Artificial Intelligence cannot Replace Human Skill at Embryo Transfer

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Abstract: Sixteen artificial intelligence (AI) and machine learning (ML) papers were presented at the 2018 Annual meetings of the American Society for Reproductive Medicine (Nine) and European Society for Human Reproduction and Embryology (Seven). Nearly every aspect of an IVF cycle was investigated, including sperm morphology, sperm identification, identification of empty or oocyte containing follicles, prediction of embryo cell stages, prediction of blastulation from oocytes, scoring blastocyst quality, prediction of euploid blastocysts and live birth from blastocysts, improving the embryo selection process, and for developing algorithms for optimal IVF stimulation protocols. Moreover, AI-based methods can be implemented for other clinical aspects of IVF, such as assessing patient reproductive potential and individualizing gonadotropin stimulation protocols. As AI has the capability to analyze "big" data, the ultimate goal will be to apply AI tools to the analysis of all embryological, clinical, and genetic data in an effort to provide patient-tailored treatments. Embryo Transfer is the only step of IVF that is outside the realm of AI & ML. Embryo Transfer success is presently human skill dependent and deep machine learning may one day intrude into this sacred space with the advent of specialized humanoid robots. Embryo transfer is arguably the rate limiting step in the sequential events that complete an IVF cycle. Many variables play a role in the success of embryo transfer, including catheter type, atraumatic technique, and the use of sonography guidance. In this clinical review we will cover the contemporary research goals of AI & ML as well as the variables influencing Embryo Transfer success.

Keywords: Artificial Intelligence, Embryo, Ultrasound, Algorithm, IVF, Embryo Transfer, Deep Machine Learning.

INTRODUCTION

An increasing trend in research funding towards artificial intelligence (AI) & deep machine learning (ML) has re-animated huge expectations for future applications. According to the earliest proponents of AI in IVF, embryo evaluation and selection embody the aggregate manifestation of the entire *in vitro* fertilization (IVF) process. It aims to choose the "best" embryos from the larger cohort of fertilized eggs, the majority of which will be determined to be not viable either because of abnormal development or due to chromosomal abnormalities. Indeed, it is generally acknowledged that even after embryo selection based on morphology, time-lapse microscopic photography, or embryo biopsy with preimplantation genetic testing (PGT-A), implantation rates in the human are difficult to predict. Recently, several artificial intelligence (AI)-based methods have emerged as objective, standardized, and efficient tools for evaluating human embryos. Artificial Intelligence (AI) and Machine Learning (ML) are clearly emerging technologies in Medically Assisted Reproduction (MAR) and would benefit from early application of reporting standards (1).

Culturing of human embryos in optimal conditions is crucial for a successful *in vitro* fertilization (IVF) program. In addition, the capacity to assess and grade embryos correctly will allow for transfer of the potentially 'best' embryo first, thereby shortening the time to pregnancy. It will also encourage and facilitate the implementation of single embryo transfers (SET), thereby increasing maternal & fetal safety. Time-lapse technology (TLT) introduces the concept of stable culture conditions, in connection with the possibility of continuous viewing and documenting of the embryo throughout its development. However, so far, even when embryo quality scoring is based on large datasets, or when using TLT, the morphokinetic scores are still mainly based on subjective and intermittent annotations of morphology and set timings. Also, the application of strong algorithms for widespread use is hampered by large variations in culture conditions between individual IVF laboratory protocols. New methodology, involving deep machine learning, where every image from the time-lapse documentation is analyzed by an algorithm, looking for patterns that link to outcome, may in the future provide a more accurate and non-biased embryo selection process (2).

Embryo transfer is a key stage in IVF, in which the skillset of the gynecologist itself determines the outcome. Few advances have occurred in the last few decades with regard to the actual procedure of Embryo Transfer. Studies conducted thus far have focused on factors and interventions taking place before, during (with simulators) and after this procedure. Numerous methods, including the use of ultrasound guidance for proper catheter placement in the endometrial cavity, have been suggested as more effective techniques of embryo transfer (3-5). The moot question is which factors and interventions have thus far been proven to increase pregnancy rates and live birth rates. In this article, we will review the evidence relating to the most important variables influencing embryo transfer techniques in a systematic manner with a view to provide practical recommendations to practitioners involved in medically assisted reproduction (MAR).

DISCUSSION

Why is Embryo Transfer (ET) Human Skill-Dependent?

