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Title:

BLASTOCYST COLLAPSE AND DOWNGRADING OF INNER CELL MASS MORPHOLOGY SCORE AFTER VITRIFICATION-WARMING IS PREDICTIVE OF REDUCED IMPLANTATION AND INCREASED EARLY PREGNANCY LOSS

Authors:

L Sekhon, C Briton-Jones, JA Lee, M Duke, AB Copperman, T Mukherjee

Affiliations:

1. Reproductive Medicine Associates of New York, 635 Madison Ave 10th Floor New York, New York, United States, 10022
2. Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, Klingenstein Pavilion 1176 Fifth Avenue 9th Floor New York, New York, United States, 10029

Objective:

The ability to cryopreserve and genetically screen embryos has increased cumulative pregnancy rates and confidence in embryo banking. Compared to fresh ET cycles, endometrial receptivity and placentation appear to be enhanced by the more physiologic hormonal milieu of FET cycles. Whether the influence of vitrification-warming on the morphology of euploid blastocysts impacts their implantation potential is not well characterized. This study examines whether changes in morphology grading, after vitrification-warming, correlate with clinical outcome, using a study model controlling for endometrial environment and embryonic ploidy.

Design:

Retrospective, cohort study

Materials and Methods:

The study included patients that underwent transfer of single, euploid, frozen-thawed blastocysts from July 2011 to February 2017. Blastocyst morphologic grading was determined, using a modified Gardner-Schoolcraft scale, at two time points: 1) prior to vitrification and 2) after warming, 1 to 3 hours prior to FET. Patients were binned into 4 categories, according to whether warmed blastocyst morphology 1) improved, 2) downgraded, 3) remained the same or 4) inner

cell mass (ICM) and trophectoderm (TE) could not be assessed due to blastocyst collapse. Chi-square and multivariate binary logistic regression (controlling for oocyte age, age at transfer, BMI, endometrial thickness and day of biopsy) was performed to assess the effect of morphology grade change on clinical outcome (implantation, clinical pregnancy, early pregnancy loss) after FET.

Results:

A total of 2,026 single, euploid FET cycles were included. Blastocysts with discordant changes in morphology before and after freezing (n=135) were excluded from the initial analysis. Compared with patients whose blastocyst morphology remained the same after warming, those with downgraded overall score or inability to score ICM/TE due to collapse had significantly reduced implantation and clinical pregnancy rates (Table 1). Overall improvement in morphology grade led to implantation and clinical pregnancy rates comparable to blastocysts that maintained their pre-freeze grade after warming. Downgrading and inability to assess post-warming ICM grade were associated with the largest reduction in implantation (OR 0.39 [95% CI 0.21-0.67], p=0.0008; OR 0.38 [95% CI 0.21-0.72], p=0.0028) and clinical pregnancy rate (OR 0.44 [95% CI 0.25-0.77], p=0.0043; OR 0.39 [95% CI 0.20-0.74], p=0.0042) and a significant increase in EPL (OR OR 2.46 [95% CI 1.21-5.01], p=0.0128; OR 2.80 [95% CI 1.26-6.23], p=0.012), respectively. Improvement and downgrading in TE score did not impact clinical outcome. However, inability to assess post-warming TE grade was associated with reduced implantation (OR 0.42 [95% CI 0.22-0.78], p=0.0064), clinical pregnancy (OR 0.41 [95% CI 0.22-0.80], p=0.0082) and increased odds of EPL OR 2.75 [95% CI 1.23-6.1], p=0.0135.

Conclusion:

Observation of dynamic changes in morphological grading may provide insight into an embryo's ability to adapt to and recover from pre-implantation, microenvironmental stress faced during vitrification and warming. A reduction in ICM morphology grade conferred a negative prognosis, whereas a downgraded trophectoderm had no significant impact on clinical outcome. The risk of implantation failure and early pregnancy loss increased after transfer of warmed blastocysts whose ICM and trophectoderm could not be graded due to failure to reexpand prior to FET. The association between post-warming blastocyst collapse and poorer outcomes suggests that rapid recovery and re-expansion after warming is associated with superior developmental competence and may serve as a clinical marker of embryo quality.

Support:

None

CHANGE IN MORPHOLOGICAL GRADE	IMPROVE n=509	DOWNGRADE n=169	SAME n=1176	COULD NOT ASSESS n=37	P value
Implantation	57.8%* (294/509)	49.7%*$^{+}$ (84/169)	62.8%$^{+o}$ (738/1176)	43.2%^{o} (16/37)	*0.067 $^{+}$0.001 ^{o}0.015
Clinical pregnancy	54.2%* (276/509)	46.2%*$^{+}$ (78/169)	57.7%$^{+o}$ (679/1176)	40.5%^{o} (15/37)	*0.068 ^{o}0.037 $^{+}$0.0046
Early pregnancy loss	15.5% (79/509)	18.9% (32/169)	17.3% (203/1176)	21.6% (8/37)	NS
EXPANSION	**n=540**	**n=7**	**n=1479**	**n/a**	
Implantation	56.5% (305/540)	57.1% (4/7)	60.9% (900/1479)	--	NS
Clinical pregnancy	52.8% (285/540)	57.1% (4/7)	56.1% (830/1479)	--	NS
Early pregnancy loss	15.9% (86/540)	28.6% (2/7)	17.4% (257/1479)	--	NS
ICM	**n=109**	**n=61**	**n=1807**	**n=49**	
Implantation	60.6%*$^{+}$ (66/109)	34.4%*^{o} (21/61)	61.0%$^{o\wedge}$ (1102/1807)	40.8%$^{+\wedge}$ (20/49)	*0.001 $^{+}$0.02 ^{o}<0.0001 $^{\wedge}$0.004
Clinical pregnancy	56.9%*$^{+}$ (62/109)	32.8%$^{+o}$ (20/61)	56.4%$^{o\wedge}$ (1019/1807)	36.7%*$^{\wedge}$ (18/49)	*0.019 $^{+}$0.003 ^{o} 0.0002 $^{\wedge}$0.006
Early pregnancy loss	14.7% (16/109)	22.9% (14/61)	16.8% (303/1807)	24.5% (12/49)	NS
TROPHECTODERM	**n=56**	**n=248**	**n=1669**	**n=49**	
Implantation	64.3%* (36/56)	56.0%^{o} (139/248)	60.6%$^{+}$ (1012/1669)	40.8%*$^{+o}$ (20/49)	*0.016 $^{+}$0.005 ^{o}0.05
Clinical pregnancy	58.9%* (33/56)	52.0%^{o} (129/248)	56.1%$^{+}$ (937/1669)	36.7%*$^{+o}$ (18/49)	*0.02 $^{+}$0.007 ^{o} 0.05
Early pregnancy loss	19.6% (11/56)	16.1% (40/248)	16.8% (280/1669)	24.5% (12/49)	NS