Improved outcomes after blastocyst-stage frozen-thawed embryo transfers compared with cleavage stage: a Society for Assisted Reproductive Technologies Clinical Outcomes Reporting System study

Emily C. Holden, M.D.,[a] Banafsheh N. Kashani, M.D.,[a] Sara S. Morelli, M.D., Ph.D.,[a,b] Donald Alderson, M.S.,[c] Sangita K. Jindal, Ph.D., H.C.L.D.,[d] Pamela A. Ohman-Strickland, Ph.D.,[e] and Peter G. McGovern, M.D.[a,b]

[a] Obstetrics, Gynecology and Women's Health, Rutgers—New Jersey Medical School, Newark, New Jersey; [b] University Reproductive Associates, Hasbrouck Heights; [c] Rutgers University Biostatistics and Epidemiology Services Center, Rutgers University, Newark, New Jersey; [d] Montefiore's Institute for Reproductive Medicine and Health, Hartsdale, New York; and [e] Biostatistics, Rutgers School of Public Health, Piscataway, New Jersey

Objective: To investigate whether there is a difference in obstetrical and perinatal outcomes in blastocyst frozen-thawed embryo transfers (FETs) compared with cleavage-stage FET.

Design: A retrospective cohort study.

Setting: Not applicable.

Patient(s): Women undergoing autologous FETs at either the blastocyst stage (n = 118,572) or the cleavage stage (n = 117,619) reported to the Society for Assisted Reproductive Technology in the years 2004–2013.

Intervention(s): None.

Main Outcome Measure(s): Live birth, gestational age, birth weight, miscarriage.

Result(s): After controlling for confounders, there were a 49% increased odds of live birth after blastocyst-stage FET compared with cleavage-stage FET (odds ratio [OR] = 1.49; 95% confidence interval [CI], 1.44, 1.54). Additionally, blastocyst FET was associated with a 68% (OR = 1.68; 95% CI, 1.63, 1.74) increased odds of clinical pregnancy and an 7% (OR = 0.93; 95% CI, 0.88, 0.92) decreased odds of miscarriage. There was also a 16% increased odds of preterm delivery (OR = 1.16; 95% CI, 1.06, 1.27) after blastocyst FET but no difference in birth weights.

Conclusion(s): In patients undergoing FET, blastocyst-stage transfer is associated with higher live-birth rates when compared with cleavage-stage transfers. Furthermore, perinatal outcomes are similar between the groups. (Fertil Steril® 2018;110:89–94. ©2018 by American Society for Reproductive Medicine.)

This abstract is available in Spanish at the end of the article.

Key Words: Blastocyst, cleavage, frozen embryo transfer

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Assisted reproductive technologies (ART) and IVF specifically have now resulted in many thousands of successful pregnancies each year. In the United States, it is estimated that 1.6% of infants born every year are conceived using ART (1). In recent years, with the advent of vitrification and improved IVF cycle outcomes after blastocyst transfer (2), there has been an increase in blastocyst-stage frozen-thawed embryo transfers (FETs). However, there is little high-quality evidence comparing obstetrical and perinatal outcomes of cleavage-stage FETs to blastocyst-stage FETs, as noted in a 2016 Cochrane review (2).

Most studies comparing cleavage-stage FET to blastocyst-stage FET suggest no difference in cycle outcomes (3–11). Despite insufficient data to support blastocyst-stage FET, many IVF clinics have implemented blastocyst FET for their patients. It is well known that pregnancies conceived through IVF are at increased risk for obstetrical and neonatal complications including preterm delivery and low birth weight (12). While these risks may be mitigated in FET cycles (13, 14), it is important to determine whether there are significant differences in outcomes between blastocyst-stage and cleavage-stage FETs.

Using the Society for Assisted Reproductive Technologies Clinical Outcomes Reporting System (SART-CORS) database, the aim of this study was to investigate whether there is a difference in obstetrical and perinatal outcomes in FET cycles among cleavage-stage versus blastocyst-stage embryos. We hypothesized that blastocyst-stage FETs have better pregnancy outcomes, specifically higher numbers of live births and fewer preterm deliveries. In addition, we hypothesized that birth weights are higher in live births that resulted from blastocyst-stage FETs.

