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Original Research

A New Nomogram to Predict Spontaneous Pregnancy after Laparoscopy Combining Hysteroscopy in Women with Minimal to Mild Endometriosis-Associated Infertility

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Abstract

Background: Endometriosis is common in reproductive age women, which contributes to infertility. This study aims to build a model including antimüllerian hormone (AMH) to predict spontaneous pregnancy within one year after laparoscopy combined with hysteroscopy in women with minimal to mild endometriosis-associated infertility. **Methods**: There were 220 women included in the study, and a generalized linear model was constructed. The women enrolled in the study were experienced symptoms of endometriosis, and underwent combined laparoscopy and hysteroscopy between January and September 2016. All participants were diagnosed with minimal to mild endometriosis following surgery. **Results**: The predictive power (sensitivity, specificity, area under the curve (AUC)) of the model for spontaneous pregnancy rate after surgery was measured and compared with the endometriosis fertility index (EFI). The AUC for prediction model of postoperative spontaneous pregnancy was 0.697 (95% confidence interval (95% CI): 0.626–0.768). The best cut-off point was 0.629 (sensitivity: 78.4%; specificity: 54.5%). While the AUC for EFI as the spontaneous pregnancy predictor was 0.573 (95% CI: 0.498–0.648). The best cut-off point was 7.5 (sensitivity: 42.3%; specificity: 74.8%). **Conclusions**: We suggest that laparoscopy combined with hysteroscopy may offer better fertility outcomes to patients with minimal to mild endometriosis-associated infertility. The nomogram visualized the points of variate in the generalized linear model may provide a simple and convenient method for clinicians in making decisions for individual patients.

Keywords: antimüllerian hormone; laparoscopy combined with hysteroscopy; minimal to mild endometriosis; spontaneous pregnancy; prediction model

1. Introduction

Endometriosis is common in reproductive age women, characterized by the presence of ectopic endometrial implants [1]. The stages of endometriosis were assessed by the revised American Fertility Society (rAFS) scores, with total score <16 defined as minimal and mild stages of endometriosis [2]. It has been demonstrated that the probability of spontaneous pregnancy in women with minimal/mild endometriosis was significantly lower than women with unexplained infertility [3]. Laparoscopic surgery is widely used for treating mild to moderate endometriosis-associated infertility patients. Meta-analysis demonstrated that laparoscopic surgery is an improved method compared to diagnostic laparoscopy when live birthrate and ongoing pregnancy after 20 weeks were considered [4].

Currently, there are many clinical prediction models and biomarkers for women with infertility or subfertility to explore a reliable method to assess the probability of pregnancy [5,6]. Among them, the most commonly used method for estimating the pregnancy rate of women with endometriosis-associated infertility is biomarker interleukin-6 (IL6) [7] and the endometriosis fertility index (EFI) [8–10], which includes age, duration of infertility, prior pregnancy, least function (LF) score, rAFS endometriosis lesion and total score. However, declined ovarian reserve is an increasing consideration of reduced fertility [11]. Antimüllerian hormone (AMH) is considered a reliable independent marker of ovarian reserve [12]. To date, only a few publications have focused on the relationship between AMH and spontaneous conception [13–15]. Previous studies have shown a significantly higher frequency of endometrial polyps in women with endometriotic infertility [16,17]. It has been revealed in a meta-analysis that identifying and removing endometrial polyps via hysteroscopy will be clinically helpful to treat endometriosis-related infertility [18].

Therefore, a new model including AMH and endometrial polyps is needed to assess the spontaneous pregnancy rate after surgery in women suffering from minimal/mild endometriosis associated infertility.

2. Materials and Methods

This retrospective study reviewed infertile women with one or more symptoms of endometriosis such as dys-

