Abstract Details

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Abstract title:

Time of morulation and trophectoderm quality are associated with live birth after euploid blastocyst transfer: a multicenter study

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Study question:

Does the morphodynamic characterization of human euploid blastocysts' preimplantation development increase the prognostic value upon their reproductive competence?

Summary answer:
Time of morulation (tM) and trophectoderm (TE) quality after blastulation (tB) increase the prediction upon euploid blastocysts' chance to result in a live birth (LB).

What is known already:
To date, the definition of a normal chromosomal constitution through comprehensive-chromosome-testing represents a powerful predictive parameter upon blastocyst's reproductive potential. However, more than 40-50% of euploid blastocysts fail to implant. The assessment of preimplantation embryo development via time-lapse has been broadly investigated to find a possible correlation between morphokinetic parameters and the clinical outcomes after IVF. Although, some conflicting data and limited evidence have been shown. The predictive value of morphokinetics during IVF cycles including preimplantation-genetic-testing of aneuploidies (PGT-A) has been instead limitedly investigated, and therefore needs further assessment.

Study design, size, duration:
In Phase1, 511 first single embryo transfers (SETs) of vitrified-warmed euploid blastocysts (N=147 center1; N=364 center2; training set) from 1069 PGT-A cycles between January-2016 and September-2017 were retrospectively recruited. A predictive model of LB was defined. In Phase2, this model was tested in a validation set including 319 consecutive SETs from 546 PGT-A cycle performed between September-2017 and June-2018 in 3 IVF centers. The ongoing pregnancy rate (OPR) was defined as primary outcome.

Participants/materials, setting, methods:
Only cycles conducted through continuous media in time-lapse incubator were included. In Phase1, all timings of development up to tSB (starting-blastulation) were compared among implanted and non-implanted euploid blastocysts. Static assessment of TE and inner cell mass (ICM) at tB was also performed. Logistic regressions outlined the parameters associated with LB. The model was applied to the validation set in Phase2 and its predictivity estimated through Receiver operating characteristic (ROC) curve analysis.

Main results and the role of chance:
The average LB rate after euploid SET in Phase1 was 40%, consistent at both centers. The euploid blastocysts resulting in a LB at both centers showed a concordant significantly faster development than non-implanted/miscarried ones for tPB2, t4, t5, t8, s3, cc3, tM and tSB. Similarly, a high-quality ICM and the TE at tB were concordant as positively associated with a LB. However, the multivariate logistic regression outlined only tM and TE quality as putative predictors. Therefore, we defined 80hr as the cut-

off tM, corresponding to the 50th percentile of prediction of a LB after vitrified-warmed SET in the training set. A model was then created based on TE quality (high or low) and tM (<80hr or ≥80hr), which showed a significant AUC of 0.65 from the ROC curve analysis. The predictive model was validated on an independent dataset composed of 319 euploid SETs from 3 different IVF centers. The euploid blastocysts characterized by a high-quality TE at tB and a tM <80hr resulted in an OPR of 61.2% (N=41/67), while those with low-quality TE at tB and a tM≥80hr resulted in an OPR of 30.0% (N=15/50; p<0.01). However, the ROC curve showed a poorly clinically-significant AUC of 0.59.

Limitations, reasons for caution:
This model is limited to euploid blastocysts produced from a population of patients indicated to PGT-A and cultured in continuous media with oxygen control in time-lapse incubators. Moreover, time-lapse timings beyond tSB were not accounted due to different blastocyst biopsy approaches adopted, namely with and without zona-opening in day3.

Wider implications of the findings:
The reproducibility of predictive models based on time-lapse parameters is highly dependent on culture conditions, that must be consistent. Moreover, these data by shedding light on the time of morulation, incite future investigations of this crucial phase of preimplantation development. A stage entailing massive morphological, cellular and molecular changes.

Trial registration number:
None.

Keywords:
morula stage
time-lapse microscopy
embryo selection
euploid
blastocyst