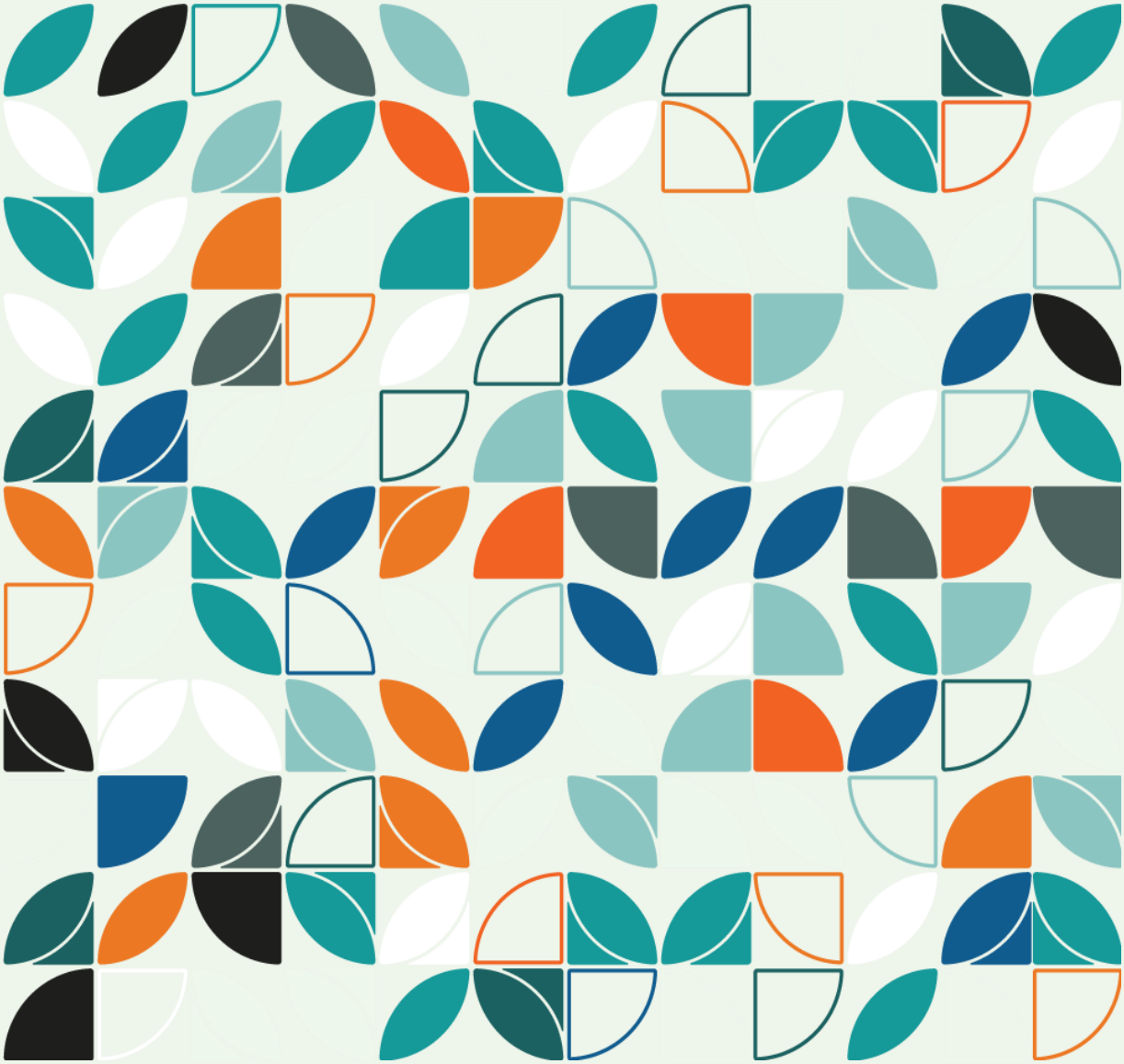
Chloe

Fairtility

Fairtility's Clinical Studies 2021 - 2024

Research using CHLOE™



Contents

Executive Summary

USING CHLOE EQ™ integrated with the EMR and the time-lapse incubator:
- increases embryologist efficiency by 33%,
- increases the capacity of cycles embryologists can treat by 50% &
- reduces risk,
- Reduction of 41% of time required per cycle.

CHLOE agreement with embryologists for PN assessment 91-97%

Clinic	CRGH	Juana Crespo			Fertility	Reproferty	HSFC, CRGH, Plymouth, Kings
Country	UK	Spain			Brazil	Brazil	UK
Study	25	26	08	31	36	36	11
	468/483		166/179	2360/2591	606/641	195/197	5664/6048
PN agreement	92%	93%	93%	91%	95%	99%	94%

CHLOE agreement with embryologists for MORPHOKINETIC assessment Strong /Very strong

Clinic	Fertilitat	Primordia	Reproferty	Fertility	Juana Crespo	Memorial	CARE	USF	Cornell	HSFC	CRGH	Plymouth	Kings
Country	Brazil	Brazil	Brazil	Brazil	Spain	Turkey	UK	USA	USA	Multicenter UK			
Study	36	36	36	36	26, 08, 05	04, 05, 01	03, 05	38	32	12			
tPNf		1.0		0.959	0.69	0.78-0.92	0.77-0.92	0.856	0.65	0.97	0.63	0.95	0.66
t2	0.889	0.932	0.997	0.927	0.64	0.85-0.91	0.73-0.85	0.920	0.9	0.84	0.87	0.92	0.74
t3	0.873	0.998	0.945	0.912	0.76	0.81-0.89	0.79-0.81	0.601	0.76	0.8	0.81	0.84	0.84
t4	0.746	0.997	0.942	0.958	0.61	0.73-0.83	0.65-0.73		0.83	0.89	0.87	0.74	0.76
t5	0.809	0.998	0.928	0.972	0.77	0.81-0.83	0.80-0.81		0.79	0.76	0.89	0.78	0.73
t6		0.999		0.950	0.74	0.82-0.86	0.79-0.82		0.80	0.77	0.68	0.74	0.69
t7		1.0		0.894	0.63	0.63-0.74	0.69-0.74		0.82	0.72	0.76	0.8	0.8
t8		1.0		0.900	0.68	0.68	0.68		0.84	0.73	0.79	0.72	0.83
t9		0.995				0.66-0.71	0.69-0.71		0.74	0.74	0.76	0.78	
tM		0.954		0.903	0.78	0.71-0.85	0.78-0.85		0.81		0.85	0.67	
tsB		0.998		0.981	0.93	0.92	0.90-0.92		0.95	0.75	0.89	0.9	0.92
tB	0.941	0.951	0.964	0.973	0.93	0.91	0.87-0.91	0.899	0.86	0.74	0.92	0.92	0.95
teB		0.971			0.80	0.79-0.83	0.79-0.83		0.61		0.6	0.96	

CHLOE BLAST score is predictive of BLASTULATION AUC 0.84-0.96

Clinic	Memorial	CRGH	Juana Crespo	Next Clinics Murcia	Crespo, Memorial, NEXT, Generalife, CRGH, Alpha, IASO	Gravida	Reproferty Fertility Fertilitat Primordia	CRGH Kings Plymouth HSFC	IVF London
Country	Turkey	UK	Spain	Spain	Multi	Spain	Brazil	UK	UK
Blastulation	0.96 n=5392	0.89 n=3269	0.84 n=179	0.84 n=179	0.86 n=4266	0.91	0.91 n=792	0.87-0.92 n=8368	0.86 n=1328

CHLOE EQ score is predictive of UTILISATION AUC 0.84-0.96

Clinic	Juana Crespo	Reproferty Fertility Fertilitat Primordia	CRGH Kings Plymouth HSFC	IASO	IVF London	UZ Brussels
Country	Spain	Brazil	UK	Greece	UK	Belgium
Utilisation	0.90	0.90 n=792	0.88-0.96 n=8368	0.94 n=1425	0.88 n=1328	0.84 n=1153

CHLOE EQ score is predictive of IMPLANTATION AUC 0.63-0.76

Clinic	Soroka & Hadassah	Soroka, NYU, Hadassah	Crespo, Memorial, Next, Generalife, CRGH, Alpha, IASO	Dijon	Gravida	Juana Crespo	CRGH	UZ Brussels
Country	Israel	Israel USA	Multi	France	Spain	Spain	UK	Belgium
Implantation	0.69 n=608	0.66	0.76 n=535	0.68	0.75	0.64	0.63 n=113	0.65 n=141

CHLOE EQ score is predictive of PLOIDY AUC 0.60-0.96

Clinic	Memorial	IASO	Crespo, Memorial, Next, Generalife, CRGH, Alpha, IASO	Gravida	Juana Crespo	Genesis Reproferty Fertility Fertilitat	USF	CRGH	IVF London	Bernabeu	UZ Brussels
Country	Turkey	Greece	Multi	Spain	Spain	Brazil	USA	UK	UK	Spain	Belgium
Ploidy	0.96 n=5392	0.66 n=915	0.61 n=1463	0.96	0.64	0.65	0.6 n=1711	0.60	0.64 n=1328	0.63 n=224	0.60 n=54

CHLOE EQ score correlates with LIVE BIRTH

Clinic	Cornell	Memorial
Country	USA	Turkey
Live birth vs Not live birth	CHLOE EQ Score 0.93±0.2 n=42 vs 0.87±0.2 n=36, p=0.08	tB correlated with live birth prediction 104.57 ± 7.03 vs 106.46 ± 7.12 , p=0.037

USING CHLOE OQ™ integrated with the EMR and the time-lapse incubator:

- Assess eggs within the **safety of the incubator**,
- Mitigate human mix-up errors with **secure traceability**
- Capture images automatically **saving you time**,
- Enable **personalized family planning** for your patients.

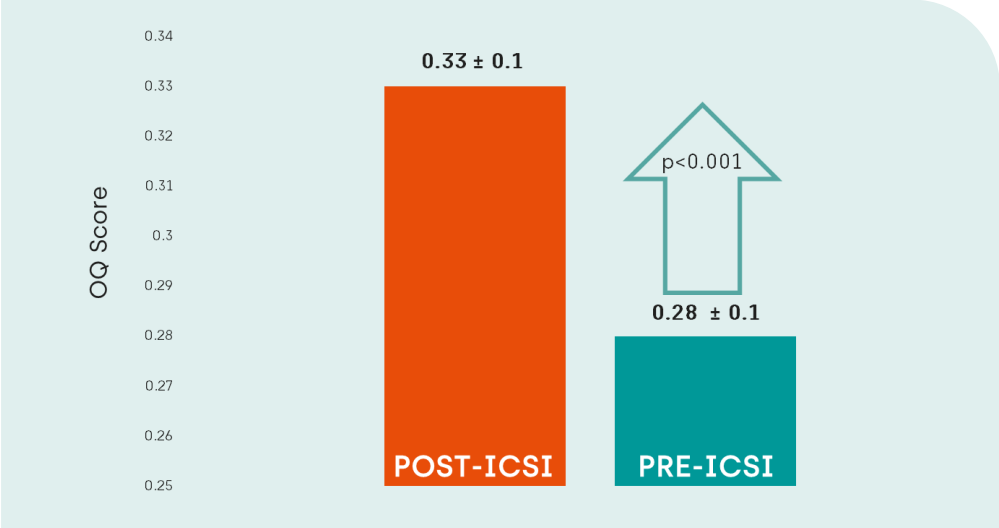
CHLOE OQ score is predictive of BLASTULATION

Clinic	Alpha	CRGH	IASO	London women's
Country	Malaysia	UK	UK	UK
Prediction of blastulation (AUC)	0.60, n=1151	0.61 n=80	0.70 n=30	0.66 n=1449

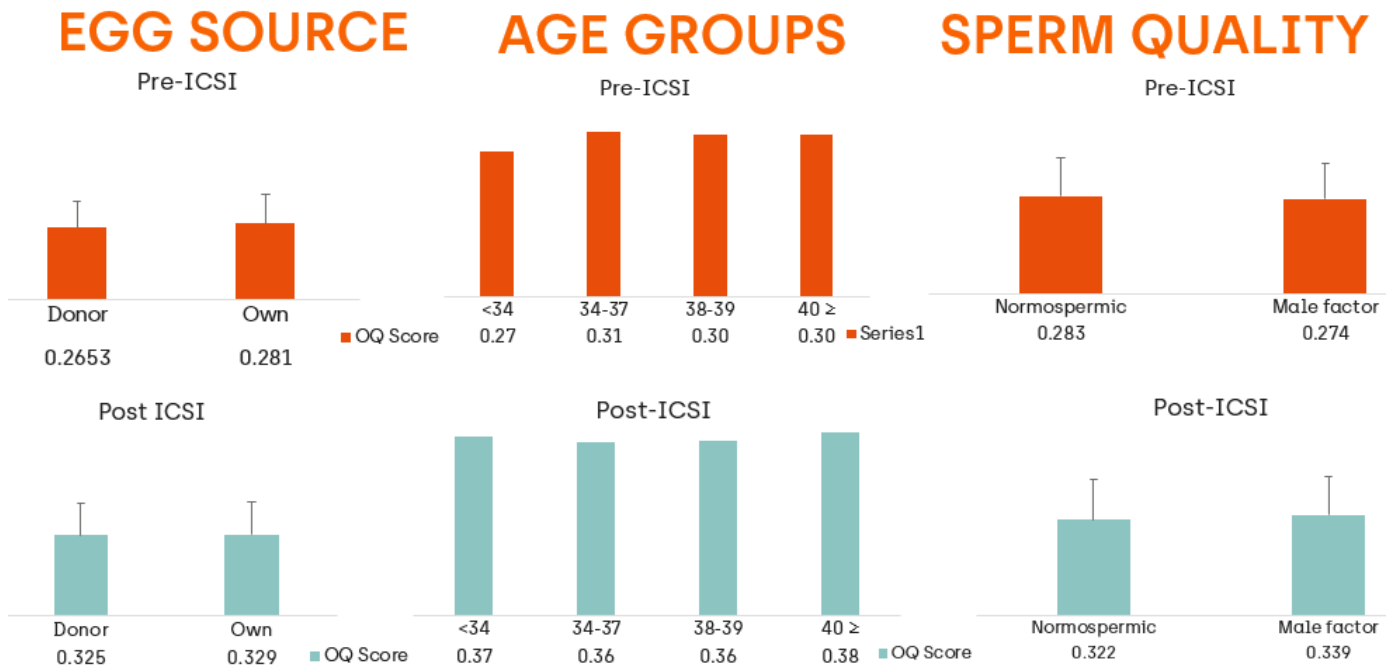
Multi-centre Study; Pre-ICSI images only

Clinic	Alpha	IASO	CRGH	Overall
n	1151	83	30	1264
Blastocyst Rate	63%	60%	57%	63%
% improvement in prediction over random	21%	25%	40%	22%
Efficacy of prediction of blastulation (AUC)	0.6	0.61	0.7	0.6
Accuracy	61%	63%	70%	61%
Sensitivity	67%	64%	88%	67%
Odds ratio	2.0	2.7	6.4	2.1

Pre-ICSI, Post-ICSI images. Confounders, suggesting how an oocyte responds to ICSI contributes to prediction of blastulation.



Egg source, male factor and age did not affect CHLOE-OQ Score.



Single center study with donor warmed oocytes

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ABSTRACTS

Automatic annotations

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Prediction of blastulation, ploidy, implantation, Live birth

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Clinics involved

Fertilitat	Brazil
Fertility FIV	Brazil
Primordia	Brazil
Reproferty	Brazil
Genesis	Brazil
UZ Brussels	Belgium
Dijon	France
Institute Of Life-IASO	Greece
GeneraLife	Italy, Spain
Hausken	Norway
Alpha	Spain
Gravida	Spain
CREA	Spain
Juana Crespo	Spain
Dexeus	Spain
IVIRMA	Spain
Next Clinics, Murcia	Spain
Memorial	Turkey
Avenues	United Kingdom
CARE Fertility	United Kingdom
CRGH	United Kingdom
HSFC	United Kingdom
London women's	United Kingdom
Evewell	United Kingdom
Plymouth	United Kingdom
Kings	United Kingdom
City	United Kingdom
Cornell	USA
USF	USA
Kindbody	USA
NYU	USA

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1. Study presented at ASRM 2022 2. Kindbody Study, 2023

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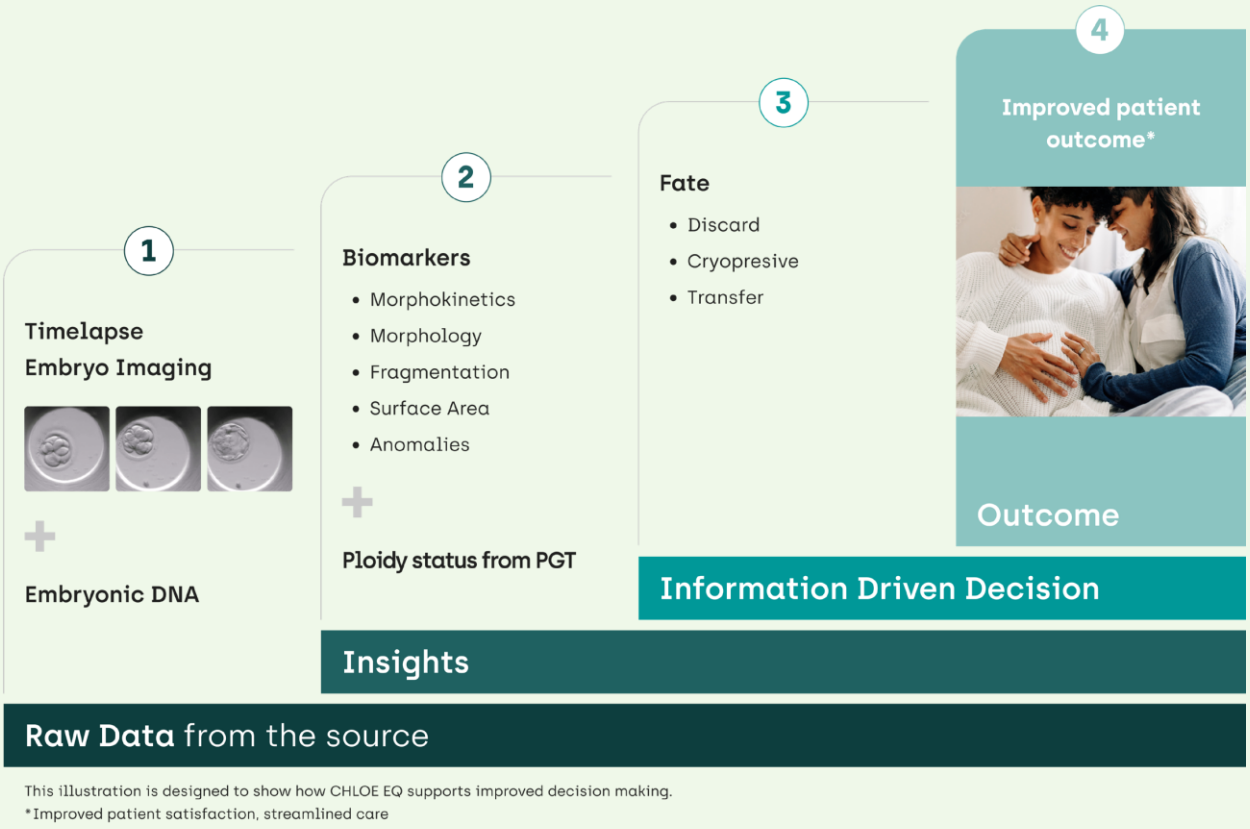

This illustration is designed to show how CHLOE EQ supports improved decision making.
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"Working with Chloe has been tremendously inspiring as we get to see the underlying biology that helps us understand which embryo should be prioritized for transfer. **The ability to grade embryos and populate data in the EMR, automatically, saves precious time for our embryologists."**

Eros Nikitos
Lab Director, Institute of Life – IASO MaternityHospital Athens, Greece

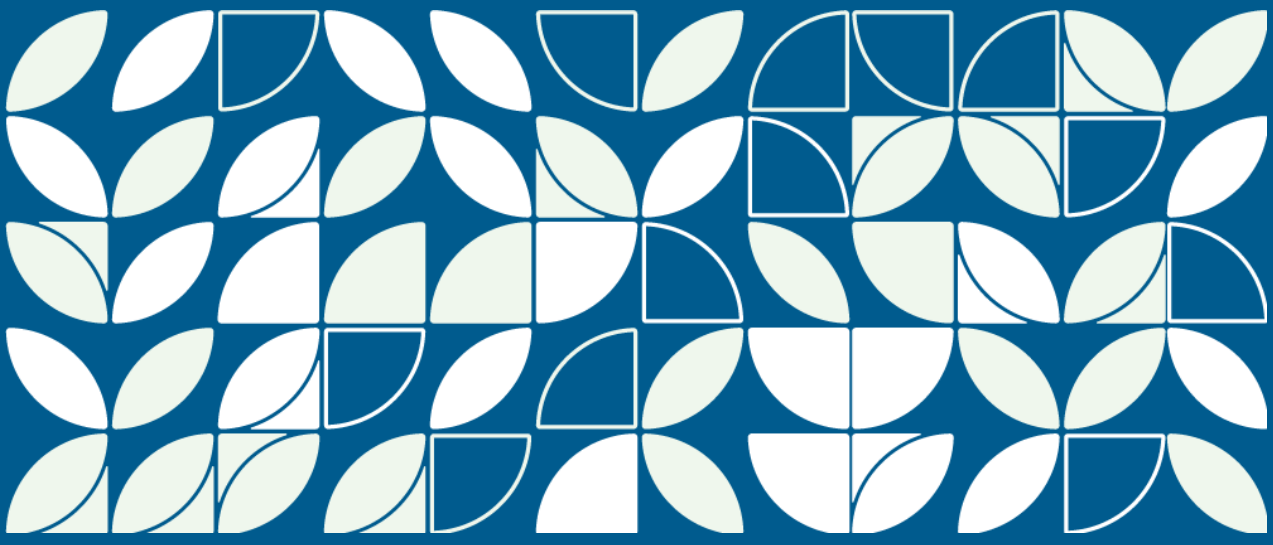
"At NextFertility Murcia, we use CHLOE to help us select the embryos to be transferred in an objective way. **Through CHLOE we can send patients a link that allows them to follow the development of their embryos and thus, be more informed."**

Emilio Gomes Sanches,
IVF Lab manager at Next Fertility Murcia, Spain

"At IVF LONDON we love Chloe EQ™ as it enables us to share information with our patients which allows them to follow the development of their embryos in real time, be more informed and have meaningful conversations with our care team in the clinic"

Alpesh Doshi,
Consultant Embryologist and Founder at IVF London

Published papers



Human Reproduction

How slow is too slow? A comprehensive portrait of Day 7 blastocysts and their clinical value standardized through artificial intelligence

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Clinica Valle Giulia, GeneraLife IVF, Rome, Italy 2 The Alexander Grass Center for Bioengineering, School of Computer Science and Engineering, Hebrew University of Jerusalem, Jerusalem, Israel 3 Fairtilty Ltd, Tel Aviv, Israel 4 IVF Unit, Department of Obstetrics and Gynecology, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel 5 Fertility and IVF Unit, Department of Obstetrics and Gynecology, Soroka University Medical Center and the Faculty of Health Sciences Ben-Gurion University of the Negev, Beer-Sheva, Israel 6 Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Urbino, Ital.

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ABSTRACT

Study question: What is the clinical value of Day 7 blastocysts?

Summary answer: Ending embryo culture at 144 hours post-insemination (h.p.i.; i.e. 6 days) would involve 7.3% and 4.4% relative reductions in the number of patients obtaining euploid blastocysts and live birth(s) (LBs), respectively.

What is known already: Many studies showed that Day 7 blastocysts are clinically valuable, although less euploid and less competent than faster-growing embryos. Nevertheless, a large variability exists in: (i) the definition of 'Day 7'; (ii) the criteria to culture embryos to Day 7; (iii) the clinical setting; (iv) the local regulation; and/or (v) the culture strategies and incubators. Here, we aimed to iron out these differences and portray Day 7 blastocysts with the lowest possible risk of bias. To this end, we have also adopted an artificial intelligence (AI)-powered software to automatize developmental timings annotations and standardize embryo morphological assessment.

Study design, size and duration: Observational study including 1966 blastocysts obtained from 681 patients cultured in a time-lapse incubator between January 2013 and December 2020 at a private Italian IVF center.

Participants/materials, setting, methods: According to Italian Law 40/2004, embryos were not selected based on their morphology and culture to 168 h.p.i. is standard care at our center. ICSI, continuous culture with Day 5 media refresh, trophectoderm biopsy without assisted hatching and comprehensive chromosome testing (CCT) to diagnose full-chromosome non-mosaic aneuploidies, were all performed. Blastocysts were clustered in six groups based on the time of biopsy in h.p.i. at 12 hr intervals starting from 168 h.p.i. Blastocyst quality was assessed using Gardner's scheme and confirmed with AI-powered software. AI was also used to automatically annotate the time of expanding blastocyst (tEB) and the hours elapsing between this moment and the achievement of full expansion when blastocysts were biopsied and vitrified. Also, blastocyst area at tEB and at the time of biopsy was automatically assessed, as well as the hour of the working day when the procedure was performed. The main outcomes were the euploidy rate and the LB rate (LBR) per vitrified-warmed euploid single blastocyst transfer. The results were adjusted for confounders through multivariate logistic regressions. To increase their generalizability, the main outcomes were reported also based on a 144-h.p.i. cutoff (i.e. 6 exact days from ICSI). Based on this cutoff, all the main patient outcomes (i.e. number of patients obtaining blastocysts, euploid blastocysts, LBs, with supernumerary blastocysts without a LB and with surplus blastocysts after an LB) were also reported versus the standard care (>168 h.p.i.). All hypothetical relative reductions were calculated.

Main results and the role of chance: A total of 14.6% of the blastocysts reached full expansion beyond 144 h.p.i. (5.9% in the range 144–156 h.p.i., 7.9% in the range 156–168 h.p.i. and 0.8% beyond 168 h.p.i.). Slower blastocysts were of a worse quality based on the evaluation of both embryologists and AI. Both later tEB and longer time between tEB and full blastocyst expansion concurred to Day 7 development, quite independently of blastocyst quality. Slower growing blastocysts were slightly larger than faster-growing ones at the time of biopsy, but no difference was reported in the risk of hatching, mainly because two dedicated slots have been set along the working day for these procedures. The lower euploidy rate among Day 7 blastocysts is due to their worse morphology and more advanced oocyte age, rather than to a slower development per se. Conversely, the lower LBR was significant even after adjusting for confounders, with a first relevant decrease for blastocysts biopsied in the range 132–144 h.p.i. (N ¼ 76/208, 36.5% versus N ¼ 114/215, 53.0% in the control, multivariate odds ratio 0.61, 95% CI 0.40–0.92, adjusted-P ¼ 0.02), and a second step for blastocysts biopsied in the range 156–168 h.p.i. (N ¼ 3/21, 14.3%, multivariate odds ratio: 0.24, 95% CI 0.07–0.88, adjusted-P ¼ 0.03). Nevertheless,

when the cutoff was set at 144 h.p.i., no significant difference was reported. In this patient population, ending embryo culture at 144 h.p.i. would have caused 10.6%, 7.3%, 4.4%, 13.7% and 5.2% relative reductions in the number of patients obtaining blastocysts, euploid blastocysts, LBs, supernumerary blastocysts without an LB and surplus blastocysts after an LB, respectively.

Limitations, reasons for caution: Gestational and perinatal outcomes were not assessed, and a cost-effectiveness analysis is missing. Moreover, we encourage other groups to investigate this topic with different culture and biopsy protocols, as well as in different clinical settings and regulatory contexts.

Wider implications of the findings: In view of the increasing personalization and patient-centeredness of IVF, whenever allowed from the local regulations, the choice to culture embryos to Day 7 should be grounded on the careful evaluation of couples' reproductive history. Patients should be aware that Day 7 blastocysts are less competent than faster-growing ones; still, poor prognosis couples, couples less compliant toward other attempts in case of a failure and couples wishing for more than one child, may benefit from them. AI tools can help improving the generalizability of the evidence worldwide.

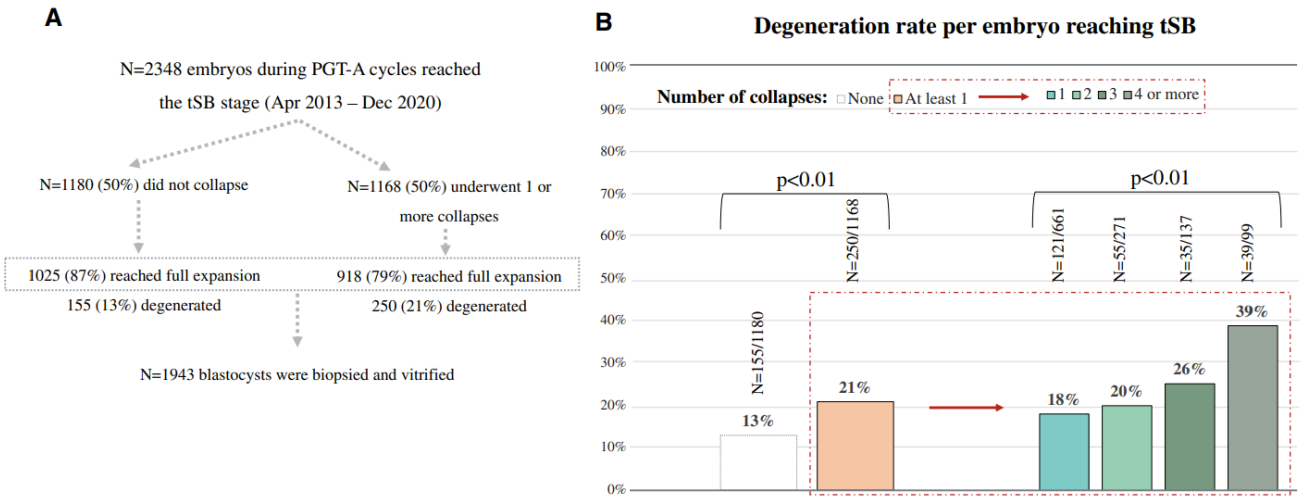


Figure 1. Study flowchart and human blastocyst degeneration rate after spontaneous collapse. (A) Blastocysts included in the investigation. (B) Degeneration rate among embryos reaching the time of starting blastulation (tSB) according to the number of collapses experienced from none to four or more. Statistical significance was assessed through Fisher's exact and chi-squared tests. PGT-A, preimplantation genetic testing for aneuploidies; Apr, April; Dec, December.

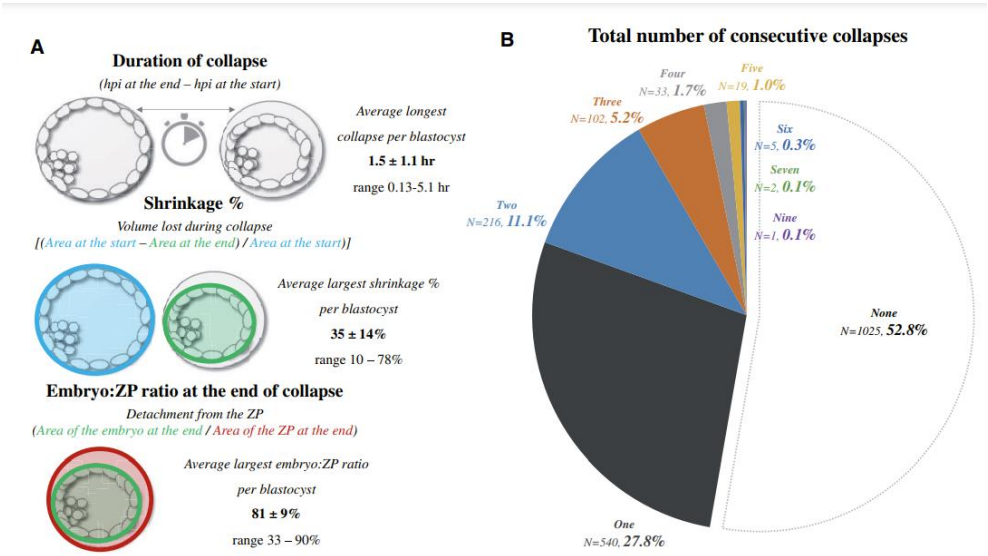


Figure 2. Main blastocysts collapse descriptive features and prevalence of spontaneous collapse(s). (A) Summary of the main features extracted from the software CHLOETM and average § SD results in our dataset. (B) Prevalence of blastocysts never collapsing and collapsing 1–9 times in our dataset. Hpi, hour post-insemination; ZP, zona pellucida.

Human Reproduction

Human blastocyst spontaneous collapse is associated with worse morphological quality and higher degeneration and aneuploidy rates: a comprehensive analysis standardized through artificial intelligence

Danilo Cimadomo, Anabella Marconetto, Samuele Trio, Viviana Chiappetta, Federica Innocenti, Laura Albricci, Itay Erlich, Assaf Ben-Meir, Iris Har-Vardi, Ben Kantor, Anat Sakov, Giovanni Coticchio, Andrea Borini, Filippo Maria Ubaldi, Laura Rienzi
Human Reproduction. 2022 Aug 8;deac175.

ABSTRACT

Study question: What are the factors associated with human blastocyst spontaneous collapse and the consequences of this event?

Summary answer: Approximately 50% of blastocysts collapsed, especially when non-viable, morphologically poor and/or aneuploid.

What is known already: Time-lapse microscopy (TLM) is a powerful tool to observe preimplantation development dynamics. Lately, artificial intelligence (AI) has been harnessed to automate and standardize such observations. Here, we adopted AI to comprehensively portray blastocyst spontaneous collapse, namely the phenomenon of reduction in size of the embryo accompanied by efflux of blastocoel fluid and the detachment of the trophectoderm (TE) from the zona pellucida (ZP). Although the underlying causes are unknown, blastocyst spontaneous collapse deserves attention as a possible marker of reduced competence.

Study design, size, duration: An observational study was carried out, including 2348 TLM videos recorded during preimplantation genetic testing for aneuploidies (PGT-A, n = 720) cycles performed between January 2013 and December 2020. All embryos in the analysis at least reached the time of starting blastulation (tSB), 1943 of them reached full expansion, and were biopsied and then vitrified.

Participants/materials, setting, methods: ICSI, blastocyst culture, TE biopsy without Day 3 ZP drilling, comprehensive chromosome testing and vitrification were performed. The AI software automatically registered tSB and time of expanding blastocyst (tEB), start and end time of each collapse, time between consecutive collapses, embryo proper area, percentage of shrinkage, embryo:ZP ratio at embryo collapse, time of biopsy (t-biopsy) and related area of the fully (re-)expanded blastocyst before biopsy, time between the last collapse and biopsy. Blastocyst morphological quality was defined according to both Gardner's criteria and an AI-generated implantation score. Euploidy rate per biopsied blastocyst and live birth rate (LBR) per euploid single embryo transfer (SET) were the main outcomes. All significant associations were confirmed through regression analyses. All couple, cycle and embryo main features were also investigated for possible associations with blastocyst spontaneous collapse.

Main results and the role of chance: At least one collapsing embryo (either viable or subsequently undergoing degeneration) was recorded in 559 cycles (77.6%) and in 498 cycles (69.2%) if considering only viable blastocysts. The prevalence of blastocyst spontaneous collapse after the tSB, but before the achievement of full expansion, was 50% (N = 1168/2348), irrespective of cycle and/or couple characteristics. Blastocyst degeneration was 13% among non-collapsing embryos, while it was 18%, 20%, 26% and 39% among embryos collapsing once, twice, three times or ≥4 times, respectively. The results showed that 47.3% (N = 918/1943) of the viable blastocysts experienced at least one spontaneous collapse (ranging from 1 up to 9). Although starting from similar tSB, the number of spontaneous collapses was associated with a delay in both tEB and time of biopsy. Of note, the worse the quality of a blastocyst, the more and the longer its spontaneous collapses. Blastocyst spontaneous collapse was significantly associated with lower euploidy rates (47% in non-collapsing and 38%, 32%, 31% and 20% in blastocysts collapsing once, twice, three times or ≥4 times, respectively; multivariate odds ratio 0.78, 95%CI 0.62-0.98, adjusted $P = 0.03$). The difference in the LBR after euploid vitrified-warmed SET was not significant (46% and 39% in non-collapsing and collapsing blastocysts, respectively).

Limitations, reasons for caution: An association between chromosomal mosaicism and blastocyst collapse cannot be reliably assessed on a single TE biopsy. Gestational and perinatal outcomes were not evaluated. Other culture strategies and media should be tested for their association with blastocyst spontaneous collapse. Future studies with a larger sample size are needed to investigate putative impacts on clinical outcomes after euploid transfers.

Wider implications of the findings: These results demonstrate the synergistic power of TLM and AI to increase the throughput of embryo preimplantation development observation. They also highlight the transition from compaction to full blastocyst as a delicate morphogenetic process. Blastocyst spontaneous collapse is common and associates with inherently lower competence, but additional data are required to deepen our knowledge on its causes and consequences.

Study funding/competing interest(s): There is no external funding to report. I.E., A.B.-M., I.H.-V. and B.K. are Fairtility employees. I.E. and B.K. also have stock or stock options of Fairtility.

Trial registration number: **N/A**

Solving the "right" problems for effective machine learning driven in vitro fertilization

Itay Erlich, Assaf Ben-Meir, Iris Har-Vardi, James A. Grifo, Assaf Zaritsky

Abstract: Automated live embryo imaging has transformed in-vitro fertilization (IVF) into a data-intensive field. Unlike clinicians who rank embryos from the same IVF cycle cohort based on the embryos visual quality and determine how many embryos to transfer based on clinical factors, machine learning solutions usually combine these steps by optimizing for implantation prediction and using the same model for ranking the embryos within a cohort. Here we establish that this strategy can lead to sub-optimal selection of embryos. We reveal that despite enhancing implantation prediction, inclusion of clinical properties hampers ranking. Moreover, we find that ambiguous labels of failed implantations, due to either low quality embryos or poor clinical factors, confound both the optimal ranking and even implantation prediction. To overcome these limitations, we propose conceptual and practical steps to enhance machine-learning driven IVF solutions. These consist of separating the optimizing of implantation from ranking by focusing on visual properties for ranking, and reducing label ambiguity.

Background: In vitro fertilization (IVF) is the process where a cohort of embryos are developed in a laboratory followed by selecting a few to transfer in the patient's uterus. After approximately forty years of low-throughput, automated live embryo imaging has transformed IVF into a data-intensive field leading to the development of unbiased and automated methods that rely on machine learning for embryo assessment. These advances are now revolutionizing the field with recent retrospective papers demonstrating computational models comparable and even exceeding clinicians' performance, startups and medical companies are securing significant funds and at advanced stages of regulatory approvals. Traditionally, embryo selection is performed by clinicians ranking cohort embryos based solely on their visual qualities to estimate implantation potential, and then using non-visual clinical properties that are common to all cohort embryos to decide how many embryos to transfer. Machine learning solutions usually combine these two steps by optimizing for implantation prediction and using the same model for ranking the embryos within a cohort under the implicit assumption that training to predict implantation potential also optimizes a solution to the problem of ranking embryos from a specific cohort.

Results: In this multi-center retrospective study we analyzed over 48,000 live imaged embryos to provide evidence that the common machine-learning scheme of training a model to predict implantation and using the same model for embryo ranking is wrong. We made this point by explicitly decoupling the problems of embryo implantation prediction and ranking with a set of computational analyses. We demonstrated that: (1) Using clinical cohort-related information (oocyte age) improves embryo implantation prediction but deteriorates ranking, and that (2) The label ambiguity of the embryos that failed to implant (it is not known whether the embryo or the external factors were the reason for failure) deteriorates embryo ranking and even the ability to accurately predict implantation. Our study provides a quantitative mapping of the tradeoffs between data volume, label ambiguity and embryo quality. In a key result, we reveal that considering embryos that were excluded based on their poor visual appearance (called discarded embryos), although commonly thought as trivially discriminated from high quality embryos, enhances embryo ranking by reducing the ambiguity in their (negative) labels. These results establish the benefit of harnessing the availability of extensive data and reliable labels in discarded embryos to improve embryo ranking and implantation prediction.

Outlook: We make two practical recommendations for devising machine learning solutions to embryo selection that will open the door for future advancements by data scientists and IVF technology developers. Namely, training models for embryo ranking should: (1) focus exclusively on embryo intrinsic features. (2) include less ambiguous negative labels, such as discarded embryos. In the era of machine learning, these guidelines will shift back the traditional two-step process of optimizing embryo ranking and implantation prediction independently under the appropriate assumptions - an approach better reflecting the clinician's decision that involves the evaluation of all the embryos in the context of its cohort.

Scientific Reports. Nature

Pseudo contrastive labeling for predicting IVF embryo developmental potential

I. Erlich1,2, A. Ben-Meir2,3, I. Har-Vardi2,4, J.Grifo5, F. Wang5, C. Mccafrey5, D. McCulloh5 ,Y. Or6 & L. Wolf7*
Scientific Reports volume 12, Article number: 2488 (15 February 2022)

ABSTRACT

In vitro fertilization is typically associated with high failure rates per transfer, leading to an acute need for the identification of embryos with high developmental potential. Current methods are tailored to specific times after fertilization, often require expert inspection, and have low predictive power. Automatic methods are challenged by ambiguous labels, clinical heterogeneity, and the inability to utilize multiple developmental points. In this work, we propose a novel method that trains a classifier conditioned on the time since fertilization. This classifier is then integrated over time and its output is used to assign soft labels to pairs of samples. The classifier obtained by training on these soft labels presents a significant improvement in accuracy, even as early as 30 h post-fertilization. By integrating the classification scores, the predictive power is further improved. Our results are superior to previously reported method including the commercial KIDScore-D3 system, and a group of eight senior professionals, in classifying multiple groups of favorable embryos into groups defined as less favorable based on implantation outcomes, expert decisions based on developmental trajectories, and/or genetic tests.

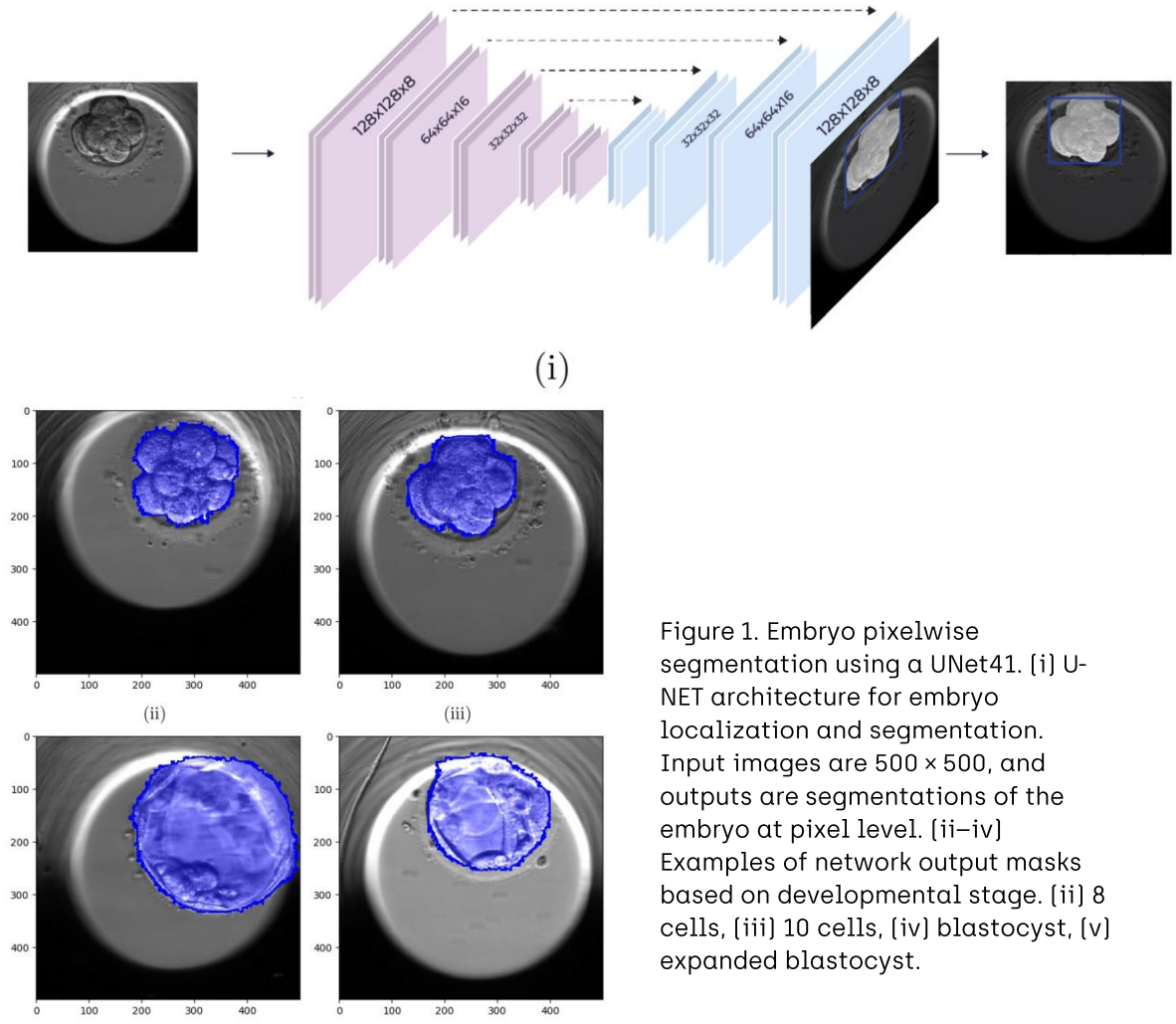


Figure 1. Embryo pixelwise segmentation using a UNet41. (i) U-NET architecture for embryo localization and segmentation. Input images are 500 × 500, and outputs are segmentations of the embryo at pixel level. (ii–iv) Examples of network output masks based on developmental stage. (ii) 8 cells, (iii) 10 cells, (iv) blastocyst, (v) expanded blastocyst.

