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Association between embryo morphological quality and birth weight for singletons conceived via autologous fresh embryo transfer: an analysis using Society for Assisted Reproductive Technology Clinical Outcomes Reporting System

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Objective: To determine if morphologically suboptimal embryo quality is associated with adverse perinatal outcomes.
Design: A retrospective cohort.
Setting: SART CORS database.
Patient(s): Singletons conceived from autologous in vitro fertilization fresh cycles.
Intervention(s): None.
Main Outcome Measure(s): Birth weight (gram), birth weight z-score, low birth weight (LBW), small for gestational age (SGA), and large for gestational age (LGA).
Result(s): Among 5,869 in vitro fertilization fresh cycles, 71.1% transferred morphologically good embryos, and 27.0% and 1.9% transferred fair and poor embryo(s), respectively. Compared with singletons conceived from good embryos, singletons from poor embryos had a higher birth weight (3,415.8 ± 562.0 vs. 3,202.7 ± 639.9). Proportions of LBW, SGA, and LGA were comparable across embryo quality groups. Multivariate regression analysis comparing perinatal outcomes from fair vs. good embryos showed no association for birth weight (0.69-gram difference; 95% CI, -24.30–25.68), birth weight z-score (Coefficient, 0.00; 95% CI, -0.07–0.08), LBW (adjusted odds ratio [aOR], 0.84; 95% CI, 0.63–1.11), SGA (aOR, 0.93; 95% CI, 0.78–1.11), and LGA (aOR, 1.07; 95% CI, 0.86–1.33). Stratified analysis, considering cleaved and blastocyst embryo transfers separately, confirmed these findings. Sensitivity analysis revealed increased odds of LGA (aOR, 1.53; 95% CI, 1.04–2.24) with fair-quality embryos only among single embryo transfer cycles.
Conclusion(s): Once a singleton live birth from fresh embryo transfer is achieved, fair morphological embryo quality is not associated with a reduction in birth weight or increased risks of LBW, SGA, and LGA. (Fertil Steril® 2022;118:715-23. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Embryo quality, embryo morphology, birth weight, singleton perinatal outcomes, IVF autologous fresh transfer

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Received February 22, 2022; revised June 14, 2022; accepted June 15, 2022; published online August 5, 2022.
M.L. has nothing to disclose. B.S. holds a patent on a diagnostic kit to determine quality of human oocytes; Vice Chair LGBT Special Interest Group ASRM. V.L.B. reports grants from NIH, consulting fees from IBSA, payment for expert testimony, and presidential chain of the Society for Assisted Reproductive Technology.
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Fertility and Sterility® Vol. 118, No. 4, October 2022 0015-0282/$36.00
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https://doi.org/10.1016/j.fertnstert.2022.06.017

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Multiple studies have documented that embryo morphological quality plays a critical role in the success of in vitro fertilization (IVF) treatment; specifically, an embryo with top quality is associated with a significantly higher likelihood of successful implantation and later live birth (1–5). Most studies suggest that the implantation rate is lower for poor-quality embryos (6). A few studies, which examined ongoing pregnancy rates among embryos with documented implantation, reported no statistical difference in rates of clinical pregnancy and live birth for poor vs. good or fair-quality embryos (2). In clinical practice, it is not uncommon that only embryos with suboptimal quality are available for transfer, and these embryos are transferred when no other embryos are available (7–9).

Although implantation and live birth may occur from the transfer of embryos with suboptimal morphologic quality (2, 4, 7, 10), only a few studies have examined whether live birth after the transfer of a poor or fair-quality embryo is associated with adverse birth outcomes (1, 9, 11–14).

The *Society for Assisted Reproductive Technology* (SART) is the primary organization of professionals dedicated to the practice of assisted reproductive technologies in the United States. The member clinics of SART report their data using the SART Clinical Outcomes Reporting System (SART CORS). In SART CORS, embryos are categorized on the basis of the descriptions of "good, fair, and poor" categories included in the instructions provided to clinics who enter the data. Using a national database, the current study aims to examine whether embryo quality is associated with perinatal outcomes of birth weight, birth weight z-score (Z-score), low birth weight (LBW), small for gestational age (SGA), and large for gestational age (LGA). This study will also evaluate whether these relationships differ by embryo developmental stage. Because of the increased risk of adverse outcomes with multiple gestations (15–17), this analysis is limited to singleton births.

