The association between rapidly dividing embryos and embryonic euploidy detected via next generation sequencing (NGS)

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OBJECTIVE

Previous research has suggested that rapid embryo development may be a strong predictor of outcomes. Rapid cell division of the early embryo was thought to be “chaotic,” and cleavage stage embryos with > 8 cells thought to have poor developmental potential. However, others have found that early cleavage embryos have higher implantation rates. Studies evaluating the relationship between cleavage development and embryonic aneuploidy are limited by use of older technologies. Thus, our goal was to assess whether rapid cell division of an early embryo is correlated with copy number variation and embryonic competence via next generation sequencing (NGS).

DESIGN

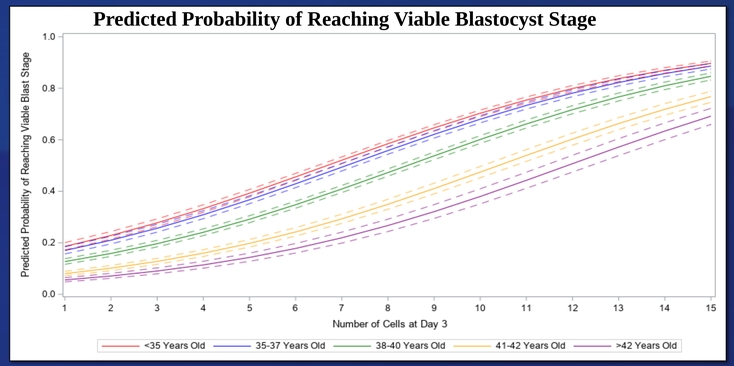
Retrospective cohort study

MATERIALS AND METHODS

- The study included patients at a single academic center who underwent in vitro fertilization and had at least one embryo that reached cleavage stage from 2016 to 2019.
- Day 3 embryos were divided into 3 groups: slow (< 6 cells), intermediate (6-8 cells), and fast (>8 cells).
- Our primary outcome was euploidy as diagnosed by trophectoderm (TE) biopsy for preimplantation genetic testing for aneuploidy (PGT-A). All tested embryos were evaluated using NGS.
- Secondary outcomes included number of blastocysts, biopsied blastocysts, ongoing pregnancy/live births (OP/LB), and clinical losses (CL).
- Data were analyzed using students ANOVA, chi square tests, and a multivariate logistic regression, with p<0.05 considered significant.

RESULTS

	Slow (N = 5651)	Intermediate (N = 23,907)	Fast (N = 11,358)	p-value	OR with 95% CI	Adjusted p-value
Blastocysts	30.30% (1,712/5,651)	77.50% (18,528/23,907)	80.08% (9,095/11,358)	<0.0001	1.30 (1.28-1.31)	<0.0001
Biopsied blastocyst rate	9.68% (547/5,651)	46.89% (11,209/23,907)	52.22% (5,932/11,358)	<0.001	1.28 (1.27-1.30)	<0.0001
Euploid rate	47.71% (261/547)	49.07% (5,500/11,209)	50.76% (3,011/5,932)	0.07	1.02 (1.00-1.04)	0.02
OP/LB rate	39.06% (25/64)	53.52% (1,004/1,876)	53.00% (556/1,049)	0.07	0.97 (0.82-1.14)	0.69
Clinical loss rate	12.82% (5/39)	12.47% (175/1403)	12.83% (101/787)	0.97	1.02 (0.77-1.35)	0.91



- 40,916 Day 3 embryos from 3,565 patients were assessed
- In our unadjusted analysis, there were significant differences between slow (n=5,651), intermediate (n=23,907), and fast (n=11,358) Day 3 embryos that developed to blastocysts (30.30%; 77.50%; 80.08%, p <0.0001) and that were biopsied (9.68%; 46.89%; 52.22%, p <0.0001). Euploidy was similar among groups (47.71%; 49.07%; 50.76, p = 0.07). A sub-analysis of intermediate vs fast embryos showed a higher rate of euploidy in the fast group (p=0.04).
- After adjusting for confounders, and using the intermediate group as a control, fast Day 3 embryos were significantly associated with increased odds of reaching blastocyst stage (OR 1.30, CI 1.28-1.31, p < 0.0001) and having blastocysts that were eligible for TE biopsy (OR 1.28, CI 1.27-1.30, p <0.0001).
- Finally,fast growing Day 3 embryos were equally likely to be diagnosed as euploid when compared with intermediate growing embryos (OR 1.02, CI 1.00-1.04, p = 0.02). There was no association between fast growing Day 3 embryos and odds of OP/LB (OR 0.97, CI 0.82-1.14, p = 0.69) or CL (OR 1.02, CI 0.77-1.35, p = 0.91).
- Finally, we categorized patients according to SART age groups and observed a higher predicted probability of an embryo reach blast stage for younger compared to older patient groups. Odds of an embryo reaching viable blast is 30% higher for each increase in cell count at day 3, controlling for all other covariates.

CONCLUSIONS

- Rapidly dividing cleavage embryos perform as well as, if not better than, intermediate or slow growing cleavage embryos.
- Prior studies of rapidly dividing embryos may have witnessed embryo/endometrial dyssynchrony and not necessarily implantation failure related to embryonic competence.
- Our study demonstrated that rapidly dividing embryos have high rates of euploidy and clinical potential.
- Morphokinetic measurements combined with genomic and non-genomic markers provide the ideal support to optimize embryo selection and improve patient outcomes.