Cryopreserved oocyte versus fresh oocyte assisted reproductive technology cycles, United States, 2013

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Objective: To compare characteristics, explore predictors, and compare assisted reproductive technology (ART) cycle, transfer, and pregnancy outcomes of autologous and donor cryopreserved oocyte cycles with fresh oocyte cycles.
Design: Retrospective cohort study from the National ART Surveillance System.
Setting: Fertility treatment centers.
Patient(s): Fresh embryo cycles initiated in 2013 utilizing embryos created with fresh and cryopreserved, autologous and donor oocytes.
Intervention(s): Cryopreservation of oocytes versus fresh.
Main Outcomes Measure(s): Cancellation, implantation, pregnancy, miscarriage, and live birth rates per cycle, transfer, and/or pregnancy.
Result(s): There was no evidence of differences in cancellation, implantation, pregnancy, miscarriage, or live birth rates between autologous fresh and cryopreserved oocyte cycles. Donor cryopreserved oocyte cycles had a decreased risk of cancellation before transfer (adjusted risk ratio [aRR] 0.74, 95% confidence interval [CI] 0.57–0.96) as well as decreased likelihood of pregnancy (aRR 0.88, 95% CI 0.81–0.95) and live birth (aRR 0.87, 95% CI 0.80–0.95); however, there was no evidence of differences in implantation, pregnancy, or live birth rates when cycles were restricted to those proceeding to transfer. Donor cryopreserved oocyte cycles proceeding to pregnancy had a decreased risk of miscarriage (aRR 0.75, 95% CI 0.58–0.97) and higher live birth rate (aRR 1.05, 95% CI 1.01–1.09) with the transfer of one embryo, but higher miscarriage rate (aRR 1.28, 95% CI 1.07–1.54) and lower live birth rate (aRR 0.95, 95% CI 0.92–0.99) with the transfer of two or more.
Conclusion(s): There was no evidence of differences in ART outcomes between autologous fresh and cryopreserved oocyte cycles. There was evidence of differences in per-cycle and per-pregnancy outcomes between donor cryopreserved and fresh oocyte cycles, but not in per-transfer outcomes. (Fertil Steril® 2017;107:110–8. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology (ART), egg freezing, in vitro fertilization (IVF), vitrification

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Although embryo cryopreservation has been available for several decades, oocyte cryopreservation until recently was considered experimental owing to the fragility of the single cell and its inability to tolerate the slow-freezing process. With the growing availability and acceptance of vitrification (rapid freezing) and new evidence suggesting that oocytes can tolerate the vitrification process, the Practice Committee of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology determined that oocyte vitrification and thawing should no longer be considered experimental as of October 2012 (1).

Oocyte cryopreservation has increased in recent years (2) and is an important component of fertility preservation. Fertility preservation may be

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necessary for women undergoing treatment for cancer or other medical conditions that affect future fertility potential (1). Fertility preservation also is used for women who plan to delay childbearing, because pregnancy rates are more strongly influenced by the age of an oocyte at the time of retrieval than the age of a woman trying to achieve pregnancy (3, 4). Oocyte cryopreservation also is useful for ART cycles involving donor oocytes. Oocyte cryopreservation allows for simplification of the donor process, because the use of cryopreserved oocytes allows for the formation of egg banks and eliminates the need to align the timing of oocyte retrieval from a donor with the transfer of embryos to a recipient (1). In addition, it simplifies splitting donor oocytes from one donor among multiple recipients.

Although ART cycles using cryopreserved oocytes still represent a small proportion of all ART cycles conducted in the United States, we expect the number of these cycles to continue to increase. At the same time, little is known about the effectiveness of cycles involving previously cryopreserved oocytes. In this study, among fresh embryo cycles, we aimed to explore the characteristics of cryopreserved oocyte cycles and to compare the characteristics of cycles using cryopreserved oocytes with those using fresh oocytes using a national database. We also aimed to calculate live birth rates for cryopreserved and fresh oocyte cycles according to patient and cycle characteristics and compare outcomes of cycles using cryopreserved oocytes with those using fresh oocytes.

MATERIALS AND METHODS

Data Source and Definitions

We analyzed 105,517 fresh embryo cycles initiated in 2013, including 422 autologous cryopreserved oocyte cycles, 93,181 autologous fresh oocyte cycles, 2,223 donor cryopreserved oocyte cycles, and 9,691 donor fresh oocyte cycles, as reported to the Centers for Disease Control and Prevention's National ART Surveillance System (NASS). The NASS contains data from 467 US clinics that performed assisted reproductive technology (ART) cycles in 2013 and accounts for approximately 98% of all ART cycles conducted in the United States (5). Fresh embryo cycles are cycles with the intent to transfer an embryo created during the current cycle; fresh oocyte cycles are cycles with the intent to transfer embryos derived from oocytes retrieved during the current cycle; and cryopreserved oocyte cycles are cycles in which oocytes that were previously frozen are thawed with the intent of fertilizing the oocytes and transferring the resulting embryo(s) to the patient during the current cycle. Autologous cycles use oocytes belonging to the patient, whereas donor cycles use oocytes provided for the patient (the recipient) by a donor (6, 7). Frozen embryo cycles, or cycles with the intent to transfer a thawed embryo that was cryopreserved during a previous cycle, were excluded from analysis, because the state of the oocyte (fresh or cryopreserved) is not collected in NASS for these cycles (n = 55,506). Donor embryos, or those embryos left over from a patient's ART treatment that are then donated to another patient, were excluded from analysis (n = 1,460) (5). Additionally, a small number of cycles of mixed type were removed from analysis (n = 726).

