Comparison of perinatal outcomes following frozen embryo transfer cycles using autologous versus donor oocytes in women 40 to 43 years old: analysis of SART CORS data

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Abstract

Objective To study the differences in perinatal outcomes after frozen embryo transfer cycles using autologous or donor oocytes in women of advanced maternal age.

Design Historical cohort study.

Setting US national database from the Society of Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) from 2009 to 2013.

Patient(s) Women at 40–43 years of age undergoing autologous frozen embryo transfers (a-FET) or donor oocyte frozen embryo transfers (d-FET) resulting in singleton pregnancies that were entered in the SART CORS database from 2009 to 2013.

Results a-FET resulted in 4402 singleton live births whereas d-FET resulted in 2703 singleton live births. d-FET resulted in a higher risk of preterm births (< 37 weeks), with adjusted odds ratio (aOR) 1.33 (95% CI 1.02–1.75), but similar risk of small for gestational age (SGA), with aOR 1.75 (95% CI 0.85–3.7), when compared to a-FET. However, when only single blastocyst transfer cycles are considered, d-FET and a-FET showed no difference in preterm births or other adverse perinatal outcomes.

Conclusions Singletons resulting from d-FET are at increased risk for perinatal morbidity. However, the risk was diminished in single blastocyst transfer cycles. Our study supports the current American Society for Reproductive Medicine (ASRM) guidelines of transferring a single blastocyst in d-FET cycles.

Keywords Donor oocyte · Frozen embryo transfer · Pregnancy outcome · SART CORS · Advanced maternal age

Introduction

Changes in the social, cultural, and professional attitudes in the last several decades have led to a trend of delayed female reproduction. The mean maternal age of the first live birth has increased from 24.9 years in 2000 to 26.3 years in 2014 [1]. Diminished ovarian reserve associated with advanced

maternal age and iatrogenic causes such as cancer treatments have resulted in a greater utilization of oocyte donation as a means for assisted reproduction. In 2015, oocyte donation encompassed 9.8% of all Assisted Reproductive Technology (ART) cycles reported to the Society for Assisted Reproductive Technologies Clinic Outcome Reporting System (SART CORS) with an average live birth rate of 46.2% [2]. Although now a commonly used technique, data showing perinatal safety and outcomes of babies born following oocyte donation are still lacking. In women of advanced maternal age, there is a well-documented linear relationship between increasing age and risk of genetic abnormalities as well as obstetrical complications, such as preeclampsia, gestational diabetes, preterm delivery, small for gestational age, intrauterine growth restriction, and cesarean section [3–5]. However, the mechanisms underlying this age-related deterioration in neonatal and obstetric outcomes are unclear. Proposed mechanisms include poor oocyte quality resulting from ovarian aging, unfavorable uterine environment, co-

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morbidities associated with advanced maternal age, or a combination of these factors.

Mixed results have been found in previously published studies on perinatal outcomes from donor oocyte ART cycles. Dude et al. demonstrated an increased risk for preterm deliveries among donor oocyte recipient cycles. In that study, donor oocyte cycles were found to have a higher risk for small for gestational age newborns, but this was likely related to the higher proportion of preterm deliveries [6]. Similarly, other studies have found increased rates of prematurity in donor oocyte cycles [7–9]. Contrary to these findings, two age-matched studies comparing women undergoing autologous or donor oocyte ART cycles found no difference in preterm deliveries or SGA; however, they were limited by small sample sizes [10, 11]. Notably, a recent meta-analysis found that donor oocyte cycles are at higher risk of adverse perinatal outcomes including preterm deliveries, SGA, and low birth weight [12]. However, the heterogeneous patient population and ART cycle characteristics included in these studies deter our interpretation of the data, leaving the above stated question of the impact of age on neonatal and obstetric outcomes unanswered.

The objective of this study is to compare the perinatal outcomes from singleton pregnancies in patients of advanced age (40–43 years of age) undergoing autologous frozen embryo transfers (a-FET) or embryo transfers using donor oocytes (d-FET). Only FET cycles were included in order to control for the uterine hormonal environment between the two groups. A narrow age range helped to control the general maternal health as a confounding factor in the analyses.

