Middle East Fertility Society Journal

RESEARCH Open Access

Using artificial intelligence to predict the intrauterine insemination success rate among infertile couples

Azadeh Akbari Sene[1], Zahra Zandieh[1], Mojgan Soflaei[1], Hamid Mokhtari Torshizi[2*] and Kourosh Sheibani[3]

Abstract

Background: To evaluate the use of artificial intelligence (AI) in predicting the success rate of intrauterine insemination (IUI) treatment among infertile couples and also to determine the importance of each of the parameters affecting IUI success. This study was a retrospective cohort study in which information from 380 infertile couples undergoing IUI treatment (190 cases resulting in positive pregnancy test and 190 cases of failed IUI) including underlying factors, female factors, sperm parameters at the beginning of the treatment cycle, and fertility results were collected from 2013 to 2019 and evaluated to determine the effectiveness of AI in predicting IUI success.

Results: We used the most important factors influencing the success of IUI as a neural network input. With the help of a three-layer neural network, the accuracy of the AI to predict the success rate of IUI was 71.92% and the sensitivity and specificity were 76.19% and 66.67%, respectively. The effect of each of the predictive factors was obtained by calculating the ROC curve and determining the cut-off point.

Conclusions: The morphology, total motility, and progressive motility of the sperm were found to be the most important predictive factors for IUI success. In this study, we concluded that by predicting IUI success rate, artificial intelligence can help clinicians choose individualized treatment for infertile couples and to shorten the time to pregnancy.

Keywords: Artificial intelligence, Machine learning, Infertility, Intrauterine insemination, Time to pregnancy

Background

According to the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) as well as the World Health Organization (WHO), infertility is defined as fail to achieve pregnancy following sexual intercourse for 12 months or more if the person avoids any contraception methods [1–3]. Infertility can be considered as an important life crisis that might lead to psychological problems and serious stressful experiences for infertile couples [4, 5].

Today, with advances in infertility treatment, various methods are used to treat infertile couples. Among the methods used in the treatment of infertility is the intrauterine insemination (IUI), which is used in the treatment of infertility with male, cervical, ovarian, and immunological factors and infertility with unexplained etiologies, which account for about 40% of infertility causes [6]. This is a cheap, easy to use, and a relatively non-invasive method compared to other methods of infertility treatment, but a wide success rate for this method has been reported in different studies [7].

Infertility treatment methods are time-consuming and impose a lot of financial and psychological costs on infertile couples. Choosing the right treatment protocol and predicting the results of assisted reproduction can significantly reduce these costs and help infertility professionals

*Correspondence: hamidmokhtari.t@gmail.com
[2] Biomedical Engineering and Physics Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Full list of author information is available at the end of the article

and infertile couples to shorten the time to pregnancy (TTP). Since several factors might affect the IUI success, it is difficult to predict its success. Various studies have evaluated the effectiveness of factors influencing the IUI success, using one or more factors and usual methods of statistical analysis. The results of these studies show that none of the sperm parameters or female factors alone are sufficient to predict the success rate of IUI [8, 9].

Because several factors seem to be influential in predicting the outcome of IUI at the same time, using machine learning algorithms can be a more effective step in this direction. Machine learning algorithms such as artificial neural networks (ANN) can be useful in predicting the success of IUI due to their efficient performance and high computational speed. Several studies on IVF prediction using machine learning algorithms have been conducted in recent years [10–14]; but to our knowledge, no significant effort has been made to utilize these methods in the case of IUI. In the present study, we used ANN as a tool to predict the success of IUI and the impact of different parameters on its final outcome. In order to shorten the time between the patients' admission and pregnancy, the right treatment method should be chosen based on the personal parameters of each individual patient. Using our predicting method, doctors will be able to adopt the most appropriate treatment for infertile couples and if the chances of IUI success are estimated to be low the patient should become a candidate for other assisted reproductive technology (ART) treatments.