MATERIAL AND METHODS

All IVF cycles reported to SART-CORS over a 10-year period (2004–13) were evaluated. Data were collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493 [15]). Ninety-five percent of IVF cycles in the United States are reported through the SART registry (16). Validation of the data collected through SART-CORS occurs annually. Some clinics have on-site visits for chart review based on an algorithm for clinic selection. During the site visit, data reported by the clinic were compared with information recorded in patients' charts. In a recent review of validation of site visit results, 90.9% (10/11) of the data fields selected were found to have discrepancy rates of ≤5% (17).

Only frozen, autologous cycles were included in the analysis. Exclusion criteria included fresh IVF cycles and IVF cycles using donor oocytes. Furthermore, only cycles with treatment and pregnancy outcomes were included. The primary study outcome assessed was live-birth rate. Secondary study outcomes included clinical pregnancy and miscarriage rates, preterm delivery, birth weights, and stillbirths. Demographic criteria from the cycles were also collected.

The following associated SART-defined terms and definitions were used in this study. *Live birth* is defined as a fetus showing signs of life after delivery. *Clinical intrauterine gestation* is defined as an intrauterine pregnancy visible on ultrasound. *Stillbirth* is defined as a birth at 18 weeks or later from the date of transfer in which no fetus showed signs of life after delivery. *Preterm delivery* is defined as a delivery before 37 weeks of gestation. *Low birth weight* infants are those with a birth weight less than 2,500 g and *very low birth weight* infants are those with a birth weight less than 1,500 g. Analyses also looked at weights greater than 4,000 and 4,500 g.

Statistical analysis was performed using both SAS 9.4, SAS Institute and Microsoft Excel, version 14.7.6. $P<.05$ was considered statistically significant. Adjusted and unadjusted associations between outcomes and blastocyst stage (vs. cleavage stage) were examined using generalized estimating equations using logit links for binary outcomes and identity links for continuous outcomes. These models adjust tests for repeated measures from women with multiple treatment cycles and assume equicorrelation between observations belonging to the same woman. Perinatal outcomes were evaluated among cycles with one live birth. Cochran-Mantel-Haenszel tests examined bivariate associations between perinatal weights and blastocyst (vs. cleavage) stage. Again, generalized linear models examined associations. Sensitivity analyses evaluated all associations adjusted for reporting year to evaluate the possibility that improved outcomes are due to improved medical practices rather than use of blastocyst over cleavage stage. This study was approved by the Rutgers Health Sciences Institutional Review Board and the SART Research Committee before the release of the data to our institution.

RESULTS

A total of 236,191 FET cycles from 171,901 patients (with between one and 13 cycles per patient) that occurred from 2004 through 2013 were analyzed. All cycles performed before 2006 were cleavage-stage FETs. Blastocyst-stage FET cycles were first reported in 2006 and comprised 12% of all FET cycles. Blastocyst-stage FETs continued to increase yearly thereafter, rising to 78% in 2013. Use of blastocyst-stage FETs significantly increased over time ($P<.0001$), as seen in Supplemental Figure 1.

Regional data on FET trends became available in 2010. For the purpose of analyzing regional use of blastocyst FET over time, the United States was broken up into four regions: midwest, northeast, south, and west. The south had the highest use of blastocyst FETs in 2010. The northeast region had the lowest use in 2010 (58%) but grew to the highest by 2013 (81%). Within each of the four regions, rates of blastocyst FET use significantly increased over time ($P<.0001$), as seen in Supplemental Figure 2.

Demographic data from the FET cycles are shown in Table 1. Although there were statistically significant differences in the demographic characteristics between blastocyst-stage and cleavage-stage FET cycles in terms of age, body mass index (BMI), gravidity, parity, maximum serum FSH, and prior IVF cycles ($P<.0001$), differences were not large enough to be clinically meaningful and likely secondary to our large sample size. Cleavage-stage FET cycles

TABLE 1

Demographic data for FET cycles from 2004 through 2013.

Variable	Cleavage stage (n = 117, 619)	Blastocyst stage (n = 118, 572)	P value
Maternal age, y	33.8	33.4	<.0001
BMI, kg/m^2	25.2	25.1	.0051
Smoking status, %	7.2	5.2	<.0001
Maximum serum FSH, IU/mL	7.3	7.4	<.0001
Gravidity	1.4	1.5	<.0001
Prior full-term birth	0.7	0.6	<.0001
Prior preterm birth	0.1	0.1	<.0001
No. of embryos thawed	3.4	2.3	<.0001
No. of embryos transferred	2.3	1.8	<.0001
Prior fresh cycles	1.5	1.6	<.0001
Prior frozen cycles	0.5	0.5	<.0001

Note: Values are expressed as the mean. *P* values are the result of generalized estimating equation models, accounting for repeated cycles within women, with identity links for continuous outcomes and logit (log-odds) links for binary outcomes. It should be noted that due to the relatively large sample sizes, most differences are statistically significant. However, this does not indicate that the difference is practically significant or meaningful in a clinical setting.

