INDIAN FERTILITY SOCIETY

SIG Newsletter

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SIG Embryology

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MORPHOKINETICS

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INTRODUCTION

Morphokinetics, a term combining "morpho" (form/shape) [1] and "kinetics" (movement) [2], refers to the time-specific morphological changes that occur during cell development. Morphokinetics in the context of embryo development refers to the time-specific morphological changes that occur during the early stages of embryo development, particularly in the context of in vitro fertilization (IVF) treatments. This dynamic approach provides crucial information on the development of fertilized eggs, aiding in the selection of embryos with high implantation potential for IVF treatments.

In classical morphological evaluation, embryos are taken out of the incubator for a few minutes each day to be statically and singly observed under a microscope. In contrast, time-lapse systems enable continuous monitoring through images captured 4-6 times per hour, all while the embryos remain inside the incubator.[3]

HOW DOES IT DIFFER ?

Standard Vs Timelapse

COMPARISON

During in vitro culture, embryos are commonly assessed through morphological grading to predict their developmental competence and potential for implantation. This assessment involves evaluating various features such as the morphology of Pronuclei (PN) and nucleoli, the number and size of blastomeres at specific stages, fragmentation, multinucleation, blastocyst expansion, and the appearance of the inner cell mass (ICM) and trophoectoderm (TE) [4-9]

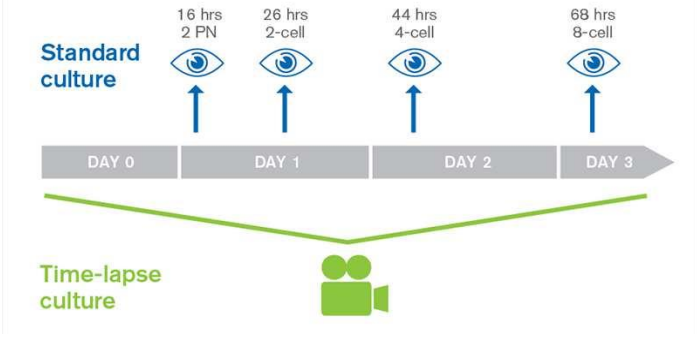


Figure 1 :Standard embryo culture vs time lapse technology [10]

Traditional morphological evaluation occurs at static time points, offering a "snap-shot" of the embryo's development. However, this method often requires physically removing embryos from the incubator, exposing them to temperature, pH, and oxygen level fluctuations. Additionally, it has limited ability to predict developmental competence and ongoing pregnancy, with significant intra- and inter-observer variability [11,12]

To standardize morphological evaluations across laboratories, a consensus on the timing and characteristics of morphology assessment for human embryos was published by ESHRE and the Alpha Scientists in Reproductive Medicine [13]. While this was a positive step, the static nature of morphology evaluation still presents limitations.

TIME LAPSE VS CONVENTIONAL CULTURE

EVOLUTION OF TIME LAPSE

Though time-lapse technology [TLT] has been part of Assisted Reproductive Technology (ART) for many years [14], it wasn't until 2010 that TLT evolved from merely observing human embryos in culture to becoming a tool for selection and prediction. Wong et al. detailed an algorithm capable of predicting blastocyst formation by the second day of embryo culture, based on cell division timings [15].

The year 2011 marked TLT's official introduction into embryology laboratories, correlating embryo implantation with specific cell division timing parameters and introducing the term 'morphokinetics' [16]. The advent of TLT has enabled increased observations and dynamic assessments of developing embryos. Simultaneously, TLT provides an uninterrupted culture environment, reducing the need for embryo handling and exposure to external conditions [17]

HOW TIME LAPSE WORKS?