We compared characteristics and outcomes of cycles utilizing fresh and cryopreserved oocytes, both autologous and donor, among all cycles started, among all cycles proceeding to retrieval (i.e., excluding cycles canceled before retrieval), among all cycles proceeding to transfer (i.e., excluding cycles canceled before retrieval or transfer), and among all cycles resulting in pregnancy (i.e., excluding canceled cycles or cycles for which a pregnancy was not achieved).

Assisted reproductive technology cycle-level characteristics explored in this study included clinic size, patient age, obstetric history, and reason for ART. Retrieval characteristics included age of the woman providing the oocyte at time of retrieval; number of oocytes retrieved; use of intracytoplasmic sperm injection (ICSI, the injection of a single sperm directly into an oocyte); and number of embryos cryopreserved at the end of the ART cycle for potential future use. Transfer characteristics included use of assisted hatching (a micromanipulation technique designed to enhance implantation); number of embryos transferred; and embryo stage at transfer, either cleavage (2 to 3 days after fertilization) or blastocyst (5 to 6 days after fertilization) (6, 7).

Outcomes of ART cycles explored in this study included cancellation, in which an ART cycle is stopped after the start of ovarian stimulation or monitoring but before the retrieval of an oocyte and/or the transfer of an embryo; the number of embryos achieving implantation (number of fetuses) per the number of embryos transferred; pregnancy; miscarriage; and birth of at least one live-born infant (6, 7).

Statistical Analysis

We compared cycle-, retrieval-, and transfer-level characteristics of cryopreserved and fresh oocyte cycles, both among autologous and donor cycles, using a Rao-Scott χ^2 test, which adjusts for clustering of the data by clinic. We calculated live birth rates for cryopreserved and fresh oocyte cycles, both among autologous and donor cycles, according to the cycle- and transfer-level characteristics listed above. We explored whether these characteristics were significantly associated with live birth using unadjusted log binomial regression models with generalized estimating equations to account for clustering by clinic.

We assessed ART treatment outcomes, including cancellations, pregnancies, and live births among all ART cycles; implantation, pregnancy, and live births among all ART transfers; and miscarriage and live births among all ART pregnancies. Comparisons were made between fresh and cryopreserved oocyte cycles stratified by oocyte source (autologous or donor). Outcomes were modeled using unadjusted and adjusted log binomial or Poisson regression with generalized estimating equations. For outcomes among all cycles, we adjusted for significant risk factors from the set of all possible cycle-level risk factors; for outcomes among transfers and pregnancies, we adjusted for significant risk factors from the set of all possible cycle-, retrieval-, and transfer-level risk factors. Significant risk factors were determined using backward model building. Finally, we considered all

interactions between the independent variable of interest (fresh or cryopreserved oocyte) and each of the other independent variables. We retained those interactions that were significant in the adjusted models and that affected the interpretation of the comparison between fresh and cryopreserved oocyte cycles. We did not include age of the woman providing the oocyte at time of retrieval in the adjusted models owing to 24% and 21% missing values among cryopreserved autologous and donor oocyte cycles, respectively; however, we did check to determine whether the inclusion of this variable affected results and reported differences within the text. We did not adjust for variables that were not available for all cycle types, such as embryo stage at transfer, which was only available for fresh oocyte cycles.

All statistical analysis was conducted in SAS v. 9.3 (SAS Institute). Statistical significance was determined using $\alpha = 0.05$. This study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention.

RESULTS

Characteristics of Cryopreserved and Fresh, Autologous, and Donor Cycles

Among patients using their own oocytes, those using cryopreserved oocytes were more likely to be ≥40 years old, have no prior births, and have one or more prior ART cycle(s) as compared with those using fresh oocytes (Table 1). They also were less likely to have tubal factor and unexplained infertility but more likely to have ART treatment due to some other reason. They were more likely to attend a larger clinic (≥500 cycles), have ≥11 oocytes retrieved, use ICSI and assisted hatching, have zero embryos cryopreserved, and have only one embryo transferred. Cryopreserved donor oocyte cycles were more likely to be conducted among recipients ≥40 years old and using oocytes retrieved from women <30 years old than fresh donor oocyte cycles. They also were more likely to be conducted among recipients who attended a larger clinic, used ICSI and assisted hatching, and had zero embryos cryopreserved.

Live Birth Rates by Patient and Treatment Characteristics

The only factor significantly associated with live birth among autologous cryopreserved oocyte cycles was cryopreservation of at least one embryo (Table 2). Autologous fresh oocyte cycles had higher rates of live birth among patients of younger age, and patients with no prior pregnancies, births, or ART cycles. Live birth rates varied among autologous fresh oocyte cycles by reason for ART use: rates were significantly higher when the reason for ART was endometriosis, ovulation disorder, male factor infertility, or unexplained infertility, and lower for diminished ovarian reserve, tubal factor infertility, uterine factor infertility, or "other" reason. Autologous fresh oocyte cycles also had higher rates of live birth when ≥11 oocytes were retrieved, at least one embryo from the cycle was cryopreserved, assisted hatching was not used, two or more embryos were transferred, or blastocyst embryos were transferred.