MATERIALS AND METHODS

Study Population

This retrospective cohort study was performed using the SART CORS database, which contains the data that 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). The SART CORS data are validated annually, with some clinics having on-site visits for chart review on the basis of an algorithm for clinic selection. During each visit, data reported by the clinic are compared with the information recorded in the patients' charts. Of 11 data fields selected for validation, 10 were found to have discrepancy rates of $\leq 5\%$ (18).

All autologous IVF cycles with fresh embryo transfer resulting in a live birth with outcome data confirmed by direct physician/hospital review of medical records from 2008–2013 were included in the initial data set (n = 34,031). Cycles with multiple births (n = 21,772) were subsequently excluded. We focused on singleton live births because birth outcomes from multiple pregnancies are influenced by many factors related to the presence of >1 fetus, making it challenging to detangle the effects of embryo quality from those because of multiple gestations. We limited the analysis to fresh cycles because embryo quality was only available for fresh transfers. Because it is impossible to determine which embryo led to live birth if there were embryos transferred of different quality, we excluded cycles transferring more than 2 embryos or those transferring 2 embryos of different quality (n = 5,818).

To facilitate subsequent analysis stratified by embryo developmental stage, we further excluded cycles with the transfer of an embryo identified as one-cell (n = 150) or morula (n = 391). Among cycles with the transfer of 2 embryos, we removed cycles with embryos with different developmental stages at transfer (n = 6). Because of extremely low viability and high neonatal mortality, cycles with gestational age <23 weeks, almost all (95%) developed from good-quality embryos, were further excluded (n = 20) (19). Lastly, cycles with neonate of clinically impossible birth weight (n = 1, >10,000 g) and with gestational age >44 weeks (n = 4) were removed because of the unavailability of birth weight reference as documented by Talge et al. (20). The final analytical sample included 5,869 cycles (Supplemental Fig. 1, available online).

Predictor and Outcome Measures

The key predictor is overall embryo gradings (poor vs. fair vs. good) collected from the field of embryo morphology reported in SART CORS. The embryologist assigned a quality grade for embryo morphology in each clinic using specific criteria provided by SART. These criteria consider the embryo's characteristics, such as fragmentation, symmetry, inner cell mass (ICM), or trophectoderm quality. The good-fair-poor rating is used for both cleaved embryos and blastocysts, but the specific criteria used for the rating differ for cleaved embryos compared with blastocysts (21). The validity of this good-fair-poor rating has been reported and validated by multiple studies demonstrating a positive relationship between live birth rate and transfer of good-quality embryos (21–27). Perinatal outcomes were analyzed as birth weight (continuous: in gram), birth weight z-score (continuous), LBW defined as birth weight <2,500 gram (no vs. yes), SGA defined as birth weight <10% for gestational age and sex (no vs. yes), and LGA defined as birth weight >90% for gestational age and sex (no vs. yes). Singleton birth weight z-scores and categorization of SGA and LGA were calculated and operationalized per standardized singleton birth weight national data reported by Talge et al. (20). Specifically, the birth weight z-score for each singleton was derived by subtracting the gestational age- and sex-specific mean birth weight value from the singleton's birth weight (in grams) and then dividing the resulting value by gestational age- and sex-specific SD.

Data Analysis

Covariates (maternal age, body mass index [BMI] [normal {ref} vs. underweight, overweight, obese], race [Caucasian {ref} vs. American Indian or Alaska Native, Asian, African American, Hispanic or Latino, Native Hawaiian], miscarriage

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TABLE 1

Maternal demographics, obstetric history, and in vitro fertilization fresh treatment cycle parameters among study population.