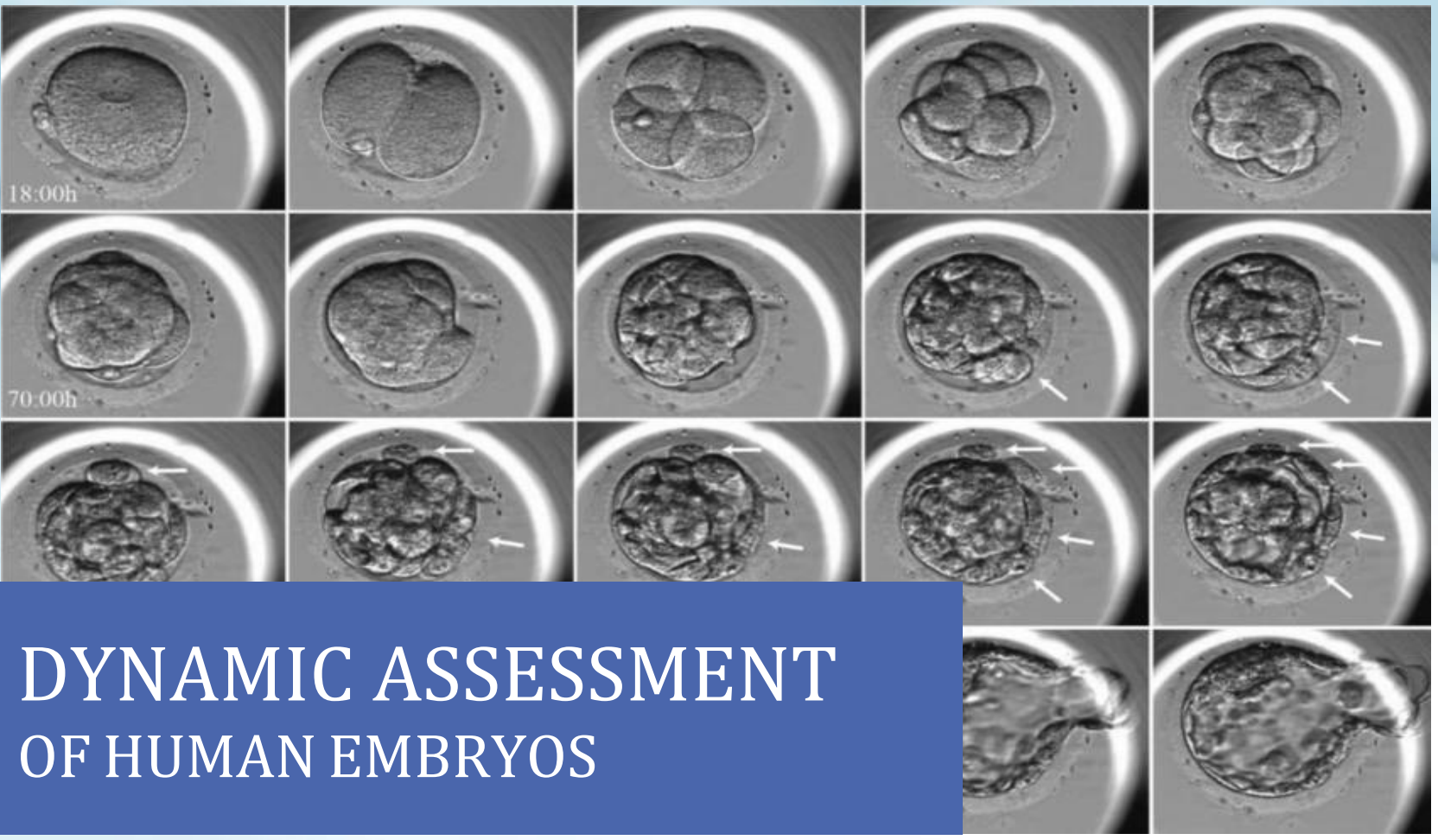
Salient features

Image Recording: The TLT incubator captures images of embryo development at regular intervals, typically every 5 to 15 minutes.

Continuous Monitoring: This continuous monitoring allows embryologists to observe the embryos' development without disturbing their environment.

Assessment Software: Some TLT systems come with specialized computer programs. These programs analyze the images and track changes in the embryos' shape and structure over time.

Ranking Embryos: Based on the data collected, the software can rank embryos according to their developmental milestones and morpho kinetics (timing of cell divisions and other events). [18]



DYNAMIC ASSESSMENT OF HUMAN EMBRYOS

Picture Caption: To make your document look professionally produced, Word provides header, footer, cover page, and text box designs that complement each other.