Donor cryopreserved oocyte cycles had higher rates of live birth among recipients with no prior ART cycles or if at least one embryo was cryopreserved. Rates of live birth were higher among donor fresh oocyte cycles when recipients were 30–34 years of age or had an ovulatory disorder, when the woman providing the oocyte was aged <35 years, or when the ART treatment cycle involved the retrieval of ≥11 oocytes, the cryopreservation of at least one embryo, the transfer of two or more embryos, or the transfer of blastocyst embryos. Live birth rates were lower among donor fresh oocyte cycles when recipients had tubal factor infertility.

Outcomes of Cryopreserved Oocyte Cycles Compared with Fresh Oocyte Cycles

When comparing outcomes of autologous cryopreserved oocyte cycles with autologous fresh oocyte cycles, after adjusting for significant covariates, cryopreserved oocyte cycles, transfers, and pregnancies showed no evidence of any difference in the rates of cancellation, implantation, pregnancy, miscarriage, or live birth (Table 3).

When comparing the outcomes of all donor cryopreserved oocyte cycles with all donor fresh oocyte cycles, cryopreserved oocyte cycles had lower cancellation rates before transfer (8.5% vs. 11.5%; adjusted risk ratio [aRR] 0.74, 95% confidence interval [CI] 0.57–0.96), lower pregnancy rates (51.1% vs. 58.5%; aRR 0.88, 95% CI 0.81–0.95), and lower live birth rates (43.0% vs. 49.4%; aRR 0.87, 95% CI 0.80–0.95) after adjusting for significant covariates. However, there was no evidence of a significant difference in implantation, pregnancy, or live birth rate between cryopreserved and fresh oocytes cycles when the cycles were restricted to only those proceeding to transfer.

Among cycles resulting in pregnancy, if the number of embryos transferred was not considered, there was no evidence of a significant difference in miscarriage or live birth rates between cryopreserved and fresh donor oocyte cycles. However, cryopreserved donor oocyte transfers resulting in pregnancy had lower miscarriage rates (12.1% vs. 16.2%; aRR 0.75, 95% CI 0.58–0.97) and higher live birth rates (86.4% vs. 81.9%; aRR 1.05, 95% CI 1.01–1.09) if only one embryo was transferred but higher miscarriage rates (15.9% vs. 12.4%; aRR 1.28, 95% CI 1.07–1.54) and lower live birth rates (82.6% vs. 85.8%; aRR 0.95, 95% CI 0.92–0.99) if two or more embryos were transferred compared with fresh donor oocyte transfers resulting in pregnancy. In additional analysis, when controlling for oocyte age at retrieval, there was no evidence of a difference in live birth rates among single embryo transfers (results not shown).

DISCUSSION

Among patients using their own oocytes, we found no evidence of any significant difference in cancellation, implantation, pregnancy, miscarriage, or live birth rates if the oocytes were previously frozen as compared with fresh. Among patients using donor oocytes, although there were some differences in per-cycle outcomes (cancellation, pregnancy, and live birth rates) and per-pregnancy outcomes (miscarriage and live birth) between cryopreserved and fresh oocyte cycles,

TABLE 1

Characteristics of autologous and donor fresh embryo cycles started in 2013, comparing cryopreserved oocyte and fresh oocyte cycles.

