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Determination of Cut Off for Endometrial Thickness in Couples with Unexplained Infertility: Trustable AI

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Abstract. 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. We aimed to analyze the impact of endometrial thickness on the ongoing pregnancy rate in couples with unexplained infertility. A total of 729 couples with unexplained infertility were included in this study. A random forest model (RFM) and logistic regression (LRM) were used to predict pregnancy. Evaluation of the performance of RFM and LRM was based on classification criteria and ROC curve, Odd Ratio for ongoing Pregnancy by EMT categorized. The results showed that RFM outperformed the LRM in IVF/ICSI and IUI treatments, obtaining the highest accuracy. We 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 two treatments. In addition, Endometrial thickness was not statistically significantly different from CPR and FHR in both treatments.

Keywords. Machine learning, Endometrial thickness, Unexplained, Prediction model

1. Introduction

Infertility was considered after the second half of the 19th century B. C., and various causes and treatments were gradually introduced for it [2]. The cause of infertility, such as male and female factors, unexplained infertility, genetic factors, or a combination of these factors, are considered. Unexplained infertility is a factor in which standard tests such as tubing and ovulation and sperm testing are standard for a couple but still infertile

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[11]. Unexplained factor makes up about 15 to 30% of infertile couples [1]. Endometrial thickness (EMT) factor is also one of the essential factors in influencing pregnancy rates for treatments that have been evaluated in various articles [3; 4; 6; 7; 12]. For example, in study, Quaas et al. (2021) evaluated the effect of EMT on pregnancy under ovarian stimulation protocol used in IUI treatment for couples with unexplained infertility [10]. Herein, we examined EMT and its effect on pregnancy in IUI and IVF/ ICSI treatments. Also, our study applied a machine learning perspective to construct a superior model to evaluate the impact of EMT on pregnancy rate.

2. Materials and Methods

2.1. Patient selection

Couples treated from two infertility centers were included in this study. Infertility treatments using sperm or eggs donated and surrogate uterus were also excluded from the study. A total of 729 couples (952 treatment cycles) with unexplained infertility, include 641 IUI cycles (500 couples) with unexplained infertility and 311 IVF/ICSI cycles (229 couples). Only the first three treatment cycles were considered. Some of data for IVF/ICSI and IUI can be seen in Table 1 and Table 2, respectively. This study was approved by the Institutional Review Board (IRB code: IR.MUMS.MEDICAL.REC. 1399.060.) of Mashhad University of Medical Sciences.

Table 1. Some of Clinical characteristics of patients admitted to infertility centers(IVF/ICSI).

Characteristic	Successful FHR (N=88)	Unsuccessful FHR (N=412)	Successful CPR (N=99)	Unsuccessful CPR (N=401)	Total (N=500)	*p*-value (CPR outcome)	*p*-value (FHR outcome)
Female Age	28.1 ± 5.2	29.5±5.4	27.9 ± 5.1	29.6±5.48	29.2±5.4	0.06[a]	0.02[a*]
FSH(mIU/ml)	7.4±2.8	6.6±3.2	7.3±2.7	6.6±3.2	6.8±0.4	0.11 [a]	0.04 [a*]

Table 2. Some of Clinical characteristics of patients admitted to infertility centers (IUI).

Characteristic	Successful FHR (N=68)	Unsuccessful FHR (N=161)	Successful CPR (N=78)	Unsuccessful CPR (N=151)	Total (N=229)	*p*-value (CPR outcome)	*p*-value (FHR outcome)
Female Age	29.7±5.4	29.7±5.4	31.3±6.4	31.02±5.8	31.3±5.9	0.09 [a]	0.6 [a]
FSH(mIU/ml)	8.15±5.3	8.15±5.3	8.7±10.7	8.3±4.5	8.52±6.2	0.1 [a]	0

Abbreviation. FSH: Follicle Stimulation Hormone, BMI: Body Mass Index, * Significant features (*p*-value <0.05), [a] Examined by student's t-test

2.2. Prediction Model

To establish the model, we used two well-known and Logistic Regression Model (LRM) as the non-parametric model and Random Forest Model(RFM) as a parametric model. After that, we evaluated the results by k-fold cross-validation (k=5) for the models. We validated the results by IUI dataset. Moreover, we obtained optimal cut-off for EMT by statistical test. Moreover, we described EMT categorized in terms of ongoing pregnancy and clinical pregnancy and the optimal cut-off for EMT.