TYPES OF TIME LAPSE SYSTEM

Time-lapse systems used in assisted reproductive technology are typically classified into two types: open and closed systems. The open system, a traditional box-type incubator, houses a camera inside to capture images of developing embryos at regular intervals. In contrast, the closed system integrates time-lapse technology directly into a bench top incubator. This setup enables continuous monitoring of embryo development without the need to remove them from the optimal culturing environment. Clinics may choose between these systems based on their specific requirements and preferences. [19]

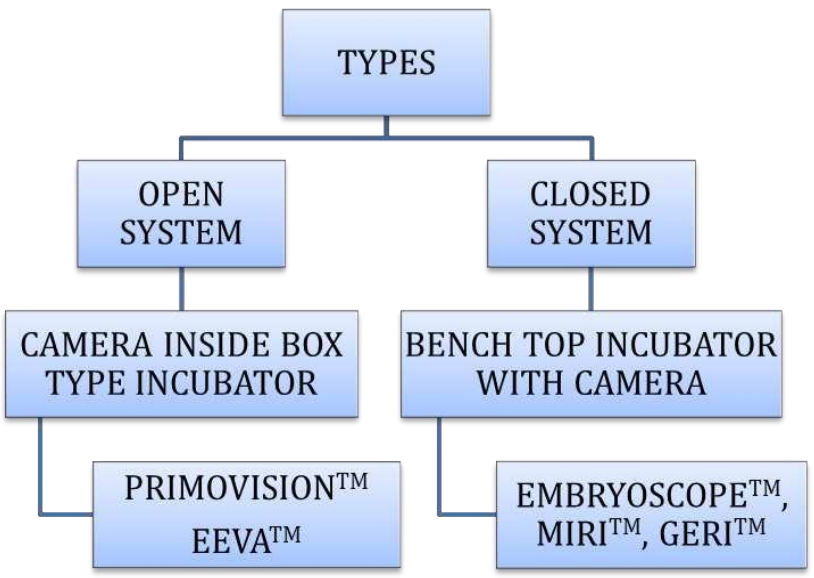


FIGURE 2 : TYPES OF TIME LAPSE

ADVANTAGES OF TIME LAPSE TECHNOLOGY

Dynamic assessment of embryos:

It provides a dynamic observation of embryo development, as opposed to static observation, allowing for a more comprehensive understanding of the process.[20]

Good Quality Images

High-resolution images obtained at frequent time points provide greater detail of the events involved in embryo development, aiding in more accurate embryo selection.

Reduce Human Error:
It reduces the degree of human error in embryo selection by providing more time for evaluation and reducing time pressure.

Minimize the damage to the embryos:
By minimizing fluctuations in optimal culture conditions, potential damage to otherwise viable embryos is reduced. [21]

Reduced Risk of Multiple Gestation:
Selecting a single embryo with the highest potential reduces the likelihood of multiple gestations, which can limit future complications. [22]

What can be missed without Time lapse?

Traditional embryo culture and static morphological assessment might fail to detect certain aspects, whichcan only be identified through time-lapse monitoring.

- Direct Unequal
- CleavageReverse Cleavage

DIRECT UNEQUAL CLEAVAGE

Defined as the abrupt cleavage of one blastomere into three daughter blastomeres or an interval of cell cycles less than five hours, Direct Unequal Cleavage (DUC) is a phenomenon commonly observed in tripronuclear human oocytes. While a normal cell cycle typically lasts between 10 to 15 hours, DUC is characterized by extremely short cell cycles with incomplete DNA replication, which may lead to an unequal distribution of DNA to blastomeres.

Direct unequal cleavage (DUC) refers to three specific scenarios:

- DUC 1 refers to abnormal cleavage occurs after syngamy (1-cell stage), resulting in the formation of 3-4 blastomeres instead of the typical 2 blastomeres. (DUC- 1 Figure 3)
- DUC 2 means abnormal cleavage occurs at the 2-cell stage, resulting in the formation of 5 or 6 blastomeres instead of the expected 4 blastomeres. (DUC 2 Figure 4)
- Direct unequal cleavage 3 (DUC – 3) refers to abnormal cleavage happens at the 4-cell stage, resulting in the formation of 9 or more blastomeres. (DUC 3 Figure 5)
- DUC Plus embryos is a term used to refer the embryo with multiple direct unequal cleavage like DUC1,DUC2,DUC3.

