Live birth and multiple birth rates in US in vitro fertilization treatment using donor oocytes: a comparison of single-embryo transfer and double-embryo transfer

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Abstract

Objective To compare live birth rates (LBRs) and multiple birth rates (MBRs) between elective single-embryo transfer (eSET) and double-embryo transfer (DET) in donor oocyte in vitro fertilization (IVF) treatments in both a cycle-level and clinic-level analysis.

Methods Donor oocyte IVF treatments performed by US IVF clinics reporting to the Centers for Disease Control and Prevention in 2013–2014 were included in the analysis. Primary outcomes included LBR and MBR. Secondary outcomes included gestational age at delivery (GA) and birth weight (BW) of offspring. These outcomes were evaluated on an individual cycle level as well as on the clinic level.

Results In multivariable models, LBR did not change significantly as clinics utilized eSET more frequently. MBR decreased significantly as utilization of eSET increased, from 39% MBR in clinics that utilized eSET 0–9% of the time to 7% MBR in clinics that used eSET 70% of the time ($P < .0001$). Mean BW and GA of IVF-conceived offspring both increased as clinics utilized eSET more frequently (2778 to 3185 g [$P < .0001$] and 37.5 to 38.5 weeks [$P = .02$] for clinics with the lowest and highest eSET utilization, respectively).

Conclusions US IVF clinics utilizing eSET with higher frequencies have clinically comparable LBRs and significantly lower MBRs than clinics with lower-frequency eSET utilization. Mean offspring BW and GA increased with higher eSET utilization, further confirming the improved safety of this practice.

Keywords Elective single-embryo transfer · Live birth rate · Multiple birth rate · Donor oocyte · IVF

Introduction

Use of donated oocytes for in vitro fertilization (IVF) treatment increases the chance of pregnancy and live birth for infertility patients who have poor oocyte quality or quantity,

often due to older female partner age. In fact, donor oocyte IVF typically has the highest live birth rates (LBRs) of any IVF treatment, with LBRs consistently over 50% in the USA [1]. Due to the increasing age of women interested in child-bearing, relatively high live birth rates, and the increasing availability of cryopreserved oocyte “banks” making treatment easier and less expensive than in the past, the number of treatment cycles using donor oocytes has steadily increased in the USA during the last two decades and there is no sign this trend is changing [1, 2].

Most women using donor oocytes are over 40 years old, and with increasing age comes increasing risk for adverse neonatal and maternal outcomes, including perinatal mortality, preterm birth, fetal growth restriction, gestational diabetes, cesarean delivery, and maternal intensive care unit admission [3, 4]. Compounding these risks are the well-documented

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dangers associated with multiple-gestation pregnancies, the most significant of which are preterm delivery and perinatal death [5]. Acknowledging these risks, the American Society for Reproductive Medicine recommends transferring a single embryo when oocyte donor age is less than 35 years [6]. Despite this, elective single-embryo transfer (eSET; meaning there were at least two embryos available but, electively, only one was transferred, with the others cryopreserved) was used in less than 35% of all transfers using donor oocytes in 2014 [6, 7]. This failure to follow recommendations resulted in nearly one multiple birth for every three live births (30.5% rate of multiple birth outcome) from donor oocyte IVF treatment, with one third of all resulting live births occurring before term [1, 7].

There is pressure for clinics to perform multiple-embryo transfer to improve the possibility of a live birth, especially in a competitive environment where clinics may be unwilling to risk a lower publicly reported LBR, even with the use of donor oocytes. Patients contribute to this pressure as they often associate eSET with a lower pregnancy rate and may not fully understand the risks associated with multiple-gestation pregnancy. In our program, we found that while implementing a single-embryo transfer (SET) policy, we could maintain high LBRs while dramatically decreasing the MBR in both autologous and donor oocyte cycles [8].

The objective of this study was to compare the most recently available data on LBRs and MBRs between eSET and DET in donor oocyte IVF treatment nationwide in an effort to evaluate the assumptions behind DET.