Scientific reports, Nature

An artificial intelligence algorithm for automated blastocyst morphometric parameters demonstrates a positive association with implantation potential

Yael Fruchter-Goldmeier, Ben Kantor, Assaf Ben-Meir, Tamar Wainstock, Itay Erlich, Eliahu Levitas, Yoel Shufaro, Onit Sapir & Iris Har-Vardi

ABSTRACT

Blastocyst selection is primarily based on morphological scoring systems and morphokinetic data.
These methods involve subjective grading and time-consuming techniques. Artifcial intelligence allows for objective and quick blastocyst selection. In this study, 608 blastocysts were selected for transfer using morphokinetics and Gardner criteria. Retrospectively, morphometric parameters of blastocyst size, inner cell mass (ICM) size, ICM-to-blastocyst size ratio, and ICM shape were automatically measured by a semantic segmentation neural network model. The model was trained on 1506 videos with 102 videos for validation with no overlap between the ICM and trophectoderm models. Univariable logistic analysis found blastocyst size and ICM-to-blastocyst size ratio to be signifcantly associated with implantation potential. Multivariable regression analysis, adjusted for woman age, found blastocyst size to be signifcantly associated with implantation potential. The odds of implantation increased by 1.74 for embryos with a blastocyst size greater than the mean (147 ± 19.1 μm). The performance of the algorithm was represented by an area under the curve of 0.70 ($p < 0.01$). In conclusion, this study supports the association of a large blastocyst size with higher implantation potential and suggests that automatically measured blastocyst morphometrics can be used as a precise, consistent, and time-saving tool for improving blastocyst selection.

Automatic annotations

Morphokinetics
PN
DUCs

Study 01: ASRM 2022 – Memorial

Strong agreement between manual and Artificial Intelligence (AI) supports automated annotations of time-lapse cultured embryos at a single fertility clinic

Yelke, H., Kahraman, S., Kumtepe, Y., Hickman, C., Brualla, A. & Derrick, R.

Published by Fertility & Sterility

Clinic: Memorial (Turkey)

Objective: To determine whether automated annotations by an AI-based tool(Chloe EQ, Fairtility) is consistent with the annotations by experienced embryologists.

Materials and methods: Retrospective comparative analysis with 3415 time-lapse videos collected between 2019 and 2020 from ICSI embryos. Videos were annotated manually by an experienced embryologist and automatically using CHLOE(Fairtility), an Artificial Intelligence (AI) based tool. Level of agreement was quantified using Intra Class Correlation(ICC) and Bland-Altman(BA) analysis method was used to evaluate and calculate the percentage of points outside the limits of agreement. The difference between human vs CHLOE was calculated.

Results:

- ICC and CCC demonstrated very strong (tPNf, t2, t3, t5, t6, tsB, tB) and strong (tPNa, t4, t7, t8, t9, tM, tEB) levels of agreement between experienced embryologists and CHLOE EQ morphokinetic annotations.
- The percentage of embryos within the limits exceeded 93% for all morphokinetic parameters, and reached as high as 99% for tPNf.
- There was no difference in the mean±standard deviation between CHLOE and embryologists throughout all morphokinetic parameters.
- The fact that the algorithm was not trained in this dataset before validation suggests its capability to generalise.

Conclusions: Automated annotation is consistent with manual annotation by experienced embryologists, with at least a strong level of agreement between embryologists and CHLOE.

Impact statement: Manual annotations are time consuming and prone to inter and intra operator variation. Robust automatic annotation tools, such as CHLOE(Fairtility) can be used to enhance the IVF laboratory's embryo selection process, allowing for more parameters to be included in the decision, whilst being efficient with the embryologist's time.

Events	n	CHLOE EQ		Embryologist		ICC	Level of agreement	Time frame including 80% of embryos	Percentage of embryos within BA limits
		Mean	SD	Mean	SD				
tPNa	3415	8.44	3.69	8.69	3.26	0.78	STRONG	2	96
tPNf	3467	24.57	5.32	24.79	5.02	0.89	VERY STRONG	0.5	99
t2	3486	27.57	5.89	27.64	5.62	0.91	VERY STRONG	0.4	98
t3	3458	36.85	7.29	37.33	6.9	0.89	VERY STRONG	0.8	95
t4	3397	41.36	9.39	39.77	7.6	0.73	STRONG	1.5	96
t5	3333	49.38	9.62	48.84	9.49	0.83	VERY STRONG	1.5	94
t6	3257	53.24	9.54	53.06	9.52	0.86	VERY STRONG	1.8	94
t7	3123	58.42	12.13	55.92	9.91	0.63	STRONG	3.2	95
t8	2993	62.89	12.91	59.65	10.99	0.68	STRONG	8.2	95
t9	2932	71.80	11.23	68.34	11.85	0.66	STRONG	10.6	95
tM	2553	84.66	9.67	89.81	9.75	0.71	STRONG	9	94
tSB	2278	98.65	8.36	99.24	8.62	0.92	VERY STRONG	3.2	95
tB	1899	105.47	7.94	105.52	7.85	0.91	VERY STRONG	3.4	94
tEB	647	110.45	7.94	110.54	7.78	0.79	STRONG	5.8	93

Study 02: ESHRE 2022 – Next Fertility

Artificial intelligence system detects "goldilocks" morphokinetic zone for embryos transferred or frozen in time-lapse videos

J.A. Castilla1, N. Almunia2, A. Brualla3, R. Jiménez4, A.M. Villaquirán4, I. Har-vardi5, A. Ben-Meir5, E. Gomez2.

Published by Human Reproduction

Clinic: NEXT CLINIC MURCIA (Spain)

Question: Are there specific morphokinetic time points which can be used to determine whether an embryo should be discarded?

Answer: Morphokinetic ranges where embryos will be discarded rather than transferred or cryopreserved, can be defined using time-lapse annotations automatically generated with artificial intelligence (AI).

What is known already?: Time-lapse incubation has changed the way embryos are selected. Instead of static daily observations, continuous monitoring of embryos allows for generation of morphokinetic parameters which quantify the pace of development. However, annotations by humans have been shown to incur operator variations and are time-consuming to perform. AI can automatically annotate embryos with equivalence in accuracy to experienced embryologists. Although most embryo selection methods are designed to identify the embryo with the highest chance of becoming a live healthy baby, the ability to identify embryos that will not be suitable for treatment is equally important for clinical decision making.

Study design, size, duration: This is a prospective, observational, cohort study. Time-lapse videos from 142 embryos from a private fertility clinic in Spain were automatically annotated using CHLOE (Fairtility), an AI-based software. 185 cleaved embryos cultured in 2021 at a private fertility clinic were included in the analysis. CHLOE automatically generated the following morphokinetic parameters: tPNa, tPNf, t2, t3, t4, t5, t6, t7, t8, t9+, tM, tSB, tB, tEB.

Participants/ materials, setting, methods: Embryos analysed came from donor and own oocyte's treatments where ICSI was performed. Selected embryos were analysed using CHLOE, to automatically identify morphokinetic parameters. The distribution for each morphokinetic parameter was compared between fates (data presented for transferred vs frozen vs discarded as mean+-standard deviation, 2-sided t-test). Each continuous morphokinetic parameter was categorised according to the ranges where embryo utilisation was futile (<1%), optimal (maximum utilisation rate) or reduced utilisation rate (between optimal and futile).

Main results and the role of chance:

- Every morphokinetic parameter the difference in event time between frozen+transferred vs discarded embryos was statistically significant($p<0.003$).
- It became apparent that a goldilocks zone appeared, with the distribution of these embryos according to time. The proportion of embryos transferred or frozen peaked, and the number discarded was at its minimum. It was able to determine the optimal vs futile time ranges, Table 1).

Limitations, reasons for caution: This is a single centre study. Further work will (i) test the limits across different clinics, with different geographical demographic variations, and varied clinical practices, to understand how these factors affect the limits between futile and optimal ranges of morphokinetics, and (ii) assess clinical outputs (implantation, ploidy, live birth).

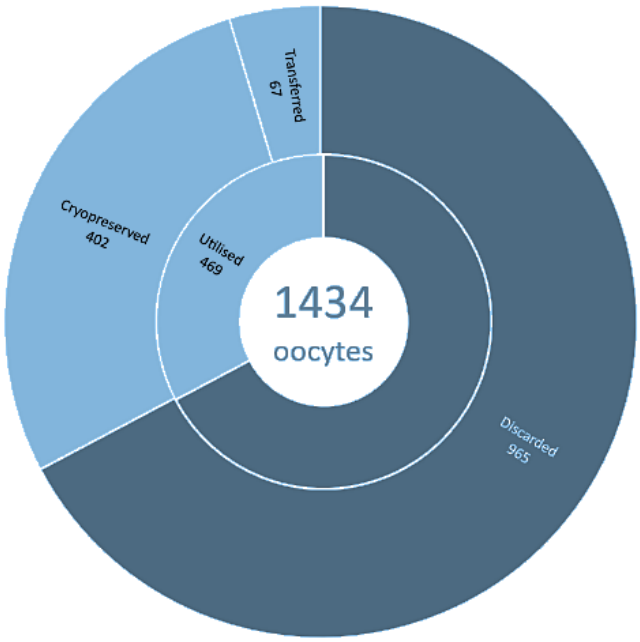
Wider implications of the findings: Identifying objective ranges for determining when an embryo is not suitable for treatment will help reduce variation between and within embryologists and clinics; will avoid overly optimistic decisions which waste time and resources and increase patient's emotional burden, and increase professional confidence when selecting embryos for discarding, transfer or freezing

Table 1. Optimal vs futile time ranges for maximum and minimum utilisation.

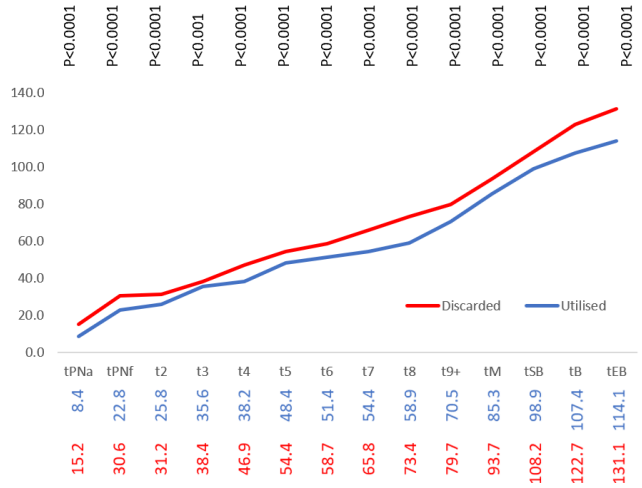
Event	Max utilization rate (optimal time range)	Minimum utilization rate (futile time range)
tPNa	4.4-8.8 hours	<4.4, >13.7 hours
tPNf	19.1-23.3 hours	<9.4, >28.9 hours
T2	23.-36.4 hours	<19.9, >33.6 hours
T3	32.1-37.4 hours	>24.6, >43 hours
T4	34-40.2 hours	<29.5, >55 hours
T5	42.7-52 hours	<33.7, >63.5 hours
T6	45-4-54.2 hours	45-4-54.2 hours
T7	47.8-56.7 hours	<42.8,>77.5 hours
T8	49.2-64.5 hours	<44.5,>82.5 hours
T9+	64.1-74.2 hours	<57, >90 hours
tM	76.6-92.6 hours	<64.7, >104.2 hours
tSB	91.2-105 hours	<81.3,>113.8 hours
tB	97.2-111.2 hours	<92,>118.7 hours
tEB	103.4-116.7 hours	<94.7,>122.5 hours

Table 2. Agreement in determination of embryo stage (CHLOE vs Embryologist)

		Agreement	Disagreement	Agreement Rate
Day 1 – 18hpi	N=60	60	0	100%
Day 2 - 44hpi	N=41	37	4	90%
Day 3 - 68hpi	N=30	26	4	87%
Day 5 – 116hpi	N=22	22	0	100%

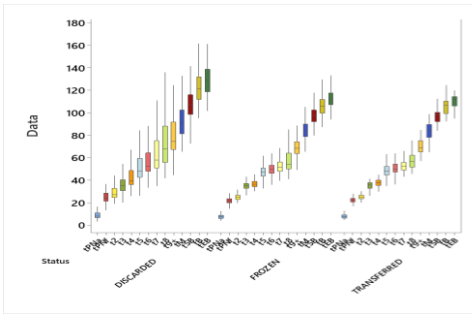


For every morphokinetic parameter the difference in event time between utilised vs discarded embryos was statistically significant.

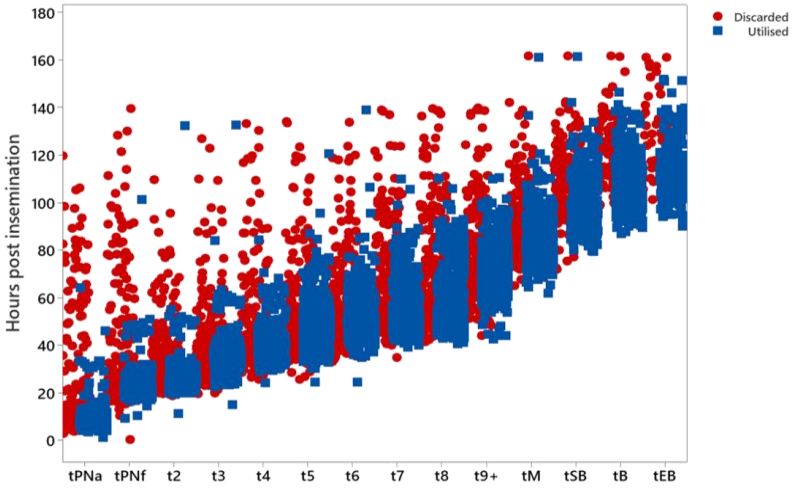


Discarded embryos have a significantly **slower** rate of division than those **utilised**

Time variation is greater in vitrified embryos than in transferred embryos



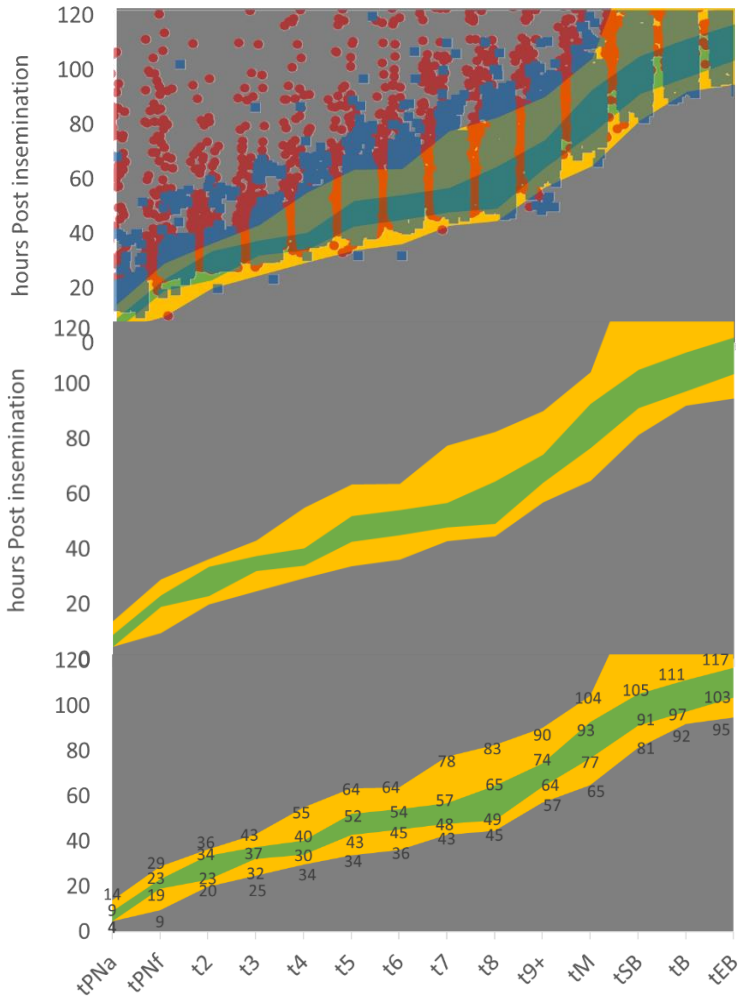
Time variation in the different morphokinetic events is greater in discarded embryos than in utilised embryos



Optimal proportion of embryos utilised

Reduced proportion of embryos utilised

Futile chance of embryos being utilised (<1%)



Study 03: ESHRE 2022 - CARE

An assessment of agreement between automated embryo annotation, through artificial intelligence, and manual embryo annotation.

Authors: Barrie1, R. Smith1, C. Hickman2, I. Erlich2, A. Campbell1.

Published by Human Reproduction

Clinic: CARE (United Kingdom)

Question: How strong is the agreement between embryo morphokinetic annotations performed by experienced embryologists compared to an automated embryo annotation system based on artificial intelligence (AI)?

Answer: Agreement between manual and automated annotation as determined by the interclass correlation coefficient (ICC) revealed strong or very strong agreement for all analysed morphokinetic variables.

What is known already?:

- Transitioning from time-lapse imaging to embryo selection for transfer, freezing or discard involves annotation.
- Numerical data can be used as input to selection models quantifying embryo viability.
- Currently, embryos are manually annotated by the embryologist which can be subjective and time-consuming.
- There is the additional challenge of operator variation, despite the development of standardised definitions and quality assurance schemes.
- AI may help resolve these challenges.

Study design, size, duration: Retrospective comparative analysis, including 2442 embryos from IVF and ICSI cycles, from four private fertility clinics belonging to the same group in the UK. All the embryos cultured in a time-lapse incubator (EmbryoScope,Vitrolife) between January 2016 and 2019 were included in the study. Manual annotations (MA) versus automated annotations (AA) were compared using a two-way, mixed interclass correlation coefficient (ICC), which produced five categories of agreement, very weak(0-0.20), weak(0.21-0.40), moderate(0.41-0.60), strong(0.61-0.80), very strong(0.81-1.00).

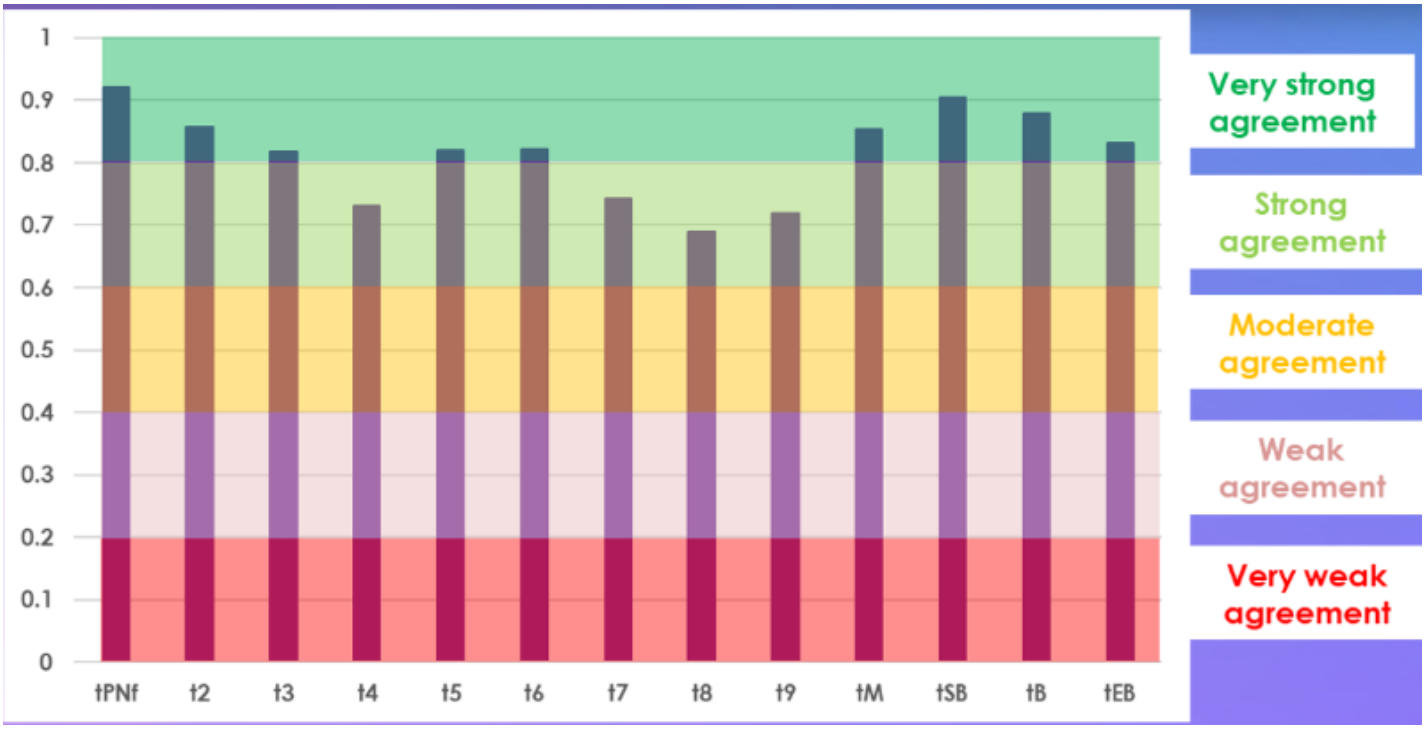
Participants/ materials, setting, methods: Videos were manually annotated by experienced embryologists from pronuclei fading (tPNf) to time of expanded blastocyst (tEB) with all cell stages annotated in between (time to two-cell (t2), three-cell (t3), four-cell (t4), five-cell (t5), six-cell (t6), seven-cell (t7), eight-cell (t8), nine-cell (t9), morula (tM), start of blastulation (tSB) and full blastocyst (tB)). Blind to human annotations, and without any training, the same videos were annotated by CHLOE (Fairtility) to produce automated annotation data.

Main results and the role of chance:

- AA did not provide a result for 15.4% of the MA (3235/21,008).
- Very strong agreement (0.81-1.00) between MA and AA was found for tPNf, t2, t3, t5, t6, tM, tSB, tB, tEB.
- Strong agreement (0.61-0.80) was found for t4, t7, t8 and t9+.
- For t2 outliers (n=14,6%), the average time difference was 5.97h(range;5.50-24.44h). All embryos with a t2 outlier were classed as either poor(PQ) or average quality(AQ).
- The t5 outliers (n=45,19%) had an average time difference of 2.84h(range;9.33-36.69h). 96%(n=43) of these embryos were classed as PQ(n=25,56%) or AQ(n=18,40%).
- Outliers for t8 (138,58%) were, on average, 17.53h different between MA and AA(range;12.68-40.35h). 94%(n=130) of these embryos were classed as PQ(n=77,56%) or AQ(n=53,38%).
- The tSB outliers (n=28,12%) had an average time difference of 3.58h(range;0.71-14.39h). 89%(n=25) of these embryos were classed as PQ(n=16,57%) or AQ(n=9,32%) (Figure 1).
- Finally, outliers associated with tB (n=44, 18%) had an average time difference of 6.39h(range;0.02-33.67h). 95%(n=42) of these embryos were classed as PQ(n=38,86%) or AQ(n=4,9%).
- Almost 15%(n=40) of the embryos had outliers in more than one of the five morphokinetic parameters.

Limitations, reasons for caution: The findings for this study reflect the capabilities of a specific AI-based annotation algorithm against the practice in multiple clinics in the same group and country. The automated annotation algorithm was not trained on this dataset prior to validation, which is encouraging for generalisability.

Wider implications of the findings: AI is ideally suited to resolve annotation challenges. This study demonstrates that where embryo quality is poor, annotation could be skewed both when performed manually and automatically. Once robustness is demonstrated, AI tools such as CHLOE, may allow clinics to process clinical data efficiently, objectively and consistently.



Carefertility

A. Barrie[1], R. Smith[1], C. Hickman[2], I. Erlick[2], A. Campbell[1]
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An assessment of agreement between automated embryo annotation, through artif intelligence, and manual embryo annotation

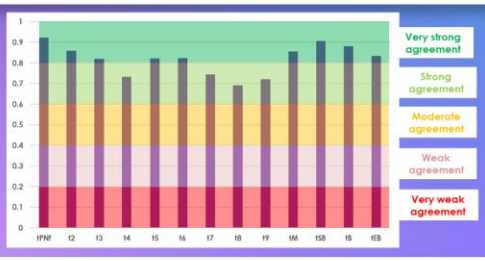
Study question
How strong is the agreement between embryo morphokinetic annotations performed by experienced embryologists compared to an automated embryo annotation system based on artificial intelligence (AI)?

Study answer
Agreement between manual and automated annotation as determined by the interclass correlation coefficient (ICC) revealed strong or very strong agreement for all analysed morphokinetic variables.

What is known already?
Transitioning from time-lapse imaging to embryo selection for transfer, freezing or discard involves annotation; the action of converting images to numerical data. Numerical data can be used as input to selection models quantifying embryo viability. Currently, embryos are manually annotated by the embryologist which can be subjective and time-consuming. As such, clinics prioritise a manageable number of variables to annotate, leading to a range of clinic practices. There is the additional challenge of operator variation, despite the development of standardised definitions and quality assurance schemes. AI may help resolve these challenges.

Study design, size and duration
Retrospective comparative analysis, including 2442 embryos from IVF and ICSI cycles, from four private fertility clinics belonging to the same group in the the embryos cultured in a time-lapse incubator (EmbryoScope,Vitrolife) between January 2016 and 2019 were included in the study. Manual annotations (versus automated annotations (AA) were compared using a two-way, mixed interclass correlation coefficient (ICC), which produced five categories of agre very weak(0-0.20), weak(0.21-0.40), moderate(0.41-0.60), strong(0.61-0.80), very strong(0.81-1.00).

Participants/materials, setting, methods
Videos were manually annotated by experienced embryologists from pronuclei fading (tPNf) to time of expanded blastocyst (tEB) with all cell stages annot in between (time to two-cell (t2), three-cell (t3), four-cell (t4), five-cell (t5), six-cell (t6), seven-cell (t7), eight-cell (t8), nine-cell (t9), morula (tM), start of blastulation (tSB) and full blastocyst (tB)). Blind to human annotations, and without any training, the same videos were annotated by CHLOE (Fairtility) to produce automated annotation data.



AGREEMENT BETWEEN MANUAL AND AUTOMATED ANNOTATION REVEALED STRONG OR VERY STRONG AGREEMENT FOR ALL ANALYSED MORPHOKINETIC VARIABLES!

Conclusions
The findings for this study reflect the capabilities of a specific AI-based annotation algorithm against the practice in multiple clinics in the same group ar country. The automated annotation algorithm was not trained on this dataset prior to validation, which is encouraging for generalisability. AI is ideally su to resolve annotation challenges. This study demonstrates that where embryo quality is poor, annotation could be skewed both when performed manua and automatically. Once robustness is demonstrated, AI tools such as CHLOE, may allow clinics to process clinical data efficiently, objectively and consis

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Study 04: ESHRE 2022 – GeneraLife

Elucidation of blastocyst collapse and its consequences: a comprehensive artificial intelligence-powered analysis of 1943 embryos from 643 couples

Authors: D Cimadomo, A Marconetto, F Innocenti, S Trio, V Chiappetta, D Soscia, L Albricci, L Dovere, A Giancani, R Maggiulli, I Erlich, A Ben-Meir, I Har-Vardi, F.M Ubaldi, L Rienzi

Published by Human Reproduction

Clinic: Generalife (Italy)

Question: What are the causes and consequences of blastocyst collapse?

Answer: ~50% of blastocysts collapsed, especially if they are aneuploid and/or morphologically-poor. Yet, no impact on the live-birth-rate (LBR) per vitrified-warmed euploid single-embryo-transfer (SET) was reported.

What is known already?: Time-lapse-microscopy (TLM) is a powerful tool to describe the peculiar dynamics of preimplantation development. Lately, artificial intelligence (AI) has been also implemented to automatize and standardize such description. Here, we adopted AI to comprehensively portray blastocyst collapse, namely the phenomenon of embryo contraction with an efflux of blastocoel fluid and the detachment of the trophectoderm (TE) from the Zona Pellucida (ZP). Although, the causes of this event are still undetermined, small blastocyst contractions have been reported beneficial for the hatching process, while a full collapse has been associated with lower competence.

Study design, size, duration: Observational study including 1943 blastocysts from 643 couples cultured in the Embryoscope between January-2013 and December-2020. TE biopsy without day3 ZP drilling and comprehensive-chromosome-testing were performed. The Fairtility® software automatically registered: (i)time of starting-blastulation (tSB), (ii)starting and ending time of each collapse (tSC and tEC), (iii)blastocysts' areas, (iv)shrinkage% [(area at SC – area at EC)/area at SC)], (v)embryo:ZP ratio at EC (area of the collapsed embryo/area of the ZP), and (vi)time of biopsy (t-biopsy).

Participants/ materials, setting, methods: Blastocyst quality was defined according to Istanbul Consensus (11, excellent; 12-21, good; 22-13-31, average; 33-23-32, poor) and with the Fairtility implantation score (IS) as well, i.e., a continuous variable from 0 to 1 generated by the KID+ software based on the TLM videos of preimplantation development. The main outcome was the LBR per euploid SET adjusted for confounders through logistic regressions. All couple and embryo features were also investigated for their association with blastocyst collapse.

Main results and the role of chance: 47.3% of the blastocysts collapsed 1- to 9-times (interval between collapses: 4-8hr), and 73% of the couples had ≥1 collapsed blastocyst (1.8±1.1, range:1-8). No couple feature, though, was associated with blastocyst collapse. The longest collapses lasted 1.5±1.1 (0.13-5.1)hr, while the largest shrinkage% and embryo:ZP ratio at EC were 35±14% (10-78%) and 81±9% (33-90%), respectively. In ~50-60% of collapses a 20-40% blastocyst volume reduction was registered, 40-60% or 20-40% in ~15-30%, 60-80% in 0-4%. In case of multiple collapses, the first three involved smaller shrinkages. Blastocysts undergoing ≥1 collapse showed similar tSB as not-collapsing blastocysts, but progressively longer tEB and t-biopsy. The earlier the first event, the more the consecutive collapses. Notably, the poorer the morphology, the higher the risk (excellent, good, average, and poor not-collapsing blastocysts were 64%,50%,44% and 37%), number (e.g.,≥4 collapses were 0.4%,2%,4% and 8%) and duration (1.2±1.0,1.4±1.0,1.6±1.1 and 1.9±1.3hr) of blastocyst collapse. Collapsing blastocysts were significantly less euploid than non-collapsing (35% vs 47%; multivariate-OR:0.75,95%CI 0.6-0.92,p<0.01); conversely, their LBR per euploid SET (39% vs 46%) and miscarriage rate per clinical pregnancy (17% vs 11%), were not significantly different (adjusted-OR:1.0,95%CI 0.69-1.48,p=0.96 and adjusted-OR:1.65,95%CI 0.79-3.42,p=0.18, respectively). All data were confirmed also by defining blastocyst quality through the Fairtility IS.

Limitations, reasons for caution: Gestational and perinatal outcomes were not assessed. Other culture strategies and media shall be assessed for their association with blastocyst collapse. Perhaps, future studies from other groups and with a larger sample size might unveil a significant impact on the clinical outcomes.

Wider implications of the findings: Collapse is common and delays blastocyst full-expansion. Moreover, poor morphology and aneuploidies involve a higher risk of collapse(s); however, no impact was reported on the clinical outcomes after euploid SET. AI appears to increase the throughput of the analysis, but additional data are required to research the causes of collapse.

Study 05: ESHRE 2022 - Generalife

How slow is too slow? A comprehensive portrait of Day 7 blastocysts and their clinical value standardized through artificial intelligence

Authors: Cimadomo D, Soscia D, Casciani V, Innocenti F, Trio S, Chiappetta V, Albricci L, Maggiulli R, Erlich I, Ben-Meir A, Har-Vardi I, Vaiarelli A , Ubaldi M & Rienzi L.

Published by Human Reproduction

Study question: What is the clinical value of Day 7 blastocysts?

Summary answer: Ending embryo culture at 144 hours post-insemination (h.p.i.; i.e. 6 days) would involve 7.3% and 4.4% relative reductions in the number of patients obtaining euploid blastocysts and live birth(s) (LBs), respectively.

What is known already: Many studies showed that Day 7 blastocysts are clinically valuable, although less euploid and less competent than faster-growing embryos. A large variability exists in: (i) the definition of 'Day 7'; (ii) the criteria to culture embryos to Day 7; (iii) the clinical setting; (iv) the local regulation; and/or (v) the culture strategies and incubators. Here, we aimed to iron out these differences and portray Day 7 blastocysts with the lowest possible risk of bias. To this end, we have also adopted an artificial intelligence (AI)-powered software to automatize developmental timings annotations and standardize embryo morphological assessment.

Study design, size and duration: Observational study including 1966 blastocysts obtained from 681 patients cultured in a time-lapse incubator between January 2013 and December 2020 at a private Italian IVF center.

Participants/ materials, setting, methods: According to Italian Law 40/2004, embryos were not selected based on their morphology and culture to 168 h.p.i. is standard care at our center. ICSI, continuous culture with Day 5 media refresh, trophectoderm biopsy without assisted hatching and comprehensive chromosome testing (CCT) to diagnose full-chromosome non-mosaic aneuploidies, were all performed. Blastocysts were clustered in six groups based on the time of biopsy in h.p.i. at 12 hr intervals starting from 168 h.p.i. Blastocyst quality was assessed using Gardner's scheme and confirmed with AI-powered software. AI was also used to automatically annotate the time of expanding blastocyst (tEB) and the hours elapsing between this moment and the achievement of full expansion when blastocysts were biopsied and vitrified. Also, blastocyst area at tEB and at the time of biopsy was automatically assessed, as well as the hour of the working day when the procedure was performed. The main outcomes were the euploidy rate and the LB rate (LBR) per vitrified-warmed euploid single blastocyst transfer. The results were adjusted for confounders through multivariate logistic regressions. To increase their generalizability, the main outcomes were reported also based on a 144-h.p.i. cutoff (i.e. 6 exact days from ICSI). Based on this cutoff, all the main patient outcomes (i.e. number of patients obtaining blastocysts, euploid blastocysts, LBs, with supernumerary blastocysts without a LB and with surplus blastocysts after an LB) were also reported versus the standard care (>168 h.p.i.). All hypothetical relative reductions were calculated.

Main results and the role of chance: A total of 14.6% of the blastocysts reached full expansion beyond 144 h.p.i. (5.9% in the range 144–156 h.p.i., 7.9% in the range 156–168 h.p.i. and 0.8% beyond 168 h.p.i.). Slower blastocysts were of a worse quality based on the evaluation of both embryologists and AI. Both later tEB and longer time between tEB and full blastocyst expansion concurred to Day 7 development, quite independently of blastocyst quality. Slower growing blastocysts were slightly larger than faster-growing ones at the time of biopsy, but no difference was reported in the risk of hatching, mainly because two dedicated slots have been set along the working day for these procedures. The lower euploidy rate among Day 7 blastocysts is due to their worse morphology and more advanced oocyte age, rather than to a slower development per se. Conversely, the lower LBR was significant even after adjusting for confounders, with a first relevant decrease for blastocysts biopsied in the range 132–144 h.p.i. (N ¼ 76/208, 36.5% versus N ¼ 114/215, 53.0% in the control, multivariate odds ratio 0.61, 95% CI 0.40–0.92, adjusted-P ¼ 0.02), and a second step for blastocysts biopsied in the range 156–168 h.p.i. (N ¼ 3/21, 14.3%, multivariate odds ratio: 0.24, 95% CI 0.07–0.88, adjusted-P ¼ 0.03). Nevertheless, when the cutoff was set at 144 h.p.i., no significant difference was reported. In this patient population, ending embryo culture at 144 h.p.i. would have caused 10.6%, 7.3%, 4.4%, 13.7% and 5.2% relative reductions in the number of patients obtaining blastocysts, euploid blastocysts, LBs, supernumerary blastocysts without an LB and surplus blastocysts after an LB, respectively.

Limitations, reasons for caution: Gestational and perinatal outcomes were not assessed, and a cost-effectiveness analysis is missing.

Wider implications of the findings: In view of the increasing personalization and patient-centeredness of IVF, whenever allowed from the local regulations, the choice to culture embryos to Day 7 should be grounded on the careful evaluation of couples' reproductive history. Patients should be aware that Day 7 blastocysts are less competent than faster growing ones; poor prognosis couples, couples less compliant toward other attempts in case of a failure and couples wishing for more than one child, may benefit from them. AI tools can help improving the generalizability of the evidence worldwide.

Study 06: Pronucleo 2022 - Reproferty

Identifying the optimal morphokinetic range for euploid embryos using CHLOE-EQ, an AI-based embryology assistant

Authors: Gomes M, Zepeda, A.; Brualla, A.; Hickman, C.

Best abstract of Pronucleo congress 2022

Objective: To identify the optimal time-range of morphokinetic events in euploid embryos compared to aneuploids using CHLOE-EQ an AI automatic embryo assessment assistant.

Study design: Retrospective, observational study of 143 time-lapse embryos from a private fertility clinic in Brazil in 2022. Comparator between human and CHLOE-EQ (AI-based embryo assessment tool).

Methods: Embryo time-lapse videos were automatically annotated using CHLOE-EQ (Fairtility) for morphokinetics, PN number and anomalies. The frequency distribution for each morphokinetic parameter was compared between euploid and aneuploid embryos to establish ranges for optimal euploidy rate. The ranges between optimal (maximum euploidy rate) and all embryos were compared (paired t-test). Level of agreement between CHLOE-EQ and embryologist was assessed for morphokinetics (ICC) and PN assessment (Kappa). Efficacy of predictions of CHLOE-EQ scores were assessed (AUC).

Results: For each morphokinetic event, an optimal range for identification of euploids compared to aneuploids was identified (tPNf:21.6-27.5;t2:24.8-30.2;t3:35.9-42.5;t4:36.8-44.5;t5:48.7-65.1;t6:49.6-66.3;t7:52.5-68.8;t8:56.6-79.5;t9:65.9-90.4;tM:80.3-96.8;tsB:91.6-109.8;tB:97.7-107.5). Optimal range of euploid embryos was smaller than the total range for all embryos (p<0.001):tPNf (5.87 vs 34.99),t2(5.37 vs 37.35),t3(6.62 vs 74.52), t4(7.77 vs 39.21), t5(16.4 vs 68.61),t6(16.72 vs 67.58),t7(16.31 vs 66.36),t8(22.89 vs 51.51),t9(24.48 vs 44.24),tM(16.46-49.03),tSB(18.27-53.14),tB(9.81-51.1) and a reduced euploid rate was found outside of the optimal range (p<0.001). The accuracy of PN assessment was 99% (195/197). Agreement between experienced embryologists and CHLOE-EQ was very strong in all morphokinetic events (AUC 0.928-0.997). CHLOE-BLAST Score was predictive of blastulation (AUC=0.99), whilst CHLOE-EQ Score was predictive of utilisation (AUC 0.96), selection for transfer (AUC=0.85), euploidy (AUC=0.67) and CHLOE Ranking was predictive of utilisation (AUC=0.86) and selection for transfer (AUC=0.86).

Limitations: Retrospective assessment of a single clinic. Only blastocysts deemed suitable for biopsy were assessed for ploidy, therefore, the ploidy rate of non-blastocysts or inferior quality embryos is unknown, creating a potential bias regarding the lower cutoff threshold for optimal ranges.

Conclusion: CHLOE-EQ can identify the optimal morphokinetic time range to maximise the chance of an embryo being euploid, a potentially valuable biomarker for embryo selection, especially within the context of a PGT-A program, potentially providing consistency in embryo selection for biopsy.

Study 07: ASRM 2022 – Juana Crespo, CARE, Memorial

Why spend time doing manual annotations when CHLOE EQ™'S automatic annotations are comparable to that of experienced embryologists? A multi-centre comparative study

Adriana Brualla Mora, Amy Barrie, Rachel Smith, Alison J Campbell, Clara Miret Lucio, Marta Lozano, Semra Kahraman, Yesim Kumtepev Colakoglu, Anat Sakov, Iris Har-Vardi, Assaf Ben-Meir & Cristina Hickman.

Published by Fertility & Sterility

Clinic: Juana Crespo (España), CARE (United Kingdom), Memorial (Turkey).

Type: Retrospective Cohort Study (includes comparator groups)

Objective: To assess the agreement between manual and CHLOE EQ morphokinetic annotations.

Materials and methods: Time-lapse videos from 5402 embryos from 1092 patients from 3 clinics from 3

countries (UKN=328 cycles; Spain N=309 cycles; Turkey N=455 cycles) were annotated manually by experienced embryologists and by CHLOE EQ (Fairtility). CHLOE EQ is a transparent AI tool that supports embryologists in making clinical decisions from time-lapse videos. The agreement between manual and CHLOE EQ annotations were quantified using Concordance Correlation Coefficient (CCC) for each morphokinetic event, as well as through a confusion matrix.

Results:

- Overall, the level of agreement across all morphokinetic parameters was at least strong (tPNf, t2,t3, t4, t6, t7, t8, t9, tM, teB), if not very strong (t5, tsB, tB).
- Across all 3 clinics, the level of agreement for all morphokientic parameters assessed was at least strong.

Conclusions: CHLOE EQ automatic annotation of human embryos is comparable to human manual annotations. This finding was found to be consistent in three different independent clinics, suggesting that the algorithm, which was blindly tested without prior training, can be generalised across different clinics worldwide.

Impact statement: The ability to automatically annotate time-lapse embryos using AI algorithms such as CHLOE EQ presents an opportunity to save precious embryologist time whilst increasing the granularity and immediacy of data captured to support clinical and operational decision making in an IVF clinic. The automatic annotation further provides an international morphokinetic language, resolving inter and intra operator variation.

Table 1. Level of agreement between CHLOE automatic annotations and manual annotations by experienced embryologists in 3 clinics.

Event	Overall	Degree of agreement with experienced embryologists	Clinic 1	Clinic 2	Clinic 3
tPNf	0.77	Strong	0.92	0.69	0.91
t2	0.73	Strong	0.86	0.64	0.91
t3	0.79	Strong	0.81	0.76	0.88
t4	0.65	Strong	0.7	0.61	0.78
t5	0.8	Very strong	0.82	0.77	0.85
t6	0.79	Strong	0.82	0.74	0.85
t7	0.69	Strong	0.74	0.63	0.85
t8	0.68	Strong	0.67	0.68	0.72
t9	0.69	Strong	0.71		0.61
tM	0.78	Strong	0.77	0.78	0.78
tSB	0.92	Very strong	0.9	0.93	0.91
tB	0.91	Very strong	0.88	0.93	0.92
tEB	0.79	Strong	0.82	0.8	0.48

Characterising Direct Unequal Cleavage using CHLOE-EQ

Braga D, Setti A, Vingris L, Guilherme, P, Lo Turco E, Vergueiro T, Zepeda A, Brualla, A, Edson Borges Jr, Hickman C.

Clinic: Fertility FIV (Brazil)

Objective: Direct Unequal Cleavage (DUCs) has been associated with reduced embryo viability in terms of blastulation, ploidy and implantation. The objective of this study was to assess whether DUCs are associated with oocyte quality, whether DUCs have an impact on multinucleation or blastocyst quality.

Methods: Retrospective assessment of time-lapse data from a single clinic using manual annotation of oocyte quality and automatic detection of DUC using CHLOE-EQ (Fairtility, Israel), an artificial intelligence (AI) based assistant that supports embryologists with embryo assessment. Categorical data was assessed using Chi-square test.

Results: (Table 1) DUCs had a compromised ability to blastulate compared to non-DUCs (DUC: 68% (21/31) vs non-DUCs: 94% (289/307), p<0.001). DUCs were not associated with the presence of a smooth endoplasmic reticulum (SER) in the oocyte (6% (6/98) of DUCs were derived from SER oocytes vs 5% (20/388) of non-DUCs, NS). DUCs were not associated with whether the oocyte was dark, granular, homogeneous, had an inclusion or was normal (NS). All DUCs had thick zona pellucida (9/9) compared to 68% of non-DUCs (15/22, p=0.054). DUCs were more likely to have a non-uniform zona pellucida compared to non-DUCs (DUCs: 7% (6/82) vs non-DUCs: 18% (66/366), p=0.01). DUCs were 4-fold less likely to be multinucleated at the 2-cell stage than non-DUCs (DUC: 7% (2/29) vs non-DUCs: 30% (91/305), p=0.03). DUCs were 7-fold more likely to be multinucleated at the 4-cell stage than non-DUCs (DUC: 7% (2/29) vs non-DUCs: 1% (3/302), p=0.06), although this difference did not reach significance. DUCs are more likely to have C-grade quality trophectoderm at the blastocyst stage than non-DUCs (DUC: 53% (10/19) vs non-DUCs 26% (75/285), p<0.05); although the ICM quality was unaffected (DUC: 16% (3/19) vs non-DUCs 14% (39/285), NS). Patient age was not associated with DUCs (p=0.4).

Conclusion: Given the growing evidence that DUCs have compromised viability, it is important to understand the biology in how DUCs impact embryo selection. The ability to use AI to detect DUCs to avoid such important information being missed during embryo selection can assist embryologists in maximising their efficacy of embryo selection.

Keywords: DUC, CHLOE-EQ, embryo selection, oocyte quality

Table 1. DUCs vs Non DUCs

	DUCs	Non DUCs
Blastulation	68%(21/31), p<0.001	94%(289/307), p<0.001
Smooth endoplasmic reticulum (SER) in the oocyte	6% (6/98), NS	5%(20/388), NS
Thick zona pellucida	100% (9/9), p=0.054	68% (15/22, p=0.054
Non-uniform zona pellucida	7%(6/82), p=0.01	18%(66/366), p=0.01
Multinucleated at the 2 cell stage	7%(2/29), p=0.03	30%(91/305), p=0.03
Multinucleated at the 4 cell	7%(2/29), p=0.06	1%(3/302), p=0.06
C-grade quality trophectoderm	53% (10/19), p<0.05	26% (75/285), p<0.05]
ICM Quality	16% (3/19), NS	14% (39/285), NS

Study 09: SEF 2022 – Juana Crespo

¿ES FIABLE LA CLASIFICACIÓN EMBRIONARIA GENERADA POR UN SISTEMA DE INTELIGENCIA ARTIFICIAL (IA)?