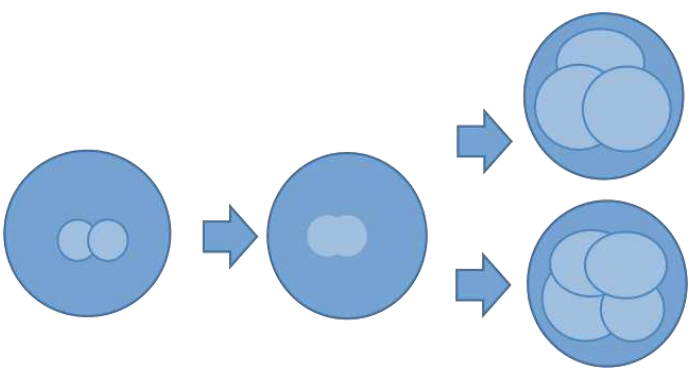


Figure 3 : Diagrammatic Representation Of Direct Unequal Cleavage 1 (DUC 1)

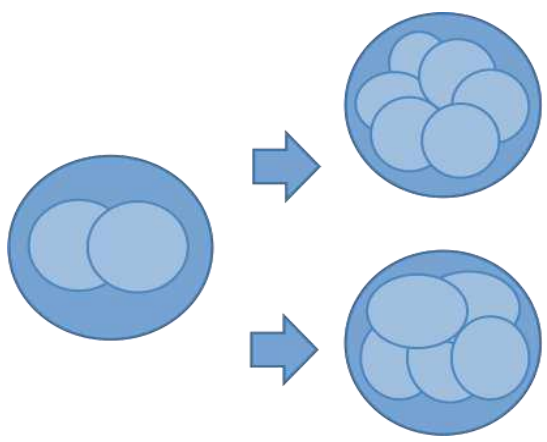


Figure 4 : Diagrammatic Representation Of Direct Unequal Cleavage 2 (DUC-2)

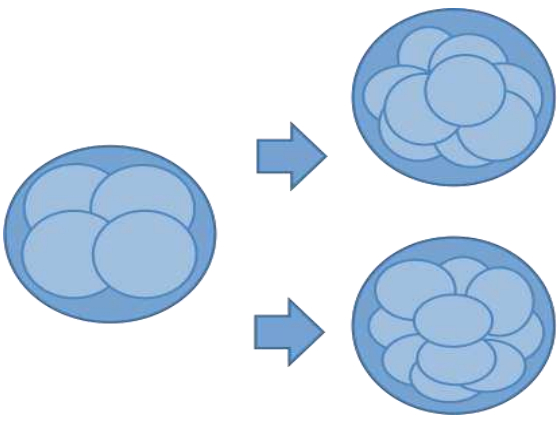


Figure 5 : Diagrammatic Representation Of Direct Unequal Cleavage 2 (DUC-3)

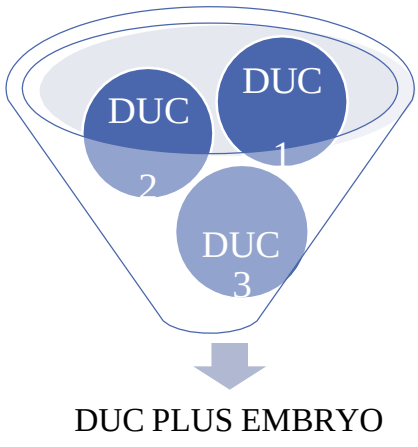


Figure 6 : Diagrammatic Representation Of Direct Unequal Cleavage DUC Plus

IMPACT OF DIRECT CLEAVAGE ON IMPLANTATION & PLOIDY STATUS

Qiansheng Zhan et al in 2016 analyzed 21,261 embryos from 3,155 cycles using time lapse and reported that total incidence of DUC per embryo in first three cleavage was 26.1% and is more common in multinucleated embryos. Generally, as the severity of DUC increases from DUC-1 to DUC-3 and then to multiple DUC embryos, there is a decrease in the rate of blastocyst formation. Similarly, the implantation rate is reduced, particularly with DUC-3 and to a lesser extent with DUC-2.

However, despite these differences in blastocyst formation and implantation rates, studies have shown that the live birth rate after blastocyst transfer from DUC embryos is similar. Interestingly, no live births have been reported from DUC-1 and DUC Plus embryos.