3. Results

RFM predicted 89.9% and 79.4% from positive clinical pregnancy and positive ongoing pregnancy in patients under IVF/ICSI treatment and 82.6% and 73.5% in patients under IUI treatment, respectively. Also, RFM and LRM predicted ongoing pregnancy for IVF/ICSI treatment with, respectively Accuracy .69 and .65, Precision (PPV) .48 and .47 Recall .70 and .65, F-Score .57 and .55. Moreover, RFM and LRM predict ongoing pregnancy in IUI treatment, with Accuracy .82 and .80, PPV.77 and .67, Recall .82 and .81, F-Score .76 and .73. Accuracy values for models can be seen in Figure 1. A for IVF/ICSI and in Figure 1. C. for IUI. Area Under the Curve (AUC) values in the K-Fold process can be seen for IVF/ICSI in Figure 1. B. and in Figure 1.D. for IUI.

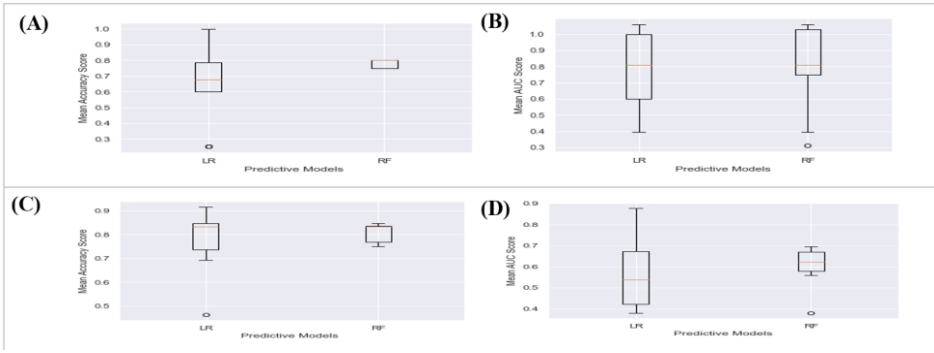

Figure 1. Comparison Accuracy and AUC respectively (A) and (B) for IVF/ICSI, (C) and (D) for IUI.

Also, we displayed relationship of EMT and pregnancy in Figure 2. Highest pregnancy rate (clinical and ongoing) is obtained 7.99-8.99 mm for IUI and 8.99-9.99 for IVF/ICSI treatment in Figure 2. A and Figure 2. B, respectively.

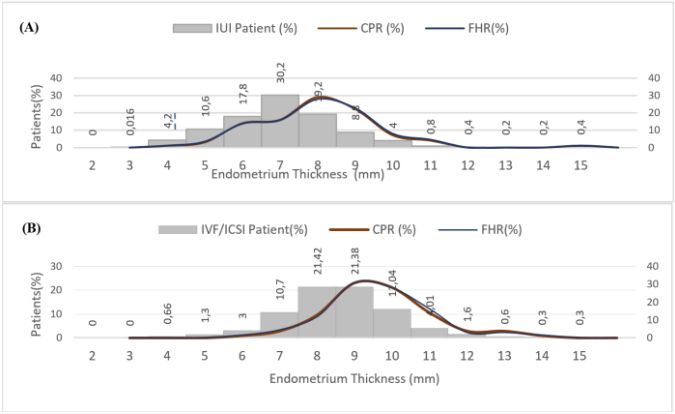

Figure 2. Relationship of Endometrium Thickness with CPR and FHR (A) for IUI; (B) for IVF/ICSI; Clinical pregnancy mean a pregnancy diagnosed by ultra-sonographic visualization of one or more gestational sacs. The clinical pregnancy rate (CPR) in IVF/ICSI is 34.6% (78/229), and for IUI is 19.8% (99/500).