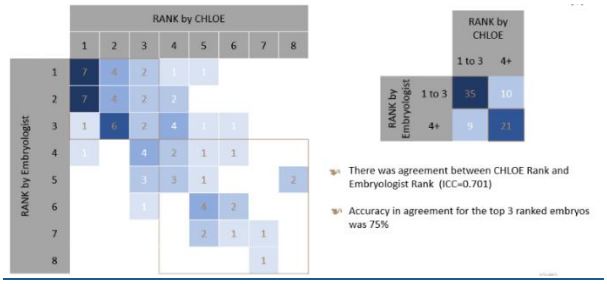
Clínica: Juana Crespo (Spain)

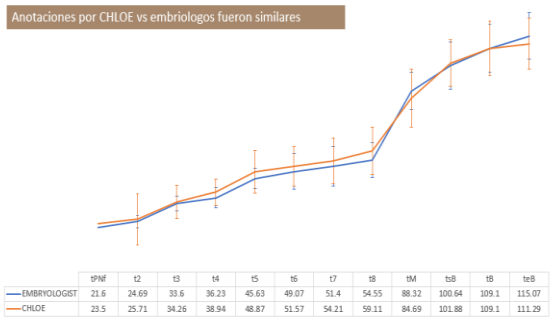
Introducción: En la actualidad, los eventos morfocinéticos de los embriones se anotan de forma manual durante el desarrollo embrionario, por lo que existe variabilidad inter e intra-centro. La decisión de qué embrión transferir, congelar o descartar depende directamente de estas anotaciones. Es importante desarrollar una herramienta que aporte consistencia y precisión en las anotaciones, y así facilitar la toma de decisiones.

Material y Métodos: Se realizó un análisis de cohorte retrospectivo sobre 179 videos de timelapse(Embryoscope,Vitrolife) recopilados en 2021. Los eventos morfocinéticos de los embriones fueron anotados tanto manual como automáticamente por CHLOE (IA,Fairtility). Mediante el coeficiente de correlación-intraclase (CCI), se compararon ambas anotaciones, y se calculó la proporción de correcciones realizadas sobre el número de pronúcleos. También se evaluó la precisión del sistema(IA) en la predicción de blastulación a las 44horas de cultivo utilizando el AUC como métrica de eficacia. El uso de embriones (transferidosVScongeladosVSdescartados) se comparó con la clasificación de embriones generada por CHLOE.

Resultados: La concordancia en la anotación de los PNs entre CHLOE y los embriólogos fue del 93%, con una tasa de corrección del 7% (n=179).

- La gran mayoría de las variables morfocinéticas mostraron una concordancia muy fuerte, con un rango CCI de(0.81-1.00). Las variables t6 y tM obtuvieron una concordancia fuerte, con un ICC de (0.61-0.8). t4 obtuvo una concordancia moderada(0.5).
- CHLOE obtuvo una predicción de la blastulación en Día 3 de cultivo con un nivel de sensibilidad del 0.77 y especificidad 0.83(AUC:0.84,p<0.0001).
- La clasificación generada por CHLOE se correlacionó con las decisiones del embriólogo sobre congelar, transferir o descartar embriones, con una alta sensibilidad de 0.88 y una especificidad del 0.67(AUC: 0,84,p<0,0001).





Conclusiones: La IA proporciona una herramienta objetiva y eficaz para apoyar la toma de decisiones de los embriólogos, y realizar anotaciones morfocinéticas automáticas con precisión.

Study 10: SEF 2022 – Next Clinic Murcia

Análisis del desarrollo y ploidía de embriones con Direct Unequal Cleavage en las primeras divisiones celulares (DUC). ¿Debemos descartarlos?

Autores: Gómez E, Brualla A, Almunia N, Jiménez R, Villaquirán A, Derrick R, Erlich I, Hickman C.

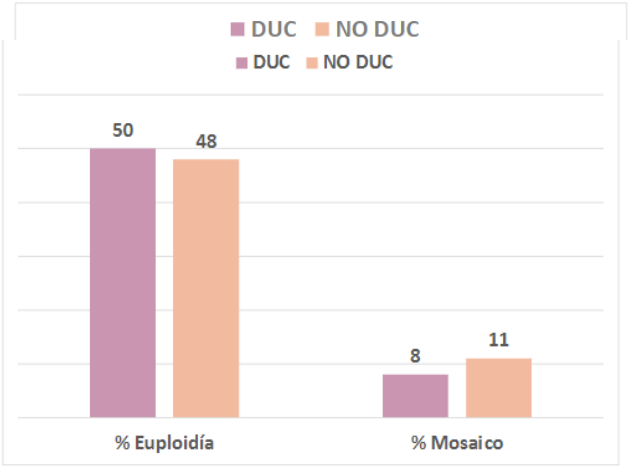
Clínica: NEXT CLINIC MURCIA (España)

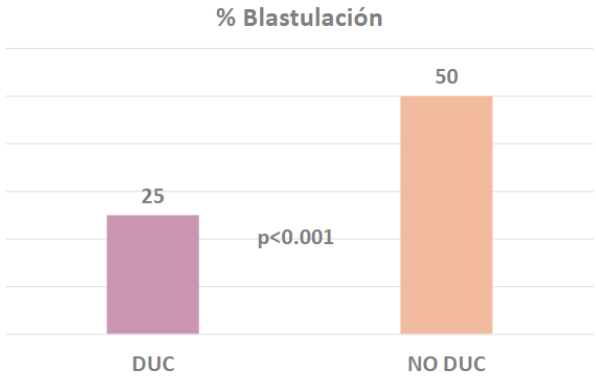
Introducción: A veces una blastómera se divide en tres o más células, es la *Direct Unequal Cleavage* (DUC). Cuando este fenómeno tiene lugar durante las primeras divisiones embrionarias, el embrión podría estar afectado por una distribución desigual del ADN en las blastómeras, debido a una replicación incompleta y a una citocinesis anómala. Así, los DUC podrían tener un impacto negativo sobre la tasa de blastulación, de desarrollo y de ploidía embrionaria.
El objetivo del presente estudio es evaluar la capacidad de desarrollo de estos embrionarios, así como su ploidía en comparación con los que no presentan DUC.

Material y Métodos: Se realizó un análisis retrospectivo de 693 videos de *timelapse* (Embryoscope, Vitrolife) recopilados entre 2018 y 2020. Los videos fueron procesados usando una herramienta de inteligencia artificial, CHOLE (Fairtility), y se compilaron automáticamente las siguientes características: DUC, blastulación, calidad morfológica de la masa celular interna (MCI) y trofoectodermo (TE). Los datos obtenidos, así como el resultado del PGT-A, de los embriones que presentaron DUC, identificado por el sistema CHOLE, se compararon mediante una chi-cuadrado con los noDUC.

Resultados: Se analizaron 693 embriones, el 29% presentaron DUC. Éstos tuvieron una tasa de blastulación menor que los noDUC (25% vs 50%, p<0.001). Al analizar la calidad de la MCI obtuvimos que en los embriones DUC el 7% presentaton una MCI adecuada y el 9% un trofoectodermo correcto, frente al 33% y al 35% de los noDUC (p<0,001). Los blastocistos DUC (n=38) y los no-DUC (n=292) tuvieron una tasa de euploidía (50 vs 43%) y mosaicismo (8 vs 11%) similar.

Conclusiones: Los embriones DUC tienen una tasa de blastulación y calidad embrionaria menor, pero los que llegan a blastocisto presentan una tasa de euploidía y mosaicismo similar a los no-DUC. Ésto podría indicar que los embriones DUC que llegan a blastocisto eliminarían las células con una composición cromosómica errónea.





Study 11: SEF 2022 – Next Clinic Murcia

¿PODEMOS DETERMINAR RANGOS DE PARÁMETROS MORFOCINÉTICOS PARA ESTABLECER QUÉ EMBRIONES SERÁN CAPACES DE ALCANZAR UN ESTADO ÓPTIMO DE DESARROLLO?

Autores: Gómez E, Brualla A, Almunia N, Jiménez R, Villaquirán A, Derrick R, Erlich I, Hickman C.

Clínica: NEXT CLINIC MURCIA (España)

Introducción: El cultivo de los embriones en incubadores timelapse ha cambiado la forma en que se seleccionan los embriones. El seguimiento continuo de los embriones permite establecer parámetros morfocinéticos para cuantificar el ritmo de desarrollo. Aunque la mayoría de los métodos de selección de embriones están diseñados para identificar el embrión con la mayor probabilidad de convertirse en un bebé nacido vivo sano, la capacidad de identificar embriones que no tendrán la capacidad de progresar su desarrollo es igualmente importante para la toma de decisiones clínicas.

Material y métodos: Se analizaron 185 embriones cultivados en 2021 en un incubador timelapse (Embryoscope, Vitrolife), y se analizaron los parámetros morfocinéticos con CHLOE (Faitility), un software basado en Inteligencia Artificial. Se comparó la distribución de cada parámetro morfocinético entre los distintos destinos (transferidos vs congelado vs descartado como media+-desviación estándar, test-t bilateral). Cada parámetro morfocinético continuo se clasificó según los rangos en los que la utilización de embriones fue inútil (<1%), óptima (tasa de utilización máxima) o tasa de utilización reducida (entre óptima e inútil).

Resultados: Para cada parámetro morfocinético, la diferencia en el tiempo del evento entre los embriones congelados y transferidos frente a los descartados fue estadísticamente significativa (P<0.003). Los resultados detallan el punto de tiempo (media (DS) de congelado y transferido frente a la media (DS) descartado, p-valor) en horas para cada

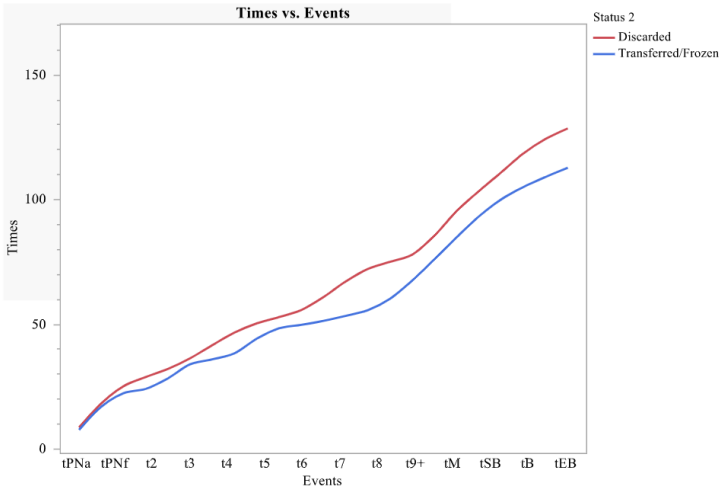
La dispersión de los embriones descartados es mayor en los utilizados

(24.92(2.71)vs33.78(16.17),p<0.0001), **t3** (34.62(4.03)vs42.58(22),p=0.0024), **t4** (37.29(4.31)vs48.29(20.29,p<0.0001), **t5** (47.03(6.47)vs55.32(22.63),p=0029), **t6** (49.54(5.63)vs60.56(22.20),p<0.0001), **t7** (53.1(7.86)vs69.13(24.54),p<0.0001), **t8** (57.78(9.78)vs77.33(25.79),p<0.0001), **t9+** (69.14(7.39)vs81.9(21.96),p<0.0001), **tM** (83.9(8.72)vs96.08(16.88),p<0.0001), **tSB** (97.89(7.55)vs105.38(11.38),p=0.0005), **tB** (105.74(7)vs113.25(15.53),p=0.0002), **eEB** (110.65(7.58)vs120.47(11.36),p=0.0031).

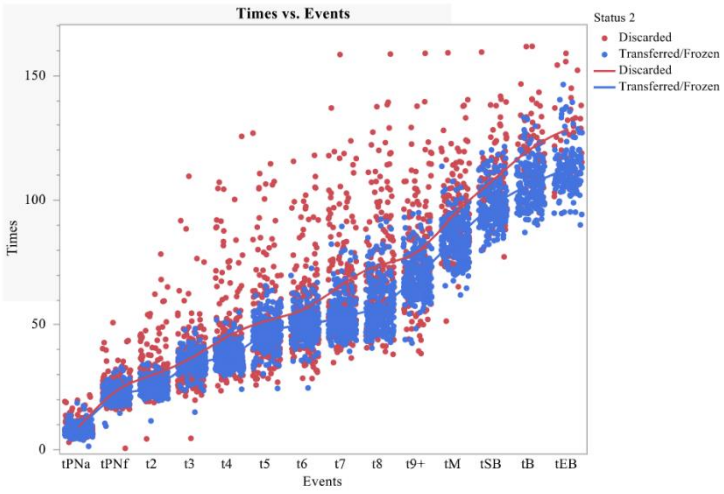
Al observar la distribución exacta de estos embriones según el tiempo, se determinaron intervalos de tiempo óptimos e intervalos de tiempo fútiles, que eran zonas donde la proporción de embriones transferidos-congelados o descartados alcanzaban su punto máximo.

Conclusiones: La identificación de rangos objetivos para determinar cuando un embrión no es adecuado para el tratamiento puede reducir la variación entre embriólogos y centros, y permitirá una mayor optimización de los recursos.

Los embriones descartados presentan un ritmo de división más lento que los utilizados



La dispersión de los embriones descartados es mayor en los utilizados



Study 12: PCRS 2022 – IVFF

A three-way comparison of annotations by embryologists, guided annotation (Vitrolife) and CHLOE-EQ (Fairtility)

AUTHORS: Miller K, Grunwald, A, Berntsen J, Zepeda A, Hickman C

Background: Time-lapse has improved efficiency in the IVF lab by bringing flexibility of when embryo evaluations need to take place. However, manual annotations of morphokinetic parameters required for KIDScore algorithm are time-consuming. Guided Annotations (Vitrolife) and CHLOE-EQ (Fairtility) are two solutions that automate morphokinetic annotations.

Objective: The purpose of this study was to compare annotations by embryologists, Guided Annotations and CHLOE-EQ.

Materials and methods: 1696 embryos were retrospectively annotated by a embryologist and retrospectively annotated by Guided Annotation (Vitrolife) and by CHLOE-EQ (Fairtility). The embryologist and reducing the cost per cycle. Increased accuracy and consistency associated with automated annotations reduces the comparison of annotations between the three methods of annotation (Embryologist, Guided Annotation, CHLOE-EQ) were compared with each other using intra class correlation coefficient. The agreement level was categorised as poor (<0.4), moderate (0.4-0.6), strong (0.6-0.8) and very strong (0.8+).

Results: Overall, automatic annotations by CHLOE-EQ and Guided Annotation have at least a moderate agreement with human embryologists. CHLOE-EQ and Guided Annotations have a very strong level of agreement with each other for all morphokinetics. The automatic annotations have the benefit of providing the full range of morphokinetic annotations, whilst humans only annotate the morphokinetics required for IDASCORE.

Conclusion: Automatic annotation brings consistency to embryo evaluation whilst saving time. Both Guided Annotations and CHLOE EQ have a very strong level of agreement demonstrating robustness and efficacy in both of these methods of automated annotation.

Impact statement: This is the first study assessing two automatic annotation solutions with human annotations. Automatic annotations improve efficiency in the lab, increasing the number of cycles possible per

risk of transferring an embryo with lower chance of achieving a healthy live birth.

	CHLOE-EQ vs embryologists	VITROLIFE vs embryologists	CHLOE-EQ vs vitrolife
tPNf	0.856 Very Strong	0.651 Strong	0.945 Very Strong
T2	0.920 Very Strong	0.689 Strong	0.988 Very Strong
T3	0.601 Strong	0.540 Moderate	0.910 Very Strong
T4	0.511 Moderate	0.534 Moderate	0.850 Very Strong
T5	0.525 Moderate	0.478 Moderate	0.879 Very Strong
T6	Not assessed	Not assessed	0.887 Very Strong
T7	Not assessed	Not assessed	0.855 Very Strong
T8	Not assessed	Not assessed	0.802 Very Strong
tSB	Not assessed	Not assessed	0.940 Very Strong
tB	0.899 Very Strong	0.903 Very Strong	0.971 Very Strong
teB	Not assessed	Not assessed	0.956 Very Strong

Study 13: ASRM 2023 - EVEWELL

Embryo selection by AI: are we playing fair? Interrogating the sex bias question through embryo developmental morphokinetics and PGT-A data.

Authors: Teodora Popa, Matthew Lau, Chloe He, Colin Davies, Christian Ottolini, Helen O'Neill

Clinic : Evewell

Background: With the advent of modern assisted reproductive technologies (ART), artificial intelligence (AI) algorithms have been increasingly employed to assess and predict embryo quality based on morphokinetic parameters. However, these algorithms assume identical parameter values for male and female embryos, potentially introducing sex bias in AI-driven embryo assessment. Consequently, it is essential to investigate whether there are significant differences in developmental morphokinetics between male and female embryos, as any disparities could impact the accuracy and fairness of AI-based embryo selection.

Objective: Time-lapse has improved efficiency in the IVF lab by bringing flexibility of when embryo evaluations need to take place. However, manual annotations of morphokinetic parameters required for KIDSCORE algorithm are time-consuming. Guided Annotations (Vitrolife) and CHLOE-EQ (Fairtility) are two solutions that automate morphokinetic annotations. The purpose of this study was to compare annotations by embryologists, Guided Annotations and CHLOE-EQ.

Materials and Methods: We conducted a retrospective cohort study using time-lapse imaging data as well as PGT-A outcomes from 1,638 euploid embryos, comprising 844 male (XY) and 794 female (XX) embryos. We analysed two parameters commonly used to determine embryo quality:

- Morphokinetic timing, where parameters were compared between sexes using t-tests; however, the primary focus was on a 5-fold cross-validated multivariate logistic regression model, which assessed the predictability between sex and these parameters.
- Cleavage patterns to identify any sex-specific differences in the frequency and occurrence of various cleavage events.

Results: Our analysis found no significant statistical differences (with significance considered at $p < 0.05$) in morphokinetic timing parameters or cleavage patterns between male and female embryos. Additionally, the logistic regression model returned an accuracy of 52.1, and an average area under curve (AUC) of 0.530 across the 5-folds.

Conclusion: The project's findings support the continued use of sex-unadjusted AI algorithms for embryo selection, as no significant differences were observed, and the predictive power of the logistic regression model proved to be low. We conclude that current AI-driven embryo assessment tools are not likely to be inherently biased with respect to embryo sex and can be employed to improve ART outcomes while promoting fair and accurate embryo selection processes.

Study 14: British fertility 2023 - HSFC, CRGH, PLYMOUTH

Multi-centre assessment of the efficacy of CHLOE-EQ (Fairtility) in automatically assessing zygotes on day 1

AUTHORS: Samantha Knight, Mina Vasilic, Plymouth, Alexa Zepeda, Noam Bergelson, Adriana Brualla, Cristina Hickman.

Introduction: To assess how well CHLOE-EQ, an artificial intelligence (AI) based embryo assessment support tool, is able to assess the number of pronucleates (PN) in a zygote compared to embryologists, and whether this capability is generalised across different clinics.

Method: Time-lapse images of 6048 zygotes from three different clinics (Clinic 1: n=518, Clinic 2: n=307, Clinic 3: n=5223) were prospectively assessed by clinical embryologists on day 1 as per routine clinical procedures. Blind to human assessment, all zygote time-lapse videos were retrospectively assessed by CHLOE-EQ (Fairtility). Number of PNs was categorised as 0,1,2,3+ and the level of agreement was quantified in two was: (1) accuracy = total agreement / total number of zygotes assessed; (2) Kappa agreement across all categories (Kappa score +- 95% confidence interval). Data was assessed for each individual clinic as well as overall. Accuracy was further assessed for 2PN specifically.

Results: Overall level of agreement across all clinics was 94% (5664/6048), with similar ($p<0.05$) levels of agreement between the three clinics (1: 95%, 491/518; 2: 90%, 275/307; 3: 94%, 4898/5223). The overall accuracy for 2PNs was 95% (5761/6048) which was similar ($p<0.05$) between the three clinics (1: 96%, 499/518; 2: 91%, 278/307; 3: 95%, 4984/5223).

The kappa agreement overall was almost perfect [0.834(0.819-0.850)]. This was consistent across the individual clinics which had at least substantial agreement between CHLOE-EQ and embryologist PN assessment [1: 0.846 (0.791-0.900); 2: 0.748 (0.668-0.827) ; 3:0.839 (0.822-0.855)]. The agreement observed was significantly higher than the agreement expected by chance (chance vs actual: 1:66%vs95%; 2:59%vs90%; 3:61%vs94%;$p<0.001$).

Conclusion: CHLOE-EQ has at least strong level of agreement with the PN assessment by human embryologists. Further studies will assess the nature of the few disagreements observed. The high agreement allows for increased consistency between operators, automatic EMR data entry, and automatic KPI assessment.

Multi-centre assessment of the efficacy of CHLOE-EQ (Fairtility) in automatically assessing zygotes on Day 1

Knight, Samantha[1]; Joshi, Raj[1]; Venkataraman, Suvir[1]; Venkat, Geetha[1]; Cawood, Suzanne[2]; Vasilic, Mina[2]; Mahews, Rebecca[3];Dodge, Sally[3]; Thompson, Andrew[4]; Mania, Anastasia[5]; Ippokras, Sarris[5]; Zepeda, Alexa[6]; Bergelson, Noam[6]; Brualla, Adriana[6];Hickman, Cristina[6]

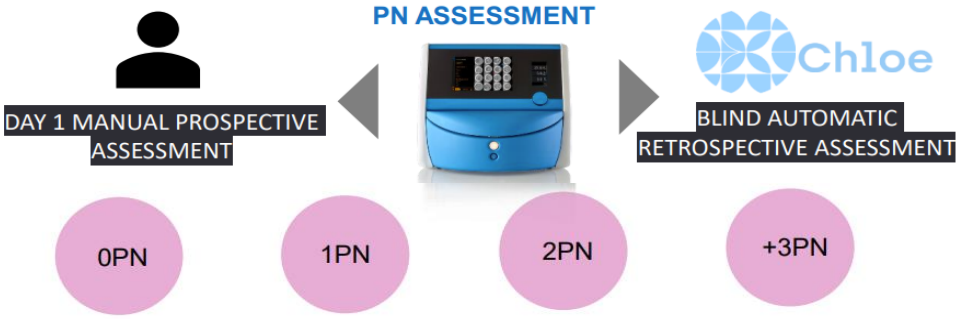
[1]Harley Street Ferlity Clinic, United Kingdom
[2]CRGH, United Kingdom
[3]CRGW Plymouth, United Kingdom ; [4]CRGW, United Kingdom
[5]Kings Fertility, United Kingdom
[6]Fairtility, Israel

Objective

TO COMPARE MANUAL ASSESSMENT OF PRONUCLEATES IN TIME-LAPSE IMAGES WITH AUTOMATIC ASSESSMENT USING ARTIFICIAL INTELLIGENCE IN 3 CLINICS

Methods

Time-lapse images of 6048 zygotes (Clinic 1: n=518, Clinic 2: n=307, Clinic 3: n=5223).



Level of agreement was quantified in:
(1) accuracy = total agreement / total number of zygotes assessed
(2) Kappa agreement across all categories (Kappa score +- 95% confidence interval).

Results

- Overall level of agreement across all clinics was 94%, with similar ($p<0.05$) levels of agreement between the three clinics
- The overall accuracy for 2PNs was 95% which was similar ($p<0.05$) between the three clinics
- The kappa agreement overall was almost perfect across the individual clinics which had at least substantial agreement between CHLOE-EQ and embryologist PN assessment
- The agreement observed was significantly higher than the agreement expected by chance (chance vs actual: 1:66%vs95%; 2:59%vs90%; 3:61%vs94%;$p<0.001$)

	Overall	Clinic 1	Clinic 2	Clinic 3
PN Level of agreement	94% 5664/6048 p<0.05	95% 491/518 p<0.05	90% 275/307 p<0.05	94% 4898/5223 p<0.05
Overall accuracy for 2PNs	95% 5761/6048 p<0.05	96% 499/518 p<0.05	91% 278/307 p<0.05	95% 4984/5223 p<0.05
Kappa PN agreement	0.834 (0.819-0.850)	0.846 (0.791-0.900)	0.748 (0.668-0.827)	0.839 (0.822-0.855)

Conclusion

- CHLOE-EQ has at least a strong level of agreement with the PN assessment by human embryologists
- Further studies will assess the nature of the few disagreements observed
- The high agreement allows for increased consistency between operators, automatic EMR data entry, and automatic KPI assessment

Study 15: British fertility 2023 – PLYMOUTH, CRGH, HSFC

USING ARTIFICIAL INTELLIGENCE TO AUTOMATICALLY ANOTATE TIME-LAPSE VIDEOS: saving precious time

Authors: Plymouth, CRGH, HSFC, Alexa Zepeda, Noam Bergelson, Adriana Brualla, Cristina Hickman

Introduction: The aim of this study was to compare the manual annotation by embryologists with the automated annotation by an AI-based decision support tool (CHLOE-EQ, Fairtility).

Methods: 8368 embryos from ICSI/IVF cycles cultured in Embryoscope incubators from 2021 to 2022 at 4 clinics (n=362, 5591, 653, 1762) were annotated as per routine clinical practice. The same videos were blindly assessed retrospectively using CHLOE-EQ (Fairtility). Lin's concordance correlation coefficient (CCC) were calculated between CHLOE-EQ and embryologist annotation times for each of the morphokinetic parameters assessed using two-way model for agreement. Five categories of agreement were determined based on CCC score; very weak

(0-0.20), weak (0.21-0.40), moderate (0.41-0.60), strong (0.61-0.80) and very strong (0.81-1.00). The level of agreement was quantified separately for each clinic and presented as (clinic 1, clinic 2, clinic 3, clinic 4).

Results: All the CCC for all the morphokinetics across all 4 clinics were at least strong level of agreement between CHLOE-EQ and human embryologists: tPNf (0.97, 0.63, 0.95, 0.66), t2 (0.84, 0.87, 0.92, 0.74), t3 (0.8, 0.81, 0.84, 0.84),t4 (0.89, 0.87, 0.74, 0.76), t5 (0.76, 0.89, 0.78, 0.73), t6 (0.77, 0.68, 0.74, 0.69), t7 (0.72, 0.76, 0.80, 0.80), t8 (0.73, 0.79, 0.72, 0.83), tsB (0.75, 0.89, 0.9, 0.92), tB (0.74, 0.92, 0.92, 0.95).

Conclusion: Manual annotations are time-consuming and subjective, prone to inter and intra operator variation. CHLOE-EQ automatic annotation is equivalent to the annotation by experienced embryologists. This equivalence has been demonstrated across different clinics with different types of patients and following different protocols. Automatic annotations help save precious embryology time.

Using Artificial Intelligence to automatically annotate time-lapse videos: saving precious embryology time

Matthews, Rebecca[1]; Doidge, Sally[1]; Thompson, Andrew[2]; Cawood, Suzanne[3]; Vasilic, Mina[3]; Knight, Samantha[4]; Joshi, Raj[4]; Mania,Anastasia[5]; Sarris, Ippokras[5]; Zepeda, Alexa[6]; Bergelson, Noam[6]; Brualla, Adriana[6]; Hickman, Cristina[6]

[1]CRGW Plymouth, United Kingdom ; [2]CRGW, United Kingdom ; [3]CRGH, United Kingdom ; [4]Harley Street Fertility Clinic, United Kingdom; [5]Kings Fertility, United Kingdom ; [6]Fairtility, United Kingdom

Background and Aim

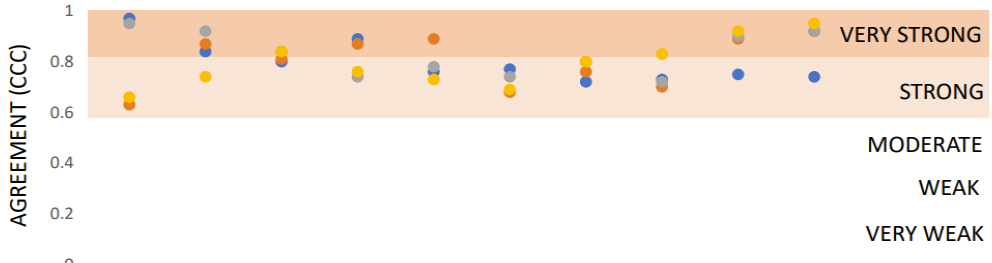
- Manual annotations for embryo grading and selection are time-consuming.
- These annotations are subjective and prone to inter/intra operator variation.
- There is a need to automate annotations to bring consistency to this process.
- Automatic annotations will save precious embryology time which can be used doing other tasks.
- **The aim of this study was to determine the correlation of the AI automatic annotations from CHLOE-EQ against the manual annotations performed by embryologists.**

Methods

- Retrospective video timelapse footage was collected from 8368 embryos over 4 UK clinics (n=362, 5591, 653, 1762).
- The embryos were from fresh ICSI/IVF cycles cultured from 2021 to 2022.
- Lin's concordance correlation coefficient (CCC) was calculated between CHLOE-EQ and embryologist annotation times for each of the morphokinetic parameters assessed using two-way model for agreement.
- Five categories of agreement were determined based on CCC score; very weak (0-0.20), weak (0.21-0.40), moderate (0.41-0.60), strong (0.61-0.80) and very strong (0.81-1.00).

Results

The CCCs for each morphokinetics parameter, across all 4 clinics, show strong agreement between CHLOE-EQ and human embryologists.



	tPNf	t2	t3	t4	t5	t6	t7	t8	tSB	tB
Clinic 1	0.97	0.84	0.8	0.89	0.76	0.77	0.72	0.73	0.75	0.74
Clinic 2	0.63	0.87	0.81	0.87	0.89	0.68	0.76	0.7	0.89	0.92
Clinic 3	0.95	0.92	0.84	0.74	0.78	0.74	0.8	0.72	0.9	0.92
Clinic 4	0.66	0.74	0.84	0.76	0.73	0.69	0.8	0.83	0.92	0.95

Conclusion

- CHLOE-EQ automatic annotation is equivalent to the annotation by experienced embryologists at all 4 clinics.
- Automatic annotations have the potential to help save embryologists a lot of time, improving efficiency.

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Study 16: British fertility 2023 – CRGH, HSFC, PLYMOUTH, KINGS

CHLOE-EQ Score: a novel biomarker of embryo viability

Authors: Suzanne Cawood, Mina Vasilic, Samantha Knight, Raj Joshi, Rebecca Matthews, Sally Dodge, Andrew Thompson, Anastasia Mania, Ippokratis Sarris, Alexa Zepeda, Noam Bergelson, Adriana Brualla, Cristina Hickman

Introduction: Artificial Intelligence (AI) based tools have promised to improve embryo viability prediction. There is a need to validate these promises before introducing AI technologies into clinical practice. The objective was to validate the ability of CHLOE-EQ to predict embryo utilisation, decision for transfer, ploidy and clinical pregnancy.

Methods: CHLOE EQ score combines morphological and morphokinetic AI algorithms, trained on over 100,000 embryo videos, to assist in embryo selection. From January 2021 to July 2022, 8368 embryos were cultured in embryoscopes across four different clinics: clinic 1 (n=362), clinic 2 (n=5591), clinic 3 (n=653), clinic 4 (n=1762). Efficacy of prediction of CHLOE-EQ score for embryo utilisation, decision for transfer, ploidy and clinical pregnancy for each individual clinic was assessed using Binary logistic regression and quantified using the area under the curve (AUC). Data presented as (mean AUC across the four clinic ± standard deviation: clinic 1, clinic2, clinic 3, clinic 4). Ploidy and clinical pregnancy data was only available for clinic 2.

CHLOE RANK (proposed ranking in order of priority for transfer) and CHLOE BLAST score were assessed relative to blastulation and utilisation.

Results: CHLOE-EQ score was predictive of embryo utilisation (0.89±0.01: 0.90, 0.88, 0.88, 0.96), decision for transfer (AUC=0.75±0.12: 0.64, 0.72, 0.89, 0.81), ploidy (AUC=0.60) and clinical pregnancy (AUC=0.72).

CHLOE BLAST score was predictive of blastulation (0.88±0.02: 0.91, 0.87, 0.87, 0.92) and decision for transfer (0.86±0.08: 0.91, 0.9, 0.76, 0.74). CHLOE RANK was predictive of utilisation (0.88±0.01: 0.89, 0.92, 0.82, 0.81).

There was no significant difference in the efficacy of prediction between the different clinics for CHLOE EQ, CHLOE BLAST or CHLOE RANK (p>0.05).

Conclusion: CHLOE-EQ is consistently predictive of embryo viability across different clinics, suggesting that CHLOE-EQ could be a valuable biomarker to support clinical decisions regarding transfer, cryopreservation or discarding.

CHLOE-EQ Score: a novel biomarker of embryo viability

Cawood, Suzanne[1]; Vasilic, Mina[1]; Knight, Samantha[2]; Joshi, Raj[2]; Mahews, Rebecca[3]; Thompson, Andrew[4]; Mania, Anastasia[5];Sarris, Ippokras[5]; Zepeda, Alexa[6]; Bergelson, Noam[6]; Brualla, Adriana[6]; Hickman, Cristina[6]

[1]CRGH, United Kingdom ;
[2]Harley Street Ferlity Clinic, United Kingdom ;
[3]CRGW Plymouth, United Kingdom ;
[4]CRGW, United Kingdom ;
[5]Kings Ferlity, United Kingdom ;
[6]Fairlity, United Kingdom ;

Background

- Arficial Intelligence (AI) based tools have promised to improve embryo viability prediction
- There is a need to validate these promises before introducing AI technologies into clinical practice
- The objective was to validate the ability of CHLOE-EQ to predict embryo ulisation, decision for transfer, ploidy and clinical pregnancy

Methods

- CHLOE EQ score combines morphological and morphokinec AI algorithms, trained on over 100,000 embryo videos, to assist in embryo selection
- 8368 embryos were cultured in embryoscopes across four different clinics: clinic 1 (n=362), clinic 2 (n=5591), clinic 3 (n=653), clinic 4 (n=1762)
- Efficacy of prediction of CHLOE-EQ score for embryo utilisation, decision for transfer, ploidy and clinical pregnancy for each individual clinic was assessed using Binary logisc regression and quantified using the area under the curve (AUC)

Results

- CHLOE-EQ score was predictive of
  - embryo utilisation
  - decision for transfer
  - ploidy &
  - clinical pregnancy
- CHLOE BLAST score was predictive of
  - blastulation &
  - decision for transfer.
- CHLOE RANK was predictive of utilisation

		AUC				
		Overall	Clinic 1	Clinic2	Clinic 3	Clinic 4
CHLOE EQ	Embryo utilization	0.89 ±0.01	0.90	0.88	0.88	0.96
	Decision for transfer	0.75 ±0.12	0.64	0.72	0.89	0.81
	Ploidy			0.60		
	Clinical pregnancy			0.72		
CHLOE BLAST	Blastulation	0.88 ±0.02	0.91	0.87	0.87	0.92
	Decision for transfer prediction	0.86 ±0.08	0.91,	0.9	0.76	0.74
CHLOE RANK	Embryo utilization	0.88 ±0.01	0.89	0.92	0.82	0.81

- There was no significant difference in the efficacy of prediction between the different clinics for CHLOE EQ, CHLOE BLAST or CHLOE RANK (p>0.05)

Conclusion

CHLOE-EQ is consistently predictive of embryo viability across different clinics, suggesting that CHLOE-EQ could be a valuable biomarker to support clinical decisions regarding transfer, cryopreservation or discarding

Study 17: ESHRE 2023 – IVF London

Morphokinetic Goldilocks: identifying the optimal morphokinetic range (not too fast, and not too slow) to identify embryos with optimal chance of being euploid

Authors: Sareena Sharma; Zepeda, A.; Brualla, A.; Hickman, C.

Published by Human Reproduction

Study Question: Can CHLOE-EQ, an AI embryo assessment support tool, automatically identify the optimal time-range of morphokinetic events where chance of euploidy is maximized?

Study Answer: Embryos that are within the normal morphokinetic range have increased chances of being euploid compared to embryos developing at a pace outside the optimal range.

What is known already?: The introduction of time-lapse technologies in IVF has revealed quantitative and qualitative morphokinetic parameters that predict embryo viability (ESHRE Workshop group, 2020), but their assessment is time-consuming and subjective. Artificial Intelligence (AI) based tools, such as CHLOE-EQ (Fairtility), are ideally suited to automatically annotate morphokinetics as part of a range of tools to quantify embryo quality and detect abnormalities. There have been several attempts in the literature to predict ploidy with morphokinetics. We postulated that embryos that develop at a normal pace (not too fast and not too slow) would be more likely to be euploid.

Study design, size and duration: Retrospective case-controlled study of 1328 time-lapse videos collected in 2022 from IVF and ICSI embryos from a private single fertility clinic. 142 of those were biopsied and genetically tested by NGS. The embryos were automatically assessed by CHLOE-EQ (Fairtility), an AI embryologist support tool.

Participants/materials, setting, methods: Time-lapse videos were automatically annotated using CHLOE-EQ(Fairtility) for morphokinetics, number of pronucleates and anomalies. The frequency distribution for each morphokinetic parameter was compared between euploid and aneuploid embryos to establish ranges for optimal euploidy rate. The ranges between optimal (maximum euploidy rate) and sub-optimal (outside optimal range) were compared (t-test). Efficacy of blastocyst, utilisation and ploidy prediction by CHLOE blast score at 68hpi and CHLOE-EQ score were assessed using the area under the curve (AUC).

Main Results and the role of chance: For each morphokinetic event, an optimal range for identification of euploids was identified (tPNf:21.37-25.78; t2:24.01-28.6; t3:34.07-39.20; t4:35.5-40.64; t5:46.12-53.92; t6:48.77-55.63; t7:50.22-57.45; t8:52-60.21; t9:67.35-75.55; tM:78.49-89.08; tsB:92.20-102.39; tB:99.54-109.83; tEB:106.42-120.38). Optimal range of euploid embryos was smaller than the total range for all embryos ($p<0.001$): tPNf (0.27vs152.36), t2(5.52vs158.96), t3(22.7vs159.29), t4(30.38vs167.96), t5(32.02vs168.29), t6(35.58vs155.44), t7(41.04vs157.65), t8(41.37vs158.06), t9(48.85vs158.39), tM(56.4vs163.89), tSB(84.74vs173.26), tB(93.01vs168.62); tEB(95.96vs164). Embryos with optimal ranges across morphokinetic events had a higher euploidy rate than embryos with suboptimal ranges [50% (11/20), 35.35% (35/99), NS].

CHLOE-BLAST Score at 68hpi was predictive of blastulation (AUC=0.86), whilst CHLOE-EQ Score was predictive of utilisation (AUC 0.88) and euploidy (AUC=0.64) and CHLOE Ranking was predictive of utilisation (AUC=0.91) and selection for transfer (AUC=0.80).

Limitations: This is a single-center, retrospective study, where only the blastocysts deemed suitable for biopsy were assessed for ploidy. Therefore, the ploidy rate of non-blastocysts or inferior quality embryos is unknown, creating a potential bias regarding the lower cutoff threshold for optimal ranges.

Wider implications: CHLOE-EQ can identify the optimal morphokinetic time range to maximise the chance of an embryo being euploid, a potentially valuable biomarker for embryo assessment, selection, managing patients expectations down to individual embryos, and helping reduce the chance of viable embryos being discarded.

Study 18: ESHRE 2023 – Instituto Bernabeu

The first study to assess the clinical efficacy of CHLOE-EQ on the assessment of embryo viability of embryos cultured in a GERI time-lapse incubator

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Published by Human Reproduction

Study Question: Can an automatic AI scoring system predict ploidy, live birth and utilization? Are there differences in AI scoring between donor and own gametes?

Study Answer: CHLOE-EQ Score is directly associated with oocyte quality, ploidy, utilization, live birth, embryo quality, DUCs, blastulation and selection for transfer.

What is known already?: The integration of AI algorithms, such as CHLOE-EQ, into different Time-lapse systems requires clinical and biological validation. Geri Time-lapse videos have given embryologists more insight into embryo development. Analyzing this information manually requires time and introduces risk of error. To tackle this issue, AI solutions like CHLOE-EQ (Fairtility) can be used to automatically assess video datapoints. CHLOE-EQ provides an embryo quality score that has been shown to predict embryo viability and ploidy, providing clarity on the underlying biological factors. Before introducing AI tools in clinical practice, it is crucial to confirm their efficacy and validate with clinical data.

Study design, size and duration: A retrospective cohort analysis was conducted at a private clinic in Spain from April 2021 to November 2022, involving the review of 3196 Geri time-lapse videos with a subset of known ploidy and live birth outcomes. The correlation of CHLOE-EQ score with ASEBIR clinic grading was evaluated. As well as with DUCs, oocyte quality, sperm source, blastulation, utilization, selection for transfer, ploidy and live birth.

Participants/materials, setting, methods: Geri time-lapse videos were automatically analyzed by CHLOE-EQ (Fairtility). CHLOE-EQ score was assessed in relation to laboratory (ploidy, clinic ASEBIR embryo scoring, utilization, selection for transfer) and clinical outcomes (live birth), as well as between own vs donor gametes (own eggs >40y vs donor eggs and testicular sperm vs donor sperm) using descriptive statistics and t-test. The accuracy of prediction was measured using binary logistic regression (AUC).

Main Results and the role of chance: CHLOE-EQ score was positively correlated with ASEBIR embryo quality (A:8.7±1.9, n=349 >B:6.8±2.9, n=470 > C: 5.1±3.0, n=124 > D:1.3±2.1,n=751; p<0.05). Non-DUCs had higher CHLOE-EQ Score than DUCs (5.3±3.8,n=1798 vs 1.9±0.38,n=643,p<0.001). CHLOE-EQ Score was unaffected by the quality of the sperm sample, with similar CHLOE-EQ scores between donor sperm and testicular derived sperm (4.1±3.9,n=335 vs 3.4±4.2,n=56, respectively, NS).

Embryos that blastulated (yes vs no: 5.4±3.7,n=1996 vs 0.6±2.1,n=309, p<0.001), were utilized (7.4±0.28,n=911, vs 1.0±2.1, n=1309, p<0.001), selected for transfer (8.7±2.4,n=153 vs 3.3±3.7, n=2067, p<0.001), were euploid (7.5±2.5,n=72 vs 6.3±3,n=152, p=0.001) and resulted in live births (4.4±4.1, n=332 vs 3.8±4, n=499, p=0.02) had a higher CHLOE-EQ score than embryos that did not.

CHLOE-EQ Score is higher in embryos derived from oocytes from donors than own eggs, suggesting that oocyte quality affects CHLOE-EQ score (4.0±4, n=1189 vs 2.7±3.4, n=356).

CHLOE-EQ Score is predictive of utilization (AUC=0.95,n=2220,baseline=41%,p<0.001), euploidy (AUC=0.63,n=224,baseline=32.1%,p=0.003), blastulation (AUC=0.94, n=2305, baseline=86.6%, p<0.001) and selection for transfer (AUC=0.89, n=2220, baseline=41%,p<0.001).

Limitations: This is a retrospective single-center study in which embryos for transfer were selected by human embryologists, and forms part of program to validate the responsible integration of AI into clinical practice in each individual clinic.

Wider implications: This is the first study presenting the efficacy of prediction of CHLOE-EQ with GERI data. AI tools have the potential to improve consistency, efficiency, and accuracy of embryo assessment and selection. CHLOE-EQ predicts through quantitative and qualitative morphological and morphokinetics information, resulting in more personalized care for each individual embryo.

Study 19: ESHRE 2023 – Fertility FIV

Abnormal Oocytes are more likely to lead to abnormal embryo divisions (Direct Unequal Cleavage, DUC), but do not compromise embryo quality as assessed using CHLOE-EQ score

Authors: 1 Borges, E.; Setti, A.; Braga, D.; Verguiro, T. ; 3 Zepeda, A.; Brualla, A.; Hickman, C. 1 Fertility FIV, Brazil 2 Embriologica, Brazil 3 Fairtility, Israel

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Study question: Do oocyte dysmorphisms lead to abnormal embryo divisions and compromised embryo quality?

Study answer: Oocyte cytoplasmic abnormalities (granularity, Smooth Endoplasmic Reticulum,SER) did not affect CHLOE-EQ score; whilst zona abnormalities (thickness and unevenness) and SER tend to lead to DUCs.

What is known already? Oocyte dysmorphisms include extracytoplasmic (zona pellucida (ZP) evenness and thickness) and cytoplasmic abnormalities (SERs, inclusions, darkness, granularity). The impact of these abnormalities on embryo development and viability as reported in the literature is contradictory. CHLOE-EQ score is an Artificial Intelligence (AI) based algorithm designed to support embryologists in assessing embryo viability, and has previously been demonstrated to automatically detect embryo development anomalies (such as DUCs), to be predictive of blastulation, utilisation, selection for transfer, ploidy, implantation and live birth. Therefore, CHLOE-EQ is a metric of embryo viability. The impact of oocyte dysmorphisms on CHLOE-EQ and DUCs is poorly understood.

Study design, size and duration: Retrospective cohort analysis of 742 embryo time-lapse videos, cultured at a private fertility clinic between June and July 2022.

Participants/materials, setting, methods: The clinic provided annotations on extracytoplasmic abnormalities (ZP thickness and uniformity) and cytoplasmic abnormalities (SERs, inclusions, darkness, granularity). CHLOE-EQ (Fairtility) automatically annotated morphokinetics and DUCs and further quantified embryo viability scores (CHLOE-EQ and Blast Score).

Main Results and the role of chance: CHLOE-EQ score was not affected by the oocyte having cytoplasmic abnormalities (no vs yes: 4.2±4, n=122vs4.1±4,n=359,NS): dark (4.1±4,n=476vs3.1±4,n=5,NS), granular (4.1±4,n=179vs4.1±4,n=302,NS), SER (4.1±4,n=455vs3.8±4,n=26, NS), inclusion (4.1±4,n=430vs4.1±4,n=51,NS); or ZP abnormalities (overall (4.2±4,n=379vs3.7±4,n=102,NS), non-uniformity (4.1±4,n=409vs4.2±4,n=72,NS), thick ZP (4.2±4,n=457vs2.8±4,n=24,NS), thin ZP(4.1±4,n=475vs2.1±4,n=6,NS).

DUC embryos were two times more likely to be derived from oocytes with thick ZP (9/98, 9%oocytes) than oocytes without thick ZP (15/383, 3.9%, p=0.03). DUCs were more likely to have a non-uniform ZP compared to non-DUCs (DUCs: 7%(7/98) vs Non-DUCs: 17%(65/383), p=0.015). DUCs were not associated with the following oocyte cytoplasmic dysmorphias: SER (DUC vs Non-DUCs: 6/98,6% vs 20/388,5%,NS), dark (0/98 vs 5/383, NS), granular (61/98 vs 241vs383, NS), inclusions (11/98 vs 40/383, NS). DUCs had lower blastulation rate than non-DUCs (DUC:1.8%(2/113) vs Non-DUCs:77%(298/389), p<0.001). DUCs were 4-fold less likely to be multinucleated at the 2 cell stage than non-DUCs (DUC: 7%(2/29)vsNon-DUCs: 30%(91/305), p=0.03). DUCs were 7-fold more likely to be multinucleated at the 4 cell stage than non-DUCs (DUC: 7%(2/29)vs Non-DUCs:1%(3/302), p=0.06). Patient age was not associated with DUCs (DUCs: 36.9±4 vs non-DUCs:37.1±4, NS).