Moreover, there seems to be a correlation between DUC severity and euploid rate, with euploid rates gradually increasing from DUC-1 (13.3%) to DUC-2 (19.5%), DUC-3 (33.3%), and finally to non-DUC embryos (45.6%) in Day 3 biopsied embryo. The trend of decrease in euploidy disappeared in Day5 embryo biopsy. [23]

REVERSE CLEAVAGE:

- Reverse Cleavage is an abnormal division refers to the refusion of two separate cells into one cell before 8 cells. (Figure7)

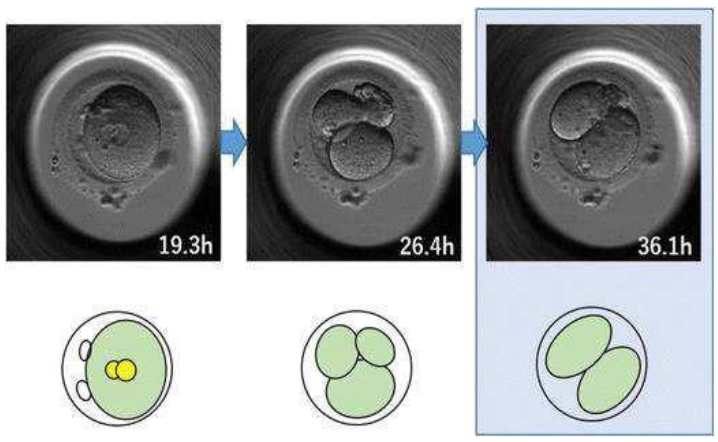


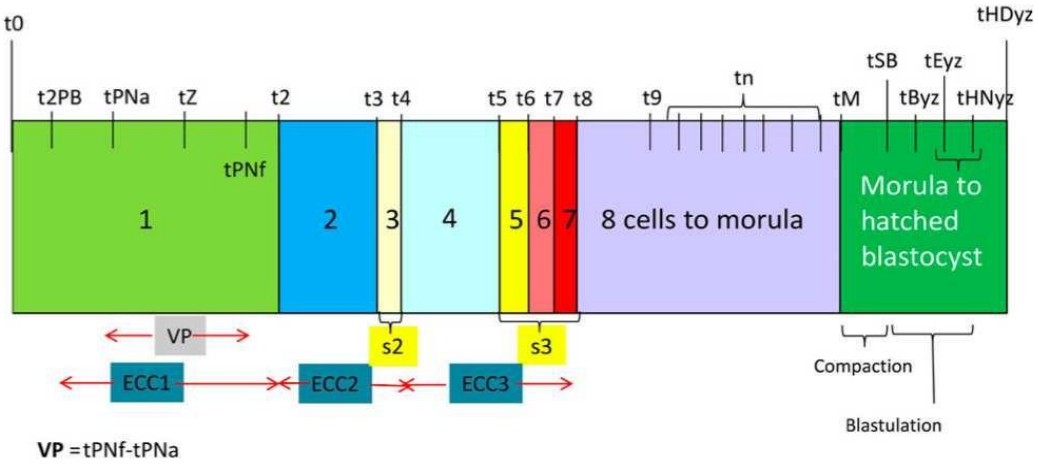
Figure 7: Reverse Cleavage[24]

MORPHOKINETICS – CAN IT PREDICT ANEUPLOIDY ?

In a study involving 405 time-lapse preimplantation genetic testing (TL-PGT) cycles and 1,467 blastocysts, researchers found that the incidence of reverse cleavage (RC) was similar among all biopsied embryos, with no significant difference. However, the blastocyst quality of the RC-positive (RC+) group was generally lower than that of the RC-negative (RC) group.

Interestingly, the number of RC occurrences was not associated with embryo ploidy status. Furthermore, the chromosomal euploid of cleavage-stage embryos exhibiting the RC phenomenon and developing to the blastocyst stage was not significantly different fro m that of cleavage-normal blastocysts. Based on these findings, the study suggests that RC embryos should not be discarded. [25] Hickman et al [26], Quera et al [27]and Desai et al [28] have also shown that reverse cleavage has no impact on ploidy status.