Patients and methods

Study design and population

After Institutional Review Board and SART Research Committee approval, a population-based historical cohort study of ART cycles from the SART CORS database from 2009 to 2013 was performed. Inclusion criteria were women 40–43 years of age undergoing a-FET or d-FET cycles. Cycles undergoing preimplantation genetic testing (PGT), cycles with more than 1 neonate born, neonates < 24 weeks or < 500 g or without recorded outcomes, were excluded. Variables analyzed included age, race, BMI, smoking status, etiology of infertility, maximum historical early follicular phase FSH, gravidity, parity, history of prior preterm births, number of embryos transferred, day of embryo transfer (cleavage vs. blastocyst stage), implantation rate, vanishing twins, clinical pregnancy rate, pregnancy loss rate, live birth rate, preterm birth rate, stillborn rate, small for gestational age, and number of live born babies. Small for gestational age (< 10% expected weight for gestational age) was obtained by

using birth weight and controlling for the gestational age, using the World Health Organization weight percentiles calculator [13]. Preterm birth was defined as birth before 37 weeks of gestation and extremely preterm birth was defined as birth before 28 weeks of gestation. We controlled for the following confounding variables: age, BMI, smoking status, gravidity, prior full-term births, prior preterm births, number of embryos transferred, vanishing twins, blastocyst transfer, and single blastocyst transfer.

Outcome measures

The primary outcome measure was preterm birth rate. Secondary outcomes included the rates for small for gestational age, low birth weight, and pregnancy loss. A sub-analysis of patients undergoing single blastocyst transfer was performed.

Statistical analysis

Stata 12.1 was used for statistical analyses. Student's *t* test was used to compare continuous data that were normally distributed. Fisher's exact and Chi-square tests, as appropriate, were used to compare categorical data. Generalized Estimating Equations (GEE) were used to control for repeated cycles from a single patient and to control for possible confounders as listed above. Outcomes were reported as adjusted odds ratios (aOR) with 95% confidence intervals. Statistical significance was set at $p < 0.05$.

Results

Between 2009 and 2013, a total of 156,873 ART cycles were performed in patients 40–43 years of age. Of these, 21,637 were a-FET and 10,125 were d-FET cycles, resulting in 18,653 and 8447 transfers respectively. Demographic and ART cycle characteristics of patients who underwent embryo transfers are presented in Table 1. Patients undergoing a-FET were slightly younger than patients undergoing d-FET cycles (41.1 ± 1.1 vs. 41.7 ± 1.1 , $p < 0.0001$) and were less likely to be of the white race (44.3% vs. 48.4%, $p < 0.001$). Of note, in a-FET cycles, the age at the time of embryo cryopreservation that resulted in live births was even younger (39.6 ± 3.5), and 2.5% of these a-FET live births resulted from embryos frozen at maternal age of less than 35 years. Patients undergoing a-FET cycles were also less likely to undergo SET (16.3% vs. 21.7%, $p < 0.0001$) or blastocyst transfer (54.5% vs. 64%, $p < 0.0001$), and more likely to have a higher number of embryos transferred (1.8 ± 1.1 vs. 1.6 ± 0.9 , $p < 0.0001$).

A total of 3602 clinical pregnancies (42.6% per transfer) were achieved in the d-FET group, resulting in 2669 live births and 870 pregnancy losses (Table 2). A total of 6622 clinical pregnancies (35.5% per transfer) led to 4402 live

Table 1 Demographic and ART characteristics of transferred cycles

	a-FET <i>n</i> = 18,653	d-FET* <i>n</i> = 8447	<i>p</i> value
Age (years)	41.1 (± 1.1)	41.7 (± 1.1)	< .0001
BMI (kg/m ²)	25.3 (± 5.6)	25.2 (± 5.6)	0.95
Ever smoker	1215 (7.4%)	543 (7.4%)	0.90
Race, <i>N</i> (%)			
- Black/African America	1049 (5.6%)	371 (4.4%)	0.002
- Hispanic/Latino	1083 (5.8%)	293 (3.5%)	< .0001
- Asian	1804 (9.7%)	674 (8.0%)	0.001
- White/Caucasian	8269 (44.3%)	4084 (48.4%)	< .0001
- Other	92 (0.5%)	31 (0.4%)	0.30
- Not entered	6356 (34.1%)	2994 (35.4%)	0.03
Maximum baseline FSH (mIU/ml)	8.9 (± 6.5)	15.3 (± 17.1)	< .0001
Gravidity	1.9 (± 1.7)	1.9 (± 1.7)	0.33
Prior full-term births	0.7 (± 0.9)	0.6 (± 0.8)	< .0001
Prior preterm births	0.13 (± 0.38)	0.11 (± 0.33)	0.01
Number of total embryos transferred	1.8 (± 1.1)	1.6 (± 0.9)	< .0001
Blastocyst transfer	10,183 (54.5%)	5409 (64.0%)	< .0001
Single blastocyst transfer	1820 (16.3%)	1172 (21.7%)	< .0001
Vanishing twins	257 (5.9%)	130 (4.9%)	0.08

