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Editorial

Time-Lapse Imaging: Why Are There So Few Randomized Controlled Trials?

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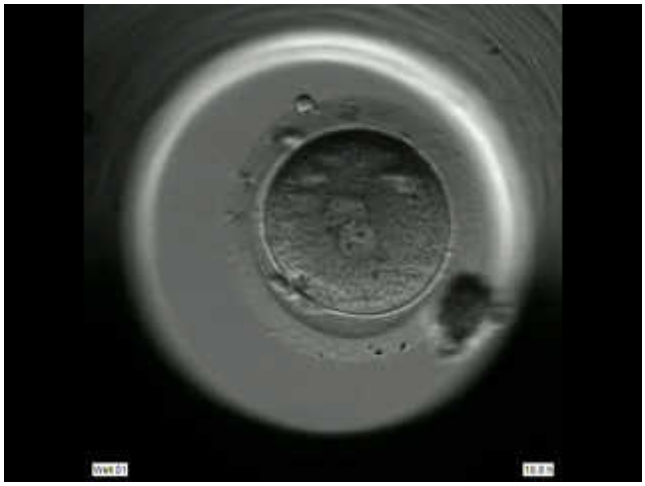
As researchers in human clinical embryology, we all know about the fascination what new ideas in the field of assisted reproduction impose on us. Usually it is a short step from learning about something new starting our own research activities in order to elaborate on how to try and implement them into routine. This has happened with microinjection, which after being developed for DNA transfer into pronuclei for animal research attracted attention in the human IVF field and resulted in techniques like SUZI (subzonal insemination) [1] and finally ICSI (intracytoplasmic sperm injection) [2]. Another technology that challenged our field was vitrification and although the principle was known for decades [3], the implementation process of vitrification for freezing of oocytes and embryos was a very fast one [4].

The recent introduction of time-lapse technology is also based on the pioneering work of embryologists like Diane Payne [5] and Yasuyuki Mio [6], just to name a few. Since then time-lapse has emerged as a technology that is considered to have the potential to change how embryologists look upon embryos in search of the one embryo with the best implantation chance [7] and chance to result in live birth. While time-lapse imaging is increasingly used in many laboratories around the globe, the clinical benefit of this technology is under discussion and especially randomized clinical trials are requested [8].

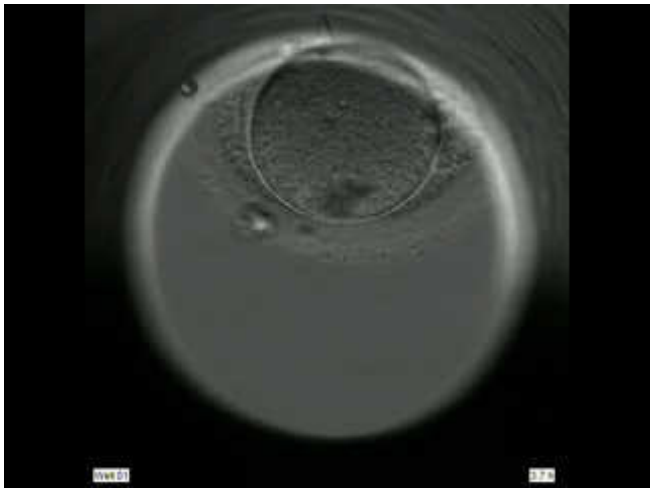
Being a time-lapse user myself, I experienced first hand the change the technology made in the laboratories where I applied this technique. The logical benefit of applying time-lapse imaging systems was obvious for me due to undisturbed culture that supported constant incubation parameters. Identifying embryos with aberrant cleavage patterns or morphology characteristics - that I would have never been able to spot without time-lapse - further strengthened this perception. However, from the point of view of clinical evidence such perception is considered anecdotal, as it is observational and not based on clinical data obtained by a RCT (Videos 1 and 2).

As time-lapse was first used clinically in 2009, question began to arise about randomized clinical trials (RCTs) to prove that the technology worked on a general basis. Talking to others in the field it became obvious, that private clinics that invest in such technology are not interested in performing RCTs. This is partly due to limited resources in a business oriented setting. But I also learned that clinics that use the technology – and sometimes even in combination with their own specific selection criteria – will not necessarily test these criteria in a RCT if they see improved results. RCT´s usually require large numbers of patients, unless the benefit gained is so huge, that a small sample size will be sufficient – which is usually not the case in the field of ART. And RCTs may take a long time during which knowledge will change and eventually more favorable parameters will be proposed which means that there is a chance that the RCT will either not be completely relevant upon completion or based on "aged" standards.

