



DISCLAIMER

- Niels B. Ramsing is an **employee** and **shareholder** in Vitrolife AB
- Vitrolife AB develop, produce and sell the EmbryoScope™ the first *time-lapse incubation system* approved for clinical use in IVF.

- Chief Technology Officer, Ph.D.
 - Developing and testing the EmbryoScope since 2004.







2004 2005 2005 2007 2009




IMPROVED OUTCOMES USING TIME-LAPSE

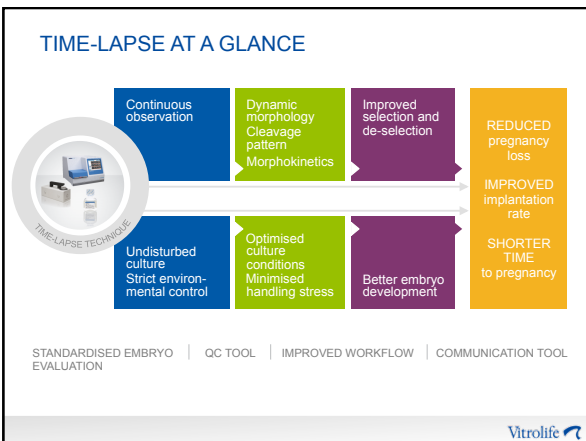
Clinical benefits from using Time-lapse

-  **IMPROVED** implantation rate^{1, 2, 3, 4}
-  **REDUCED** pregnancy loss^{1, 5, 6}
-  **SHORTENED** time to pregnancy¹

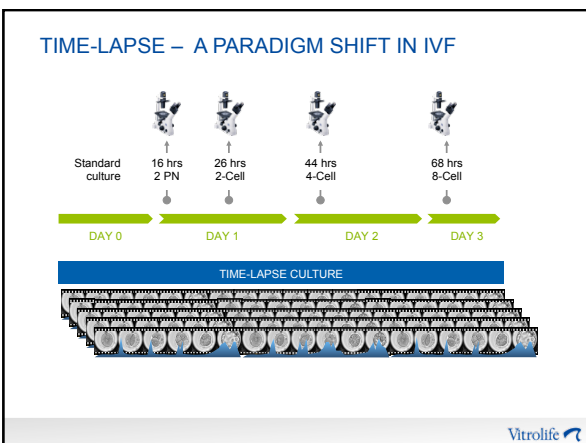


1. Rubio et al (2014) Fertil Steril 102 (5):1287-1294 e1295. 2. Menouar et al (2012) Fertil Steril 98 (6):1481-1489 e1410. 3. Kovacs et al (2013) Fertil Steril 99 (3):590-594. 4. Srigstad et al (2015) J Assist Reprod Genet 8. Barak et al (2013) Fertil Steril 100 (2):5248. 5. Vitrolife metaanalysis of Kathanan et al (2013). 6. Rappaport Stern, Cell Biochem Biophys 75:243-248. Kovacs et al (2013) and Rubio, et al (2014).









WHY USE TIME-LAPSE IN IVF?

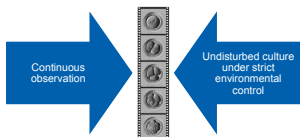
What do you get?

- | | |
|---------------------------------------|------------------------------------|
| 1 Solving the observational dilemma | Improved outcomes |
| 2 More embryo information | |
| 3 Undisturbed culture | |
| 4 Standardised embryo evaluation | |
| 5 Tool for QC | Additional benefits for the clinic |
| 6 Flexibility in workflow | |
| 7 Tool for communication | |



1 | Solving the observational dilemma

DILEMMA
You want as much info as possible to select embryos for transfer and cryopreservation, but you want to avoid disturbing embryo development



SOLUTION
Minimise embryo disturbance while maximising information needed for embryo selection/ de-selection



2 | More embryo information

DYNAMIC MORPHOLOGY

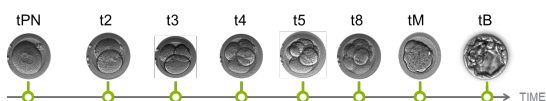
Continuously changing morphology can be seen with time-lapse

CLEAVAGE PATTERN

Abnormal cleavage patterns can be distinguished with time-lapse

MORPHO-KINETICS

Timing of events



2.1 | More embryo information – Dynamic morphology

DYNAMIC MORPHOLOGY

- Z-score of the zygote - arrangement of pronuclear precursor bodies
- Fragmentation – changing appearance of fragments with time
- Multinucleation – proper number of nuclei at 2- and 4-cell stages
- Symmetry of blastomeres
- Correct blastocyst morphology at optimal timing



