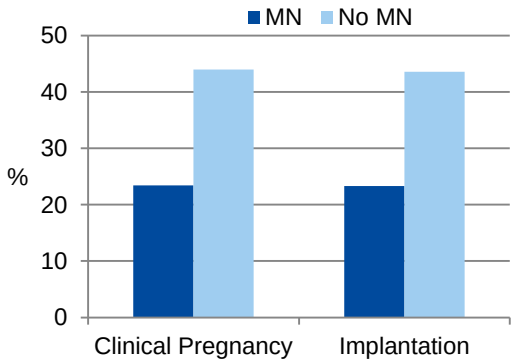
Effect and prevalence of embryo developmental traits

Without time-lapse certain embryo developmental traits that negatively influence clinical outcome in IVF are missed. Morphology has long been known to be dynamic, but without observing it through a dynamic technology it is not quantifiable. Similarly, certain developmental patterns and kinetic benchmarks can be indicators of embryo viability and are only quantifiable through a dynamic imaging tehnology.
This technote summarizes the prevalence and effect of developmental traits which can only be observed using time-lapse technolgy based on published data.

Multinucleation: impact on clinical outcome

Using time-lapse technology nuclear status of developing embryos can be quantified and multinucleation identified. A recently published study demonstrated the significantly reduced clinical pregnancy rates (23.4% vs 44%) and implantation rates (23.3% vs. 43.6%) for transfers with multinucleated vs transfers without any multinucleated embryos respectively. Up to 72% of multinucleated embryos were missed when observing embryos only at traditional time limits for embryo assessment.



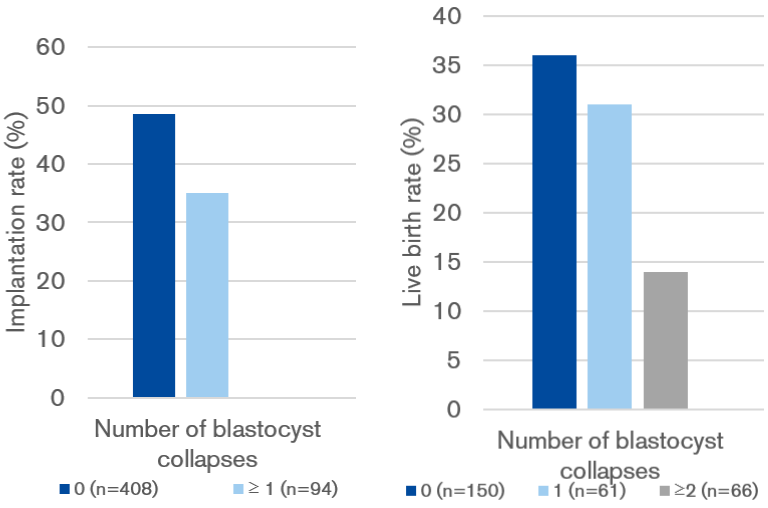
Data from Ergin, E.G., et al., Fertil Steril(2014): 102(4)

Time-lapse user since 2009 says:

"Our analysis of transfer cycles and embryo multinucleation shows that in transfers where no blastomeres were multinucleated at the 2-cell stage the KIDpositive percentage was substantially higher (62.3% and 60.7% higher for FHB and LB, respectively) than for transfers were at least one blastomere was multinucleated. This trend is the same at the 4-cell stage. Without time-lapse we would not have been able to observe this valuable indicator of embryo potential in 82 and 65 percent of cases, respectively." says Kirsten Simonsen and John Kirk from Maigaard Fertilitetsklinik, Aarhus, Denmark (data from May 2010 to Febr. 2016)

Appearance can be deceiving – developmental history adds another level of information to blastocyst morphology

The introduction of time-lapse into clinical IVF has revealed several new aspects of how embryo morphology is perceived. Even blastocysts high morphology scores by traditional grading may not always implant and part of the reason for that may be due to their developmental history. Besides adverse cleavage patterns, blastocyst collapse has been investigated with time-lapse. Analysis shows that the number of times a blastocyst collapses is strongly correlated to outcome rates of embryos with known outcome data, the results are depicted below and indicate that embryos that show blastocyst collapse can be downgraded if alternatives are available for transfer. Blastocyst collapse can only be quantified with time-lapse.



Data from Marcos, J., et al., Hum Reprod(2015): 30(11) (left) and Bodri, D., et al., Fertil Steril(2016): 105(6)

Impact and incidence of direct cleavage – a developmental trait that may be misinterpreted without time-lapse

In traditional embryo evaluation, there is often a preference for embryos that exhibit faster cleavage than others. But in certain developmental patterns fast developmental pace is not a positive trait. This is the case for the "direct cleavage" phenomenon which covers embryos for which one or more blastomeres divides to more than two daughter blastomeres at any stage. An analysis of 2494 embryos performed by Vitrolife demonstrates that 63% of embryos exhibiting direct cleavage from one to three cells would not have been detected by conventional static monitoring at 27 to 29 hours after fertilization.

The incidence and impact of direct cleavage is depicted in the studies below.

12%

Of all embryos exhibited direct cleavage at 1st, 2nd or 3rd cleavage division

Impaired development and high chromosomal abnormality rate

(89% of direct cleavage embryos)

Zaninovic et al. (ASRM2013: P327)

13.7%

Of embryos exhibited direct cleavage

Significantly reduced clinical pregnancy rate

(1% vs 13.1% of embryos were known to implant for direct cleavage vs non-direct cleavage embryos, respectively)

Rubio et al. (2012): FertilSteril 98(6)

Time-lapse user since 2012 says:

"Time-lapse allows us to identify embryos with abnormal cleavage patterns. We have the policy of not transferring embryos that cleave directly from one to three cells or embryos that exhibit fusing blastomeres with associated nucleation errors. This policy is part of our success in improving our relative live birth rates per transferred embryo by 29%" says Shabana Sayed, IVF Laboratory manager at Klinikk Hausken, Bergen and Haugesund, Norway (data compared from before (2009-2011) and after (2012-2015) implementation of the EmbryoScope time-lapse system)

Reverse cleavage – significant affects embryo potential

With time-lapse abnormal cleavage patterns can be identified. Reverse cleavage – the phenomenon where a blastomere cleaves into two daughter blastomeres that then fuse – is a cleavage pattern that is only observable by time-lapse and therefore has only been studied in recent years. In one study, 153 embryos were incubated and analysed with time-lapse. In 27,4% of these had at least one complete or partial reverse cleavage during the first three cleavage cycles. Embryos exhibiting reverse cleavage had an implantation rate of 0% whereas the implantation rate for embryos that did not reverse cleave was 22,1%.

27,4%

Of 153 embryos exhibited reverse cleavage at least once during cell cycles 1, 2 and 3

0% of these implanted

(compared to 22,1% of non-reverse cleavage embryos)

Liu, Y. et al., Fertil Steril(2014): 102(5)

Blastomere exclusion

Recently, time-lapse users have reported the observance of blastomere exclusion e.g. during morulation. Excluded blastomeres can be followed only with time-lapse in order to observe their development after exclusion to assess whether they re-integrate and become part of the blastocyst formation or not. Blastomere exclusion has been suggested to be part of a kind of correction mechanism*, however further studies are needed to confirm this. (*Lagalla et al.; Hum.Reprod. (2015): 30(suppl 1): i3)