Materials and methods

Cycle-level analysis stratified by embryo stage at transfer and use or non-use of preimplantation genetic screening or diagnosis

We obtained study approval from the Institutional Review Board of the Centers for Disease Control and Prevention (CDC). Using data collected by the CDC's National Assisted Reproductive Technology Surveillance System (NASS), we identified all cycles with the transfer of at least one embryo produced from a donor oocyte in 2013 and 2014, $n = 38,260$. We excluded cryopreserved embryo transfers (ETs) ($n = 17,806$) because information on embryo stage at transfer, use of preimplantation genetic screening or diagnosis (PGS/D), or the source of the donor oocyte (cryopreserved or fresh) was not reported for these cycles. We also excluded cycles where a cryopreserved donor oocyte was used because it was not possible to determine whether a cryopreserved ET or fresh ET was performed or whether PGS/D was utilized ($n = 4616$). Additionally, we excluded 1346 gestational carrier

cycles, 1067 cycles that were not eSET or DET, 220 in which day of ET was not defined, and 16 cycles with missing information regarding use of PGS/D. We excluded cleavage stage transfers that utilized PGS/D ($n = 2$). This left a final sample size of 13,187 fresh ET cycles using embryos created with a fresh donor oocyte. We defined eSET as the transfer of a single embryo when at least one additional embryo was cryopreserved.

We stratified data by embryo stage at transfer (cleavage [days 2–3] versus blastocyst [days 5–6]) and calculated LBRs and MBRs for eligible ETs using eSET versus DET over the 2-year reporting period. LBR was defined as the live birth (at > 20 weeks gestational age [GA]) of at least one child divided by all ETs in a given group (cleavage stage or blastocyst stage). MBR was defined as the percentage of twin and higher-order multiple births among all live births. We also explored secondary outcomes including GA and birthweight at delivery (BW). Preterm delivery was defined as < 37 weeks gestation. For both blastocyst and cleavage stage transfers, we further stratified cycles by recipient age (< 40, 40–45, and > 45 years old) and compared LBRs for eSET versus DET. Two-sample *t* tests, chi-square tests, Fisher's exact tests, and Wilcoxon rank sum tests were used to compare outcomes for eSET and DET cycles.

For blastocyst transfers only, we stratified analyses by use or non-use of PGS/D and compared LBRs, MBRs, and miscarriage rates, defined as the number of clinical pregnancies ending in spontaneous loss prior to completion of 20 weeks gestation divided by the total number of clinical pregnancies.

Adjusted live birth rate estimate by number of embryos available for transfer

For blastocyst transfers only, we estimated adjusted live birth rates (aLBRs) for eSET and DET based on total number of embryos available (2, 3, 4+). The aLBR included the number of embryos transferred plus the number cryopreserved and was calculated using multivariable predicted marginal proportions from logistic regression models including recipient age, number of donor oocytes retrieved, and parity, and accounted for clustering by clinic.

Clinic-level analysis stratified by frequency of eSET use

This analysis included all NASS reporting assisted reproductive technology (ART) clinics that performed at least one fresh ET from a fresh donor oocyte in 2013 or 2014, regardless of clinic size ($n = 436$ clinics, $n = 14,471$ cycles). This represented 88% of all clinics reporting to the CDC in those years. We calculated each clinic's eSET rate

using the total number of cycles that qualified as an eSET divided by the total number of ETs in a clinic. We grouped clinics into the following eSET rate categories: 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and $\geq 70\%$ and assessed LBR and MBR by clinic eSET category. We also investigated average infant BW and GA at delivery per clinic eSET category. We used analysis of variance to assess relevant clinic-specific and patient demographic variables. We constructed linear models to estimate adjusted means for clinic-level LBRs and MBRs for our clinic eSET rate categories and retained all clinic-level covariates that were significant ($P < .05$). For clinic LBR models, retained covariates included average recipient age, frequency of blastocyst transfer, proportion of cycles with non-Hispanic black race/ethnicity, proportion of cycles with Hispanic ethnicity, and frequency of PGS/D. For MBR models, covariates included recipient age and frequency of blastocyst transfer.