	Autologous cycles					Donor cycles				
	Cryopreserved oocyte[a] cycles		Fresh oocyte cycles			Cryopreserved oocyte[a] cycles		Fresh oocyte cycles		
Characteristic	**n**	**%**	**n**	**%**	***P* value**	**n**	**%**	**n**	**%**	***P* value**
All cycles	422	100.0	93,181	100.0		2,223	100.0	9,691	100.0	
Patient age at cycle start (y)					<.001					<.001
<30	47	11.1	10,864	11.7		27	1.2	282	2.9	
30–34	105	24.9	29,097	31.2		155	7.0	845	8.7	
35–39	111	26.3	32,066	34.4		416	18.7	1,972	20.4	
≥40	159	37.7	21,154	22.7		1,625	73.1	6,591	68.0	
No. of prior pregnancies[b]					.47					.76
0	206	48.9	43,240	46.5		898	40.6	3,851	39.9	
≥1	215	51.1	49,824	53.5		1,313	59.4	5,803	60.1	
No. of prior births[b]					.01					.87
0	334	79.3	67,257	72.3		1,610	72.9	7,064	73.2	
≥1	87	20.7	25,767	27.7		598	27.1	2,584	26.8	
No. of prior ART cycles[b]					<.001					.25
0	62	14.7	53,649	57.7		1,026	46.2	4,092	42.3	
≥1	360	85.3	39,378	42.3		1,197	53.8	5,587	57.5	
Reason for ART										
Diminished ovarian reserve	105	24.9	27,385	29.4	.14	1,799	80.9	7,371	76.1	.11
Endometriosis	31	7.3	8,849	9.5	.22	109	4.9	521	5.4	.64
Ovulation disorder	53	12.6	12,339	13.2	.77	60	2.7	277	2.9	.82
Tubal factor	37	8.8	13,399	14.4	.002	149	6.7	677	7.0	.80
Uterine factor	21	5.0	4,526	4.9	.92	120	5.4	605	6.2	.51
Male factor	165	39.1	32,529	34.9	.32	320	14.4	1,578	16.3	.21
Other	120	28.4	11,960	12.8	<.001	333	15.0	1,846	19.0	.06
Unexplained	26	6.2	13,746	14.8	<.001	133	6.0	426	4.4	.30
Clinic size					<.001					<.001
0–99 cycles	8	1.9	3,936	4.2		9	0.4	327	3.4	
100–199 cycles	13	3.1	9,668	10.4		62	2.8	882	9.1	
200–499 cycles	52	12.3	20,484	22.0		210	9.4	2,133	22.0	
≥500 cycles	349	82.7	59,093	63.4		1,942	87.4	6,349	65.5	
Retrievals only[c]	382	100.0	84,264	100.0		2,136	100.0	9,265	100.0	
Age of woman providing oocyte at time of retrieval (y)[b]					.07					<.001
<30	50	17.3	10,204	12.1		1,484	88.1	7,025	83.7	
30–34	96	33.2	27,328	32.4		199	11.8	1,192	14.2	
≥35	143	49.5	46,732	55.5		—[d]	—[d]	172	2.1	
No. of oocytes retrieved					<.001					—
0–10	75	30.7	40,979	48.6		—[e]	—[e]	1,168	12.6	
≥11	169	69.3	43,285	51.4		—[e]	—[e]	8,097	87.4	
Intracytoplasmic sperm injection[b]	368	97.1	63,835	76.4	<.001	2,124	99.4	7,356	79.5	<.001
No. of embryos cryopreserved[b]					<.001					<.001
0	291	76.6	44,813	54.0		1,063	49.8	1,927	21.0	
≥1	89	23.4	38,215	46.0		1,073	50.2	7,250	79.0	
Transfers only[f]	327	100.0	72,993	100.0		2,033	100.0	8,565	100.0	
Assisted hatching	204	62.4	28,455	39.0	<.001	1,500	73.8	1,586	18.5	<.001
No. of embryos transferred[b]					.02					.11
1	99	30.3	17,173	23.5		799	39.3	2,549	29.8	
≥2	228	69.7	55,820	76.5		1,234	60.7	6,016	70.2	
Embryo stage[b]					—					—
Cleavage (2–3 d)	—[g]	—[g]	32,170	44.1		—[e]	—[e]	1,351	15.8	
Blastocyst (5–6 d)	—[g]	—[g]	39,428	54.1		—[e]	—[e]	7,032	82.3	
Other	—[g]	—[g]	1,306	1.8		—[e]	—[e]	158	1.9	

[a] Cycles started in 2013 where cryopreserved oocytes are thawed with the intent of fertilizing the oocytes and transferring the resulting embryos to the patient.
[b] Missing <1% for prior pregnancies, prior births, prior ART cycles, ICSI; missing 1% for cryopreservation; missing 3% for embryo stage among fresh transfers; missing 9% for oocyte source age among fresh donor retrievals; missing ≥20% for oocyte source age, number of oocytes retrieved, and length of freeze among cryopreserved autologous retrievals and oocyte source age among cryopreserved donor retrievals.
[c] Percentages are among noncanceled cycles (retrievals) only.
[d] Suppressed for confidentiality. Either count was between 1 and 5 or cell contents allowed for the calculation of a count between 1 and 5.
[e] Donor cycles could not be linked to retrieval.
[f] Percentages are among cycles with at least one embryo transferred.
[g] Autologous cycles could be linked to a retrieval, but embryo stage was only available for retrievals resulting in transfer (i.e., not banking cycles).

Crawford. Cryopreserved oocyte cycles. Fertil Steril 2016.

TABLE 2

Live birth rates by cycle- and transfer-level characteristics among autologous and donor, cryopreserved and fresh oocyte cycles started in 2013.