OTHER MORPHOKINETIC PARAMETERS IN TIMELAPSE



VP =tPNf-tPNa
ECC1 =t2 – tPB2
ECC2 =t4 - t2
ECC3 = t8 - t4
s2 = t4 - t3
s3 = t8 - t5

Compaction = tM - tSC
Blastulation = tB– tSB

Figure 8 : Schematic representation of the blastomere cell cycles(cc) and the rounds of divisions herein defined as embryo cell cycles (ECC), resulting in the doubling from two to four, and from four to eight, cells. The cell cycle for blastomere 'a', is calculated as t3 2 t2 and documented as cc2a, and for blastomere b as t4 2 t2, and documented as cc2b. The cell cycle whereby the embryo reaches four cells from two cells (ECC2) is also calculated (t4 2 t2). [29]

CELL DIVISION TIMIMGS RECORDED IN TIMELAPSE

Timings	
Time	**Definitions of expected events**
t0	Time of IVF or mid-time of micro/injection (ICSI/IMSI)
tPB2	The second polar body is completely detached from the oolemma
tPN	Fertilization status is confirmed
tPNa	Appearance of individual pronuclei; tPN1a, tPN2a; tPN3a..
tPNf	Time of pronuclei disappearance ; tPN1f; tPN2f. . .
tZ	Time of PN scoring
t2 to t9	Two to nine discrete cells
tSC	First evidence of compaction
tMf/p	End of compaction process (last frame before cavity formation) 'f' corresponds to fully compacted; 'p' corresponds to partial compaction
tSB	Initiation of blastulation.
tByz	Full blastocyst (last frame before zona starts to thin) 'y' corresponds to morphology of inner cell mass; 'z' corresponds to morphology of trophectoderm cells
tEyz	Initiation of expansion; first frame of zona thinning
tHNyz	Herniation; end of expansion phase and initiation of hatching process
tHDyz	Fully hatched blastocyst

Each timing defines the first time lapse frame in which the expected phenomenon is observed or detected.

Figure 9 : Cell cycle Timings recorded by Time lapse [29]

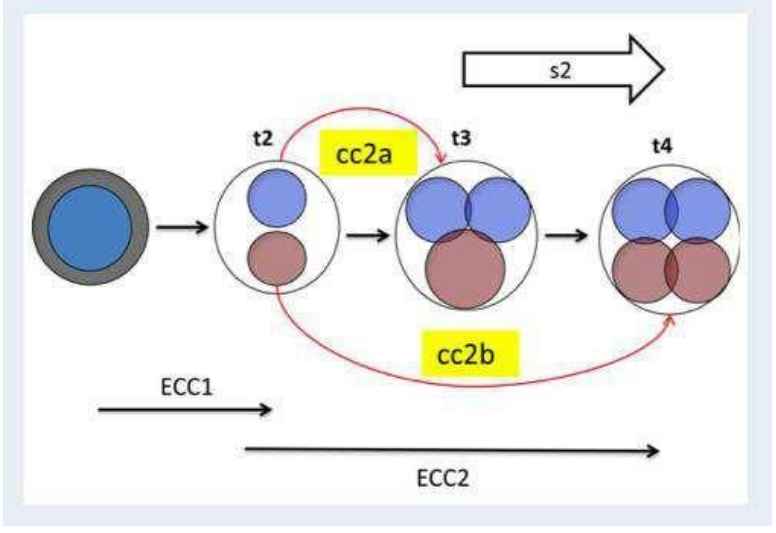


Figure 9 : Cell cycle 1 & 2 – Diagrammatic representation [29]

