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Review on Embryo Selection Based on Morphology Using Machine Learning Methods

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Abstract

In vitro fertilization (IVF) offers a great help to infertile couple that are trying to conceive baby. However, the success rate of IVF is still relatively low (38%). A critical factor that influences the success of IVF is the quality of the embryo. The most viable embryo would be chosen to be transferred based on the morphology or appearance of the embryo. Embryologist would have to observe the morphology of embryo before selecting the most viable embryo to be transferred into woman uterus. There are two types of embryo assessment based on morphology, traditional morphology assessment and time-lapse imaging. In traditional morphology assessment, embryologists observe and evaluate the embryo based on grading system available. Meanwhile, in time-lapse imaging, embryo assessment could be done without disturbing embryo culture. Evaluation of the embryos using traditional morphological evaluation and time-lapse were still subjective. Researchers are trying to integrate machine learning into the IVF procedure to increase its success rate. Therefore, the aim of this review is to summarize the available literature regarding the use of morphology for the selection of viable embryo in IVF using machine learning.

Keywords: *Embryo selection, IVF, machine learning, morphology, time-lapse monitoring*

1 Introduction

Being able to have their own baby is probably the dream of every couple. However, there are some unfortunate couples that are not being able to conceive their own baby due to infertility. According to the World Health Organization

(WHO) [1], infertility is referred as a disease of reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. The desire to conceive a baby still can be achieved with the aid of in vitro fertilization (IVF) which is the most commonly assisted reproductive technologies (ART) used to overcome the male, female or both fertility problems [2].

In vitro fertilization, IVF is a type of treatment that priorities precision in the entire procedure. A slight error could affect the success rate of IVF. The treatment initially begins with the ovarian stimulation where medications are given to stimulate multiple eggs and the response of the ovaries is monitored with regular ultrasounds and blood tests. The process is then followed by trigger injection of human chorionic gonadotropin (hCG) to aid the egg’s final maturation and loosening it from the follicle wall. Exact timing for during this process is crucial as the egg retrieval need to take place 34 to 36 hours after the final injection. The following step that follows would be the egg retrieval where the eggs is removed and will later be fertilized with sperm in laboratory. Then, the fertilized egg, called embryo will be selected to return to the womb to grow. Pregnancy blood test would take place fourteen days after the embryo transfer to indicate the success or failure of the IVF procedure.

Earlier in the beginning of IVF being used to treat infertility, multiple embryo transfer is done to increase the success rate of IVF. However, the risks of multiple pregnancies from the multiple embryo transfer have been acknowledged as it can endanger both mother and baby. Thus, it became a global trend to reduce the embryo being transferred and choose the most viable one instead [3, 4]. The process of choosing the most viable embryo is what we call embryo selection. The best embryo is chosen by the embryologist based on its appearance or its morphology. The morphological assessment is done by grading the number and size of cells, its development and other factors as well. With a defined scoring system, the most viable embryo can be chosen and will most likely increase the IVF success rate.

Assessment of embryo by morphological characteristic has been a useful tool in IVF procedure. There are two types of embryo selection approaches that ware based on morphological characteristic, traditional embryo selection and time-lapse imaging (Fig. 1). In traditional morphological evaluation, embryo would be taken out of incubator in a timely manner to assess the embryo developmental process. On the other hand, time-lapse imaging was introduced as a tool to improve the traditional embryo selection process. With time-lapse imaging, it enables the embryologist to monitor the embryo development without disturbing the embryo culture and this method shows a promising result in improving the pregnancy rate [5].

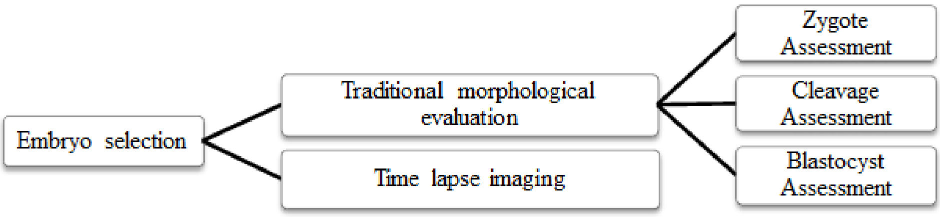

Fig 1: Embryo selection methods

Other method to improve the IVF success rate is to utilize machine learning algorithm to improve the existing procedure. As known, machine learning technique is capable of improving the performance through the interpretation of data in the medical application. In assisted reproductive technologies, researchers have come out with various machine learning algorithm or model to improve the IVF success rate. It is also reported that machine learning are able to improve the pregnancy rate of the IVF procedure [6]. Within the past decade, researchers already integrated machine learning into embryo selection process based on morphological characteristic on both traditional morphological evaluation and time-lapse imaging. Therefore, the aim of this review is to summarize available literature regarding the use of morphology for the selection of viable embryo in IVF using machine learning method.

