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Machine Learning Approaches to predict Intra-Uterine Insemination Success Rate- Application of Artificial Intelligence in Infertility

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Abstract: **Introduction:** Assisted Reproductive Technology (ART) has been widely utilized for infertility management. Despite its low success rate, Intra-Uterine Insemination (IUI) is one of the first alternatives and most important approaches regarding many cases of infertility treatment. Given the numerous influencing factors and limitations associated with time and resources, the development of a reliable model to predict the success rate of ART methods can significantly contribute to decision-making processes. **Materials and methods:** We reviewed the demographic, clinical, and laboratory data regarding 157 IUI treatment cycles among 124 women using their partner's sperm from May2017 to June2019. Primary outcome measures were clinical pregnancy and live birth. Some prediction models were constructed and compared to the logistic regression analysis. **Result:** Woman's mean age was 30.1 ± 5.2 years and the infertility had a female cause in 24.3% of the cases, male cause in 32.6% of cases, and combined causes in 32.6% of the cases. Concerning the first IUI cycle, the clinical pregnancy rate per cycle was 16.9% (N= 21). Data were prepared according to cross-industry standard process for data mining (CRISP-DM) methodology, and the following models were fitted to the data: J48 Decision Tree, Perceptron Multilayer (MLP) Neural Network, Support Vector Machine (SVM) with radial basis function (RBF) kernel, K-Nearest Neighbors (KNN) with one neighborhood, and Bayesian Network. J48 Decision Tree, with a sensitivity of 95% and specificity of 98%, had the most optimal performance, and the KNN model was the weakest one. **Conclusion:** To predict the results of IUI as a simple and less invasive therapy for infertile couples, some models were applied based on artificial intelligence and J48 Decision Tree was recommended.

Keywords: Artificial intelligence, Assisted Reproductive Technology (ART), Decision tree, Infertility, Insemination, neural network

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1. Introduction

Based on a global survey, 8-12% of couples in the reproductive age range worldwide (1-4) and up to 20.2% of the Iranian population (5), face infertility. Over the past 40 years, Assisted Reproductive Technology (ART) has been widely uti-

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lized by healthcare providers for the management of infertility. ART includes all fertility treatments in which either eggs or embryos are handled.
More advanced ART techniques, such as In Vitro Fertilization (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI) have been developed over the past decades. However, due to its characteristics of being less invasive and less costly, Intra-Uterine Insemination (IUI) is considered an important approach and a first choice in many infertility cases. Some indications include male subfertility, cervical factor infertility, human immunodeficiency virus (HIV) infection, requirement of donor sperm, and immunological infertility (6-10).
Although IUI is more affordable and less invasive when compared to other ART methods, the pregnancy success rate is relatively low in each cycle (11). According to the European Society of Human Reproduction and Embryology, although IUI success in terms of pregnancy rate per cycle differs based on various factors, it can reach up to 16.4%. (12, 13) This rate was reported 16.5% and 22% in two Iranian population-based studies (14, 15). Several factors have been associated with the likelihood of successful pregnancy following IUI. woman's age, ovarian reserve and stimulation, Human Chorionic Gonadotropin Therapy, duration and cause of infertility, endometrial thickness, and the number of high-quality motile spermatozoa (16-20) are examples of such factors.
Due to the limitations associated with time, money, and facilities, it is highly necessary to develop a reliable model to predict the success rate of ART methods based on variable individual factors to assist us in the decision-making process. Artificial intelligence (AI) refers to complex software that performs tasks in a way similar to human brains, often by sensing and responding to a feature of their environment. Numerous methods based on statistical models and AI have been proposed for this purpose. However, in terms of IUI, a vast majority of these methods are based on conventional statistical models such as logistic regression, and no standard and reliable method for modeling IUI outcomes has been developed so far (21-23).
Over the recent years, along with the dramatic increase in biomedical data volume and complexity and the breakthroughs in the field of computer sciences, there is a tendency to utilize computer-based prediction models and artificial intelligence (AI) systems in medical fields. Artificial intelligence is identified as a machine's intellectual capability to display information by combining learning, self-adapting, and predicting systems (24, 25). The increase in the factors affecting the success of ART methods, including IUI, has dramatically augmented the amount of biomedical data individually required to predict the clinical outcome. This makes it almost impossible for conventional statistical methods to be effectively used for this purpose, thereby calling for a more sophisticated method to facilitate effective data analysis. With their complex algorithms, AI systems can detect and learn the potential pattern and connections among a huge amount of biomedical data. (26-28) These machines are already being used in various fields of medical sciences, such as pharmacology, cardiology, oncology, neurology, stem cells, and immune therapies. (29-36).
Numerous studies have been performed to predict pregnancy after IVF and embryo classification or selection using AI. However, the literature related to the application of AI to IUI outcome prediction is rather limited (37-39). Therefore, we aimed to design a dynamic model to predict IUI outcomes based on Artificial Intelligence.