Many patient and embryo factors influence the outcome of assisted reproductive technology (ART) treatment. The predictors for a successful ART cycle

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include female age, ovarian reserve, embryo quality, endometrial receptivity, and the embryo transfer (ET) technique. ET, the final step of ART, has recently been noted as a crucial step affecting ART success. Factors affecting pregnancy rates following ET include either abdominal or transvaginal ultrasound guidance, ease of passage of ET transfer, catheter type and build, the transfer technique, the catheter-loading technique, blood or mucus inside or outside the catheter lumen, retained embryos, mock transfer, the physician's training & experience, and catheter tip location. Despite the lack of consensus regarding the optimal ET technique, it is generally recommended that during ET, the disruption of the endometrium and the induction of uterine contractions should be avoided (5). The exposure of embryos to the ambient conditions should be minimized, and the embryo(s) should be placed at a pre-determined optimal position within the fundal region of the uterine cavity.

Numerous published papers now document that the ET procedure has an impact on pregnancy and delivery rates after IVF. Difficult transfers should be avoided, as they reduce implantation and pregnancy rates. A total of 7,714 ETs were analyzed by Kava-Braverman *et al*. (6). The clinical pregnancy rate (CPR) was significantly higher in the cases of easy ET compared with difficult ET (38.2% vs. 27.1%). Each instrumentation needed to successfully deposit the embryos in the fundus involved a progressive reduction in the CPR: use of outer catheter sheath (odds ratio [OR] 0.89; 95% confidence interval [CI] 0.79-1.01), use of Wallace stylet (OR 0.71; 95% CI 0.62-0.81), use of tenaculum (OR 0.54; 95% CI 0.36-0.79). Poor ultrasound visualization significantly diminished the CPR. The CPR decreased progressively with the use of additional maneuvers during ET (6).

Importance of Training Physicians for Embryo Transfer

Training residents and fellows is the single most important factor in contemporary reproductive medicine that separates man from machines. A recent study by McQueen *et al*. revealed striking differences between fellowship programs regarding the adequacy of ET technique training; nearly one-half of third-year fellows had performed fewer than ten ETs. With appropriate supervision & training, there is no difference in live birth rate between ETs performed by fellows and attending physicians (7). The authors suggested that efforts should be made to address barriers and set minimums for the number of transfers performed during fellowship (7).

Ramaiah *et al.* assessed the value of the American Society for Reproductive Medicine Embryo Transfer Certificate Course in confidence and skill building for performing a live embryo transfer (ET) (8). The main study outcomes included ET simulation scores of all exercises analyzed at various points of the training and self-assessed confidence before and after the completion of the Embryo Transfer Certificate Course based on a 6-point Likert scale and association of both with extent of prior live ET experience and year of the Reproductive Endocrine (REI) fellowship. The American Society for Reproductive Medicine Embryo Transfer Certificate Course data analysis demonstrated the effectiveness of simulator-based ET training for REI fellows across their 3 years of training, regardless of prior experience with live ET (8).

WHAT ARE THE MAIN VARIABLES ACCORDING TO CONTEMPORARY EVIDENCE BASED MEDICINE (EBM) INFLUENCING EMBRYO TRANSFER SUCCESS?

Depth of Placement of Embryos under Ultrasound Guidance at ET

Placing the embryos at 10-20 mm from the fundus and at an endometrial thickness of more than 7 mm is recommended for good clinical pregnancy outcomes (9). Davar *et al*'s recent study suggested that the depth of intrauterine embryo placement at a distance of 25 ± 5 mm below the fundal endometrial surface give better IVF results (10).

Pacchiarotti *et al's* results also suggest that the depth of embryo replacement may be an important variable in embryo transfer technique (11). The authors recommend transferring at least more than 10mm away from fundus. Pregnancy rates and ongoing PRs are higher if the embryos are replaced at a distance >10 mm from the top of the fundus. In addition, because significantly more embryos were replaced in cycles where the transfers occurred at a distance of >20 mm, a distance>10 mm to <20 mm seems to be the best site for embryo transfer to achieve higher PRs (11).

The objective of Santos *et al's* study was to determine the influence of the embryo placement depth on the endometrial cavity in relation to the pregnancy rates, after frozen-thawed embryo transfers performed under ultrasound guidance (12). The patients were classified according to three variables: <10mm, 10 to 15mm and >15mm. Clinical and ongoing pregnancy rates were higher in the 10-15mm and >15mm Groups, when compared to the <10mm Group; there was no statistical difference between the groups in terms of miscarriage and live birth rates. They performed a subsequent analysis, using the same sample of patients, comparing only the <10mm and ≥10mm variables. The ≥10mm Group had better reproductive outcomes, with higher clinical and ongoing pregnancy rates. The authors concluded that pregnancy rates are influenced by the embryo transfer site, and better results can be achieved when the tip of the catheter is placed in the central area of the endometrial cavity, especially when the distance from the endometrial fundus is >10mm (12).