The paper organization is given as follows. Section 2 provides background on traditional morphological evaluation and time-lapse imaging. Machine learning approaches to the embryo selection based on morphology is on Section 3. Discussion on embryo selection approaches is given in Section 4. Lastly, section 5 will conclude the machine learning approaches in embryo selection based on morphological characteristics.

2 Background

2.1 Traditional Morphology Evaluation

In embryo selection, the most used practice in choosing embryo with best quality is traditional morphological evaluation. In this traditional method, assessing embryo before transfer into woman uterus is done based on morphological characteristic of the embryo. Morphology is the study of structure or form. In the field of biology, morphology refers to the study of the shapes and arrangement of parts of organisms, in order to determine their function, their development, and how they may have been shaped by evolution. In simpler words, morphology can be inferred by observing the appearance and structure of the cell. In the clinical practice of embryo selection using traditional morphological evaluation, the development of embryo after intra cytoplasmic sperm injection would be observed in a timely manner. The observation would be done by removing the embryo out of incubator and followed by static evaluation of morphological characteristic under the light microscope.

Embryo development competence is the key to a successful IVF procedure. In order to ease the process of determining the embryo with a high quality and with the most potential to result in pregnancy, the score of morphological features such as number of cells, grade of fragmentation, cell size and multi-nucleation for cleavage stage embryo, status of inner cell mass and trophectoderm for blastocyst stage embryo [7] are included for the evaluation of embryo. Grading schemes ware introduced to accelerate the process. Embryologist can rely on the grading scheme during the process of observing the embryo. The grading schemes for embryo selection differ based on the stage of development of embryo.

2.1.1 Zygote Assessment

The evaluation of zygotes or pronuclear is the first step in the grading of embryo. Features such as number, equality, size and distribution of nucleoli, pronuclear size and alignment, the time of pronuclear breakdown and presence or absence of cytoplasmic halo [8, 9, 10] are used to classify the zygotes. The zygote assessment is also known as zygote score (Z-score) which is an established scoring system for the zygote at approximately 16 to 18 hour after insemination happen. Z-score have been proven to be useful in the a few studies and obtained positive results [11, 12]. However, there are also studies that indicate that the zygote score does not really contribute to the process of embryo selection [13, 14].

2.1.2 Cleavage Assessment

Cleavage stage of embryo assessment is widely being used to evaluate the embryo quality. The morphological criteria that should be consider as reported by “Advanced Fertility Center of Chicago" in [15] are first the cell number, followed by cell regularity or degree of blastomere size equality (uneven blastomere cleavage), degree of fragmentation and also the presence of multi-nucleation. Another additional factor to be considered for embryo grading and selection for transfers include the presence of vacuoles, granularity and thickness of the zona pellucida. The usefulness of cleavage stage assessment also has already being discussed before and have been proven for playing an important role in embryo selection [16].

2.1.3 Blastocyst Assessment

The evaluation of embryo at four or five days after fertilization is called blastocyst stage assessment. In IVF treatment, some clinics choose to transfer embryo in cleavage stage while some prefers to push embryo into blastocyst stage. The quality assessment of blastocyst stage can be distinguished by checking the two cell types, inner cell mass (ICM) and trophectoderm (TE) and the fluid cavity [15]. Gardner et al in [17] introduced three separates scoring for each blastocyst which are score for blastocyst expansion, ICM quality grade and TE quality grade. The final score of each blastocyst would be composed of these score.

With all the different types of scoring system to assist the morphological evaluation of the embryo, the process of embryo selection should be easier. However, there are some issues that also arise such as inter-observer and intra-observer variability [18, 19]. Regardless of how well the embryologist did, this can still result in uncertainty due to the background and experiences of the embryologist as grading process is subjective.