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were found to have more smokers than blastocyst FET cycles (7.2% compared with 5.25%, *P*<.0001). Cleavage-stage FET cycles also had fewer single ETs compared with the blastocyst FET cycles (5.4% vs. 20.2%, *P*<.0001).

Blastocyst FET cycles had significantly increased cumulative pregnancy rates (60.6% vs. 47.7%), clinical intrauterine gestations (48.5% vs. 37.4%), and live-birth rates (37.9% vs. 28.8%) when compared with cleavage-stage FET cycles (*P*<.0001; Table 2). Improved success for blastocyst-stage FET was achieved using both fewer embryos thawed (*P*<.0001) and fewer embryos transferred (*P*<.0001; Table 2). When controlling for maternal age at embryo freeze, BMI, smoking, prior IVF cycles, maximum serum FSH, and number of embryos transferred to the uterus, blastocyst-stage FET resulted in 49% increased odds of a live birth compared with cleavage-stage FET (odds ratio [OR] = 1.49;

TABLE 2

Unadjusted cycle outcome data of all FET cycles included in the analysis.

Outcome	Cleavage stage (n = 117, 619)	Blastocyst stage (n = 118, 572)	P value
Live birth	28.8	37.9	<.0001
Cumulative pregnancy	47.7	60.6	<.0001
Biochemical pregnancy	9.8	11.6	<.0001
Clinical intrauterine gestation	37.4	48.5	<.0001
Ectopic pregnancy	0.5	0.4	.026
Heterotopic pregnancy	0.02	0.03	.44
One live birth[a]	77.4	77.8	.0025
Two live births[a]	21.2	21.4	
Three or more live births[a]	1.4	0.8	

Note: All data are percentages. *P* values are derived from generalized linear models, accounting for repeated cycles within women, with logit links. Number of live births calculated out of those with at least one live birth.
[a] *P* value for number of live births derived from Cochran-Mantel-Haenszel χ^2 test.

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TABLE 3

Comparison of perinatal outcomes of live births are shown from pregnancies resulting in one live birth.

Outcome	Cleavage stage	Blastocyst stage	P value
Gestational age at delivery, wk	38.7	38.6	.030
Birth weight, g	3,368	3,367	.87
Highest birth weight (>4,500 g), %	2.0	2.1	.91
High birth weight (>4,000 g, <4,500 g), %	10.4	10.1	
Normal birth weight (>2,500 g, <4,000 g), %	80.3	80.7	
Low birth weight (>2,000 g, <2,500 g), %	5.6	5.6	
Very low birth weight (<2,000 g), %	1.6	1.6	

Note: P values are the result of generalized estimating equations or Cochran-Mantel-Haenszel χ^2 as appropriate.

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95% confidence interval [CI], 1.44, 1.54) (Table 4). Similar results were seen for clinical pregnancy rates, in which blastocyst-stage FET resulted in 68% increased odds of having a live clinical pregnancy compared with cleavage-stage FET (OR = 1.68; 95% CI, 1.63, 1.74) (Table 4). There were also 7% lower odds of miscarriage after blastocyst FET when controlling for the above factors (OR = 0.93; 95% CI, 0.88, 0.98) (Table 4). No differences were seen in ectopic pregnancy or heterotopic pregnancy rates (*P*=.42 and *P*=.50, respectively).

When adjusting analyses by year of procedure, results retained direction of associations and significance levels. In some cases, the ORs were somewhat attenuated given the strong level of multicollinearity between the year and use of blastocyst versus cleavage stage.

Perinatal outcomes of blastocyst-stage compared with cleavage-stage FET for patients with one live birth are shown in Table 3. Mean gestational age at delivery for blastocyst-stage FET was 270.8 days compared with 271.1 days for cleavage-stage FETs. Mean birth weights were 3,368 g compared with 3,367 g for cleavage stage compared with blastocyst stage, respectively. In singleton pregnancies, after adjusting for maternal age at freezing, BMI, smoking, prior fresh IVF cycles, and maximum serum FSH, there were 16% increased odds of having a delivery before 37 weeks after blastocyst FET compared with cleavage-stage FET (OR = 1.16; 95% CI, 1.06, 1.27) (Table 4), but no significant change in odds of having a birth weight less than 2,500 g (OR = 0.95; 95% CI, 0.85, 1.06) (Table 4). The mean rate of neonatal death was 0.7% and 0.5% for cleavage-stage and blastocyst-stage FET, respectively (*P*=.0077). However, after adjusting for the above confounders, there was no difference in odds of neonatal death between the groups (OR = 0.78; 95% CI, 0.55, 1.12). Cleavage-stage FETs were found to have a 0.4% still birth rate compared with 0.5% in blastocyst-stage FETs (*P*=.17).