Limitations: This was a retrospective-single clinic study. Causality is not determined.

Wider implications: Given the growing evidence that DUCs have compromised viability, it is important to understand the biology of how DUCs are connected to oocyte quality. Using AI to detect DUCs to avoid critical information being missed during embryo assessment can assist embryologists in maximising their efficacy of embryo selection.

Study 20: ESHRE 2023 – GeneraLife

Comprehensive artificial intelligence-powered investigation of blastocyst expansion dynamics: associations with competence

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Study question: Are blastocyst expansion dynamics from time of starting blastulation (tSB) to time of biopsy (t-biopsy) indicative of embryo competence?

Summary answer: Early expansion dynamics across 5hours after tB, embryo-proper area (emb-A), zona-pellucida-area (zp-A), ZP-thickness (zp-T) at t-biopsy and their t-biopsy/tB ratios are associated with competence.

What is known already: Blastocyst expansion is the very first morphogenetic event common to several species. Time-lapse-technology (TLT) implementation in IVF allowed deeper understanding of blastocyst expansion process. Some studies leveraged TLT and Artificial-Intelligence to investigate blastocyst expansion timings and dynamics for their association with embryo competence. Huang's group, in particular, designed a quantitative standard expansion assay (qSEA) showing promising results. However, data about qSEA reproducibility are missing. Here we comprehensively investigated the expansion processes between tSB and t-biopsy through Artificial-Intelligence, and adapted the qSEA to our setting that encompasses PGT-A without day3-hatching and single-euploid-blastocyst-transfer.

Study design, size, duration: Retrospective study including 2184 blastocysts cultured in EmbryoScope during 786 PGT-A cycles conducted across 2013-2020. Videos were analyzed through an Artificial-Intelligence-powered tool (CHLOE™, Fairtility). The software automatically extracted timings in hours-post-insemination and measures as proportions of video frames occupied by each feature under investigation (single pixel=300µm; wells' area=90,000µm2) recorded every 30min from tSB. These data were tested for their association with euploidy and live-birth after 548 euploid transfers via multivariate regressions.

Participants/materials, setting, methods: ICSI, trophectoderm biopsy on fully-expanded blastocysts without day3 zp drilling, and qPCR/NGS to assess full-chromosome non-mosaic aneuploidies were performed. The timings assessed were tSB, tB, tEB and t-biopsy (=end of video). At these timings and every 30min across 5hours after tSB the software recorded the following measures emb-A, zp-A, zp-T, inner-cell-mass area (ICM-A), and ICM-to-trophectoderm ratio. Also increase/decrease ratios for all measures between timings were assessed. Putative confounders (e.g., maternal age, blastocyst quality) were considered.

Main results and the role of chance: Larger emb-A and zp-A at t-biopsy and zp-T at both tEB and t-biopsy were associated with euploidy. Similarly, the ratios zp-A at t-biopsy/zp-A at both tB and tEB highlighted a larger expansion among euploid blastocysts versus aneuploid. All these differences were confirmed when adjusting for maternal age, morphological quality and tB ($p<0.01$). zp-A t-biopsy/tB ratio (aneuploid:+68.8% versus euploid:+79.9%) showed a more relevant association than final zp-A at t-biopsy per se (24082±5763 versus 25438±5969µm2). The ratios zp-T at t-biopsy/zp-T at both tB and tEB were also significantly associated with euploidy, even when adjusting for confounders ($p<0.01$). However, in this case zp-T at t-biopsy (8.1±3.2 versus 7.1±2.7µm) per se showed a stronger association than zp-T t-biopsy/tB ratio (-50% versus -55%). ICM-A and ICM-to-trophectoderm ratio showed no association with euploidy. All areas, ratios, and measures showed no association with LBs (N=233) among 548 euploid transfers. The qSEA every 30min from tB outlined different early expansion dynamics between euploid and aneuploid embryos, with the former expanding more (larger areas and thinner zp) and sooner. The differences in the two groups became significant already after 2.5-3 hours, due to a rather constant expansion rate in both groups, but faster among euploid blastocysts. The same significant trend was reported for euploid blastocysts resulting in a LB versus not.

Limitations, reasons for caution: Retrospective single-center study. Previous studies on qSEA were based on 10 measurements every hour from tB, instead of 10 measurements every 30min. To properly assess the association between expansion dynamics and timings with LB, more transfers are required. To outline a predictive power, instead, a prospective randomized design is warranted.

Wider implications of the findings: Blastocyst expansion dynamics, timings and ratios measured through Artificial-Intelligence, already during the 5hours following tB, provide objective quantitative data associated with embryo competence. qSEA is a promising clinical strategy, user-friendly and easily applicable, that deserves further appraisal. Basic research on the mechanisms that govern blastocyst expansion processes is warranted.

Study 21: Fairtility - CRGH

Green (normal), amber (reduced viability) and red (severely reduced viability): a novel simple traffic-light classification for morphokinetics associated with pregnancy outcome and euploidy

Authors: Mina Vasilic, Alexa Zepeda, Adriana Brualla, Noam Bergelson, Cristina Hickman

Study Question: What is the clinical significance of the morphokinetic traffic light categorisation on embryo viability?

Study Answer: Embryos selected for transfer, euploid embryos and embryos that lead to pregnancy tend to be classified as green in this novel traffic light classification using CHLOE-EQ.

What is known already? Time-lapse (TL) incubators have provided embryologists with more information to determine the fate of embryos, leading to varying clinical practices between clinics in prioritizing this information. CHLOE-EQ is an AI-embryologist support tool, that automatically provides CHLOE-EQ Score, an embryo viability score, that analyses valuable data points of TL videos and provide implantation prediction. CHLOE-EQ uses a novel traffic light categorization for morphokinetics that allows embryologists to quickly see which embryos are developing normally at a glance. The objective of this study was to assess the traffic light system in a real clinical setting.

Study design, size and duration: 147 embryos with known clinical outcomes were assessed to compare CHLOE-EQ score among pregnant and not pregnant patients. CHLOE-EQ embryoviewer provides cut-offs for each morphokinetic event (red=severely reduced viability, amber=reduced viability and green=normal). The objective of the study was to validate these cut-offs against pregnancy outcome. This validation was also performed in another study with 566 embryos with known ploidy and CHLOE-EQ Score.

Participants/materials, setting, methods: CHLOE-EQ score was assessed in relation to clinical pregnancy and ploidy using descriptive statistics and t-test. The prediction of clinical and ongoing pregnancy was measured using binary logistic regression (AUC). CHLOE EQ Score was classified and validated as: High CHLOE-EQ ≥8/10 and low Score <8/10. Morphokinetic events from tPNf to tEB were analysed; and their correlation with clinical pregnancy and ploidy assessed. Only embryos that had at least 7 morphokinetic annotations were included.

Main Results and the role of chance: Within embryos selected for transfer, CHLOE-EQ Score was higher for embryos leading to a pregnancy compared to non-pregnancy [7.66±2.26 (n=45) vs 6.44±2.86 (n=68), p<0.01]. Patients with high CHLOE-EQ score had higher rates of clinical pregnancy, although this difference did not reach significance [49% (26/53) vs 32.2% (19/59), NS]. Patient age did not differ among high and low CHLOE-EQ score [35.98±3.79 vs 36.68±3.87, p=0.33]. CHLOE-EQ Score was directly correlated with embryo euploidy (euploid: 5.34±2.73, n=252 vs aneuploid: 4.41±2.86, n=314, p<0.001)

All transferred embryos had mostly green morphokinetics (120/120), regardless of clinical outcome. Embryos that were suitable for biopsy had mostly green morphokinetic events (97.1%, 583/600). Euploid embryos had mostly green morphokinetics (96.9% 252/260). Embryos that were discarded had mostly red morphokinetics.

CHLOE-EQ traffic light categorisation is predictive of clinical and ongoing pregnancy (AUC=0.63, n=113, baseline=40%, p<0.02; AUC=0.66, n=113, baseline=38%, p=0.005) and euploidy (AUC=0.60, n=566, baseline=44.5%, p<0.001)

Limitations: This study is conducted at a single center using retrospective data and embryos selected for transfer by human embryologists.

Wider implications: Traffic light system to classify embryos based on morphokinetics is simple and easily understandable, irrespective of embryologist seniority or experience with time-lapse, allowing embryologists to see at a glance whether embryos are developing normally, saving time and mitigating the risk of important embryo anomalies being missed when deciding embryo fate.

Study 22: ESHRE 2023 - Next Fertility

Morphokinetics and blastocyst biomarkers analysis and comparison of triamniotic monochorionic triplets using Artificial Intelligence after fresh single embryo transfer.

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Published by Human Reproduction

Study question: Can AI reduce the twin and triplet monozygotic pregnancies rate, following elective single embryo transfer (eSET)?

Summary answer: AI can automatically annotate morphokinetic developments and other biomarkers. Embryos leading multiple monozygotic pregnancy have slower cell divisions and larger ICM than monoamniotic embryos.

What is known already: Monozygotic twin (MZT) and monozygotic triplet (MTP) pregnancies are a rare phenomenon in spontaneous pregnancies, but the incidence increases significantly when pregnancies are achieved by assisted reproductive technology (ART); 0.4% vs. 1.56% MZTs, and 0.004% vs. 0.048% MTPs. It is unclear what mechanisms cause an embryo to split into two or three, although several have been proposed such as culture to blastocyst, decompacting ICMs, frozen-warmed embryo transfers, assisted hatching and even ICSI. In order to study this split phenomenon, time-lapse imaging has been used to discover any signs of embryo division.

Study design, size, duration: This is a retrospective assessment of a total of 8 embryos from 2018 to 2022 that led to single pregnancy (n=4), twin pregnancy (n=3) and triple pregnancy (n=1) following a fresh single embryo transfer. All embryos were inseminated using ICSI technique, and assisted hatching was performed before fresh transfer.

Participants/materials, setting, methods: Using CHLOE (Fairtility, Tel Aviv) we automatically assessed the morphokinetics, blastocyst biomarkers and scores. Singletons and multiple pregnancy were compared in terms of morphokinetics (t-test) and surface area of ICM, ICM diameter, ICM area/embryo area ratio, ICM shape and CHLOE embryo quality score were compared using ANOVA test.

Main results and the role of chance: Embryos that led to multiple pregnancies had slower embryo development than embryos that led to singletons (single vs multiple: t2: 22.1+-2 vs 25.2+-2, p=0.04; t3: 32.56+-2.65 vs 36.98 +-1.48, p=0.01; t5: 44.09+-4.84 vs 50.37+-0.69, p=0.02; t6: 47.26+-3.87 vs 53.59+-2.40, p=0.01; t7: 48.76+-4.04 vs 55.15+-3, p=0.02; t8: 50.18+-4.27 vs 57.55+-1.5, p=0.008; t9: 63.27+-3.76 vs 73.04+-5.33, p=0.03). Embryos leading to triplets were slower than twins which were in turn slower than singletons (single vs twins vs triplets: t4: 33.86+-3.41 vs 37.69+-1.61 vs 48.95, p=0.007; t8: 50.18+-4.27 vs 58.07+-1.29 vs 55.96, p=0.04; t9: 63.27+-3.76 vs 71.23+-4.81 vs 78.44, p=0.01).

Embryos that led to multiple pregnancies had a larger ICM to embryo surface area ratio (single vs multiple: 0.14+-0.08 vs 0.27+-0.06, p=0.04) and smaller embryo diameter (single vs multiple: 177.2+-16.5 vs 138.15+-8.25, p=0.003).

We didn't find statistically significant differences between the groups in CHLOE EQ score (single vs multiple: 0.97 vs 0.76, p=0.36), Blast score (single vs multiple: 0.87+-0.06 vs 0.78+-0.13, p=0.26), CHLOE Rank, Trophectoderm quality, ICM Area (single vs multiple: 3629+-1361 vs 4151 +- 569, p=0.48) and ICM shape (single vs multiple: 1.64+-0.45 vs 1.27+-0.12, p=0.15).

Limitations, reasons for caution: The main limitation of this study is the number of cases included in the study, as we studied one triplet, 3 twins and 4 single pregnancies.

Wider implications of the findings: This might be the first time that AI has been used to analyse the behaviour of embryos that resulted in multiple pregnancy. The transfer of a slowly dividing embryo and / or with a large ICM could result in a multiple pregnancy.

Study 23: ESHRE 2023 – Juana Crespo

Not all DUCs are the same: Impact of DUC type on the blastulation, utilization and ploidy

Authors: M. Lozano, A. Brualla, A. Zepeda, C. Hickman, N. Bergelson, M. Escriba, M. Benavent, A. Garcia, J. Crespo, J. Teruel

Published by Human Reproduction

Study Question: We have identified six categories of DUCs as identified automatically by CHLOE-EQ. Do these DUC categories differ in embryo competency?

Summary Answer: DUC-1, Major chaotic DUC and Fragmented DUC have compromised blastulation, utilization and ploidy, compared to DUC2, minor chaotic DUC and not-direct DUC.

What is known already: CHLOE-EQ (Fairtility, an AI-based support tool) automatically annotates embryo morphokinetics and identifies embryo division anomalies, such as Direct Unequal Cleavage(DUCs). DUCs are defined as less than 5 hours from two cells to three cells. DUCs have been associated with being severely compromised, with lower chance of blastulating, being utilized, euploid, implanting or leading to live birth. In some clinics, DUCs are automatically discarded. Other clinics reported euploids and live births from DUC embryos, raising questions as to whether there are different types of DUCs with different competencies. In this study, we identified 6 types of DUCs and assessed their viability.

Study design, size, duration: Retrospective cohort study that took place between March to July 2022 at a private fertility clinic in Spain. This study included 1032 time-lapse videos of embryos with Direct unequal cleavage (DUCs) as identified by CHLOE-EQ. CHLOE-EQ defines DUCs as (t3-t2)<5 hours. DUCS annotated by CHLOE-EQ were classified into 6 types by embryologists.

Participants/materials, setting methods: DUC1(direct division from the 1-cell to 3 or more, without a visible 2-cell stage); DUC2 (Direct Division from 2-cells where either cell divides directly from one to three cells); Minor Chaotic DUC (asynchronous irregular divisions: cells still countable);

Major chaotic DUC (asynchronous irregular divisions: cells/fragments are too chaotic to count); Fragmented DUC1 (resembles a DUC1, but the third 'cell' is a fragment); Not direct DUC (quick division from 1 cell to 2cells to 3cells).

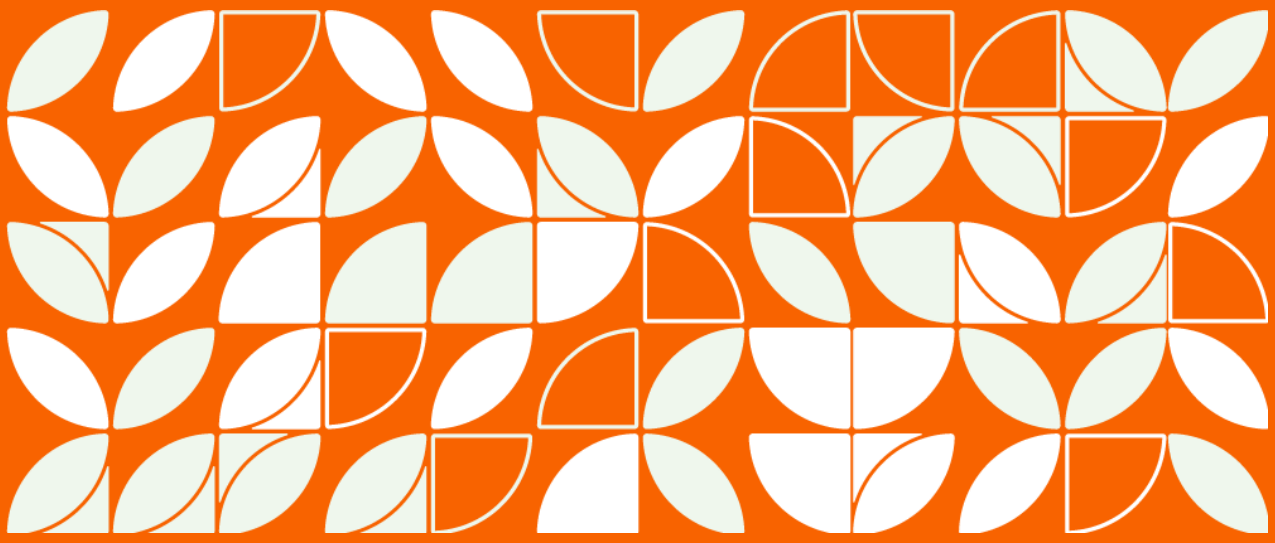
Main results and the role of chance: CHLOE-EQ correctly identified 97.4%(875/898) of 2PN DUCs, based on the definition of DUC (t3-t2<5). Most DUCs annotated by CHLOE-EQ, were classified by embryologists as minor chaotic [25%(231/921)], followed by DUC 1 [20.3%(187/921)], Not direct DUCs [18.1%(167/921)], major chaotic DUCs [14.6%(135/921)], DUC 2 [14%(129/921)], and lastly, fragmented DUC1 [7.8%(72/921)]. The average t3-t2 time did not differ between the six groups (1.6,1.5,1.5,1.6,1.5,1.6, respectively, p>0.05). Among DUC embryos, Minor chaotic DUCs [85%(110/129)] and Not direct DUCs [66.9%(109/163)] and DUC2 [57%(73/128)] had similar blastulation rates (p>0.05) and utilization rates [DUC2:44.2% (57/129), Minor Chaotics: 37.7%(87/231), Not Direct DUCs: 56.3%(94/167), p>0.05]. These three groups had a higher blastulation rate than DUC1 [20.1% (37/184)], Major chaotic [21.6% (29/134)], Fragmented DUC1 [19.7% (14/71), p<0.05)] and a higher utilization rate than DUC1 [11.8% (22/187)], Major chaotic [14% (19/135)], Fragmented DUC1 [11.1%(8/72), p<0.05)]. Type of DUC was not affected by Age(p>0.05). Four live births from single embryo transfer of DUC embryos were recorded in this dataset.

Limitation, reasons for caution: DUCs were assessed by a single embryologist, further studies will assess intra and inter-operator variation in DUC classification across various clinics. It was particularly challenging to differentiate between fragments and cells. This study is ongoing to further understand implication of DUC types on clinical outcome.

Wider implication of the findings: Given that different DUC types have varied competency levels, the results of this study encourage embryologists not to discard DUC embryos simply because they are DUCs. It is important to assess the type of DUC when determining the fate of the embryo and when managing the expectation of affected patients.

Prediction

Blastulation
Implantation
Ploidy prediction



Study 24: ESHRE 2022 – Memorial

Simplifying the complexity of time-lapse decisions with AI: CHLOE (Fairtility) can automatically annotate morphokinetics and predict blastulation (at 30hpi), pregnancy and ongoing clinical pregnancy

H.K. Yelke, G. Ozkara, B. Yuksel, Y. Kumtepe Colakoglu, M. Aygun, A. Brualla, I. Erlich, C. Hickman, S. Selimoglu, B. Okten, S. Kahraman.

Published by Human Reproduction

Clinic: Memorial (Turkey)

Question: What is CHLOE's (Fairtility) efficacy of prediction of blastulation (at 30hpi), pregnancy and ongoing clinical pregnancy following single embryo transfer (SET)?

Answer: CHLOE(Fairtility) algorithms are effective predictors of blastulation, ploidy, pregnancy, implantation and ongoing clinical pregnancy.

What is known already? There are differences in clinical practice between clinics.

Challenges:

- Interoperator inconsistencies and time-consuming manual annotations time-lapse videos.
- AI-based uses predictors to predict blastulation and implantation, whilst providing transparency to which biological characteristics have led to that determination.
- There is a need to validate AI tools before their incorporation into clinical practice.

Study design, size, duration: Single centre study that took place between 2017-2020, at a private fertility clinic in Turkey. This was a retrospective cohort analysis that reviewed 6748 time-lapse videos containing 5392 cleaved embryos, 3763 blastocysts, 877 single embryo transfers (SET) with known ongoing pregnancy outcome, 306 euploid SETs and 25 mosaic embryo SETs with known ongoing pregnancy outcome. CHLOE Blastocyst Score and CHLOE EQ score efficacy of prediction of clinical outcomes was quantified using the metric AUC.

Participants/ materials, setting, methods: Time-lapse videos were assessed using CHLOE (Fairtility), an AI based tool, to quantify quantitative and qualitative morphokinetics (including automated annotations of tPNa,tPNf,t2,t3,t4,t5,t6,t7,t8,t9,tM,tSB,tB,tEB), CHLOE EQ score and CHLOE blastocyst score (calculated at 30hpi) relative to laboratory (ploidy results, blastulation) and clinical outcomes (biochemical, clinical and ongoing clinical pregnancy) following overall SET and SET of non-PGTA embryos. Binary logistic regression was used to calculate area under the curve (AUC) as a measure of prediction efficacy.

Main results and the role of chance:

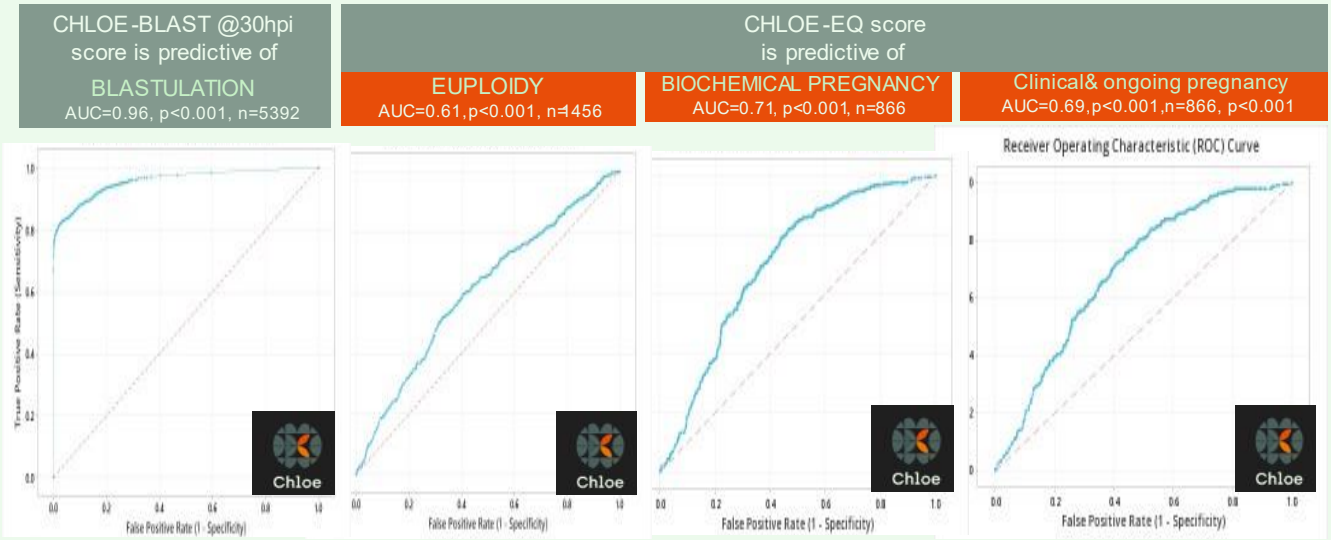
- Blastulation score assessment of cleaved embryos was predictive of blastulation (AUC=0.96, baseline=70% n=5392, p<0.001, Figure 1).
- Following PGT-A, CHLOE EQ Score was predictive of euploids (AUC=0.61, baseline=34%, n=1456, p<0.001, Figure 2), despite the fact the algorithm was not trained on prediction of ploidy (EUPLOIDS FAIL TO IMPLANT). Embryos classified as mosaics (AUC=0.5, baseline=19%, n=1456, p>0.05).
- Following SET, CHLOE EQ score was predictive of biochemical (Figure 3), clinical and ongoing pregnancy rate (Table 1, Figure 4).
- Following SET of non-PGT-A embryos, CHLOE EQ score decreased with increasing patient age (p<0.001), but the difference in mean EQ score between positive and negative ongoing pregnancy was not affected by age (NS). The type of aneuploidy (monosomy, trisomy, segmental) did not affect EQ score or Blastulation score (p>0.05).
- CHLOE EQ score prediction of outcome was higher for non-PGT-A transfers than overall transfers for biochemical, Clinical and ongoing pregnancy (Table 1), despite lower baselines.

Limitations, reasons for caution: This is a single centre study, using retrospective data where embryos were selected for transfer by human embryologists. The study is part of a larger framework for responsible incorporation of AI into clinical practice through robust validation.

Wider implications of the findings: AI-based tools have the potential of increasing consistency, efficiency and efficacy of embryo selection. The additional information on quantitative and qualitative morphokinetics that AI tools such as CHLOE provide, bring transparency to the prediction, allowing for improvement in personalisation of care down to each individual embr

Table 1. CHLOE EQ Score prediction of Biochemical, clinical and ongoing pregnancy.

CHLOE-EQ prediction of		AUC	Baseline	N	
Biochemical Pregnancy	PGTA	0.73	33%	535	P<0.001
	Overall	0.71	49%	866	P<0.001
Clinical & Ongoing Pregnancy	Non-PGTA	0.76	24%	535	P<0.001
	Overall	0.69	37%	866	P<0.001



Study 25: ESHRE 2022 - IASO

Challenges with comparing different commercially available Artificial Intelligence (AI) systems on the same data set of time-lapse selected euploid blastocysts

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Published by Human Reproduction

Clinic: IASO (Greece).

Study question: To identify challenges in choosing a robust AI following comparative validation with data already pre-selected with established embryos selection tools: blastulation, morphology, time-lapse, PGTA.

Summary answer: Challenges included: bias; assessment against outcomes AI models were not trained on; performance metrics prioritisation; statistical methodology; continuous data cutoffs for binary clinical decision making.

What is known already:

- AI is commercially available to be incorporated into routine practice to support embryo selection decision-making.
  Different clinical practices and demographics are used to train AI models.
- Fertility professionals require robust methods of validation to responsibly implement AI-based tools.
- Unbiased and robust frameworks for comparing AI systems in the same dataset are needed.
- Validating AI in a dataset of time-lapse selected euploid blastocysts using all the current methods of embryo selection currently available is the toughest assessment possible and has not previously been performed.

Study design, size, duration:This study uses a retrospectively timelapse dataset collected from 2018-2021 at a single private fertility clinic. The dataset included 915 blastocysts which underwent PGTA (913 results: 381 euploids, 528 aneuploids, 4 mosaics) and 46 euploids transferred with known bhcg and ongoing clinical outcome (of which 40 resulted to live birth). Following a prospective, comparative, observational, cohort study design, blastocysts were blindly scored using the CHLOE(FAIRTILITY) and another commercially available AI system, referred to as 'AI-2'.

Participants/materials, setting, methods:Patients aged 24-47years (average 35.4). Blastocysts selected for biopsy and transfer based on morphology and KIDScore (Vitrolife). Both AI systems were tested in the data set blindly, without any training. Correlation Regression analysis assessed correlation with KIDSCORE and relative to each AI system. Efficacy of prediction (using metrics AUC, Accuracy, Sensitivity, Specificity and Informedness) of outcomes (ploidy, biochemical and clinical pregnancy) were assessed for both AI models (CHLOEvsAI-2) by two independent statisticians to establish significance.

Main results and the role of chance:

Figure 1. CHLOE EQ Score prediction of ploidy.

- Regression analysis demonstrated no correlation between KIDSCORE and AI-2 or between CHLOE(FAIRTILITY) and AI-2. CHLOE(FAIRTILITY) correlated with KIDSCORE (Table 1).
- AI-2 was not predictive of ploidy (Euploids vs Aneuploids+mosaic: AUC=0.5,p=0.6). CHLOE(Fairtility) was predictive of ploidy(AUC=0.66,p<0.001).
- Neither AI-2 or CHLOE(Fairtility) predicted which embryo the human embryologist prioritised for transfer. CHLOE(Fairtility) was more specific than AI-2 for predicting selection for transfer and ploidy, and they were equally as sensitive.
- There was no difference detected in efficacy of prediction of biochemical and ongoing clinical pregnancy (Table 2) by AI-2 or CHLOE.
- CHLOE(Fairtility) was more sensitive, and less specific than AI-2 for predicting biochemical pregnancy and more sensitive but equally as specific for predicting clinical pregnancy.
- Informedness was positive for both CHLOE(Fairtility) and AI-2 in predicting all outcomes assessed. Informedness was greater for AI-2 for predicting morphology(AI-2vsCHLOE:0.16vs0.31,p<0.05), transfer, ploidy and equivalent for predicting biochemical and clinical pregnancy (Table 2).

Limitations, reasons for caution: In this single clinic study, both algorithms were assessed against outcomes (live birth following transfer of time-lapse cultured euploid blastocysts) for which they were not trained on: AI-2(designed for ploidy prediction) and CHLOE(FAIRTILITY, implantation prediction of non PGTA embryos) and no clinic data was used for training.

Wider implications of the findings: The only way to decide which AI model is more useful is by a direct comparison of two or more models on the same dataset with same outcomes and metrics, as recommended by TRIPOD. To date, this is the first publication comparing multiple commercial AI models on the same dataset.

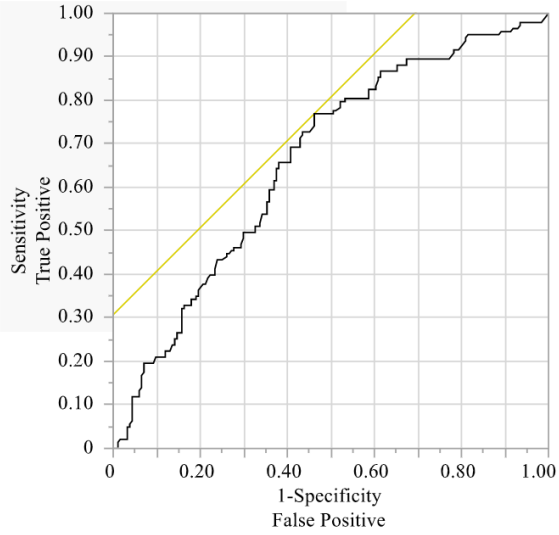


Table 1. Correlation between KIDScore, AI-2 and CHLOE for Prediction of ploidy

Correlation	Prediction of ploidy
KIDSCORE vs AI-2	r2=0.3%,p=0.5
AI-2 vs CHLOE	r2=0.03%,p=0.9
CHLOE vs KIDSCORE	r2=29%,p<0.001

Table 2. AI-2 vs CHLOE for prediction of ploidy, embryo transfer, biochemical pregnancy, ongoing and clinical pregnancy.

	Prediction of ploidy	Embryo transfer	Prediction of biochemical	Prediction of ongoing and clinical pregnancy
AI-2 vs CHLOE	specificity/sensitivity 0.54/0.77vs0.23/0.87, p<0.05/NS Informedness: 0.10vs0.31,p<0.05	accuracy:0.31vs0.49, p<0.00001 specificity/sensitivity 0.44/0.80vs0.17/0.93, p<0.05 Informedness: 0.11vs0.24,p<0.05	accuracy:0.52vs0.67,NS specificity/sensitivity 0.36/0.81vs0.86/0.38, p<0.05 Informedness: 0.23vs0.17,NS	accuracy:0.53vs0.78,NS specificity/sensitivity 0.33/0.88vs0.83/0.46, p<0.05 Informedness: 0.29vs0.22,NS

Study 26: ESHRE 2022 - CRGH

Impact of Direct Unequal Cleavage (DUC) on embryo development, blastocyst formation and ploidy - artificial intelligence (AI) analysis.

Authors: A. Florek, R. Odia, S. Theodorou, M. Duran, W. Saab, V. Seshadri, P. Serhal, C. Hickman, A. Brualla Mora, R. Derrick,M. Gaunt.

Published by Human Reproduction

Clinic: CRGH (United Kingdom)

Question: Do DUCs significantly impact embryo development? In particular, morphokinetics, grading, and Pre-implantation Genetic Testing for Aneuploidy (PGT-A) outcome? Is this analysis corroborated by artificial intelligence?

Answer: DUC embryos develop slower, have lower rates of blastulation and lower CHLOE (Fairtility) scores for blastulation and implantation. However, occasionally euploid blastocysts form from DUCs.

What is known already?:

- Time-lapse technology enables the identification of DUCs during embryo development. Previous research associates DUCs with poorer blastulation, implantation, and ploidy outcomes.
- DUCs are rarely transferred.
- Whether DUC embryos should be automatically discarded or deprioritised is an ongoing debate which leads to inconsistency in clinical practices across fertility centres.
- AI image processing algorithms may assist embryologists in the identification of DUCs.

Study design, size, duration: A retrospective single-centre study of normally-fertilised embryos cultured in time-lapse incubators throughout 2019--2021. We reviewed 9284 time-lapse videos using an AI image processing tool (CHLOE, Fairtility), and assessed DUC embryo outcomes (ploidy, blastulation, and blastocyst quality). Additionally, we analysed pronuclei data searching for possible causes of DUCs.

Participants/ materials, setting, methods: CHLOE (Fairtility) software analysed time-lapse videos identifying pronuclei, DUCs, and blastulation; recording all morphokinetic time points (tPNa,tPNf,t2,t3,t4,t5,t6,t7,t8,t9,tM, tSB,tB,tEB), morphological grades for the inner cell mass (ICM) and trophectoderm, blastocyst size at 116hpi; and assessing the likelihood of blastulation (at 30hpi) and implantation. We evaluated the statistical significance for all variables using t-tests (continuous variables) and chi-squared tests (categorical variables). We quantified the two pronuclei (2PN) detection efficacy using four metrics: accuracy, sensitivity, specificity, and informedness.

Main results and the role of chance:

- All the embryos analysed (n=9284), 35% showed DUCs (n=3269).
- Blastulation was significantly higher in non-DUC versus DUC embryos (Table 1)
- ICM quality and trophectoderm quality were significantly higher in non-DUC than in DUC embryos (Table 1).
- DUC embryos were 6 hours slower than non-DUC embryos.
- Implantation EQ score and blastulation score were lower for DUC embryos than for non-DUC embryos (Table 1).
- CHLOE automatic PN assessment agreed with human annotation in 92% of cases (TP=388,TN=5,FP=29,FN=7).
- CHLOE Blastocyst prediction at 30hpi had an AUC of 0.89 (Figure 1).
- The embryologist agreed on 97% of all 483 embryos that CHLOE classified as DUC. Discrepancies arose from CHLOE misclassifying fragments as blastomeres. Further studies warranted.

Limitations, reasons for caution: Differentiating between fragments and blastomeres within the 5 hours from the first division proves challenging for embryologists and, especially, AI algorithms. Hence, some embryos' DUC status may be misclassified. Additionally, our sample sizes are limited and larger sizes are needed to corroborate our findings, especially those pertaining to ploidy status.

Wider implications of the findings: DUC embryos are associated with poorer outcomes and DUC status should be integrated into embryo classification frameworks. Nevertheless, some DUC embryos prove to be euploid. Hence, DUC embryos should not excluded from culture at cleavage stage and instead be allowed to reach blastocyst stage before assessing their suitability for transfer/vitrification/PGT-A.

	DUC	Non DUCs
Implantation EQ Score	[0.14(0.24] p<0.0001	0.46(0.36), p<0.0001
Blastulation Score	0.4(0.46] p<0.0001	0.75(0.4] p<0.0001
Euploidy rate	27.2% (12/44).	-
Blastulation	49%, p<0.0001	76%, p<0.0001
ICM Quality A,B,C,D	3%,4%,16%,47%, p<0.001	24%,13%,19%,21%, p<0.001
Trophectoderm quality A, B, C, D	2%,7%,14%,52%, p<0.0001	20%,21%,15%,23%, p<0.0001

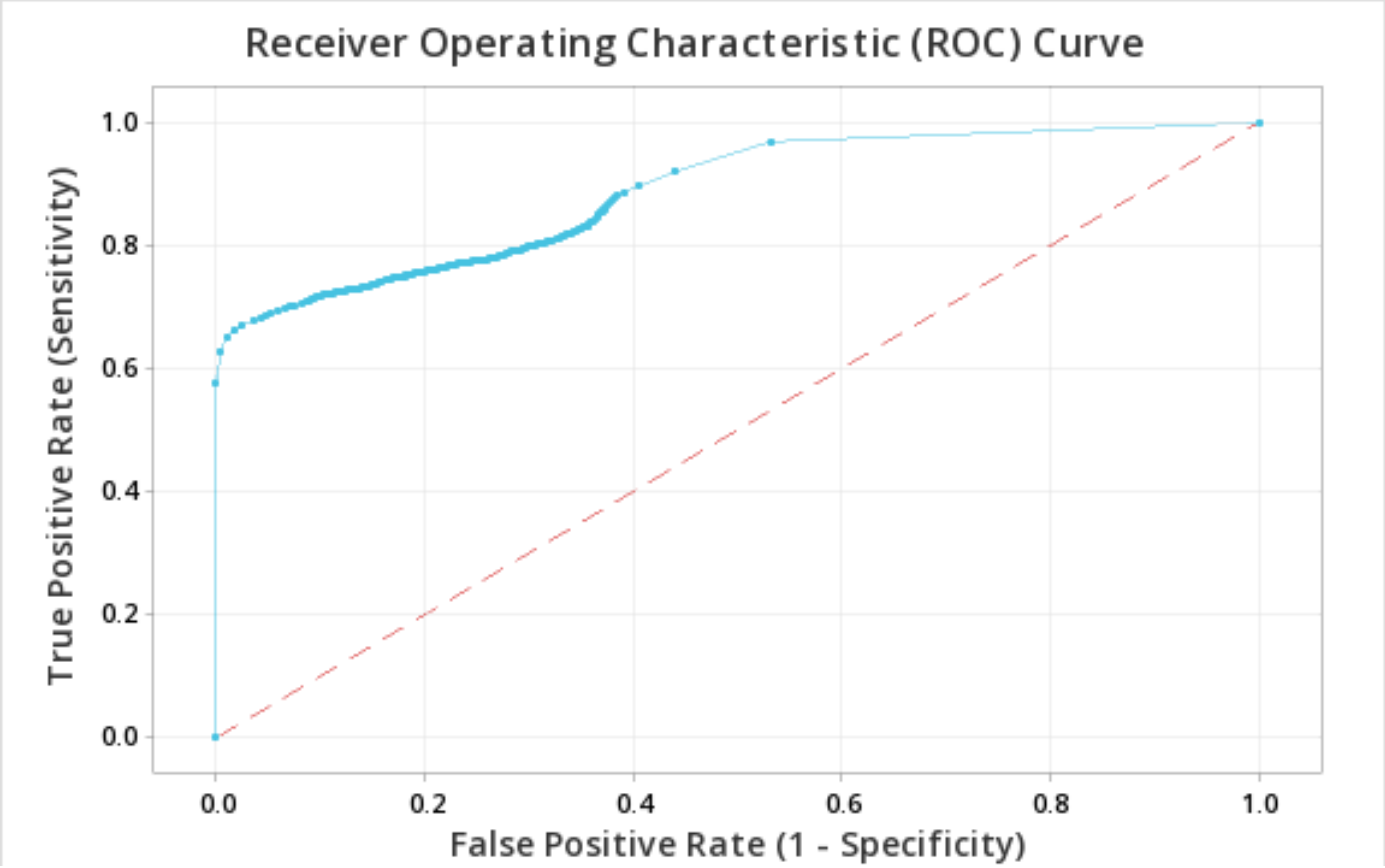


Figure 1. CHLOE EQ Blast Score and Blastocyst prediction. AUC-0.8872

The Centre for Reproductive & Genetic Health

Impact of Direct Unequal Cleavage (DUC) on embryo development, blastocyst formation and ploidy - artificial intelligence (AI) analysis.

A. Florek[1] 1, R. Odia[1], S. Theodorou[1], M. Duran[1], W. Saab[1], V. Seshadri[1], P. Serhal[1], C. Hickman[2], A. Brualla Mora[2], R. Derrick[2], M. Gaunt[1]. 1-The Centre for Genetic & Reproductive Health CRGH, London, UK. 2- Fairtility, Tel Aviv-Yafo, Israel.

Study question

Does direct unequal cleavage impact embryo development? In particular, morphokinetics, grading, and ploidy status? Can we answer these questions using artificial intelligence?

Summary answer

DUC embryos develop slower, have lower blastulation rates, and lower CHLOE (Fairtility) blastulation and implantation scores. However, DUC embryos occasionally develop into euploid blastocysts.

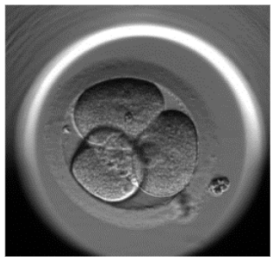


Figure 1. Image showing Direct Unequal Cleavage (DUC). An abnormal cleavage of one blastomere into three daughter blastomeres or an interval of first two cell cycles occurring within less than five hours.

Fairtility

Materials and method

A retrospective single-centre study of normally-fertilised embryos cultured in time-lapse incubators throughout 2019--2021. We reviewed 9284 time-lapse videos using an AI image processing tool (CHLOE, Fairtility). It analysed the videos, identifying pronuclei, DUCs (Figure 1), and blastulation; recording morphokinetic time points (tPNa, tPNf, t2, t3, t4, t5, t6, t7, t8, t9, tM, tSB, tB, tEB), morphological grades for the inner cell mass (ICM) and trophectoderm (TE). We assessed 465 DUC embryo outcomes (fate, ploidy, blastulation, and blastocyst quality). Statistical significance was evaluated using t-tests (continuous variables) and chi-squared tests (categorical variables).

Main results

Of all the embryos analysed (n=9284), 35% showed DUCs (n=3269). Blastulation was significantly higher in non-DUC than DUC embryos (76% and 49%, p<0.0001). For the embryos that blastulated, ICM and TE quality was significantly higher in non-DUC than in DUC embryos (Figure 2, p<0.001).

DUC embryos reached t3 faster than non-DUC ones [Mean(SD): 34h(15h) and 39h(10h), p<0.0001]. However, t5 was similar for both cohorts [52h(21h) and 51h(12h), NS]. For all further morphokinetic milestones, DUC embryos were six hours slower than non-DUC ones.

DUC embryos with known ploidy status had a euploidy rate of 25.5% (12/47). However, the few DUC embryos with high morphokinetic grades had a higher euploidy rate of 66.7% (4/6).

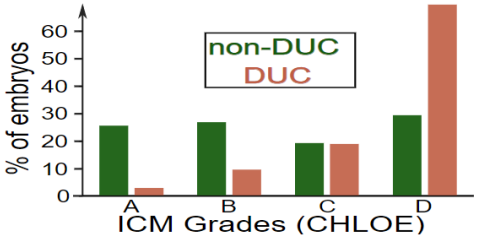


Figure 2a. Inner cell mass quality.

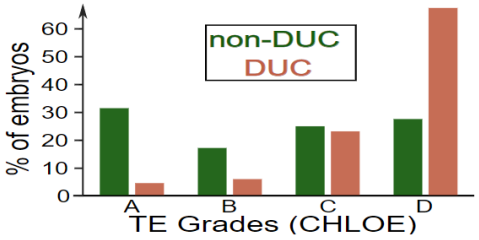


Figure 2b. Trophectoderm quality.

Implantation score [0.14(0.24) and 0.46(0.36), p<0.0001] and blastulation score [0.4(0.46) and 0.75(0.4), p<0.0001] were lower for DUC embryos than for non-DUC embryos.

Conclusions

DUC embryos are associated with poor grades and outcomes. DUC status should be integrated into embryo classification frameworks. Nevertheless, some DUC embryos prove to be euploid. Hence, DUC embryos should not be excluded from culture at cleavage stage and instead be allowed to reach blastocyst stage before assessing their suitability for transfer, vitrification, or biopsy for genetic testing.

Study 27: ESHRE 2022 – Juana Crespo

A validation study for artificial intelligence (AI) compared with manual annotation, using donor eggs reveals that AI accurately predicts blastulation

Authors: J Teruel Lopez, C Miret Lucio, M Lozano Zamora, M Escribá Suarez, M Benavent Martínez, J Crespo Simó, I Erlich, M Tran, N Bergelson

Published by Human Reproduction

Clinic: Juana Crespo (Spain)

Question: Are the annotations produced by AI comparable to manual annotations? Does AI accurately assess fertilisation checks, and predict embryo usage and blastulation compared to embryologists?

Answer: Automatic annotations by AI was consistent with manual annotations. AI implantation algorithms had strong prediction of blastulation and embryo usage.

What is known already?:

- Embryos are manually annotated for specific morphokinetic features during embryo development. This is a labour-intensive process, and dependent on training and experience, leading to inter and intra clinic variation.
- Decision to transfer, freeze or discard embryos relies heavily on these annotations.
- AI has demonstrated to provide consistency and accuracy in annotation and produce scores that can facilitate decisions around embryo usage.
- Validation is needed before its integration into clinical practice.

Study design, size, duration: Retrospective cohort study, that took place between September to December 2021 at a private fertility clinic in Spain. To control for embryo variability, this study only included 179 time-lapse videos for embryos created from donor eggs. This was based on the understanding that donor eggs are more likely to produce better quality blastocysts and embryos and thus will give the most optimal conditions for annotation in a validation framework.

Participants/ materials, setting, methods: The same time-lapse cultured embryos were annotated manually and automatically by CHLOE(Fairtility, an AI-based tool). Manual and CHLOE annotations were compared to assess the strength of agreement (i) using intra-class correlation (ICC), and (ii) the proportion of corrections required at the pronuclei (PN) stage. AI accuracy in predicting blastulation at 30hours, and blastulation before 116 hours, was also assessed using AUC as the efficacy metric. Embryo usage was compared with the AI-generated ranking of embryos.