In Ivanovski *et al's* study, the transfer catheter was advanced to a defined distance from the uterine fundus, up to the point estimated for transfer: 10 +/- 2.5 mm and 15 +/- 2.5 mm respectively in A and B group. Analysis of their results demonstrated that pregnancy rate was significantly influenced by transfer distance from the fundus where the pregnancy rate decreases from 46.2% in group B to 28.8% in group A ($p < 0.05$) (13).

Speed of Injection at the Time of ET

Catheter injection speed affects depth and placement of the embryo into the uterine cavity and is shown to be highly variable in, and between, subjects in a manually performed embryo transfer. In an effort to standardize the injection speed during embryo transfer, Caanen *et al.* developed an automated transfer pump: the pump-regulated embryo transfer (PRET) device (14). In a randomized controlled trial, they aimed to investigate if standardization of the injection speed and pressure with this PRET results in a better controlled positioning of the transferred embryo(s). Five hundred ninety-nine embryo transfer cycles were randomly assigned to the PRET or manual transfer. Positioning of the embryo(s) into the uterine cavity was measured with ultrasound. The PRET device generated a significantly smaller variance of the positioning of the embryo(s) into the uterine cavity. This resulted in an ongoing pregnancy rate of 21% in the PRET versus 17% in the manual ($p = 0.22$) transfer group. The PRET results in better controlled positioning of the embryo(s), and it also gives the opportunity to standardize embryo transfer (14).

Mo *et al.* set up a study to evaluate the location of transferred embryos under various parameters during embryo transfer in *in vitro* fertilization (IVF) by applying an *in vitro* experimental model for embryo transfer (ET) (15). Mock ET simulations were conducted with a lab model of the uterine cavity. Embryo transfer catheter was loaded with a sequence of air and liquid volumes as well as development-arrested embryos donated by patients. The transfer procedure was recorded using a high-definition video camera. The medium speed-injected embryos were usually located in the static region while fast- and slow-speed injected embryos were mostly localized at the uterine fundus and the cervical region, respectively. The probability of embryo separation from the air-bubble interface increased from 11.1% in slow injection cases to 29.6% and 48.1% in the medium and fast injection cases, respectively. The authors suggested that faster injection of embryos into a retroverted uterus usually results in the embryo dissociating from the air bubble (15).

Measurement of Utero-Cervical Length before ET

Bakas *et al.* examined the accuracy of embryo transfer based on the previous measurement of the utero-cervical length (16). All patients had transvaginal ultrasound measurement of utero-cervical length prior to embryo transfer and measurement of embryo distance (intrauterine air bubbles) from fundal surface of uterine cavity and internal cervical os immediately after embryo transfer. Primary outcome was to estimate the accuracy of embryo transfer based on the measurement of the embryo distance from middle of uterine cavity after embryo transfer and secondary outcome was to assess the effect of embryo distance from uterine fundus and internal cervical os to clinical pregnancy rate. The study concluded that ET by a single operator with the previous measurement of utero-cervical length and estimation of embryo transfer position will be very accurate (16).

Preload or Afterload at ETs

Preload direct ETs with soft catheters under ultrasound guidance is currently considered the best procedure (17-18). A prospective randomized unblinded controlled clinical trial by Levi Setti *et al,* included 352 ultrasound-guided ETs assigned to either direct ET or afterload ET (19). The primary outcome was the rate of difficult or suboptimal transfers defined as: advancement of the outer sheath (specific for the direct transfer), multiple attempts, use of force, required manipulation, use of a stylet or tenaculum, dilatation, or use of a different catheter. The secondary outcome was clinical pregnancy rate. The rate of difficult transfers was significantly higher in the direct ET group compared with the afterload ET group, although a wide variation was observed among operators (19).

Retention of Embryos at ET

The retention of the embryo in the transfer catheter after embryo transfer (ET) during *in vitro* fertilization is a common feature, encountered by even the most experienced IVF physicians, and embryos retained in the embryo transfer catheter or within its sleeve require a repeat embryo transfer (20-21). The exact mechanism of embryo retention has not been explained. Therefore, Kozikowska *et al's* study aimed to investigate the mechanism of embryo retention in the catheter during embryo transfer by using a transparent uterus model equipped with pressure sensors and a video recorder (22). Their results indicated that pressure changes in the uterine cavity during ET can influence the distribution of the transferred fluid containing the embryo. Under certain conditions, the transferred fluid can flow backward in the catheter, which may lead to retention of the embryo in the catheter.

ET Catheter Type

An Argentinian study (23) aimed to compare the use of semi-rigid and flexible catheters in terms of pregnancy rate and level of difficulty of the embryo transfer (ET) procedure. The results suggested that a softer catheter may help with difficult ETs (23).