Methods

This study was a historical cohort study including infertile couples referred to Shahid Akbarabadi Hospital IVF Center, Tehran, Iran, between 2013 and 2019 that underwent IUI. The study was approved by the ethics committee of Iran University of Medical Sciences, Tehran, Iran (code IR.IUMS.FMD.REC.1398.126). In this 6-year period, a total of 948 couples underwent IUI treatment in our center, of which 190 couples had successful IUI treatment based on serum BHCG (chemical pregnancy) results. All these successful cases and 190 couples with unsuccessful IUI results based on negative BHCG test were included in the present study. Inclusion criteria included age between 20 and 40 years, the presence of at least one open fallopian tube in hysterosalpingography or laparoscopy, at least ten million per milliliter of total motile sperms, sperm motility of more than 30%, and sperm normal morphology of more than 4%. The exclusion criteria were age over 40 years, advanced pelvic endometriosis, obstruction of both fallopian tubes, congenital or acquired uterine abnormalities, the presence of underlying medical condition, and severe sperm abnormality.

The information from patients entering the study including basic demographic information and data related to the history of previous pregnancies were collected through interviews and recorded in a specially designed questionnaire. Physical examination and laboratory measurements were also recorded. Possible influential parameters in IUI success rate including female age, male age, body mass index (BMI), follicle-stimulating hormone (FSH) level, anti-mullerian-hormone (AMH) level, sperm count, sperm morphology, sperm motility, progressive sperm motility before the preparation process, cause of infertility, type of infertility, duration of infertility, previous successful pregnancy history, patency of one or both fallopian tubes, history of miscarriage, and history of previous successful or unsuccessful IUI were selected as neural network inputs.

Neural network modeling

The neural network model used in the present study was a three-layer feedforward neural network classifier, including an input layer, a middle layer and an output layer (Fig. 1). This structure was strengthened using recursive error method with the help of sigmoid nonlinear relationships between the layers. We allocated 70% of data to the network training, 15% to testing, and 15% to validation of the network. We used the cross-sectional entropy method between the actual response and the neural network response as a way to minimize the loss function. The cross-sectional entropy formula in the two-class classifications was expressed by the following equation:

$$e_{\text{cross-entropy}} = -\frac{1}{N}\sum_{i=1}^{N}\left[y_i \log \hat{y}_i + (1-y_i)\log(1-\hat{y}_i)\right]$$

$\sum$ used as the operator for summation, N the number of samples, y output of system, and $\hat{y} = 1/(1+e^{y})$, and e = Euler's number.

Examining the effectiveness of each input

In order to understand the importance of each input parameter in the success of IUI, the weight matrix between the layers of the neural network, based on Yang's work was calculated utilizing the MATLAB software [15].

Results

Table 1 shows the demographic findings of patients entering the study and their male partners. The designed network accuracy was best achieved with 14 neurons in

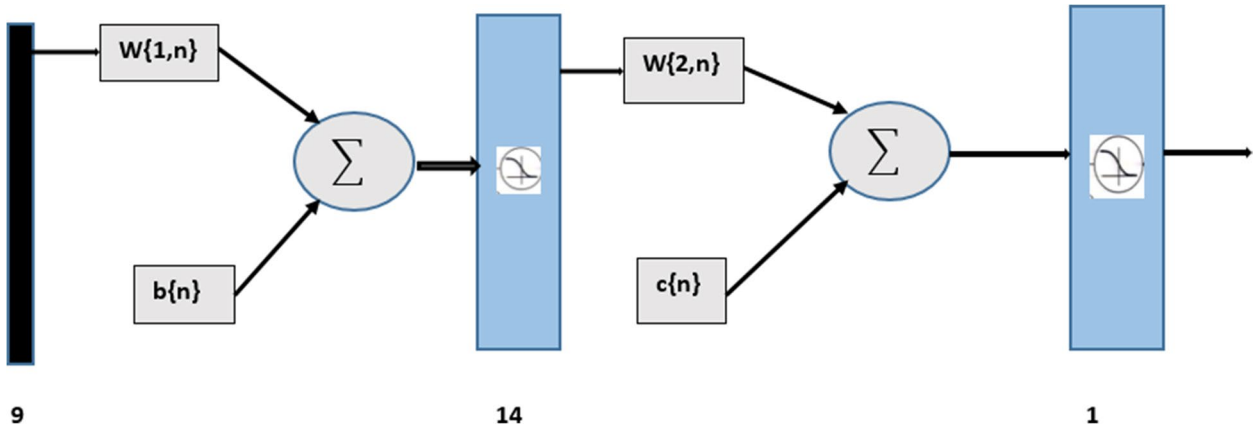

Fig. 1 The structure of the basic model. (W, b, and c are weight matrix between layers. The symbol inside the rectangle means the sigmoid function)