All-inclusive clinic-level analysis (fresh and cryopreserved ETs) stratified by frequency of SET use

Lastly, we performed an all-inclusive clinic-level analysis ($n = 462$ clinics, $n = 40,904$ cycles). This included all clinics that performed any donor oocyte cycles—including fresh and cryopreserved donor oocytes as well as fresh and cryopreserved ETs over the same 2-year period. Given previously mentioned limitations, we were unable to discern embryo stage at transfer or whether PGS/D was used. We also have incomplete data on supernumerary embryos available in cryopreserved ET cycles, and thus, we report the SET rate more broadly rather than the eSET rate.

Statistical analyses were conducted using SAS version 9.4 and SUDAAN version 11.0. P values $< .05$ were considered statistically significant.

Results

Cycle-level analysis stratified by embryo stage at transfer and use or non-use of PGS/D: blastocyst ET

PGS/D data excluded

This analysis included 3697 eSET and 6998 DET cycles using fresh blastocysts from fresh donor oocytes excluding cycles using PGS/D. See Table 1 for patient and treatment cycle characteristics. LBR and MBR for eSET versus DET were 54.6 versus 62.0% ($P < .0001$) and 1.3 versus 47.9% ($P < .0001$), respectively. In the eSET group, 14.8% of all deliveries were preterm compared to 38.3%

in the DET group ($P < .0001$); average BW was significantly higher in the eSET versus DET group (3220 versus 2627 g, $P < .0001$). LBR decreased with increasing age in recipients receiving eSET (58.4% in women < 40 years old to 47.8% in women > 45 years old, $P < .0001$), as well as in those undergoing DET (64.4% in women < 40 years old to 56.6% in women > 45 years old, $P < .0001$) (data not shown). aLBRs for eSET and DET were similar when there were only two embryos available to transfer (49.6 versus 52.8%, $P = .33$) and were higher with DET when three or more embryos were available for transfer (52.8 versus 59.2%, $P = .02$).

PGS/D data only

PGS/D was utilized in 312 eSET and 349 DET fresh blastocyst donor cycles (data not shown). The eSET rate was higher in PGS/D cycles compared to non-PGS/D cycles (47.2 versus 34.6%, $P < .0001$). Use of PGS/D was not associated with differences in the LBR, MBR, or miscarriage rate when compared to cycles that did not include PGS/D in either eSET or DET cycles. eSET cycles with PGS/D had a LBR of 56.4 versus 54.6% in cycles without PGS/D ($P = .55$). MBR (1.3 versus 0% for eSET cycles with and without PGS/D, respectively, $P = .16$) and miscarriage rates (14.4 versus 15.5% for eSET cycles with and without PGS/D, respectively, $P = .66$) were also similar between groups. When comparing DET with PGS/D to DET without PGS/D, LBRs were similar (62.0 versus 57.6%, $P = .10$), as were miscarriage rates (10.5 versus 11.3%, $P = .72$), while MBRs were lower with PGS/D (40.8 versus 47.9%, $P = .05$). When comparing eSET versus DET treatment cycles utilizing PGS/D, eSET and DET had similar LBR (56.4% for eSET versus 57.6% for DET, $P = .76$), whereas MBR was much lower with eSET (0% for eSET versus 40.8% for DET, $P < .0001$). Miscarriage rates were also similar between groups (14.4% for eSET versus 10.5% for DET, $P = .22$).