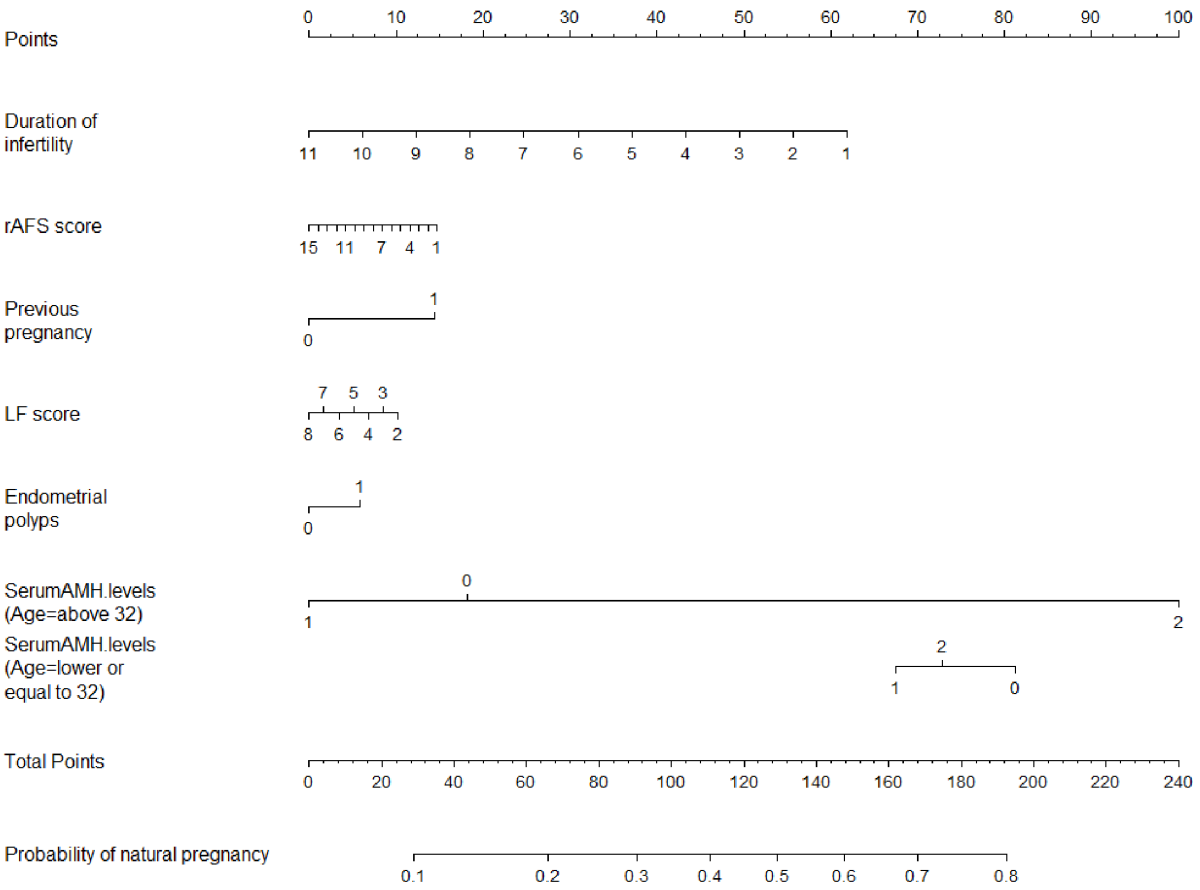

Fig. 1. Nomogram for predicting the individual probability of spontaneous pregnancy in infertile women with minimal to mild endometriosis. Note: Group 0: AMH $\leq$4 ng/mL, Group 1: 4 ng/mL $<$ AMH $\leq$ 6 ng/mL, and Group 2: AMH $>$6 ng/mL. AMH, antimüllerian hormone; rAFS, revised American Fertility Society; LF, least function.

menorrhea, dyspareunia, and chronic pelvic pain, or with the finding of a posterior fornix tenderness nodule found by gynecologic examination. They were diagnosed with minimal/mild endometriosis by laparoscopy combined with hysteroscopy and been treated during the operation between January and September 2016 in West China Second University Hospital of Sichuan University. The basic information from medical history and operative documents were reviewed and collected. According to intraoperative findings, we assessed the stages of endometriosis by rAFS, with a score of $<$16 defined as minimal or mild endometriosis. Diagnosis of fallopian tube patency, lysis of adhesions, and ablation and resection of endometriosis were accomplished laparoscopically. Hysteroscopy was performed as a routine in order to detect the existence and removal of polyps. This study was approved by the Ethics Committee of West China Second University Hospital of Sichuan University (approval code: 2019-067); and all participants signed consent forms. The inclusion criteria included regular menstrual cycles, rAFS score less than 16, no other infertility factors such as polycystic ovary syndrome (PCOS), hydrosalpinx, adenomyosis, male infertility factor, and no hormonal treatment 3 months prior to surgery. All couples had a normal sex life and failed conception without any contraception for more than 1 year. Exclusion criteria included the presence of endometrial hyperplasia, those who underwent assisted reproduction techniques, or who utilized contraception for 1 year after removal of uterine fibroids. There were 241 patients included in the study. The follow-up was performed by telephone or outpatient visit every month after surgery, and lasted for 1 year. For those who became pregnant during that interval, the follow-up period was extended until delivery, and the pregnancy outcomes were recorded. Pregnancy was defined as β -HCG (human chorionic gonadotropin) level over 25 IU/L. Women with a negative serum pregnancy test were not considered to be pregnant at the end of 1 year's follow-up. There were 21 patients (8.7%) lost to follow-up with the main reason being a change of phone number. The remaining 220 women were analyzed.