Table 1 Demographic findings of patients entering the study and their male partners

Parameter		Mean (±SD)
Female age (year)		30.99 (±4.7)
Female BMI (kg/m)		25.68 (±4.3)
FSH (IU/L)		6.03 (±3.5)
AMH (ng/ml)		3.82 (±3.6)
Male age (year)		34.81 (±5.2)
Sperm count (million per milliliter)		55.39 (±38)
Parameter		Percent
Total sperm motility (percent)		45.31%
Sperm progressive motility (percent)		29.58%
Sperm morphology (percent)	≤4%	69.4%
	>4%	30.6%

the middle layer. The accuracy, sensitivity, and specificity were equal to 71.92%, 76.19%, and 67.66%, respectively.

While the results indicate that our model can perform well as a predicting tool, another of our stated goals was to find the extent each underlying factor influences the IUI success. This helps physicians who do not have access to neural network algorithms or other intelligent algorithms to make the best decision in choosing the IUI method. In the first step, the effectiveness of each of the prognostic factors was calculated based on the area under the ROC curve and the cut-points were determined (Table 2). In the second step, scoring was performed using the artificial intelligence method. Table 3 shows the calculation of the impact of each of the prognostic factors affecting the success of IUI using the artificial intelligence method.

Table 2 Study of probable predictive factors with the help of statistical analysis

Risk factor	ROC (AUC)	Cut-off	Sensitivity	Specificity
Progressive sperm motility (%)	0.593	6.14	54.77	65.79
Total sperm motile count (%)	0.572	30.75	41.71	75.26
Previous Successful IUI treatment (yes/no)	0.538	_	_	_
Male age (year)	0.53	31	77.39	33.16
Infertility duration (year)	0.524	4.5	32.16	76.84
Total sperm count (106)	0.522	49.5	55.28	52.63
Patency of fallopian tubes (one/both)	0.52	_	_	_
Normal sperm morphology (%)	0.517	0.675	12.56	95.26
Female age (year)	0.516	27	77.89	27.37
Type of fertility (primary or secondary)	0.515	_	_	_
AMH (ng/ml)	0.515	2	32.66	75.26
Previous successful ongoing pregnancy (number of successful ongoing pregnancy)	0.505	1	26.6	76.3
Abortion history (yes/no)	0.5	_	_	_
BMI (kg/m^2)	0.5	24.45	34.67	55.26
FSH (IU/mL)	0.5	5.45	51.76	53.16

Table 3 Scoring prognostic factors with the help of artificial neural networks

Risk factor	
Normal sperm morphology	0.198023
Total sperm motility	0.164762
Progressive sperm motility	0.132263
Fallopian tubes condition	0.098004
Abortion history	0.05446
Previous unsuccessful IUI	0.048595
History of previous live birth	0.04088
Female age	0.03941
Type of infertility	0.036119
Male age	0.032112
BMI	0.031406
Etiology of infertility	0.028339
FSH	0.02782
Sperm count	0.025603
AMH	0.022267
Infertility duration	0.019938

Discussion

Intrauterine insemination (IUI) is a commonly used non-invasive and affordable procedure to treat infertility caused by different underlying causes such as male subfertility, unexplained infertility, ovulatory dysfunction, and cervical factor infertility [16]. The overall success rate of IUI varies, with pregnancy rates ranging from as low as 2.7% to as high as 66% [17]. Despite the improvements in semen preparation and controlled ovarian stimulation techniques, the success rates reported for IUI are lower than the rates reported for other ART procedures [18]. Data from the European Society of Human Reproduction and Embryology indicates that the pregnancy rate per IUI cycle has remained stable for many years at about 12% [19–21]. Several prognostic factors that help determine the IUI treatment outcome have been identified including the woman's age, cause and duration of infertility, mature follicle number, endometrial thickness, number of sperm inseminated, sperm morphology, and progressive motile sperm count [18]. In the present study, we evaluated the impact of multiple baseline parameters which might affect the IUI success rate at the beginning of the cycle, without including the intra-cycle characteristics, to devise a method to provide an individualized infertility treatment plan and a proper counseling regarding the chance of achieving pregnancy. The purpose was to select the couples with higher success probability for IUI treatment and use other ART methods for those individuals with less success probability. This strategy would help us to shorten the time to pregnancy (TTP) as an extremely important goal for every modern infertility clinic. Considering multiple prognostic factors for IUI success, machine learning, and artificial intelligence (AI) showed promising results in selecting the best candidates for IUI in order to optimize TTP.