1. Handerson et al (2001), Hum Reprod 16 (2):313-318. 2. Yakin et al (2005), Fertil Steril 83 (1):245-245. 3. Montoye et al (2011), Placenta 32 Suppl 3 S252-256. 4. Datta et al (2014), J Clin Endocrinol Metab 109(10):2551-2556. 5. Coughlin et al (2014), Fertil Steril 102 (4): 1026-1033. 6. Handerson et al (2002), Reprod Biomed Online 5 (1):36-38. 7. Datta et al (2014), Reprod Biol Endocrinol 12:54. Vitrolife

2.2 | More embryo information – Cleavage patterns

DO NOT MISS OUT ON KEY EMBRYO DEVELOPMENT EVENTS

- Almost 20% of embryos divide incorrectly or have abnormal cleavage
- Embryos with uneven cleavages have reduced potential of becoming a baby
- Distinguish normal and abnormal cleavage patterns

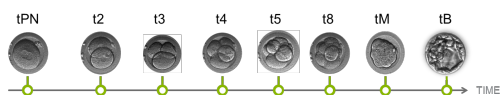


1. Aljukh et al (2011), Nat Commun 2:417. 2. Messinger et al (2011), Hum Reprod 26 (10):2668-2671. 3. Mo et al (2008), Am J Obstet Gynecol 199 (5):660-665. 4. Pilschke et al (2010), Reprod Biomed Online 21 (4):533-536. 5. Rubio et al (2012), Fertil Steril 98 (5):1436-1438. 6. Hinkka et al (2012), Clinica Gynecol 77 (1): 52-57. Vitrolife

2.3 | More information – Morphokinetics

MORPHOKINETICS – timing of events


Correlation with outcome potential



1. Hinkka et al (2012), Clinica Gynecol 77 (1):52-57. 2. Rubio et al (2014), Fertil Steril 102 (5):1267-1264. 3. Messinger et al (2012), Fertil Steril 98 (5): 1481-1484. 4. Chamayou et al (2013), J Assist Reprod Genet 30 (5):703-710. 5. Campbell et al (2013), Reprod Biomed Online 27 (2):140-148. 6. Datta et al (2014), Reprod Biol Endocrinol 12:54. 7. Calabrese (2015), J Assist Reprod Genet 30 (1):27-35. 8. Rappin et al (2015), Hum Reprod 30(2):276-283. Vitrolife

3 | Undisturbed culture

- Less handling ¹
- Embryos in a stable environment
- Supports better embryo development ^{2,3}
- Less light exposure than standard evaluation ⁴




1. Zhang et al (2010). *Reprod Biomed Online* 20 (4):510-515. 2. Rubio et al (2014). *Fertil Steril* 102 (5):1287-1294. 3. Kahraman et al (2013). *J Reprod Steril Cell Biotechnol* 3:55-61. 4. Li et al (2014). *J Assist Reprod Genet* 31 (7):795-801

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4 | Standardised embryo evaluation

- Standardising the knowledge within the lab
- Embryo scoring can be more standardised and less dependent on subjective assessment
- Interoperator dependence can be lowered¹




1. Sundvall et al (2013). *Hum Reprod* 28 (12):3215-3221

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5 | Tool for QC

INCREASED SAFETY

- More than one person can score and evaluate embryo development
- All development data saved – ability to re-evaluate if complications or questions appears
- Lab QC possible- early warning system for issues with the culture system¹⁻³



1. Wolff et al (2013). *Hum Reprod* 28 (7):1776-1782. 2. Morbeck et al (2014a). *Fertil Steril* 102 (3):759-766. 3. Morbeck et al (2014b). *J Assist Reprod Genet* 31 (12):1703-1713

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6 | Flexibility in workflow

OBSERVATIONS ARE NOT CONNECTED TO FIXED TIME-POINTS

- Reduce the morning rush hour
- Evaluate embryos when you have time
- Free up resources

You can plan your workload better

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7 | Tool for communication



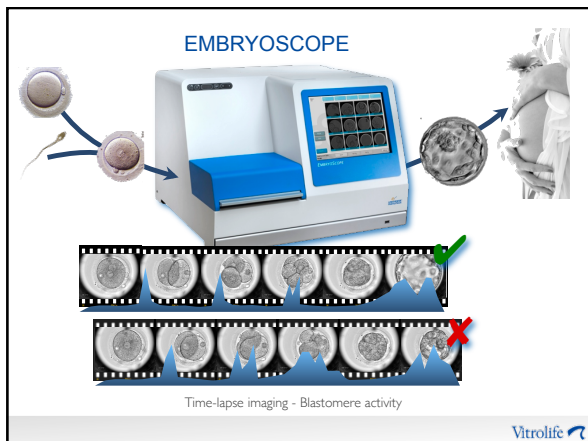
- ♥ Facilitate communication between doctors, embryologists and patients
- ♥ Increase level of understanding
- ♥ Facilitates training of new embryologists