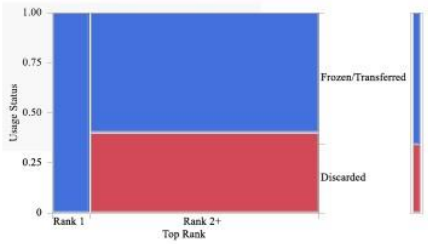
Main results and the role of chance:

- AI ranking accurately correlated with embryologist decisions to freeze, transfer or discard embryos, with an overall high sensitivity 0.88 and specificity 0.67, (AUC: 0.84,p<0.0001).
- The majority of morphokinetic variables showed a very-strong agreement. Only t4 (0.5) showed a moderate agreement. All other variables fell within a strong ICC of (0.61-0.8). There were no very weak (0-0.2) or weak (0.21-0.4) variables (Table 1).
- PN agreement between AI and embryologists was 93%.
- A rank of 1 was seen in 14%(n=113) of embryos, all of which were frozen or transferred. Some embryos that scored a rank of 2 were discarded, but this was significantly lower than those that scored a rank of 3 or more (3%vs32%,p=0.0004).
- AI predicted blastulation on day 3 with a high level of sensitivity 0.77 and specificity 0.82, (AUC: 0.84,p<0.0001). Furthermore, the blastulation score given on day 3 was a predictor of blastulation before 116 hours with a high sensitivity 0.77 and specificity 0.80, (AUC: 0.81,p<0.0001, Figure 1).

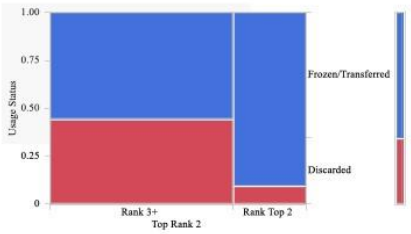
Limitations, reasons for caution: This study only included embryos from donor eggs. Furthermore, this study occurred at a single site and is planned to be replicated at several clinics. Where there are discrepancies between human and AI, further studies are required to determine the ground truth.

Wider implications of the findings: This study demonstrates an AI framework to safely introduce AI in the fertility clinic. AI will accurately annotate embryos and give reliable scores to predict good quality blastulation, and inform decisions around embryo usage determination. AI provides a time-effective, objective tool in decision-making, with the potential to optimise success, cost and emotional burden to our patients.

UTILIZATION BY TOP RANK

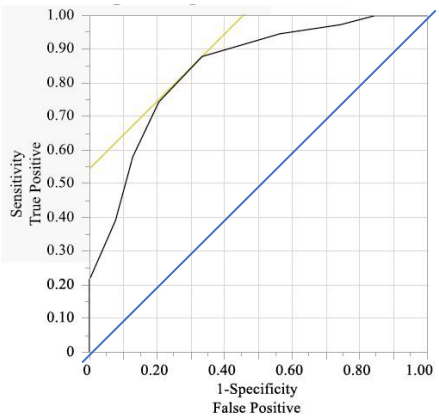


UTILIZATION BY TOP 2 RANK



PREDICTION OF USAGE FROM RANK

p value	AUC	Sensitivity	Specificity
<0.0001	0.84	0.88	0.66



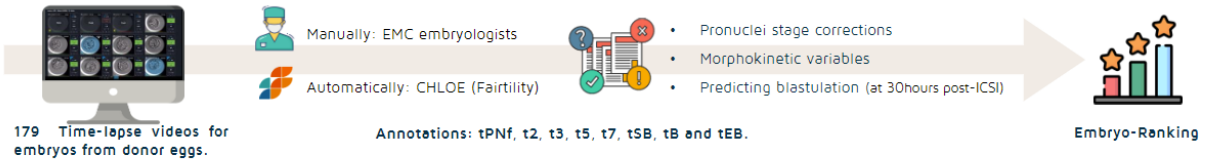
Prediction of usage from rank CHLOE vs embryologists

A validation study for artificial intelligence (AI) compared with manual annotation, using donor eggs reveals that AI accurately predicts blastulation

J. Teruel[1], C. Miret[1], M.Lozano[1], M. Escribá[1], M.Benavent[1], J. Crespo[1], I.Erlich[2], M.Tran[2], N.Bergelson[2]
1.Equipo Medico Crespo, Valencia, Spain 2.Fairtility, Clinical, Tel Aviv, Israel

STUDY DESIGN

Retrospective cohort study, that took place between September to December 2021 at a private fertility clinic in Spain.



179 Time-lapse videos for embryos from donor eggs.

Annotations: tPNf, t2, t3, t5, t7, tSB, tB and tEB.

Embryo-Ranking

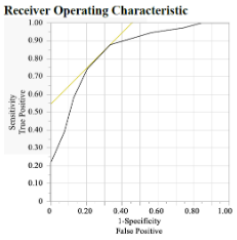
MAIN RESULTS

The majority of **morphokinetic variables** showed a very-strong ICC (0.81-1.00) or strong ICC (0.61-0.8) agreement.

EVENT	tPN	T2	T3	T4	T8	tM	tSB	tB	tEB
ICC	0,69	0,64	0,76	0,61	0,68	0,78	0,93	0,93	0,80

PN agreement between AI and embryologists was 93%: PN's had to be corrected by an embryologist only 7%(n=179) of the time.

AI **predicted blastulation** on day 3 with a high level of sensitivity 0.77 and specificity 0.82, (AUC: 0.84,p<0.0001). The blastulation score given on day 3 was a predictor of blastulation before 116 hours with a high sensitivity 0.77 and specificity 0.80, (AUC: 0.81,p<0.0001).

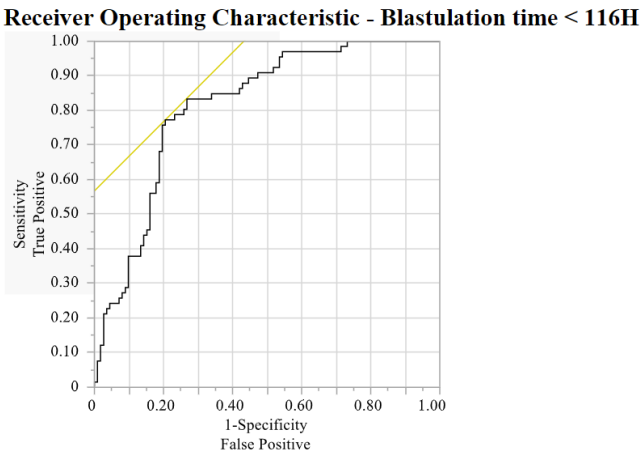


Similarly, AI-generated ranking accurately correlated with embryologist decisions to freeze, transfer or discard embryos, with an overall high sensitivity 0.88 and specificity 0.67, (AUC: 0.84,p<0.0001). A rank of 1 was seen in 14%(n=113) of embryos, all of which were frozen or transferred. Some embryos that scored a rank of 2 were discarded, but this was significantly lower than those that scored a rank of 3 or more (3%vs32%,p=0.0004).

Table 1. ICC Morphokinetic events. Agreement between CHLOE and embryologists

Event	ICC	CCC
tPNf	0.93	0.93
t2	0.91	0.91
t3	0.87	0.87
t4	0.49	0.48
t5	0.89	0.89
t6	0.78	0.78
t7	0.81	0.81
t8	0.74	0.74
tM	0.74	0.74
tSB	0.91	0.91
tB	0.95	0.95
tEB	0.86	0.86

Figure 2. Blastulation prediction by CHLOE. AUC – 0.81



Study 28: ESHRE 2022 - Next Fertility

An analysis of qualitative and quantitative morphokinetic: Parameters automatically annotated using CHLOE (Fairtility), an AI-based tool, finds AI score predictive of blastulation and ploidy

Authors: E Gómez, A Brualla-Mora, N Almunia, R Jiménez, C Hickman, I Har-vardi, A.M Villaquirán

Published by Human Reproduction

Clinic: NEXT CLINIC MURCIA (Spain)

Question: What is the relationship between qualitative and quantitative morphokinetic parameters automatically annotated using CHLOE(Fairtility), an AI-based tool.

Answer: CHLOE score is associated with ploidy. DUC embryos have lower blastulation, form fewer good blastocysts, have increased fragmentation, slower development, lower implantation than non-DUCs.

What is known already?:

- Time-lapse technologies in IVF has led to the discovery of quantitiative and qualitative morphokinetic parameters which are predictive of embryo viability (ESHRE Workshop group, 2020).
- Challenges of annotating videos manually: (i)operator variation, (ii)time-consuming; (iii)complexity of how to prioritise numerous features when determining which embryos to transfer, freeze or discard.
- CHLOE (Fairtility) is an AI-based tool designed to automatically capture these parameters from the time-lapse videos, removing the "black box" associated with AI.
- CHLOE brings transparency and support to the embryologist responsible for the decision, thus enhancing personalisation of care down to each individual embryo.

Study design, size, duration: Prospective cohort analysis on time-lapse data retrospectively collected at a single private fertility clinic in Spain between 2018-2020. 693 videos were automatically annotated (without training) using the CHLOE Artificial Intelligence (AI) tool for the following quantitative features: tPNa,tPNf,t2,t3,t4,t5,t6,t7,t8,t9,tM,tsB,tB,teB, size of ICM; and the following qualitative parameters: number of pronucleates, morphological quality of Inner Cell Mass and Trophectoderm (CHLOE Morphological scoring), identification of unusual embryo cleavages i.e. Direct Uneven Cleavage (DUCs), amongst other features.

Participants/ materials, setting, methods: All embryos were cultured using the Embryoscope (Vitrolife) incubator. Using a range of algorithms, CHLOE generated a prediction of blastulation (at 30hpi) and implantation which were compared to outcome (blastocysts vs non-blastocysts; euploids vs Aneuploids&Mosaics; Mosaics vs euploids&aneuploids). Embryos identified as DUCS by CHLOE were compared with non-DUCs in terms of outcomes and in terms of endpoints generated by CHLOE (parametric continuous data assessed using 2-tail t-test, categorical data using chi-square).

Main results and the role of chance:

- Within all cleaved embryos analysed (n=693), 29% were DUCs. DUC embryos were less likely to blastulate, had a higher proportion of embryos with severe fragmentation, less likely to be suitable for biopsy, lower blastulation prediction score, lower implantation prediction EQ score and slower embryo development across the all morphokinetic time-points assessed(p<0.001), except for t5 (NS); than non-DUCs. DUCs and non-DUCs had similar proportion of 1,2,3PNs (Table 1, Figure 1).
- Within embryos that blastulated (n=581), 25% were DUCs. DUC blastocysts were less likely to have a good quality ICM or a good quality trophectoderm, lower implantation EQ score and slower embryo development across the following morphokinetics time-points than non-DUC blastocysts. DUCs (n=38) and non-DUC (n=292) blastocysts had similar euploidy rate, mosaicism rate and similar ratio of Euploids:Aneuploid:Mosaics (Table 1).
- Blastulation score was predictive of blastulation (AUC of 0.91, p<0.001). Mosaic embryos had similar implantation score to non-mosaics (0.61vs0.67, NS). Euploid embryos had a higher implantation score than aneuploid blastocysts (0.71bs0.62, p<0.02), so implantation EQ score was predictive of ploidy.

Limitations, reasons for caution: This study involved the validation of (i) a specific AI based tool which may not be generalised across other AI tools; (ii) in a single centre. Results obtained did not involve training, suggestive of CHLOE's ability to generalise across clinics. Presenting a framework for responsibly incorporating AI into clinical practice.

Wider implications of the findings: CHLOE can simplify the processing of time-lapse data to effectively, consistently and efficiently quantify parameters that can help explain a comprehensive prediction of embryo viability. This provides a useful tool which will ultimately assist clinicians with selecting the most optimal embryos for transfer, and avoid wastage from discarding viable embryos.

CLEAVED EMBRYOS	DUC	Non-DUCs
Blastulation	25%, p<0.001	50%, p<0.001
Fragmentation	26%, p<0.001	3%, p<0.001
Suitability for biopsy	23%, p<0.001	87%, p<0.001
Blastulation Score	0.53, p<0.001	0.76, p<0.001
Implantation EQ Score	0.21, p<0.001	0.48, p<0.001
1, 2, 3 PN	5,83,5%, NS	7,84,3%, NS
BLASTULATED EMBRYOS		
Good quality ICM	7%, p<0.001	33%, p<0.001
Good quality trophectoderm	9%, p<0.05	35%, p<0.05
Implantation EQ Score	0.29 ,p<0.05	0.52, ,p<0.05
Euploid rate	50%, NS	43%, NS
Mosaicism	8%, NS	11%, NS
Ratio Euploids:Aneuploid:Mosaics	19:16:3, NS	126:133:33, NS

AN ANALYSIS OF QUALITATIVE AND QUANTITATIVE MORPHOKINETIC PARAMETERS AUTOMATICALLY ANNOTATED USING CHLOE (FAIRTILITY), AN AI-BASED TOOL, FINDS AI SCORE PREDICTIVE OF BLASTULATION AND PLOIDY

[1]Emilio Gómez, [2]Adriana Brualla, [1]Nuria Almunia, [1]Rebeca Jiménez, [2]Cristina Hickman, [2]Iris Har-vardi, [1]Ana Mª Villaquirán.

[1] Next Fertility Murcia. Murcia (España) [2] Fairtility, Tel Aviv (Israel)

INTRODUCTION

The introduction of time-lapse technologies in IVF has led to the discovery of quantitative and qualitative morphokinetic parameters which are predictive of embryo viability. The challenges of annotating videos manually remain: operator variation, time-consuming, etc. CHLOE (Fairtility) is an AI-based tool designed to automatically capture these parameters from the time-lapse videos.

Our **objective** was to find if there is a relationship between qualitative and quantitative morphokinetic parameters automatically annotated using CHLOE.

MATERIALS & METHODS

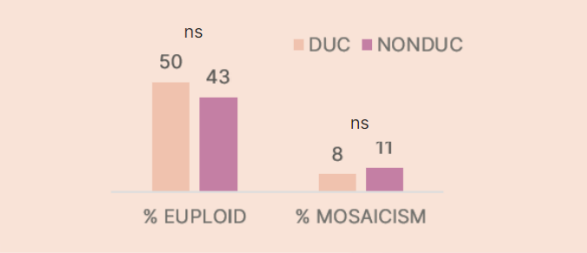
Prospective cohort analysis on time-lapse data retrospectively collected at a single private fertility clinic in Spain (Next Fertility Murcia) between 2018-2020. 693 videos were automatically annotated (without training) using the CHLOE Artificial Intelligence (AI) tool for all morphokinetic events number of pronucleates, morphological quality of Inner Cell Mass and Trophectoderm (CHLOE Morphological scoring), identification of unusual embryo cleavages i.e. Direct Uneven Cleavage (DUCs), amongst other features.

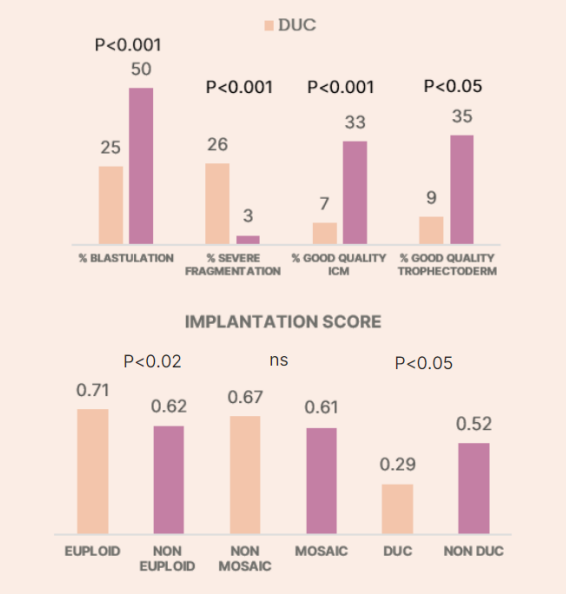
All embryos were cultured using the Embryoscope (Vitrolife) incubator. Using a range of algorithms, CHLOE generated a prediction of blastulation (at 30hpi) and implantation which were compared to outcome (blastocysts vs non-blastocysts; (blastocysts vs non-blastocysts; euploids vs Aneuploids & Mosaics; Mosaics vs euploids & aneuploids). Embryos identified as DUCS by CHLOE were compared with non-DUCs in terms of outcomes and in terms of endpoints generated by CHLOE (parametric continuous data assessed using 2-tail t-test, categorical data using chi-square).

RESULTS

Blastulation score was predictive of blastulation (AUC of 0.91, p<0.001). Within all cleaved embryos analysed (n=693), 29% were DUCs. DUC embryos were less likely to blastulate (DUC vs NonDUC: 25 vs 50%, p<0.001), had a higher proportion of embryos with severe fragmentation (26% vs 3%,p<0.001), less likely to be suitable for biopsy (23 vs 87%, p<0.001) lower blastulation prediction score (0.53 vs 0.76,p<0.001), lower implantation prediction score (0.21 vs 0.48,p<0.001) and slower embryo development across the all morphokinetic time-points assessed (p<0.001), except for t5 (NS); than non-DUC. DUC and non-DUC had similar proportion of 1,2,3 PNs (5,83,5%vs 7,84,3%, NS). In embryos that blastulated (n=581), DUC blastocysts were less likely to have a good quality ICM (7 vs 33%, p<0.001) or a good quality trophectoderm (9 vs 35%, p<0.05), lower implantation score (0.29 vs 0.52,p<0.05) and slower embryo development across the following morphokinetics time-points than non-DUC blastocysts.

DUCs (n=38) and non-DUC (n=292) blastocysts had similar euploidy rate (50 vs 43%, NS), mosaicism rate (8 vs 11%, NS), and similar ratio of Euploids:Aneuploid:Mosaics (19:16:3 vs 126:133:33, NS). One DUC embryo was transferred, leading to an ongoing clinical pregnancy.





CONCLUSIONS

CHLOE can simplify the processing of time-lapse data to effectively, consistently, and efficiently quantify parameters that can help explain a comprehensive prediction of embryo viability. This provides a useful tool which will ultimately assist clinicians with selecting the most optimal embryos for transfer and avoid wastage from discarding viable embryos. This study involved the validation of (i) a specific AI based tool which may not be generalised across other AI tools; (ii) in a single centre. Results obtained did not involve training, suggestive of CHLOE's ability to generalise across clinics. Presenting a framework for responsibly incorporating AI into clinical practice.

Study 29: ESHRE 2022 – Soroka & Hadassah

An analysis of automated morphometric measurements finds that a combination of a large blastocyst size and a short tB-tSB time interval doubles the implantation rate

Authors: I. Har-Vardi, Y. Fruchter-Goldmeier, A. Ben-Meir, T. Wainstock, I. Erlich, E. Levitas, Y. Shufaro, O. Sapir, B. Kantor

Published by Human Reproduction

Clinic: Soroka (Israel), Hadassah (Israel)

Study question: Are automated blastocyst morphometric measurements combined with morphokinetic pattern associated with implantation rate?

Summary answer: Automated blastocyst morphometric measurements combined with morphokinetic pattern demonstrated that a larger blastocyst size and a shorter time-interval tB-tSB are associated with higher implantation potential.

What is known already:

- Optimization of embryo selection is important for increasing implantation potential. Transfer of a high quality blastocyst based on conventional morphological parameters has been shown to improve IVF clinical outcome.
- Novel parameters of blastocyst quality including morphokinetics from time-lapse monitoring and manual analysis of morphometric parameters have demonstrated promising results regarding implantation potential.
- Manual measurements of morphometric parameters is time-consuming task and is subjected to intra- and inter-observer variations. The introduction of automated morphometric measurements would remove subjective blastocyst analysis and further improve implantation rates.

Study design, size, and duration: A nested retrospective case control analysis of 608 day-5 transferred blastocysts was conducted and included women who underwent IVF treatment in three public IVF units between 2014 and 2017.

Participants/materials, setting, methods: Automated morphometric blastocyst analysis was measured at the mean time of tEB-tPNf (85.82 h) by training a pixel-wise segmentation model (MaskRCNN) on time-lapse videos. Morphometric blastocyst parameters included the following: blastocyst size (μm), inner cell mass (ICM) size (μm), ICM to blastocyst size ratio, and ICM shape. Annotation variables included all the time intervals (hours) from time of pronuclei fading (tPNf) to the expanded blastocyst (tEB).

Main results and the role of chance:

- The mean blastocyst size for implanted embryos was significantly larger compared to non-implanted embryos.
- The mean interval times of tSB-tPNf, tB-tPNf, tEB-tPNf, tB-tSB, and tEB-tSB were significantly shorter (Table 1).
- In a multivariable logistic model: ICM size, blastocyst size, tB-tSB, and woman age on implantation potential, blastocyst size was found to be positively associated with implantation potential, while tB-tSB and woman age were found to be negatively associated (Table 2).
- Blastocyst size larger than the mean and a tB-tSB interval shorter than the mean had a 2.028 greater chance of implantation compared to blastocysts that did not meet these criteria (OR=2.028, 95% CI 1.420-2.894, p<0.001).
- In a multivariable logistic model adjusted for woman age, the chance for implantation among blastocysts meeting the aforementioned criteria was 1.7 greater (adjusted OR 1.714, 95% CI 1.182-2.485, p=0.005). The AUC value for implantation prediction was 0.69 (p<0.01).

Limitations, reasons for caution: The study's limitations include its retrospective nature and the absence of some patient characteristics. Wider implications of the findings: A blastocyst selection based on the combination of automated blastocyst size measurements and manual tB-tSB time interval may increase implantation rate two-fold. The inclusion of automated morphometric measurements to the blastocyst selection algorithm may reduce intra- and inter-observer variations and should be incorporated into models for implantation prediction.

Table 1. Mean Interval times and implantation potential

	Implanted embryos	Non-implanted embryos
Blastocyst size	152.10 ±19.22µm, p<0.001	144.25±18.52µm, p<0.001
INTERVALS		
tSB-tPNf	72.10±5.60h, p=0.016	73.30±5.80h, p=0.016
tB-tPNf	80.08±5.96h, p<0.001	82.54±5.92h, p<0.001
tEB-tPNf	84.95±5.43h, p=0.001	86.58±4.93h, p=0.001
tB-tSB	8.21±2.90h, p<0.001	9.49±3.62h, p<0.001
tEB-tSB	13.50±3.00h, p=0.001	14.58±3.75h, p=0.001

Table 2. Implantation potential assessment

	Implantation
Blastocyst size	OR=1.017, 95% CI 1.006-1.027, p=0.002
tB-tSB	OR=0.918, 95% CI 0.861-0.980, p=0.010
Woman age	OR=0.903, 95% CI 0.874-0.932, p<0.001

Study 30: ASRM 2022 – Soroka & NYU Langone

CHLOE EQ™ Effectively and automatically predicts embryo implantation across all patient age groups by combining morphokinetic and morphology algorithms over culture

timeAuthors: Itay Erlich, PhD, Rishabh Hariharan, BSc, Iris Har-Vardi, PhD, Michelle Tran, BS, Gilad Karavani, MD, Eliahu Levitas, MD, James A Grifo, MD, PhD, Fang WANG, PhD, Cristina Hickman, PhD and Assaf Ben-Meir, MD.

Published by Fertility & Sterility

Clinic: Soroka (Israel), NYU Langone Health (USA).

Type: Retrospective Cohort Study

Objective: To determine (a) whether a morphokinetic machine learning model can automatically annotate embryo morphokinetics comparably to embryologists; (b) the efficacy of prediction of implantation by CHLOE EQ; (c) how the efficacy of prediction of implantation bymorphological & machine and combined (CHLOE EQ) learning models are affected by increased culture time and (d) patient age.

Materials and methods: 36,561 human-annotated time-lapse videos, including 6,938 embryos with known implantation, were used to assess 3 separate machine learning algorithms, automatically quantifying (i) morphokinetics, (ii) morphology, (iii) combined morphokinetics and morphology (CHLOE EQ Automated annotation at 15 morphokinetic stages were assessed and compared to manual annotations by experienced embryologists. All 3 algorithms dynamically scored embryos throughout culture time to predict implantation potential. Efficacy of prediction over time was assessed as area under the curve (AUC). Culture time, patient age, & implantation status were assessed as confounders.

Results:

- CHLOE annotation was comparable to manual annotation of embryos (r>0. 95).
- Morphological, morphokinetic and CHLOE were effective predictors of implantation throughout culture time (AUC>0.66, accuracy of >0.61,p<0.001).
- For all 3 models, AUC for implantation prediction increased with increased culture time, particularly up to the morula stage (p<0.001).
- Both patient & embryo age affected AUC at different culture times (p<0.001).
- Embryo stage impacted automatic morphokinetic annotation accuracy (p<0.001).
- Morphology analysis had the highest AUC after 100hpi & in patients >37 years. Morphokinetic assessment at 116hpi had the highest sensitivity (0.8) and negative predictive value (0.78), whilst morphology had a greater specificity (0.64) and positive predictive value (0.55).
- Combined into CHLOE, these models lead to significantly improved prediction of implantation, particularly for the younger population (<33years) and within 90hpi.

Conclusions: CHLOE combines morphokinetic & morphology algorithms over culture time to effectively and automatically predict embryo implantation across all patient age groups; whilst automatically annotating morphokinetic parameters with comparable accuracy to experienced embryologists, saving embryology time. CHLOE continuously learns with increasing culture time and is particularly effective in the younger population where larger number of embryos make it harder to select the best embryo for a single embryo transfer.

Impact statement: The transparency of machine learning algorithms is essential to allow healthcare professionals to effectively incorporate such tools into clinical decisions & practice. Itis important to translate the mathematics of the models into explainable & clear biology that can be trusted, understood & relied on. CHLOE incorporates biologically relevant biomarkers of prediction (morphology and morphokinetics) to save embryology time in processing time-lapse data and improve clinical decisions through an enhanced prediction efficacy & consistency.

Study 31: ASRM 2022 – Crespo, Memorial, NEXT CLINIC MURCIA, CRGH, IASO, Generalife, Alpha

Transparent prediction of blastulation, ploidy and implantation: an international multisite validation at six independent clinics

Authors: Assaf Ben-Meir, MD., Clara Miret Lucio, MSc, Marta Lozano, MSc, Rabi Ahmed-Odia, M.SC.,Semra Kahraman, Prof. MD, Yesim Kumtepe Colakoglu, M.Sc, Hakan Kadir Yelke, M.SC.,Triantafillos Triantafillou, PhD, Emilio Gomez, PH.D., Danilo Cimadomo, PhD, Adelle Yun XinLim, M.SC., Adriana Brualla Mora, MSc, Iris Har-Vardi, PhD, Anat Sakov, PhD and Cristina Hickman, PhD.

Published by Fertility & Sterility

Clinics: Juana Crespo (Spain), Memorial (Turkey), NEXT CLINIC MURCIA (Spain), Generalife (Rome), CRGH (United Kingdom), Alpha IVF (Malaysia), IASO (Greece).

Type: Retrospective Cohort Study (includes comparator groups)

Objective: To assess the ability of CHLOE EQ (Fairtility) to predict blastulation, utilization, ploidy & implantation at 6 independent clinics.

Materials and methods: Time-lapse videos from 4603 embryos, 627 cycles, 6 clinics, 4 countries were retrospectively assessed using CHLOE: a transparent AI tool that supports embryologists in making clinical decisions from time-lapse videos. CHLOE combines a plethora of machine learning algorithms, three of which were trained to predict embryo utilization (CHLOEBLAST score, CHLOE RANK) and implantation (CHLOE EQ score) from as early as 30hpi.Logistic regression assessed the efficacy of prediction at 68hpi for blastulation (by 116hpi and overall), ploidy and implantation. The algorithms were assessed blindly without prior training to demonstrate generalisation.

Results: Table 1

- Overall, BLAST score was predictive of blastulation (AUC=0.86: 0.84-0.93, n=4266, p<0.001).
- CHLOE ranking was predictive of embryo utilization (AUC=0.68: 0.68-0.71, n=4719, p<0.001).
- CHLOE EQ score was predictive of ploidy (AUC=0.61, n=1463, p<0.001) and implantation(AUC=0.76, n=535, p<0.001, Table 1).

Conclusions: CHLOE BLAST score at 68hpi is predictive of blastulation & utilization. CHLOE ranking is predictive of embryo utilization. CHLOE EQ score is predictive of both ploidy and implantation.

Impact statement: The ability to accurately and consistently predict blastulation, utilization, ploidy and implantation potential as early as 30hpi instantaneously is essential towards improving personalised care, enhancing the management of patient expectations, managing blastocyst biopsy and vitrification workload later in the week, determining which embryos to prioritise for biopsy, transfer and cryopreservation, ensuring viable embryos are not discarded and determining the best embryo transfer strategy for each individual embryo for each individual patient.

Table 1. CHLOEs Scores and predictive models.

Blastulation prediction	Embryo utilization prediction	Ploidy prediction	Implantation prediction
CHLOE BLAST SCORE (AUC=0.86: 0.84-0.93, n=4266, p<0.001	CHLOE ranking AUC=0.68: 0.68-0.71, n=4719, p<0.001	CHLOE EQ SCORE AUC=0.61, n=1463, p<0.001	CHLOE EQ SCORE AUC=0.76, n=535, p<0.001

Event	ICC				Degree of Agreement with experienced embryologists			
	Overall	Clinic A-D	Clinic E	Clinic F	OVERALL	Clinic A-D	Clinic E	Clinic F
tPNf	0.77	0.92	0.69	0.91	Strong	Very Strong	Strong	Very Strong
t2	0.73	0.86	0.64	0.91	Strong	Very Strong	Strong	Very Strong
t3	0.79	0.81	0.76	0.88	Strong	Very Strong	Strong	Very Strong
t4	0.65	0.7	0.61	0.78	Strong	Strong	Strong	Strong
t5	0.8	0.82	0.77	0.85	Very Strong	Very Strong	Strong	Very Strong
t6	0.79	0.82	0.74	0.85	Strong	Very Strong	Strong	Very Strong
t7	0.69	0.74	0.63	0.85	Strong	Strong	Strong	Very Strong
t8	0.68	0.67	0.68	0.72	Strong	Strong	Strong	Strong
t9	0.69	0.71	Not assessed	0.61	Strong	Strong	Not assessed	Strong
tM	0.78	0.77	0.78	0.78	Strong	Strong	Strong	Strong
tSB	0.92	0.9	0.93	0.91	Very Strong	Very Strong	Very Strong	Very Strong
tB	0.91	0.88	0.93	0.92	Very Strong	Very Strong	Very Strong	Very Strong
tEB	0.79	0.82	0.8	0.68	Strong	Very Strong	Very Strong	Strong

Study 32: ASRM 2022 – Juana Crespo

Can CHLOE EQ™, An ai-based embryologist assistant tool, automaticallypredict whether an embryo will blastulate, be utilised and/or implant on day 3?

Authors: Clara Miret Lucio, MSc, Marta Lozano, MSc, Adriana Brualla Mora, MSc, Anat Sakov, PhD and Cristina Hickman, PhD, [1]Juana Crespo, Valencia, Spain, [2]Fairtility, Sant Cugat Del Valles,Spain, [3]Fairtility, Israel, [4]Fairtility, United Kingdom

Published by Fertility & Sterility

Clinic: Juana Crespo (Spain)

Type: Retrospective Cohort Study (includes comparator groups)

Objective: To compare automatic annotations, pronucleate (PN) detection, blastulation & utilisation prediction by CHLOE EQ (FAIRTILITY, an AI-based embryologist assistant tool) and experienced embryologists.

Materials and methods: A retrospective cohort study (June 2021 to March 2022) of 2851time-lapse cultured embryos from 309 patients. Embryos were annotated by experienced embryologists, & automatically by CHLOE. Manual & automatic morphokinetic annotations and PN count were compared to establish strength of agreement using intra-class correlation (ICC).CHLOE's efficacy of prediction of blastulation (by end of culture & by 116hpi) was assessed using AUC as the efficacy metric. Embryo utilization was compared with ranking by CHLOE.

Table 1. Morphokinetic parameter annotation level of agreement between CHLOE and embryologists

Morphokinetic parameters	ICC	Level of agreement
tPNf	0.69 n=2165	STRONG
T2	0.64 n=2201	STRONG
T3	0.76n=2307	STRONG
t4	0.61 n=1730	STRONG
t5	0.77 n=1707	STRONG
t8	0.68 n=1612	STRONG
tM	0.78 n=1367	STRONG
tSB	0.93 n=1246	VERY STRONG
tB	0.93 n=1059	VERY STRONG
tEB	0.8 n=656	VERY STRONG

Results:

- All morphokinetic parameters demonstrated a very strong or strong level of agreement with none showing moderate, week or very week agreement (Table 1).
- PN agreement between embryologists and CHLOE was 91% (2360/2591). CHLOE agreed with experienced embryologistsin the determination of normal (2PN) fertilization in 94% of 2PNs as established by experienced embryologists (2095/2223), demonstrating a high level of agreement. CHLOE Blast Score was predictive of overall blastulation as well as blastulation by 116hpi.
- CHLOE-generated embryo ranking was predictive of embryo utilization (Table 2). Out of the 297 embryos ranked 1 by CHLOE, most (91%) were transferred or frozen; a lower utilization proportion was observed for embryos ranked 3 or more(49% , p<0.001).

Conclusions: CHLOE automatic annotation of embryos; determination of cell number, assessment of stage of embryo development, and determination of number of PNs were comparable to human manual annotations. Moreover, CHLOE accurately predicted blastulation and embryo utilisation on day 2 (as early as 30hpi) as well as on day 3. Embryos ranked by CHLOE are in agreement with embryo utilisation decisions made by experienced embryologists.

Impact statement: Automatic assessment of embryos cultured in time-lapse and direct integration between CHLOE, the time-lapse incubator and the electronic medical record (EMR)provides opportunities for automatic data-capture directly from the source: saving embryology time, reducing transcription error risks; improving the fluidity of information between stakeholders and improving transparency in operational intelligence through automatic and live KPI monitoring. CHLOE-supported clinics can increase the number of cycles capacity per embryologist with the potential to reduce operational costs and make IVF treatment more financially accessible. CHLOE provides a time-efficient, objective tool to support the embryologist in clinical decision-making, with the potential to optimize success, cost and emotional burden to our patient.

Table 2. Prediction of blastulation and embryo utilization by CHLOE

Overall Blastulation prediction	Prediction of Blastulation by 116 hpi	Embryo utilization prediction
CHLOE BLAST SCORE AUC=0.83; sensitivity=0.69, specificity=0.78, p<0.001	CHLOE BLAST SCORE AUC=0.82; sensitivity=0.65, specificity=0.85, p<0.001	CHLOE Embryo Ranking AUC=0.79; sensitivity=0.76, specificity=0.67

Study 33: ASRM 2022 – Cornell

Turning the black box into a glass box: use of transparent artificial intelligence to understand biological markers useful for embryo selection

Authors: Cristina Hickman, PhD, Nikica Zaninovic, Ph.D., Jonas Malmsten, D.P.S., Qiansheng Zhan,Ph.D., Adriana Brualla Mora, MSc, Iris Har-Vardi, PhD and Assaf Ben-Meir, MD.

Published in Fertility & Sterility

Clinic: Cornell (USA)

Type: Retrospective Cohort Study (includes comparator groups)

Objective: To compare biomarkers automatically annotated by CHLOE EQ (Fairtility) with human annotations, and to better understand their biological relevance.

Materials and methods: 799 day 5 Time-lapse (TL) videos were retrospectively assessed, morphologically graded and ranked by five experienced embryologists before being assessed by CHLOE for automatic detection of a range of biomarkers.

Results:

- CHLOE EQ score was directly related to ranking by all embryologists (p<0.001). Embryologists rarely agreed with each other (103/799- 12.9%).
- Implanted embryos had a higher CHLOE EQ score compared to embryos that did not implant. Euploids had higher CHLOE EQ score than aneuploid/mosaics. The difference in CHLOE EQ score between embryos leading to LB and not approached significance (Table 1).
- Good quality embryos, as determined by CHLOE, were more likely to be euploid (51%vs 35%,p<0.001), more likely to implant (71% vs 33%) and more likely to lead to a LB (58% vs 22%) than poor/fair quality embryos.
- There was very strong and strong levels of agreement between human and CHLOE EQ morphokinetic annotations (Table 2).
- 12% of blastocysts were identified as DUCs by CHLOE (97/799). DUC blastocysts had lower euploidy rate (31%, 29/94) compared to non-DUC blastocysts (49%, 332/684, p<0.001). 2% of A-graded ICM blastocysts were DUCs which was a five-fold lower proportion than B graded (10%)and C-graded (50%) ICM blastocysts (p<0.001).22% of embryos were identified has having severe fragmentation by CHLOE (179/799).
- Euploid embryos had a larger diameter at 114hpi (166±24 n=359 vs 154±23um n=403, p<0.001), compared to aneuploid and mosaic embryos. The embryos with an A-graded ICM had a significantly (p<0.001) larger embryo diameter (179±18µm, n=114) than embryos graded B(157±18µm, n=165) or C (153±22, n=12) by embryologists. There is a negative relationship between diameter at 114hpi & tsB (r=-0.7, p<0.001) & tB(r=-0.7, p<0.001).
- 21% (169/799) of blastocysts collapsed once, 4% (30/799) twice and 0.5% (4/799) 3 times. The severity of the collapse increased with increasing number of collapses (1 collapse: median 23%;2: 29%, 3:31%; p=0.001).

Conclusions: CHLOE can automatically quantify: (a) blastocyst diameter (which increases with expansion); when the blastocyst is expanded; (b) proportion of blastocyst that collapses and the number of times a blastocyst collapses; (c) DUC,(d) fragmentation and (e) morphokinetics (comparable to human manual annotations).

Impact statement: Automatic TL quantification allows for a consistent embryo assessment; better fluidity of information between the lab, REI, patient & clinic management; reducing operational costs whilst increasing standards of care through transparency.

Table 1. CHLOE EQ Score comparison in implanted embryos, euploids and live birth

	CHLOE EQ Score
Implanted embryos vs not implanted	0.94±0.2 n=56, vs 0.85±0.3 n=28, p<0.001
Euploid embryos vs Aneuploid/mosaics	0.85±0.2 n=360 vs 0.76±0.3 n=410, p<0.001
Live Birth vs not live birth	0.93±0.2 n=42 vs 0.87±0.2 n=36, (p=0.08).

Table 2. Level of agreement in morphokinetic parameter annotations. CHLOE vs embryologists.

Morphokinetic parameters	CCC	
tPNf	0.65	STRONG
t2	0.9	VERY STRONG
t3	0.76	STRONG
t4	0.83	VERY STRONG
T5	0.79	STRONG
T6	0.80	VERY STRONG
T7	0.82	VERY STRONG
t8	0.84	VERY STRONG
T9	0.74	STRONG
tM	0.81	VERY STRONG
tSB	0.95	VERY STRONG
tB	0.86	VERY STRONG
teB	0.61	STRONG

Study 34. Alpha 2022 – Dijon

Use of CHLOE-EQ to select embryos for transfer at the Cleavage stage: a pilot study using paired sibling embryos with known implantation

Authors: Patricia Fauque, David Taub, Noam Bergelson, Cristina Hickman.

Clinic: Dijon (France)

Authors: DIJON TEAM1; David Taub2, Noam Bergelson2, Cristina Hickman2

Introduction: Cleavage transfer, although cost effective, cannot benefit from blastocyst-related embryo selection benefits. Artificial Intelligence (AI) algorithms as tools to support embryo selection have mostly been assessed in blastocyst programs. We propose a unique validation model based on separately-transferred paired sibling embryos.

Method:

- 193 cleavage embryos were transferred (n=27), cryopreserved (n=92) or discarded (n=74). Time-lapse videos were retrospectively assessed using CHLOE-EQ (Fairtility), an embryology assistant automatically, quantifying morphokinetics, identifying anomalies such as Direct Uneven Cleavages (DUC), scoring and ranking the embryos based on CHLOE-EQ score at 40hpi. CHLOE-EQ score was compared between different embryo fates (discarded/transferred/frozen; Kruskal Wallis). Ranking of embryos for transfer by CHLOE-EQ vs embryologists were compared (Kappa Cohen's agreement).
- A paired analysis was performed in a subset following the inclusion criteria: patients with at least one pregnancy, at least two transfers, with both fresh and frozen transfers derived from the same egg collection. Cleavage embryos were selected for fresh transfer following morphological evaluation of embryos on either day 2 (n=8) or day 3(n=3). Subsequent frozen cycles were transferred on day 3 (n=26). 37 embryos from 10 patients were transferred in either fresh (n=11) or frozen (n=26) cycles. 17 lead to a pregnancy.

Results:

- Of the five DUC embryos transferred, none of them led to a pregnancy, compared to 33% (23/69) pregnancy rate observed with transferred non-DUC embryos.
- Fresh transferred embryos had a higher EQ score compared to embryos cryopreserved or discarded (Table 1).
- There was fair agreement between CHLOE-EQ and the embryologist on which embryo was selected to transfer in the first cycle (73% agreement, 51/70, Kappa=0.3, p<0.001).
- In the paired analysis, the AUCs for CHLOE ranking and embryologist ranking for prediction on implantation were comparable (embryologists AUC=0.675 vs CHLOE EQ AUC of 0.682, NS).

Table 1. CHLOE EQ and embryo fate.

Embryo fate	CHLOE EQ Score
Fresh Transfer	0.41±0.2, n=27, p<0.001
Cryopreserved	0.32±0.2, n=92, p<0.001
Discarded	0.18±0.21, n=73, p<0.001

Conclusion: CHLOE-EQ has comparable embryo selection performance to experienced human embryologists at 40 hpi. The AI based algorithm is able to identify anomalies in embryo development automatically, ensuring consistency and effectiveness in the critical decisions made during embryo selection. The paired analysis used is a unique method to assess and validate embryo selection performance

Study 35. Alpha 2022 – Gravida

Automatic assessment of Time-Lapse videos using CHLOE-EQ can automate KPI assessment to validate the operational performance of an IVF Clinic

Authors: Gravida TEAM; Adriana Brualla, Noam Bergelson, Cristina Hickman

Clinic: Gravida (Spain)

Introduction: There is a need for tools that process the raw time-lapse data into information that can be useful not only for embryo selection, but also for monitoring and quality assuring operations. CHLOE (Fairtility) is an AI software that automatically annotates time-lapse videos, generating live and ongoing Key Performance Indicators (KPIs).

Methods: Case study of CHLOE-EQ automatically calculating KPIs for a single clinic. From 200 embryos, 51 blastocysts underwent PGT-A (23 euploids, 24 aneuploids, 4 mosaics, 7 euploids transferred). Time-lapse videos were assessed retrospectively using CHLOE-EQ, annotating all morphokinetic events, abnormalities, generating CHLOE BLAST score, CHLOE-EQ score and rank. Overall fertilisation (OFR, at least 2PNs per inseminated oocyte); normal fertilisation (NFR,2PN per inseminated oocyte); 1PN (1PNR); Polyploidy (PR, 3+PN per inseminated oocyte); non-fertilised (Non-FR); Cleavage (CR, cleaved embryos per 2PN); Blastulation rates (BR, blastocysts per 2PN cultured to day 5-7).

Results:

- CHLOE-EQ demonstrated that all the KPIs assessed were within normal range: OFR (70%, 54/197); NFR (68%, 134/197); 1PNR(3%, 5/197); PR (2%, 4/197); Non-FR (27%, 54/197); CR (100%); BR (69%, 93/134).
- CHLOE Blast score at 68hpi was predictive of blastulation. CHLOE-EQ score and ranking were predictive of implantation and euploidy (Table 1).
- CHLOE-EQ association with embryo viability suggests it could be monitored as a KPI. Average CHLOE-EQ score across all embryos was 4.78±3.7.
- Only 8.9% (3/34) of DUC embryos blastulated vs. 87% (90/104) of the non-DUC embryos ($p<0.001$). These suggest that the proportion of DUCs (22%, 44/200) may also be a useful biomarker to assess operational performance.

Conclusion: Automatic KPI assessment from time-lapse images is a unique use of AI that goes beyond the more common embryo selection functionality. By turning raw time-lapse data into KPIs that are biologically and operationally relevant, it is possible to either reassure clinics that operational KPIs are within the normal range, or help identify non-conformities before they impact treatment outcome. In this way, AI can help save embryology time, reduce process-related risk, and create an early anomaly detection and prevention to ensure clinics always operate at the highest possible standards. blast prediction at 68hpi, implantation prediction of automatic CHLOE-EQ score, implantation prediction of Chloe Rank, euploidy prediction by CHLOE-EQ score and by rank. Also, blastulation rate and euploidy from DUC embryos was assessed and compared to non-DUCs.

Table 1. CHLOE Score and prediction models: Blastulation, implantation and ploidy.

Prediction models	CHLOE Scores
Blastulation prediction	CHLOE Blast score at 68hpi (AUC= 0.80)
Implantation prediction	CHLOE-EQ score (AUC=0.75) and Embryo ranking (AUC= 0.96)
Euploidy prediction	CHLOE-EQ score (AUC=0.64 and Embryo ranking (AUC=0.65)

Study 36: Alpha 2022 – Juana Crespo

CHLOE (Fairtility) can automatically annotate images from time-lapse cultured embryos for Pronucleate (PN) count, Morphokinetics and Ranking according to ploidy and implantation potential, with at least a strong agreement compared to experienced embryologists

Authors: JUANA CRESPO TEAM; ADRIANA BRUALLA, Noam Bergelson, Cristina Hickman

Clinic: Juana Crespo (Spain)

Introduction: Time-lapse culture of embryos increased the amount of information available from embryos to help prioritise embryos for treatment. Manual annotations of time-lapse images are time-consuming, prone to human error and inconsistencies. Artificial Intelligence support tools, such as CHLOE-EQ, have the potential to improve efficacy of selection, efficiency of time-lapse data processing, reduce process related risk and increase consistency in clinical decision making. To bring these benefits into reality, it is first necessary to validate CHLOE-EQ's ability to process time-lapse data.

Method: 1038 embryos were cultured in a time-lapse incubator and assessed for morphokinetics, pronucleate count and suitability for treatment by experienced embryologists. Of these, 448 were assessed for ploidy (101 euploids, 50 mosaics, 290 aneuploids, 7 failed amplification). Blind to human assessments, CHLOE-EQ (an AI assistant to support embryologists processing time-lapse images) was used to automatically assess morphokinetics, PN count and generate CHLOE viability scores: CHLOE Blast Score (designed to predict utilisation) and CHLOE EQ Score (designed to predict implantation). The agreement between embryologists and CHLOE was assessed using Concordance Correlation Coefficient (CCC, continuous data) and Kappa agreement (categorical data). Predictive performance was assessed using Binary Logistic Regression (Area under the ROC Curve, AUC).

