Transfers of lower quality embryos based on morphological appearance result in appreciable live birth rates: a Canadian center's experience

Ingrid Lai, M.D.,[a,b] Michael Neal, M.Sc.,[b] Nicole Gervais, M.A.,[a,c] Shilpa Amin, M.D.,[a,b] Evan Taerk, M.D.,[a,b] and Mehrnoosh Faghih, M.D.[a,b]

[a] Department of Obstetrics and Gynecology, Division of Gynecologic Reproductive Endocrinology and Infertility, McMaster University, Hamilton, Ontario, Canada; [b] Ontario Network of Experts in Fertility (ONE Fertility), Burlington, Ontario, Canada; and [c] Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada

Objective: To determine the reproductive outcomes resulting from transfer of lower-grade blastocysts to support the practice of cryopreserving and transferring lower-grade embryos.
Design: Retrospective chart review.
Setting: Single infertility center.
Patient(s): Women who have undergone a fresh (n = 570) or frozen (n = 885) transfer of a single blastocyst embryo between December 2013 and December 2018.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome was live birth rate. The secondary outcomes included implantation rate, ongoing pregnancy rate, associations with inner cell mass (ICM) and trophectoderm epithelium (TE) grades determined by morphological assessment, and antenatal/perinatal complications.
Results: Reproductive outcomes directly correlated with embryo quality. Transfers of AA embryos resulted in a 41.4% live birth rate compared to 31.1% for BB embryos and 13.3% for CC embryos. The TE grade was significantly associated with the live birth rate. Embryos with a TE grade of "B" had an odds ratio of 0.677 and embryos with a TE grade of "C" had an odds ratio of 0.394 compared to embryos with a TE grade of "A" for live birth.
Conclusion: Embryos with a TE "C" grade should be considered for transfer and cryopreservation, as they are shown to result in appreciable live birth rates. Such treatment should involve a thorough discussion with patients, however, as these live birth rates are significantly lower than those associated with higher-grade embryos. (Fertil Steril Rep® 2020;1:264–9. ©2020 by American Society for Reproductive Medicine.)
Key Words: Lower-grade embryo, live birth rate

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Preimplantation embryo development follows a predictable pattern, with competent embryos reaching the blastocyst stage by day 5 or 6 after fertilization. By the blastocyst stage, cells have differentiated into two distinct cell lines. One cell line is the inner cell mass (ICM), and this inner cluster of cells develops into the fetus. The other cell line is the trophectoderm epithelium (TE), and this outer sheet of cells forms the extra-embryonic components. These components, together with a fluid-filled cavity known as the blastocoel, make up a blastocyst, which is an advanced preimplantation embryo.

It is common for embryologists in North America to use Gardner and Schoolcraft's Blastocyst Scoring System for morphological assessment of embryos (1). This system consists of a number indicating the degree of blastocoel or blastocyst expansion (1 = early blastocyst, blastocoel <50% volume; 2 = blastocyst, blastocoel >50% volume; 3 = full blastocyst, 100% blastocoel expansion; 4 = expanded blastocyst; 5

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Reprint requests: Ingrid Lai, M.D., 3210 Harvester Road, Burlington, Ontario, Canada, L7N 3T1 (E-mail: ingrid.lai@medportal.ca).

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= hatching blastocyst; 6 = hatched blastocyst), followed by a letter grade designating the quantity and quality of the ICM (A = many cells tightly compacted; B = several cells loosely adhered; C = very few cells; D = no cells or degenerate or necrotic cells), and a second letter grade designating the quantity and quality of the TE (A = continuous layer of small identical cells; B = noncontinuous layer with fewer cells; C = noncontinuous layer with few small cells and large cells; D = sparse distribution of large or flat or degenerate cells). Thus, there are nine combinations of embryo grades for blastocysts that are not degenerated: AA, AB, BA, BB, AC, CA, BC, CB, and CC. The goal of the scoring system is to aid in the selection of embryos with high implantation potential, to improve reproductive outcomes. Higher-grade embryos are more likely euploid, and although some embryo scores are well accepted as having implantation potential (e.g., AA is the best, and AB is better than AC), other scores are less clear-cut (2–4). Furthermore, lower-grade embryos may be euploid, albeit at a lower rate (2, 5).