DISCUSSION

This study is the first national database analysis comparing trends in use and outcomes after cleavage-stage and

TABLE 4

Adjusted outcome data for frozen ET cycles.

Outcome	Adjusted odds ratios	Confidence interval
Live birth	1.49	1.44, 1.54
Clinical pregnancy rate	1.68	1.63, 1.74
Miscarriage rate	0.93	0.88, 0.98
Preterm delivery <37 wk gestation	1.16	1.06, 1.27
Birth weight <2,500 g	0.95	0.85, 1.06

Note: Analyses controlled for maternal age at embryo freeze, BMI, smoking, prior IVF cycles, maximum serum FSH, and number of embryos transferred to the uterus. Live birth, clinical pregnancy rate, and miscarriage rate included all frozen ET cycles. Preterm delivery and birth-weight analyses included singleton pregnancies only.

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blastocyst-stage FET. It is also the largest cohort study to date comparing the two and the only study to incorporate perinatal outcomes into its analysis. Additionally, our primary outcome of live-birth rate was not analyzed in most earlier publications on this topic.

Our results demonstrate a significant increase in live-birth rates with blastocyst FET compared with cleavage-stage FET, even when controlling for confounders. Similarly, we found significantly higher clinical pregnancy rates as well as decreased odds of miscarriage after blastocyst FET. Our results are similar to those reported in previous studies comparing outcomes after fresh blastocyst-stage transfers to fresh cleavage-stage transfers (2, 8) and are likely secondary to embryo self-selection and improved synchronization between the embryo and the endometrium in blastocyst transfer cycles.

Additional secondary outcomes of this study included preterm delivery rates, birth weights, and stillbirths. There was no difference in mean gestational age at delivery. After controlling for maternal factors, slightly increased odds of having a preterm delivery in the blastocyst FET group compared with cleavage-stage FET were noted. Despite these small increased odds, no difference was found in the odds of having a low birth weight infant. These findings suggest that the increased odds of having a preterm delivery may not be clinically meaningful.

There have been few studies analyzing pregnancy outcomes between blastocyst and cleavage-stage FET. There are three published randomized control trials, all with less than 100 cycles in each comparison group and all before the advent of vitrification (3, 6, 18). The remainder of studies are mostly retrospective, except for one prospective observational study (8). Most studies comparing blastocyst-stage and cleavage-stage FETs have demonstrated no significant difference in cycle outcomes (3–11), with one small randomized control trial favoring cleavage-stage FET (18). There have only been two studies to date that favor blastocyst-stage FET over cleavage-stage FET (19, 20). Our study provides further evidence in support of the ongoing national trend toward blastocyst-stage over cleavage-stage FET. Despite most clinics performing blastocyst-stage FETs, cleavage-stage FETs are still being performed in up to 20% of clinics. Our results should encourage physicians to continue to shift their practices toward more blastocyst-stage FETs and away from cleavage-stage FETs.

Our study limitations include its retrospective nature, the rapid change in IVF practices and technologies that occurred over the study period, and the limitations of the SART-CORS data set. It is not possible to know how many embryos were cryopreserved by slow freeze technology or by vitrification during this study period; therefore, this confounding variable cannot be controlled in the analysis. We were also unable to determine whether blastocyst transfers led to embryo loss when compared with cleavage-stage transfers. It is possible that the best-quality embryos were transferred back to the patient during a fresh cycle, while secondary-quality embryos were cryopreserved during the earlier years analyzed in this data set. These FET cycles are grouped with more recent FET cycles whereby all embryos may have been frozen, including the best-quality embryos, a shift in practice patterns that cannot be controlled for in analysis. The increasing use of pre-implantation genetic testing has not been included as a variable in this analysis. In our data set, the few number of cycles recorded as having undergone preimplantation genetic screening or diagnosis precluded us from performing meaningful analysis.