	Overall (N = 5,869) N (%)	Good (N = 4,172) N (%)	Fair (N = 1,586) N (%)	Poor (N = 111) N (%)
Year of treatment cycle[a,b,c]				
2008	609 (10.38)	463 (11.10)	141 (8.89)	5 (4.50)
2009	811 (13.82)	516 (12.37)	261 (16.46)	34 (30.63)
2010	995 (16.95)	705 (16.90)	270 (17.02)	20 (18.02)
2011	1,007 (17.16)	706 (16.92)	285 (17.97)	16 (14.41)
2012	1,204 (20.51)	867 (20.78)	319 (20.11)	18 (16.22)
2013	1,243 (21.18)	915 (21.93)	310 (19.55)	18 (16.22)
Maternal age at the start of treatment cycle[a,d]				
Mean ± SD	32.71 ± 3.83	32.59 ± 3.80	32.99 ± 3.84	33.50 ± 4.62
Maternal race				
White	4,496 (76.61)	3,199 (76.68)	1,207 (76.10)	90 (81.08)
American Indian or Alaska native	9 (0.15)	9 (0.22)	0 (0.00)	0 (0.00)
Asian	655 (11.16)	470 (11.27)	175 (11.03)	10 (9.01)
African American	302 (5.15)	205 (4.91)	89 (5.61)	8 (7.21)
Hispanic/Latino	385 (6.56)	271 (6.50)	111 (7.00)	3 (2.70)
Native Hawaiian	22 (0.37)	18 (0.43)	4 (0.25)	0 (0.00)
BMI				
Normal	2,843 (48.44)	2,021 (48.44)	777 (48.99)	45 (40.54)
Underweight	141 (2.40)	105 (2.52)	33 (2.08)	3 (2.70)
Overweight	1,172 (19.97)	817 (19.58)	332 (20.93)	23 (20.72)
Obese	809 (13.78)	558 (13.37)	237 (14.94)	14 (12.61)
Missing	904 (15.40)	671 (16.08)	207 (13.05)	26 (23.42)
Smoking (3 mo before the treatment cycle)[a,e]				
Average none or <1 cigarette	4,265 (72.67)	2,918 (69.94)	1,263 (79.63)	84 (75.68)
Average 1–9 cigarettes	49 (0.83)	41 (0.98)	8 (0.50)	0 (0.00)
Average 10–20 cigarettes	22 (0.37)	19 (0.46)	3 (0.19)	0 (0.00)
Average >20 cigarettes	5 (0.09)	5 (0.12)	0 (0.00)	0 (0.00)
Missing	1,528 (26.04)	1,189 (28.50)	312 (19.67)	27 (24.32)
Parity				
Nulliparous	3,016 (51.39)	2,186 (52.40)	780 (49.18)	50 (45.05)
Parous	2,848 (48.53)	1,983 (47.53)	804 (50.69)	61 (54.95)
Missing	5 (0.09)	3 (0.07)	2 (0.13)	0 (0.00)
Miscarriage[a]				
No	2,439 (41.56)	1,781 (42.69)	617 (38.90)	41 (36.94)
Yes	1,390 (23.68)	988 (23.68)	375 (23.64)	27 (24.32)
Missing	2,040 (34.76)	1,403 (33.63)	594 (37.45)	43 (38.74)
Infertility diagnosis[b,c]				
Male factor	1,405 (23.94)	990 (23.73)	388 (24.46)	27 (24.32)
Diminished ovarian reserve	435 (7.41)	305 (7.31)	112 (7.06)	18 (16.22)
Uterine factor	109 (1.86)	84 (2.01)	22 (1.39)	3 (2.70)
Endometriosis	477 (8.13)	358 (8.58)	111 (7.00)	8 (7.21)
PCOS	1,121 (19.10)	776 (18.60)	330 (20.81)	15 (13.51)
Tubal factor	954 (16.25)	703 (16.85)	238 (15.01)	13 (11.71)
Multiple diagnoses (≥2, including "other")	467 (7.96)	313 (7.50)	139 (8.76)	15 (13.51)
Unexplained	901 (15.35)	643 (15.41)	246 (15.51)	12 (10.81)
Treatment protocol[a,b]				
Agonist suppression	3,209 (54.68)	2,381 (57.07)	781 (49.24)	47 (42.34)
Agonist flare	404 (6.88)	298 (7.14)	92 (5.80)	14 (12.61)
Antagonist suppression	2,090 (35.61)	1,376 (32.98)	668 (42.12)	46 (41.44)
Missing	166 (2.83)	117 (2.80)	45 (2.84)	4 (3.60)
Ovarian stimulation (d)[a,b,d]				
Mean ± SD	11.71 ± 2.60	11.63 ± 2.72	11.90 ± 2.27	12.06 ± 2.17
FSH dosage[b,e]				
Mean ± SD	2,702.06 ± 1,391.04	2,656.94 ± 1,340.55	2,790.50 ± 1,488.28	3,126.20 ± 1,664.85
Assisted hatching[a,b,c]				
None	4,425 (75.40)	3,272 (78.43)	1,098 (69.23)	55 (49.55)
All transferred embryos	1,296 (22.08)	857 (20.54)	405 (25.54)	34 (30.63)
Some embryos	147 (2.50)	42 (1.01)	83 (5.23)	22 (19.82)
Missing	1 (0.02)	1 (0.02)	0 (0.00)	0 (0.00)
ICSI[a]				
None	1,684 (28.69)	1,104 (26.46)	543 (34.24)	37 (33.33)
All mature oocytes	3,789 (64.56)	2,739 (65.65)	979 (61.73)	71 (63.96)
Some oocytes	396 (6.75)	`329 (7.89)	64 (4.04)	3 (2.70)

