oocytes in adjusted models (51% [frozen] vs. 48% [fresh], aRR 0.83, 95% CI 0.8–0.87). Additionally, an increase in biochemical pregnancy loss was observed with frozen-donor oocyte cycles (8.6% [frozen] vs. 5.6% [fresh], aRR 1.22, 95% CI 1.05–1.43). Although not statistically significant, a trend toward a higher proportion of clinical miscarriage was noted with frozen-thawed oocytes compared with fresh (17.4% [frozen] vs. 12.6% [fresh], aRR 1.07, 95% CI 0.97–1.19).

Additionally, there was a significantly higher proportion of high-birthweight infants noted after transfer of frozen-

TABLE 2

Clinical outcomes for frozen autologous oocytes relative to fresh autologous oocytes.

Outcome	Fresh autologous oocytes (n = 139,181)	Frozen autologous oocytes (n = 553)	RR (95% CI)	aRR (95% CI)[a]
Pregnancy outcomes				
Biochemical pregnancy loss	8,016 (5.8)	38 (6.9)	1.19 (0.88, 1.62)	1.28 (0.93, 1.76)
Clinical pregnancy loss	15,190 (10.9)	62 (11.2)	1.03 (0.81, 1.3)	1.03 (0.81, 1.31)
Clinical pregnancy	43,120 (31)	156 (28.2)	0.91 (0.8, 1.04)	0.91 (0.79, 1.04)
Live birth	35,774 (25.7)	132 (23.9)	0.93 (0.8, 1.08)	0.93 (0.79, 1.09)
Pregnancy plurality, n (%)				
Singleton	27,457 (76.8)	110 (83.3)	Reference	Reference
Multiple	8,317 (23.2)	22 (16.7)	0.72 (0.49, 1.05)	0.96 (0.63, 1.46)
Birthweight, n (%)				
Normal birthweight[b]	29,565 (67.2)	102 (67.1)	Reference	Reference
Low birthweight[b]	12,480 (28.4)	31 (20.4)	0.79 (0.58, 1.07)	0.92 (0.65, 1.31)
High birthweight[b]	1,961 (4.5)	19 (12.5)	2.52 (1.67, 3.82)	2.67 (1.65, 4.3)
Singleton birthweight, n (%)				
Normal Birthweight[b]	22,666 (83.1)	80 (72.7)	Reference	Reference
Low birthweight[b]	2,694 (9.9)	11 (10)	1.14 (0.65, 1.98)	1.13 (0.56, 2.27)
High birthweight[b]	1,926 (7.1)	19 (17.3)	2.45 (1.63, 3.68)	2.77 (1.74, 4.42)

aRR = adjusted relative risk ratio; CI = confidence interval; RR = relative risk ratio.
[a] Models were adjusted for maternal age, body mass index, smoking status, parity, infertility diagnosis (male infertility, endometriosis, polycystic ovary syndrome, diminished ovarian reserve, tubal factor, uterine, unexplained, other), number of embryos transferred, and preimplantation genetic testing.
[b] Low birthweight was defined as <2,500 g; normal birthweight was defined as ≥2,500 g and ≤3,999 g; and high birthweight was defined as >4,000 g.

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thawed donor oocytes compared with fresh donor oocytes (6.2% [frozen] vs. 4.6% [fresh], aRR 1.42, 95% CI 1.1–1.83); this finding remained when restricted to singleton gestations (9.4% [frozen] vs. 7.8% [fresh], aRR 1.38, 95% CI 1.07–1.77). There were no differences noted in the proportion of low-birthweight infants overall (29.5% [frozen] vs. 32.9% [fresh], aRR 1.03, 95% CI 0.94–1.12) or among singleton gestations only (12.6% [frozen] vs. 11.8% [fresh], aRR 1.15, 95% CI 0.94–1.41).

DISCUSSION

To our knowledge, this is the largest study to date, analyzing clinical and neonatal outcomes between frozen and fresh oocytes after fresh ET, in both donor and autologous oocyte cycles. In our study, notable differences in clinical and neonatal outcomes were observed. Specifically, our study found a higher incidence of high-birthweight infants after the use of frozen relative to fresh oocytes in both autologous and donor cycles. Additionally, we observed a decrease in LB and clinical pregnancy and an increase in biochemical pregnancy loss after the use of frozen oocytes in donors, but not autologous cycles.

