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Application of Machine Learning and Artificial Intelligence Techniques for IVF Analysis and Prediction

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ABSTRACT

Infertility is the combination of factors that prevent pregnancy. It involves a lot of care and expertise while selecting the best embryo to lead to a successful pregnancy. Assistive reproductive technology (ART) helps to solve this issue. In vitro fertilization (IVF) is one of the methods of ART which is very popular. Artificial intelligence will have digital revolution and manifold advances in the field of reproductive medicine and will eventually provide immense benefits to infertile patients. The main aim of this article is to focus on the methods that can predict the accuracy of pregnancy without human intervention. It provides successful studies conducted by using machine learning techniques. This easily enables doctors to understand the behavior of the attributes which are suitable for the treatment. Blastocyst images can be deployed for the detection and prediction of the best embryo which has the maximum chance of a successful pregnancy. This pioneering work gives one a view into how this field could benefit the future generation.

KEYWORDS

ART, Artificial Intelligence, Blastocyst, Deep Learning, Embryo Grading, Embryo Selection, IVF, Machine Learning Techniques, Neural Networks

INTRODUCTION

It involves a lot of care and expertise while selecting the best embryo or the factors which lead to a successful pregnancy. The embryologist plays a vital role by establishing reproductive assistance and clinical help from the fertility consultant, in the initial stages of diagnosis of a couple who come for IVF treatment. The culture of

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eggs, sperm and embryos are examined under medical conditions. The main aim is to understand, plan and regulate the defects that are contemplated before fertilization. Embryologists study the embryo morphology including embryo grading, embryo freezing, selecting the best embryo for implantation (Uyar, 2009). Processing an embryo for the fertilization is called a cycle. The embryologists freeze the embryos until they get the best results. Implantation failure occurs when the IVF process cannot be successful even after repetitive embryo transfers (Koot, 2016). Manual embryo grading is a tedious and time-consuming job. It will be easy if a machine can do this process without human intervention. With this thought using artificial intelligence (AI) and deep learning techniques, it is very helpful in determining the best embryo that can be induced (Malinowski, 2014).

The three methods through which IVF can be obtained using AI and ML techniques:

- Building a model to know what the success rate of IVF treatment will be and whether to continue with it or not;
- Predicting the accuracy as to in how many cycles IVF can be successful;
- Selecting the best quality embryo, which increases the chance of pregnancy even before IVF treatment.

In this review, the following sections will help in knowing different Machine Learning and AI techniques and their contributions towards the infertility treatment. In view of this survey, the data has been collected from different search engines and from the previous publications.

THEORETICAL BACKGROUND

According to statistical survey, Infertility is faced by more than 10% of the world population (Haimovici, 2018). Infertility is the inability to achieve pregnancy after one year of unprotected intercourse due to many combinations of factors. On determining the infertility aspect of a couple, an appropriate assisted reproduction treatment is applied in order to conceive a pregnancy successfully. The quality of embryos and oocytes is predicted by using artificial intelligence methods. IVF is one of the types of ART, where man's sperm and woman's egg is nourished under medical conditions and then it is inserted into the women's uterus (Gerris, 2004; Raef, 2019). The reasons for infertility are blocked fallopian tubes, diabetes, age, smoking, alcohol consumption, irregular mensural cycles, hormonal deficiencies, low sperm count, certain genetic diseases, etc. (Haimovici, 2018; Crawford, 2015).

ART has many techniques to deal with different types of issues:

1. In vitro Fertilization (IVF): It is the most successful technique of ART
2. Intrauterine Insemination (IUI): Fertilization of eggs is done inside the woman's uterus. The success rate is low when compared to IVF. But it is affordable

3. Intracytoplasmic Sperm Injection (ICSI): By taking the eggs from a woman's body and injecting sperm to one of the eggs, when it fertilizes it is transferred to the woman's uterus. This is the best technique for sperm related issues (Alizadeh, 2014)
4. Intrafallopian Transfer: Unlike the other techniques the eggs are fertilized inside the fallopian tubes of a woman. This is the best choice for women who suffer from fallopian tube issues which can be performed in two different types:
   a. Gamete Intrafallopian Transfer (GIT);
   b. Zygote Intrafallopian Transfer (ZIT);
5. Surrogacy;
6. Test tube baby.

Aneuploidy is the assessment of chromosomes which leads to fertility. Infertility occurs when the count of chromosomes differ which causes miscarriages in 60% of the people (Miyagi, 2019). So, there is a method called Comprehensive Chromosome Screening (CSS) which mainly deals with chromosome abnormalities. It enumerates the chances of getting pregnant. The parameters that are needed for the blastocyst evaluation mainly depends on the chromosomes that are mapped with blastocyst morphology (Capalbo, 2014). This enables the chances of implantation which leads to a healthy pregnancy.