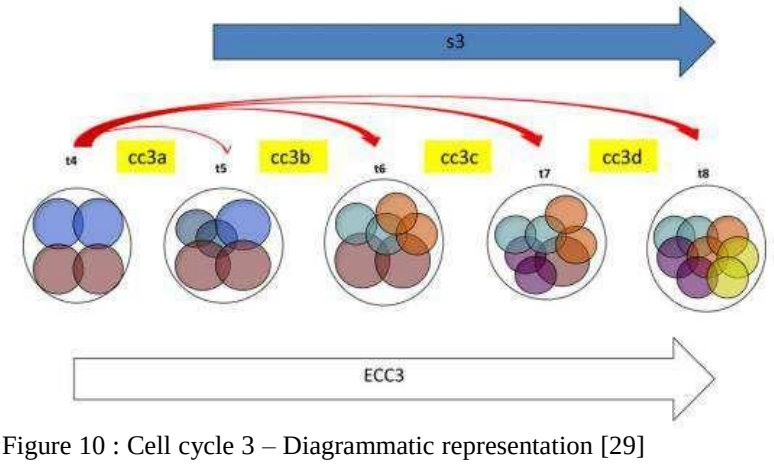


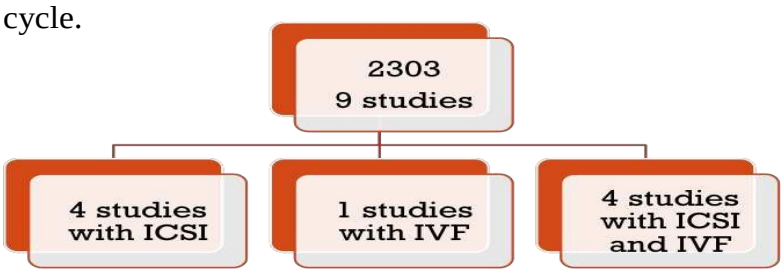
Figure 10 : Cell cycle 3 – Diagrammatic representation [29]

IS THE FREQUENT LIGHT EXPOSURE SAFE?

The EmbryoScope™ imaging system uses low-intensity red light (635 nm) and does not emit low-wavelength light (<550 nm), which has been shown to hinder embryo development [30,31]. This system's light exposure comprises only about 15% of the light encounteredin a normal IVF microscope [17]. Two studies compared the effects of repeated, short, low -intensity light exposure used for time-lapse imaging with the longer, less frequent exposure to higher intensity light used for routine microscopic observation of embryo morphology. These studies, conducted on embryos from fresh oocytes derived from donors or infertile patients, respectively,
demonstrated the safety of embryo culture in time-lapse systems versus conventional incubation [32,33]

What does the COCHRANE REVIEW says .....

It included 9 studies with 2303 cycles. Out of which 4 studies were conducted with ICSI cycle and other 4 included both IVF and ICSI and only one study with IVF cycle.



COCHRANE REVIEW published in 2019, which is considered as high-quality evidence included 9 studies. Among the 9 studies, all studies included autologous oocytes and only one study by Rubio et al included both autologous and donor oocyte program. Overall, there is currently insufficient high-quality evidence regarding the rates of live birth or ongoing pregnancy, miscarriage, stillbirth, or clinical pregnancy to determine a clear advantage between time-lapse systems (TLS), with or without embryo selection software, and conventional methods. [34]

The use of Time-Lapse incubation and imaging is not recommended for improving the chances of conception for most fertility patients, whether automated or manually analyzed. Overall, the findings from moderate to high-quality evidence suggest that this add-on does not affect the treatment outcome. [35]

WHAT ARE THE STRENGTHS & WEAKNESS IN TIME LAPSE TECHNOLOGY ?