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TABLE 1

Continued.

	Overall (N = 5,869) N (%)	Good (N = 4,172) N (%)	Fair (N = 1,586) N (%)	Poor (N = 111) N (%)
PGT[b,c]				
None	5,784 (98.55)	4,111 (98.54)	1,568 (98.87)	105 (94.59)
All embryos	50 (0.85)	33 (0.79)	12 (0.76)	5 (4.50)
Some embryos	35 (0.60)	28 (0.67)	6 (0.38)	1 (0.90)
No. of embryos transferred				
Single	1,714 (29.20)	1,235 (29.60)	451 (28.44)	28 (25.23)
Double	4,155 (70.80)	2,937 (70.40)	1,135 (71.56)	83 (74.77)
Embryo developmental stage at transfer[a,b]				
Cleaved embryo	2,610 (44.47)	1,659 (39.77)	884 (55.74)	67 (60.36)
Blastocyst	3,259 (55.53)	2,513 (60.23)	702 (44.26)	44 (39.64)

Note: Mean ± SD for continuous variables and N (%) for binary or categorical variables. BMI = body mass index; FSH = follicle stimulating hormone; ICSI = intracytoplasmic sperm injections; PCOS = polycystic ovary syndrome; PGT = preimplantation genetic testing.
[a] Comparison between good vs. fair reaches statistical significance after Bonferroni correction.
[b] Comparison between good vs. poor reaches statistical significance after Bonferroni correction.
[c] Comparison between fair vs. poor reaches statistical significance after Bonferroni correction.
[d] Dunn' test.
[e] Fisher's exact test.

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history [yes vs. no], parity [nulliparous {ref} vs. parous], infertility etiology [male factor {ref} vs. diminished ovarian reserve, uterine factor, endometriosis, polycystic ovary syndrome, tubal factor, multiple diagnoses (≥2, including "other"), unexplained], gestational age [in days], infant sex [male {ref} vs. female]) were determined on the basis of existing literature (28–34). We first examined the amount and pattern of missingness on all analytical variables. The percentage of missingness ranged from 0.09% (parity) to 34.76% (miscarriage) across the study population. Under the assumption of missing at random, we performed multiple imputations by chained equation. Missing values on continuous variables were imputed through predictive mean matching and logistic regression for binary outcomes, multinomial logistic regression for nominal categorical variables, and ordinal logistic regression for ordinal variables. Variables with completely observed values (reported cycle year, maternal age at the start of treatment, maternal race, infertility diagnosis, source of sperm, whether being performed intracytoplasmic sperm injection, preimplantation genetic testing, embryo quality and developmental stage at transfer, gestational age) were used as auxiliary variables for imputation. A total of 50 imputed data sets were generated for subsequent regression analyses.

Descriptive analysis was conducted on the preimputed data set. The χ^2 test and Dunn's test, a nonparametric multiple comparison procedure, were performed to collect pairwise comparisons on categorical and continuous variables, respectively, across the 3 embryo quality groups (35). We applied Bonferroni correction for P values for multiple testing. Considering that birth weight outcomes significantly differed by gestational lengths and the preferences for blastocyst transfers in clinical practices, we stratified the analyses by the length of gestation (preterm vs. term) and embryo stage at transfer (cleavage vs. blastocyst). Preterm birth was defined as a gestational age <37 weeks. Because of the limited number of live births from the transfer of morphologically poor embryos (1.9% of our sample), we focused regression analyses on cycles that included the transfer of fair or good (reference group) embryos. Unadjusted and adjusted linear regressions were performed on the imputed data sets to model continuous outcomes (birth weight [in gram] and z-score), and unadjusted as well as adjusted logistic regressions were conducted to model binary outcomes (LBW, SGA, and LGA). In multivariate analyses, we adjusted for a panel of covariates (reported cycle year, maternal age and race, BMI, parity, history of miscarriage, infertility diagnosis, number of transferred embryos, embryo developmental stage, gestational age [in days], infant sex) for all outcomes evaluated, except for SGA and LGA, wherein the gestational age was removed from the covariates, considering the construction of both outcomes already accounted for the gestational duration.