Results:

- All morphokinetic parameters assessed had at least a strong level of agreement between experienced embryologists and CHLOE (Very strong agreement; Strong agreement, Table 1).
- PN count agreement between embryologists and CHLOE-EQ was very high (accuracy 912/950 =96%; Kappa=0.83).
- CHLOE Blast score at 68hpi was predictive of blastulation (AUC 0.754, Figure 1) and embryo utilisation (AUC 0.814). CHLOE-EQ score was predictive of embryo utilisation (AUC 0.899), euploidy (AUC 0.644, Figure 2) and failure to amplify (AUC 0.66). CHLOE-EQ score was not significantly predictive of mosaicism (AUC 0.564, NS).
- CHLOE-EQ score increased from embryos that were discarded to cryopreserved to transferred. CHLOE-EQ score increased from embryos that were aneuploid to mosaic to euploid (Table 2).

Conclusion: CHLOE automatically annotates time-lapse raw data for embryo viability assessment according to ploidy and implantation potential, with at least a strong agreement compared to embryologists.

Figure 1. CHLOE Blast Score and prediction of Blastulation. AUC – 0.75

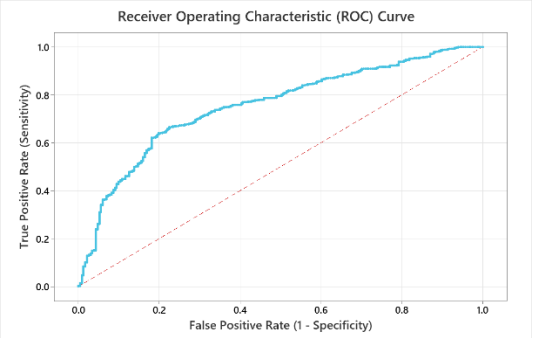


Figure 2. CHLOE EQ and prediction of ploidy. AUC – 0.64

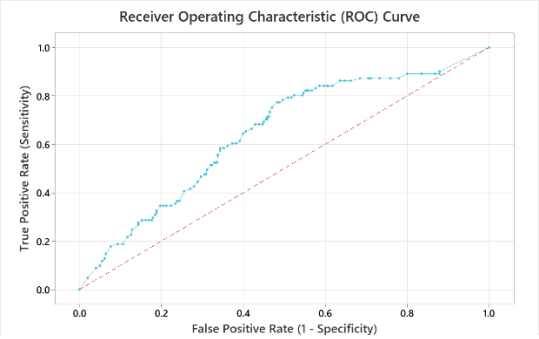


Table 1. Level of agreement between CHLOE and embryologists

Morphokinetic parameters	CCC	
tPNf	0.813	VERY STRONG
t2	0.849	VERY STRONG
t3	0.784	STRONG
t4	0.752	STRONG
t5	0.866	VERY STRONG
t6	0.854	VERY STRONG
T7	0.706	STRONG
t8	0.742	STRONG
tM	0.828	VERY STRONG
tSB	0.947	VERY STRONG
tB	0.898	VERY STRONG
teB	0.715	STRONG

Table 2. CHLOE EQ Score in embryo fate and ploidy.

	CHLOE EQ Score
Fresh Transfer vs cryopreserved vs Discarded	7.9, n=1 vs 4.3+-3.3, n=456 vs 0.41+- 0.1, n=574, p<0.001
Aneuploid vs Mosaic vs euploids	3.7+- 3.3, n=290 vs 3.7+- 3.3, n=290 vs 5.7+-3.2, n=101

Study 37: CBRA 2022 - Reproferty, Fertility FIV, Fertilitat, Primordia, Embriologica, Fairtility

Multicentre validation of CHLOE-EQ: An embryo assessment assistant based on Artificial Intelligence (AI)

Authors: MOURA B, ZEPEDA A, BRUALLA, A, HICKMAN, C.

Clinics: Reproferty, Fertility FIV, Fertilitat, Primordia, Embriologica, Fairtility

Objective: CHLOE-EQ is an embryo assessment assistant that automatically processes time-lapse videos using AI with the objective to increase consistency, efficacy of prediction whilst saving valuable embryologist time. The purpose of this study was to compare the assessment of embryoscope time-lapse videos by experienced embryologists with CHLOE-EQ (Fairtility) across four independent clinics.

Methods: Following culture of embryos in a time-lapse incubator (Embryoscope, Vitrolife) at four clinics (Clinic A N=147, Clinic B N=40, Clinic C N=143, Clinic D N=462); experienced embryologists prospectively assessed the number of pronucleates, morphokinetics, inner cell mass (ICM) and trophectoderm quality and determined which embryos should be utilised or discarded as per routine clinical practice. The same time-lapse videos were retrospectively assessed by CHLOE-EQ (Fairtility), blind to the human assessments. Intra-Correlation Coefficient (ICC) was used to quantify the level of agreement between Embryologist and CHLOE for morphokinetics: Very weak (0-0.2), weak (0.2-0.4), moderate (0.4-0.6), strong (0.6-0.8), very strong (0.8-1). Agreement of PN assessment by CHLOE and Embryologists was assessed using Kappa score. Efficacy of prediction of blastulation, utilisation, selection for transfer and ploidy was assessed against CHLOE-Blast Score and CHLOE EQ Score and CHLOE RANK using Binary logistic regression. Each of the assessments was analysed per clinic, and overall across all five clinics.

Results:

- All morphokinetics had a very strong agreement between CHLOE and embryologist annotations.
- At the individual clinic level, the lowest level of agreement was moderate for tPNa in clinic A and strong for t4 in clinic A: all other clinics had a very strong level of agreement between embryologist and CHLOE for all remaining morphokientics.
- Overall accuracy of PN assessment was 96%, with a kappa agreement 0.87 (very strong).
- Across all clinics, CHLOE BLAST Score was predictive of blastulation (AUC=0.77-0.99, p<0.001), CHLOE EQ Score was predictive of utilisation (AUC 0.81-0.91), selection for transfer (AUC 0.70-0.85), euploidy (AUC=0.65-0.75) and CHLOE Ranking was predictive of utilisation (AUC=0.70-0.86) and selection for transfer (AUC=0.85-0.86).

Conclusion: CHLOE-EQ can automatically annotate morphokinetics, count pronucleates and identify blastulation with a strong level of agreement with experienced embryologists across different clinics, bringing a consistent language of embryo assessment that can be generalised to different clinics using time-lapse incubation. Incorporating AI based tools such as CHLOE in a time-lapse clinics can help improve consistency in embryo assessment, efficacy of prediction of embryo viability whilst saving valuable

Table 1. CHLOEs algorithms predictive of viability (AUC)

	Clinic A	Clinic B	Clinic C	Clinic D	Overall
CHLOE BLAST SCORE prediction of blastulation	0.88	0.92	0.99	0.77	0.91
CHLOE EQ SCORE prediction of utilisation	0.87	0.81	0.96	0.91	0.90
CHLOE EQ Score prediction of selection for transfer	0.70		0.85	0.70	0.75
CHLOE EQ Score prediction of euploidy	0.75		0.67	0.65	0.65
CHLOE RANK prediction of utilisation	0.72	0.70	0.86	0.71	0.71
CHLOE RANK prediction of selection for transfer	0.86		0.86	0.85	0.85

Table 2. Very strong agreement between CHLOE and embryologists

Morphokinetics	Clinic A	Clinic B	Clinic C	Clinic D	Overall
tPNa	0.503	0.973		0.809	0.808
tPNf		1.0		0.959	0.969
t2	0.889	0.932	0.997	0.927	0.917
t3	0.873	0.998	0.945	0.912	0.915
t4	0.746	0.997	0.942	0.958	0.836
t5	0.809	0.998	0.928	0.972	0.895
t6		0.999		0.950	0.958
t7		1.0		0.894	0.911
t8		1.0		0.900	0.917
t9		0.995			0.995
tM		0.954		0.903	0.912
tsB		0.998		0.981	0.983
tB	0.941	0.951	0.964	0.973	0.962
teB		0.971			0.971
PN accuracy			99% [195/197]	95% [606/641]	96% [801/838]

Study 38: CBRA 2022 - Genesis

Using CHLOE-EQ to automatically monitor embryo development, identify abnormal embryos and monitor Vienna Consensus Key Performance Indicators (KPIs)

Authors: Oliveira Rocha I, Zepeda, A.; Brualla, A.; Hickman, C.

Clinic: Genesis (Brazil)

Objective: To automatically assess Vienna Consensus KPIs and identify abnormal embryos (pronucleate and cell division abnormalities) and understand the implications towards pace of embryo development.

Methodology: Following insemination, 387 zygotes from 41 patients were cultured in a time-lapse incubator (Embryoscope, Vitrolife, Sweden). CHLOE-EQ (Fairtility, Israel) was used to automatically assess time-lapse videos. CHLOE-EQ is an Artificial Intelligence (AI) based assistant that supports embryo evaluation. Embryos were cultured following routine clinical procedures. CHLOE-EQ was used to identify pronucleates (PNs), Direct Unequal Cleavage (DUCs), blastulation and morphokinetic parameters. Morphokinetic development for different PN anomalies were assessed using Kruskal Wallis. Proportion of anomalies versus blastulation were assessed using Chi-square. Key performance indicators were compared with competency value as published in the Vienna Consensus (ESHRE SIG et al., 2017).

Results:

- 387 zygotes (average 9 zygotes per patient), CHLOE-EQ was able to assess PN count in 97.4% of the zygotes.
- Normal fertilisation rate (2PN/zygotes assessed) was 66% (247/377); polyploidy rate (3PN/zygotes assessed) was 5.6% (21/377); 1PN rate was 5.8% (22/377); Degeneration rate was 8% (31/377) and fertilisation rate (two or more PN/zygotes assessed) was 71%.
- Blastulation per cleaved embryo was 50% (140/281).
- None of the DUCs were able to form a blastocyst, whilst non-DUCs had a 71% (140/198) blastulation rate.
- Severe fragmentation was observed in 2% (5/247) of 2PNs and 14% (3/22) of 1PNs and none of the 3PNs.
- 1PN embryos were less likely to blastulate than 2PN and 3PN embryos (Table 1).
- 2PNs had significantly faster morphokinetic median timings to t2 (p=0.046), t3 (p=0.008), t4 (p<0.001), t5 (p<0.001), t6(p<0.001), t7(p<0.001), t8(p<0.001), t9(p<0.001), tM (p=0.026). This difference was no longer significant at the blastocyst stages (tsB (p=0.055), tB (p=0.3) and teB(p=0.3)).

Conclusion: With no human input, CHLOE-EQ is able to automatically process time-lapse videos into data that is useful for monitoring laboratory operational KPIs as well an opportunity to learn from the data. Many IVF clinics follow the policy of a blanket discard of 1PN and DUC embryos which are not considered for treatment. However, recent publications have suggested that these unusual embryos may be considered for treatment when they follow a normal pace of embryo development all the way to the blastocyst stage. CHLOE-EQ can help identify these embryos, and further identify when these embryos are developing normally by automatically tracking their morphokinetics and supporting the embryologist in determining when unusual embryos should be considered for treatment, thus avoiding the discarding of potentially viable embryos and protecting the cumulative chances of success to individual patients.

	Blastulation	DUCs
1PN	24%(4/17), p<0.05	41% (9/22)
2PN	52% (126/244), p<0.05	28% (70/247)
3PN	50%(10/20), p<0.05	19% (4/21)

Study 39: Fairtility – IVFF

CHLOE-EQ score is a useful biomarker to assess, validate and monitor different genetic providers in the same IVF clinic

Authors: MILLER K, ZEPEDA, A., HICKMAN, C.

Clinic: IVFF (USA)

Introduction: When establishing whether an embryo is euploid, genetic providers vary in their choice of platforms, protocols, and definitions of cut-offs between euploid, aneuploid and mosaics. The purpose of this study was to investigate in a single clinic working with multiple genetic providers whether the genetic provider affected the efficacy of ploidy prediction using the same AI-based predictive algorithm for ploidy. The AI-based algorithm used has been shown to be an effective predictor of implantation and ploidy elsewhere.

Methods: Retrospective assessment of 1711 time-lapse cultured blastocysts biopsied and sent for PGT-A analysis to four separate and independent genetic providers. CHLOE-EQ is an AI-based embryology assistant that automatically analyses time-lapse videos, extracting biomarkers useful for embryo selection. CHLOE-EQ's efficacy of prediction of whether an embryo was diagnosed as euploid or chaotic was compared using binary logistic regression and quantified using Area Under the Curve (AUC). AUCs of different genetic providers were compared.

Results:

- Overall, the efficacy of prediction of euploidy of CHLOE-EQ was AUC=0.6 (n=1711). The efficacy of prediction of euploidy by CHLOE-EQ varied between the genetic providers (Table 1).
- Overall, the efficacy of prediction of chaotic aneuploidy of CHLOE-EQ was AUC=0.6 (n=970). The efficacy of prediction of chaotic aneuploidy by CHLOE-EQ varied between the genetic providers (Table 2).

Conclusion: This study has demonstrated that the efficacy of prediction of ploidy by AI-based algorithms varies between genetic providers in the same clinic.

Impact statement: CHLOE-EQ score is a useful biomarker to assess, validate and monitor different genetic providers in the same clinic, allowing the IVF clinic to better understand the different definitions of euploidy provided by different genetic providers.

Table 1. Prediction of ploidy variation between genetic providers.

Genetic providers	Prediction of ploidy of CHLOE EQ
1	AUC=0.7 (n=57)
2	AUC=0.6 (N=1635)
3	AUC=0.5 (n=13)
4	AUC=0.8 (n=6; p<0.001)
Overall	AUC=0.6 (n=1711)

Table 2. Prediction of chaotic aneuploidy variation between genetic providers.

Genetic providers	Prediction of chaotic aneuploidy by CHLOE EQ
1	AUC=0.7 (n=36)
2	AUC=0.6 (N=924)
3	Not reported
4	Not reported
Overall	AUC=0.6 (n=970)

Study 40: ASRM 2021 – Soroka & Hadassah

The association between implantation rate and automated measurements of embryo annotation and blastocyst geometry.

Authors: Iris Har-Vardi, Assaf Ben-Meir, Tamar Wainstock, Eliahu Levitas, Ben Kantor.

Published by Fertility & Sterility

Clinic: Soroka, Hadassah (Israel)

Objective: To study the possible association between implantation rate and automated annotation of embryo morphokinetic events and blastocyst geometry.

Materials and Methods:

- A nested retrospective case-control analysis of 499 single day-5 transferred blastocysts was conducted. Automatic annotation was performed by using a neural network.
- Annotation variables included time intervals (hours) from time of tPNf-tEB.
- Blastocyst geometry was measured at the mean time of tPNf-tEB (86.09 h) and included the following parameters: Inner Cell Mass (ICM) area (μm²), ICM diameter (μm), ICM shape (long diameter divided by short diameter), blastocyst size (μm) and ICM to blastocyst size ratio.

Results:

- The mean interval times of tSB-tPNf, tB-tPNf, tEB-tPNf and tEB-tSB were significantly shorter for implanted embryos compared to non-implanted embryos (Table 1).
- The mean blastocyst size for the implanted embryos was significantly larger compared to non-implanted embryos (157.53±15.9 μM versus 151.80±15.8 μM respectively, p=0.001).
- No statistically significant differences were found between implanted and non-implanted blastocysts for the remaining morphokinetic and blastocyst geometrical parameters.
- Mean embryo size of women aged <35 was larger compared to embryos of women aged ≥ 35 (154.97±16.2 vs 151.34±15.6 respectively, p=0.014), and the time interval tEB-tSB was shorter among younger versus older women (13.82±4.3 vs 15.59±5.5 respectively, p=0.001).
- In a multi variable logistic model, which adjusted for maternal age and blastocyst size, the interval time tSB-tEB was found to be negatively associated with implantation rates (adjusted OR=0.94, 95%CI 0.89-0.99, p=0.012).
- Embryo size was found to be positively associated with implantation rates (adjusted OR= 1.01, 95%CI 1.00-1.03, p=0.037).

Conclusions: Automated embryo annotation and blastocyst geometry demonstrated that a larger blastocyst size and a shorter time interval tSB-tEB are associated with increased implantation potential.

Impact Statement: To the best of our knowledge, this is the first study to investigate the effect of automated morphokinetic annotation and blastocyst geometry on implantation potential. This approach can be used as an advanced and highly effective tool for day-5 blastocyst selection and should be incorporated into a model for implantation prediction.

Table 1. Morphokinetic Interval times comparison. Implanted vs Non implanted.

Interval event times	Implanted embryos	Non-implanted	p
tSB-tPNf	71.50±4.7	72.74±4.9	p=0.007
tB-tPNf	78.37±4.5	80.00±4.5	p=0.011
tEB-tPNf	84.79±4.9	86.94±5.6	p=0.001
tEB-tSB	13.46±3.9	15.0±5.2	p=0.02

Study 41: ASRM 2021 – NYU Langone, Soroka & Hadassah

A machine learning based morphology versus automatic morphokinetic algorithms for implantation prediction

Authors: Assaf Ben-Meir, Iris Har-vardi, Gilad Karavani, Eliahu Levitas, James A. Grifo, Fang Wang, Itay Erlich

Published by Fertility & Sterility

Clinic: NYU Langone (USA), Soroka (Israel) and Hadassah (Israel)

Objective: To validate implantation prediction models using artificial intelligence algorithms (AI) to compare results from morphology recognition data, automatic morphokinetics events evaluation or a combination of both data in a retrospective multi-center study.

Materials and Methods: The automatic morphokinetic evaluation tool was trained on 36561 annotated embryos obtained between 2014 – 2019 (34132 in training set and 2429 in test set). Morphokinetic annotation and morphology evaluation of 6938 embryos with known implantation data (KID) were used to train and test CHLOE, an AI algorithm. The training set consisted of 6363 embryos (1078 KID-positive and 5285 KID-negative). The blind test set consisted of 575 embryos (171 KID-positive and 404 KID-negative). The embryos were scored for implantation potential by CHLOE based on automatic evaluation of morphokinetic and morphology data. We compared our combined morphokinetic and morphology model to models that only take in morphokinetic events or the last frame of embryo development.

Results:

- In this study we demonstrated:
- A machine-learning based automatic annotation of embryo development events (r2=0.95).
- A robust implantation prediction tool evaluating (AUC) continuously every hour from 30 to 116 hpi with progressive improvement and maximal AUC of 0.65 at 116 hours.
- After morula stage it showed better prediction with AUC of 0.68 at 116 hours.
- Combining both algorithms revealed that morphokinetics annotation added value until the start of blastulation (around 90 hours).
- After the start of blastulation, the combined tool was similar in AUC to morphology alone with AUC of 0.68 at 116 hours.

Conclusions: Assessment of blastocyst morphology is sufficient for most of its competence evaluation. However, prediction at cleavage stage is better when incorporating morphokinetic data into morphology evaluation.

Impact Statement: Given the high degree of inter- and intra-observer variability and subjectivity in morphokinetic and morphology assessment among embryologists, time-lapse automatic annotations combined with AI models are a way to standardize and objectively quantitate embryo competence.

Keywords: Artificial intelligence, embryo selection, time-lapse image, morphokinetics annotation

Study 42: SEF 2022 - DEXEUS

Valoración de un nuevo sistema basado en inteligencia artificial para el analisis del desarrollo embrionario y la selección del mejor blastocisto a transferir

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Clínica: Dexeus (España)

Introducción: La utilización de incubadores Time-lapse ha permitido disponer de mayor información para la evaluación y selección embrionaria. La incorporación de algoritmos para determinar los embriones con mayor probabilidad de implantación fue el paso siguiente para optimizar y estandarizar las decisiones. Actualmente con la incorporación de la Inteligencia Artificial (IA) dichas herramientas podrán ir mejorando a medida que vayan registrándose nuevos casos. El objetivo del estudio es valorar un nuevo sistema de selección embrionaria basado en IA y su adecuación a los nuevos parámetros de la clasificación ASEBIR2021.

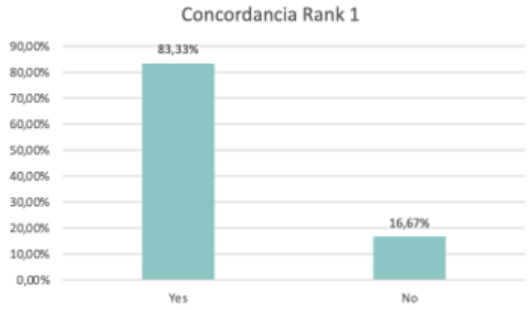
Material y métodos: Estudio piloto observacional retrospectivo de 60 ovocitos microinyectados y cultivados en Embryoscope TM correspondientes a 5 pacientes. El desarrollo embrionario y selección del embrión a transferir fue realizado por embriólogos experimentados. A su vez, todas las imágenes registradas fueron analizadas por el nuevo software Chloe TM que proporcionó información de las divisiones y principales eventos, y del pronóstico de implantación de cada embrión. Se analizó el grado de correspondencia entre ambos sistemas.

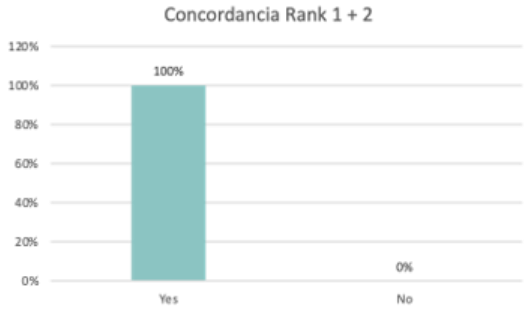
Resultados: La correspondencia en cuanto a la fecundación a las 18h post ICSI fue 100% (60/60).

- El estadio embrionario a las 44h y 68h coincidió en 87% (67/77) de las anotaciones, siendo en todos los casos la diferencia de 1 única célula. El estadio a las 116h coincidió 100% (25/25).
- La correspondencia en la selección del primer blastocisto a transferir fue 83% (5/6) no siendo la diferencia relevante ya que el embrión transferido fue el TOP2 del ranquin propuesto.
- La medición automatizada del grado de expansión del blastocisto, área de la MCI y número de células del trofectodermo permitió incorporar la nueva clasificación ASEBIR2021 al sistema.

Conclusiones: El nuevo sistema de análisis y selección embrionario basado en IA ha demostrado ser de gran efectividad proporcionando estandarización de las observaciones, mayor rapidez y capacidad de adaptación a la incorporación de nuevos parámetros de selección.

Grado de concordancia en la selección embrionaria





Study 43: PCRS 2022 – IVFF

CHLOE-EQ score is a useful biomarker to assess, validate and monitor different genetic providers in the same IVF clinic

Authors: MILLER K, GRUNWALD A, ZEPEDA A, HICKMAN C.

Clinic: IVFF

Introduction: When establishing whether an embryo is euploid, genetic providers vary in their choice of platforms, protocols, and definitions of cut-offs between euploid, aneuploid and mosaics. The purpose of this study was to investigate in a single clinic working with multiple genetic providers whether the genetic provider affected the efficacy of ploidy prediction using the same AI-based predictive algorithm for ploidy. The AI-based algorithm used has been shown to be an effective predictor of implantation and ploidy elsewhere.

Methods: Retrospective assessment of 1711 time-lapse cultured blastocysts biopsied and sent for PGT-A analysis to four separate and independent genetic providers. CHLOE-EQ is an AI-based embryology assistant that automatically analyses time-lapse videos, extracting biomarkers useful for embryo selection. CHLOE-EQ's efficacy of prediction of whether an embryo was diagnosed as euploid or chaotic was compared using binary logistic regression and quantified using Area Under the Curve (AUC). AUCs of different genetic providers were compared.

Results: Overall, the efficacy of prediction of euploidy of CHLOE-EQ was AUC=0.6 (n=1711). The efficacy of prediction of euploidy by CHLOE-EQ varied between the genetic providers from 0.5 to 0.8: 1: AUC=0.7 (n=57); 2: AUC=0.6 (N=1635); 3: AUC=0.5 (n=13); 4: AUC=0.8 (n=6; $p<0.001$).

Overall, the efficacy of prediction of chaotic aneuploidy of CHLOE-EQ was AUC=0.6 (n=970). The efficacy of prediction of chaotic aneuploidy by CHLOE-EQ varied between the genetic providers: 1: AUC=0.7 (n=36); 2: AUC=0.6 (N=924); Genetic Providers 3 and 4 did not report any chaotics.

The patients whose embryos were assessed by each of the genetic providers had similar age ($p>0.05$).

Conclusion: This study has demonstrated that the efficacy of prediction of ploidy by AI-based algorithms varies between genetic providers in the same clinic.

Impact statement: CHLOE-EQ score is a useful biomarker to assess, validate and monitor different genetic providers in the same clinic, allowing the IVF clinic to better understand the different definitions of euploidy provided by different genetic providers.

Study 44: ESHRE 2023 – Memorial

The impact of CHLOE-EQ and embryologist seniority on the ability and confidence to predict ploidy

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Published by Human Reproduction

Study question: Can embryologists and CHLOE-EQ predict ploidy? Does their confidence and ability to predict vary with embryologist seniority?

Summary answer: High inter-observer variability between embryologists on prediction of ploidy. CHLOE-EQ provided a consistent prediction of ploidy.

What is known already: Previous studies have demonstrated the value of using Artificial Intelligence (AI)-based tools, such as CHLOE-EQ (Fairtility), to support, quantify and standardize embryo assessment. CHLOE-EQ uses AI-based algorithms to predict implantation. Recent studies have demonstrated that the algorithms also have ploidy predictive capabilities. Little is known about the ability of human embryologists to predict ploidy of blastocysts deemed suitable for biopsy, and whether this ability to predict varies with seniority or confidence level.

Study design, size, duration: Cohort study including 141 patients treated in a Memorial Sisli Hospital ART and Reproductive Genetics Center between January 2020-August 2022, with at least 4 blastocysts with different PGT-A results per cycle, leading to a total of 734 embryos. The same blastocysts were blindly assessed by CHLOE-EQ and by a senior and a junior embryologists working in the same clinic. Intraobserver variance of senior embryologist was also evaluated.

Participants/materials, setting, methods: Embryologists were asked to predict whether a blastocyst was euploid or aneuploid, their confidence of this determination (confident, neutral, not confident), the rank of the embryos based on chance of being euploid. The same embryos were assessed using CHLOE-EQ, scoring embryos from 0 to 10. The extent of mosaicism (from 35-70%) was quantified. Trophectoderm biopsy was performed to embryos at least 3BB, four low quality blastocysts (Aneuploid:5AC,4AC,6CB; Euploid:2AA) were also included into the study.

Main results and the role of chance: The average patient age was 33±4 years (ranging from 22 to 39 years). Embryologists agreed on euploid prediction in a minority of blastocysts(48%,324/670). Agreement of the senior embryologist on same embryos in a different time was higher (Kappa=0.42,moderate) than with the junior embryologist (Kappa=0.19(slight)/0.26(fair)), suggesting seniority affected prediction consistency. CHLOE-EQ ranking had fair agreement with the embryologists (Kappa=0.22,0.22,0.23), bringing consistency to prediction irrespective of seniority. Confidence was not affected by seniority (senior vs junior: 'Confident'/'Neutral'/'Not confident':60/26/14% vs 57/27/16% vs 66/24/10%,NS). Efficacy of prediction of ploidy reduced with junior embryologist (senior: AUC=0.58,0.57 vs junior:AUC=0.55). The senior embryologist was able to predict ploidy with a greater accuracy when 'confident' (AUC=0.60,n=441,p<0.001) compared with 'not confident' (AUC=0.50,n=107,NS). This was not the case with the junior embryologist ('Confident' AUC=0.56,NS vs 'Not Confident' AUC=0.54,NS). Euploidy rate was greater in high scoring embryos(CHLOE-EQ 5.1-10) than low(0-5) scoring (60%, 272/457 vs 48%,135/280;p<0.005,AUC=0.58). This was maintained in blastocysts where the senior embryologist was 'confident'(64% vs 54%) and 'not confident' (57% vs 36%), showing consistency in assessment irrespective of confidence. CHLOE-EQ score reduced with increasing degree of mosaicism (Euploid 6.3±2; Mosaic<35% 5.98±2.87; Mosaic>50% 4.31±2.80; Mosaic>70% 2.85±4;p=0.04). Euploid embryos had a higher CHLOE-EQ score than aneuploid/mosaic embryos (6.3±2, n=396 vs 5.78±2,n=319;p=0.008).

Limitations, reasons for caution: Mostly optimal quality blastocysts were included in this study. There is a need to better understand the role of Artificial Intelligence in improving consistency of selection of blastocysts for biopsy, and to extend this study for viable lower quality blastocysts to be included rather than discarded.

Wider implications of the findings: Effective prediction of ploidy can (i) improve biopsy criteria so that viable embryos are not discarded, (ii) reduce the cost of PGT-A by prioritizing embryos with increased chances of being euploid. CHLOE-EQ's ploidy prediction improved consistency can support both PGT-A programs, and cycles where PGT-A is not an option.

Study 45: ESHRE 2023 – Juana Crespo

Assessment of ongoing clinical outcomes prediction of an AI system on retrospective SET data

Authors: Teruel Lopez J, Miret Lucio C, Lozano Zamora M, Crespo J, Brualla, A.; Zepeda, A.; Hickman, C.

Published by Human Reproduction

Study Question: Would patients with fresh and frozen embryo transfer had achieved pregnancy before if the embryo was chosen by AI?

Study Answer: CHLOE (AI) can predict pregnancy, ongoing clinical pregnancy, and miscarriage following a single embryo transfer (SET).

What is known already?: The use of time-lapse incubators has provided embryologists with more information to evaluate embryo development, resulting in varying clinical practices among clinics in prioritizing this information. However, manual annotation of time-lapse videos is time-consuming and prone to interoperator inconsistencies. To overcome these challenges, AI tools like CHLOE (Fairtility) can be utilized. CHLOE uses AI-based predictors to predict implantation and provides clarity on the biological factors driving these predictions. However, before incorporating AI tools into clinical practice, it is important to validate their effectiveness.

Study design, size and duration: Single study center that took place between July of 2021 and December 2022 at a private clinic in Spain. This was a retrospective cohort analysis that reviewed 118 time-lapse videos from single fresh embryo transfers and 92 time-lapse videos from single frozen embryo transfers with known ongoing clinical pregnancy outcome. CHLOE EQ score and CHLOE Rank efficacy of prediction of clinical outcomes and miscarriage was quantified using the metric AUC.

Participants/materials, setting, methods: Time-lapse videos were evaluated using CHLOE (Fairtility), an AI tool, to determine CHLOE EQ score and rank related to clinical outcomes (biochemical pregnancy, clinical pregnancy, and miscarriage) following fresh and frozen SET. CHLOE rank and embryology were compared with chi-square and AUC was calculated with logistic regression to measure prediction accuracy. T-test was used to check differences in CHLOE EQ score in different outcomes.

Main Results and the role of chance: Embryologist vs CHLOE Ranking weren't significant (p>0.05). In fresh SET the mean EQ score was 7.76, and in frozen SET was 7.07. Following fresh SET, CHLOE EQ score was not-significantly predictive of biochemical pregnancy (AUC=0.53, n=104, p=0.462), clinical pregnancy (AUC=0.51, n=79, p=0.949), and miscarriage rate (AUC=0.50, n=68, p=0.949); CHLOE Ranking was more predictive than embryologist rank for biochemical pregnancy (embryologist vs CHLOE rank: AUC=0.51, p>0.05 vs AUC=0.61, p>0.05), clinical pregnancy (embryologist vs CHLOE rank: AUC= 0.51, p>0.05 vs AUC=0.70, p>0.05) and miscarriage rate (embryologist vs CHLOE rank: AUC= 0.51, p>0.05 vs AUC=0.75, p>0.025). Following frozen SET, only top 1 embryos ranked by embryologists were transferred, and CHLOE EQ score was predictive of biochemical pregnancy (AUC=0.60, n=85, p=0.213), clinical pregnancy (AUC=0.64, n=60, p=0.919), and miscarriage rate (AUC=0.87, n=52, p=0.437); CHLOE Ranking was predictive of biochemical pregnancy (AUC=0.59, p>0.05), clinical pregnancy (AUC= 0.64, p>0.05) and miscarriage rate (AUC= 0.90, p>0.05).

Limitations: This study is a single-center retrospective analysis where embryos were chosen for transfer by human embryologists and is part of a broader effort to validate the responsible integration of AI into clinical practice.

Wider implications: The use of AI-based tools has the possibility to enhance the consistency, efficiency, and effectiveness of embryo selection. The information from quantitative and qualitative morphokinetics provided by AI tools like CHLOE brings greater clarity to predictions, enabling more personalized care for each individual embryo.

Study 46: ESHRE 2023 - IVIRMA

Using artificial intelligence platform coupled to an existing time system; external validation of an automatic embryo score to assist in selection

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Published by Human Reproduction

Study question: How does a novel artificial intelligence-based embryo evaluation system work in Geri® time-lapse systems?

Summary answer: Automatic score provided by CHLOETM for embryos cultured in Geri® was associated with conventional morphology, euploidy, implantation and live birth.

What is known already: Artificial intelligence has been making headway in assisted reproduction in recent years. Many companies have developed different models for automated embryo evaluation and selection, such as CHLOE™ software (Fairtility, Israel). According to the developers, it is an orchestration of cutting-edge morphological and morphokinetic AI algorithms, trained over 100,000 embryo videos and tens of millions of images. Different laboratories validated its use in specific time-lapse systems (Embryoscope, Vitrolife), and the results were shown in previous international congresses. However, this is the first time that an objective and independent review of CHLOETM has been performed on Geri® (Genea Biomedx, Australia) time-lapse system.

Study design, size, duration: This retrospective analysis included 3,568 embryos from 417 patients that underwent IVF treatments in a single center. Embryos were cultured in Geri® (Genea Biomedx, Australia) time-lapse systems and routinely evaluated by senior embryologists according to the ASEBIR criteria (from A-high quality to D-low quality and excluded embryos). Then, embryos were automatically scored by CHLOETM from 0 to 1.

Participants/materials, settings, methods: Automatic embryo score was compared with conventional morphology (n=3,568 embryos), ploidy (n=467 embryos), and clinical outcomes for single blastocyst transfers (n=461).

Main results and the role of chance: The comparison between the embryo score provided by CHLOE™ and the category assigned by embryologists showed a direct association*. The means were 0.97 ± 0.10 for A (n=123); 0.89 ± 0.21 for B (n=842); 0.74 ± 0.30 for C (n=607), 0.24 ± 0.31 for D (n=997) and 0.15 ± 0.25 for excluded embryos (n=403). Regarding the chromosomal status, embryos with normal content had significantly higher score than abnormal ones. Following results are presented per quartiles of similar sample size: the euploidy rates were 35.9% for score £ 0.81 (n=117), 40.8% for score 0.81-0.96 (n=120), 48% for score 0.96-0.99 (n=125) and 58.1% for score >0.99 (n=105)*. Implanted embryos achieved significantly higher marks than non-implanted embryos: 0.93±0.15 (n=251) vs. 0.85±0.25 (n=210)*. Also, automatic embryo score was higher for embryos that led to a live birth than those that did not: 0.94±0.15 (n=188) vs. 0.86±0.24 (n=243)*. Focusing on top quality embryos (A+B), the score means were 0.94 ± 0.16 for implanted good quality embryos 0.88 ± 0.22 for non-implanted ones*.

*p<0.05

Limitations, reasons for caution: This project is limited by its retrospective and single-center nature. Multicenter validation would be necessary to ensure it is a safe and effective method of embryo assessment.

Wider implications of the findings: In addition to verifying that automatic scoring agrees with embryologists, this study demonstrated CHLOE's ability to distinguish between potential embryos with similar morphological characteristics. Therefore, CHLOE EQTM score may help embryologists make decisions.

Study 47: Fairtility – UZ Brussels

Validation of the CHLOE-EQ tool for embryo evaluation and selection.

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Unsubmitted.

Study question: What is the agreement of embryo utilization and selection rates between the CHLOE-EQ AI-based tool and the manual method by competent embryologists?

Summary answer: CHLOE-EQ and embryologists agreed on pronuclear assessment. CHLOE-EQ score was predictive of blastulation and utilization rates.

What is known already: Embryo evaluation and selection is a time-consuming, subjective process requiring intensive training as it relies on static morphological assessment. Due to the limitations of static morphological assessment, time-lapse imaging was introduced in the IVF lab. To improve the selection process for embryos with the highest chance of implantation, artificial intelligence (AI) was initiated as a standardized and objective tool for embryo evaluation and selection. Due to its deep learning capabilities, AI has the ability to look at parameters overlooked by the human eye. The predictive capabilities of AI are constantly being studied.

Study design, size, duration: A retrospective study analyzing embryos cultured in an Embryscope+ time-lapse incubator between September and December 2022. Embryos were graded by skilled embryologists using the adapted Gardner morphological assessment in use at a university fertility-center. Fertilization, decisions to transfer, cryopreserve or discard were based on morphological scoring and internal guidelines. Fertilization, utilization rates and implantation rates were analyzed comparing the CHLOE-EQ automated scoring and the manual scoring. Embryo quality scores were calculated for the AI-tool.

Materials, methods: All embryos (n=1554) were manually assessed by at the fertility-clinic. The same embryos were assessed by CHLOE-EQ (Fairtility). The agreement between embryologists and CHLOE-EQ was calculated for pronuclear (PN) assessment. AI's accuracy in predicting blastulation, utilization, ploidy and implantation rates (for both CHLOE EQ score and CHLOE Blast score (at 68hpi)) were assessed using binary logistic regression (AUC). The AI-generated embryo ranking was compared to the utilization.

Main results and the role of chance: CHLOE-EQ and embryologists agreed on pronuclear count in 89.9% of putative zygotes (1297/1442), with only 10.1% requiring correction. Most of the disagreements involved over-counting PNs (n=89) compared to under-counting (n=60) relative to embryologists. CHLOE-EQ correctly identified 2PNs in 94.9% of the 2PN embryos (1094/1153) relative to the embryologist annotations.

At 68hpi, CHLOE-Blast score was predictive of blastulation (AUC:0.80 ,n=1153, baseline=56.5%,p<0.001) and utilization (AUC:0.79, n=1153,baseline=49.2%,p<0.001).

The AI-generated embryo ranking showed a strong correlation with the embryologists' decision to freeze, transfer, or discard embryos (AUC:0.74, n=1153, baseline=49.2%, p<0.001).

CHLOE-EQ score was not able to predict pregnancy (AUC:0.65, n=141, baseline=43.2%, p=0.01) and ploidy status (AUC:0.60, n=54, baseline=40.7%, p=0.21), However, it could predict utilization (AUC:0.84 n=1153, baseline=49.2%, p<0.001).

A significant higher CHLOE-EQ score was noted for embryos that blastulated (6±3.65,n=651 vs 1.45±3.18, n=502, p<0.001), embryos that were utilized (6.73±3.77, n=567 vs 1.46±2.51, n=586, p<0.001), embryos selected for transfer (7.15±3.62, n=142 vs 3.61±4, n=1011, p<0.001) as well as embryos that implanted (8±3.19, n=61 vs 6.41±3.8, n=80, p=0.01). Higher CHLOE-EQ scores, although not significant, were also found for embryos that were euploid (6.35±3.6, n=22 vs 5.12±3.6, n=16, p=0.22).

Limitations, reasons for caution: Data were retrospective and observational. Clinical pregnancy rates and (cumulative) live birth rates were not assessed. Moreover some cycles had no fresh transfer. Larger datasets are required to assess pregnancy and ploidy predictions. In cases of discrepancies between embryologists and AI, further studies are required to determine the ground truth.

Wider implications of the findings: AI can accurately assess pronuclear formation and has good predictive capabilities for blastulation and utilization rates. The AI-tool provides useful and reliable scores to assist the IVF-lab in deciding embryo fates. However, further validation on larger sample size is required before implementation in the clinical setting.

Study 48: Fairtility – IASO

Reimagining KPI monitoring with CHLOE-KPI: Using Artificial Intelligence to automatically assess Vienna Consensus Key Performance Indicators to quantify operational performance

T. Triantafillou1; Alexa Zepeda, Adriana Brualla, Cristina Hickman

Clinic: IASO (Greece)

Study Question: Can an AI-based algorithm be used to automatically assess operational performance of an IVF lab based on Vienna Consensus key performance indicators?

Study Answer: CHLOE-KPI can automatically quantify Vienna Consensus traditional KPIs. CHLOE-EQ's ability to predict embryo viability makes it a useful automatic biomarker to monitor operational performance sensitively.

What is known already?: Key Performance Indicators (KPIs) are objective measures for systematically monitoring and evaluating the IVF laboratory's contribution to patient care, a critical element of every IVF clinic Quality Management System. KPIs currently rely on definitions which are simple to assess (fertilisation, cleavage, blastulation), and we do not routinely use other biomarkers to monitor operations (such as morphokinetics or CHLOE-EQ score). Manual assessment of morphokinetics is time-consuming and prone to inter and intra-operator variation, posing challenges to introducing these as routine KPIs for monitoring IVF laboratory performance. CHLOE-KPI may provide an opportunity to derive more sensitive KPIs for detecting operational non-conformances.

Study design, size and duration: Retrospective comparative analysis with 3417 time-lapse videos of putative zygotes collected between January and December 2022, from IVF and ICSI embryos from a private single fertility clinic. CHLOE-KPI was used to automatically detect Vienna consensus KPIs.

Participants/materials, setting, methods: 3417 putative zygotes were assessed by CHLOE-KPI to provide Vienna Consensus KPIs: overall fertilization rate, normal fertilization rate, polyploidy rate, 1PN, degeneration rate, DUC rate, day 5 blastulation rate and overall blastulation rate. CHLOE-EQ was verified as a biomarker to predict for embryo viability using binary logistic regression (AUC).

Main Results and the role of chance: Overall fertilization rate (2+PN/zygotes assessed) was 76.2% (2604/3417); Normal fertilisation rate (2PN/zygotes assessed) was 73.4% (2508/3417); polyploidy rate (3PN/zygotes assessed) was 2.8% (96/3417); 1PN rate was 5.3% (181/3417); Day 5 and overall blastulation rate were found to be within the Vienna Consensus KPIs [50.8% (1275/2508), 56.2% (1409/2508)]. All of these automatically collected KPIs were found to be within the normal range. Morphokinetics were also automatically collected and monitored over time. CHLOE-EQ Score was predictive of utilization (AUC=0.94, n=1425, p<0.001), selection for transfer (AUC=0.74, n=1425, p<0.001), blastulation (0.87, n=3417, p<0.001) and ploidy (AUC=0.55, n=760, p=0.11)

Limitations: There is a need to redefine the Vienna consensus within the context of CHLOE-KPI: to establish optimal frequency and time-points assessment, quantify live KPI monitoring, normalize patient confounders and measure individual biomarkers to predict sub-optimal culture conditions leading to reduced clinical outcome and known changes to the culture environment.

Wider implications: CHLOE-KPI can provide KPI insights to detect and prevent non conformances before they get a chance to affect clinical outcome. Early prevention of operational anomalies provides an opportunity to improve standards of care. Automatic KPI monitoring driven by AI may be the key for standardizing and optimising care.

Study 49: BRITISH FERTILITY 2024 – Hausken

Assessment of stimulation protocol's effect on embryo quality and clinical outcome and how artificial intelligence (AI) might help monitor different clinical practices.

Authors: Shabana Sayed, Anat Safran, Adriana Brualla, Alexa Zepeda, Cristina Hickman

Clinic: Hausken (Norway).

Objective: Assessment of the effect of type of stimulation on clinical outcome and embryo quality as assessed by an AI algorithm.

Study Answer: Antagonist derived embryos are faster, have higher quality and were associated with higher pregnancy rate than agonist derived embryos.

Methods: Retrospective comparative analysis with 1248 time-lapse videos collected between May-October 2022 from IVF and ICSI embryos from a private single fertility clinic. Embryo videos were automatically assessed by CHLOE-EQ (Fairtility), an AI embryologist support tool.

The assessment of the effect of stimulation protocols (antagonist vs long agonist) on clinical outcome and embryo quality, measured by an AI embryo quality score was performed using t-test.

Embryo development was assessed by comparing morphokinetic events at hours post insemination in each group: antagonist vs long agonist (t-test). Demographic bias was measured using t-test.

Results Type of stimulation protocol was significantly associated with AI embryo quality Score and embryo development, with antagonist protocol derived embryos being faster (t4, t9,tM and tSB (p=<0.05) and having a higher embryo quality score compared to long agonist protocol (1.6 +/- 3 vs 0.3 +/- 1, p<0.001). Antagonist protocol derived embryos led to higher pregnancy rate (67%, n=20) compared to Long agonist protocol-derived embryos (25%, n=5, p=NS).

Antagonist and Agonist derived embryos came from patients of similar age (35 +/- 5.4 vs 35.4 +/- 6.9, p=NS). However, BMI was higher for antagonist compared to agonist (25.15 +/- 4.5 vs 22.15 +/- 3.05, p=<0.001). Pregnancy rate and embryo quality did not differ among patients with overweight or obesity (p=NS). Comorbidities were evenly distributed among both groups of patients.

Conclusions: Antagonist derived embryos are faster, have higher quality and were associated with higher pregnancy rate than agonist derived embryos. AI can provide monitoring of clinical practices to determine if protocols influence in clinical outcomes and KPIs.

Study 50: BRITISH FERTILITY 2024 – HSFC

Identifying the optimal morphokinetic range for euploid embryos using an Artificial Intelligence (AI) based embryologist tool.

Authors: Samantha Knight, Raj Joshi, Geetha Venkat, Suvir Venakataraman, Alexa Zepeda, Cristina Hickman

Objective: To assess CHLOE-EQs prediction of ploidy and identify the optimal time-range of morphokinetic events in euploid embryos using an AI automatic embryo assessment tool.

Methods: Retrospective cohort study assessing 52 time-lapse (TL) embryo videos with known ploidy and 166 TL-videos with unknown ploidy. The prediction of euploidy by CHLOE-EQ Score, an embryo quality AI score, was assessed with binary logistic regression (AUC). The morphokinetic events (tPNa-tEB) were automatically annotated in hours post insemination (hpi) using CHLOE-EQ (Fairtility). The frequency distribution for each morphokinetic parameter was compared between euploid embryos and embryos with unknown ploidy. Optimal range was established based on interquartile range (Q1-Q3) of euploid embryos. The interquartile ranges of euploid embryos and all embryos (unknown ploidy) were compared with t-test.