The finding of a higher incidence of high-birthweight infants after fresh transfer of embryos created from frozen compared with fresh autologous oocytes is consistent with the recent data from both observational studies and randomized controlled clinical trials that suggest a higher incidence of large for gestational age and high-birthweight infants after frozen compared with fresh ET (11, 14, 15). Specifically, recent data suggest that hormonally programmed frozen ETs are associated with a higher rate of large for gestational age and macrosomia compared with natural or stimulated frozen ETs (13).

Therefore, it is possible to attribute at least some of the increase in high birthweight observed in the frozen autologous oocyte group to the uterine hormonal environment. Women who undergo fresh transfer with fresh oocytes have recently had ovarian stimulation to super-ovulate the ovaries in preparation for oocyte retrieval, whereas women who use frozen autologous oocytes by default have a different uterine environment. Their uterus is prepared for frozen ET either by hormonal programming with exogenous estrogen and progesterone (likely the vast majority) or the embryo is transferred in a natural or stimulated ovulation cycle (13, 14).

Our second analysis, which included transfers of fresh embryos created from fresh or frozen-donor oocytes into intended parent recipients, serves as a control for the endometrial environment, which may have been a confounding factor in the autologous oocyte analysis. Intended parent recipients in donor cycles undergo similar uterine preparation, whether the embryo source used is a fresh or frozen-donor oocyte. In this analysis, our study also reports a higher incidence of high-birthweight infants in pregnancies resulting from frozen-donor oocytes, albeit of a lower magnitude compared with that observed with frozen autologous oocytes. This finding of increased birthweight with frozen-donor oocytes deserves further study. When confirmed in future studies, it is important because it suggests a possible impact of oocyte freezing on subsequent neonatal birth weight that cannot be entirely explained by the endometrial environment alone.

Another important finding of our study is that in the donor oocyte analysis, there was a lower proportion of LB among fresh transfers that used frozen-donor oocytes. Our finding is similar to a study recently published by Whynott et al. (22) that also observed lower LB with frozen-donor oocytes compared with fresh donor oocytes. Our study also noted a decrease in clinical pregnancy as well as a higher proportion of biochemical pregnancy loss in the adjusted analysis among transfers using frozen-donor eggs.

TABLE 3

Clinical outcomes for frozen-donor oocytes relative to fresh donor oocytes among intended parent recipients.

Outcome	Fresh donor oocyte and parent recipient (n = 11,482)	Frozen-donor oocyte and parent recipient (n = 3,490)	RR (95% CI)	aRR (95% CI)[a]
Pregnancy outcomes, n (%)				
Biochemical Pregnancy loss	645 (5.6)	301 (8.6)	1.54 (1.35, 1.75)	1.22 (1.05, 1.43)
Clinical miscarriage	1,443 (12.6)	607 (17.4)	1.38 (1.27, 1.51)	1.07 (0.97, 1.19)
Clinical pregnancy	5,528 (48.1)	1,780 (51)	1.06 (1.02, 1.1)	0.83 (0.8, 0.87)
Live birth	4,703 (41)	1,465 (42)	1.02 (0.98, 1.07)	0.81 (0.77, 0.85)
Pregnancy plurality, n (%)				
Singleton	3,397 (72.2)	1,158 (79)	Reference	Reference
Multiple	1,306 (27.8)	307 (21)	0.75 (0.68, 0.84)	0.92 (0.81, 1.03)
Birthweight, n (%)				
Normal birthweight[b]	3,738 (62.5)	1,130 (64.4)	Reference	Reference
Low birthweight[b]	1,966 (32.9)	518 (29.5)	0.91 (0.84, 0.99)	1.03 (0.94, 1.12)
High birthweight[b]	274 (4.6)	108 (6.2)	1.28 (1.03, 1.58)	1.42 (1.1, 1.83)
Singleton birthweight, n (%)				
Normal birthweight[b]	2,715 (80.4)	892 (78)	Reference	Reference
Low birthweight[b]	398 (11.8)	144 (12.6)	1.09 (0.91, 1.3)	1.15 (0.94, 1.41)
High birthweight[b]	264 (7.8)	108 (9.4)	1.22 (0.99, 1.51)	1.38 (1.07, 1.77)