2. Materials and methods

We reviewed the demographic, clinical, and laboratory data regarding 157 IUI treatment cycles in 124 women referred to the infertility ward of Taleghani hospital located in Tehran, Iran, in this retrospective cohort study. The records from May 2017 to June 2019 were registered for training the network and can be used for prediction.
Inclusion criteria was all the couples who underwent IUI in this time period. Exclusion criteria were severe sperm parameters abnormality, Globozoospermia, teratozoospermia, cryptozoospermia as male factors and obstruction of fallopian tube by any reasons, unexplained infertility and advanced age as female factors and the patients with missing data. Successful treatment was considered as live birth in the couples who used maximum three times IUI technique. Failure to fertilization, still birth and abortion after three times are described as unsuccessful treatment due to our center protocols.
The infertility evaluation of each patient included history, physical examination, two semen analyses, and measurement of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-müllerian hormone (AMH), and prolactin (PRL) (normal range 2.5 to 17 ng/ml). The hormonal ovulatory management for each IUI cycle, semen analyses, and IUI protocol were the same for all couples. IUI protocol starts with clomiphene citrate 100mg or letrozole 5mg for 5 days then followed by recombinant FSH 75 or 150 IU one or two injections.
All patients signed an informed consent before being enrolled in the study. The study protocol was approved by our institutional review board of research and the ethics committee of Shahid Beheshti University of Medical Sciences (ethics code: Ir.sbmu.RETECH.REC.1396.628). This study was conducted in accordance with the 1967 Declaration of Helsinki and its later amendments. Primary outcome measures were clinical pregnancy and live birth. Some prediction models were constructed and compared to the logistic regression analysis.

3. Results

In the first IUI cycle, women's mean age was 30.1±5.2 years, and the mean body mass index (BMI) was 25.5±3.6 kg/m2. Infertility had a female cause in 24.3% of the cases (broken down into polycystic ovary syndrome (PCOS), pelvic endometriosis, cervical infertility, and fallopian tube anomalies to name a few), a male cause in 32.6% of the cases, and combined male and female causes in 32.6% of the cases. In 10.5% of the cases, no cause could be observed. Based on the first IUI cycle, the clinical pregnancy rate per cycle was 16.9% (N= 21). Table 1 illustrates the statistical indices related to the study variables.

3.1. Prediction models

Following data preparation according to cross-industry standard process for data mining (CRISP-DM) methodology, the following models were fitted to the data; J48 Decision Tree, Perceptron Multilayer (MLP) Neural Network, Support Vector Machine (SVM) with radial basis function (RBF) kernel, K-Nearest Neighbors with 1 neighborhood, and Bayesian Network. In these models, optimal parameters for modeling were selected from a set of parameters through five-fold cross-validation. To evaluate the results of the models, the Leave-One-Out evaluation scheme was employed. The procedure (IUI) result was considered as the target variables and other variables as inputs. Table 2 summarizes the results of the model evaluation.

Comparison of the executed models showed that J48 Decision Tree had the best performance while the KNN model was the weakest. The rules derived from the j48 Decision tree are shown in figure 1.

The tree structure of the above rules is as Figure 2.