Results: CHLOE-EQ Score was predictive of euploidy (n=52, AUC=0.71, baseline=44%, $p<0.05$). For each morphokinetic event, an optimal range for identification of euploids was identified in hpi. (tPNa:17.1-18.7; tPNf: 22.3-25.5; t2:25.2-28.2; t3: 36.4-39.7; t4:36.9-41; t5:49.2-54.9; t6:51.6-56.9; t7:51.9-57.4; t8:53.6-66.4; t9:68.5-80.7; tM:78.2-92.3; tSB:91.4-104; tB:98.9-113.3; tEB:104.6-119.9). Optimal range of euploid embryos was smaller than the interquartile range for all embryos ($p<0.05$): tPNa(1.6 vs 10.4), tPNf(3.2 vs 5.1), t2(3 vs 5.7), t3(3.3 vs 7.8), t4(4.1 vs 6.2), t5(5.7 vs 10.4), t6(5.3 vs 11.5), t7(5.5 vs 13.7), t8(12.8 vs 17.9), t9(12.2 vs 16), tM(14.1 vs 14.8), tSB(12.6 vs 13.4), tB(14.4 vs 15.2); tEB(15.3 vs 18.9).

Conclusion: CHLOE-EQ can identify the optimal morphokinetic time range to maximise the chance of identifying a euploid embryo; a potentially valuable biomarker for embryo selection, especially within the context of a PGT-A program, to provide consistency in embryo selection for biopsy and to help reduce the chance of viable embryos being discarded.

Study 51: ASEBIR 2023 – INSTITUTO BERNABEU

Clinical validation of an automatic score of artificial intelligence (CHLOE EQ) and its relationship with euploidy and gametes

Authors: Jorge Ten, Adriana Brualla, Alexa Zepeda, Cristina Hickman

Introduction: Embryo selection is a critical aspect in assisted reproduction, and the integration of artificial intelligence into incubation systems, such as the Geri, can significantly improve the accuracy and efficiency of the process. Fairtility's CHLOE AI application, integrated with time-lapse incubators, has proven to be a useful tool for embryo evaluation and selection in the IVF laboratory. The CHLOE EQ Score considers multiple morphological and kinetic criteria to assess embryo quality and predict its implantation potential.

Objectives: This study aimed to validate the CHLOE EQ score in relation to euploidy and gametes. Comparing embryo quality by CHLOE EQ score in euploid and aneuploid embryos, likewise, between own and donor oocytes, between asthenozoospermic semen, between embryos from donor and own semen, between embryos from ejaculate semen and testicular / epididymal semen, and embryo quality between semen samples with normospermia and hypospermia. With these objectives, we sought to determine the efficacy of the CHLOE EQ score in the evaluation of embryo quality in IVF cycles and identify factors that could affect this quality.

Material and Methods: A total of 3,529 embryos and 2,147 donor oocytes and 1,464 oocytes from women undergoing IVF cycles at our center were included in the study. CHLOE EQ score was measured in all embryos as a marker of embryo quality. Embryo quality (t-test) was compared between euploid and aneuploid embryos. Likewise, between embryos from ejaculate semen and testicular/epididymal semen, between embryos with asthenozoospermia (<32% vs. >32%), between embryos from donor and own semen, and between semen samples with normospermia and hypospermia. The prediction of euploidy was analyzed by logistic regression (AUC).

Results: The CHLOE EQ score in euploid embryos was higher compared to aneuploid embryos (0.7±0.33, n=112 vs 0.59 ± 0.35, n=225, p=0.004), and was also predictive of euploidy (AUC=0.62, n=337, p=0.006).

The CHLOE EQ score in donor oocytes was significantly higher than in own oocytes (0.42±0.42 vs 0.35±0.39, p<0.001). Embryos from ejaculated semen showed significantly higher embryo quality than embryos from testicular/epididymal semen (0.39±0.41 vs 0.32±0.39, p=0.03). Embryos from semen with an adequate percentage of motility showed a significantly higher embryo quality than embryos from semen with a lower percentage of motility (0.40±0.41 vs 0.36±0.41, p=0.008). No significant differences were found in embryo quality between embryos from donor and own sperm, or between sperm samples with normospermia and hypospermia.

Conclusions : The CHLOE EQ score is a useful tool for assessing embryo quality in IVF cycles, as well as for predicting euploidy. Donor oocytes and embryos from ejaculated semen showed significantly higher embryo quality than own oocytes and embryos from testicular/epididymal semen. In addition, embryos from semen with an adequate percentage of motility showed a significantly higher embryo quality than embryos from semen with a lower percentage of motility. These findings indicate that CHLOE EQ may be a useful instrument for assessing possible factors related to embryo quality. In addition to providing an indicator of embryo quality in an automated, personalized and efficient way.

Study 52: ASEBIR 2023 – NEXT FERTILITY

Evaluation of the relationship between trophectoderm quality and MCI and euploidy in embryos in IVF through CHLOE EQ

Authors: Emilio Gomez, Alexa Zepeda, Adriana Brualla, Cristina Hickman.

Introduction: Embryo selection in the context of IVF is essential to maximize the chances of success. In this sense, the evaluation of trophectoderm quality and MCI are important to identify euploid embryos. Recently, a new selection tool has been developed, the CHLOE EQ score, which is based on the evaluation of the morphokinetic and morphological characteristics of the embryo using Artificial Intelligence. The aim of this study was to investigate whether trophectoderm quality and MCI are related to euploidy and CHLOE EQ score in IVF embryos.

Materials and methods: A retrospective study was conducted in which a total of 393 embryos from IVF cycles were included. The quality of trophectoderm and MCI in embryos was evaluated according to Gardner's criteria. Chromosome analysis using PGT-A was performed to determine euploidy. The CHLOE EQ score was used to assess the morphological quality of the embryo. The Chi-square test was used to calculate the relationship between the quality of trophectoderm and MCI and euploidy. To compare the quality of the trophectoderm and MCI and CHLOE EQ, the Kruskal-Wallis test was used. Finally, binary logistic regression was used and AUC was calculated to assess whether CHLOE EQ was predictive of euploidy.

Objectives: The objective of this study was to evaluate the relationship between trophectoderm and MCI quality and euploidy, and to determine whether the CHLOE EQ score is predictive of euploidy.

Results: The results showed that the CHLOE EQ score is a significant predictor of euploidy, with an AUC of 0.57, n=574, p=0.003. In addition, a significant difference was found between trophectoderm and MCI quality and euploidy. Category A embryos had an euploidy rate of 70%, while category D embryos had an euploidy rate of 34.6% (p=0.001 for both comparisons). A significant difference was also found between trophectoderm and MCI quality and CHLOE EQ score. Category A embryos had a significantly higher CHLOE EQ score than category D embryos (9.2 vs. 4.6 for trophectoderm, and 9.2 vs. 0.4 for MCI, p<0.001 for both comparisons).

Conclusion: In conclusion, the results of this study suggest that the CHLOE EQ score is a significant predictor of euploidy in IVF embryos. In addition, trophectoderm quality and MCI were found to be related to euploidy and CHLOE EQ score. These findings may be useful for improving embryo selection in IVF cycles and improving treatment success rates.

Study 53: Fairtility – Hadassah & Sorroka

Decoupling implantation prediction and embryo ranking in machine learning: the impact of clinical data and discarded embryos

Authors: Itay Erlich Sotirios, H Saravelos, Cristina Hickman, Assaf Ben-Meir2,5, Iris Har-Vardi, James A. Grifo, Semra Kahraman, Assaf Zaritsky

Objective: To determine whether data derived from (i) clinical characteristics shared among sibling embryos and (ii) discarded embryos, are relevant for (a) implantation prediction and (b) embryo ranking.

Design: Multi-center, retrospective cohort analysis using machine learning algorithms.

Subjects: Time-lapse data derived from 57,850 embryos cultured to at least day 5 from 9,795 patients from 5 clinics.

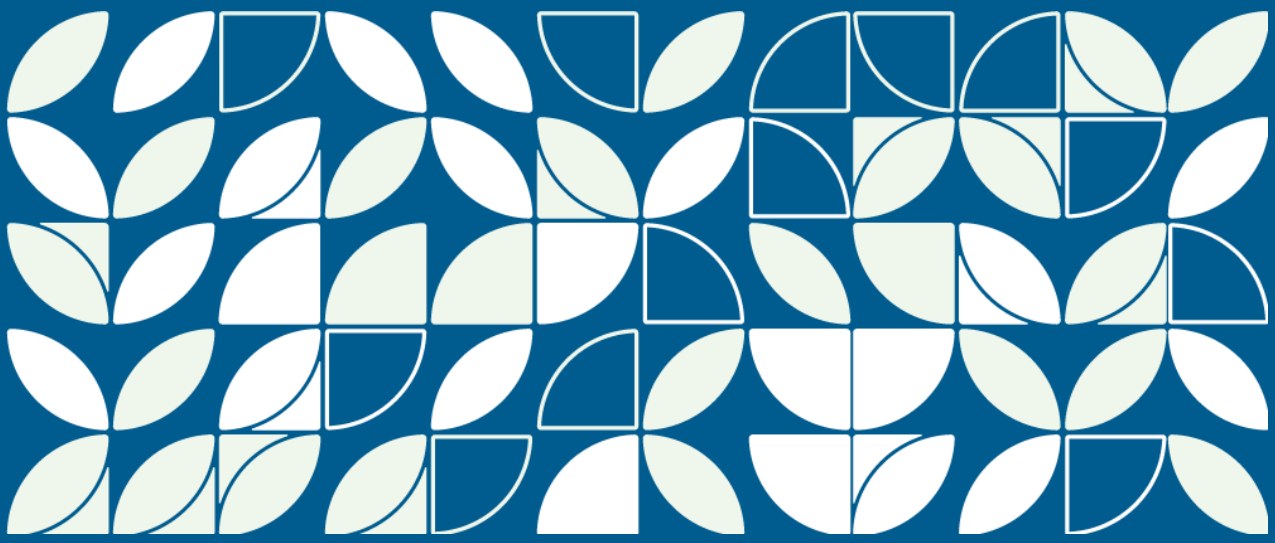
Exposure: Embryos were classified into 4 groups: a) implanted blastocysts; b) blastocysts transferred but not implanted; c) discarded blastocysts; d) discarded non-blastocysts. Implanted blastocysts were labelled as positive, while all other groups were labelled as negative in varying combinations of binary outputs (positive vs negative): (1) a vs b; (2) a vs c; (3) a vs d; (4) a vs c and d; (5) a vs b and c and d (without including clinical characteristics); (6) a vs b and c and d (including clinical characteristics). Clinical characteristics included oocyte donor age, endometrial thickness, previous treatments, endometrial preparation, and body mass index. For each binary group, included data was used to train, validate and test two separate machine learning algorithms automatically quantifying morphokinetics (time-series image input) and morphology (single image input). For each binary group, the models were assessed for (i) implantation prediction on the binary classification tasks of (1) a vs. b; (2) a vs. c; (3) a vs. c and d; (4) a vs. b and c and d; and (ii) embryo ranking on cohorts composed of (1) a and c; (2) a and c and d.

Main outcome measures: Efficacy of implantation prediction was quantified using the area under the curve (AUC) at different culture times. Embryo ranking efficacy was assessed using the number of embryo transfer cycles (nETs) required to achieve a pregnancy at different culture times.

Results: Morphology algorithms outperformed morphokinetic algorithms in terms of implantation prediction ($p<0.001$). The inclusion of clinical characteristic data improved implantation prediction ($p<0.001$), whilst deteriorating embryo ranking efficacy in sub-cohorts with between 2 and 8 embryos ($p<0.001$). The inclusion of discarded embryos as a negative labels along with the non-implanted embryos, improved implantation prediction and embryo ranking when compared to models that included only non-implanting embryos as the negative label ($p<0.001$).

Conclusion: To maximize clinical efficacy, transferred and discarded embryos should be included when training machine learning algorithms for implantation prediction and ranking. Moreover, patient clinical characteristics should be included for implantation prediction but excluded from embryo ranking.

Live birth prediction



Study 54: ESHRE 2022 – Mermorial

Can AI be used as a tool in the evaluation of the risk of pregnancy loss after euploid single embryo transfer?

Published by Human Reproduction

Clinic: Memorial (Turkey)

Question: Can AI be used as a tool in the evaluation of the risk of pregnancy loss after euploid embryo transfer?

Answer: AI-annotated tSB (time to start blastulation) and tB (time to formation of full blastocyst) were predictive of miscarriage and live birth.

What is known already?: Despite the advantage of PGT-A in preventing miscarriages, a pregnancy loss still can occur after the transfer of a chromosomally normal embryo. Unfortunately in the literature there are no clear criteria indicating which morphologically good euploid embryos may be at risk of resulting in pregnancy loss.

Study design, size, duration: Retrospective cohort analysis of 455 euploid embryos allowing for the analysis of a range of variables for prediction of live birth or miscarriage from ICSI cycles, that were cultured in the Embryoscope (Vitrolife) at a single clinic (Istanbul Memorial Hospital, ART and Reproductive Genetics Center), and transferred between 2017-2020. This is the largest reported AI study to date predicting outcome in euploid SETs.

Participants/ materials, setting, methods: Patients were aged 24-44 years. Each morphokinetic feature was annotated manually and by CHLOE-(Fairtility), and pregnancy outcomes were evaluated.

Main results and the role of chance:

- AI annotations: average time (Mean+-Standard deviation (SD)) for tSB (98+-7vs97+-7,p<0.05) and tB (106+-7vs105+-7,p=0.02) were significantly longer in patients who miscarried compared to those that did not.
- Embryos that aborted and led to live birth had an equal proportion of Direct unequal cleavage (respectively, DUCs assessed by humans 7/46 vs 67/402, NS; and by CHLOE: 5/31 vs 69/424, NS)
- DUCS were more easily recognised by AI with an incidence of (81%vs7%,(n=53),p<0.0001). There was no significant difference between the presence of DUCS and pregnancy outcome.
- Clinical factors that significantly influenced the outcome of an euploid SET: method of endometrial preparation, with miscarriage being significantly lower in patients who had a natural cycle compared with oestrogen preparation in a frozen embryo transfer (FET, 46%vs54%(n=74),p<0.001).
- Miscarriage was higher in patients who had a lower endometrial thickness (9+-2vs10+-2,p<0.002). There was a significant increased risk of miscarriage with increasing number of previous attempts for both fresh (6+-3vs5+-2,p<0.0003) and FET trials (2+-1vs3+-1,p<0.0001).
- Miscarriage rates were equivalent for All other clinical features analysed did not significantly affect live birth outcome following SET of euploid embryos.

Limitations, reasons for caution: Retrospective data using embryos selected for transfer using KIDSCORE and morphology.

Wider implications of the findings: AI-annotated tSB and tB can be added to the already existing range of available evaluation methods for embryo viability and functions which can predict the risk of miscarriage after euploid embryo transfer.

Table 1: Time-lapse annotations automatically generated using Artificial Intelligence[AI] according to pregnancy outcome [Data presented as mean±SD hours, p<0.05 is considered statistically significant. tPNa: time to Pn appearance, tPNf: time to Pn fading, t2: time to two cells, t3: time to three cells, t4: time to four cells, t5: time to five cells, t6: time to six cells, t7: time to seven cells, t8: time to eight cells, t9: time to nine cells, tM: time to morula, tSB: time to start blastulation, tB: time to blastocyst and tEB: time to expanded blastocyst]

	pregnancy loss mean±SD	Live birth mean±SD	P
tPNa	7.89 ± 2.84	7.66 ± 2.32	0.455
tPNf	23.77 ± 2.93	23.35 ± 2.92	0.255
t2	26.52 ± 2.90	26.01 ± 2.96	0.172
t3	37.52 ± 4.56	36.89 ± 4.04	0.229
t4	38.83 ± 3.87	38.76 ± 4.69	0.897
t5	50.19 ± 6.76	49.98 ± 5.48	0.780
t6	52.97 ± 5.47	52.17 ± 5.48	0.252
t7	55.23 ± 5.79	54.79 ± 6.64	0.598
t8	58.64 ± 7.26	58.19 ± 8.71	0.677
t9	71.19 ± 7.34	70.98 ± 7.45	0.823
tM	85.92 ± 7.31	85.17 ± 7.78	0.448
tSB	98.48 ± 6.72	97.03 ± 6.94	0.101
tB	106.46 ± 7.12	104.57 ± 7.03	0.037
tEB	112.86 ± 6.45	112.54 ± 6.85	0.825
Direct cleavage (%n)	6.8%	6.8%	0.983
Blastulation score	0.97 ± 0.16	0.97 ± 0.15	0.974
Implantation score	0.74 ± 0.24	0.77 ± 0.22	0.317

Study 55: ASRM 2022 – Cornell

Inner cell mass surface area automatically detected using CHLOE EQ ™ (Fairtility), an ai-based embryology support tool, is associated with embryo grading, embryo ranking, ploidy and live birth outcome

Authors: Cristina Hickman, PhD1, Assaf Ben-Meir, MD.2, Iris Har-Vardi, PhD3, Adriana Brualla Mora, MSc4, Jonas Malmsten, D.P.S.5, Qiansheng Zhan, Ph.D.5 and Nikica Zaninovic, Ph.D

Published by Fertility & Sterility

Clinics: Cornell (USA)

Type: Retrospective Cohort Study (includes comparator groups)

Objective: To assess the biological relevance of inner cell mass (ICM) surface area with regards to embryo grading and ranking by experienced embryologists, and ploidy, clinical and live birth outcome.

Materials and methods: CHLOE EQTM (Fairtility) is a transparent Artificial Intelligent (AI) tool that supports embryologists in making clinical decisions from time-lapse incubation videos. CHLOE EQTM(Fairtility) can automatically detect and quantify biomarkers, such as ICM surface area, which may be relevant for embryo selection. 799 embryos were cultured to day 5, of which 758 were assessed using PGT-A, and 78 were transferred with known live birth outcomes. The time-lapse videos were retrospectively assessed, morphologically graded and ranked by five experienced embryologists from around the world before being assessed by CHLOE EQTM. Cart classification was used to identify the optimal decision tree nodes based on live birth outcome. 291 embryos had the same ICM Gardner grading by the 5 embryologists: these were compared to ICM surface area (Kruskal walls). Data presented as mean± standard deviation (SD).

Results: Of the 291 embryos with agreed Gardner ICM grading by the 5 embryologists:

- A grade blastocysts had an overall larger ICM compared to B and C grade blastocysts (A vs. B/C: 30542±8949µm2 n=114 vs 28875±2981µm2, n=177, p<0.001, Figure 1).
- ICM surface area reduced with increasing embryo rank, as established by the embryologists (p<0.001).
- Euploid embryos had a larger ICM surface area at 114hpi (29735±7060µm2 n=359 vs. 28686±5112µm2 n=403, p<0.001), and equivalent ICM roundness (1.08±0.1 n=359 vs 1.07±0.1 n=403, NS) compared to aneuploid and mosaic embryos.

- Live birth rate per embryo transferred was directly affected by ICM surface area, with the highest live birth rate where the ICM was between 28703µm2 and 34010µm2 (77.4%, n=31) compared to greater than 34010µm2 or less than 28703µm2 (38%, n=47, p<0.001).

Conclusions: The optimal size of the ICM (between 28730 and 34010µm2) may indicate the optimal ratio of epiblast and hypoblast cells within. Moreover, a small ICM may have insufficient cells whilst a large ICM may have compromised communication leading to compromised cell differentiation required for viability. Therefore, the ICM is expected to be between 28703 and 34010um2 to maximise live birth potential.

Impact statement: ICM grading is currently qualitative and subjective. Quantitative assessment of the surface area of the ICM is a clear example of how Artificial Intelligence can be used to improve embryo assessment and selection, by improving the granularity and consistency of information in an efficient manner that can be easily introduced into a busy IVF laboratory setting.

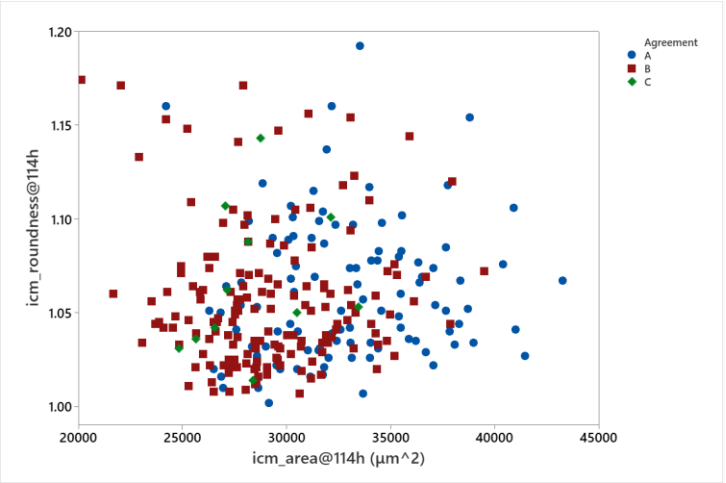


Figure 1. ICM grading agreement between CHLOE and embryologists.

Study 56: ESHRE 2022 – Generalife

Uncovering the value of day 7 blastocysts using artificial intelligence on time lapse videos

Authors: Danilo Cimadomo, Daria Soscia, Valentina Casciani, Federica Innocenti, Samuele Trio, Viviana Chiappetta, Laura Albricci, Roberta Maggiulli, Itay Erlich, Assaf Ben-Meir Iris Har-vardi, Alberto Vaiarelli, Filippo Maria Ubaldi, Laura Rienzi.

Published by Human Reproduction

Clinic: Generalife (Rome)

Study question: What is the clinical value of day 7 blastocysts?

Summary answer: Ending embryo culture at 144 hours-post-insemination (hpi) would involve 7.3%- and 4.4%-relative reductions in the patients obtaining euploid blastocysts and live birth(s) (LBs), respectively.

What is known already: Many studies showed that day 7 blastocysts are clinically valuable although less euploid and less competent than faster growing embryos. Nevertheless, a large variability exists in: (i) the definition of "day 7"; (ii) the criteria to culture embryos to day 7; (iii) the clinical setting; (iv) the local regulation; and/or (v) the culture strategies and incubators. Here, we aimed to iron out these differences and portray day 7 blastocysts with the lowest possible risk of bias. To this end, we have also adopted an artificial intelligence (AI)-powered software to automatize developmental timings annotations and standardize embryo morphological assessment.

Study design, size and duration: Observational study including 1966 blastocysts obtained from 681 patients cultured in a time lapse incubator between January 2013 and December 2020 at a private Italian IVF center.

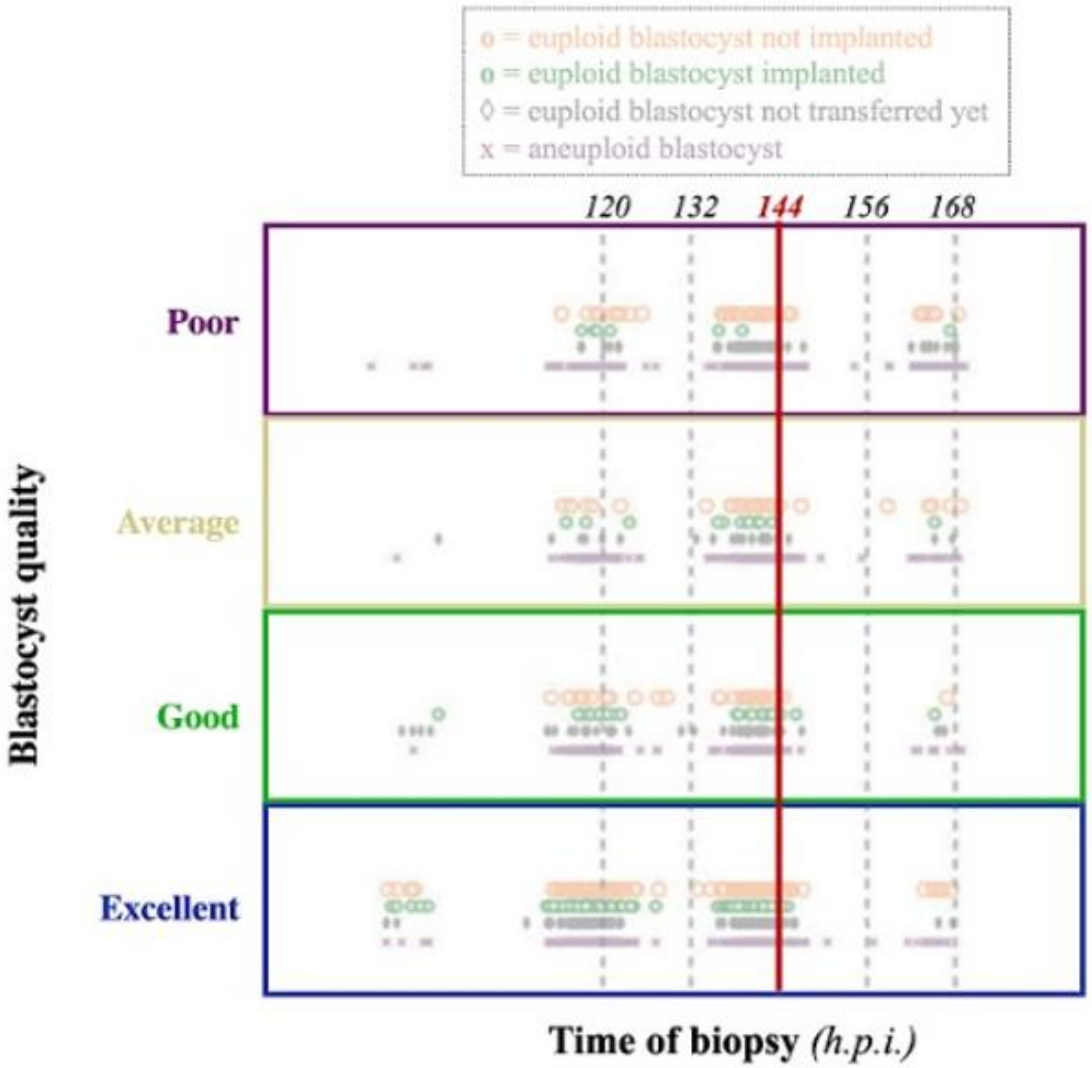
Participants/materials, setting, methods: Trophectoderm biopsy without hatching and comprehensive-chromosome-testing were performed. Blastocysts were clustered in six groups based on the time-of-biopsy every 12hr from <120hpi (control) to >168hpi. Blastocyst quality, time-of-expanding-blastocyst (tEB) and duration of expansion were annotated through AI and confirmed manually. The main outcomes were euploidy-rate and LB-rate (LBR) per transfer. Lastly, patients obtaining (euploid) blastocysts, LBs, and supernumerary blastocysts, were reported based on a hypothetical 144hpi cut-off, and all relative reductions calculated.

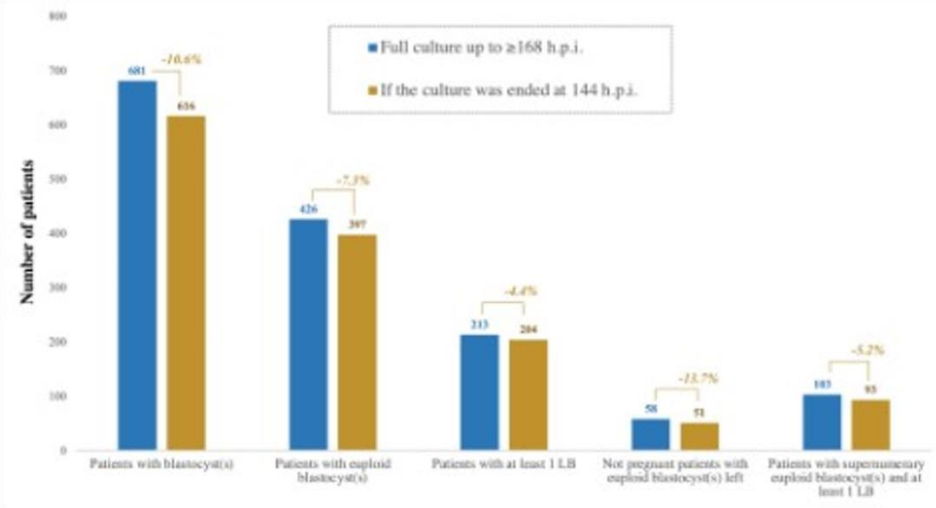
Main results and the role of chance:

- 14.6% of the blastocysts reached full expansion beyond 144hpi (5.9% between 144-156hpi, 7.9% between 156-168hpi, and 0.8% >168hpi). Slower blastocysts were of a worse quality based on the evaluation of both embryologists and AI.
- Both longer tEB and a longer duration of expansion coincided with day7 development, independent of embryo quality.
- Lower euploidy rate among day7 blastocysts is due to their worse morphology and more advanced oocyte age, rather than to a slower development *per se*.
- Lower LBR was significant even after adjusting for confounders, with a first relevant decrease for blastocysts biopsied in the range 132-144hpi (N=76/208, 36.5% versus N=114/215, 53.0% in the control, multivariate-OR: 0.61, 95%CI 0.40-0.92, adjusted-p=0.02), and a second step for blastocysts biopsied in the range 156-168hpi (N=3/21, 14.3%, multivariate-OR: 0.24, 95%CI 0.07-0.88, adjusted-p=0.03). Nevertheless, when the cut-off was set at 144hpi, no significant difference was reported.
- Ending embryo culture at 144hpi would have caused 10.6%-, 7.3%-, 4.4%-, 13.7%-, and 5.2%-relative reductions in the number of patients obtaining blastocysts, euploid blastocysts, LBs, supernumerary blastocysts without a LB and after a LB, respectively.

Limitations, reasons for caution: Gestational and perinatal outcomes were not assessed, and a cost-effectiveness analysis was not performed. We encourage the production of these data in other clinical settings and regulatory contexts.

Wider implications of the findings: Day7 culture shall be supported following a careful case-by-case evaluation. Patients shall be aware of their lower competence, yet day7 blastocysts are valuable for poor-prognosis couples, couples less compliant towards other attempts in case of failures, and couples wishing for second children. AI may improve the generalizability of these evidence.


o = euploid blastocyst not implanted
o = euploid blastocyst implanted
◊ = euploid blastocyst not transferred yet
x = aneuploid blastocyst
120
132
144
156
168
Poor
Average
Good
Excellent
Blastocyst quality
Time of biopsy (h.p.i.)


Full culture up to ≥168 h.p.i.
If the culture was ended at 144 h.p.i.
Number of patients
681
636
-10.6%
426
397
-7.3%
213
204
-4.4%
58
51
-13.7%
103
93
-5.2%
Patients with blastocyst(s)
Patients with euploid blastocyst(s)
Patients with at least 1 LB
Not pregnant patients with euploid blastocyst(s) left
Patients with supernumerary euploid blastocyst(s) and at least 1 LB

Study 57: Fairtility – BRITISH FERTILITY 2024

AI and manually annotated biomarkers associated with blastulation and Live birth (LB) outcome.

Katherine Galdaba, Alexa Zepeda, Cristina Hickman

Objective: To identify CHLOE-captured and manually annotated biomarkers associated with LB and/ or blastulation outcome.

Materials and methods: Retrospective cohort study using time-lapse videos of 1491 embryos from 3 clinics, with known LB and blastulation outcomes. Biomarkers automatically annotated by CHLOE: DUC, fragmentation, PN count, embryo area and diameter, zona pellucida (ZP) thickness and perivitelline (PVS) space size. Biomarkers manually annotated using Darwin software: ≥50% fragmentation and configuration. Biomarkers were compared with LB and/ or blastulation outcomes (Mann-Whitney and chi-squared test)

Results: CHLOE-captured PN count and PVS size were associated with blastulation outcome, 2PN embryos and a smaller PVS size at 26hpi (<5.5 μm) and 44hpi (<5 μm) had increased blastulation rates (BLR) compared to 1PN embryos (82%,n=440 vs 44%,n=16,p<0.001) and a larger PVS size (26hpi:≥5.5 μm; 44hpi:≥5 μm) (26hpi: 72%,n=246 vs 63%, n=400,p<0.05; 44hpi: 73%,n=319 vs 61%,n=328,p<0.01). CHLOE-captured fragmentation, embryo area, diameter and ZP thickness were not associated with blastulation outcome, and DUC vs non-DUC (47%, N=47 vs 61%,n=329) and 1PN vs 2PN (69%, n=13 vs 62%,n=789) were not associated with LB outcome (p=NS).

≥50% fragmentation and planar configurations had reduced BLRs compared to <50% fragmentation and tetrahedral configurations [(55%,n=132 vs 70%,n=516), (81%,n=172 vs 90%,n=209,p<0.05)].These biomarkers were not associated with LB outcome [(55%,n=55 vs 60%, n=321),(57%,n=148 vs 61%,n=171, p=NS)]. 4-cell stage multinucleation vs non-multinucleated was not associated with BLRs nor LB [(86%,n=36 vs 84%,n=393), (62%,n=29 vs 59%,n=290),p=NS]

Conclusion: PN count, PVS size, ≥50% fragmentation and 4-cell stage cell configuration are associated with blastulation outcome. No biomarkers were found to be associated with LB. Manual assessments of embryos are time-consuming and subjective. AI detects biomarkers that are logistically impossible to detect manually. The use of CHLOE-captured biomarkers can be implemented during embryo assessment to assist in embryo selection.

Study 58: ESHRE 2022 – Memorial

Predicting live birth(LB) outcome from 455 Single Embryo Transfers (SET) of euploid embryos:

Combining time-lapse annotations automatically generated using Artificial Intelligence(AI) with clinical features

Question:

Can AI predict live birth outcomes, compared with manual morphological assessments, for euploid embryo transfers,(ETs)? Which clinical features influence the live birth outcome of transferred euploid embryos?

Answer:

For euploid SETs, AI-annotated tSB and tB, endometrial preparation, thickness and number of previous transfers were predictive of miscarriage and live birth.

What is known already?:

Increasing proportion of patients seeking fertility care do not struggle to get pregnant, instead struggle to carry a pregnancy to term. Recurrent miscarriage affects 1-2% of women. Thus, new treatments are required to improve their chances of reaching live birth.
Aneuploidy is the primary cause of miscarriage. Most AI studies predicting outcome have ploidy or implantation as their endpoints. This is the largest reported AI study to date predicting outcome in euploid SETs, allowing for the analysis of a range of variables (from the embryo and the uterus) for prediction of live birth or miscarriage.

Study design, size, duration:

Prospective cohort analysis of 455 euploid embryos, from IVF and ICSI cycles, that were cultured in the Embryoscope(Vitrolife) at a single clinic, and transferred between 2017-2020.

Participants/ materials, setting, methods:

Patients were aged 24-44 years. Each morphokinetic feature was annotated manually and by CHLOE-(Fairtility), and correlated with; biochemical and clinical pregnancy, miscarriage and live birth rates.
The influence of various clinical factors were evaluated: type of infertility (female factor, combined, unexplained, genetic and male factor infertility), recurrent pregnancy loss, endometrial adenomas, polycystic ovaries, AMH, age, BMI, duration of infertility, method of endometrial preparation, endometrial thickness, and previous number of trials.

Main results and the role of chance:

When annotated using AI, the average time (Mean+-Standard deviation (SD)) for tSB (98+-7vs97+-7,p<0.05) and tB (106+-7vs105+-7,p=0.02) were significantly longer in patients who miscarried compared to those that did not.
Embryos that aborted and led to live birth had an equal proportion of Direct unequal cleavage (respectively, DUCs assessed by humans 7/46 vs 67/402, NS; and by CHLOE: 5/31 vs 69/424, NS)
DUCS were more easily recognised by AI with an incidence of (81%vs7%,(n=53),p<0.0001). There was no significant difference between the presence of DUCS and pregnancy outcome.
Clinical factors that significantly influenced the outcome of an euploid SET included the method of endometrial preparation, with miscarriage being significantly lower in patients who had a natural cycle compared with oestrogen preparation in a frozen embryo transfer (FET, 46%vs54%(n=74),p<0.001). Similarly, miscarriage was higher in patients who had a lower endometrial thickness (9+-2vs10+-2,p<0.002). There was a significant increased risk of miscarriage with increasing number of previous attempts for both fresh (6+-3vs5+-2,p<0.0003) and FET trials (2+-1vs3+-1,p<0.0001).
Miscarriage rates were equivalent for All other clinical features analysed did not significantly affect live birth outcome following SET of euploid embryos.

Limitations, reasons for caution:

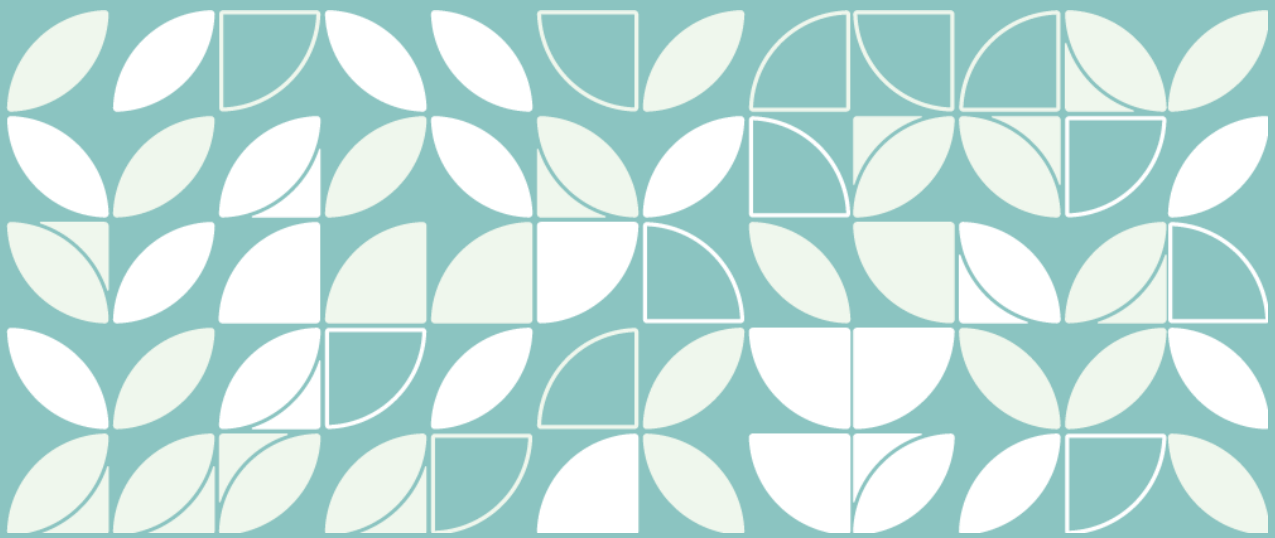
Retrospective data using embryos selected for transfer using KIDSCORE and morphology.

Wider implications of the findings:

Differentiating between euploid embryos that lead to live birth or miscarry is difficult. We have identified features that can be used in combination to predict success of euploid ETs. This will help manage patient expectations, minimise the emotional and financial burden of ART and inform decisions around proceeding or starting new transfer cycles.

CHLOE-EQ KPIs

Risk reduction
Saving time



Study 59: ESHRE 2022 – IASO

FMEA analysis of an automatic integration of time-lapse incubators into electronic medical records using CHLOE (Fairtility) shows risk reduction through automation of data capture and processing.

T. Triantallou, C. HIckman, R. Derick, M. Tran, E. Nikitos, G. Kontopoulos, I. Vasilopoulos, K. Kostaras, D. Mpotzaki.Institute Of Life- IASO, IVF, Athens, Greece.Fairtility, Fairtility, Tel Aviv, Israel.

Published by Human Reproduction

Clinic: IASO (Greece)

Study question: Can integrations and automatic data processing between time-lapse incubators and EMRs reduce the risks associated with manual moving of data from time-lapse incubators to EMRs

Summary answer: Redesigning data workflow using CHLOE(Fairtility) decreased risk occurrence and increased risk detection possibilities associated with embryo classification and selection to freeze, biopsy, transfer and discard.

What is known already: Decisions are made from information derived from time-lapse incubators. Clinically, embryologists decide which embryos(and when) are suitable for transfer, cryopreservation, biopsy, or discarding based on data derived from time-lapse incubators, manually annotated and summarised into the electronic medical record (EMR) where further information useful for embryo selection is stored. Manual movement of data from time-lapse incubators to EMRs is time-consuming, administrative, reduces the granularity of the data available and incurs risk of human-error inaccuracies. These challenges limit the possibilities of how this data can be used to optimise clinical decisions, improve the patient experience and proactively detect operational anomalies.

Study design, size, duration: Failure mode effects analysis (FMEA) analysis was carried out on the workflow integration into a large (>5000 cycles per annum) IVF centre following ESHRE guidelines for laboratory and time-lapse practice (ESHRE,2015,2020), comparing before and after the introduction of CHLOE(Fairtility). The FMEA analysis evaluated the possible data capture, processing and associated clinical decision risks from embryos entering to leaving the time-lapse incubator. The Risk Priority Number (RPN=likelihood x severity x detection of incidence) was calculated for each failure mode (Rienzi,2015).

Participants/materials, setting, methods: Through authenticated REST API calls according to the OpenAPI standard, CHLOE(Fairtility) linked the treatment unique identier from the EMR(LIVO, inhouse developed) to the time-lapse incubator, automatically processed the time-lapse data, captured quantitative and qualitative information (such as morphokinetic time points, PNs, cleavage and blastocyst morphological grades, unusual embryo developmental anomalies and prediction scores for blastulation and implantation)and automatically loaded into the EMR.

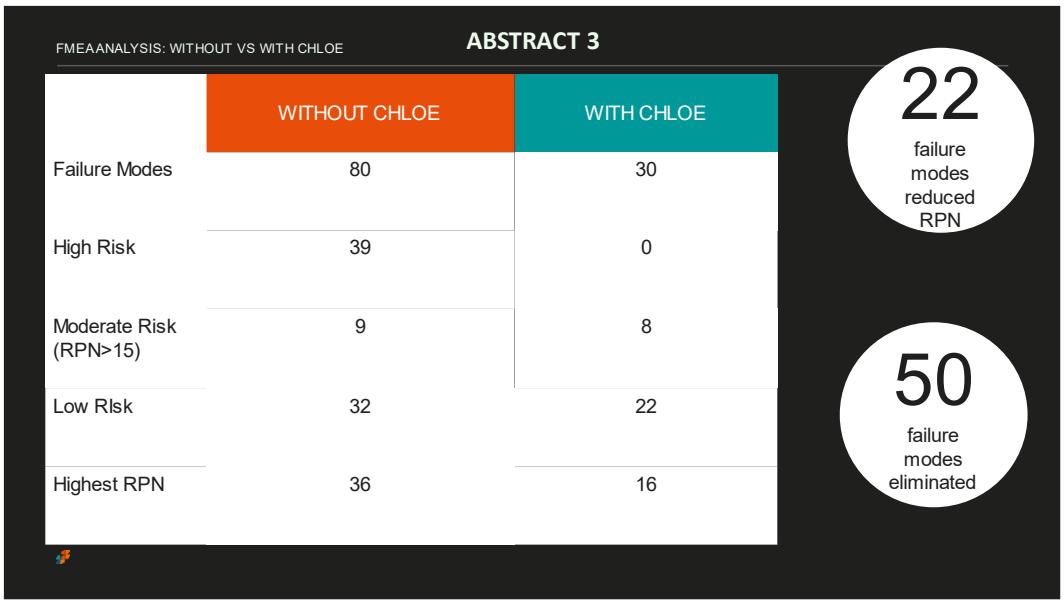
Main results and the role of chance:

- Before CHLOE(Fairtility), 8 process phases were identified, with 81 associated failure modes.
- 45 risks were given a moderate RPN (RPN>15, i.e. data entry error into the EMR; image feature detection missed (i.e. 2PNs, Inner Cell Mass, incorrectly diagnosing fragments as cells and vice versa; incorrectly diagnosing vacuoles as a PNs, asynchronous PNs missed),with consequences including inaccurate KPI monitoring (n=20, RPN=4); reduced patient experience and increased stress(n=18, RPN range 3-16); wrong embryo being selected (n=42, RPN range 8-36).
- Wrong embryo selection had three possible consequences: viable embryo discarded leading to a reduction in efficacy of treatment; viable embryo not prioritised for transfer causing reduced chance of pregnancy, or increased time to pregnancy, increasing cost and emotional burden); euploid embryo not prioritised for biopsy, increasing cost.
- Overall, RPN ranged from 3 to 36. After CHLOE(Fairtility), 51 failure modes were eliminated completely, including quantitative and qualitative morphokinetic annotations, entering data into the EMR for daily embryo grades, and embryo fate decisions.
- 22 failure modes had reduced RPN, including blastocyst morphological grading, number of PNs, identification of unusual embryo cleavages; with30 low RPNs and 6 moderate RPNs. Implementation of CHLOE(Fairtility) reduced the highest RPN from 36 to 16.
- Limitations, reasons for caution: FMEA is a proactive method to identify potential incidents in order to develop strategies to mitigate risks, forming part of a framework for responsible innovation. The likelihood of

incidences were estimated based on a PUBMED literature review, personal experience and the experience of colleagues.

Wider implications of the findings: CHLOE(Fairtility) has the potential to eliminate risks that exist when manually moving data from time-lapse incubators to EMRs: time-consuming, administrative, reduced data granularity and human-error-based inaccuracies. CHLOE(Fairtility) optimises clinical decisions, providing an opportunity for personalised patient care, improved patient engagement, and the potential to detect operational non-conformities before impacting clinicall

Figure 1. Risk with and without CHLOE



Study 60: ASRM 2O22 – FAIRTILITY

COMPREHENSIVE COMPARISON OF NUMBER OF EMBRYOLOGY HOURS PER CYCLE AND RISK BEFORE AND AFTER INTRODUCTION OF CHLOE EQ (FAIRTILITY) INTO A 100% TIME-LAPSE IVF CLINIC

Authors: Cristina Hickman, Michelle Tran, Noam Bergelson, Assaf Ben-Meir, Iris Har-Vardi, Yael Kfir, Adriana Brualla Mora

Published by Fertility & Sterility

OBJECTIVE: To consider how staffing requirements & risk in an IVF lab change with the introduction of CHLOE EQ (Fairtility).

MATERIALS AND METHODS: Systematic analysis of embryology process steps & associated time & risks before & after introduction of CHLOE into a lab operating 100% time-lapse incubation. Risk quantification using Failure Mode Effects Analysis (FMEA) and embryology hours per cycle calculated based on the summation of average time required per process step. Main outcome is the number of cycles capacity per embryologist.