In Canada, preimplantation genetic testing for aneuploidy (PGT-A) is not routinely performed; rather, it is typically reserved for certain patient populations, such as those with recurrent pregnancy loss. Without PGT-A, embryo grade by morphological assessment remains an important tool in embryo selection for transfer. Furthermore, embryo grade is shown to influence pregnancy rates even in euploid embryos confirmed by PGT-A (6). There are fertility centers across Canada that discard lower-grade embryos such as CC embryos. Some patients may have only lower-grade embryos available for transfer. Since the initiation of vitrification for embryo cryopreservation in December 2013, ONE Fertility (Burlington, Ontario, Canada) has been cryopreserving and transferring CC grade embryos. We have observed that the rates of pregnancy and live birth resulting from the transfer of CC embryos are not negligible. As such, this study aims to establish a deeper understanding of the pregnancy and live birth rates resulting from these embryo transfers to allow better patient counseling and to support a practice to cryopreserve lower-grade embryos.

MATERIALS AND METHODS

Approval was obtained from the Hamilton Integrated Research Ethics Board (HiREB # 5635-C) to perform this retrospective chart review. This study reviewed treatment cycles consisting of single-embryo transfers between December 13, 2013, and December 13, 2018, at ONE Fertility in Burlington, Ontario, Canada. Data were collected from clinic electronic medical records and the Better Outcomes Registry and Network (BORN) database (registry of maternal, neonatal, and childhood outcomes in Ontario).

Inclusion criteria consisted of women of any age, any number of in vitro fertilization (IVF) cycles, embryos from autologous or donor oocytes, cryopreservation by vitrification, fresh or frozen single-embryo transfer, and nonovulatory (medicated) protocol prior to frozen embryo transfer to minimize variability in duration of progesterone exposure. Rates of pregnancy and live birth decline with each 1-mm decrease in endometrial thickness <7 mm (7); as such, all patients in this study had an endometrial thickness ≥7 mm prior to embryo transfer. Exclusion criteria consisted of nonblastocyst embryos, blastocyst embryos without a grade based on Gardner and Schoolcraft's system (e.g., "early blastocyst"), nonvitrification method of cryopreservation, and ovulatory (natural cycle) protocol prior to frozen embryo transfer.

TABLE 1

Distribution of cases by embryo grade.

Embryo grade	Fresh ET	Frozen ET
AA	204 (35.8%)	178 (20.1%)
AB	131 (23.0%)	135 (15.2%)
BA	37 (6.5%)	78 (8.8%)
BB	158 (27.7%)	312 (35.3%)
AC	2 (0.35%)	5 (0.6%)
CA	0 (0%)	0 (0%)
BC	30 (5.3%)	70 (7.9%)
CB	2 (0.35%)	38 (4.3%)
CC	6 (1.0%)	69 (7.8%)

Note: ET = embryo transfer; n = absolute number of embryos; % = percentage of an embryo grade in the ET group.

Lai. Clinical outcomes of lower-grade embryos. Fertil Steril Rep 2020.

Data were collected on reproductive age (age at time of embryo creation, age at time of embryo transfer), infertility diagnosis, morphological grade using Gardner and Schoolcraft's system (expansion stage, ICM grade, TE grade), transfer type (fresh or frozen), pregnancy rate (positive β-hCG test), implantation rate (number of gestational sacs present by 6 weeks' gestational age divided by number of embryos transferred), clinical pregnancy rate (number of gestational sacs with sonographic evidence of fetal heartbeat beyond 6 weeks' gestational age divided by number of embryos transferred), ongoing pregnancy rate (pregnancy beyond 20 weeks' gestational age), live birth rate (number of live offspring delivered divided by number of embryos transferred), and complications. All clinical outcomes were identified through the BORN database. Antenatal or perinatal complications potentially relevant to this study included the following: genetic abnormalities, fetal anomalies or birth defects, gestational diabetes, gestational hypertension or preeclampsia, placental issues (placenta previa, invasive placentation, other placental issues), intrauterine fetal demise (IUFD) or stillbirth, intrauterine growth restriction, low birth weight <2500 g, large for gestational age >4000 g, and preterm labor/delivery or preterm premature rupture of membranes.