The patterns discovered by the Decision Tree for those who have a successful treatment are as follows: If the infertility period is less than five years and there is no uterus disease, the result will be successful. These conditions existed in 22 couples (Rule Support), with 91% (Rule Confidence) having a successful outcome. Because 17% of the studied couples had successful treatment results, this pattern presents the chances of achieving successful treatment more than 5 (lift index). This indicates that infertility period and uterus disease had a substantial impact on the treatment outcome.

Moreover, the following two patterns were found for couples whose treatment fails;

If the infertility period is more than 5 years, the result will be unsuccessful. These conditions were established in 98 couples (Rule Support), 99% (Rule Confidence) of couples with unsuccessful treatment. The lift index in this rule is 1.2.

In another pattern, if the infertility period is more than 5 years, and the condition of the uterus disease is "endometriosis" and "polyp", the treatment result will be unsuccessful. Support for this rule is 4, and its 100% confidence and lift indicator is 1.2. Due to the low support of this rule, it can be said that its generalizability is not as high as the two other rules.

In the logistic regression, only the infertility period coefficient was significant (p-value <0.001). This coefficient is -3.75 with a standard error of 1.07. According to the infertility period, the odds ratio is 0.02, based on which with the annual increase in infertility period, the chances of a successful outcome are reduced by 98%. The 95% confidence interval shows that this chance drop is 80% to 99.7%.

In general, it can be concluded that among the statistical models and machine learning methods, the decision tree had the highest overall accuracy, sensitivity, and specificity. This can be caused by the greedy search of the decision tree model to find the variable with the highest amount of information about the response variable. In other models, due to the simultaneous presence of independent variables in model learning, the high number of input variables and their interdependence can lead to poor learning and reduced model performance. Furthermore, according to the tree rules and the infertility period coefficient in the logistic regression model, this variable had a high degree of information concerning the outcome of the treatment.

After testing the relationship between the input variables and clinical pregnancy, these variables were used to create a logistic regression. Correct prediction rates were greater in neural network conjectures compared to the logistic regression model.

4. Discussion

Since IUI is the least invasive procedure in ARTs, it should be considered as the first-line treatment for those infertility cases where IUI is indicated. The overall success of IUI varies, with pregnancy rates ranging from as low as 2.7% to as high as 66% (14). Based on the previously-discussed reasons, developing a reliable model to predict the success rate of ART methods has been always of interest for infertility experts. On the other hand, the data used to predict the infertility outcome in such cases are fragmented. This is mostly because patient data is obtained from several sources, and more importantly, both male and female factors are required for the final results (40).

So far, several studies have been conducted to provide models capable of analyzing the value of parameters to predict the IUI cycle or procedure outcome (41-43). These models are mostly based on logistic regression and able to identify and assess the impact of various prognostic factors contributing to the IUI. The main known factors that affect the outcome of IUI technique are as follows: female and male ages, body mass index (BMI) in women (<25 kg/m²), length and type (secondary) of infertility, sperm motility and normal sperm morphology count, number of follicles larger than or equal to 14 mm, serum FSH and Estradiol (E2) level, frequency of uterine contractions, and type of insemination treatment (41, 44-48). By summing up all these studies, it is concluded that IUI results can be optimized under certain conditions, and the variance in the achieved pregnancy rate might be due to performing IUI under non-identical conditions where the presence of any of these factors can affect the outcome. None of these studies, on the other hand, has provided a reliable model for predicting the procedure outcome based on individuals' data. In this study, J48 Decision Tree, MLP Neural Network, SVM with RBF kernel, KNN with one neighborhood, and Bayesian Network. J48 Decision Tree, with a sensitivity of 95% and specificity of 98%, had the most optimal performance, and the KNN model was the weakest one.

In a systematic review by Leushuis et al., of the 29 prediction models identified in reproductive medicine, only 8 were externally validated. This means that the validity was assessed in populations other than the one in which the model was used, and only three had good predictive performance (Stolwijk et al., 1996; Templeton et al., 1996; Hunault et al., 2002a) and applicable as a reliable guide for decision making in fertility treatment (49). Among these three studies, only one was about IUI outcome prediction. They developed a model based on logistic regression analysis and showed that by identifying and selecting prognostic factors, their proposed model was able to distinguish between couples with good or poor prognosis (50).