Data presented as mean ± SD for continuous data and *n* (%) for categorical data

*In d-FET cycles, characteristics of the donor oocyte recipients are reported

births and 2120 pregnancy losses in the a-FET group. As expected, d-FET cycles resulted in a higher live birth rate

per transfer than a-FET cycles in this age group (31.6% vs. 23.6%, $p < 0.0001$; aOR 1.41, 95% CI 1.23–1.59). Also,

Table 2 Pregnancy outcomes

Pregnancy outcome	a-FET (<i>n</i> = 18,653)	d-FET (<i>n</i> = 8447)	<i>p</i> value
Gestational age*			
- 24–27 weeks	32 (0.7%)	27 (1.0%)	0.20
- 28–34 weeks	163 (3.7%)	153 (5.7%)	< .0001
- 35–36 weeks	673 (15.2%)	431 (16.1%)	0.33
- 37–41 weeks	3459 (78.3%)	2024 (75.8%)	0.01
- > 41 weeks	90 (2.0%)	42 (1.56%)	0.16
Clinical pregnancies	6622 (35.5%)	3602 (42.6%)	< .0001
Ectopic pregnancies	78 (0.4%)	44 (0.5%)	0.24
Biochemical pregnancies	2132 (11.4%)	1000 (11.8%)	0.32
Live births	4402 (23.6%)	2669 (31.6%)	< .0001
Pregnancy losses	2120 (11.4%)	870 (10.3%)	0.01
Stillbirths	22 (0.1%)	19 (0.2%)	0.03
Number of heart beats on ultrasound	1.1 (± 0.3)	1.1 (± 0.3)	0.13
Number of baby per live birth	1.0 (± 0.05)	1.0 (± 0.05)	0.63
Weight in grams*			
- < 2500	296 (6.8%)	280 (10.6%)	< .0001
- 2500–4500	3955 (90.8%)	2314 (87.8%)	< .0001
- > 4500	106 (2.4%)	43 (1.6%)	0.03
Small for gestational age*	94 (2.2%)	71 (2.7%)	0.24

*Percentages were calculated based on live births. (The other percentages were calculated based on the total number of transfers)

unsurprisingly, d-FET had lower rates of pregnancy loss than a-FET cycles (10.3% vs. 11.4% per transfer, $p = 0.01$; aOR 0.77, 95% CI 0.64–0.93) (Tables 2 and 3).

Compared to a-FET group, the d-FET group had higher preterm birth rates (22.8% vs 19.6%, $p < 0.001$) and higher rates of low birth weight (10.6% vs 6.8%, $p < 0.0001$) (Table 2). After adjusting for confounders, we found that the increased risk for preterm births and low birth weight in the d-FET group remained significant (aOR 1.33, 95% CI 1.02–1.75, and aOR 1.92, 95% CI 1.26–2.86, respectively) (Table 3). Interestingly, once the gestational age was taken into account for low birth weight cases, we did not find a difference in the rate for SGA between the d-FET and a-FET cycles (2.7% vs 2.2%, $p = 0.24$; aOR 1.75, 95% CI 0.85–3.70) (Tables 2 and 3).