Traditional embryo selection based on morphology has an advantages in the clinical routine as it is the most used method and it is already established a significant improvements in implantation rates and success rate of IVF [20]. The researchers continue doing research on how to improve the scoring system by adding new morphological markers into the existing scoring system. There is still a room for improvement in the morphological evaluation and studies nowadays focus on utilizing new technologies to enhance the morphology evaluation.

2.2 Time-lapse Imaging

In the conventional morphology evaluation or traditional morphological evaluation, in order to capture more development information of the embryo, embryologist has to frequently remove the embryo out of incubator. This practice is not practical as it could damage or disturb the embryo development or embryo culture. The introduction of time-lapse imaging able to tackle the issue as it allows continuous monitoring of embryo development. Observer or the embryologist is able to acquire frequent images of embryo. Thus, this allows the embryologist to have a better idea of the timing and duration of the morphological events that occur. With the continuous monitoring, it replaces the previous static observation into a quantitative dynamic measurement of development which is also referred as morphokinetics [7]. Morpho in morphokinetics refers to form or shape while kinetics means movement. So overall, morphokinetics refers to time specific morphological changes during embryo development providing dynamic information on a fertilized egg or embryo.

Advancement of technology led to the development of instrument that consists of incubator and a built in camera. This specific arrangement was built for time-lapse [21]. Meanwhile, a time-lapse system consist of three main components; an incubator, an optical microscope and a software program. With these three components integrated as one system, a continuous surveillance is provided while optimal culture of embryo remains undisturbed [22]. Improvement in the terms of observation of embryo development from the incorporation of morphokinetics features will lead to better understanding of the embryo development. Recently, new kinetic markers and their correlations with embryo quality and implantation potential have been discovered [21, 23, 24, 25] and a retrospective studies have shown significant correlations between morphokinetic variables and embryo viability [23, 24, 25, 26, 27, 28, 29, 30].

Time lapse imaging or time lapse system in general offers several benefits that include not only the exact determination of cell divisions, but also a closer monitoring of morphological events correlated with embryo development and IVF outcomes [22]. The ability to obtain the high resolution images at frequent time points provides greater detail of the events involved embryo development stage [31]. Protecting the embryo culture is the most important thing that embryologist need to keep in mind as it sensitive. With time-lapse, embryologist is no longer under pressure to quickly evaluate the embryo development as time-lapse are equipped with built in camera to capture the development. Thus, this reduces the degree of human error [32].

Both traditional morphological evaluation and time-lapse imaging can be used to evaluate the embryo quality. In clinical routine, traditional morphological evaluation has the advantage as it is widely being used in the clinical procedure. Subjectivity in traditional morphological evaluation leads to the need for improvement which results into the introduction to time-lapse imaging. Even though time-lapse imaging provide embryologist with more embryo developmental information, however, not every IVF laboratories are equipped with time-lapse imaging and subjectivity in evaluation still exist in time-lapse imaging. Therefore, any new approaches to improve the morphological embryo selection are greatly being explored. One of the approaches being used is machine learning.

3 Machine Learning Approaches

Recent advancement and future perspectives of machine learning techniques offer promising applications in real life problems. As known, machine learning had significantly improved their applicability in real-world medical [58] and non-medical problems [57]. Varies studies on application of machine learning have been reported until today on IVF. Table 1 shows the varieties of machine learning model in IVF.

Prediction is one of the machine learning applications in IVF. There were different types of prediction reported such as implantation prediction [33, 34, 35, 36], IVF outcome prediction [37], live birth prediction [38, 39] and miscarriage prediction [40]. Apart from that, there were also studies that focus on determining the IVF success rate [41, 42, 43, 44], while some focus on selecting the right embryo [45, 46, 47, 48, 49, 50, 51, 52]. Different types of methods were reported for each of the applications and the precision or accuracy of each models proposed were calculated. The major challenge in IVF setting is to determine the best looking embryo with the best quality in embryo selection process. Therefore, researchers were trying to integrate different types of machine learning model into the area of embryo selection.

Machine learning was integrated into the traditional morphological evaluation and into time-lapse imaging so that in could result in better embryo assessment. In traditional morphological evaluation, studies in [45] and [46] proposed an intelligent decision support system based on supervised classification to aid the selection of the most promising embryo. In the conventional method, experts or embryologists are needed to determine the embryo quality. Bayesian classification model with a reduce subset of features variable of embryo morphology and clinical data was proposed to provide a decision support for the embryo selection [45]. With the decision support system, embryologist could easily focus on the embryo suggested by the machine learning model to be transferred into the uterus.

