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TIME LAPSE MICROSCOPY IN ASSISTED REPRODUCTION

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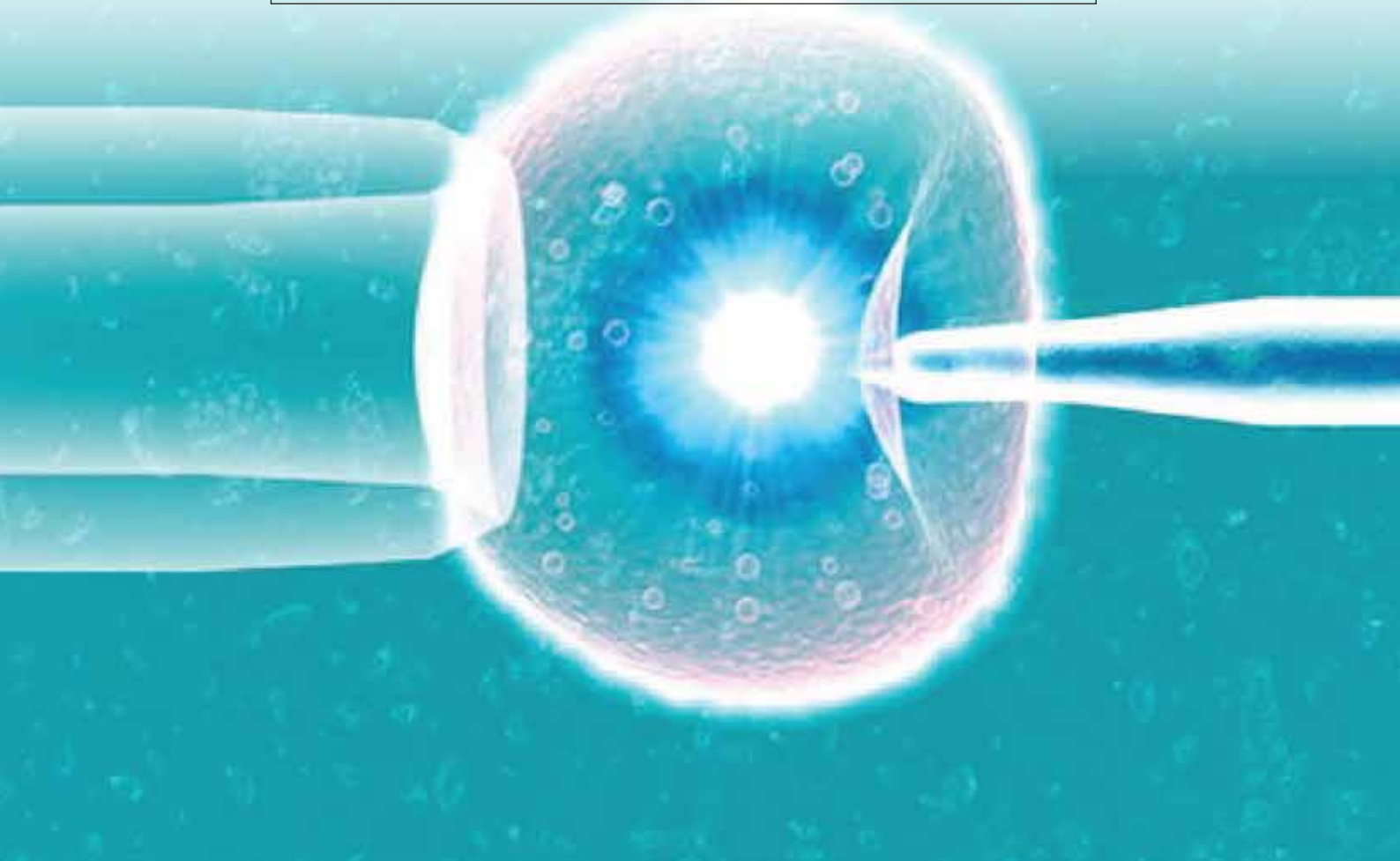

Messages

Dr Gouri Devi

President
Indian Fertility Society

Dear Friends,

In continuation with our endeavor to address the controversies in embryology practice, we would like to present the second volume of our journal "Fertilis". In this volume, we deal with 'Time lapse microscopy'. This technology has been available since 1997 when Payne used the technology to study the events occurring between 17 and 20 h after ICSI, including second polar body extrusion, and the appearance of pronuclei (PN).

Coincidentally, due to its equivocal impact on improving clinical pregnancy rate and high cost, it has not become a regular feature in various IVF labs across the world. Here, we review the positives as well as shortcomings of time-lapse microscopy and underline its utility in clinical practice.