Statistical Analyses

Statistical analyses were run using IBM SPSS Statistics 25 software (IBM SPSS, Armonk, NY). Descriptive statistical analyses (means, frequencies, percentages) were performed. Pearson χ^2 tests were performed to compare the Not C/C and AC/BC/CC comparisons. Binomial logistical regressions were performed on outcome measures to assess the strength of associations of age, ICM grade, TE grade, and transfer type on outcomes.

TABLE 2

χ^2 Test results comparing embryos with any C rating to those without a C rating.

	Embryos with a C rating			Embryos with no C rating			*P*	
	n	% of Total	% of Previous successes	n	% of Total	% of Previous successes	Of Total	Of previous successes
Positive β-hCG rates	94	42.3	42.3	729	59.2	59.2	<.001	n/a
Implantation rates	69	31.1	73.4 (69/94)	582	47.2	79.8 (582/729)	<.001	0.188
Clinical pregnancy rates	54	24.3	78.3 (54/69)	526	42.7	90.4 (526/582)	<.001	0.003
Ongoing pregnancy rates	46	20.7	85.2 (46/54)	459	37.2	87.3 (459/526)	<.001	0.665
Live birth rates	45	20.3	97.8 (45/46)	456	37.0	99.3 (456/459)	<.001	0.041

Note: n/a = not applicable.

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RESULTS

Cases by Type of Embryo Transfer

We reviewed 3159 embryo transfers (ET) that met the inclusion criteria over the 5-year period. Of the 1625 cases in the fresh ET group, 570 cases (35.1%) met eligibility criteria and had complete data regarding reproductive outcomes. Of the 1534 cases in the frozen ET group, 885 cases (57.7%) met eligibility criteria and had complete data regarding reproductive outcomes.

Cases by Embryo Grading

Cases were categorized according to their embryo grades as outlined in Table 1. The most frequent embryo grades in both ET groups were AA and BB (n = absolute number of embryos; % = percentage of an embryo grade in the ET group): fresh ET group AA, n = 204 (35.8%), and BB, n = 158 (27.7%); frozen ET group BB, n = 312 (35.3%) and AA, n = 178 (20.1%). There were no CA embryos in the study.

Demographic Data

Demographic variables were compared between groups. In the fresh ET group, the mean maternal age (± standard deviation [SD]) at time of ET was 34.5 ± 3.9 years. In the frozen ET group, the mean (± SD) oocyte age at time of embryo creation was 34.0 ± 4.0 years, and the mean (± SD) maternal age at time of ET was 34.0 ± 3.9 years.

Regarding the infertility diagnoses, it was possible for patients to have multiple contributing factors. The most common indications for IVF in this study were male factor infertility (n = 657), diminished ovarian reserve (DOR) or advanced reproductive age (ARA) (n = 415), and ovulatory dysfunction (n = 415). The primary comparison was between groups based on embryo grades (e.g., AA, AB, etc.) and secondary comparison was between groups based on transfer type (fresh vs. frozen). The number of cases of each infertility diagnosis is outlined in Supplemental Table 1.

In the fresh ET group, across all diagnoses, AA tended to be the most frequent grade (32.3%–48.8%). In the frozen ET group, across all diagnoses, BB tended to be the most frequent grade (28.3%– 50%). More CC embryos appeared in the frozen ET group regardless of diagnosis, as these were given the lowest priority for transfer and would be transferred in a fresh ET cycle only if no higher-grade embryo were available. As such, CC embryos were found in the fresh ET group 0%–2.0% of the time (mean 0.56%) and in the frozen ET group 0%–12.1% of the time (mean 5.74%).

