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Title

HOW DOES MORPHOLOGIC ASSESSMENT CORRELATE WITH IMPLANTATION OF EUPLOID EMBRYOS?

Authors

T.G. Nazem[1,2]; L. Sekhon[1,2]; J. A. Lee[1]; J. Overbey[2]; S. Pan[2]; M. Duke[1]; C. Briton-Jones[1]; M. Whitehouse[1]; A.B. Copperman[1,2] D.E. Stein[1,3]

Affiliations

1. Reproductive Medicine Associates of New York, 635 Madison Ave. 10th Floor New York, NY, United States, 10022
2. Department of Obstetrics and Gynecology and Reproductive Science, Mount Sinai School of Medicine, Klingenstein Pavilion, 9th Floor 1176 Fifth Ave. New York, NY, United States, 10029
3. Department of Obstetrics and Gynecology,, Icahn School of Medicine at Mount Sinai West, 1000 10th Ave. 10th Floor, New York, New York, United States, 10019

Objective

Pre-implantation genetic testing (PGT) has revolutionized the process of embryo selection, resulting in improved implantation and live birth rates from in vitro fertilization (IVF). In the absence of PGT, assessment and grading of embryo morphology has been the primary method of selection, despite being subjective and not standardized in the industry. This study evaluated whether the composite morphologic grade and/or a particular developmental component (i.e. expansion stage (EXP), inner cell mass (ICM), or trophectoderm (TE)) in euploid embryos undergoing single frozen embryo transfer (FET) is associated with improved IVF outcomes.

Design

Retrospective cohort study

Materials and Methods

The study included patients who underwent autologous IVF cycles and subsequent single, euploid FET between 2012 and 2017. A Gardner grading system was used to evaluate embryos before TE biopsy and vitrification, and again after rewarming prior to FET. Embryos unable to be graded after rewarming were excluded from analysis. TE biopsy and PGT using next-generation sequencing, array comparative genomic hybridization or quantitative PCR was performed on all embryos. Embryo age at time of biopsy, vitrification and FET were all included in analysis. Clinical pregnancy (CP) was confirmed by presence of fetal cardiac activity on ultrasound. A mixed-effect logistic regression model was used for analysis of clinical outcomes, including CP, ongoing pregnancy (OP), and early pregnancy loss (EPL) based on a composite morphologic grade and separately for EXP, ICM and TE. A random intercept term was added to account for subjects that contributed more than one embryo.

Results

A total of 1,517 embryos from 1,154 subjects were included for analysis. ICM grade was the greatest predictor of pregnancy outcomes when evaluated separate from TE and EXP as well as part of the composite morphologic grade [Table 1]. Embryos with an ICM grade of A compared to C had a 4-fold increase in odds of CP (95%CI 2.37-8.17) and a higher CP rate (61.9% vs. 28.2%, $p<0.01$) and 3-fold greater likelihood of OP (95%CI 1.78-6.04) and OP rate (55.2% vs. 26.8%, $p<0.01$). Embryos with an ICM grade of A compared to B had 1.5 (95% CI 1.2-2.0) times and 1.7 (95% CI 1.3-2.2) times higher chance of CP and OP, respectively. EPL was 8.6 times more likely with an ICM grade of C compared to A (95%CI 4.1-18.1), and 3.6 times more likely with an ICM grade of C compared to B (95% CI 1.8-8.3).

Conclusion

Prior to the advent of from genetic testing, morphologic assessment was essential for selection of optimal embryos. Genomic testing has revolutionized the field, but has not entirely replaced microscopic assessment of embryonic morphokinetics. Our large study convincingly demonstrates that among euploid embryos, ICM morphology is the best predictor of implantation. An embryo with an ICM grade of A has up to a 4 times higher likelihood of resulting in CP and a 3-fold higher chance of achieving an OP as compared to lesser grades. Conversely, embryos with an ICM of C were more likely to result in EPL. While ICM may be the most important morphologic component used to select an embryo for FET, a composite score may provide additional guidance as EXP and TE also play a role in an embryo's implantation potential. These results confirm that assessment of embryo morphology by a trained embryologist is essential for embryo selection, even in an era or routine PGT. A combination of genomics and morphokinetics is needed to optimize pregnancy outcomes in FET cycles.

Support

None.

Table 1.

Likelihood of IVF Outcomes based on Composite Morphologic Grade compared to 6AA Embryo

Clinical Pregnancy					
	ICM	A	B	C	
EXPANSION					TE
4		1.46*	0.96	0.33*	A
		1.48*	0.97	0.34*	B
		0.92	0.61*	0.21*	C
5		1.58*	1.03	0.36*	A
		1.60*	1.04	0.36*	B
		1.00	0.65	0.23*	C
6		Reference	0.65*	0.23*	A
		1.01	0.66*	0.23*	B
		0.63*	0.41*	0.14*	C
Ongoing Pregnancy					
	ICM	A	B	C	
EXPANSION					TE
4		1.44*	0.85	0.44*	A
		1.37	0.81	0.43*	B
		0.91	0.54*	0.28*	C
5		1.33	0.79	0.41*	A
		1.27	0.75	0.39*	B
		0.85	0.50*	0.26*	C
6		Reference	0.59*	0.30*	A
		0.95	0.56*	0.29*	B
		0.64*	0.37*	0.19*	C
Early Pregnancy Loss					
	ICM	A	B	C	
EXPANSION					TE
4		0.78	1.72	6.73*	A
		0.65	1.43	5.60*	B
		0.85	1.87	7.32*	C

5		0.82 0.68 0.89	1.80 1.50 1.95	7.03* 5.85* 7.64*	A B C
6		Reference 0.83 1.09	2.19* 1.83* 2.38*	8.58* 7.14* 9.33*	A B C

*If P<0.05