Conclusion

Blastocyst-stage FET is superior to cleavage-stage FET with regards to increasing live-birth rates and decreasing miscarriage rates. In addition to improved cycle outcomes, perinatal outcomes after blastocyst-stage FET are comparable to cleavage-stage FET. These findings provide strong evidence in support of the safety and efficacy of blastocyst-stage FET.

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Mejores resultados después de transferencias de embriones congelados-descongelados en estadio de blastocisto en comparación con embriones en estadio de segmentación: Un estudio del Sistema de Informes de Resultados Clínicos de la Sociedad para las Tecnologías de Reproducción Asistida

Objetivo: Investigar si existen diferencias en los resultados obstétricos y perinatales al comparar las transferencias de embriones congelados (TECs) en estadio de blastocisto vs las TEC en estadio de segmentación.

Diseño: : Estudio retrospectivo de cohortes.

Configuración: No aplicable.

Pacientes: Mujeres que se realizaron TECs autólogas tanto en estadio de blastocisto (n=118572) como en estadio de segmentación (n=117619), cuyos ciclos fueron reportados a la Sociedad para la Tecnología de la Reproducción Asistida (Society for Assisted Reproductive Technology) durante los años 2004-2013.

Intervención: Ninguna.

Principales medidas de resultados: Nacidos vivos, edad gestacional, peso al nacimiento, aborto.

Resultados: Después de controlar los factores de confusión, se observó un 49% más de probabilidades de nacidos vivos después de TEC en estadio de blastocisto comparado con TEC en estadio de segmentación (odds ratio [OR]= 1,49; intervalo de confianza del 95% [IC] 1,44; 1,54). Además, la TEC de blastocistos se asoció con un 68% (OR = 1,68; IC 95%; 1,63; 1,74) de incremento de las probabilidades de gestación clínica, y disminuyeron las probabilidades de aborto involuntario en un 7% (OR = 0,93; IC 95%; 0,88; 0,92). También se observó un 16% de aumento de las probabilidades de parto prematuro (OR = 1,16; IC del 95%; 1,06; 1,27) después del TEC con blastocisto, pero sin diferencias en el peso al nacimiento.

Conclusiones: En los pacientes sometidos a TEC, la transferencia en estadio de blastocisto se asocia a mayores tasas de nacidos vivos en comparación con las transferencias en estadio de segmentación. Por otro lado, los resultados perinatales son similares en ambos grupos.
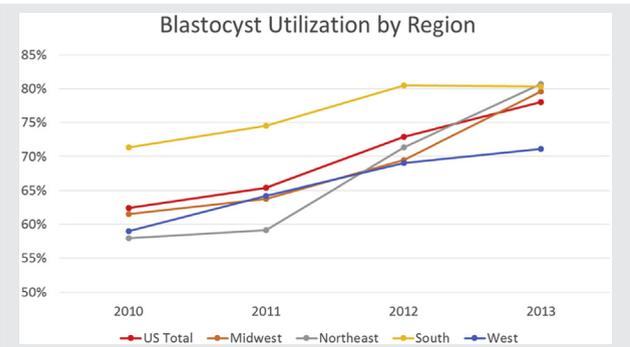
SUPPLEMENTAL FIGURE 1
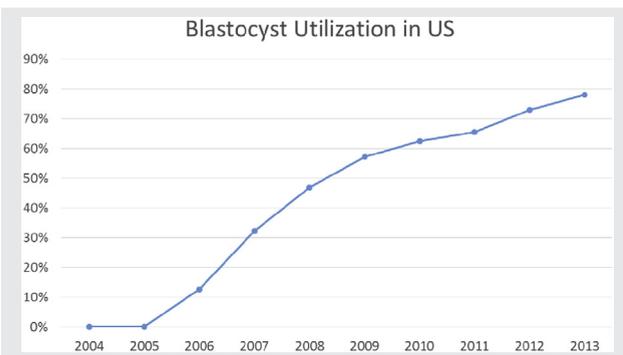
Blastocyst use over time is shown. There was no use in 2004 and 2005. Usage in 2006 was 12%, increasing in each year afterward, up to 78% in 2013. The use over time was significantly different ($P<.0001$) based on a χ^2 test.

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SUPPLEMENTAL FIGURE 2

Blastocyst use by region is shown. Data were available only from 2010 forward. The south region had the highest level in 2010. The northeast region had the lowest use in 2010 but grew to the highest by 2013. Within each of the four regions, the rates significantly changed over time (*P* values for each region <.0001) based on a χ^2 tests.

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