In addition, we did not adjust for smoking status (3 months before the treatment cycle) because of minimal variability in the imputed data sets (yes vs. no: 2% vs. 98%). To further account for possible differed perinatal outcomes between survivor singletons from vanishing twin syndrome and true singletons from the beginning of pregnancy, we conducted sensitivity analyses on all outcomes within single embryo transfer cycles (Supplemental Table 1, available online). Furthermore, we performed an analysis including all non-preimplantation genetic testing (PGT) cycles, and the results were unchanged (Supplemental Table 2, available online). All regression analyses accounted for correlations from multiple cycles within the same woman by clustering on novel patient ID. Two-sided $P<.05$ was considered statistically significant. Statistical analyses were performed using Stata Version SE 15.1 (StataCorp LLC, College Station, TX).

This study was approved by the Stanford University Institutional Review Board and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies (36).

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TABLE 2

Pregnancy and neonatal outcomes from singleton live births after in vitro fertilization fresh cycles by embryo morphology grading.

	Overall (N = 5,869) N (%)	Good (N = 4,172) N (%)	Fair (N = 1,586) N (%)	Poor (N=111) N (%)
Gestational age (y)				
Days (Mean ± SD)[a]	270.93 ± 16.82	270.51 ± 17.32	271.79 ± 15.61	274.14 ± 13.34
Weeks (Mean ± SD)	38.69 ± 2.42	38.64 ± 2.49	38.81 ± 2.24	39.10 ± 1.93
Infant sex				
Male	2,931 (49.94)	2,065 (49.50)	800 (50.44)	66 (59.46)
Female	2,904 (49.48)	2,080 (49.86)	780 (49.18)	44 (39.64)
Missing	34 (0.58)	27 (0.65)	6 (0.38)	1 (0.90)
Birth weight (g)[a,b]				
Mean ± SD	3,216.89 ± 627.50	3,202.72 ± 639.89	3,240.38 ± 595.37	3,415.80 ± 561.95
Birth weight Z-score				
Mean ± SD	-0.23 ± 1.27	-0.23 ± 1.27	-0.22 ± 1.27	-0.01 ± 1.41
LBW (<2,500 g)	595 (10.14)	448 (10.74)	142 (8.95)	5 (4.50)
SGA	786 (13.39)	575 (13.78)	203 (12.80)	8 (7.21)
LGA	502 (8.55)	345 (8.27)	142 (8.95)	15 (13.51)

Note: Mean ± SD for continuous variables and N (%) for binary or categorical variables. LBW = low birth weight; LGA= large for gestational age; SGA = small for gestational age.
[a] Comparison between good vs. poor reaches statistical significance after Bonferroni correction.
[b] Comparison between fair vs. poor reaches statistical significance after Bonferroni correction.

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RESULTS

After applying the exclusion criteria at each data cleaning stage, we included an analytical sample of 5,869 singleton births resulting from fresh embryo transfer cycles (Supplemental Figure 1).

Descriptive analysis revealed the distributions of maternal demographics, obstetric history, and cycle-related parameters among all cycles and stratified subgroups by embryo quality (Table 1). Of the 5,869 live births, 4,172 (71.1%) resulted from the transfer of morphologically good-quality embryos whereas 1,586 (27.0%) and 111 (1.9%) were conceived from fair or poor-quality embryos, respectively. Three-quarters of women were Caucasian, with approximately one-tenth Asian. Approximately half of all the women had a normal BMI. The distribution of race and BMI did not differ by embryo quality. The top 3 leading infertility diagnoses were male factor (23.9%), polycystic ovary syndrome (19.1%), and tubal factor (16.3%). Although some observations differed in terms of statistical significance, distributions of infertility diagnoses and ovarian stimulation duration did not significantly differ clinically between embryo quality groups. Women who transferred morphologically fair embryos were on an average half a year older than those with good-quality embryos (33.0 ± 3.9 vs. 32.6 ± 3.8; $P<.001$). Compared with the women who transferred good embryo(s), women who transferred fair embryo(s) were less likely to have previous miscarriages (38.9% vs. 42.7%; $P=.012$).