aRR = adjusted relative risk ratio; CI = confidence interval; RR = relative risk ratio.
[a] Models were adjusted for maternal age, body mass index, smoking status, parity, infertility diagnosis (male infertility, endometriosis, polycystic ovary syndrome, diminished ovarian reserve, tubal factor, uterine, unexplained, and other), number of embryos transferred, and preimplantation genetic testing.
[b] Low birthweight was defined as <2,500 g; normal birthweight was defined as ≥2,500 g and ≤3,999 g; and high birthweight was defined as >4,000 g.

Burks. Outcomes with frozen vs. fresh oocytes. Fertil Steril Rep 2024.

Importantly, these same findings were not found in our analysis that compared fresh and frozen autologous oocytes. There are several potential explanations for these findings. First, it should be reassuring that in a large database study, there was no decrease in LB noted among women cryopreserving and using their own oocytes. Second, there are important differences between autologous and donor oocyte cycles that may impact clinical outcomes. Stimulation parameters may differ between donor cycles that are destined for fresh or frozen donation because there is an incentive to get as many eggs as possible from a donation cycle, particularly those in which donor eggs are frozen in "lots" for donor banks (24). Finally, we cannot rule out that there is an impact of the freezing process itself on the oocyte's viability potential that we are observing in the donor egg population.

Whether vitrification itself has an impact on either the embryo or the egg is not well understood. To investigate potential changes to the embryo after vitrification, researchers have examined embryonic and placental gene expression. Animal studies have reported disorganized changes to embryonic cytoskeletal structure after vitrification (25, 26). Additionally, differences in both epigenetic markers and gene expression have been reported between fresh and frozen embryos in both human and animal models (18–20). A recent study demonstrated that vitrification and trophectoderm biopsy have cumulative effects on embryonic gene expression in multiple critical pathways in a mouse model (27). Furthermore, several genes along these critical pathways were identified as possible mediators of some of the clinical differences seen after fresh and frozen ET in this study. Given the increasing use and demand for both embryo and oocyte cryopreservation, combined with the observed differences in neonatal outcomes after the transfer of fresh and frozen embryos that have already been noted in clinical studies, further studies examining the effects of vitrification are warranted.

This study has many strengths, including the use of a large national registry that allowed analysis of frozen and fresh oocytes in both autologous and donor oocyte cycles. The inclusion of both autologous and donor cycles allows for a systematic assessment of the impact of vitrification on the oocyte in different populations and uterine environments.

However, as a retrospective database study, our study does have some inherent limitations. An important limitation is the reliability and type of data that was reported. For example, we were unable to ascertain the number of oocytes that were retrieved between groups. Additionally, we did not assess the cumulative pregnancy rate because only the first ETs were included in our analysis. We intentionally did not include frozen ET cycles because our goal was to isolate the variable of oocyte vitrification, although this can be a subject of future study. Additionally, ICSI was not controlled for in our analysis because it was considered to be an inherent feature of oocyte freezing, which results in a hardened zona pellucida that requires ICSI for fertilization (28–30). Assisted hatching was not included in our analysis for similar reasons. Finally, we recognized that our sample sizes for frozen oocytes are smaller than fresh, but because of the increased demand and popularity of egg freezing, larger sample sizes of both autologous and donor-frozen eggs should be available in the near future for assessment.

CONCLUSIONS

In conclusion, our study's findings of an increased incidence of high-birthweight infants after frozen oocyte ET in both autologous and donor populations raise important questions

about oocyte vitrification that deserve further study and cannot be entirely attributed to differences in the endometrial environment. Additionally, although it is reassuring that no difference in LB was observed between fresh and frozen autologous oocytes, the finding of a decreased likelihood of LB after frozen-donor oocytes compared with fresh donor oocytes is an important finding as more patients seek to use frozen oocytes for donor egg cycles. Future research should be directed toward LB success with the use of frozen-donor oocytes, with the hope that this will provide clinicians with the needed information to provide individualized patient care and counseling as it pertains to their prognosis.

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Declaration of Interests

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