Cycle-level analysis stratified by embryo stage at transfer: cleavage ET

There were 138 eSET and 1693 DET cycles using a cleavage-stage fresh ET utilizing a fresh donor oocyte, excluding PGS/D (data not shown). Average donor age and recipient age were 27 and 41, respectively. LBR did not differ significantly between eSET versus DET (41.3% eSET compared to 44.8% DET, $P = .43$), whereas MBR was significantly higher in the DET group (1.8% eSET versus 29.8% DET, $P < .0001$). eSET was associated with a significantly higher BW than DET (3078 g eSET versus 2796 g DET, $P = .02$). Rate of preterm delivery was significantly lower in eSET (15.8%) versus DET (30.1%; $P = .02$). LBR did not differ by age in recipients receiving

Table 1 Patient characteristics and outcomes of fresh blastocyst (days 5–6) embryo transfer cycles using a fresh donor oocyte in 2013 and 2014, by use of elective single-embryo transfer (eSET) versus double-embryo transfer (DET), excluding cycles that included preimplantation genetic screening/diagnosis (PGS/D)

	eSET (<i>n</i> = 3697)	DET (<i>n</i> = 6998)	<i>P</i> value
Donor age (years), mean (SD)	26.1 (3.2) missing = 5%	26.2 (3.5) missing = 10%	.28
Recipient age (years), mean (SD)	41.4 (5.0)	40.8 (5.42)	<.0001
Body mass index, mean (SD)	25.3 (5.4) missing = 17%	25.8 (5.7) missing = 21%	<.0001
Gravidity, mean (SD)	1.3 (1.6)	1.4 (1.7)	.04
Gravidity, median (IQR)	1.0 (2.0)	1.0 (2.0)	.18
Parity, mean (SD)	0.4 (0.7)	0.4 (0.9)	.01
Parity, median (IQR)	0 (0)	0 (0)	.31
Race/ethnicity			.002
% non-Hispanic white	46.8	46.9	
% non-Hispanic black	4.2	5.1	
% Asian	9.4	8.6	
% Hispanic	3.7	5.1	
% unknown/other	35.8	34.3	
% using ICSI	78.9	80.1	.16
No. of oocytes retrieved, mean (SD)	23.7(10.1)	21.9 (10.3)	<.0001
No. of embryos cryopreserved, mean (SD)	5.7 (4.2)	4.3 (4.3)	<.0001
Implantation rate ^a	65.8	54.0	<.0001
Clinical pregnancy rate ^b	66.0	71.2	<.0001
Live birth rate ^b	54.6	62.0	<.0001
Multiple birth rate ^c	1.3	47.9	<.0001
Number of triplet pregnancies	0	28	<.0001
Rate of preterm deliveries ^c	14.8	38.3	<.0001
Gestational age ^c (weeks), mean (SD)	38.5 (2.6)	36.9 (3.4)	<.0001
% < 24 weeks	0.4	0.9	<.0001
% 24–27 weeks	0.5	1.5	
% 28–31 weeks	1.5	5.0	
% 32–36 weeks	12.5	30.8	
% > 37.0 weeks	85.2	61.7	
Birth weight ^d (g), mean (SD)	3220 (665)	2627 (749)	<.0001
% ≥ 2500 g	88.1	57.2	
% < 2500 g	9.6	35.8	
% < 1500 g	2.3	7.0	

eSET elective single-embryo transfer, DET double-embryo transfer, SD standard deviation, IQR interquartile range, ICSI intracytoplasmic sperm injection

^a Calculated as the number of embryos implanted divided by the total number of embryos transferred, excluding PGD/PGS cycles; if number of fetal heartbeats and number of live and stillborn infants was missing, then implantation rate was considered missing

^b Among transfers. A clinical intrauterine pregnancy requires an ultrasound-confirmed gestational sac within the uterus or the documented occurrence of a birth, spontaneous abortion, or induced abortion in cases of missing ultrasound data. Clinical pregnancies include all gestational sacs regardless of whether or not a heartbeat is observed or a fetal pole is established

^c Among live-birth deliveries

^d Among live-born infants

eSET (45.9% in women < 40 years old to 44.1% in women > 45 years old, *P* = .64) or in those undergoing DET (43.6% in women < 40 years old to 45.9% in women > 45 years old, *P* = .78) (data not shown). As PGS/D was rarely performed on cleavage-stage embryos, these data were not included in the analysis.