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EMBRYOSCOPE: IMAGE ACQUISITION AND INCUBATION

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EMBRYOSCOPE TIME-LAPSE SYSTEM

- #1**
IVF solution for time-lapse embryo imaging, the most widely used system worldwide
- Global collaboration** with leading doctors and embryologists
- CE & FDA 510(k)**
CE Class IIa medical device since 2009 and FDA 510(k) cleared in 2011
- Education**
Extensive training and knowledge building
- 11 years of research** and proven results with international validation

- More than **330,000 cycles** worldwide in 46 countries (Dec 2014)
- Product development based on input from hundreds of leading scientists
- First time-lapse system** approved for clinical use in Europe and USA!
- More than **40 workshops** with 1250 participants have been held worldwide.
- ASRM/ESHRE since – 2005**, 164 posters, 72 oral abstracts and more than 30 peer reviewed papers using EmbryoScope technology

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EMBRYOSCOPE™ TIME-LAPSE SYSTEM

EmbryoScope™ time-lapse incubator

ES Server

Thin client computer runs EmbryoViewer® Software

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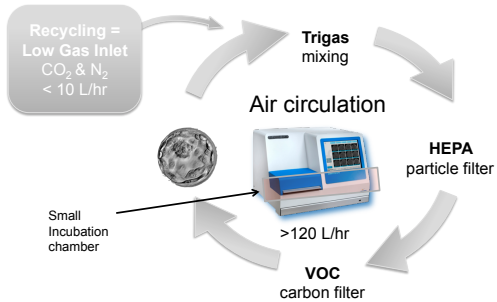
EMBRYOSCOPE TIME-LAPSE SYSTEM

- Combines the Embryo culture incubator and the camera in a **single unit**
 - Instant and continuous **monitoring of embryo** development.
 - Instant and continuous **monitoring of incubation** conditions for laboratory QC and vigilance.
- Advanced and intuitive software tools
 - **Easy analysis** of embryo development
 - **Comparison** of embryo morphokinetics



EXCELLENT EMBRYO CULTURE

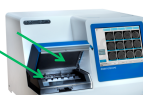
Stable incubation without removing embryos



FEATURES OF EMBRYOSCOPE TIME-LAPSE INCUBATOR



- Continuous purification of air flow**
- HEPA/VOC filter ensures cleanest environment for embryo development.



- Two stage temperature control**
- Direct heat to the EmbryoSlide culture dish as well as temperature control of incubation chamber.
 - Temperature virtually unchanged by opening and closing
 - Temperature not affected by laboratory temperature change.



FEATURES OF EMBRYOSCOPE TIME-LAPSE INCUBATOR



Integrated gas mixer

- Select your own gas mix. Simple and economical implementation of reduced O₂ culture. Avoid costs associated with high usage of N₂



Re-cycling of the gas = low gas consumption

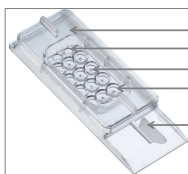
Ideal for QC

- Continuous log of of incubation conditions



EMBRYOSCOPE™ TIME-LAPSE INCUBATOR CAPACITY

- 6 EmbryoSlide® culture dishes per instrument
- 12 embryos per culture dish



- Lid ensures low evaporation
- Flushing wells*
- Microwell
- Outer well with micronumeral for identification
- Handling fin for safe transfer between workplaces