	Autologous cycles				Donor cycles			
	Cryopreserved oocyte[a] cycles		Fresh oocyte cycles		Cryopreserved oocyte[a] cycles		Fresh oocyte cycles	
Characteristic	Live birth, n (%)	*P* value	Live birth, n (%)	*P* value	Live birth, n (%)	*P* value	Live birth, n (%)	*P* value
All cycles	100 (23.7)		27,266 (29.3)		955 (43.0)		4,789 (49.4)	
Patient age at cycle start (y)		.11		< .001		.11		.005
<30	13 (27.7)		4,621 (42.5)		8 (29.6)		135 (47.9)	
30–34	27 (25.7)		11,314 (38.9)		65 (41.9)		465 (55.0)	
35–39	32 (28.8)		9,069 (28.3)		196 (47.1)		1,004 (50.9)	
≥40	28 (17.6)		2,262 (10.7)		686 (42.2)		3,184 (48.3)	
No. of prior pregnancies[b]		.48		< .001		.61		.87
0	52 (25.2)		13,320 (30.8)		394 (43.9)		1,897 (49.3)	
≥1	48 (22.3)		13,919 (27.9)		557 (42.4)		2,871 (49.5)	
No. of prior births[b]		.13		.01		.45		.27
0	84 (25.1)		19,889 (29.6)		684 (42.5)		3,460 (49.0)	
≥1	16 (18.4)		7,336 (28.5)		265 (44.3)		1,306 (50.5)	
No. of prior ART cycles[b]		.33		< .001		.03		.99
0	18 (29.0)		17,709 (33.0)		467 (45.5)		2,023 (49.4)	
≥1	82 (22.8)		9,509 (24.2)		488 (40.8)		2,761 (49.4)	
Reason for ART								
Diminished ovarian reserve	19 (18.1)	.16	4,762 (17.4)	< .001	774 (43.0)	.89	3,627 (49.2)	.66
No diminished ovarian reserve	81 (25.6)		22,504 (34.2)		181 (42.7)		1,162 (50.1)	
Endometriosis	7 (22.6)	.88	2,775 (31.4)	< .001	46 (42.2)	.88	255 (48.9)	.84
No endometriosis	93 (23.8)		24,491 (29.0)		909 (43.0)		4,534 (49.4)	
Ovulation disorder	16 (30.2)	.20	4,610 (37.4)	< .001	32 (53.3)	.05	158 (57.0)	.01
No ovulation disorder	84 (22.8)		22,656 (28.0)		923 (42.7)		4,631 (49.2)	
Tubal factor	—[d]	.05	3,793 (28.3)	.04	59 (39.6)	.37	286 (42.2)	.01
No tubal factor	96 (24.9)		23,473 (29.4)		896 (43.2)		4,503 (50.0)	
Uterine factor	SUPP	.06	1,046 (23.1)	< .001	55 (45.8)	.63	279 (46.1)	.15
No uterine factor	98 (24.4)		26,220 (29.6)		900 (42.8)		4,510 (49.6)	
Male factor	49 (29.7)	.07	10,850 (33.4)	< .001	143 (44.7)	.52	802 (50.8)	.33
No male factor	51 (19.8)		16,416 (27.1)		812 (42.7)		3,987 (49.1)	
Other	23 (19.2)	.20	2,861 (23.9)	< .001	149 (44.7)	.48	930 (50.4)	.57
No other	77 (25.5)		24,405 (30.0)		806 (42.6)		3,859 (49.2)	
Unexplained	—[d]	.26	4,621 (33.6)	< .001	52 (39.1)	.44	194 (45.5)	.47
No unexplained	96 (24.2)		22,645 (28.5)		903 (43.2)		4,595 (49.6)	
Clinic size		.86		.13		.20		.34
0-99 cycles	—[d]		1,129 (26.7)		SUPP		138 (42.2)	
100-199 cycles	—[d]		2,946 (30.5)		21 (33.9)		431 (48.9)	
200-499 cycles	14 (26.9)		6,357 (31.0)		80 (38.1)		1,055 (49.5)	
≥500 cycles	80 (22.9)		16,834 (28.5)		852 (43.9)		3,165 (49.9)	
Transfers only[c]	100 (30.6)		27,265 (37.4)		955 (47.0)		4,788 (55.9)	
Age of woman providing oocyte at time of retrieval (y)[b]		.33		< .001		.93		.02
<30	13 (30.2)		4,549 (50.1)		687 (48.6)		3,654 (56.3)	
30–34	30 (34.9)		11,320 (46.4)		91 (47.2)		625 (56.4)	
≥35	30 (25.2)		11,396 (28.8)		—[d] (50.0)		68 (43.0)	
No. of oocytes retrieved[c]		.18		< .001		—		< .001
0–10	14 (23.3)		10,257 (29.7)		—[e]		487 (47.7)	
≥11	48 (32.7)		17,008 (44.3)		—[e]		4,301 (57.0)	
Intracytoplasmic sperm injection		.92		.46		.38		.08
Yes	98 (30.5)		20,745 (37.2)		951 (47.0)		3,768 (55.1)	
No	—[d]		6,515 (37.8)		—[d]		1,018 (59.0)	
No. of embryos cryopreserved[b]		.001		< .001		< .001		< .001
0	61 (24.6)		10,878 (27.4)		384 (38.9)		786 (44.6)	
≥1	39 (50.6)		16,295 (49.5)		571 (54.6)		3,965 (58.8)	
Assisted hatching		.30		< .001		.13		.07
Yes	58 (28.4)		8,306 (29.2)		683 (45.5)		798 (50.3)	
No	42 (34.1)		18,959 (42.6)		272 (51.0)		3,990 (57.2)	
No. of embryos transferred[b]		.07		< .001		.98		.001
1	24 (24.2)		5,897 (34.3)		375 (46.9)		1,324 (51.9)	
≥2	76 (33.3)		21,368 (38.3)		580 (47.0)		3,464 (57.6)	

Crawford. Cryopreserved oocyte cycles. Fertil Steril 2016.

TABLE 2

Continued.