Softer catheters, as also reported by other authors (5,24-25), resulted in better implantation rates.

ET Catheter Rotation during Withdrawal

Literature suggested that catheter rotation during an ET could discharge mucus entrapped in the embryo to neutralize embryo displacement. The aim of Eftekhar *et al's* study was to compare the outcome of frozen embryo transfer (FET) based on catheter rotation during withdrawal (26). Patients were divided into two groups (n = 120/each), including A) the rotation treatment group (360°) that underwent ET using catheter rotation and B) the control group including the subjects who experienced ET with no catheter rotation. Their results demonstrated that catheter rotation during withdrawal increased the implantation rate and clinical pregnancy (26).

Maintenance of Tight Temperature Control during ET

Twenty-nine simulated embryo transfer procedures were carried out across five clinics. A thermocouple probe was used for standardized measurements inside each of the ET catheters to record the changes in temperature that occur in the time period between loading the catheter and placing the catheter in the uterus. In all cases, the temperature at the loaded catheter tip fell rapidly to ambient temperature during transit from the embryo transfer workstation in the IVF lab to the ET procedure room. Considering the sensitivity of the pre-implantation embryo to its immediate environment, the rapid and profound drop in temperatures observed at the catheter tip that houses the embryo during its transit from the IVF laboratory to the uterine environment may affect embryo viability and health (27). The authors suggested that the issue be addressed to ensure that the tight temperature control continues throughout the embryo transfer procedure and could improve clinical outcomes (27). We may use pre-heated, thermo-couple embedded ET catheters in the future.

ARTIFICIAL INTELLIGENCE & MACHINE LEARNING IN IVF

Artificial intelligence (AI) systems have been proposed for reproductive medicine since 1997. Although AI is the main driver of emerging research in reproduction, such as Robotics, Big Data, and internet of things, it will continue to be the engine for technological breakthroughs for the near future (28).

Over the past years, the assisted reproductive technologies (ARTs) have been accompanied by constant innovations. For instance, intracytoplasmic sperm injection (ICSI), time-lapse monitoring of the embryonic morphokinetics, and PGT-A are innovative techniques that increased pregnancy rates. Trending strongly is the use of artificial intelligence (AI) techniques in the embryo or spermatozoa selection.

In vitro fertilization has been regarded as a forefront solution in treating infertility for over four decades, yet its effectiveness has remained relatively low. This could be attributed to the lack of advancements for the method of observing and selecting the most viable embryos for implantation. The conventional morphological assessment of embryos exhibits inevitable drawbacks which include time- and effort-consuming, and imminent risks of bias associated with subjective assessments performed by individual embryologists. A combination of these disadvantages, undeterred by the introduction of the time-lapse incubator technology, has been considered as a prominent contributor to the less preferable success rate of IVF cycles. Nonetheless, a recent surge of AI-based solutions for tasks automation in IVF has been observed. An AI-powered assistant could improve the efficiency of performing certain tasks in addition to offering accurate algorithms that can inculcate objectivity and decrease subjectivity of the decision-making processes (29).

Predictive modeling has become a distinct subdiscipline of reproductive medicine, and researchers and clinicians are just learning the skills and expertise to evaluate artificial intelligence (AI) algorithms. Diagnostic tests and model predictions are subject to evaluation. The performance of AI models and their potential clinical utility hinge on the quality and size of the databases used, the types and distribution of data, and the particular AI method applied. Additionally, when images are involved, the method of capturing, preprocessing, and treatment and accurate labeling of images becomes an important component of AI modeling. Inconsistent image treatment or inaccurate labeling of images can lead to an inconsistent database, resulting in poor AI accuracy (30).

Artificial Intelligence for Sperm Selection in ART

Although *in vitro* fertilization (IVF) facilitates the job of spermatozoa, a universally acceptable means of sperm selection is yet to be developed. No objective or reliable sperm quality indicators have been established and sperm selection is, to a great extent, based on subjective qualitative evaluation. An ideal method for sperm selection in ART should be noninvasive and cost-effective and allow the identification of high-quality spermatozoa and yield better outcomes in terms of pregnancy and live birth rates. Microfluidic devices, omics profiling, micronuclei studies, sperm plasma membrane markers, and other techniques, such as Magnetic Activated Cell Sorting (MACS), Raman micro-spectroscopy, and artificial intelligence systems offer fresh approaches to an old problem (31).