* New Design – pending clearance by FDA



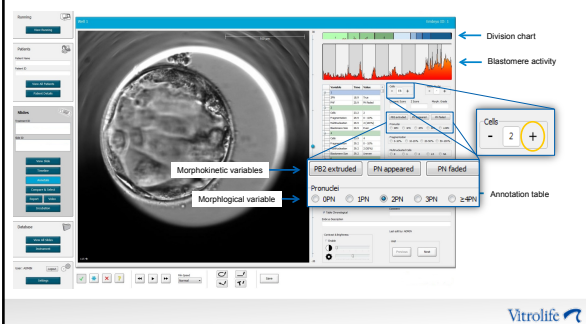


EMBRYOVIEWER: EMBRYO SELECTION

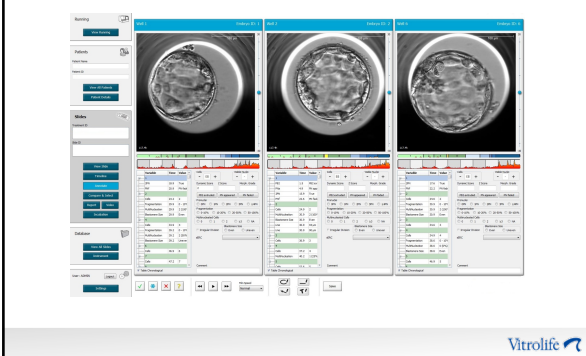


FEATURES OF EMBRYVIEWER SOFTWARE

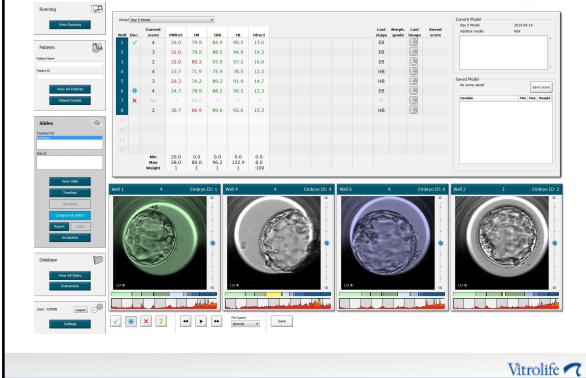
Intuitive embryo evaluation interface (Annotation tool) developed using input from leading embryologists worldwide



FEATURES OF EMBRYVIEWER SOFTWARE SIDE BY SIDE COMPARISON



COMPARE AND SELECT – USER DEFINED SCORING ALGORITHM



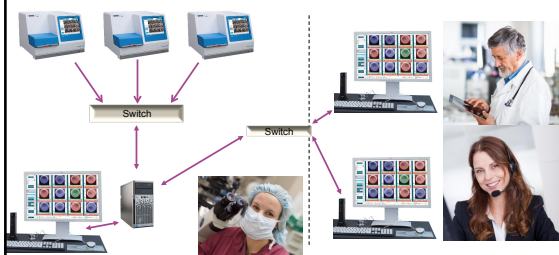
EMBRYOVIEWER SOFTWARE KEY FEATURES

- Annotation tool to mark morphokinetic and morphological events
- Digitalization
- Flexible annotation strategy
- Compare and Select tool for better selection
- Creation of models – clinic specific
- Report and video generation



FEATURES OF EMBRYOSCOPE SERVER

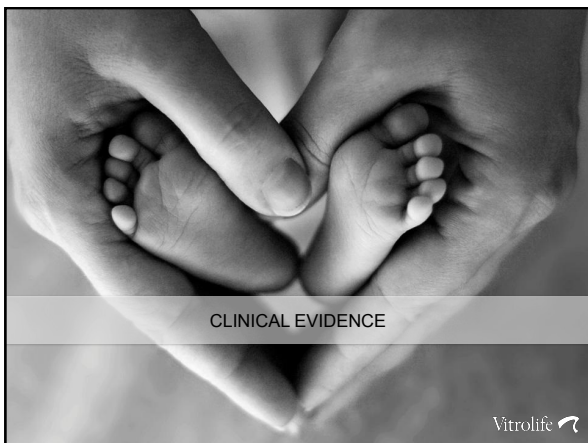
Centralized data, multiple viewing stations



Laboratory

Office/consulting area





CLINICAL EVIDENCE



NEW TECHNIQUE – NEW TERMINOLOGY

Timeline stages: tPN, t2, t3, t4, t5, t8, tM, tB

Dynamic morphology

Continuously changing morphology can be seen with time-lapse

Morphokinetics

Timing of events

Cleavage pattern

Abnormal cleavage patterns can be distinguished with time-lapse

Annotation

Registration in software of specific developmental or morphological events

TIME →

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More embryo information – Dynamic morphology

MULTINUCLEATION: IMPACT ON CLINICAL OUTCOME

Outcome	MN (%)	No MN (%)
Clinical Pregnancy	~23	~45
Implantation	~23	~45

Legend:
 ■ MN
 ■ No MN

Statistics:
 n= 145 patients (MN)
 n= 366 patients (no MN)
 Transferred embryos retrospectively checked for MN at 2-cell stage by time-lapse images

Key Findings:
 Only 27.6% of multinucleated embryos were identified within traditional time limits for embryo assessment
 Multinucleation significantly reduced clinical pregnancy rate and implantation rate

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

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More embryo information – Dynamic morphology

MULTINUCLEATION: INCIDENCE

In house analysis of 2494 embryos of which 318 were multinucleated

Multinucleation at 4-cell stage resulted in 25% lower implantation rate

23% of occurrences were missed by static evaluation time points

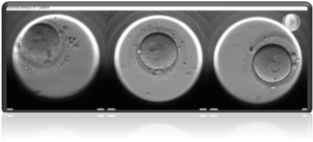
Data on file

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2.2.1 More information – Cleavage patterns

REVERSE CLEAVAGE: IMPACT ON OUTCOME

- Occurred in 27.4% of embryos
- Reduced implantation potential:
0% for RC embryos versus 22.1% for non-RC embryos



Liu et al. Fertil Steril 2014; 102 (2):298-300