Today, the use of machine learning techniques due to their superior performance compared to other statistical methods in predicting, modeling, and classifying biomedical systems has increasingly attracted the attention of medical researchers. Logistics and linear regression methods are not able to classify nonlinear and complex problems. Although machine learning techniques including neural networks are widely used in medical sciences, their most significant success has been in diagnosis and predicting the treatment results, including the predicting the success of infertility treatments. At present, machine learning algorithms in the field of infertility are commonly used to predict the success of IVF/ART. This may be due to the high cost and more sophisticated IVF techniques compared to IUI.

Wołczyński et al. in a retrospective study including 1007 infertility treatment cycles among 899 patients undergoing IVF/ICSI/ET designed a three-layer neural network that included 45 neurons in the input layer, 14 neurons in the latent layer and a single output neuron to predict the results of the treatment cycles. Using their model, the treatment cycle outcomes were correctly predicted in 68.5% of cases. Pregnancy was accurately confirmed in 49.1% of cases and abortion in 86.5% of cases [22]. Also it was possible to predict the failure of treatment with almost 90% certainty. Vogiatzi et al. collected data from 257 infertile couples who were treated during 426 IVF/ICSI cycles from 2010 to 2017 and designed an artificial intelligence network. This model was able to predict the results of the treatment cycles with 76.7% sensitivity and 73.4% specificity [14]. To the best of our knowledge, no previous study has been published on the performance of artificial intelligence to predict the success of IUI, and our study is the first report in this field. Trial and error in performing IUI without the help of robust predictor algorithms may lead to high financial costs, wasting the time, and psychological crises for infertile couples, so the study of machine learning methods can be very helpful.

We also determined the importance of each possible prognostic factor on IUI success rate. In our study, among all the baseline parameters, sperm characteristics (normal morphology, total motility, and total progressive motility) had the highest impact on conceiving chance after IUI. In agreement with our results, Butcher et al., Pereira et al., and Nikbakht also found that sperm morphology and progressive motility play an important role in IUI success rate [23–25]. One of the earliest studies on the sperm parameters' predictive value on

IUI success rate by Badawy et al. [26] reported that IUI has little chance of success when the number of motile spermatozoa inseminated is <5 × 10 [6] or normal sperm morphology is <30%. They also reported a lower chance of IUI success for women older than 35 years. In another study, Zadehmodarres et al. [27] concluded that IUI is a convenient and useful treatment option in women with younger age (<30 years), fewer treatment cycles, and lower infertility duration (4 years). Another study in Iran showed that total motile sperm count of 5×10^6 to < 10×10^6, normal sperm morphology of ≥ 5%, and number of motile sperm inseminated of ≥ 10×10^6 are useful prognostic factors for IUI success rate [24]. Bahadur et al. [28] emphasized that greater than 3 million progressive motile sperm in the insemination are related with higher IUI success rate.

In contrast to our findings, Sicchieri et al. [21] reported that female patient age was the only variable significantly correlated with IUI success rate and found no association between sperm progressive motility and pregnancy rate.