Reproductive Outcomes

The impact of a C rating. Simple analyses were conducted to compare the outcomes of lower-grade embryos to those of higher-grade embryos. Our sample was split into two groups: those with a C grade anywhere in the rating (i.e., AC, BC, CA, CB, CC) versus those without (i.e., AA, AB, BA, BB). We ran χ^2 tests to assess the differences between these groups. The results are outlined in Table 2. We included comparisons between the groups on the total sample and the subsample of those who continued to the next stage (e.g., must have implantation to have clinical pregnancy). The results show that significantly fewer embryos with a C rating resulted in a positive β-hCG, and the rates of success dropped off even more for clinical pregnancies and live births, although not for implantation or ongoing pregnancies.

The main objective of this study was to determine the degree of clinical success after transfer of CC embryos, thus providing data to aid in the decision to transfer or to cryopreserve these embryos rather than to discard them. Comparisons were made of the transfer and birth outcomes between CC embryos and [1] AA embryos, as these are the highest-graded embryos and most frequent in the fresh ET group, and [2] BB embryos, as these are most frequent in the frozen ET group.

Table 3 outlines the rates of reproductive success for AA, BB, and CC embryos. As anticipated, CC embryos have a lower rate of all indicators of reproductive success compared to AA and BB embryos. With respect to the key indicator of interest, live birth rate, CC embryos appear to be about one-third as likely (13.3%) to result in a live birth as AA embryos (41.4%), with BB embryos' success rate falling between the two (31.1%).

Associations with reproductive success. Binomial regressions were conducted to ascertain whether reproductive success was associated with the variables of ICM and TE grade, transfer type, and female age. For live birth, the regression analysis was statistically significant [χ^2 (6) = 107.04, $P<.001$]. Analyses of these variables explained 9.8%

TABLE 3

Rates of various indicators of reproductive success among AA, BB, and CC embryos.

	AA embryos (n = 382)	BB embryos (n = 470)	CC embryos (n = 75)
Positive β-hCG rates	63.1%	54.6%	36.0%
Implantation rates	50.8%	43.0%	22.7%
Clinical pregnancy rates	46.6%	37.2%	17.3%
Ongoing pregnancy rates	42.1%	31.1%	14.7%
Live birth rates	41.4%	31.1%	13.3%

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TABLE 4

Binomial logistic regression for likelihood of live birth based on embryo grade, transfer type, and age.

						95% CI for odds ratio	
	B	SE	Wald	df	*P*	Odds ratio	Lower	Upper
A ICM			1.183	2	.554			
B ICM	0.061	0.133	0.207	1	.649	1.063	0.818	1.380
C ICM	–0.229	0.302	0.571	1	.450	0.796	0.440	1.439
A TE			15.858	2	<.001			
B TE	–0.390	0.134	8.485	1	.004	0.677	0.521	0.880
C TE	–0.932	0.251	13.731	1	<.001	0.394	0.241	0.645
Age	–0.107	0.015	51.495	1	<.001	0.898	0.873	0.925
Frozen ET	–0.474	0.120	15.503	1	<.001	0.623	0.492	0.788
Constant	3.563	0.521	46.697	1	<.001	35.257		

Note: CI = confidence interval; ET = embryo transfer; ICM = inner cell mass; SE = standard error; TE = trophectoderm epithelium.

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(Nagelkerke R^2) of the variance in live births, and correctly classified 67.1% of the outcomes. Sensitivity was 19.8%, specificity was 91.9%; positive predictive value was 56.2%, and negative predictive value was 68.5%. Three of these four variables were statistically significant: TE grade, female age, and transfer type (fresh or frozen) (Table 4). Compared to embryos with a TE grade of "A," embryos with a TE grade of "B" had about two-thirds the odds of achieving a successful live birth, and embryos with a TE grade of "C" had one-third the odds of achieving a successful live birth. Likelihood of achieving a successful live birth goes down as age goes up, and frozen ETs had 0.60 times the odds of ending in a live birth compared to fresh ETs. The regression analyses for other indicators of reproductive success were similar, and all were statistically significant.

