No benefit to pregnancy or livebirth by time-lapse-based embryo selection in IVF

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Since the birth of the first child via in-vitro fertilisation (IVF) in 1978, the rate of IVF has been a steadily increasing technique.[1] Today more than 10 million children have been born after IVF worldwide and up to 7·7% of children in Europe and 4·7% in the USA are born after IVF.[2–4] Pregnancy rates occurring via IVF have have improved enormously since the 2010s, partly due to improved cryopreservation techniques and blastocyst culture.[5] Moreover, perinatal risks for the children have decreased, mainly via the introduction and implementation of single-embryo transfer, which decreases incidence of multiple births substantially.[6]

New methods are continuously being introduced to improve pregnancy rates and livebirth rates. The commercial interest in this area is not small. Patients, in their urgent wish for a child, are often more than willing to test new techniques, even without evidence of any increased benefits and also when they have to pay for the procedure themselves.

Numerous so-called add-ons, defined as optional procedures aiming to increase success but without proven benefit, most often at an additional cost for the patient, have been introduced in IVF.[7] Most of these add-ons have not been tested in adequately designed trials. The few that have been tested in large, randomised trials have not shown to be of any benefit for the patients.

Time-lapse technology, being considered such an add on, was introduced to the market in the 2010s.[8] In time-lapse incubators, embryo development is documented by built-in cameras that take images at fixed time intervals, resulting in videos that can be analysed by embryologists, computer software, or artificial intelligence. The systems thereby enable uninterrupted culture, avoiding potential adverse effects of changes in temperature and pH. Some systems also include a time-lapse based algorithm for selection of the most viable embryo, aiming to improve pregnancy rates and livebirth rates.

The rationale behind time-lapse using uninterrupted culture might sound logical, with the advantage of maintaining the developing embryo in a stable environment. In addition, using a huge amount of embryo development data instead of a few static evaluations for selection of the most viable embryo might seem beneficial. However, well designed, large, randomised trials are scarce despite wide use of the time-lapse technique.[9]

Kieslinger and colleagues[10] did a well designed, three-armed, multicentre, double-blind, randomised trial in the Netherlands. The authors used broad inclusion criteria to ensure generalisability, including a maternal age of up to 42 years and no limitation in the number of follicles available. 1731 couples were randomly assigned to one of three groups: the time-lapse early embryo viability assessment (EEVA; TLE) group with EEVA time-lapse selection algorithm and uninterrupted culture condition; the time-lapse routine (TLR) group with time-lapse uninterrupted culture and routine morphological embryo selection; and the control group with routine embryo selection and interrupted culture. Single embryo transfer on day 3 was used. Cumulative ongoing pregnancy rate (including fresh transfer and frozen–thawed transfers from the same oocyte retrieval within 1 year) and ongoing pregnancy rate after the fresh, single embryo transfer in good prognosis patients were the primary

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outcomes. No significant difference in the 12-month cumulative ongoing pregnancy rate was observed between the three groups, with 50·8% (293 of 577) for TLE, 50·9% (295 of 579) for TLR, and 49·4% (284 of 575) for the control group (TLE *vs* TLR odds ratio [OR] 0·99, 95% CI 0·79–1·25; TLR *vs* control 1·06, 0·84–1·33; and TLE *vs* control 1·06, 0·84–1·33; p=0·85). Cumulative livebirth rates were 48·7% (281 of 577) for the time-lapse EEVA group, 48·4% (280 of 579) for the time-lapse routine group, and 48·2% (277 of 575) for the control group (TLE *vs* TLR OR 1·01, 95% CI 0·81–1·28; and TLR *vs* control 1·01, 0·80–1·27; TLE *vs* control 1·02, 0·81–1·29). Ongoing pregnancy rate after fresh embryo transfer in good prognosis patients did not differ between groups, nor did time to pregnancy.

The strength of this study is that it is randomised, including a large and unselected population and using single embryo transfer. A further strength is focusing on an important topic, in view of the frequent use of add-ons in IVF. The main limitation is that ongoing pregnancy is the primary outcome, not livebirth. Livebirth is considered the most relevant outcome in IVF. Further embryo selection is still primarily based on subjective assessment.

Kieslinger and colleagues concluded that neither time-lapse-based embryo selection using the EEVA test nor uninterrupted culture conditions in a time-lapse incubator improved clinical outcomes, such as cumulative ongoing pregnancy rate or livebirth rates compared with routine methods. The authors argue that despite different culture systems and algorithms, any new selection method is unlikely to increase cumulative pregnancy or livebirth rates. Using today's efficient cryopreservation technique very few embryos are lost, and eventually the most viable embryo will be transferred.

The present study shows how the introduction of innovations in routine clinical practice of reproductive medicine often precedes the randomised controlled trials that should evaluate them. Time-lapse selection might have other advantages in logistic and validation processes in the IVF laboratory; however, cost-effectiveness needs to be evaluated critically in future studies.

We declare no competing interests.

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