Characteristic	Autologous cycles: Cryopreserved oocyte[a] cycles Live birth, n (%)	P value	Autologous cycles: Fresh oocyte cycles Live birth, n (%)	P value	Donor cycles: Cryopreserved oocyte[a] cycles Live birth, n (%)	P value	Donor cycles: Fresh oocyte cycles Live birth, n (%)	P value
Embryo stage[b]		—		<.001		—		<.001
Cleavage (2–3 d)	—[f]		8,726 (27.1)		—[e]		583 (43.2)	
Blastocyst (5–6 d)	—[f]		18,132 (46.0)		—[e]		4,112 (58.5)	
Other	—[f]		374 (28.6)		—[e]		83 (52.5)	

[a] Cycles started in 2013 where cryopreserved oocytes are thawed with the intent of fertilizing the oocytes and transferring the resulting embryos to the patient.
[b] Missing <1% for prior pregnancies, prior births, prior ART cycles, ICSI; missing 1% for cryopreservation; missing 3% for embryo stage among fresh transfers; missing 9% for retrieval age among fresh donor retrievals; missing ≥20% for retrieval age, number of oocytes retrieved, and length of freeze among frozen autologous retrievals and retrieval age among frozen donor retrievals.
[c] Percentages are among cycles transferring at least one embryo.
[d] Suppressed for confidentiality. Either count was between 1 and 5 or cell contents allowed for the calculation of a count between 1 and 5.
[e] Donor cycles could not be linked to a retrieval.
[f] Autologous cycles could be linked to a retrieval, but embryo stage was only available for retrievals resulting in transfer (i.e. not banking cycles).

Crawford. Cryopreserved oocyte cycles. Fertil Steril 2016.

there was no evidence of any difference in implantation, pregnancy, or live birth rates among transfers.

Cryopreserved oocyte cycles among patients using donor oocytes had a decreased risk of cancellation before transfer, as well as a decreased likelihood of pregnancy and live birth compared with fresh oocyte cycles when all cycles were considered; however, there was no evidence of any significant difference in outcomes when the analysis was restricted only to cycles proceeding to transfer. This difference in results between all cycles (including canceled cycles) and only cycles proceeding to ET may reflect the removal of canceled cycles because the cancellation rate differed between cryopreserved and fresh oocyte cycles, or the difference in variables considered for adjustment. Transfer-level variables, such as the number of embryos transferred and the number of embryos cryopreserved, were not considered as possible covariates in the cycle-level models because they had missing values for all cycles that did not proceed to retrieval and/or transfer. Many of these variables are important predictors of success and were retained as significant covariates in the transfer-level models.

In addition, for cycles among patients using donor oocytes, there was no evidence of a significant difference in miscarriage or live birth per pregnancy between cryopreserved and fresh oocyte cycles when number of embryos transferred was not considered. However, among all cycles resulting in pregnancy after the transfer of only one embryo, there was a decreased risk of miscarriage and an increased likelihood of live birth, whereas among all cycles resulting in pregnancy after the transfer of two or more embryos, there was an increased risk of miscarriage and a decreased likelihood of live birth for cryopreserved oocyte cycles compared with fresh oocyte cycles. The source of the difference in risk according to the number of embryos transferred is not immediately apparent; however, it could reflect differences in embryo stage or quality, which were not adjusted for during modeling. Goldman et al. (8) and Almodin et al. (9) showed that oocyte cryopreservation may negatively affect the development of an embryo to blastocyst stage; however, Garcia et al. (10) showed no evidence of a difference in cleavage or blastocyst development between fresh and cryopreserved oocyte cycles.

When looking for significant differences in ART cycle, transfer, and pregnancy outcomes between fresh and cryopreserved oocyte cycles, it is notable that although many of the associations were not significant after adjustment for other covariates (see footnotes in Table 3 for a complete list of covariates), many of the differences were significant before adjustment. Although the set of covariates included for adjustment for each outcome differed, for autologous cycles and transfers, patient age and the number of prior ART cycles were significant covariates in all models and seemed to explain the variability in outcomes between fresh and cryopreserved oocyte cycles. In addition, for autologous and donor transfers, the number of embryos cryopreserved and the use of assisted hatching were significant covariates in all models and seemed to explain the variability in outcomes between fresh and cryopreserved oocyte cycles.

Regardless of whether patients used their own oocytes or donor oocytes, cryopreserved oocyte cycles were generally conducted among older patients, as would be expected because cryopreserved oocyte cycles among patients using their own oocytes are commonly used for planned fertility preservation, whereas cryopreserved oocyte cycles among patients using donor oocytes are commonly used when a patient has diminished ovarian reserve and their autologous oocytes will not work. The vast majority of donor cryopreserved oocyte cycles, and donor cycles in general, were conducted with oocytes retrieved from women younger than 30 years, because younger oocytes are associated with higher success rates. In addition, both autologous and donor cryopreserved oocyte cycles used ICSI and assisted hatching more frequently than autologous and donor fresh oocyte cycles, because ICSI has been identified as possibly beneficial for ART procedures involving oocytes that have been cryopreserved (11). Finally, fewer embryos were cryopreserved in cycles using autologous and donor cryopreserved oocytes compared with fresh oocyte cycles. It is likely that fewer cryopreserved oocytes are thawed

TABLE 3

Outcomes of autologous and donor cycles started in 2013, comparing cryopreserved oocyte and fresh oocyte cycles.