Higher ICM grades did not appear to correlate with reproductive success, although conclusions cannot be drawn, given that only seven AC embryos were included in the study, in comparison with 100 BC embryos and 75 CC embryos. The pregnancy rates were 28.6%, 42.0%, and 36.0%; implantation rates were 14.3%, 34.0%, and 22.7%; clinical pregnancy rates were 14.3%, 27.0%, and 17.3%; ongoing pregnancy rates were 14.3%, 23.0% and 14.7%; and live birth rates were 14.3%, 23.0%, and 13.3% for AC, BC, and CC embryos, respectively.

Complications. We looked at broad categories of antepartum and postpartum complications to determine rates at which complications occurred in different embryo grade groups. There were 505 cases of ongoing pregnancies in the study. In women with ongoing pregnancies, the group containing one or more "C" grade in the embryo included 17 (37.0%) women with a complication, whereas the group with no "C" grade in the embryo included 172 (37.6%) women with a complication. This difference was not statistically significant. We attempted an analysis to look for patterns of complications based on embryo grade, transfer type, and female age, but the analysis results failed to reach significance.

The most frequent complications were gestational diabetes (n = 45; 8.9%), gestational hypertension or preeclampsia (n = 31; 6.1%), and placental issues (n = 29; 5.7%). Other complications included fetal anomalies or birth defects (n = 16; 3.2%), IUGR (n = 14; 2.8%), genetic abnormalities (n = 4; 0.8%), and IUFD or stillbirth (n = 2; 0.4%).

Direct effects on the fetus are of significance to patients. The 16 cases of fetal anomalies or birth defects, the most frequent being cardiac in nature, consisted of six AA embryos, five BB embryos, three AB embryos, one BA embryo, and one BC embryo. None were CC embryos. The four cases of identified genetic abnormalities consisted of two CC embryos (one case representing 33.3% of CC embryos in fresh ET and one case representing 12.5% of CC embryos in frozen ET), one AA embryo (1% of AA fresh ET), and one BB embryo (1.9% of BB fresh ET). The two cases of IUFD occurred with one AA embryo and one CC embryo, both in fresh ET cycles.

DISCUSSION

The demographics of the ET groups were similar, with the mean female age at 34 years. The most common indications

for IVF in this study (male factor, DOR or ARA, and ovulatory dysfunction) represent the most commonly reported etiologies of infertility (8).

Our study demonstrates that morphological embryo grading is strongly associated with reproductive outcomes, and, specifically, that TE grade significantly correlates with live birth rate. We first considered important measures of success in ET including rates of pregnancy, implantation, and clinical pregnancy as defined in Materials and Methods. However, the pregnancy outcomes are of greater clinical significance. Even with clinical pregnancies, there exists a risk of pregnancy loss (i.e., spontaneous or therapeutic abortion, IUFD, stillbirth). The end goal of IVF is to achieve a live birth, and as such the live birth rate is an important measure of success.

The overall live birth rate in cases resulting from transfer of CC embryos was 13.3%. This is approximately one-third the live birth rate of AA embryo pregnancies and almost one-half the live birth rate of BB embryo pregnancies. This is equivalent to 1 live birth for every 7.5 transfers of CC embryos. This is in stark contrast to a pregnancy rate of 0% associated with ET of CC embryos found in an earlier study (9). Studies by Koustas et al., and Irani et al. showed that healthy viable pregnancies and live births can result from the transfer of lower morphologically graded embryos (10, 11). As live birth rate is the most clinically relevant indicator of reproductive success, a live birth rate that is as high as 13.3% in CC embryo transfers should prompt continued cryopreservation or transfer of CC embryos in clinics that already adopt these practices, as well as prompt consideration of these practices in clinics that routinely discard or recommend against transfer of CC embryos.