RESULTS: Prior to CHLOE there were four steps for every embryo evaluation: (i) viewing the embryo development in the viewer & annotating each embryo; (ii)writing down daily embryo grade onto the treatment form; (iii) typing the daily observation into the electronic medical record (EMR); & (iv) calling and/or emailing the patient and/or Reproductive Endocrinologist (REI) to update on embryo development. These steps carry the risk of operator variation, transcription errors, embryo anomalies being missed & embryos being incorrectly graded, leading to the most viable embryo not being prioritised for transfer, viable embryos being discarded, or non-viable embryos being selected for treatment, leading to reduced pregnancy chances, increased time to

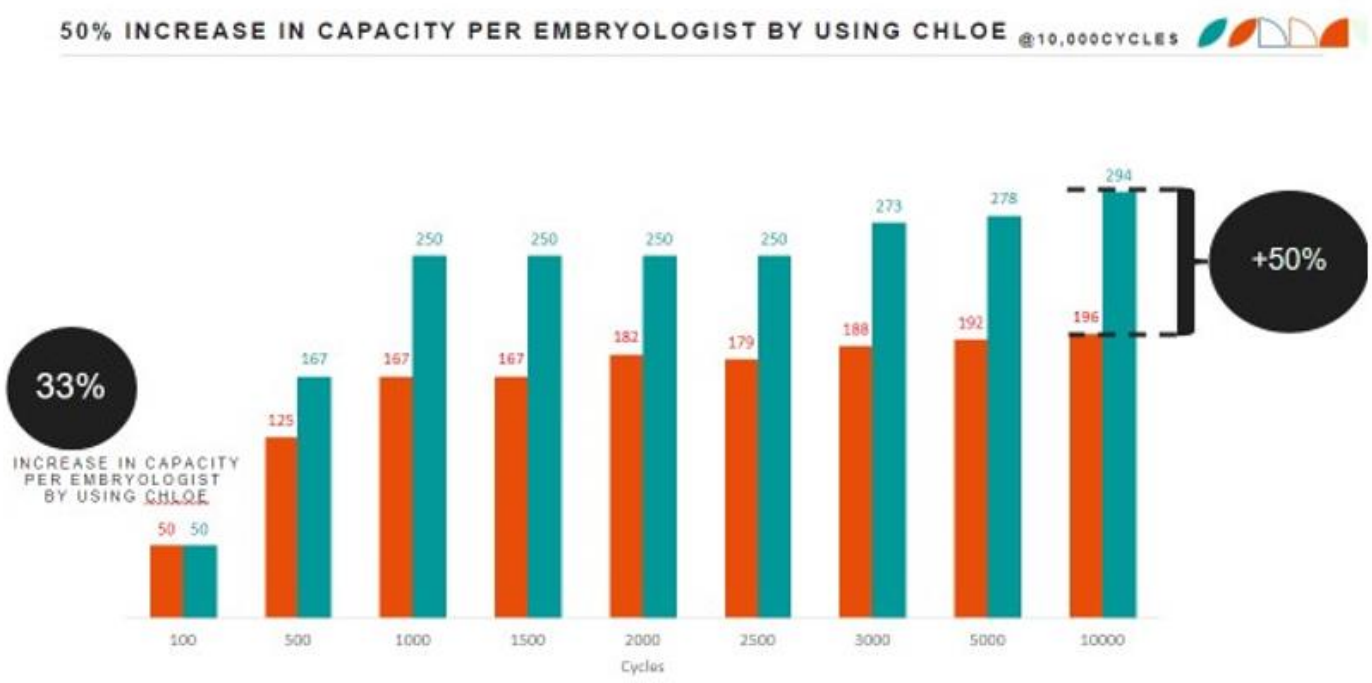
pregnancy, & unnecessary additional emotional burden & funds.

Post CHLOE, these four steps are replaced by a single step where the embryologist verifies CHLOE's automatic annotations, which are automatically integrated from the time lapse incubator (TLI), through CHLOE and directly into the EMR. Patient communication is performed as part of the verification process, with the patient receiving daily verified email reports from a single click from the CHLOE software. CHLOE removes 17 of the 24 steps, reducing time per cycle from 9.76 to 6.43 hours: a 33% reduction in time per cycle spent on mundane administrative tasks, & an associated 50% increase in embryology annual cycle capacity. In a 10,000 cycle per annum program, this represents an increase in cycle capacity per embryologist from 196 to 294 cycles/embryologist. At 1000 cycles per annum, the increase is from 167 to 250 cycles per embryologist. According to FMEA, introduction of CHLOE leads to the elimination of 50 failure modes and a further reduction in risk in 22 failure modes. The highest risk number is reduced from 36 (High) to 16 (Moderate risk).

CONCLUSIONS: Introduction of CHLOE, an AI-based embryology assistant tool that is directly integrated with TLI and with the EMR, replaces manual with automatic data capture, eliminates redundancies and reduces risk, thus leading to 50% more cycles per embryologist with less stress.

IMPACT STATEMENT: With increasing demand for IVF treatments & subsequent shortage of embryologists, embryologists worldwide are experiencing increased burnout, human error, stress and mental health issues associated with overworking. Supportive tools, such as CHLOE, can relieve this burden by increasing workflow efficiencies, embryology retention and even attraction by making embryology less administrative, safer, more effective & more enjoyable.

Figure 3. Capacity per embryologist to perform cycles with and without CHLOE



Study 61: SEF 2022 – FAIRTILITY

El análisis AMEF de una integración automática de un incubador timelapse en un Registro Médico Electrónico utilizando CHLOE (Fairtility) demuestra disminuir los riesgos a través de la automatización durante la recopilación y procesamiento de datos.

Autores: 1 Adriana Brualla, 1 Ranya Derrick, 1 Cristina Hickman, 1 Itay Erlich, 1 Noam Bergelson, 1Michelle Tan, 1 Iris Harvardi, 1Assaf Ben-Meir

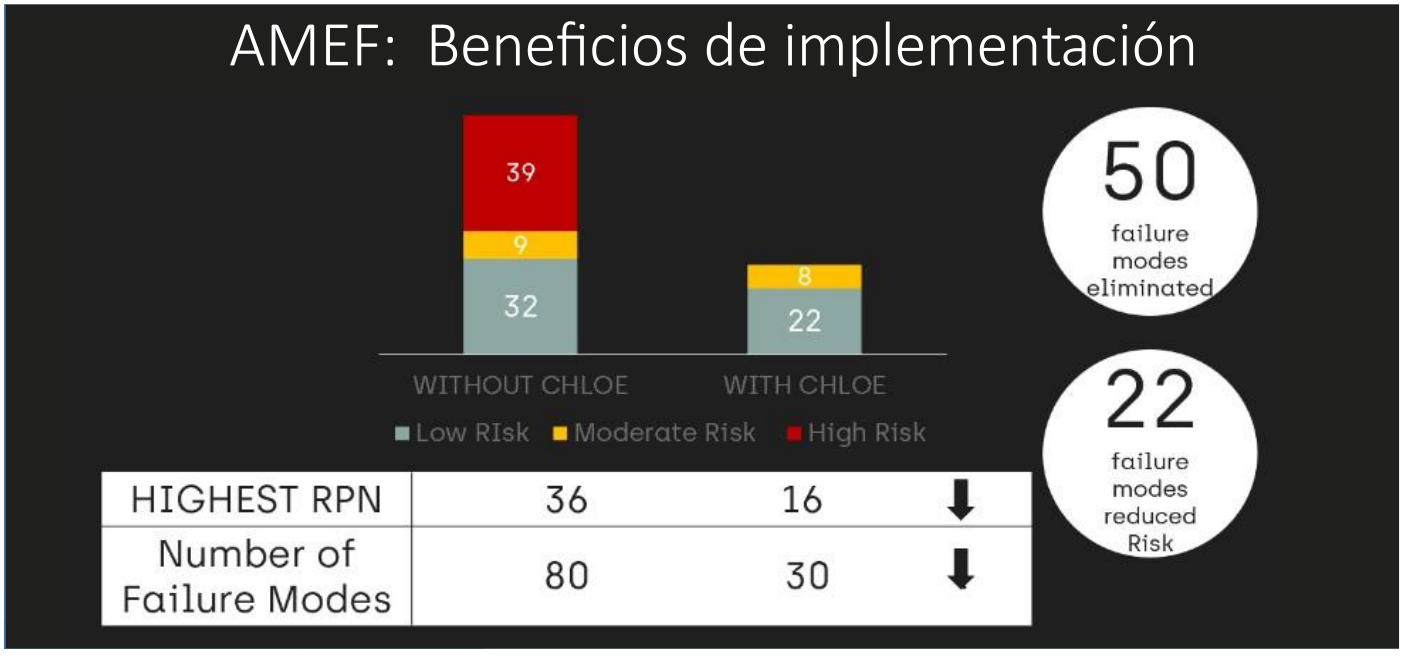
Study performed by: Fairtility, Tel Aviv (Israel)

Introducción: Los embriólogos deciden qué embriones (y cuando) transferir, criopreservar, biopsiar o descartar, en función de los datos anotados y resumidos en el registro médico electrónico(RME) durante el cultivo embrionario. El traspaso manual de datos incurre en el riesgo de imprecisiones por errores humanos. Estos desafíos limitan las posibilidades de uso de estos datos para optimizar las decisiones clínicas, mejorar la experiencia del paciente y detectar de forma proactiva anomalías operativas.

Material y Métodos: Se realizó un análisis de efectos de modo de falla(AMEF) comparando el antes y después de la introducción del CHLOE(Fairtility) en el flujo de trabajo de un centro de RA siguiendo las pautas ESHRE para laboratorio y prácticas *timelapse*(ESHRE,2015,2020). El análisis evaluó la recopilación de datos, el procesamiento y los riesgos de decisión clínica asociados desde la entrada hasta la salida de los embriones en los incubadores *timelapse*. Se calculó el Número de Prioridad de Riesgo(NPR) para cada modo de falla(Rienzi,2015). CHLOE(Fairtility) vinculó el identificador único del tratamiento del RME y procesó automáticamente los datos del *timelapse*, capturó información cuantitativa y cualitativa y actualizó automáticamente el RME.

Resultados: Se identificaron 8 fases del proceso, con 81 modos de falla asociados, entre los cuales 45 riesgos recibieron un NPR moderado (NPR>15), con consecuencias que incluían la selección del embrión equivocado(n=42,rango NPR8-36). En general, el NPR osciló entre 3-36. Después de la incorporación de CHLOE, se eliminaron por completo 51 modos de falla. Otros 22 modos de falla redujeron la NPR. La implementación de CHLOE(Fairtility) redujo el RPN más alto de 36 a 16.

Conclusiones: CHLOE(Fairtility) tiene el potencial de eliminar los riesgos asociados al traspaso de datos manual del incubador *timelapse* al RME. Además, CHLOE(Fairtility) optimiza las decisiones clínicas y permite la detección de no conformidades operativas antes de que éstas tengan un impacto clínico.



Study 62: BRITISH FERTILITY 2023 – FAIRTILITY

Lean management in the IVF clinic: using technology to eliminate wasted time in IVF lab processes whilst maximising value to patients

Authors: Hickman, Cristina ; Kfir, Yael ; Tran, Michelle ; Bergelson, Noam ; Brualla, Adriana ; Bousfiha, Meryem ; Eshed.

Introduction: To assess the amount of time embryologists spend during an average IVF cycle and explore how technology can be used to lean processes whilst improving standards of care.

Methods: 6 lab directors from 6 clinics from three countries (2 UK, 1 Spain, 3 USA) were interviewed to quantify the steps in a typical IVF cycle by following their current procedures. The lab directors were then asked to estimate the time required if they were to implement the following technologies fully integrated with CHLOE-EQ: time-lapse, electronic witnessing, electronic medical record. The total amount of time before and after CHLOE-EQ integration was compared, and the savings extrapolated to estimate their value in hourly, cycle capacity and monetary terms.

Results: Overall, the average time required per cycle before CHLOE-EQ was 15.9 hours and after CHLOE EQ was 9.4 hours, an average 41% reduction in time required per cycle (p<0.001). Before CHLOE EQ, the fastest clinic needs an average of 7.7hours per cycle, whilst the slowest needed an average of 31.5 hours per cycle. On average, cycles in the USA were more time consuming than those in Europe (mean+-st dev: 20+-10 vs. 12+-5 hours, p<0.001). After CHLOE-EQ, the fastest clinic needed an average of 6.2hours per cycle, whilst the slowest needed an average of 13.1 hours per cycle. CHLOE-EQ integrations reduced the variation in time per cycle between clinics compared to before CHLOE-EQ implementation (p<0.001). CHLOE-EQ implementation had a direct association with reduction in cost per cycle, reduction in risk, increase in capacity of cycles per embryologist. The amount saved was associated with the size of the clinic and the average salary of embryologists.

Conclusion: Introducing fully integrated digitised technologies into clinical practice can increase efficiencies, reduce risk, reduce cost and improve standards of care.

Study 63: ASEBIR 2023 – CREA

Use of CHLOE for embryo quality assessment in IVF: time saving and effectiveness.

Authors: Adriana Brualla, Alexa Zepeda, Cristina Hickman

Introduction: Embryo quality assessment is a crucial part of the in vitro fertilization (IVF) process. Manual annotations to assess embryo quality are subjective and time-consuming, which can be a challenge for IVF laboratories. CHLOE-EQ is an automated assessment tool that provides an objective and rapid assessment of embryo quality in IVF. The aim of this study was to evaluate the use of CHLOE for embryo quality assessment in IVF and compare it with manual annotations, in terms of time savings and efficacy.

Materials and methods: In this retrospective, comparative study, the use of manual annotations with the use of CHLOE-EQ (an image analysis software) was evaluated in 48 embryos. The embryo culture was followed for 6 days and the time needed for manual annotations and for the use of CHLOE on each culture day was measured.

Objectives: The main objective of this study was to evaluate whether the use of CHLOE-EQ allows significant time savings compared to manual annotations during embryo culture.

Results: The results indicate that the use of CHLOE allows a significant saving of time compared to manual annotations. The average time needed per treatment was 32 minutes and 2 seconds for manual annotations, while with CHLOE it was 21 minutes and 16 seconds, representing a time saving of 10 minutes and 46 seconds.

Regarding embryo culture, it was observed that the use of CHLOE also allowed a significant saving of time compared to manual annotations on each culture day. On Day 1 of cultivation, the mean time needed was 5 minutes and 34 seconds for manual annotations, while with CHLOE it was 3 minutes and 49 seconds. On Day 2, the average time needed was 5 minutes and 35 seconds for manual annotations, while with CHLOE it was 3 minutes and 42 seconds. On Day 3, the average time needed was 5 minutes and 21 seconds for manual annotations, while with CHLOE it was 3 minutes and 31 seconds. On Day 4, the average time needed was 5 minutes and 8 seconds for manual annotations, while with CHLOE it was 3 minutes and 23 seconds. On Day 5, the mean time needed was 5 minutes and 8 seconds for manual annotations, while with CHLOE it was 3 minutes and 21 seconds. On Day 6, the average time needed was 4 minutes and 54 seconds for manual annotations, while with CHLOE it was 3 minutes and 16 seconds. Overall, the mean total time needed per embryo was 4 minutes and 40 seconds for manual annotations and 3 minutes and 6 seconds for CHLOE.

Conclusion: The results of this study suggest that the use of CHLOE in evaluation during embryo culture can provide significant time savings compared to manual annotations. This time saving can be important in fertility clinics that handle large numbers of embryos and need accurate and efficient analysis to improve in vitro fertilization outcomes.

Study 64: ASEBIR 2023 – INSTITUTO BERNABEU

Comparación de las tasas de éxito en reproducción asistida entre dos clínicas de fertilidad en Madrid y Alicante

Jorge Ten, Adriana Brualla, Alexa Zepeda, Cristina Hickman

Introducción: La FIV es una de las técnicas más utilizadas en la reproducción asistida y su éxito depende en gran medida del rendimiento clínico de la clínica de reproducción asistida. Los indicadores clave de rendimiento (KPIs) son una herramienta útil para monitorear el rendimiento clínico en la FIV. Los KPIs pueden incluir la tasa de fecundación, la tasa de implantación, la tasa de embarazo clínico, la tasa de nacidos vivos y la calidad de los embriones, entre otros. La evaluación y el análisis de los KPIs pueden ayudar a identificar áreas de mejora y a desarrollar estrategias para mejorar el rendimiento clínico.

Objetivos: El objetivo del estudio fue comparar las tasas de éxito en la reproducción asistida entre dos clínicas de fertilidad en Madrid y Alicante y evaluar si había alguna diferencia significativa en los resultados.

Material y Métodos: Se recopilaron datos de 2872 ciclos de tratamiento en la clínica de Madrid y 800 ciclos de tratamiento en la clínica de Alicante. La edad media de los ovocitos fue 29.7 tanto en la clínica de Alicante como en la de Madrid. Se compararon las tasas de maduración in vitro de ovocitos, fecundación en 0PN, 1PN, 2PN y +3PN, la tasa de blastulación, la calidad de los blastocistos, la tasa de éxito en los tratamientos con donantes, la tasa de división de los ovocitos fecundados, y las tasas de embarazo clínico, embarazo bioquímico, nacidos vivos por transferencia embrionaria y abortos por cada embarazo.

Resultados: No hubo diferencias significativas en las tasas de maduración in vitro de ovocitos, fecundación en 0PN, 1PN, 2PN y +3PN entre las dos clínicas. La tasa general de blastulación fue significativamente mayor en Alicante (66.6%) que en Madrid (62%). La tasa de blastulación a las 116 horas de cultivo fue significativamente mayor en Alicante (58.1%) que en Madrid (52.4%). La calidad de los blastocistos también fue mejor en Alicante, ya que hubo una proporción significativamente mayor de embriones de buena y media calidad en comparación con los de Madrid. Las tasas de éxito en los tratamientos con donantes fueron significativamente mejores en Madrid en comparación con Alicante, tanto para el uso de ovocitos de donante (60.6% vs 55.5%) como para el uso de semen de donante (12.9% vs 7.9%). Hubo una diferencia significativa en la tasa de división en día 2 de cultivo de embriones fecundados entre las dos clínicas, con una tasa significativamente mayor en Alicante (95%) que en Madrid (91.6%). La tasa de éxito en la clínica de Alicante fue significativamente menor que la de Madrid en lo que respecta a los nacimientos vivos por transferencia embrionaria (23.1% vs 31.3%). No hubo diferencias significativas en las tasas de embarazo clínico por beta positiva. El promedio del EQ score de CHLOE, predictivo de implantación, en Alicante fue de 4.39, y en Madrid de 3.78.

Conclusiones: Los resultados sugieren que ambas clínicas tienen un rendimiento similar en la fertilización in vitro y la transferencia embrionaria, pero podrían haber diferencias sutiles en la calidad de los embriones y la tasa de nacidos vivos. Se requieren más estudios para investigar las causas subyacentes de estas diferencias, que podrían estar relacionadas con las diferencias demográficas de las pacientes de los dos centros. La inteligencia artificial se podría utilizar para evaluar los KPIs del consenso de Viena y detectar tempranamente no conformidades. El EQ score tiene el potencial de monitorear el rendimiento operativo clínico y de laboratorio.

Study 65: BRITISH FERTILITY 2023 – CITY FERTILITY LONDON

Using technology to enhance embryologist quality of life, reduce stress and improve standards of care

Authors: Rabi Odia; Carleen Heath; Alexa Zepeda; Noam Bergelson; Yael Kfir; Cristina Hickman

Introduction: Most embryologists in USA (ASRM,2018) and UK (ARCS,2021) experience high stress levels (89%), frequent burnout (61%) and stress-induced mental health (24%) caused by long hours, shortage of staff and lack of breaks. There is a need to implement solutions to improve quality of life and reduce stress.

Methods: CHLOE-EQ is an AI-based embryology support tool that automatically processes time-lapse data, capable of integrating with other digital tools, the foundation for a paperless laboratory. CHLOE-EQ allows for secure and remote connectivity to the time-lapse data through the embryologist's phone, and has automated and personalised patient email reports at the click of a button. We quantified the amount of time that steps in the laboratory process take during an average IVF cycle (and its associated operational and risk associated costs) and compared the time before and after CHLOE-EQ implementation. We collected feedback on ease of implementation and impact on quality of life.

Results: The average amount of time per cycle before (10.5h) and after (7.29h) CHLOE-EQ implementation was significantly reduced ($p<0.05$, 25% saving); corresponding to a 44% increase in cycle capacity per embryologist from 159 to 230 cycles. Most of the hours saved were on day 6 (D0:0.42h, D1:0.25h, D2:0.02h, D3:0.36h, D4:0h, D5:0.39h, D6:1.05h, D7:0.15h), representing total savings of 1184h per annum. Risk associated costs reduced by 87%. Embryologists reported that (i) remote access to the incubator allowed for flexibility in balancing personal life and work life, especially during the weekend; (ii) implementation of the technology into clinical practice routine was easy; (iii) increased flexibility associated with the technology reduced stress.

Conclusion: Technology was used to support embryologists with remote working and improved efficiencies in daily processes by reducing administrative burden, improving quality of life and reducing stress whilst maximising standards of care to the patient.

Using technology to enhance embryologist quality of life, reduce stress and improve standards of care

Rabi Odia; Carleen Heeth; Alexa Zepeda; Noam Bergelson; Yael Kfir; Cristina Hickman

[1]Future Life, United Kingdom
[1]Fairlity, Israel

INTRODUCTION

Most embryologists in USA (ASRM,2018) and UK (ARCS,2021) experience

89% HIGH STRESS LEVELS

61% FREQUENT BURNOUT

24% STRESS INDUCED MENTAL HEALTH

CAUSED BY: long hours, shortage of staff & lack of breaks

There is a need to implement solutions to improve quality of life and reduce stress.

METHODS

Chloe

an AI-based embryology support tool that automatically processes time-lapse data, capable of integrating with other digital tools, the foundation for a paperless laboratory.

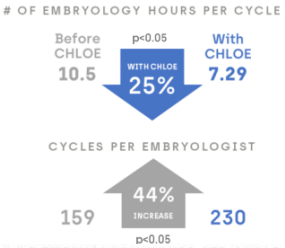
CHLOE-EQ allows for secure and remote connectivity to the time-lapse data through the embryologist's phone, and has automated and personalised patient email reports at the click of a button

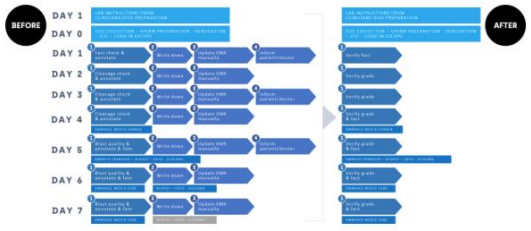
We quantified the amount of time that steps in the laboratory process take during an average IVF cycle (& its associated operational and risk associated costs)

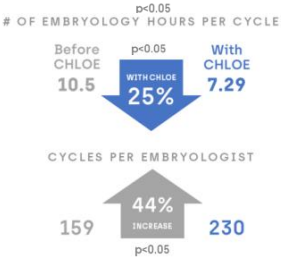
& compared the time before & after CHLOE-EQ implementation

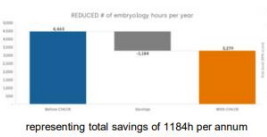
We collected feedback on ease of implementation & impact on quality of life

RESULTS

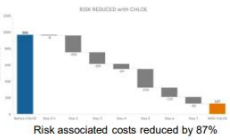








representing total savings of 1184h per annum



Risk associated costs reduced by 87%

Embryologists reported that
(i) remote access to the incubator allowed for flexibility in balancing personal life and work life, especially during the weekend
(ii) implementation of the technology into clinical practice routine was easy
(iii) increased flexibility associated with the technology reduced stress

CONCLUSION

Technology was used to support embryologists with remote working and improved efficiencies in daily processes by reducing administrative burden, improving quality of life and reducing stress whilst maximising standards of care to the patient.

Voice of the patients

Research using CHLOE EQ ™

Study 66: Fairtility – IVF LONDON

Transparency to the patient: improving patient experience, engagement and understanding by granting them real-time access to view their embryos during embryo culture

Authors: Sareena Sharma, Alpesh Doshi, Yael Kfir, Alexa Zepeda, Elinor Schmorak, Adriana Brualla, Noam Bergelson, Cristina Hickman

Study Question: Is there such a thing as too much information to patients? How do patients perceive having real-time access to embryos when embryologists share CHLOE-EQ?

Study Answer: Patients saw value in having access to real-time visuals during embryo development, improving their engagement, experience and understanding of their treatment.

What is known already?: Fertility professionals have a responsibility to manage the patient's expectations during treatment and provide the necessary support to ensure the patients are engaged with their treatment, understand the implications of decisions, and are mentally resilient. CHLOE-EQ is an AI based tool that supports embryologists in assessing and selecting embryos. At a touch of a button, embryologists are able to share, at any point of the embryo culture, any of the embryos in culture with the patient. We, therefore, need to understand how best to use this technology to support the patient in their IVF journey.

Study design, size and duration: Following IVF treatment at a private fertility clinic using CHLOE-EQ, 30 patients who were given access to their leading embryo after embryo culture were invited to complete a questionnaire. Six patients responded of which five remembered receiving the email from the clinic granting access to videos of their embryos. The response rate was 20%.

Participants/materials, setting, methods: 30% (2/6) of the respondents had previous embryo transfers. All five patients who received the email granting access to videos opened the link to view the embryos. The questions were mostly multiple choice, with one free text question for them to express any other information they wished to do so.

Main Results and the role of chance: All patients felt positive about having access to a live video of their embryos developing in real-time. Most (five) patients preferred to have access to "all of the embryos, whether progressing as expected or not". Most patients (four) would be expected to connect to the real-time access to embryo development "more than twice a day".

Having access to visual embryo information in real-time would impact positively on the patient's understanding of their IVF

treatment (all six patients: positive n=2, very positive n=4) and would make them feel calmer and more relaxed (Most patients, n=4). The patients rated highly (average 4.8/5) the overall value of having access to live embryo images during their IVF treatment alongside verbal communication with their embryologist.

Access to real-time videos of their embryos would influence the decision of half the patients (three) to come back to the same clinic for another cycle. Most (n=5) preferred to have access to the videos of their embryos developing real-time rather than after the transfer.

All patients replied that they would "absolutely" like to be informed if embryo development abnormalities were identified, with four preferring "as soon as the abnormalities are identified", and two preferring at the end of embryo culture.

Limitations: There was a low response rate (6/30) and a low sample size. Single clinic study. Embryologists must be trained on how to communicate with patients using real-time videos.

Wider implications: This is the first study quantifying feedback from patients on their perception of access to CHLOE-EQ real-time viewer. Patients saw value in having access to real-time visuals during embryo development, expressed a desire to engage with this technology, and that this would improve their experience and understanding of their treatment.

Study 67: ESHRE 2023 – Embie & Fairtility

Patients need fertility specialists to improve communication depth, quality and frequency in order to promote transparency, understanding and empathy with the patient

Authors: Yael Kfir, Ilya Mishin, Ravid Israel, Alexa Zepeda, Eran Eshed, Noam Bergelson, Assaf Ben-Meir, Iris Har-vardi, Cristina Hickman

Published by Human Reproduction

Study Question: What are the key pain-points that patients experience during fertility treatments? Based on patient perception, how can fertility clinics improve their standard of care?

Study Answer: Most patients would like to receive regular updates and more detailed explanation from their doctor, yet this happened in only half of the cases.

What is known already?: IVF treatments have an emotional, psychological and economical toll on patients. On previous studies, half the women reported that infertility is the most upsetting experience of their lives, approximately 20% of the males and females had dysfunctional emotional distress or personal difficulties. Patient's needs, pain points, expectations and education, therefore, require further research.

Study design, size and duration: An electronic survey was dispensed via the Embie mobile application or e-mail to women registered to Embie who have given their consent for communication. 98 women completed the survey from December 26th 2022 to January 15th 2023. The respondent profile was: White, Well-educated, from USA, 70% aged 31-40, 44% aged 31-35, heterosexual, tech oriented (100% Embie users), no kids, middle and upper middle class.

Participants/materials, setting, methods: The survey contained questions on demographics, IVF history, understanding of how patients choose their fertility clinic, how they educate themselves on their treatment options, how they communicate with their healthcare providers, awareness of AI, how they fund their treatment, their expectations for the clinics equipment, usage of new advanced technologies and level of involvement in their fertility care.

Main Results and the role of chance: Pricing is a pain-point for IVF patients, yet it does not affect their clinic choice, which is primarily linked to clinic location and doctor reputation. Most patients are willing to pay for modern technology. 58% of respondents state that the doctor discusses with them their chances of having a successful pregnancy, yet only 16% of women confidently know their chances of taking home a healthy baby. >90% of patients state that they would like to receive regular updates and detailed explanation from their doctor, yet this happened in only half of the cases. "Transparency of the process and decision making" is the most important tool for patients to empower themselves, followed by "answering my questions in detail". While 60% feel comfortable approaching the doctor with questions, 40% state they search for an answer prior to asking the doctor. Almost all patients expand their knowledge before and after discussions with the doctors by Internet and by approaching experienced peers. Patients expect high-tech in clinics and are ready to pay for that. 92% of patients describe at least 1 pain point with their clinic: primarily communication: inconsistent communication (39%), lack of transparency (17%), lack of understanding (12%) and lack of empathy (4%).

Limitations: The respondents mostly came from the USA and represented a non-diverse group. These findings may not generalize to other geographies or socio-economic groups.

Wider implications: The more the healthcare provider shares and involves the patient, the better the education they receive, and the less likely they will seek alternative information elsewhere which may be less medically accurate. Healthcare providers must educate themselves on the latest innovative technologies to meet patient expectations.

Study 68: ASRM 2023 – Kindbody

Transparency to the patient: improving patient experience, engagement and understanding by assessing the impact of access to own embryo videos.

AUTHORS: Jelani Roohi, Meryem Bousfiha, Alexa Zepeda, Cristina Hickman
1 Kindbody
2 Fairtility

Objective: To assess the impact of access to embryo videos on patient's IVF experience

Materials methods: An electronic survey was dispensed via the instagram account of a private fertility doctor. 72 respondents completed the survey from April 17th-21st 2023. The 12-question questionnaire assessed the desire and the needs of the respondents with regards to access to embryo images from the perspective of the respondent. The respondents completed the questionnaire unsupervised online. Respondents were not identifiable. Scale assessment questions were based on a scale from 1-5 (very negatively-very positively).

Results: 65% of respondents had at least one previous embryo transfer. The majority (75%) of respondents reported that having access to live videos of their embryos developing in real-time would have had a positive impact. The majority (74%) considered that having access to this visual information would have had a positive impact in their understanding of IVF treatment. Most (67%) patients did not feel that access to this information would cause them stress. In fact, 61% felt access to this information would make them feel calmer and more relaxed. Alongside verbal communication with the embryologist, most respondents (79%) considered this information would bring value. Most respondents (64%) considered this experience would influence their decision to come back to the same clinic for another cycle. Most respondents (71%) would like to have access to images for all embryos, 14% only the embryos developing as expected, 6% Only the leading embryo and 9% none of the embryos. 78% would like to receive daily updates, whilst 21% preferred to receive updates only on days 1 and day 5, whilst 1% only a update at end of embryo culture. The median number of times a day a patient would expect to connect to view their embryos was 2. Most respondents (74%) preferred to have access to the videos of their embryos developing in real time compared to after embryo culture is completed (14%), after pregnancy was confirmed (7%). Most (68%) would like to be informed if abnormalities were identified, whilst 29% would like to know, but only at the end of embryo culture and 3% would rather not know.

Conclusion: The majority of patients see value and have a desire to have access to real-time images of their embryos developing, reporting that this helps to improve their stress as well as improving transparency in their relationship with the IVF clinic, increasing the chance of them returning for further treatment. This communication may need to be personalized to individual patient needs.

Impact statement: IVF treatments have an emotional, psychological and economical toll on patients. Fertility professionals have a responsibility to support and manage the patients' expectations, ensuring engagement with their treatment and understanding of the implications of clinical decisions. AI tools such as CHLOE can help empower and connect patients with their own IVF journey.

Study 69: BRITISH FERTILITY 2024 - IVF LONDON

Transparency to the patient: improving patient experience, engagement and understanding by granting them access to view their embryo culture videos.

Authors: Chiranjeev Bhatia, Sareena Sharma, Alpesh Doshi, Yael Kfir, Alexa Zepeda, Elinor Schmorak, Cristina Hickman

Objective: To assess the impact of access to embryo videos on patient's IVF experience

Methods: Following IVF treatment at a private fertility clinic using CHLOE-EQ, patients were given access to their leading embryo after embryo culture. An 11-question survey was dispensed via email, 20 respondents completed the survey (January-August 2023). The questions were multiple choice based on a scale from 1-5 (very negatively-very positively). Respondents were not identifiable.

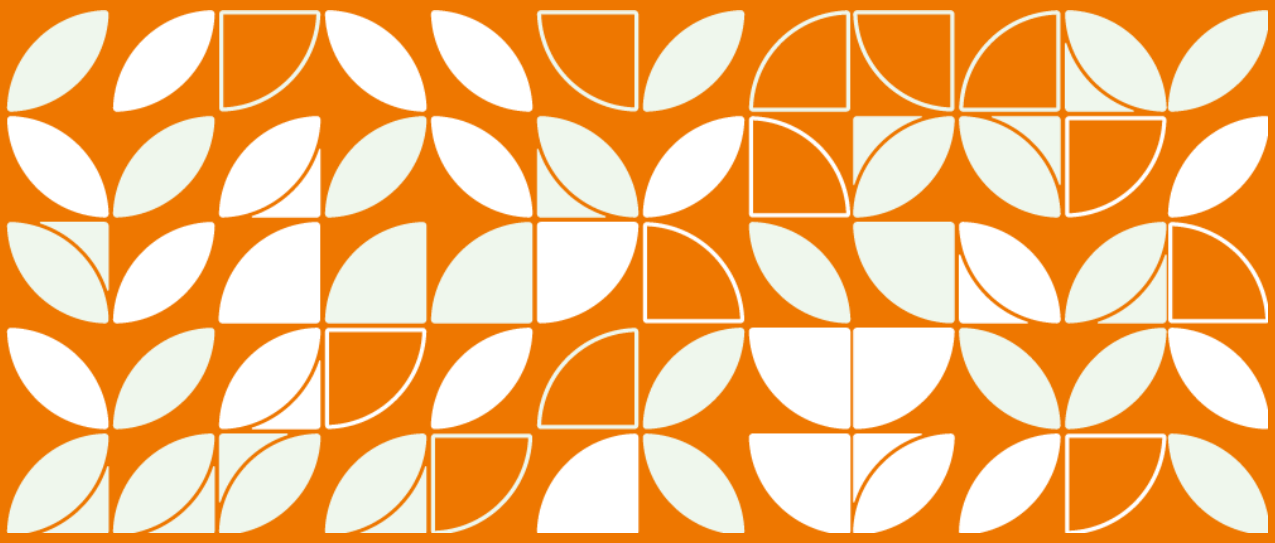
Results : All patients replied that having access to a live video of their embryos developing in real-time would have a positive impact in the understanding of their IVF treatment and 95% responded it would have a positive impact in their IVF experience.

On average, patients have accessed their embryo culture videos 22 times since March. Most patients (80%) prefer to have access to "all of the embryos, whether progressing as expected or not". Most of the patients (74%), answered they would feel "Calmer and more relaxed", 5% would feel "no effect" and 21% would feel "stressed and anxious". Most patients (95%) rated "highly" the value of having access to live embryo images during their IVF treatment alongside verbal communication with their embryologist. This experience would influence the decision of 75% of the respondents to come back to the same clinic for another cycle. Most patients (85%) replied they would like real-time access to their embryo videos with the remaining preferring after embryo culture (not real-time). Most patients (70%) would like to be informed if embryo development abnormalities are identified.

Conclusions: The majority of patients see value and have a desire to have access to real-time images of their embryos developing. This communication may need to be personalized to individual patient needs.

CHLOE OQ

Research using CHLOE EQ ™



Study 70: ESHRE 2023 – Alpha

Bringing Transparency to Oocyte Assessment: the importance of including confounders when building Artificial Intelligence (AI) based support tools to quantify oocyte viability

Authors: A.Y.X. Lim, *A. Zepeda, C. Hickman, B. Kantor.*

Published by Human Reproduction

Clinic: ALPHA

Study question: Which confounders (sperm quality, oocyte dysmorphism, culture time, images pre or post-ICSI, age) affect the ability of AI to predict blastulation based on oocyte images?

Answer: Sperm quality, oocyte dysmorphism, pre or post-ICSI image should be controlled for when building AI algorithms to predict blastulation based on oocyte images.

What is known already?
Previous studies reporting on the use of AI to predict blastulation based on oocyte images have: (i) not accounted for confounders affecting blastulation (i.e. sperm quality, culture time), and (ii) used post-ICSI images; without assessing whether the ICSI procedure affects the oocyte image as assessed by AI. Therefore, there is a risk of mislabeling viable oocytes as non-viable due to external factors, which could cause uncontrolled bias and failure to generalize when used in clinical practice. The objective was to assess how these confounders affect efficacy of prediction of blastulation from oocyte images by an AI-based oocyte assessment tool: CHLOE-OQ(Fairtility).

Study design, size and duration:
Cohort study. Images of 1281 oocytes (February to June 2022) were taken pre and post ICSI using the Embryoscope, and the embryos cultured until day 7. Oocyte donor source and age, oocyte dysmorphias and sperm quality were documented. CHLOE-OQ algorithm was trained, validated and tested in a diverse data set, accounting for pre and post ICSI image datasets, quality of oocytes, quality of sperm and patient age.

Participants/materials, setting, methods: The primary endpoint was blastulation. Sperm quality data was classified into 4 groups: (A)All (n=1281), (B)donor sperm only (n=51), (C)donor sperm and normospermic samples from men not diagnosed with male factor infertility (n=557), (D)abnormal sperm samples and other diagnosed male factor cycles (n=747). Eggs were classified by source (own/donor), and by dysmorphisms: enlarged perivitelline space, abnormal Zona pellucida, cytoplasmic abnormalities, dark, enlarged oocytes.

Main Results and the role of chance: Post-ICSI images had higher mean CHLOE-OQ score than pre ICSI images (0.28±0.1 vs 0.33±0.1, p<0.001, paired t-test). Discrepancies were particularly identified in oocytes that degenerated following ICSI, and scored 0 by CHLOE-OQ despite having higher scores pre-ICSI. Using Post-ICSI images (AUC=0.66, 95% confidence interval, CI: 0.63-0.69, n=1281) improved the efficacy of prediction of blastulation compared to pre-ICSI images (AUC=0.57: 0.53-0.60, n=1281, p<0.001), suggesting that ICSI affected the morphology of the oocyte, and how an oocyte responds to ICSI, as assessed by AI, contributes to prediction of blastulation.

Efficacy of prediction (AUC) was not affected by the quality of the sperm: (A-OVERALL 0.658 [CI(95%): 0.626-0.687]; B-Donor 0.586 [CI(95%): 0.449-0.728]; C-normospermic 0.645 [CI(95%): 0.600-0.688], D male factor 0.678 [CI(95%): 0.639-0.715]).

Oocyte features associated with low CHLOE-OQ scores were: enlarged perivitelline space, dysmorphic oocytes, abnormal Zona pellucida, cytoplasmic abnormalities and dark and enlarged oocytes. Whilst spherical oocytes with normal zona and perivitelline space were characterized as being more likely to form a blastocyst.

Limitations: This single-clinic study is retrospective. A multi-center study is underway. External factors affecting blastulation must be accounted for to avoid mislabeling of good oocytes as non-viable. There is also a need to understand oocyte dysmorphias identified by the AI algorithm to ensure biological transparency in clinical decision making.

Wider implications: Taking into account clinical and gamete confounders when building AI algorithms is a necessary strategy to ensure AI algorithms are generalized when incorporated into clinical practice, whilst reducing bias and promoting transparency in clinical decision making. The risk of not considering confounders leads to mislabeling, bias and inaccurate predictions.

Study 71: Fairtility – AVENUES

Enhancing Oncology Fertility Preservation with AI-Driven Tools: A Patient-Centric Approach to managing patient expectations

Authors: Cristina Hickman, Ahmed Amer, Anna Collins, Maximilian von Raven, Rajkumar, Lisa Stradiotto, Rami Wakim, Felicia von Reden, Sina Shahandeh, Mohsen Attia, Amin Gorgy, Lyna M Brayboy

Clinic: Avenues

Objective: To investigate the clinical and patient experience implications of utilizing AI-driven tools in oncology fertility preservation.

Case study: 41-year-old married patient diagnosed with BRCA-1 cancer, seeking pre-chemotherapy fertility preservation. NHS rejected due to high BMI. Patient accessed three pioneering AI-driven tools: (1) OVOM-INSIGHT, predicting IVF outcomes per cycle, (2) CHLOE-OQ, quantifying the ability of the egg to blastulate, (3) CHLOE-EQ, assessment of time-lapse embryo images & patient-access to patienview their embryos developing live. Virtual meetings occurred between the embryologist and the patient on days 1, 3, 5, and 7. The patient received written reports generated by AI tools. Feedback was collected 2weeks post-treatment from patient, husband, embryologist, and doctor.

Results: 11 oocytes collected, 4 mature, 6 GV (that did not mature overnight), 1 degenerated. All 4 fertilised, 3 blastocysts cryopreserved (5AA,4BC,2BC).

CHLOE-EQ identified anomaly biomarkers in 2 embryos: DUC and abnormal morphokinetics. OVOM INSIGHT predicted 15.8% chance of live birth with this cycle, with only 28% cumulative live birth over two cycles. CHLOE-OQ indicated a 68% chance of obtaining at least 3 blastocysts in this cycle. These insights guided the patient's decision to forgo a second IVF cycle before chemotherapy and start chemotherapy the day after egg collection. Patient live access to embryo development was reassuring. Virtual calls with the embryologist enhanced patient understanding. The Partner found live access helped him better connect with the treatment.

AI tools streamlined operations: embryologist only needed to attend clinic on days 0 and 6. Embryologist knew the two blastocysts would reach teb on day 6 as early as 30hpi.

Patient rated live embryo access as highly satisfying (5/5). CHLOE-EQ scores guided personalized embryo transfer strategies.

Conclusion: This study demonstrates successful integration of AI tools in oncology fertility preservation. Transparent, personalized decision-making enhanced patient experiences, streamlined operations, providing a welcomed distraction from chemotherapy.

Study 72: BRITISH FERTILITY 2024 – London women's

Does oocyte image analysis using an AI algorithm predict blastocyst formation? A single centre validation study.

Authors: Linara-Demakakou E, Porta C, McLaughlin A, Al-Hashimi B, Shah T, Zepeda A, Hickman C, Macklon N, Ahuja KK

Clinic: London women's (UK)

Objective: To assess an AI oocyte quality score prediction of blastulation using post-ICSI-images of donated warmed oocytes.

Methods: A retrospective analysis performed of anonymized time-lapse videos of 1449 warmed post-ICSI donated oocytes from 2021-2023, with known blastulation outcomes. The primary endpoint was blastulation rate. The predictive value of the AI generated CHLOE-OQ (oocyte quality) score was stratified in 4 groups. Group A OQ score >0.6, B=0.3-0.59, C=0.001-0.29, and D=0.

Blastulation rate and embryo quality in each group were compared using chi-square correlation between the CHLOE-OQ and EQ (embryo quality) and the CHLOE BLAST scores were calculated using regression analysis.

Results: CHLOE-OQ score (AUC= 0.66), Blastocyst Score at 68 hpi (AUC= 0.93) and CHLOE-EQ (AUC= 0.93) were predictive of blastulation (Baseline=65%, n=1449, p<0.001). Overall, oocytes that blastulated had a higher mean CHLOE-OQ Score (7.0 ± 2.3) than oocytes that did not blastulate (5.4±3.0, p<0.001).

Oocyte quality score corresponding to CHLOE-OQ groups showed a direct association with blastulation rate (Group A 74% (706/960), Group B 56% (151/268), Group C 43% (83/195), Group D 15% (4/26), p<0.05). Oocytes in the highest score Group had 5-fold increase in blastulation rate compared to the lowest score Group (p<0.001). The highest score Group resulted in the highest proportion of good quality embryos compared to the lowest score Group (77% (484/625) vs 0.32% (2/625), p<0.001).

No correlation was found between EQ-Score and OQ-Score (r=0.29, p>0.05).

Conclusions: CHLOE-OQ Score is predictive of blastulation. Oocytes with high OQ score had a 5-fold increase of blastulation than those with 0 score. There is no correlation between OQ and EQ-Score, suggesting that there are different biomarkers at the oocyte and embryo level to predict blastulation and implantation respectively which are independent from each other.

Study 73: BRITISH FERTILITY 2024 – CRGH

Multicenter assessment of prediction of blastulation by an Oocyte quality AI score.

Authors: Blair Sowry, Alexa Zepeda, Cristina Hickman

Clinic: CRGH

Objective: To assess CHLOE-OQ score prediction of blastulation.

Methods: Retrospective multincenter study of 1264 oocytes time-lapse videos with known blastulation outcomes. An AI oocyte quality (OQ) machine learning algorithm (CHLOE-OQ, Fairtility Ltd) provides an OQ score from 1-10. Primary endpoint was prediction of blastulation measured by AUC (binary logistic regression). An overall comparison of the mean and SD of oocytes that blastulated and not was measured with t-test. OQ Score subgroups were determined based on CART binning. Bin A: 0-8.0 and Bin B: 8.1-10. Blastulation rate in each bin was calculated (chi-square).

Results: Overall and per clinic, OQ score was predictive of blastulation (Overall AUC=0.60, Clinic 1 AUC=0.60, Clinic 2 AUC=0.61, Clinic 3 AUC=0.70). Blastulation rate between clinics did not differ [Clinic 1 63% (427/724), Clinic 2 60% (33/50), Clinic 3 13/17 (57%).

Overall, mean CHLOE-OQ Score was higher in oocytes that blastulated compared to those that did not blastulate (8.0 ± 1.6 vs 7.4 ± 2.0, p<0.001). Bin B had a higher probability of blastulation that Bin A [63.6% (506/796) vs 50.6% (276/545), p<0.001]. Showing a direct association of CHLOE OQ Score with blastulation rate.

Conclusion: CHLOE OQ is predictive of blastulation and was validated with a robust and diverse dataset. Performance was similar in 3 different clinics with different practices. CHLOE-OQ score shows a direct association with blastulation rate. The higher the score, the higher the likelihood that the oocyte may result in a blastocyst. As demonstrated overall and per bin calculations. AI-based tools for prediction of blastulation can bring clinical benefits to manage patients expectations, work organization in IVF and provide consistency in oocyte quality assessments. As well as, aiding in oocyte cryopreservation planning.

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