P-256 Time Lapse Imaging (TLI) acquired morphokinetic variables, nucleation errors and cleavage abnormalities are associated with live birth and may aid in de-selection of transfer embryos

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Study question: May the observation by TLI of morphokinetics, nucleation errors and cleavage abnormalities assist in de-selecting embryos before embryo transfer?

Summary answer: The combine predictive power of the association between the three biomarkers and live birth may aid in embryo de-selection

What is known already: Morphokinetic parameters and cleavage biomarkers are associated with treatment outcomes following *in vitro* fertilization (IVF). Nucleation errors observed by TLI have also been associated with IVF outcomes. It is also shown that nucleation error self-repair in pre-implantation embryos occurs, resulting in euploid blastocysts and live births. Biomarkers identified by TLI have been incorporated in developing algorithms to be used in selecting "the embryo" with the best potential for a live birth. However, the few randomized control studies (RCT) have not shown convincingly that TLI significantly improves live birth rate.

Study design, size, duration: Analyses of TLI data from transferred embryos, cultured in the EmbryoScope TM between June 2012 and August 2018, in a single IVF clinical setting were included. 2082 treatment cycles with Known Implantation Data (KID) for implantation and live birth were included in the analyses. Nucleation errors such as micronucleation, binucleation, and multinucleation were systematically annotated. Cleavage abnormalities such as direct cleavages, rapid and reverse cleavages were annotated for a minimum of 44 hours post insemination.

Participants/materials, setting, methods: Annotations for cleavage abnormalities, morphokinetic variables and nucleation errors, during a minimum of 44 hours, for 2959 transferred embryos were obtained from the EmbryoScope. The potential negative association between day 2 KID embryo biomarkers and implantation as well as live birth was assessed. The analyses controlled for potential confounding by adjusting for maternal age, infertility diagnosis, BMI, hormonal stimulation regime and insemination method.

Main results and the role of chance: Preliminary results were obtained regarding biomarkers in the form of nucleation errors, cleavage abnormalities and early embryo morphological attributes. Several of these biomarkers were significantly associated with implantation and live birth. Nucleation errors were associated with substantial decrease in implantation and live birth, but contrary to findings from other studies, none of the recorded nucleation error types precluded live birth. Many morphokinetically defined cleavage abnormalities were also shown to be significantly associated with implantation and live birth, with timings to 2-cells (t2) and second cell cycle (cc2) displaying the most prominent predictions for live birth probability.

Within each of the three biomarker groups, logistic regression models with implantation and live birth probability predictions displayed reasonable explanatory power regarding implantation and live birth. Combining all types of biomarkers lead to logistic regression models with substantially higher explanatory power than when the regression models only comprised a single biomarker group.

With a study of this size and *P* values for the basic findings predominantly being highly significant, the role of chance is likely to be limited. The statistical uncertainty may therefore be subordinated to the confounding caused by embryo transfer selection and further by exclusive use of embryos with known implantation

Limitations, reasons for caution: Only transferred embryos with KID data were analysed and hence the outcome of other embryos is unknown. Our study used mostly day 2 embryos, therefore generalisation up to blastocyst stage is

not possible. Our findings apply to our study cohort and may differ from findings in another clinical setting.

Wider implications of the findings: Our study provides knowledge about the role of TLI biomarkers and their potential for deselecting embryos for transfer. This will avoid transfer of lower quality embryos with lower chances of live birth. Incorporating such non-invasive de-selection strategies, alongside morphology may contribute to improving IVF outcome.

Trial registration number: NA