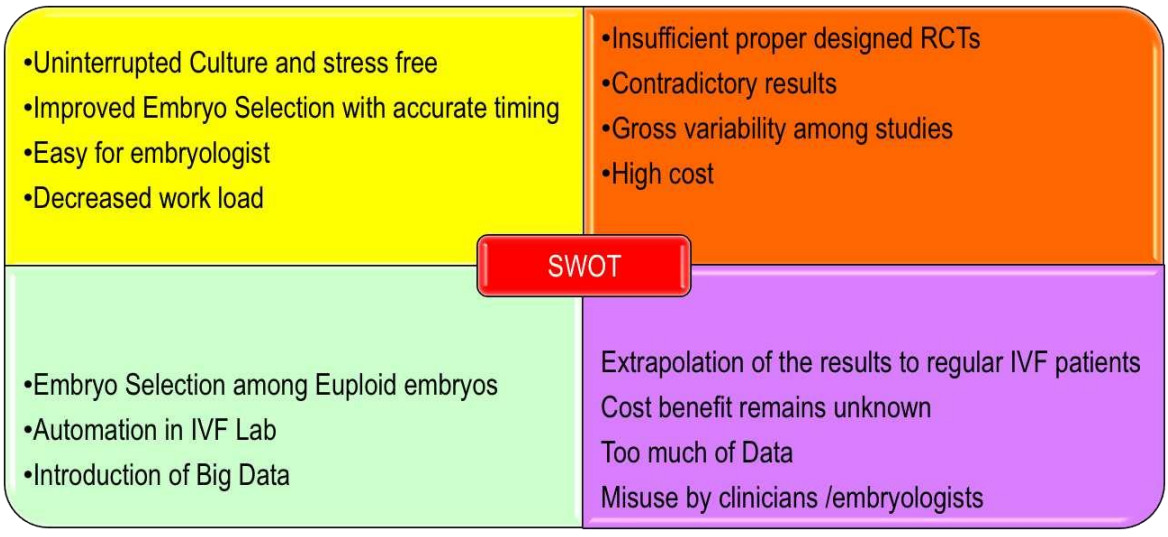


Figure 11 : Strength, Weakness, Oppurtunities & threat analysis [36]

OPTIONS AVAILABLE IN THE MARKET

	PRIMO VISION EVO	EMBRYOSCOPE	EEVA	GERI	MIRI TL	EMBRYOSCOPE PLUS
OPTICS	BRIGHT FIELD	BRIGHT FIELD	BRIGHT FIELD	BRIGHT FIELD/DARK FIELD	BRIGHT FIELD	BRIGHT FIELD
INTEGRATED INCUBATOR	NO	YES-HYBRID	NO	YES – BENCH TOP	YES – BENCH TOP	YES
FOCAL PLANES	3 -11	7	1	1	4	11
EMBRYO IMAGING	PICTURES BY USER	PICTURE EVERY 10’	PICTURE EVERY 5’	PICTURE EVERY 10’	PICTURE EVERY 5’	PICTURE EVERY 10’
CAPACITY / PATIENT	1/MICROSCOPE	6/SYSTEM	1/CAMERA	6/SYSTEM	6/SYSTEM	15
EMBRYO / PATIENT & CULTURE	6-9 INDIVIDUAL CULTURE	12 INDIVIDUAL CULTURE	12 GROUP CULTURE	16 INDIVIDUAL CULTURE	14 INDIVIDUAL CULTURE	16 INDIVIDUAL CULTURE
DATA ANALYSIS	MANUAL	MANUAL	REAL TIME AUTOATED	MANUAL / SEMI AUTOMATED	SEMI AUTOMATED	MANUAL

Table 1 : Comparison between different system available in the market [37]

HOW TO MAKE DECISION ?.....

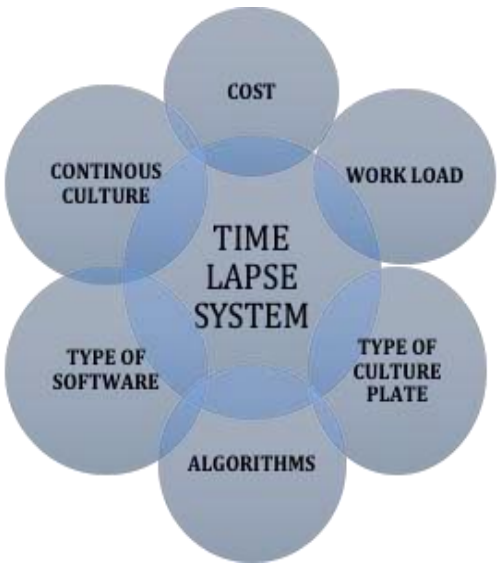


Figure 12 : Points to be considered before installation of Time lapse

LIMITATIONS:

While the benefits of morphokinetics in IVF are promising, there are limitations to consider. For example, it may not be able to deselect all abnormal embryos, and finding a universal algorithm for embryo selection remains a challenge. One notable concern is the potential for increased financial burden on patients due to the higher cost associated with this technology. Furthermore, while time lapse imaging provides detailed information on embryo development, the clinical significance of certain morphogenetic parameters remains uncertain, raising questions about their predictive value in determining embryo viability. Additionally, the reliance on algorithms for embryo selection based on morphokinetic parameters introduces the possibility of errors or misinterpretations, highlighting the need for ongoing validation and refinement of these algorithms.

CONCLUSION:

To conclude, while the morphogenetic parameter of time lapse technology holds promise for improving outcomes in IVF, its implementation should be approached cautiously, weighing the potential benefits against the associated costs and uncertainties. Continued research and clinical evaluation are essential to further elucidate the clinical utility of this technology and optimize its use in assisted reproductive practice. Stay tuned for more updates in the field of embryology.

Best regards,

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