The couple suffering from infertility, must initially undergo certain preliminary medical procedures and later follow the assistive techniques. This includes clearing the fallopian tubes with medications, accompanied by hormonal treatments. When these treatments fail, ART procedures are prescribed. But the most successful and adaptable technique is IVF. Datamining is applied in ART procedures for better results. In the year 2005 a technique, information fuzzy network along with the association rule mining is initiated which targets the real significant attribute which contributes more to the target attribute was studied (Davis, J., 2005). Tests performed in vitro means 'in the glass,' it is done outside of a living organism involving isolated tissues, organs or cells. But this is quite expensive and the number of cycles to predict the pregnancy is unknown. IVF involves stimulating and retrieving multiple mature eggs, fertilizing them under clinical conditions and implanting into the uterus after some days of fertilization. But transferring the best embryo is the main and important task of IVF. This can be done with a single or two embryo transfers in the initial cycles of the method (Gerris, 2004). Before going into detail about IVF, here are some basic terminologies that need to be understood.

The embryo begins with a single cell and divides further with time. (Rienzi, 2017) Oocyte is a cell in an ovary which may undergo meiotic division to form an ovum. An ovum is the mature female gamete in mammals, which gives rise to the embryo after fertilization. The development of embryos is done in different phases just like a normal fertile embryo, before placing a fertilized embryo into the woman's womb. The fertilization day-1 to 2 is called Zygote. The embryo in day-3 is called Multicell Embryo and by day-5 it is termed as Blastocyst. Besides developing an embryo using

IVF there are some additional techniques involved to increase the success rate of IVF. This includes:

- Ovarian Hyperstimulation: Inducing multiple follicles during ovulation
- Natural IVF: Without using any drugs for Ovarian Stimulation.
- Oocyte maturation (Rienzi, 2017; Manna, 2013)
- Eggs retrieval
- Embryo culture
- Embryo grading
- Embryo selection and finally
- Embryo transfer

RELATED WORK

Machine Learning in IVF

ML can be implemented in different types.

Supervised Learning

Here are some algorithms which have their contribution for my study.

Decision Trees

It is a classification model that incrementally builds the tree by aggregating the attributes as they have been considered as leaf nodes. It works effectively for both classification and regression. It represents the data in the tree-like structure and depicts the alternative paths to reach the leaf node, from the root node. Iterative Dichotomiser (ID3), C4.5 (successor to ID3), Classification and Regression Trees (CART), Chi-Square Automatic Iteration Detector (CHAID) are the most effective models to implement the decision trees.

ID3: This is the most effective technique to build a decision tree. Entropy and information gain are the two needed criteria for calculating ID3:

$$\text{Entropy} = -\sum_{i=1}^{n} p_i \log_2 p_i$$

While constructing the decision tree the attribute that has the highest Information gain can be considered. Gini index is used for a decision tree which must be constructed for binary attribute class labels. CART uses this technique for the construction of the tree. After construction of the tree, the main observation should be tree size, so the pre-pruning or post pruning is done to avoid the overfitting concept.

The previous study includes, Passmore's research on C5.0 Decision Tree Inducer used for feature selection, which has the improvised performance as compared to the statistical models (Passmore, 2003). Srinivas Kilambi used Logistic Regression and Principal Component Analysis (PCA) for better feature selection to improvise

the model performance (Kilambi, 2016). Cai implemented Multivariable Logistic Regression and Bootstrapping to predict the variables which affects pregnancy while performing IVF (Cai, 2011). Balogun evaluated the classification model using the Waikato Environment for Knowledge Analysis (WEKA- J48 model), for the estimation of infertility in women and is evaluated by considering 14 different attributes that are used in prediction (Balogun, 2018). Milewska and Guh tested a group of variables to predict the pregnancy, in which they implemented genetic algorithm along with Decision Tree (Milewska, 2016; Guh, 2011).

SVM Classifier

It is one of the types of classification of algorithms which predict the class labels by using hyperplanes to the good as well as bad class labels. The equation for hyperplane is W. X + b = 0, where 'W' is the weight vector, 'b' is a scalar value and 'X' is the associated attribute value. A Hybrid approach classification algorithm which is used with the comparison to Naïve Bayes and SVM has acquired better results (Malathi, 2018; Uyar, 2009). Classification of embryos, Frequency-based encoding technique has been proposed for the conversion of categorical variables and to improve the performance of SVM (Uyar, 2009), (Miyagi, 2019). Factors identification and class label prediction is a complex task in terms of IVF attributes. A method is proposed by using SVM to resolve the issue of identification (Milewski, 2012; Uyar, 2009).