A sub-group analysis of patients undergoing single blastocyst transfers revealed that d-FET had higher live birth rate per transfer when compared to a-FET (d-FET vs a-FET 50.2% vs 44.9%, respectively; aOR 1.45, 95% CI 1.06–2.00). Pregnancy loss rates were similar among both groups (d-FET vs a-FET 18.3% vs 25.6%, respectively; aOR 1.09, 95% CI 0.64–1.92). Pregnancy outcomes were similar between d-FET and a-FET cycles in this sub-group, including rates of low birth weight (d-FET vs a-FET 10.1% vs 8.2%, respectively; aOR 1.05, 95% CI 0.39–2.78), preterm birth rates (d-FET vs a-FET 14.3% vs 15.6%, respectively; aOR 0.85, 95% CI 0.44–1.64), and SGA rates (d-FET vs a-FET 10.1% vs 10.1%, respectively; aOR 0.22, 95% CI 0.02–2.17) (Tables 2 and 3).

Discussion

To our knowledge, this is the first study comparing perinatal outcomes after FET cycles using autologous versus donor oocytes in an age-matched cohort. Our study shows that d-FET cycles resulted in a higher preterm birth rate and a higher rate of low birth weight than a-FET cycles. Interestingly, this effect was not seen when analyzing only cycles with single blastocyst transfers.

Previous studies have reported mixed results when comparing oocyte donor cycles with autologous cycles. A recent meta-analysis, including seven retrospective studies, reported that donor oocyte recipient cycles were at increased risks for preterm births (OR 1.45, 95% CI 1.20–1.77) and low birth weight (OR 1.34, 95% CI 1.12–1.60), when compared to fresh autologous cycles [12]. Two of the studies that were included in the meta-analysis compared frozen autologous embryo transfers and frozen donor embryo transfers. They found a higher risk of early preterm births (gestational age < 32 weeks) and higher risk of very low birth weight (< 1500 g) in the frozen donor embryo transfer group (OR 3.3, 95% CI 1.21–9.01; and OR 1.65, 95% CI 0.92–2.96, respectively) [12]. Another large SART CORS-based retrospective study on donor oocyte recipient cycles compared to fresh autologous IVF cycles found an increased risk of preterm births (aOR 1.28, 95% CI 1.12–1.46), but a decreased risk of low birth weight when adjusted for gestational age, aOR 0.72 (95% CI 0.58–0.89), and of perinatal death (aOR 0.29, 95% CI 0.09–0.94) [6].

The strengths of our study include the following: (1) Large sample size, (2) Only FET cycles were included in order to control for the uterine hormonal environment, (3) A narrow age range (40–43 years of age) helped control for the general maternal health, and (4) Multiple possible confounding variables were controlled for in the final analyses, including age, BMI, smoking status, gravidity, prior full-term births, prior preterm births, number of embryos transferred, vanishing twins, blastocyst transfer, and single blastocyst transfer. Consistent with some of the previous studies, we also found an increased risk for low birth weight and preterm births in the d-FET cycles compared to a-FET cycles. Furthermore, although we found an increased risk of lower birth weight in the d-FET cycles, when the gestational age was considered, the SGA rates were similar between the two groups, indicating that the low birth weight was associated with the increase in preterm birth rate, in agreement with two previous studies [4, 7]. Interestingly, we found that single blastocyst transfer negated the above risks associated with

Table 3 Pregnancy outcome comparisons of all cycles and single blastocyst transfer cycles

Outcome	All d-FET vs. a-FET aOR (95% CI)	Single blastocyst transfer d-FET vs. a-FET aOR (95% CI)
Preterm births	1.33 (1.02–1.75)	1.17 (0.61–2.27)
Live birth	1.41 (1.23–1.59)	1.45 (1.06–2.00)
Pregnancy loss	0.77 (0.64–0.93)	1.09 (0.64–1.92)
Stillbirth	0.60 (0.15–2.38)	0.81 (0.05–12.50)
Low birth weight < 2500 g	1.92 (1.26–2.86)	1.05 (0.39–2.78)
Small for gestational age	1.75 (0.85–3.70)	0.22 (0.02–2.17)

Variables adjusted for in the analysis include age, BMI, smoking status, gravidity, prior full-term births, prior preterm births, number of embryos transferred, vanishing twins, blastocyst transfer, and single blastocyst transfer

donor oocyte FET cycles, resulting in similar preterm birth and SGA rates as compared to a-FET cycles. Additionally, the pregnancy loss and live birth rates were similar in the two groups after single blastocyst transfers. These sub-group analysis findings indicated that embryo quality and quantity transferred is the determining factor for perinatal outcomes in women of advanced maternal age.