Embryo contains a lot of information. The morphological characteristics of the embryo provide developmental stage of the embryo. However, to ease the embryo selection, there are also machine learning studies that try to add on new markers into embryo selection process. The study in [38] demonstrated that it is possible to develop classifier that uses machine learning techniques to predict oocyte competence by focusing on differences in the mural granulosa cell (MGC) and cumulus cell (CC) transcriptomes from follicles resulting in competent (live birth) and non-competent (no pregnancy) oocytes.

Time-lapse imaging was introduced to improve the traditional morphological assessment of embryo. It is considered as a new technology that was applied to the embryo selection procedure. With the advancement in technology, time-lapse is integrated together with the machine learning. By using the time-lapse image, a decision support tool for identifying embryo with high risk of miscarriage was developed. Therefore, embryologist could prioritize embryo for transfer based on the predicted risk [40]. The most recent trend of embryo selection in machine learning approaches utilizes Convolution Neural Network (CNN) [51, 52]. The CNN model is trained by using time-lapse images of embryos at 113 hour after insemination. Popular deep learning architecture was included into the multi-layered CNN in order to differentiate between embryos based on morphological quality [51].

Following the time-lapse trend, a novel data-driven system trained to directly predict embryo implantation probability from embryogenesis time-lapse imaging videos was developed [54]. That specific study demonstrated that, when compared to an external panel of embryologists, the algorithm results in a 12% increase of positive predictive value and a 29% increase of negative predictive value.

Both machine learning in traditional morphological evaluation and time-lapse imaging shows a promising result. New research should focus on both areas as both have it owns advantages and disadvantages.

Table 1: Machine Learning Application

Study	Methods	Machine Learning Application
Selection of human embryo for transfer by Bayesian Classifier (2008) [46]	Bayesian Classifier	Embryo selection
Bayesian classification for the selection of in vitro human embryo using morphological and clinical data (2008) [45]	Bayesian Classifier	Embryo selection
Predicting Implantation outcome from imbalanced IVF dataset (2009) [33]	Naïve Bayes	Implantation prediction
Bayesian Networks for predicting IVF Blastocyst Development(2010) [34]	Bayesian Network	Implantation prediction (based on blastocyst development)
Handling the imbalance problem of IVF implantation prediction (2010) [35]	Naïve Bayes	Implantation prediction
Nearest neighbour concept in the study of IVF ICSI/ET treatment effectiveness (2011) [41]	KNN classifier	IVF success rate
Application of Artificial Neural Network for IVF data analysis and prediction (2013) [42]	ANN (back propagation and MLP)	IVF success rate
Artificial intelligence techniques for embryo and oocyte classification (2013) [53]	Neural Network	Embryo/Oocyte classification
Competence classification of Cumulus and Granulosa Cell Transcriptome in embryo matched by morphology and female age (2016) [38]	SVM	Live birth prediction
Deep Learning enables robust assessment and selection of human blastocyst after in vitro fertilization (2018) [47]	CNN	Embryo Selection
Deep learning technique for automatic classification and analysis of human in vitro fertilization (IVF) embryo (2018) [48]	CNN	Embryo Selection
Personalized prediction of live birth prior to the first in vitro fertilization : a machine learning method (2019) [43]	Xgboost	IVF success rate (for pre-treatment)
Feasibility of predicting live birth by combining conventional embryo evaluation with artificial intelligence applied to a blastocyst image in patient classified by age (2019) [39]	CNN	Live-birth prediction
In vitro fertilization (IVF) cumulative pregnancy rate prediction from basic patient characteristics (2019) [44]	SVM	IVF success rate (for pre-treatment)
Using Deep Learning with large dataset of microscope images to develop an automated embryo grading system (2019) [49]	CNN	Embryo Selection
Selection of single potential embryo to improve the success rate of implantation in IVF procedure using machine learning techniques (2019) [50]	CNN	Embryo Selection
Prediction of implantation after blastocyst transfer in in vitro fertilization : a machine learning perspective (2019) [36]	RFM, MvLRM	Implantation prediction
Embryo selection beyond pregnancy : early prediction	XGBoost, RF	Miscarriage prediction

of first trimester miscarriage using machine learning (2020) [40]		
Evaluation of deep convolutional neural networks in classifying human embryo images based on their morphological quality (2020) [51]	CNN	Embryo Selection
Performance of deep learning based neural network in the selection of human blastocyst for implantation (2020) [52]	CNN	Embryo Selection