All-inclusive clinic-level analysis (fresh and cryopreserved ETs) stratified by frequency of SET use

Overall, 462 clinics performed at least one fresh or cryopreserved ET from either a fresh or cryopreserved donor oocyte

for a total of 40,904 cycles performed in 2013 and 2014. There was a significant increase in LBR with increasing frequency of SET utilization (from 40.8% in the 0–9% SET category to 52.5% in the $\geq 70\%$ SET category [$P = .04$]) and a significant decrease in MBR with increasing frequency of SET utilization (from 33.9% in the 0–9% SET category to 8.8% in the $\geq 70\%$ category [$P < .0001$]) (Fig. 1).

Clinic-level analysis (fresh ETs only) stratified by frequency of eSET use

Four hundred thirty-six clinics performed at least one fresh ET using a fresh donor oocyte in 2013 and 2014. A total of 14,471 treatment cycles were included in the analysis, which demonstrated significant differences in birth outcomes for eSET versus DET (Table 2). Using analysis of variance tests, BW significantly increased as eSET frequency increased (from 2778 g in the 0–9% eSET category to 3185 g in the $\geq 70\%$ eSET category, $P < .0001$); GA at delivery also increased as frequency of eSET increased (from 37.5 weeks in the 0–9% eSET category to 38.5 weeks in the $\geq 70\%$ eSET category, $P = .02$) (Table 2). There was increased frequency of blastocyst transfer with increasing eSET, ranging from 68.9% in the 0–9% eSET category to 92.4% in the $\geq 70\%$ eSET category ($P < .0001$). There was no significant difference in aLBR with increasing eSET utilization ($P = .80$) whereas the adjusted MBR was significantly reduced—from 40% among clinics in the lowest eSET category (0–9%) to 5.5% among clinics in the highest eSET category ($\geq 70\%$) ($P < .0001$) (Fig. 2).

Discussion

This study was developed to re-examine traditional beliefs regarding the purported benefits to individual patients and to IVF clinics of DET over eSET in donor oocyte IVF treatment. It is particularly important to assess treatment outcomes of donor oocyte IVF with an eye to decreasing iatrogenic risks of multiple-gestation pregnancies, as these cycles have a higher success rate due to young oocyte donor age but higher obstetrical risks in the recipient woman due to higher-than-average maternal age. There is clear evidence advanced maternal age and multiple pregnancy increase the risk for adverse obstetric and perinatal events [4, 5]. Furthermore, there is evidence that use of donor oocytes, regardless of recipient age, is an independent risk factor for adverse outcomes such as preeclampsia and preterm birth [9–11]. Thus, multiple-gestation pregnancies in women over 40 using a donor oocyte carry a dangerous combination of risks, and women who use donor oocytes represent a population that can benefit from expansion of eSET utilization [12].

Our study strongly suggests the time is now for a more concerted effort to expand eSET utilization by IVF clinics in donor oocyte treatment. Donor oocyte recipients who undergo blastocyst eSET instead of DET have MBRs that are over 35 times lower, with only a 7.4% percentage point decrease in LBR. And when using cleavage-stage embryos produced from donor oocytes, there is no difference at all in LBR with eSET compared with DET. When we include all fresh and cryopreserved donor oocyte

Fig. 1 Clinic-specific live birth rate (LBR) and multiple birth rate (MBR) for each category of single-embryo transfer (SET) rate (elective and non-elective). These data include the 463 IVF clinics that performed at least one fresh or cryopreserved embryo transfer using a fresh donor oocyte in 2013 or 2014. Total embryo transfer $n = 41,086$. $P = .04$ for LBR, $P = < .0001$ for MBR