Dr Pankaj Talwar

Secretary general
Indian Fertility Society

Dear Friends,

The ultimate goal of IVF treatment is the transfer of a single healthy embryo and subsequent birth of a healthy child. The conventional embryo selection techniques are not predictive enough to allow single embryo transfer routinely.

Scientists have tried to develop finer embryo selection tools. One of them is time-lapse imaging, which allows for continuous, non-invasive observation of embryonic development and optimizing culture conditions. The technology looks promising as it provides information on cleavage pattern, morphologic changes and dynamics of embryonic development. This could potentially help us in selecting the embryos with the highest implantation potential.

Here, we present an insightful review of literature about time-lapse microscopy, which will help you to evaluate whether the technology is useful and cost-effective for your set up.

Dr Sarabpreet Singh

Convenor
SIG (Clinical Embryology)
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Series Editor - FERTILIS

Dear Colleagues,

Time lapse imaging systems allows for continuous surveillance of early embryonic development. It has been hypothesized to improve the success rates of IVF treatment. Though, recent evidence has not shown significant improvement in live birth rates or a reduction in miscarriage rates after the use of time-lapse imaging. The positive side is that the large volume of data generated with the use of time lapse imaging will serve as a resource for further investigations.

The development of markers, which will accurately predict the blastulation rates amongst a cohort of cleavage-stage embryos or the chances of an embryo being euploid, will be a major breakthrough in embryo selection.

Time Lapse Microscopy in Assisted Reproduction

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Despite tremendous advancements in the field of assisted reproduction, the clinical pregnancy rates are still modest at about 30% per embryo transfer. It has been a constant endeavor to maximize the success rates, and for a long time, it has been presumed that transfer of more than one embryo would result in better outcomes. It is now known that transfer of multiple embryos increases the risk of multiple gestation, adverse neonatal outcomes and increases maternal morbidity. Hence, the strategy of elective single embryo transfer (eSET) was adopted, and to facilitate this,various embryo selection methods have been suggested to select the single most viable embryo which has the maximum chances of successful implantation. Time Lapse Microscopy for non-invasive embryo selection is one such technique that allows for selection and de-selection based of various morphokinetic parameters

What are the proposed morphokinetic markers of embryo competence?

Some of the putative markers of human embryo competence are:

- Faster polar body (PB) extrusion
- Synchrony in male & female PN formation
- Fast PN abuttal
- Early PN disappearance
- Duration of first cytokinesis
- First cleavage/time of 2-cell stage
- Synchrony of reappearance of nuclei after first cleavage
- Early second division
- Duration of the 2-cell stage
- Time point of 5-cell stage
- Time to start of blastulation
- Time to full blastocyst expansion[1]

It has been shown that embryos that cleave earlier and maintain a synchronized developmental speed have the highest blastulation potential, and have a higher IR.[2]

Time lapse imaging allows for ranking of the embryos according to the probability oflive birth and this hierarchical ranking for live birth prediction is proposed to have a higher discriminatory power than the standard conventional morphology assessment.[3]

Evidence

The evidence regarding the clinical utility of TLM for human embryo culture is still equivocal, and the improvement in the primary outcome measures (IR, CPR, LBR) is yet to be substantiated in larger trials.

Evidence regarding improved culture conditions

Park et al. (2015)
In a randomized controlled trial of 364 patients, it was shown that there is no difference in the number of good quality embryos amongst standard incubation and time lapse groups.[4]

Cruz et al. (2011)
No differences were found between time lapse and standard incubation as far as lab and clinical outcome was concerned.[5]

Kirkegaard et al. (2012)
In a randomized controlled trial of 676 oocytes, it was shown that there is no difference in the clinical and laboratory outcome amongst standard incubation and time lapse groups.[6]

Evidence regarding "early cleavage abnormalities"

Desai et al. (2014)
The authors found the incidence of multi nucleation and reverse cleavage to be 25%and 7% respectively, but could not find a correlation between multi nucleation and aneuploidy. They found that up to 40% of blastocysts derived from embryos with early cleaving anomalies were euploid.[7]

Lagalla et al. (2017)
It was found that up to 75% blastocysts derived from irregularly cleaving embryos were euploid, and the authors suggested an ongoing self-correction wherein the cells from irregular cleavages are extruded at the morula stage. This was substantiated in their study wherein the chromosomal assessment of the excluded cells showed chromosomal aberrations whereas the TE complement was euploid in a significant proportion of cases.[8]

Evidence regarding the notion that slower developing embryos are aneuploid

Capalbo et al. (2014)
In this study, Capalbo and Rienzi found that the euploidy level of day 5, day 6 and day 7 blastocysts was 46%, 40% and 43.5% respectively. There was no difference in ongoing pregnancy rate of euploid blastocysts according to either morphology and developmental rate.[9]