Conventional statistical models such as regression models are limited in predicting the efficacy of ART treatment. This has augmented the use of more advanced data-mining and artificial intelligence methods for the outcome prediction of infertility treatment. However, previous studies were mostly focused on the use of these methods in IVF outcome prediction (39, 51, 52) while these systems have been rarely applied to IUI.

It is in fact a simulation of the human brain via modeling the neurons in which each neuron works as a processing unit. Multi-layer perceptron (MLP) neural network is one of the most widely utilized types of networks, and its structure includes several layers (input, hidden, and output layers) each with a number of defined activity nodes and functions(53). The output of each layer is calculated using the sum of the weighed coefficients in that layer and sent to the next layer via an activity function(54). When using MLP neural network, this model requires a large data and sample size for optimal results. Because our data is not large enough, the model conducted based on MLP neural network was not the best model in our study.

Nonetheless, Milewska et al. were the pioneers in employing the more sophisticated analysis methods including artificial intelligence in predicting IUI treatment outcomes. In 2013, they provided two systems to analyze the outcomes of IUI treatment in two groups of patients with good or poor prognosis. They concluded that the k-means algorithm from the clustering methods was the most optimal alternative for the selection of patients with good prognosis, and Kohonen Neural Networks was better to use in selecting groups of patients with the least probability of pregnancy (55).

The prediction models based on XGBoost or random forest also had to be examined, but our resources were limited. The limitations of this study were the small sample size and the decrease in the use of IUI in infertile couples in the infertility wards; some physician preferred using methods that are more successful in the first line of treatment such as Intracytoplasmic sperm injection (ICSI), so we were not able to reach IUI results in many couples.

5. Conclusion

To predict the results of IUI as a simple and less invasive therapy for infertile couples, we applied some models based on artificial intelligence and recommended the use of J48 Decision Tree.

6. Appendix

6.1. Acknowledgements

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6.2. Conflict of interest

The authors declare that they have no competing interests.

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6.4. Author contribution

All the authors have the same contribution.

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Table 1: Descriptive Statistics of study variables.

	Minimum	Maximum	Mean	Standard Deviation	Median
Infertility period (year)	3.000	12.000	7.258	1.999	7.000
Male age	25.000	54.000	34.726	5.362	34.000
Menarche age	9.000	17.000	13.345	1.326	13.000
LH	1.200	52.000	8.815	7.079	8.150
Follicles number	4	26	18	6	18
AMH	0.100	21.300	7.036	4.645	5.900
FSH	1.000	28.000	6.022	4.063	5.394
Sperm count	1.000	100.000	37.829	22.082	35.000
Sperm progressive motility	12.000	100.000	74.935	22.407	80.000
Sperm morphology	1	8.5	6.250	3.511	4.000
Days after LMP	7.000	20.000	12.336	2.182	12.000
Endometer thickness	2.000	12.000	6.977	1.782	7.00

LH: Luteinizing hormone, AMH: anti-müllerian hormone, FSH: Follicle stimulating hormone,
LMP: last menstrual period.

Table 2: Classification performance of Statistical and machine learning models.

Models	Overall accuracy	Sensitivity	Specificity
J48	97%	95%	98%
Bayesian Network	95%	85%	97%
Neural Network	91%	86%	92%
SVM	97%	57%	93%
Logistic Regression	81%	81%	81%
KNN	76%	43%	82%

SVM: Support Vector Machine, KNN: K-Nearest Neighbors.

Rules for 0 - contains 2 rule(s)

Rule 1 for 0 (1.0 ;4)

if infertility period <= 5

and Uterus Disease in [polyp, endometriosis]

then 0

Rule 2 for 0 (0.99 ;98)

if infertility period > 5

then 0

Rules for 1 - contains 1 rule(s)

Rule 1 for 1 (0.909; 22)

if infertility period <= 5

and Uterus disease in [0]

then 1

*The numbers in parentheses, in front of the rules, represent the confidence and support (number of referrals).