Kresch *et al.* identified multiple new promising technologies, each with its own distinct set of benefits and limitations, to enhance chances of sperm retrieval; these include the use of multiphoton microscopy, Raman spectroscopy, and full-field optical coherence tomography during a microdissection-testicular sperm extraction procedure (32). ORBEYE and ultrasonography technologies can also serve to better visualize areas of sperm production. Finally, artificial intelligence technology can play a role in the identification of sperm and, perhaps, better-quality sperm for use with assisted reproduction.

Artificial Intelligence Aided Algorithm for Personalized Ovarian Stimulation for IVF

Letterie & Mac Donald designed a computer algorithm for *in vitro* fertilization (IVF) management and set up a study to assess the algorithm's accuracy in the day-to-day decision making during ovarian stimulation for IVF when compared to evidence-based decisions by the clinical team (33). Data were derived from monitoring during ovarian stimulation from IVF cycles. The database consisted of 2,603 cycles (1,853 autologous and 750 donor cycles) incorporating 7,376 visits for training. Input variables included estradiol concentrations in picograms per milliliter; ultrasound measurements of follicle diameters in two dimensions in millimeters; cycle day during stimulation and dose of recombinant follicle-stimulating hormone during ovarian stimulation for IVF. The main outcome measures included accuracy of the algorithm to predict four critical clinical decisions during ovarian stimulation for IVF: [1] stop stimulation or continue stimulation. If the decision was to stop, then the next automated decision was to [2] trigger or cancel. If the decision was to return, then the next key decisions were [3] number of days to follow-up and [4] whether any dosage adjustment was needed. The study described a first iteration of a predictive analytic algorithm that is highly accurate and in agreement with evidence-based decisions by expert teams during ovarian stimulation during IVF (33). These tools offer a potential platform to optimize clinical decision-making during IVF.

Siristatidis *et al*. (34) proposed a functional *in vitro* fertilization (IVF) prediction model to assist clinicians in tailoring personalized treatment of subfertile couples and improve assisted reproduction outcome. They penned down the construction and evaluation of an enhanced web-based system with a novel Artificial Neural Network (ANN) architecture and conformed input and output parameters according to the clinical and bibliographical standards, driven by a complete data set and "trained" by a network expert in an IVF setting. The system is capable to act as a routine information technology platform for the IVF unit and is capable of recalling and evaluating a vast amount of information in a rapid and automated manner to provide an objective indication on the outcome of an artificial reproductive cycle.

Can workflow during IVF be facilitated by artificial intelligence to limit monitoring during ovarian stimulation to a single day and enable level-loading of retrievals? A first-iteration algorithm described by Letterie *et al.* was designed to improve workflow, minimize visits and level-load embryology work (35). This algorithm enables decisions at three interrelated nodal points for IVF workflow management to include monitoring on the single best day, assign trigger days to enable a range of 3 days for level-loading and estimate oocyte number.

Deep Machine Learning aided Implantation Prediction Algorithms using Endometrial Thickness

Endometrial thickness in assisted reproductive techniques is one of the essential factors in the success of pregnancy. Despite extensive studies on endometrial thickness prediction, research is still needed. Mehrjerd *et al.* aimed to analyze the impact of endometrial thickness on the ongoing pregnancy rate in couples with unexplained infertility using deep machine learning & artificial intelligence based algorithms (36). A total of 729 couples with unexplained infertility were included in this study. They obtained a 7.7mm cut-off point for IUI and 9.99 mm for IVF/ICSI treatment. The results showed machine learning is a valuable tool in predicting ongoing pregnancy and is trustable via multicenter data for the two subject treatments.

Artificial Intelligence Aided Endometrial Transcriptomics Implantation Prediction Algorithms

Combining RNA sequencing data (transcriptomics) with artificial intelligence (AI) led to a clinical revolution in personalizing disease diagnosis and fostered the concept of precision medicine. Translation of endometrial transcriptomics to the clinic yielded an objective definition of the limited time period during which the maternal endometrium is receptive to an embryo, known as the window of implantation (WOI). In approximately 30% of IVF cycles in which embryo transfer is performed blindly, the WOI is displaced and embryo-endometrial synchrony is not achieved. Extending this application of endometrial transcriptomics, the endometrial receptivity analysis (ERA) test couples next-generation sequencing (NGS) to a computational predictor to identify transcriptomic signatures for each endometrial stage: proliferative (PRO), pre-receptive (PRE), receptive (R) and post-receptive (POST). In this way, personalized embryo transfer (pET) may be possible by synchronizing embryo transfer with each patient's WOI (37).

