TEN THOUSAND TIME-LAPSED TRANSFERRED EMBRYOS. WHAT HAVE WE LEARNED ABOUT HUMAN PREIMPLANTATION DEVELOPMENT IN VITRO?

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Background

Accurate embryo selection for transfer is essential to maximize the chance of successful clinical pregnancy. Several assessment methodologies exist, including morphological, morphokinetic (MK) and genetic, PGT-A. Morphology is limited by subjectivity and the introduction of automated assessment of morphology and/or kinetics promises to deliver improved accuracy and reproducibility. Observational study of human preimplantation development has been challenging due to lack of availability of embryos for research or systems to enable imaging.

Objective

This study aimed to compare MK data from a large, heterogeneous cohort of 13,670 transferred IVF and ICSI blastocysts to identify differences between embryos which resulted in a clinical pregnancy (CP+), or not (CP-), and to describe how this information may aid embryo selection in IVF.

Materials and methods

From 2011 to 2022, using EmbyoScope (Vitrolife, Sweden), the following MK variables were manually annotated for non-PGT-A ICSI and IVF embryos imaged approximately every 10 minutes through seven focal planes, following a quality assured annotation protocol: Time to; second polar body extrusion (tPB2), Pronuclear appearance and fading (tPNa and tPNf), division to 2,3,4,5,6,7,8,9 cells (t2,3,etc.), start of compaction (tSC), morula formation (tM), start of blastulation (tSB), full blastocyst (tB) and expanded blastocyst (tEB). Times were recorded in hours post insemination (hpi). For ICSI, start time was recorded midway through the procedure. For IVF, when gametes were mixed. Multicenter data were compiled from eight standardized IVF laboratories. Mean and standard deviations were calculated for CP+ and CP- embryos. Differences were compared using t-test and significance was reported <0.05. During this period, MK selection algorithms were introduced to aid embryo selection.

Results

Overall CP rates per embryo transferred were 38% for IVF and 35% for ICSI. 65% of the treatments used ICSI. For all MK variables, blastocysts resulting in CP had lower mean timings, indicating faster development compared with transferred embryos resulting in negative outcome. Mean MK timings were as follows for CP+ and CP- blastocysts respectively: tPB2:3.18 vs 3.28, tPNa:7.32 vs 7.62, tPNf:22.98 vs 23.71, t2:25.70 vs 26.44, t3:36.35 vs 36.87, t4:37.45 vs 38.57, t5:48.95 vs 49.53, t6:51.00 vs 52.78, t7:52.86 vs 55.34, t8:55.90 vs 58.81, t9:67.70 vs 69.52, tSC:77.00 vs 80.69, tM:84.46 vs 88.70, tSB:92.97 vs 96.85, tB:101.86 vs 104.93 and tEB:108.20 vs 109.44. All MK comparisons were significantly different ($p<0.01$) between the CP+ and CP- blastocysts, apart from tPB2 ($p<0.05$).

Conclusions

Time-lapse has been variably adopted in IVF clinics. Clinically viable embryos exhibit a significantly faster pace of development than their counterparts which do not result in clinical pregnancy. The differences in timings are not readily detectable with static morphological assessment. Even single morphokinetic variables have been shown to be more predictive of clinical outcome than traditional embryo morphology.[1] Morphokinetics have been used to develop algorithms for embryo selection.[2,3] Viable embryos may fail to implant due to other factors, such as endometrial. Differences in MK timings, may be more pronounced where embryo selection was based only on morphology. Further subset analyses and the inclusion of demographic and medical covariates may elucidate our understanding further. Noninvasive, reproducible, accurate assessment of dynamic embryo development lends itself to automation in modern IVF laboratories.[4]

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References

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	tPB2	tPNa	tPNf	t2	t3	t4	t5	t6	t7	t8	t9	tSC	tM	tSB	tB
Mean Pos CP (+/-SD)	3.18 (+/- 1.56)	7.32 (+/- 2.57)	22.98 (+/- 2.82)	25.7 (+/- 3.59)	36.35 (+/- 3.99)	37.45 (+/- 4)	48.95 (+/- 5.4)	51 (+/- 5.52)	52.86 (+/- 6.14)	55.9 (+/- 7.82)	67.7 (+/- 7.49)	77 (+/- 7.94)	84.46 (+/- 7.83)	92.97 (+/- 6.46)	101.86 (+/- 6.31)
Mean Neg CP (+/-SD)	3.28 (+/- 1.62)	7.62 (+/- 2.66)	23.71 (+/- 3.16)	26.44 (+/- 3.71)	36.87 (+/- 4.73)	(+/- 5.06)	49.53 (+/- 7.08)	52.78 (+/- 7.62)	55.34 (+/- 8.54)	58.81 (+/- 9.99)	69.52 (+/- 9.47)	(+/- 10.17)	88.7 (+/- 9.79)	96.85 (+/- 8.09)	104.93 (+/- 7.06)
Pvalue two tailed t test	0.0170976	6.317E-06	1.303E-41	8.7E-30	1.116E-11	1.3E-45	6.21E-08	7.3E-55	1.09E-83	9.41E-77	5.32E-28	5.2E-88	7.744E-156	1.4E-182	2.291E-115
0.05/0.01	S/NS	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S	S/S