In this study, the impact of a "C" grade was predominantly seen in the TE grade. An embryo with a TE grade of "C" was one-third as likely and a TE grade of "B" was two-thirds as likely to achieve a live birth compared to embryos with a TE grade of "A." These findings correlate with another study showing that transfers of embryos with a TE grade of "B" resulted in 29% fewer live births than those with a TE grade of "A," although that study did not address "C" grade embryos, as these were not frozen nor transferred (5). These findings are not surprising, as the TE is the most responsible for implantation and the TE grade is an independent predictor for live birth, with a higher TE grade associated with a higher live birth rate, whereas these associations are not demonstrated with the expansion stage or the ICM grade (12–19). The TE grade was also found to independently correlate with rates of pregnancy and of miscarriage (19). It is postulated that the TE grade may be a more reliable predictor, as the TE itself is more static, allowing the morphological grading to be more objective, whereas the morphological grading of the ICM is more subjective and more likely to have interobserver variability (17). Also fitting was the finding that live birth rate is inversely proportional to female reproductive age (12, 13). Of note, more live births resulted from fresh ET cycles than from frozen ET cycles in our study (frozen ET, odds ratio = 0.623). This is similar to a 2017 study showing a significantly higher live birth rate of 52.2% in the fresh ET group versus 34.4% in the frozen ET group (20). Although we did observe this difference, this study does not aim, and was not statistically powered, to address these differences between fresh and frozen transfers.

Previous studies have shown that lower morphologically graded embryos that implant and continue as clinical pregnancies have obstetric and perinatal outcomes similar to those of higher-grade embryos (21–23). This was the case in this study, in which overall complication rates were similar between the "not C grade" group and the "C grade" group. However, there were differences between CC embryos and other grade embryos with specific groups of complications. CC embryos had a higher rate of genetic abnormalities. This is even more notable, given there were two cases of genetic abnormalities in the CC embryos despite a small sample size (CC embryos with ongoing pregnancy, n = 11). This is not surprising, as CC embryos have higher rates of aneuploidy (3, 4, 24, 25). A study by Blazek et al. showed a correlation between the TE grade, although not expansion stage or ICM grade, and euploid status with euploid rates for TE grade "A" embryos of 79.31%, TE grade "B" 60.51%, and TE grade "C" 38.66% (3). Similarly, we saw this pattern with two cases of IUFD. One of the IUFDs was a pregnancy from a CC embryo, whereas the other was from an AA embryo. However, the one IUFD in the AA group represents only 1% of the AA embryos transferred in fresh cycles, whereas the one IUFD in the CC group represents 33.3% of the CC embryos transferred in fresh cycles. Unfortunately, no further information about the etiology of these IUFDs is available. Notably, a study by Herlihy et al. showed that a TE grade "C" was associated with abnormal placental histological changes, although the clinical significance of these abnormalities is unclear, as the TE grade did not translate into any major adverse perinatal outcomes (26). Interestingly, Shavit et al. showed a trend toward more adverse maternal–fetal outcomes in the pregnancies resulting from frozen ET compared to fresh ET (20). Because many more CC embryos were transferred in the frozen ET group in this study, it is possible that the differences that we observed may be due in part to the cryopreservation process. Further research into the impact of cryopreservation on pregnancy and perinatal outcomes is warranted.

This study does have some limitations, including its retrospective design. The small sample size of CC embryos, reflecting the lower likelihood of lower-grade embryos to develop to the blastocyst stage, decreases the statistical power of the study. This is also true of the low number of AC embryos and lack of CA embryos. A larger proportion of ET in the frozen group met eligibility criteria despite a similar number of ET in each group. Disproportionately more higher-grade embryos were transferred in fresh ET cycles as a result of the standard practice to transfer the highest-grade embryos available first, followed sequentially by lower-grade embryos. In our experience, almost all CC embryos survive post-thaw for ET. Subsequently, more CC embryos were frozen rather than transferred fresh, resulting in a larger number of CC embryos in the frozen ET group.