Artificial Intelligence Aided Ultrasound

Artificial Intelligence (AI) has gradually become an effective supplementary method for the assessment of female reproductive function. It has been used in clinical follicular monitoring, optimum timing for transplantation, and prediction of pregnancy outcome. Some literatures summarize the use of AI in this field, but few of them focus on the assessment of female reproductive function by AI-aided ultrasound. Chen *et al*. published the applicability, feasibility, and value of clinical application of AI in ultrasound to monitor follicles, assess endometrial receptivity, and predict the pregnancy outcome of *in vitro* fertilization and embryo transfer (IVF-ET) (38).

AI Based Algorithm using Cytoplasm Movement Velocity of Embryos to Predict Blastulation

Can artificial intelligence and advanced image analysis extract and harness novel information derived from cytoplasmic movements of the early human embryo to predict development to blastocyst? In a proof-of-principle study, 230 human preimplantation embryos were retrospectively assessed using an artificial neural network (39). After intracytoplasmic sperm injection, embryos underwent time-lapse monitoring for 44 h. For comparison, standard embryo assessment of each embryo by a single embryologist was carried out to predict development to blastocyst stage based on a single picture frame taken at 42 h of development. In the experimental approach, in embryos that developed to blastocyst or destined to arrest, cytoplasm movement velocity was recorded by time-lapse monitoring during the first 44 h of culture and analyzed with a Particle Image Velocimetry algorithm to extract quantitative information. Integration of results from artificial intelligence models with the blind operator classification, resulted in 82.6% accuracy, 79.4% sensitivity, 85.7% specificity, 84.4% precision and 81.8% F1 score. This study suggests the possibility of predicting human blastocyst development at early cleavage stages by detection of cytoplasm movement velocity and artificial intelligence analysis (39). This indicates the importance of the dynamics of the cytoplasm as a novel and valuable source of data to assess embryo viability.

Artificial Vision Morphometry Based Implantation Prediction Algorithms

Assessing the viability of a blastocyst is still empirical and non-reproducible nowadays. Chavez Badiola *et al.* developed an algorithm based on artificial vision and machine learning (and other classifiers) that predicts pregnancy from both the morphology of an embryo and the age of the patients (40). They created a system consisting of different classifiers that is fed with novel morphometric features extracted from the digital microphotographs, along with other non-morphometric data to predict pregnancy. It was evaluated using five different classifiers: probabilistic bayesian, Support Vector Machines (SVM), deep neural network, decision tree, and Random Forest (RF), using a k-fold cross validation to assess the model's generalization capabilities. Their results suggest that the system is able to predict a positive pregnancy test from a single digital image, offering a novel approach with the advantages of using a small database, being highly adaptable to different laboratory settings, and with easy integration into clinical Practice (40).

Loeweke *et al.* performed a series of analyses characterizing an artificial intelligence (AI) model for ranking blastocyst-stage embryos (41). The primary objective was to evaluate the benefit of the model for predicting clinical pregnancy, whereas the secondary objective was to identify limitations that may impact clinical use. Static images of 5,923 transferred blastocysts and 2,614 Non-transferred aneuploid blastocysts were used in the study. A bootstrapped study predicted improved pregnancy rates between +5% and +12% per site using AI compared with manual grading using an inverted microscope (41). One site that used a low-magnification stereo zoom microscope did not show predicted improvement with the AI. Visualization techniques and attribution algorithms revealed that the features learned by the AI model largely overlap with the features of manual grading systems. Two sources of bias relating to the type of microscope and presence of embryo holding micropipettes were identified and mitigated (41).

VerMilyea *et al.* have combined computer vision image processing methods and deep learning techniques to create the non-invasive Life Whisperer AI model for robust prediction of embryo viability, as measured by clinical pregnancy outcome, using single static images of Day 5 blastocysts obtained from standard optical light microscope systems (42). These studies involved analysis of retrospectively collected data including standard optical light microscope images and clinical outcomes of 8886 embryos from 11 different IVF clinics, across three different countries, between 2011 and 2018.The AI-based model was trained using static two-dimensional optical light microscope images with known clinical pregnancy outcome as measured by fetal heartbeat to provide a confidence score for prediction of pregnancy (42). The Life Whisperer AI model showed a sensitivity of 70.1% for viable embryos while maintaining a specificity of 60.5% for non-viable embryos across three independent blind test sets from different clinics. These studies demonstrated an improved predictive ability for evaluation of embryo viability when compared with embryologists' traditional morphokinetic grading methods.