Among the 5,869 live births, 44.5% were from the transfer of cleaved embryos and 55.5% from the transfer of blastocysts. The number of transferred embryos did not vary with different morphology groups. In the analysis of the total study population, the mean birth weight of neonates conceived from morphologically poor embryos was slightly greater than those developed from good (3,415.8 ± 562.0 vs. 3,202.7 ± 639.9; $P=.005$) or fair (3,415.8 ± 562.0 vs. 3,240.4 ± 595.4; $P=.024$) embryos (Table 2). Birth weight z-scores and proportions of LBW, SGA, and LGA were comparable across the 3 groups. However, the number of live births from poor-quality embryos was too small to allow regression analysis.

TABLE 3

Association between singleton neonatal outcomes and embryo morphology after transferring a single embryo or same-quality double embryos.

Embryo quality (fair vs. good)	Unadjusted		Adjusted	
Continuous outcomes	Coef.	95% CI	Coef.	95% CI
Birth weight (g)	39.40[a]	[3.97, 74.84]	0.69	[-24.30, 25.68]
Birth weight z-score	0.01	[-0.06, 0.09]	0.00	[-0.07, 0.08]
Dichotomized outcomes	OR	95% CI	aOR	95% CI
Low birth weight (<2,500 g)	0.81[a]	[0.66, 0.99]	0.84	[0.63, 1.11]
SGA (birth weight < 10%)	0.92	[0.77, 1.09]	0.93	[0.78, 1.11]
LGA (birth weight > 90%)	1.09	[0.88, 1.36]	1.07	[0.86, 1.33]

Note: Each of multivariable regression model adjusted for cycle reporting year, maternal age, race, BMI, parity, miscarriage, infertility diagnosis, number of transferred embryos, embryo developmental stage, gestational age (days), and infant sex, except for SGA and LGA, where gestational age (d) was removed from analyses. aOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; Coef. = coefficient; LGA = large for gestational age; OR = odds ratio; SGA = short for gestational age.
[a] $P<.05$.

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TABLE 4

Association between singleton neonatal outcomes and embryo morphology after transferring a single embryo or same-quality double embryos by embryo developmental stage and gestational length.

Embryo quality (fair vs. good)	Cleaved embryos[a]		Blastocysts[a]		Preterm (< 37 wks)[b]		Term (≥ 37 wks)[b]	
Continuous outcomes	Coef.	95% CI	Coef.	95% CI	Coef.	95% CI	Coef.	95% CI
Birth weight (g)	39.18[c]	[4.05,74.31]	-35.46	[-71.23,0.31]	1.21	[-77.31,79.73]	2.64	[-23.63,28.92]
Birth weight z-score	0.10	[-0.00,0.20]	-0.10	[-0.21,0.01]	0.07	[-0.16,0.30]	-0.01	[-0.09,0.07]
Dichotomized outcomes	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Low birth weight (<2,500 g)	0.68	[0.46,1.01]	1.02	[0.69,1.52]	1.07	[0.70,1.65]	0.68	[0.46,1.02]
SGA (birth weight < 10%)	0.73[c]	[0.57,0.95]	1.13	[0.89,1.43]	0.89	[0.55,1.45]	0.93	[0.76,1.12]
LGA (birth weight > 90%)	1.30	[0.95,1.77]	0.85	[0.61,1.18]	0.85	[0.39,1.85]	1.08	[0.86,1.37]

Note: BMI = body mass index; CI = confidence interval; Coef. = coefficient; LGA = large for gestational age; SGA = short for gestational age.
[a] Results adjusted for cycle reporting year, maternal age, race, BMI, parity, miscarriage, infertility diagnosis, number of transferred embryos, gestational age (days), and infant sex, except for SGA and LGA, where gestational age (days) was removed from analyses.
[b] Results adjusted for cycle reporting year, maternal age, race, BMI, parity, miscarriage, infertility diagnosis, number of transferred embryos, embryo developmental stage, gestational age (d), and infant sex, except for SGA and LGA, where gestational age (days) was removed from analyses.
[c] $P<.05$.

Li. Embryo quality and IVF birth outcomes. Fertil Steril 2022.