As a historical cohort study, our study has several limitations. Although ART outcome data submitted to SART CORS has been validated, recall bias very likely exists since all births and perinatal outcome data are self-reported. Further, most but not all clinics in the USA report to SART. Our study spans 5 years (2009–2013), during which different freezing and thawing techniques may have been used. Although it does not appear that vitrification and subsequent thawing affects perinatal outcomes [14], we cannot confirm that all cycles underwent vitrification vs. slow freeze. We had limited access to perinatal outcomes and could not include other variables that may have a direct impact on gestational age at time of delivery such as gestational hypertension, preeclampsia, or gestational diabetes [15–17]. Another limitation is that we do not have information on the age of the patient at the time the embryos were frozen in a-FET cycles.

In conclusion, our study suggests that singletons resulting from d-FET are at increased risks for perinatal morbidity. This risk is however offset when a single blastocyst is transferred. These findings therefore support the use of single embryo transfer in donor oocyte recipient cycles, in accordance with recent ASRM guidelines [18]. Future research efforts are needed to investigate the exact mechanisms associated with higher perinatal morbidity in d-FET cycles as compared to a-FET cycles, but our findings suggest that embryo quality and quantity transferred are the main determining factors for perinatal outcomes in women of advanced maternal age.

References

- Mathews TJ, Hamilton BE. Mean age of mothers is on the rise: United States, 2000–2014. *NCHS Data Brief* 2016 (232):1–8.
- Society for Assisted Reproductive Technology 2015 [Available from: www.sart.org/SART_Success_Rates/].
- Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Impact of maternal age on obstetric outcome. *Obstet Gynecol*. 2005;105(5 Pt 1):983–90.
- Jacobsson B, Ladhoff L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol*. 2004;104(4):727–33.
- Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, et al. Human aneuploidy: incidence, origin, and etiology. *Environ Mol Mutagen*. 1996;28(3):167–75.
- 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.
- Henne MB, Zhang M, Paroski S, Kelshikar B, Westphal LM. Comparison of obstetric outcomes in recipients of donor oocytes vs. women of advanced maternal age with autologous oocytes. *J Reprod Med*. 2007;52(7):585–90.
- Klatsky PC, Delaney SS, Caughey AB, Tran ND, Schattman GL, Rosenwaks Z. The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies. *Obstet Gynecol*. 2010;116(6):1387–92.
- Malchau SS, Loft A, Larsen EC, Aaris Henningsen AK, Rasmussen S, Andersen AN, et al. Perinatal outcomes in 375 children born after oocyte donation: a Danish national cohort study. *Fertil Steril*. 2013;99(6):1637–43.
- Krieg SA, Henne MB, Westphal LM. Obstetric outcomes in donor oocyte pregnancies compared with advanced maternal age in in vitro fertilization pregnancies. *Fertil Steril*. 2008;90(1):65–70.
- Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, Verheyen G, et al. Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. *Reprod Biol Endocrinol*. 2012;10:42.
- Mascarenhas M, Sunkara SK, Antonisamy B, Kamath MS. Higher risk of preterm birth and low birth weight following oocyte donation: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2017;218:60–7.
- Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gulmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. *Lancet*. 2011;377(9780):1855–61.
- Barsky M, St Marie P, Rahil T, Markenson GR, Sites CK. Are perinatal outcomes affected by blastocyst vitrification and warming? *Am J Obstet Gynecol*. 2016;215(5):603 e1–5.
- Jevé YB, Potdar N, Opoku A, Khare M. Three-arm age-matched retrospective cohort study of obstetric outcomes of donor oocyte pregnancies. *Int J Gynaecol Obstet*. 2016;133(2):156–8.
- Vidal M, Vellve K, Gonzalez-Comadran M, Robles A, Prat M, Tome M, et al. Perinatal outcomes in children born after fresh or frozen embryo transfer: a Catalan cohort study based on 14,262 newborns. *Fertil Steril*. 2017;107(4):940–7.
- Masoudian P, Nasr A, de Nanassy J, Fung-Kee-Fung K, Bainbridge SA, El Demellawy D. Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2016;214(3):328–39.
- Practice Committee of the American Society for Reproductive Medicine, Electronic address Aao, Practice Committee of the Society for Assisted Reproductive T. Guidance on the limits to the number of embryos to transfer: a committee opinion. *Fertil Steril*. 2017;107(4):901–3.