Artificial Vision Morphometry based Euploidy Prediction Algorithm

The genetics AI model was trained using static 2-dimensional optical light microscope images of Day 5 blastocysts with linked genetic metadata obtained from PGT-A (43). The endpoint was ploidy status (euploid or aneuploid) based on PGT-A results. Predictive accuracy was determined by evaluating sensitivity (correct prediction of euploid), specificity (correct prediction of aneuploid) and overall accuracy. When the blind test dataset was cleansed of poor quality and mislabeled images, overall accuracy increased to

77.4% (43). There was a significant positive correlation between AI score and the proportion of euploid embryos, with very high scoring embryos (9.0-10.0) twice as likely to be euploid than the lowest-scoring embryos (0.0-2.4). When using the genetics AI model to rank embryos in a cohort, the probability of the top-ranked embryo being euploid was 82.4%, which was 26.4% more effective than using random ranking, and ~13-19% more effective than using the Gardner score. The probability increased to 97.0% when considering the likelihood of one of the top two ranked embryos being euploid, and the probability of both top two ranked embryos being euploid was 66.4%. Additional analyses showed that the AI model generalized well to different patient demographics and could also be used for the evaluation of Day 6 embryos and for images taken using multiple time-lapse systems. Results suggested that the AI model could potentially be used to differentiate mosaic embryos based on the level of mosaicism. Results can be used to aid in prioritizing and enriching for embryos that are likely to be euploid for multiple clinical purposes, including selection for transfer in the absence of alternative genetic testing methods, selection for cryopreservation for future use or selection for further confirmatory PGT-A testing, as required. Results demonstrated predictive accuracy for embryo euploidy and showed a significant correlation between AI score and euploidy rate, based on assessment of images of blastocysts at Day 5 after IVF (43).

Time Lapse Technology Based Euploidy Prediction Algorithm

Euploid embryos displaying the normal human chromosomal complement of 46 chromosomes are preferentially selected for transfer over aneuploid embryos (abnormal complement), as they are associated with improved clinical outcomes. Currently, evaluation of embryo genetic status is most commonly performed by preimplantation genetic testing for aneuploidy (PGT-A), which involves embryo biopsy and genetic testing. The potential for embryo damage during biopsy, and the non-uniform nature of aneuploid cells in mosaic embryos, has prompted investigation of additional, non-invasive, whole embryo methods for evaluation of embryo genetic status.

TLT has the characteristics of large amount of data and non-invasiveness. If we want to accurately predict embryo ploidy status from TLT, artificial intelligence (AI) technology is a good choice. A total of 469 preimplantation genetic testing (PGT) cycles and 1803 blastocysts from April 2018 to November 2019 were included in Huang's study (44). All embryo images are captured during 5 or 6 days after fertilization before biopsy by time-lapse microscope system. All euploid embryos or aneuploid embryos were used as data sets. The euploid prediction algorithm (EPA) was able to predict euploid on the testing dataset with an area under curve (AUC) of 0.80. Their AI model named EPA can predict embryo ploidy well based on TLT data (44).

Time Lapse Technology Based Live Birth Prediction Algorithms

An AI system was created by using the Attention Branch Network associated with deep learning to predict the probability of live birth from 141,444 images recorded by time-lapse imaging of 470 transferred embryos, of which 91 resulted in live birth and 379 resulted in non-live birth that included implantation failure, biochemical pregnancy and clinical miscarriage (45). The AI system for the first time successfully visualized embryo features in focused areas that had potential to distinguish between live and non-live births. Live birth rate of embryos with good morphological quality and confidence scores higher than 0.341 was 41.1%. The authors concluded that an AI system with a confidence score that is useful for non-invasive selection of embryos that could result in live birth (45).

Based on images of embryos with known implantation data (KID), AI models have been trained to automatically score embryos related to their chance of achieving a successful implantation. Berntsen *et al.* investigated how a deep learning-based embryo selection model using only time-lapse image sequences performs across different patient ages and clinical conditions, and how it correlates with traditional morphokinetic parameters (46). The model was trained and evaluated based on a large dataset from 18 IVF centers consisting of 115,832 embryos, of which 14,644 embryos were transferred KID embryos. The fully automated iDAScore v1.0 model was shown to perform at least as good as a state-of-the-art manual embryo selection model. Moreover, full automatization of embryo scoring implies fewer manual evaluations and eliminates biases due to inter- and intraobserver variation (46).

AI Algorithm using Artificial Vision Morphometry & Spent Culture Media & for Live Birth Prediction of Euploid Embryos

Bori *et al.* set up a study aimed to develop an artificial intelligence model based on artificial neural networks (ANNs) to predict the likelihood of achieving a live birth using the proteomic profile of spent culture media and blastocyst morphology (47). This retrospective cohort study included 212 patients who underwent single blastocyst transfer at IVI Valencia. A single image of each of 186 embryos was studied, and the protein profile was analyzed in 81 samples of spent embryo culture medium from patients included in the preimplantation genetic testing program. The information extracted from the analyses was used as input data for the ANN. Three ANN architectures classified most of the embryos correctly as leading (LB+) or not leading (LB-) to a live birth: 100.0% for ANN1 (morphological variables and two proteins), 85.7% for ANN2 (morphological variables and seven proteins), and 83.3% for ANN3 (morphological variables and 25 proteins). The artificial intelligence model using information extracted from blastocyst image analysis and concentrations of interleukin-6 and matrix metalloproteinase-1 was able to predict live birth with an AUC of 1.0 (47). The model proposed in this preliminary report may provide a promising tool to select the embryo most likely to lead to a live birth in a euploid cohort. The accuracy of prediction demonstrated by this software may improve the efficacy of an assisted reproduction treatment by reducing the number of transfers per patient (47).

