Image analysis of human embryos grown in vitro as a new non-invasive tool to determine embryo health

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Study question: Which embryo criteria have the most potential for automatic monitoring and embryo quality assessment using images captured during embryo growth in vitro?

Summary answer: Detection of syngami, timing of mitosis, blastocyst formation and blastomere number are quantifiable attributes. Embryo activity and fragmentation are also detectable but not quantifiable. What is known already: Non-invasive imaging has recently made it possible to monitor embryos continuously without any known consequences to their health. It has been shown that the timing of key occurrences within the embryo can vary greatly between embryos that have similar morphological appearance at the conclusion of the recording period and that embryo morphology can change in a matter of hours, emphasizing the fact that dynamic monitoring is preferred over intermittent monitoring of embryos. Dynamic monitoring of embryos requires computerized analysis but few studies have systematically attempted to map automatically extracted embryo imaging criteria to manual detection of the same.

Study design, size, duration: Time lapse image series of human embryos fertilized in vitro were acquired as anonymized sequences donated to research with ethical approval. Images were analysed for a number of embryo trait known to correlate with embryo health. Results from computerised analysis were compared to manual detection of the same trait. The study consisted of seven studies performed on the same imaging material over a course of three years.

Participants/materials, setting, methods: Embryos were cultured in 25 l culture media (Origio, Redhill, UK) under mineral oil for up to 6 days, incubated at 37C in an atmosphere of 5%CO2, 5%O2 and 90%N2. The images were

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captured using the Embryoscope(R) time-lapse system (Vitrolife, Gothenburg, Sweden), with 9 focal depth planes, 1525 μm apart, recorded at 20 minute intervals using a HMC optical set up and a 635 nm LED as light source. Images were analyzed using Matlab(R) 7.12.0.635 (R2011a).

Main results and the role of chance: Detection accuracy of of syngami was 83%, timing of mitosis 80.8% (16 cells), blastocyst formation 71.8% and blastomere number 80.8% (16 cells). Using the timing information, it was possible to measure the time elapsed between divisions to 10.27 h (23 cells), and 1.11 h (34 cells), respectively. Detection accuracy for mitosis reduced by cell number. 100% of divisions from 1 to 2 cells were detected, 73% from 2 to 3 (or 4) cells, 30% from 3 to 4 cells, and 59% from 4 to 5 (or 6) cells. Using the timing of blastocyst and morula formation, we calculated the duration of the morula stage to 1/7 of the duration of the cleavage stage, with some patient variability. Embryo activity and fragmentation were detectable in images but the accuracy not quantifiable, due to the lack of a standardized way to measure these traits manually. The automatic counting of blastomere number was semiautomatic and required manual selection of typical images prior to analysis. The counting was tested up to the 8 cell stage, in which case the accuracy was 74.9%. The accuracy was less than for other imaging techniques, e.g. using fluorescent markers.

Limitations, reasons for caution: Images were obtained from a range of microscopy settings using different protocols for embryo cultivation and different lighting conditions in the microscopy. However, the study cohort was small (38 embryos from 7 patients from 3 laboratory settings at the largest). Wider implications of the findings: Continuous imaging of human embryos growing in vitro is being routinely generated as part of IVF cultivation. The material poses a method to study dynamic properties of embryos without having to result to experimentation on human tissue and has the possibility to provide new methods to improve IVF success rates.

Trial registration number: Ethical approval by Coventry Research Ethics Committee (04/Q2802/26) and the Human Fertilisation and Embryology Authority (R0155).