	Autologous cycles						Donor cycles					
Outcome	Cryopreserved oocyte[a] cycles (%)	Fresh oocyte cycles (%)	RR[b]	95% CI	aRR[b]	95% CI	Cryopreserved oocyte[a] cycles (%)	Fresh oocyte cycles (%)	RR[b]	95% CI	aRR[b]	95% CI
All cycles[c]												
Cancellation before retrieval/thaw[d]	9.5	9.6	0.99	0.67–1.46	0.93	0.65–1.34	3.9	4.4	0.89	0.60–1.31	0.89	0.60–1.31
Cancellation before transfer	22.5	21.6	1.04	0.83–1.31	0.91	0.75–1.09	8.5	11.5	0.74[f]	0.57–0.96[f]	0.74[f]	0.57–0.96[f]
Pregnancy	29.1	35.7	0.82[f]	0.69–0.97[f]	0.94	0.77–1.13	51.1	58.5	0.87[f]	0.81–0.95[f]	0.88[f]	0.81–0.95[f]
Live birth	23.7	29.3	0.81[f]	0.67–0.97[f]	0.94	0.75–1.17	43.0	49.4	0.87[f]	0.79–0.95[f]	0.87[f]	0.80–0.95[f]
Transfers only[e]												
Implantation	21.7	27.3	0.79[f]	0.65–0.97[f]	1.08	0.86–1.35	39.9	49.0	0.81[f]	0.73–0.91[f]	0.99	0.89–1.09
Pregnancy	37.6	45.6	0.83[f]	0.70–0.98[f]	1.06	0.89–1.25	55.9	66.1	0.85[f]	0.79–0.91[f]	0.97	0.90–1.04
Live birth	30.6	37.4	0.82[f]	0.69–0.98[f]	1.05	0.86–1.30	47.0	55.9	0.84[f]	0.78–0.91[f]	0.98	0.90–1.06
Pregnancies only[e]												
Miscarriage	15.4	15.9	0.97	0.65–1.46	0.72	0.45–1.15	14.5	13.5	1.07	0.94–1.22	1.04	0.92–1.21
1 embryo transferred	—	—	—	—	—	—	12.1	16.2	0.75[f]	0.58–0.95[f]	0.75[f]	0.58–0.97[f]
≥2 embryos transferred	—	—	—	—	—	—	15.9	12.4	1.29[f]	1.08–1.54[f]	1.28[f]	1.07–1.54[f]
Live birth	81.3	82.0	0.99	0.91–1.08	0.98	0.88–1.09	84.1	84.7	0.99	0.97–1.02	0.98	0.96–1.01
1 embryo transferred	—	—	—	—	—	—	86.4	81.9	1.06[f]	1.02–1.10[f]	1.05[f]	1.01–1.09[f]
≥2 embryos transferred	—	—	—	—	—	—	82.6	85.8	0.96[f]	0.93–1.00[f]	0.95[f]	0.92–0.99[f]

[a] Cycles started in 2013 where cryopreserved oocytes are thawed with the intent of fertilizing the oocytes and transferring the resulting embryos to the patient.
[b] Reference group = fresh oocyte.
[c] Adjusted for significant risk factors from the set of all possible cycle-level risk factors. For autologous cycles, significant covariates included patient age, number of prior pregnancies, and diagnoses of diminished ovarian reserve, endometriosis, ovulatory dysfunction, male factor, and unexplained infertility (cancellation before retrieval/thaw); patient age, number of prior pregnancies, number of prior births, and diagnoses of diminished ovarian reserve, tubal factor, male factor, other and unexplained infertility (cancellation before transfer); and patient age, number of prior pregnancies, number of prior births, number of prior ART cycles and diagnoses of diminished ovarian reserve, ovulatory dysfunction, tubal factor, uterine factor, male factor, other and unexplained infertility (pregnancy and live birth). For donor cycles, significant covariates included none (cancellation before retrieval/thaw and cancellation before transfer); patient age and diagnoses of ovulatory dysfunction and tubal factor infertility (pregnancy); patient age, number of prior births and diagnoses of ovulatory dysfunction and tubal factor infertility (live birth).
[d] Retrieval for fresh oocyte cycles and thaw for cryopreserved oocyte cycles.
[e] Adjusted for significant risk factors from the set of all possible cycle-, retrieval- and transfer-level risk factors. For autologous transfers, significant covariates included: patient age, number of prior pregnancies, number of prior births, number of prior ART cycles, diagnoses of diminished ovarian reserve, ovulatory dysfunction, tubal factor, uterine factor, and male factor infertility, use of ICSI, number of embryos cryopreserved, use of assisted hatching, and the number of embryos transferred (implantation); patient age, number of prior pregnancies, number of prior births, number of prior ART cycles, diagnoses of diminished ovarian reserve, ovulatory dysfunction, tubal factor, uterine factor, and male factor infertility, use of ICSI, number of embryos cryopreserved, use of assisted hatching, and number of embryos transferred (pregnancy); patient age, number of prior births, number of prior ART cycles, diagnoses of diminished ovarian reserve, tubal factor, uterine factor, and male factor infertility, use of ICSI, number of embryos cryopreserved, use of assisted hatching, and number of embryos transferred (live birth). For donor transfers, significant covariates included: patient age, number of prior ART cycles, tubal factor infertility, use of ICSI, number of embryos cryopreserved, use of assisted hatching, and number of embryos transferred (implantation); patient age, number of prior ART cycles, diagnoses of ovulatory dysfunction and tubal factor infertility, number of embryos cryopreserved, use of assisted hatching, number of embryos transferred, and clinic size (pregnancy); patient age, number of prior births, number of prior ART cycles, diagnoses of ovulatory dysfunction and tubal factor infertility, number of embryos cryopreserved, use of assisted hatching, and number of embryos transferred (live birth). For autologous pregnancies, significant covariates included: patient age, number of prior pregnancies, number of prior births, diagnoses of ovulatory dysfunction, uterine factor, male factor and unexplained infertility, number of embryos cryopreserved, use of assisted hatching, number of embryos transferred and clinic size (miscarriage); patient age, number of prior pregnancies, number of prior births, diagnoses of ovulatory dysfunction, tubal factor and uterine factor infertility, number of embryos cryopreserved, use of assisted hatching, and number of embryos transferred (live birth). For donor pregnancies, significant covariates included: number of prior pregnancies, number of prior births, tubal factor infertility, and number of embryos transferred (miscarriage), number of prior pregnancies, number of prior births, tubal factor infertility, number of embryos transferred, and clinic size (live birth).
[f] Statistically significant association.