Naïve Bayes Classification

This mainly works on the probabilistic model. It examines the probabilities individually for all the true and false cases and will also check for the conditional probabilities of being true or false. Malathi applied hybrid model, the results were so convincing with the highest accuracy than that of SVM and Naïve Bayes (Malathi, 2018). Differentiating the embryos in terms of implantation into the uterus is an important task. The imbalance outcome of true and false cases can be handled by Naïve Bayes Classifier (Uyar, 2010; Miyagi, 2019). Güvenir tested with Successive estimation using a ranking algorithm (SERA), which helped in finding out the attributes which mainly affect the IVF treatment (Güvenir, 2015). Embryo selection is the leading step towards the success of IVF treatment. This is evaluated by using a Naïve Bayes approach (Uyar, 2009). Md Rafiul Hassan, Sadiq Al-Insaif, M. Imtiaz Hossain, and Joarder Kamruzzaman, have analyzed different classification algorithms that contribute in prediction of IVF treatment and proposed a new feature selection technique called Hill climbing, which evaluates the important attributes that can improve the efficiency of the classifier and there by predicting infertility.

Ensemble Methods

The results produced by these methods that can be based on the combination of multiple models and bringing them together into one frame. The main methods include Bagging, Ada- Boosting, Random forest (LeBlanc, 2010). Some authors have contributed their work on these methods which is very helpful for this survey (Milewski, 2012;

Arora, 2017; Miyagi, 2019). The bootstrap aggregation method is used to increase the accuracy. Cai has compared the bootstrap with Naïve Bayes Classifier, and the result was that the Naïve Bayes Classifier has achieved the highest accuracy (Cai, 2011). Case-based reasoning is one of the methods which can evaluate different data results, where the related attributes can be identified for the fertility outcome (Jurisica, 1998).

Unsupervised Learning

It is the process of grouping of objects based on the similarity not by the class labels. Here class labels are unknown. K- Means Clustering is one of the unsupervised learning algorithms that mainly works on centroid, assigning the random data points to its nearest centroid. The intensity factors caused by the usage of drugs in infertility is analyzed using this algorithm (Alizadeh, 2004).

Association Rule Mining

It is one of the rule-based methods in machine learning techniques to observe the correlations, frequent patterns and relevant measures of interest. It mainly works on two parameters viz., support and confidence. Support is the frequency of the rule appearing in database and confidence is the number of times the rules proved to be true. This algorithm proved its efficiency in Market Basket analysis, medical diagnosis, census data, DNA and protein sequence (Davis, 2005).

Performance Evaluation of Models

Once the model is built then the results can be established with methods which will be used to visualize the assessment, such as accuracy, sensitivity, specificity, precision, recall that can evaluate the performance of the model.

For making this analysis effective the main terms that must be known are Positive and Negative tuples. In case of binary class labels, positive tuples are the *YES* conditions and negative tuples are the *NO* conditions.

The following are the basic terms:

Recall = TP/P
Positive (P) = Actual is True
Negative (N) = Actual is Negative
True Positive (TP) = Actual and Predicted are positive
False Negative (FN) = Actual is positive and predicted is negative
True Negative (TN) = Actual and predicted are negative
False Negative (FN) = Actual is negative and predicted positive

1. **Confusion Matrix:** This is the powerful evaluation tool which can analyze the performance of a classifier (Table 1);
2. **Accuracy:** The accuracy of a model can be determined based on the number of tuples that are correctly classified by the classifier:

Table 1. Confusion Matrix

	Predicted Class 1	Predicted Class 2
Actual Class 1	TP	FN
Actual Class 2	FP	TN

Accuracy = TP + TN /P+N

3. **Sensitivity:** The positive tuples that is correctly identified by the classifier:

Sensitivity = TP/P

4. **Specificity:** The negative tuples that are correctly identified by the classifier:

Specificity = TN/N

5. **Precision:** The percentage of total number of correctly classified positive tuples divided by the total number of predictive positive tuples:

Precision= TP/TP+FP

6. **Recall:** The percentage of total number of correctly classified positive tuples divided by the total number of positive tuples:

Recall= TP/TP+FN

If two classification models are used for the analysis and to compare which classification model is the best, then receiver operating characteristic curves (ROC) is widely used. This is the visualization tool, which draws a curve between True Positive Rate (TPR) and False Positive Rate (FPR). Here the TPR is Sensitivity and FPR is Specificity.