Figure 1: The rules derived from the j48 Decision tree.

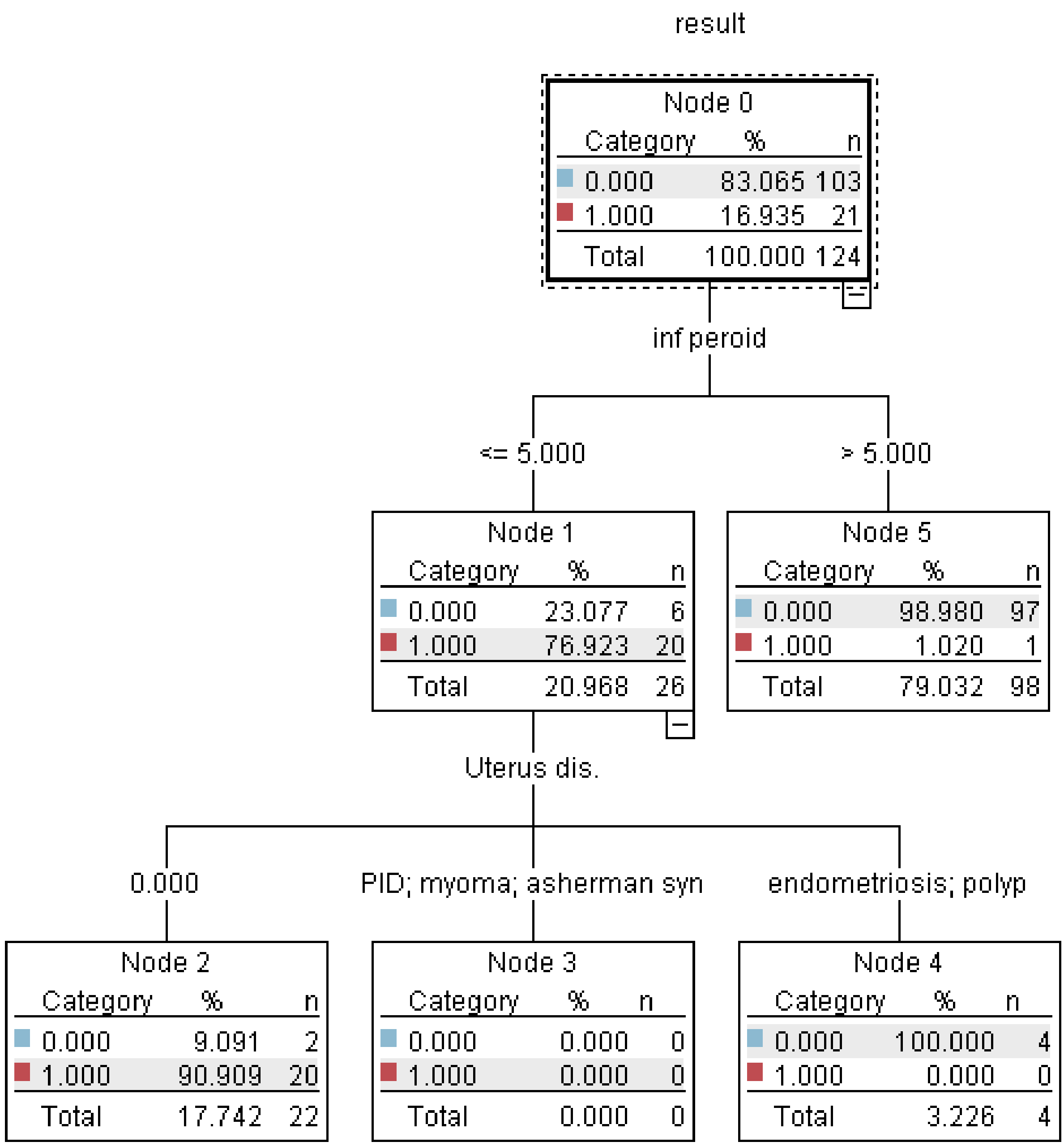

Figure 2: Tree structure of the rules.