Crawford. Cryopreserved oocyte cycles. Fertil Steril 2016.

for fertilization as compared with the average oocyte yield in a fresh cycle.

The only characteristic significantly associated with live birth for cryopreserved oocyte cycles among patients using their own oocytes was having at least one embryo cryopreserved, an indicator that multiple good-quality embryos were available for transfer; this was also a significant predictor of success for all other cycle types. Cryopreserved oocyte cycles among patients using donor oocytes had one other significant predictor of success: having no prior ART cycles. In comparison, fresh oocyte cycles had a variety of significant predictors of success both among patients using their own oocytes or donor oocytes. Differences in characteristics significantly associated with live birth between cryopreserved and fresh oocyte cycles may be due to the smaller number of cryopreserved oocyte cycles; they may also be due to the preservation of fertility when oocytes are frozen.

This study is the first national study exploring cryopreserved oocyte cycles with the ability to control for other factors that may influence success. Previous studies, many of which were clinic-specific and therefore lacking generalizability, vary in their results. Kushnir et al. (12) found that donor cryopreserved oocyte cycles had worse live birth rates than fresh oocyte cycles; however, because the study used aggregate data, it did not adjust for any factors that might affect live birth rates. Several other studies found that cryopreserved oocyte cycles had success rates that were approaching or not different from those of fresh oocyte cycles (8–10,13,14). Some additional studies compared fresh and cryopreserved oocyte cycles for sibling donations (i.e., those from the same donor but given to different recipients), such that they inherently controlled for characteristics of the donor. These studies also found that frozen oocytes cycles had similar success rates as fresh oocyte cycles (15–18).

This study is subject to several limitations. Because cryopreserved oocyte cycles only became nonexperimental in October 2012, we were only able to analyze the most recent year of ART data collected in NASS, 2013, when these cycles were first reported to the Centers for Disease Control and Prevention. As a result, and because of the low prevalence of cryopreserved oocyte cycles, the sample size was small, resulting in a lack of power to detect differences, particularly for autologous cycles. Additionally, because of some limitations in adapting an existing surveillance system to collect a new type of ART cycle, some important information, such as stage of ET, was not available for the cryopreserved oocyte cycles. Other important variables, such as embryo quality, method of cryopreservation, and mechanism for endometrial preparation also were not included in the analysis, because they are not currently collected for any cycle type in NASS. A recent review of studies comparing the method of cryopreservation found that vitrification may improve pregnancy rates over slow freezing, and therefore may be an important variable for adjustment (19). Comparisons between autologous fresh and autologous frozen oocyte cycles should be interpreted with caution owing to the difference in group sizes and our inability to account for the mechanism of endometrial preparation. As previously noted, age of the woman providing the oocyte was not controlled because of missing data; however, for donor cycles, donor eggs are usually selected from healthy, young donors, as evidenced by the similar age distributions seen in Table 1. Finally, we were unable to look at differences in results based on the reason for oocyte freezing because this field is not captured in NASS.

Oocyte cryopreservation has expanded ART treatment options for many patients, including those needing fertility preservation for medical reasons and those choosing to delay child-bearing who do not want or are unable to fertilize oocytes before freezing. With only some differences in per-cycle and per-pregnancy outcomes between donor cryopreserved and fresh oocyte cycles, our data suggest that after adjusting for other significant factors, there is limited evidence of any difference in outcomes between fresh and cryopreserved oocyte cycles, both for fresh embryo cycles using a patient's own oocytes or donor oocytes. Because oocyte cryopreservation is expected to increase, more work is needed to further explore the impact and safety, both in the short term and longer term, of fertility preservation for the purpose of deferred childbearing (1).

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