Table 2 Characteristics of US fertility clinics ($n = 436$) categorized by frequency of elective single-embryo transfer (eSET) utilization in fresh donor oocyte IVF cycles ($n = 14,471$) performed in 2013 and 2014

	Clinic eSET rate					P value ^a		
	0–9% $N = 166$	10–19% $N = 63$	20–29% $N = 58$	30–39% $N = 40$	40–49% $N = 29$	50–59% $N = 35$	60–69% $N = 11$	$\geq 70\%$ $N = 34$
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Total number of donor cycles	2942	2557	3030	1258	1000	834	2068	782
Number of donor cycles per clinic (mean)	17.7 (28.8)	40.6 (58.1)	52.2 (62.7)	31.5 (37.2)	34.5 (30.3)	23.8 (37.7)	188.0 (404.2)	23.50 (33.8)
Number of donor cycles per clinic (median, IQR)	9.5 (19.0)	25.0 (28.0)	33.5 (45.0)	17.0 (25.5)	20.0 (43.0)	11.0 (23.0)	62.0 (95.0)	9.0 (20.0)
Recipient age (years)	41.1 (3.0)	40.3 (2.1)	40.8 (1.9)	41.2 (1.5)	40.8 (1.8)	41.1 (2.6)	41.1 (1.6)	40.0 (4.3)
Race/ethnicity of clinic patients								
% non-Hispanic white	54.7 (38.6)	52.1 (32.8)	48.8 (35.8)	51.2 (32.0)	45.3 (36.5)	49.3 (32.4)	42.9 (31.2)	46.6 (38.4)
% non-Hispanic black	6.7 (15.2)	4.1 (76.5)	4.5 (8.5)	4.7 (8.5)	3.5 (6.1)	6.1 (13.1)	3.5 (4.4)	2.0 (3.8)
% Asian	6.8 (16.5)	8.4 (14.9)	5.8 (9.0)	7.1 (13.6)	6.0 (9.9)	10.5 (14.5)	16.1 (12.6)	16.7 (29.3)
% Hispanic	9.3 (20.4)	8.8 (15.8)	3.7 (5.6)	7.2 (10.9)	8.3 (19.7)	4.7 (7.8)	5.5 (9.6)	5.8 (17.2)
% other	0.1 (0.6)	0.03 (0.2)	0.2 (0.8)	0	0	0	0.1 (0.4)	0
% unknown/missing	22.4 (37.5)	26.6 (37.1)	36.9 (42.3)	29.9 (37.1)	36.9 (40.1)	29.3 (39.5)	31.9 (33.3)	28.9 (40.8)
Parity	0.5 (0.5)	0.5 (0.4)	0.4 (0.2)	0.4 (0.3)	0.4 (0.2)	0.3 (0.3)	0.3 (0.1)	0.3 (0.4)
No. of embryos transferred	2.1 (0.3)	1.9 (0.1)	1.8 (0.1)	1.6 (0.1)	1.6 (0.1)	1.5 (0.1)	1.3 (0.03)	1.1 (0.1)
% day 2–3 embryo transfers	24.4 (34.0)	20.0 (29.5)	16.0 (22.9)	11.1 (14.9)	12.3 (14.0)	10.9 (17.8)	15.6 (26.2)	5.2 (9.6)
% day 5–6 transfers	68.9 (35.19)	78.8 (29.3)	81.4 (23.4)	86.8 (15.6)	86.0 (13.6)	87.8 (17.6)	82.7 (26.4)	92.4 (11.3)
% ICSI cycles	78.4 (31.3)	78.1 (26.3)	77.4 (28.3)	83.4 (23.3)	77.7 (23.8)	76.6 (28.5)	79.6 (22.3)	73.8 (29.6)
% PGS/D cycles	6.5 (18.5)	5.2 (11.2)	3.8 (7.0)	6.3 (12.9)	4.8 (10.3)	5.1 (13.8)	5.3 (10.6)	4.0 (10.4)
Live birth rate (per cycle)	54.3 (27.6)	55.2 (13.9)	55.9 (12.8)	57.6 (18.9)	53.9 (18.2)	51.7 (26.3)	60.3 (17.6)	59.6 (28.0)
Twin birth rate (per delivery)	38.0 (30.0)	35.8 (17.1)	35.3 (18.2)	30.3 (18.4)	22.6 (3.3)	28.3 (22.6)	16.8 (7.2)	7.0 (8.2)
Triplet + birth rate (per delivery)	0.6 (4.4)	2.0 (12.6)	0.7 (1.6)	0.7 (4.0)	0.1 (0.5)	0.3 (1.4)	0.01 (0.05)	0.06 (0.3)
Average birthweight (g)	2778 (462)	2719 (306)	2758 (295)	2777 (390)	2870 (512)	2817 (426)	2964 (167)	3185 (515)
Average gestational age (weeks)	37.5 (1.7)	37.2 (1.2)	37.4 (1.3)	37.5 (1.2)	37.4 (2.7)	37.5 (1.7)	38.2 (0.6)	38.5 (1.0)