Regression results are presented in Table 3. After covariates adjustment (cycle reporting year, maternal age, race, BMI, obstetric histories [parity, miscarriage], infertility diagnosis, number of transferred embryos, embryo stage, gestational age, and infant sex) and excluding poor embryo transfer cycles, compared with good-quality embryos, we observed no association of morphologically fair embryos with birth weight (Coef, 0.69; 95% CI, -24.30–25.68), z-score (Coef: 0.00; 95% CI, -0.07–0.08), LBW (aOR, 0.84; 95% CI, 0.63–1.11), SGA (aOR, 0.93; 95% CI, 0.78–1.11), and LGA (aOR, 1.07; 95% CI, 0.86–1.33).

We next separately examined the associations by embryo developmental stage (cleaved vs. blastocyst). Stratified analyses did not infer any association of fair-quality embryo morphology with adverse neonatal outcomes for either cleaved or blastocyst embryos (Table 4). Specifically, fair cleaved embryos were associated with a higher birth weight (Coef, 39.18; 95% CI, 4.05–74.31) and decreased odds of SGA (aOR, 0.73; 95% CI, 0.57–0.95). No association between embryo morphological quality and the neonatal outcome was observed for the blastocyst transfers. Embryo morphological quality did not predict birth weight, LBW, SGA, and LGA within preterm or term births (Table 4).

Sensitivity analysis, restricting to cycles transferring one embryo to rule out the potential impact of whether there were vanishing twins, largely further confirmed our main findings. However, in this analysis restricted to the transfer of one embryo, we observed an increased odds of LGA (aOR, 1.53; 95% CI, 1.04–2.24) associated with fair- relative to good-quality embryo transfer (Supplemental Table 1). Similarly, sensitivity analyses limited to single embryo transfer cycles, excluding PGT cycles, indicated singletons from fair-quality embryos were more likely to be born LGA (aOR, 1.56; 95% CI, 1.06–2.31). But we did not observe increased odds for adverse perinatal outcomes from analyses of all non-PGT cycles, within cleaved embryo or blastocyst transfer cycles separately, or within preterm births or term births respectively (Supplemental Table 2).

DISCUSSION

The current study, using data from IVF clinics across the United States, significantly contributes to the limited body of existing literature regarding embryo quality and neonatal outcomes. In our analysis including over 5,800 fresh embryo transfer cycles with physician-confirmed singleton live births, we observed no association between suboptimal embryo quality with adverse neonatal outcomes. Specifically, we observed no decrease in birth weight and no increased risk of LBW, SGA, or LGA with the transfer of morphologically fair-quality embryos compared with the transfer of good-quality embryos. Most of the published literature is consistent with our findings. For example, our analyses are consistent with the pilot study by Oron et al. (1) indicating that the embryo quality is not associated with birth outcomes once a viable pregnancy is achieved.

In an analysis restricted to cleaved embryo transfers after adjusting for key confounders, we observed no decrease in birth weight or increased odds in LBW, SGA, or LGA with the transfer of poor cleaved embryos, consistent with two previous studies of cleaved embryo transfer in an Asian population (4, 12). Among blastocysts, we observed no relationship between embryo morphology and birth weight, consistent with the findings of some previous studies. For example, Bouillon et al. (11) also found no effect of embryo quality on LBW, SGA, or LGA in fresh blastocyst transfers. Hu et al. (9) and Bakkensen et al. (37) reported no association between poor-quality blastocysts and the risk of SGA or LGA. Finally, Li et al. (38) found that singletons and twins conceived from poor-quality blastocysts, defined as both inner cell mass (ICM) and trophectoderm (TE) graded as C, were not at increased risk of LBW compared with their peers from average-quality blastocysts.

It is difficult to directly compare the findings of our study, which included only an overall blastocyst grade, with those of Licciardi et al. (13), who used a different blastocyst grading system with separate grades for TE and ICM as well as no overall blastocyst grade. They found that infant birth weight was significantly high among those conceived from blastocysts with high ICM grading whereas no association was

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noted with TE grading. In contrast, another study, which included outcomes on the basis of ICM grades, reported that an inferior ICM grade (B or C) was associated with a reduced risk of preterm birth (37). Each of these two studies reported data from their single centers. Further study is needed to determine whether ICM grading alone has an association with perinatal outcomes.