IMPACT OF AI AND DEEP LEARNING TECHNIQUES IN IVF

As many of the techniques which had their contribution towards IVF success is mainly assessed by the attributes which have a major impact on infertility. Based on these attributes much research has been done for the prediction of the success rate of IVF using various Data mining and Machine Learning techniques. As there is scientific and computational growth over the decades Artificial Intelligence has become popular in all areas of technology. So, it has an impact on medical sciences and clinical advancements. Now all the medical applications are depending on the prediction and assessment. Siristatidis implemented logistic regression and statistical modeling for evaluation and its influence in terms of the medical perspective (Siristatidis, 2010).

Artificial Neural Network (ANN) has a complete solution where human interference is almost zero. It can analyze and predict the future. ANN is also implemented in the field of gynecology as detailed below.

AI has its mark in the field of infertility too (Siristatidis, 2011). The normal procedure in IVF is to perform the morphology of embryos with the help of an embryologist, assessing the best embryo for the implantation. Embryo grading is an important task that is carried out by the embryologists in search of the best embryo. But if the implantation fails, then the patient must go through with another cycle of assessment for the successful transfer. But a human cannot predict how many cycles that a patient must go through. By applying AI, if the microscopic images (Blastocyst) of the patient have been supplied to the machine then it will predict the best embryo which has an accurate outcome for the fertility treatment. So, from the grading of embryos to the prediction of the best embryo for the IVF cycle is done by AI. This is an automated process without human intervention. This assists the doctors as well as the embryologists to hasten their work and to minimize their time (Figure 1).

Image Source: Medical Express

The Convolution Neural Network model is proposed using image processing to detect automatically the grade of the blastocyst (Gunawan, 2019). Weill Cornell Medical University has developed a deep neural network called STORK, which enables the automation of the infertility process in terms of choosing and transferring embryos (Khosravi, 2019). The time-lapse imaging technique is used for the assessment of the best embryo development. Oocyte and embryo classification play an important role while analyzing the embryo quality. When this classification is automized by using AI technology it gives the best results as compared to ML techniques used previously (Manna, 2013). The aneuploidy (abnormalities) present in the chromosomes leads to infertility. If this can be recognized prior to the process of IVF then it can save money as well as time for the patient and fertility experts. Aneuploidy can be treated by AI. When the blastocyst image is developed and given to the AI network this can be predicted prior to the treatment (Miyagi, 2019).

AI in Embryo Grading

Embryo grading is important and time taking task of the infertility process. Where embryo features will be studied and processed for the final best embryo selection.

Figure 1. Classification of Blastocyst images using AI

Deep learning will reduce the time of embryo grading by using its techniques (Chen, 2019). The embryos used here are around one lakh and the embryo's age are 5 days are considered. The images have been divided into training, validation, and testing. A 50-layer network is used to carry out this study. The network has automatically graded the embryos and suggested the best embryo that can be transferred for the treatment. This mainly reduces the time and clinical tasks that need to be performed. Semi automized grading can be applied to verify the relevant features between the embryos that can be used for the treatment. This involves image segmentation and analysis.

AI in Embryo Classification

Embryo selection is the most important phase after the grading is done. The selection of embryo mainly depends on which day the embryo is being considered so that it has the highest chances of fertility. Cohort Embryo Selection method is being used for the assessment and it uses the time points and the day of embryos that have the highest chance of implantation (Dimitriadis, 2017). In analyzing the high-quality embryo, this is a simple and novel method.

CONCLUSION AND FUTURE SCOPE

Artificial Intelligence will fetch digital revolution and manifold advances in the field of reproductive medicine and will eventually provide immense benefits to infertile patients and to the society. The application of AI in IVF is significant and used to a great advantage for embryo grading and selection, optimizing the assessment of ovarian reserve parameters and sperm selection.

The main aim is to explore the possibility of using this new system in larger and more structured studies such as those with single-embryo transfer, including a prospective randomized trial for reaching full clinical relevance. Deep learning is applied with a convolutional neural network in the realm of AI to develop classifiers for predicting the probability of a live birth from a blastocyst image categorized by maternal age.

The existing models from the survey have identified the importance of Machine learning and Artificial Intelligence which are determined as the best predictable approaches for the ART treatments. Most of the work is done on the attributes or the constraints which affects infertility. As a proposed work, these models can be upgraded with the latest available data using the blastocyst image datasets. This pioneering work gives us a view into how this field could benefit the future generation.

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