Figure 3. A. and 3. B. indicated CPR and FHR with an error bar of 95% Confidence Intervals (CIs) by quantiles of EMT for both treatments. 22.86% and 20.15% of women undergoing IUI with EMT of 7 to 8.99 mm, obtained positive clinical and ongoing pregnancy, respectively (Figure 3. A.). Also, for IVF/ICSI treatment group, 36.56% and

33.58% of women with EMT of 8 to 9.99 mm obtained positive clinical and ongoing pregnancy, respectively (Figure 3. B.). EMT has associated with FHR based on Student T-test with (p<.001, 95% CI) for IUI and with (p=.024, 95% CI) for IVF/ICSI. Therefore, increasing EMT is statistically associated with increasing FHR before reaching the cut-off points. In addition, cut-off points for endometrial thickness have been calculated in both treatments based on Odd Ratio (OR) with a 95% confidence interval. Cut off points are obtained for IUI and IVF/ICSI treatment in 7.7 mm (OR=1.6, p-value=.05, CI: [1.08,2.7]) and 9.99 mm (OR=2.35, p-value=.03, CI: [1.05,5.9]) EMT, respectively. Statistically different is observed in EMT 9.99 mm with 4.99 – 8 mm in IVF/ICSI and EMT 7.7 mm with 3.99 – 7 mm in IUI.

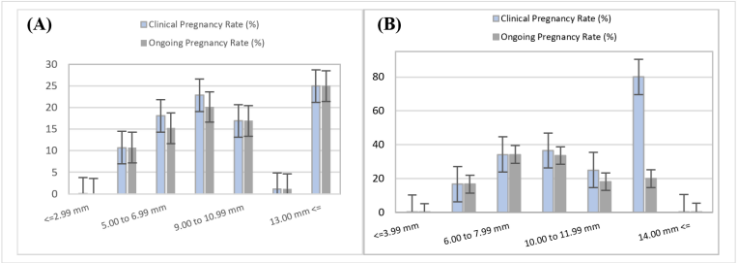

Figure 3. CPR and FHR by Percentile Endometrium Thickness in (A) for IUI and (B) for IVF/ICSI

Also, we analyzed output of the models by Shapley Additive exPlanations (SHAP) value plot [9]. The SHAP value helps interpret model prediction in terms of each feature. We draw the SHAP for RFM based on endometrial thickness for both of the treatment (See figure 4.). According to the results, endometrial thickness positively impacts RFM output for IVF/ICSI and IUI treatment

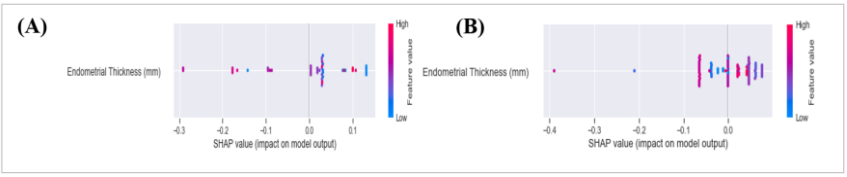

Figure 4. SHAP Value plots to show Impact of Endometrial Thickness on Model output; (A) for IVF/ICSI, (B) for IUI

4. Discussion

This is a retrospective study of 729 patients with unexplained infertility factors of IVF/ICSI and IUI treatment that led to the development of a machine learning-based model to predict the pregnancy rate. This study showed that RFM for prediction FHR and CPR have the best classification performance. In this study to examine pregnancy rate prediction, it can be seen that the use of machine learning tools can work better than the non-parametric regression model. Our study showed that clinical and ongoing pregnancy increase with increasing EMT until reaching the cut-off point. Although this increase was non-linear for both treatment methods. It showed a positive relationship between EMT and pregnancy rate. This correlation to pregnancy can be seen in similar studies [8; 9]. In contrast, some studies did not find a correlation between these two factor [12]. The fact that the study population is evaluated with different input and output

criteria can be influential. In both treatments after the cut-off, pregnancy is reduced, which may not be due to the negative effect of EMT on pregnancy. However, EMT on the day of HCG injection was a poor factor for both treatments; we obtained significant cut-off points of 7.7 and 9.99 mm in the IUI and IVF/ICSI treatments, respectively. While some similar studies obtained lower cut-off points for EMT [8; 9], some other studies obtained higher cut-off points by evaluating EMT factors per millimeters [5].

5. Conclusions

In summary, in contrast to LRM, machine learning-based models are more efficient and we found out machine learning is a valuable tool in predicting ongoing pregnancy and is trustable via multicenter data for two treatments Endometrial thickness was not statistically significantly different from CPR and FHR in both treatments. However, this difference was significant between patients with a positive FHR result in IUI and IVF/ICSI treatment.

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