Includes all clinics that reported to the National Assisted Reproductive Technology Surveillance System and performed at least one fresh embryo transfer using a fresh donor oocyte in 2013 and 2014
eSET elective single-embryo transfer, SD standard deviation, IQR interquartile range, ICSI intracytoplasmic sperm injection, PGS/D preimplantation genetic screening or diagnosis

^a P value compares means between eSET categories

Fig. 2 Clinic-specific live birth rate (LBR) and multiple birth rate (MBR) for each category of elective single-embryo transfer (eSET) rate. These data include the 436 IVF clinics that performed at least one fresh embryo transfer using a fresh donor oocyte in 2013 or 2014. Total embryo transfer $n = 14,471$. Estimated means for LBR and MBR after adjusting for significant confounding variables are shown, with 95% confidence

interval bars. $P = .80$ for LBR, $P = <.0001$ for MBR. Clinic LBR models were adjusted for average recipient age, frequency of blastocyst transfer, proportion of cycles with non-Hispanic black race/ethnicity, proportion of cycles with Hispanic ethnicity, and the frequency of PGS/D. MBR models were adjusted for recipient age and frequency of blastocyst transfer

cycles, LBRs actually increase in those clinics in the higher categories of SET utilization. When we restricted the clinic-level analysis to only fresh ETs from fresh donor oocytes, and then analyzed embryo transfers to only *elective* SETs, LBRs did not vary significantly by eSET clinic category, even among clinics performing eSET $\geq 70\%$ of the time. These data support the widespread use of eSET in donor oocyte cycles and suggest clinics can be comfortable knowing an increase in eSET utilization will not reduce LBRs.

Most likely due to the significantly lower likelihood of multiple-gestation births, birth outcomes in women receiving eSET as compared to DET were much improved in BW and GA. This held true both when treatment outcomes were evaluated on an individual cycle level and on the clinic level. Women who received eSET delivered a full week and a half later on average than women receiving DET, and their infants' mean BW was nearly 600 g higher. The rate of preterm birth was also significantly lower—14.7% in women receiving eSET compared to 38.1% in women receiving DET. Patients receiving care from clinics that utilized eSET for $\geq 70\%$ of their donor oocyte cycles had offspring deliver about a week later and with birthweights approximately 400 g higher than patients of clinics performing 0–9% of their cycles as eSET. Quite clearly, when a clinic increases their utilization of eSET, they improve neonatal health outcomes and reduce societal healthcare costs.