A major strength of our study is that it included a large study population from the national registry of SART CORS, which collects critical information on patient demographics, cycle parameters and outcomes, and pregnancy and perinatal outcomes from IVF clinics across the United States, excluding possible selection bias related to a single-center design. In addition, by focusing on fresh embryo transfer, we avoided the well-documented impacts of frozen cycles on pregnancy outcomes (39). Furthermore, considering previously reported varied pregnancy outcomes in relation to embryo stage at transfer, we conducted a stratified analysis to evaluate the association among cleaved embryos vs. blastocysts with an adequate sample per group.

Several limitations warrant consideration. Because few live births resulted from the transfer of poor-quality embryos, we cannot draw stable statistical inference from a regression analysis of perinatal outcomes comparing morphologically poor-quality embryos vs. good embryos. The criteria used to assess embryo quality may vary among embryologists, and the SART embryo quality grading system has not been further validated by inter- and intrarater reliability. However, considerable research has shown that the grading system recorded in SART CORS is reasonably linked to the live birth rate, and SART member clinics are asked to use standard definitions of good-fair-poor morphology (21–27). Lastly, we could not control for the effects caused by different embryo culture media (40, 41) and gestational complications (42, 43) that could impact perinatal outcomes because of the data unavailability in SART CORS.

CONCLUSIONS

Once a singleton live birth from fresh embryo transfer is achieved, suboptimal embryo quality is generally not associated with a reduction in birth weight or increased risks of LBW, SGA, and LGA. Among fresh single embryo transfer cycles, morphologically fair-quality embryos may be associated with an increased risk of LGA. Future studies are warranted to see if the same results are noted with transfers of embryos undergoing biopsy and preimplantation genetic testing. Additionally, investigation of the relationship between embryo quality and perinatal outcomes focused on single embryo transfer cycles is encouraged.

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34822

Acknowledgments: The authors thank SART and its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of the SART members, this research would not have been possible.

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Asociación entre la calidad embriomorfológica y el peso al nacer de los fetos únicos concebidos a través de la transferencia autóloga de embriones frescos: análisis utilizando el Sistema de Informe de Resultados Clínicos de la Sociedad de Tecnología de Reproducción Asistida.

Objetivo: Determinar si la calidad embrionaria morfológicamente subóptima se asocia con resultados perinatales adversos.

Diseño: Cohorte retrospectiva.

Entorno: Base de datos SART CORS.

Paciente(s): Hijos únicos concebidos a partir de ciclos frescos de fecundación in vitro autóloga.

Intervención(es): Ninguna.

Principales medidas de resultados: peso al nacer (gramos), puntuación z del peso al nacer, bajo peso al nacer (BPN), pequeño para la edad gestacional (PEG) y grande para la edad gestacional (GEG).

Resultados: Entre 5.869 ciclos frescos de fecundación in vitro, el 71,1 % transfirieron embriones morfológicamente buenos y el 27,0 % y el 1,9 % transfirieron embriones regulares y malos, respectivamente. En comparación con los hijos únicos concebidos a partir de buenos embriones, los hijos únicos de embriones malos tuvieron un mayor peso al nacer (3.415,8±562,0 frente a 3.202,7±639,9). Las proporciones de BPN, PEG y GEG fueron comparables entre los grupos de calidad embrionaria. El análisis de regresión multivariable que comparó los resultados perinatales de embriones aceptables versus buenos no mostró asociación para el peso al nacer (diferencia de 0,69 gramos; IC del 95 %, -24,30–25,68), puntuación z del peso al nacer (coeficiente, 0,00; IC del 95 %, -0,07 –0,08), BPN (odds ratio ajustado [ORa], 0,84; IC 95 %, 0,63–1,11), PEG (ORa, 0,93; IC 95 %, 0,78–1,11) y GEG (ORa, 1,07; IC 95 %, 0,86–1,33). El análisis estratificado, considerando por separado las transferencias de embriones escindidos y de blastocistos, confirmó estos hallazgos. El análisis de sensibilidad reveló mayores probabilidades de GEG (aOR, 1,53; IC 95 %, 1,04–2,24) con embriones de buena calidad solo entre ciclos de transferencia de un solo embrión.

Conclusión(es): Una vez que se logra un nacido vivo único a partir de la transferencia de embriones frescos, la calidad morfológica del embrión no se asocia con una reducción en el peso al nacer o mayores riesgos de BPN, PEG y GEG.

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