Whitney et al. (2019)
Whitney found that day 6 and day 7 blastocysts are euploid and give rise to live births in a significant proportion of cases (up to 40% and 36% respectively), and suggested routine culture of blastocysts till day 7 in PGS cycles.[10]

Kroener et al. (2012)
It was found that increased aneuploidy rates are not associated with delayed blastulation, though increased aneuploidy has been associated with absence of blastulation.[11]

Evidence regarding improvement of primary outcome measures

Racowsky et al. (2015)
In this meta-analysis, it was shown that there was insufficient evidence to support the use of time lapse compared with conventional incubation methods, and that TLM should remain experimental and not be charged to the patients.[12]

Chen et al. (2017)
Ten RCTs were included in this meta-analysis, and the pooled result showed no significant differences in ongoing pregnancy rate between the standard incubation and time lapse groups. In fact, the evidence favored the standard incubation group as far as CPR and LBR were concerned.[13]

Pribenszky et al. (2017)
This meta-analysis of 5 RCTs concluded that TLM improved pregnancy and live birth rates as compared to standard incubation, and reduced early pregnancy loss. However, this meta-analysis was critiqued and criticized for including RCTs with severe methodological flaws, allocation bias and concealment bias. Moreover, the authors of the meta-analysis were scientific advisors on the board of a company manufacturing one of the time lapse microscope units.[14]

Cochrane Database of Systematic Reviews (2019)
This review included 9 RCTs, and 2955 couples, and concluded that there was insufficient good quality evidence of differences in live birth and ongoing pregnancy rate, miscarriage and still birth, or clinical pregnancy to choose between TLM and conventional incubation.[15]

Evidence regarding concordance with ploidy status

Rienzi et al. (2015)
This study found no correlation between the 16 commonly used morphokinetic parameters and embryo ploidy. Embryo ranking according to a previous hierarchical classification, and then PGS failed to detect any difference in the percentage of euploid embryos according to their ranks.[16]

Reignier et al. (2018)
A review by Reignier et al including 13 studies, looking at the correlation between morphokinetics and euploidy, found that no single morphokinetic parameter could be consistently correlated for ploidy status.[17]

Potential benefits of Time Lapse Microscopy

- Foremost, TLM allows for uninterrupted embryo culture and obviates the need for removal of embryo culture dishes from the incubator for embryo assessment.
- There is a possibility of obtaining developmental data that can be used to select or deselect embryos of similar morphology on the day of embryo transfer
- TLM is an excellent quality control and research tool
- It allows for off-site data analysis
- TLM is an excellent tool for patient counseling
- It has been suggested that embryos selected by TLM result in a better implantation rate (IR), clinical pregnancy rate (CPR) and live birth rate (LBR).

However, the benefits are still debatable and needs to be substantiated by randomized controlled trials.

Potential concerns regarding use of TLM in IVF laboratory

- The safety regarding use in routine laboratory work flow needs is a concern, though it has been shown that the light exposure to the embryos during the 5 days of incubation and with a short exposure at every 10 minutes is still far lesser than that incurred during routine standard assessments.[18]
- Non-inferiority as compared to the standard method of embryo assessment is yet to be established.[4]
- The evidence for potential increase in IR, CPR and LBR is still conflicting.[11,12,14]
- There is a need for standardization of terminology and annotation used in TLM across various laboratories to eliminate heterogeneity
- Though TLM has been advocated as a tool for prediction of embryo ploidy, definite concordance is still lacking, and hence there is a potential of discarding otherwise euploid embryos.[15, 16]
- Cost effectiveness, especially in a resource poor setting, is an important consideration as the installation and running cost of the equipment is substantial.

Various Time lapse strategies available in the market

The various time lapse incubators available commercially are based on one of the three strategies: either to build an incubator around a microscope (Tokai Hit stagetop incubator), to insert a microscope in a commercially available incubator (Primovision, Eeva), or to have all items integrated in a single equipment (Embryoscope, Geri, Esco Miri).

Conclusions

In the light of the available evidence, it can be concluded that:

I. There is ample evidence to show that TLM can still not conclusively be used for improvement of primary outcome measures (IR, CBR, LBR), especially in low resource settings
II. There exist ethical dilemmas regarding offering non-evidence-based add-ons, and there is a potential of wasting embryos by discarding them solely on the basis of non-invasive testing
III. TLM may still very well be the future of embryo culture for reasons other than improved embryo culture.
IV. TLM is a promising tool, especially with the integration of Artificial Intelligence and Deep learning.

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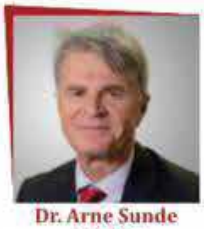
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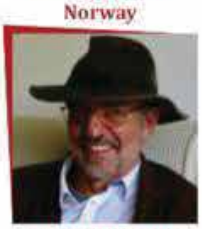
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