Furthermore, some statistically significant differences may be artifacts from the presence of a significant difference

in an earlier developmental stage (e.g., higher implantation rate in the fresh ET group), causing a ripple effect rather than a true difference.

The rate of embryo development to the blastocyst stage has also been shown to make a difference, with day 5 blastocysts significantly outperforming day 6 blastocysts with the same embryo grade for live birth rates (11). We did not differentiate between day 5 and day 6 blastocysts in our study, and further research is warranted to determine whether the rate of embryo development influenced our findings.

We focused on embryo grades and did not address the expansion stage of embryos. However, some studies showed that expansion stage did not have a significant impact on pregnancy rates and live birth rates (9, 12, 14, 16, 17). Other studies showed that embryo ploidy is a more important determinant of implantation potential than morphological grading and developmental rate (4, 24). PGT-A is the best available way to determine embryo ploidy and thus embryo quality. However, there are technical limitations associated with performing a biopsy on a TE grade C embryo due to sparse TE cells. In light of a subset of lower-grade embryos being euploid, and until TE grade C embryos can be reliably assessed for ploidy status with noninvasive PGT-A methods, one could consider transferring a TE grade C embryo while performing PGT-A on higher-quality embryos. In the absence of PGT-A, embryo grading by morphological assessment is a valuable clinical marker for selection of embryos for fresh or frozen transfer.

In conclusion, embryos with a TE "C" grade by morphological assessment should be considered for transfer and cryopreservation, as they are shown to result in appreciable live birth rates. However, these live birth rates are significantly lower than those achieved with higher-grade embryos. Our findings encourage a thorough discussion with patients to prepare their expectations of success based on the quality of the embryo being transferred.