Recently, Hansen et al. performed a secondary analysis of 2462 IUI cycles from the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial to assess the impact of some cycle characteristics of couples with unexplained infertility on live birth rate. They reported that patient discomfort during the IUI procedure was associated with a reduction in live birth rate. Also higher total motile sperm count (TMC) was associated with greater live birth rate and TMC of 15.1–20.0 million resulted in a 14.8% live birth rate, when TMC of ≤5 million resulted in only 5.5% live birth rate. They also found that most other factors associated with the performance of IUI were not significantly related to live birth rate [29]. Ainsworth et al. [3] in a retrospective cohort study aimed to define IUI cycle characteristics (female age, semen characteristics, and ovarian stimulation type) associated with viable birth. They reported that IUI is a futile treatment for women age > 43, regardless of stimulation type or inseminate motility (IM). Also very poor prognosis (viable birth rate < 5%) was reported among women who used oral medications or Clomid plus gonadotropins and were under 35 years old with IM < 49%, or between 35 and 37 years with IM < 56%, or over 38 years, and those women over 38 years who used gonadotropins only with IM < 60%. Their study also provided a nomogram to individualize counseling regarding the probability of a viable birth [3].

Based on our findings, AI is a superior tool to predict the IUI success with a good predictive value (which was more than 70% in the present study), since it utilizes

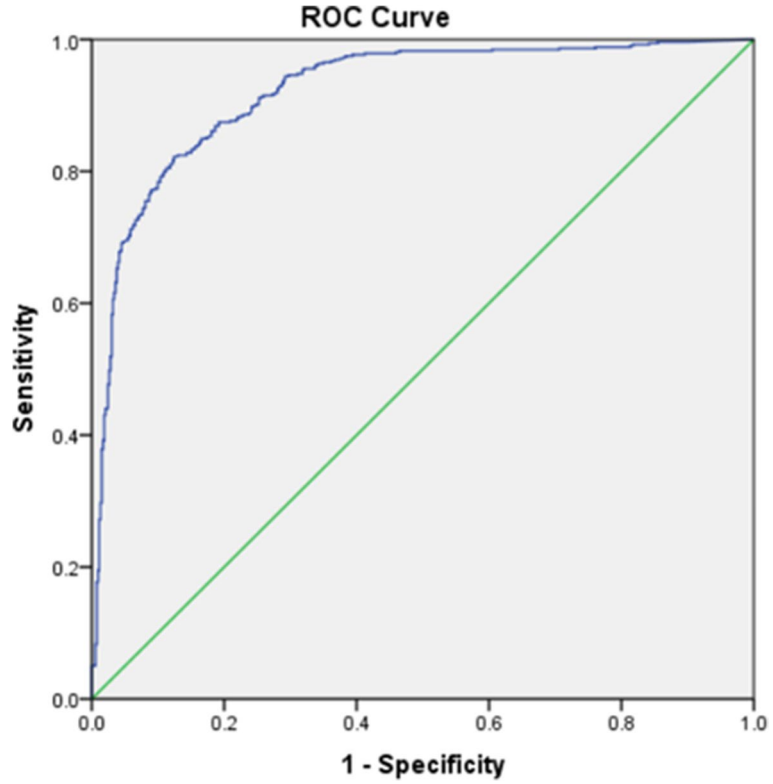

Fig. 2 Receiver-operating characteristic curves for the prediction of IUI success

multiple baseline male and female factors. Including multi-centric data from a larger group of patients and considering more possible prognostic factors might increase this predictive value in future studies. We think designing application based on machine learning can help infertility specialists to select the most appropriate patients for IUI treatment based on their personal characteristics and help to shorten the time interval to pregnancy (TTP) in future (Fig. 2).

Abbreviations

IUI: Intrauterine insemination; AI: Artificial intelligence; TMC: Total motile sperm count; ART: Assisted reproductive technology; TTP: Time to pregnancy.

Acknowledgements

The authors would like to thank the Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), Iran University of Medical Sciences (IUMS), Tehran, Iran, for their non-financial supports throughout the period of study (code: IR.IUMS.FMD.REC.1398.126).

Authors' contributions

AAS: Supervision, study design. ZZ: Data analysis, interpretation of the results. MS: Data collection. HMT: Study design, data analysis, AI design. KS: Manuscript preparation. The authors read and approved the final manuscript.

Funding

No funding.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Our study was approved by the ethics committee of Iran University of Medical Sciences, Tehran, Iran (code IR.IUMS.FMD.REC.1398.126).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), Iran University of Medical Sciences (IUMS), Tehran, Iran. [2]Biomedical Engineering and Physics Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [3]Basir Eye Health Research Center, Tehran, Iran.

Received: 20 August 2021 Accepted: 2 December 2021
Published online: 15 December 2021

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