Raw Time-Lapse Videos Based Deep Machine Learning Implantation Prediction Algorithm

The contribution of time-lapse imaging in effective embryo selection is promising. Existing algorithms for the analysis of time-lapse imaging are based on morphology and morphokinetic parameters that require subjective human annotation and thus have intrinsic inter-reader and intra-reader variability. Deep learning offers promise for the automation and standardization of embryo selection. Tran *et al.* (48) created a deep learning model named IVY, which was an objective and fully automated system that predicts the probability of FH pregnancy directly from raw time-lapse videos without the need for any manual morphokinetic annotation or blastocyst morphology assessment. This study was a retrospective analysis of time-lapse videos and clinical outcomes of 10 638 embryos from eight different IVF clinics, across four different countries, between January 2014 and December 2018.This study is a retrospective analysis demonstrating that the deep learning model has a high level of predictability of the likelihood that an embryo will implant (48).

AI Ranked Metabolic Activity Based Implantation Prediction Algorithm

Morphological and morphokinetic analyses utilized in embryo selection provide insight into developmental potential, but alone are unable to provide a direct measure of embryo physiology and inherent health. Glucose uptake is a physiological biomarker of viability and amino acid utilization is different between embryos of varying qualities. Blastocysts with higher developmental potential and a higher probability of resulting in a viable pregnancy consume higher levels of glucose and exhibit distinct amino acid profiles. Embryos were individually cultured in a time-lapse incubator system, and those reaching the blastocyst stage had their morphokinetics annotated and were each assigned a Gardner grade, KIDScore and EmbryoScore. Glucose and amino acid metabolism were measured. Clinical pregnancies were confirmed by the presence of a fetal heartbeat at 6 weeks of gestation (49). Glucose consumption was at least 40% higher in blastocysts deemed of high developmental potential using either the Gardner grade ($P < 0.01$, $n = 209$), KIDScore ($P < 0.05$, $n = 207$) or EmbryoScore ($P < 0.05$, $n = 184$), compared to less viable blastocysts and in blastocysts that resulted in a clinical pregnancy compared to those that failed to implant ($P < 0.05$, $n = 37$) 949). Additionally, duration of cavitation was inversely related to glucose consumption ($P < 0.05$, $n = 200$). Total amino acid consumption was significantly higher in blastocysts with an EmbryoScore higher than the cohort median score ($P < 0.01$, $n = 185$). Furthermore, the production of amino acids was significantly lower in blastocysts with a high Gardner grade ($P < 0.05$, $n = 209$), KIDScore ($P < 0.05$, $n = 207$) and EmbryoScore ($P < 0.01$, $n = 184$). These results confirm that metabolites, such as glucose and amino acids, are valid biomarkers of embryo viability and could therefore be used in conjunction with other systems to aid in the selection of a healthy embryo (49).

CONCLUSIONS

The goal of an IVF cycle is a healthy live-born baby. Despite the many advances in the field of assisted reproductive technologies, accurately predicting the outcome of an IVF cycle has yet to be achieved. One reason for this is the method of selecting an embryo for transfer. Morphological assessment of embryos is the traditional method of evaluating embryo quality and selecting which embryo to transfer. However, this subjective method of assessing embryos leads to inter- and intra-observer variability, resulting in less than optimal IVF success rates. To overcome this, it is common practice to transfer more than one embryo, potentially resulting in high-risk multiple pregnancies. Although time-lapse incubators and preimplantation genetic testing for aneuploidy have been introduced to help increase the chances of live birth, the outcomes remain less than ideal. Utilization of artificial intelligence (AI) has become increasingly popular in the medical field and is increasingly being leveraged in the embryology laboratory to help improve IVF outcomes (50-62). And assume we have the perfect AI + ML algorithm for prediction of the correct embryo that will implant and give rise to a live birth, you will still need a skilled gynecologist who will safely and successfully transfer this embryo into the AI+ML ranked receptive uterus. In contemporary Reproductive Medicine human beings are yet not dispensable!

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