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REFERENCES

1. Gardner D, Schoolcraft W. In vitro culture of human blastocyst. In: Janson R, Mortimer D, editors. Towards reproductive certainty: infertility and genetics beyond. Carnforth: Parthenon Press; 1999:378–88.
2. Abramov R, Antes R, Kuznyetsov V, Zaver S, Balakier H, Madjunkova S, et al. Morphological blastocyst grade is not a determinant for implantation of euploid embryos. Reprod Biomed Online 2018;36:e32–3.
3. Blazek J, Large M, Pham V, Hughes M, Gordon T. Embryo quality scoring: a correlation between trophectoderm development and aneuploidy rate in developing blastocysts. Hum Reprod 2015;30:1–2.
4. Capalbo A, Rienzi L, Cimadomo D, Maggiulli R, Elliott T, Wright G, et al. Correlation between standard blastocyst morphology, euploidy and implantation: an observational study in two centers involving 956 screened blastocysts. Hum Reprod 2014;29:1173–81.
5. Ahlström A, Westin C, Wikland M, Hardarson T. Prediction of live birth in frozen–thawed single blastocyst transfer cycles by pre-freeze and post-thaw morphology. Hum Reprod 2013;28:1199–209.
6. Zilberberg E, Nayot D, Smith RG, Meriano J, Barzilay E, Haas J, et al. Endometrial compaction (decreased thickness) in response to progesterone results in higher ongoing pregnancy rate. Fertil Steril 2019;112:e89–90.
7. Liu K, Hartman M, Hartman A, Luo Z, Mahutte N. The impact of a thin endometrial lining on fresh and frozen thaw IVF outcomes: an analysis of over 40 000 embryo transfers. Hum Reprod 2018;33:1883–8.
8. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Lippincott Williams and Wilkins; 2012.
9. Kawakami N, Aoi Y, Shindou C, Saito H, Hirata R, Hayashi N. The order of priority for embryo transfer-study of assort by blastocyst expansion, inner cell mass and trophectoderm grade. Fertil Steril 2013;100:S292.
10. Koustas G, Smith H, Sjoblom C. Avoiding cancellation of embryo transfer: embryos with poor morphology on day 5 yield pregnancies and life births. Fertil Steril 2015;104:e334.
11. Irani M, O'Neill C, Palermo GD, Xu K, Zhang C, Qin X, et al. Blastocyst development rate influences implantation and live birth rates of similarly graded euploid blastocysts. Fertil Steril 2018;110:95–102.
12. Ahlström A, Westin C, Reismer E, Wikland M, Hardarson T. Trophectoderm morphology: an important parameter for predicting live birth after single blastocyst transfer. Hum Reprod 2011;26:3289–96.
13. Onwubalili N, Brown K, Thompson SM, Jindal SK, McGovern PG. Live birth and clinical pregnancy rates after elective single embryo blastocyst transfer are strongly predicted by age and trophectoderm score. Reprod Sci 2012;19:98A.
14. Hill MJ, Richter KS, Heitmann RJ, Graham JR, Tucker MJ, DeCherney AH, et al. Trophectoderm grade predicts outcomes of single-blastocyst transfers. Fertil Steril 2013;99:1283–9.
15. Thompson SM, Onwubalili N, Brown K, Jindal SK, McGovern PG. Blastocyst expansion score and trophectoderm morphology strongly predict successful clinical pregnancy and live birth following elective single embryo blastocyst transfer (eSET): a national study. J Assist Reprod Genet 2013;30:1577–81.
16. Chen X, Zhang J, Wu X, Cao S, Zhou L, Wang Y, et al. Trophectoderm morphology predicts outcomes of pregnancy in vitrified-warmed single-blastocyst transfer cycle in a Chinese population. J Assist Reprod Genet 2014;31:1475–81.
17. Chimote N, Mehta-Chimote B, Chimote N. Trophectoderm gradation and time of transfer are robust factors governing selection of best single blastocyst for transfer to predict implantation and live births in IVF. Hum Reprod 2014;29:191–2.
18. Shah M, Kort J, Lathi R. Does blastocyst morphology predict pregnancy outcomes in euploid single embryo transfers? Fertil Steril 2015;104:e276.
19. Honnma H, Baba T, Sasaki M, Hashiba Y, Ohno H, Fukunaga T, et al. Trophectoderm morphology significantly affects the rates of ongoing pregnancy and miscarriage in frozen-thawed single-blastocyst transfer cycle in vitro fertilization. Fertil Steril 2012;98:361–7.
20. Shavit T, Oron G, Weon-Young S, Holzer H, Tulandi T. Vitrified-warmed single-embryo transfers may be associated with increased maternal complications compared with fresh single-embryo transfers. Reprod Biomed Online 2017;35:94–102.
21. Rekawek P, Friedman F, Gagbe-Togbe B, Lee J, Copperman AB. Analysis of morphology of single-embryo transfers and correlation with antepartum biomarkers and obstetric outcomes. Obstet Gynecol 2015;125:111S.
22. Sekhon L, Rodriguez-Purata J, Lee J, Briton-Jones C, Copperman A, Pavilion K. Are reproductively competent blastocysts with poor morphological grade at an increased risk for adverse perinatal outcome? Age 2016;198:116.
23. Oron G, Son W, Buckett W, Tulandi T, Holzer H. The association between embryo quality and perinatal outcome of singletons born after single embryo transfers: a pilot study. Hum Reprod 2014;29:1444–51.
24. Capalbo A, Ubaldi FM, Dusi L, Maggiulli R, Romano S, Albricci L, et al. Predictive value of blastocyst morphology beyond aneuploidy testing: evidences from a randomized non-selection study. Hum Reprod 2016;31(Suppl 1):i237–8.
25. Wang A, Kort J, Westphal L. Embryo euploidy in relation to morphology, embryo sex, and birth outcomes. Reprod Sci 2017;24:167A–8A.
26. Herlihy N, Sekhon L, Nazem T, Hernandez-Nieto C, Oliva M, Lee J, et al. Does morphologic grading of embryonic trophectoderm correlate with quality of placentation and perinatal outcome? Fertil Steril 2017;108:e376–7.