The first RCT to proof a benefit of time-lapse was published in 2014 [9]. This RCT compared time-lapse technology offered by an integrated time-lapse system in combination with a selection model to traditional embryo evaluation after culture in a standard incubator. This study



Video 1: An embryo that has a regular development with normal cell cycles from the very beginning up to the blastocyst stage.



Video 2: An embryo that is characterized by a very short 2-cell stage. The embryo divides to the 3-cell stage almost immediately and stays for a long time in the 3-cell stage. The large blastomere of the 3-cell embryo further divides into a smaller and a larger blastomere. This embryo shows an irregular cleavage and although it develops to blastocyst, it may have a lower implantation potential according to literature.

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involved more than 800 patients and showed a significant improvement for the time-lapse group but the possible bias due to a non-adequate control group and the potential simple benefit from undisturbed culture for the study group was raised in several critical reviews [10].

Cochrane published a Cochrane review [11], based on the study by Rubio et al. [9] together with two other studies [12,13], which was probably premature as the studies had different design and two of these were based on too small a sample size. The controversy on this report was taken up in a reply letter to Cochrane [14].

A recent publication by the Cleveland clinic entitled "Does the addition of time-lapse morphokinetics in the selection of embryos for transfer improve pregnancy rates? A randomized controlled trial" seemed to be the proper study many people have asked for.

The design of this study was very interesting, as it is the first time that a study addressed the question of whether or not morphokinetic analysis in an integrated time-lapse system will facilitate better results in regard to the clinical pregnancy rate compared to a control group that was incubated in the same integrated time-lapse system and where embryos were chosen by traditional morphology analysis at fixed time-points only.

The sample size justification in the study was calculated on the base of a 50% CPR, which was derived from a pilot study where the morphokinetic parameters were established and initially applied [15]. The authors expected an absolute increase of 10% by the intervention to reach a 60% CPR. With a power of 80% at an alpha of 0.05 the number of patients for randomization was set at 232. The study saw an increase in the CPR from 62.9% to 68.1%, but the statement in the publication was that the result was not significant.

While reading this publication I somehow wondered myself about that statement of the authors that the study was adequately powered to conclude no significant difference between groups - which clearly was in contrast to the statement of the sample size justification to show a significant improve of 10% in CPR. Using a publicly available sample size calculator (http://clincalc.com/Stats/SampleSize.aspx) and with the same parameters set by the authors, I calculated that the study was not properly powered from the beginning, as the calculation tool revealed that a sample size of 774 patients would have been required starting from a 50% CPR. Using only 232 patients would only give a power between 30% and 35%, i.e., in two out of three studies one would NOT see any significant difference and make the wrong conclusion, even if the actual improvement would have been the expected 10% absolute increase (i.e., 20% relative).

Because this study was underpowered right from the beginning, a statement in the abstract that the study did not reach significance is actually obsolete, as the study was not properly designed to show a significant increase. It should have been the reviewers of the Journal to identify this weakness. Furthermore the reviewers should have insisted on removing a statement on significance that can apparently not be reached if the underlying statistical calculation is wrong.

It is encouraging, that the authors do see a trend towards an improvement in CPR by adding morphokinetics to morphology assessment in a time-lapse system. Personally I would consider an absolute increase of 5% to raise the pregnancy rate from 63% to 68% a success and be justification enough to adopt such a technology.

However, to proof this increase to be significant would require a sample size of 1311 patients in each arm for a study to obtain a power of 80% to detect a significant difference at an alpha level of 5%.

The question remains: who is going to do this study? One may consider it a logical consequence that the Cleveland group may continue the study to reach sufficient power. However, as the morphokinetic model, which they initially developed, was proven to be successful and applicable it is doubtful if the clinic will take the efforts and workload to continue such a study to answer the question that is raised by others.

The 5% improvement shown in the Goodman study [16] was just achieved by adding selection criteria, meaning that the overall effect of time-lapse by adding undisturbed culture is even higher. Thus, even though from a scientific/academic standpoint an RCT is the "proper way", the overall effect, be it selection, incubation or a more flexible workflow, appears to working for many individual clinics which will continue to use this technology despite the lack of properly conducted RCTs.

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