4 Discussion

Selecting the right embryo is a very important step in IVF procedure. Most IVF centers use the traditional ways of evaluating the embryo viability which is based on static morphological assessment to select the most viable embryo. Traditional morphological evaluation provides practical advantages in clinical routine. Significant improvement in implantation rate and live birth success can be obtained by using traditional morphological evaluation. Besides, traditional morphological evaluation is inexpensive. This allows more researchers to work on improved method to be integrated into traditional morphological evaluation. Using traditional morphological evaluation, it is reliable and widely being used, but somehow, the subjectivity of assessment of embryo limits its success. The other things that is concerning is the time consuming factor of traditional morphological evaluation. Manually making assessment can only be done by taking out the embryo from the incubator repeatedly in the specific time point. This makes the process more complicated as removing embryo out of its embryo culture frequently to get more developmental information could damages the embryo.

Advancement in technology has proposed the used of time-lapse imaging in the embryo selection process. By that, it facilitates the embryo selection process. Nevertheless, time-lapse technology provides a very useable, although expensive, tool for the laboratory, with safe and stable culture conditions [55]. However, even with time-lapse imaging, implantation rates in human are still difficult to predict [56]. There is still no consensus on the clinical benefits of this technique [2]. It is important to emphasize that most fertility centers do not possess time-lapse imaging hardware [2]. High costing of such instrument causes the lack of availability of such hardware. On the other hand, in current clinical practice, embryos with the highest morphological grades are the first to be transferred, however, even with time-lapse imaging systems availability; decisions to the most viable embryo are done manually.

Machine learning model in traditional morphological evaluation used static microscopic images to evaluate the embryo [46]. Images alone do not provide enough information to the machine learning model. Thus, the model is trained together with morphological characteristic features so that the model is able to classify the embryo into a potential and non-potential embryo group. Some of the models provide a decision support system to help embryologist in decision making process of choosing the most viable embryo to be transferred into uterus. Besides, in traditional morphological evaluation, existing model were developed using Bayesian classifier. Researchers can still explore traditional morphological evaluation using other machine learning models.

As time-lapse imaging was introduced to improve traditional method, the study in machine learning also follows the trend. The recent studies in machine learning area used time-lapse imaging or time-lapse video to select the most viable embryo from cohort of embryos available. In comparison to the static microscopic images, time-lapse imaging provides more information on the developmental stage of the embryo. More data collected allows more consideration to be integrated. Thus, with machine learning model using time-lapse imaging, a more realistic decision making system to select embryo was able to developed and become a reliable machine learning model to ease morphological embryo selection process. Besides, by utilizing machine learning in time–lapse, it could lead to the patterns recognition that link the outcome of every time-lapse image [55]. Therefore, a more accurate and non-biased embryo selection could be obtained in the future.

At the moment, machine learning model utilizes either static microscopic images or time-lapse images as the training data; both in traditional morphological evaluation and time-lapse. By utilizing images, more steps are required in order to detect the morphological characteristics of the embryo. It requires experts or embryologist to verify the morphological characteristics based on the images of embryo. Therefore, the models are trained with both embryo images and morphological characteristics of the embryo. Textual data consisting of features or characteristics of embryo are still needed for the models to be able to train accurately.

Due to the complexity of embryo morphology, morphological assessment still remains as a challenge. It is hard to emulate the skill of embryologist into a fully automated system [52]. Eventhough time-lapse imaging might be the most advance technologies in embryo selection process, however, traditional morphology evaluation also shows a reliable result in embryo selection. Thus, there is opportunity to explore machine learning model that utilize textual data of morphological embryo characteristic that can be used to choose most viable embryo in traditional morphological evaluation.

5 Conclusion

Embryo selection plays the major role in increasing the success rate of IVF. Conventional assessment although shows great impact in embryo selection; the need for improvement is still there especially to eliminates subjectivity. Expensive cost in time-lapse limits the usage of time-lapse to be used further in embryo selection. With the advancement in technology, machine learning has been integrated into the embryo selection process. Various prediction models have introduced and provide a decision support system for the embryologist. There is still a room for improvement especially in developing a machine learning model for traditional morphological evaluation. Since traditional ways is reliable and inexpensive to begin with, there is a lot of opportunity and improvement that can be explored and added into the traditional morphology assessment.

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