Limitations of our study include its retrospective, observational design. Although we attempted to control for confounding variables that may have affected our primary outcomes, there may be others that cannot be assessed such as laboratory quality and experience with eSET. Furthermore, due to limitations in data reporting, we were unable to include outcomes from cryopreserved ETs or from cycles utilizing a cryopreserved donor oocyte in our cycle-level analysis. Recent publications suggest success rates are comparable for fresh and cryopreserved oocytes and cryopreserved ET has comparable, and perhaps improved, success when compared to fresh ET [13, 14]. Indeed, our analysis shows that when we include fresh and cryopreserved ETs as well as fresh and cryopreserved donor oocytes, as clinic SET rates increase, LBR actually increases whereas MBR significantly declines. Lastly, we are not able to assess cumulative pregnancy success rates in donor oocyte recipients.

Conclusions

The best outcome of IVF is a healthy singleton pregnancy, and as our findings suggest, implementing clinic-level SET policies for donor oocyte recipients will be an important step towards achieving that goal. As we struggle to find medical means of reducing preterm birth, this is a relatively simple way to reduce one of its truly iatrogenic causes. Changing

ET practices in this population has the potential to have a profound effect on the well-being of the patient, the child conceived using ART, as well as the healthcare system as a whole.

Compliance with ethical standards

We obtained study approval from the Institutional Review Board of the Centers for Disease Control and Prevention (CDC).

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

- Centers for Disease Control and Prevention ASfRM, Society for Assisted Reproductive Technology. 2014 Assisted reproductive technology national summary report. US Dept of Health and Human Services. 2016.
- Kawwass JF, Monsour M, Crawford S, Kissin DM, Session DR, Kulkarni AD, et al. Trends and outcomes for donor oocyte cycles in the United States, 2000–2010. *JAMA*. 2013;310(22):2426–34.
- Fitzpatrick KE, Tuffnell D, Kurinczuk JJ, Knight M. Pregnancy at very advanced maternal age: a UK population-based cohort study. *BJOG*. 2017;124(7):1097–106.
- Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. *Obstet Gynecol*. 2005;105(6):1410–8.
- ACOG Practice Bulletin No. 144. Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol*. 2014;123(5):1118–32.
- Practice Committee of Society for Assisted Reproductive T, Practice Committee of American Society for Reproductive M. Elective single-embryo transfer. *Fertil Steril*. 2012;97(4):835–42.
- Society for Assisted Reproductive Technology 2014 National summary report. (Accessed 9 Aug 2017 at <https://www.sartcorsonline.com/>).
- Kresowik JD, Stegmann BJ, Sparks AE, Ryan GL, van Voorhis BJ. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. *Fertil Steril*. 2011;96(6):1367–9.
- Dude AM, Yeh JS, Muasher SJ. Donor oocytes are associated with preterm birth when compared to fresh autologous in vitro fertilization cycles in singleton pregnancies. *Fertil Steril*. 2016;106(3):660–5.
- Letur H, Peigne M, Ohl J, Cedrin-Dumerin I, Mathieu-D'Argent E, Scheffler F, et al. Hypertensive pathologies and egg donation pregnancies: results of a large comparative cohort study. *Fertil Steril*. 2016;106(2):284–90.
- Storgaard M, Loft A, Bergh C, Wennerholm UB, Soderstrom-Anttila V, Romundstad LB, et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. *BJOG*. 2017;124(4):561–72.
- Simchen MJ, Shulman A, Wiser A, Zilberberg E, Schiff E. The aged uterus: multifetal pregnancy outcome after ovum donation in older women. *Hum Reprod (Oxford, England)*. 2009;24(10):2500–3.
- Crawford S, Boulet SL, Kawwass JF, Jamieson DJ, Kissin DM. Cryopreserved oocyte versus fresh oocyte assisted reproductive technology cycles, United States, 2013. *Fertil Steril*. 2017;107(1):110–8.
- Wang A, Santistevan A, Hunter Cohn K, Copperman A, Nulsen J, Miller BT, et al. Freeze-only versus fresh embryo transfer in a multicenter matched cohort study: contribution of progesterone and maternal age to success rates. *Fertility and Sterility*. 2017.