Venous blood samples were collected within 3 months before surgery. Serum AMH levels were determined by enzyme-linked immunosorbent assay (Kang Run biotechnology Co., Ltd., Guangzhou, Guangdong, China). The variation coefficient between and within batches were $<$10%.

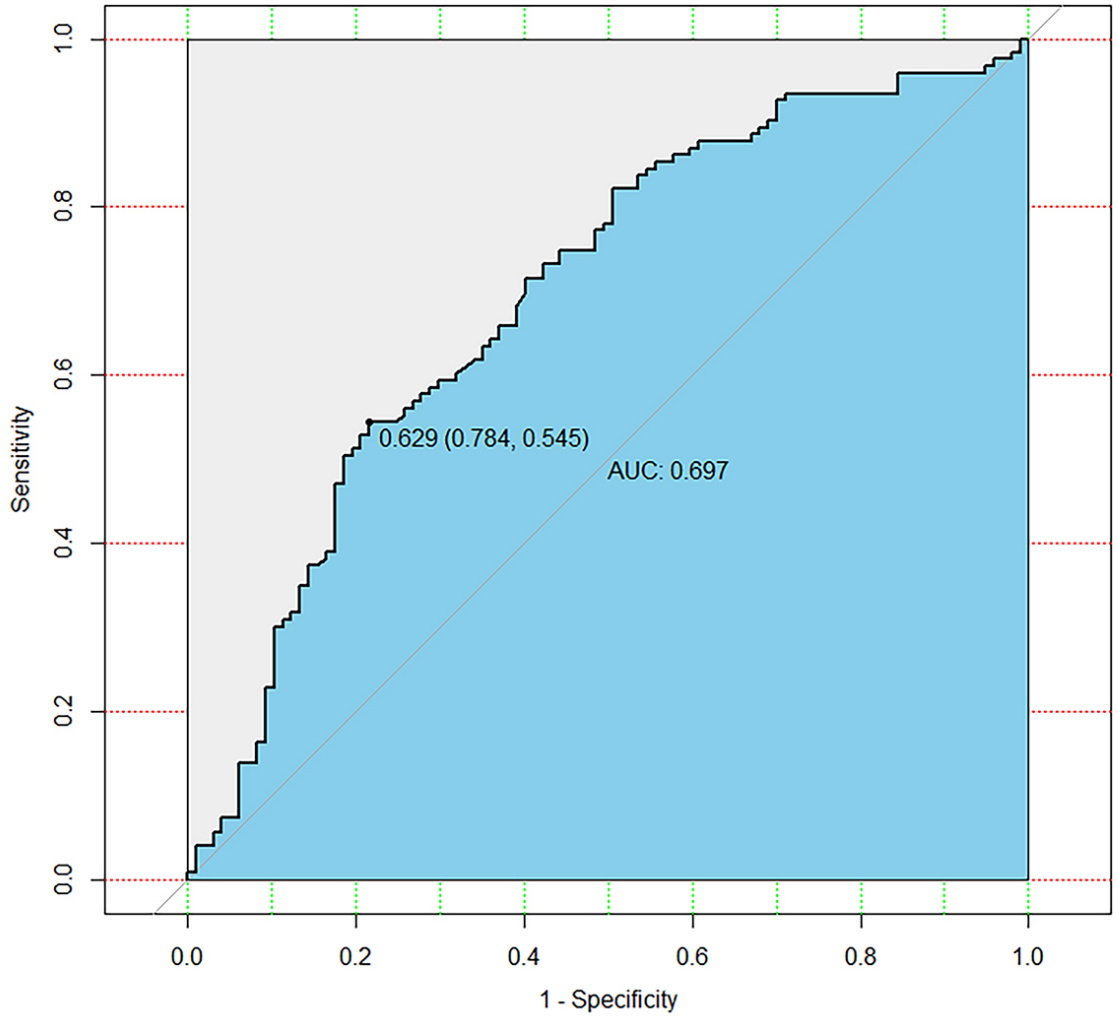

Fig. 2. Receiver operator characteristic curve. The area under the curve (AUC) for prediction model for spontaneous pregnancy was 0.697 (95% confidence interval (95% CI): 0.626–0.768). The best cut-off point was 0.629 (sensitivity: 78.4%; specificity: 54.5%).

The enrolled 220 patients were further divided into 3 subgroups according to their serum AMH levels: Group 0: AMH $\leq$4 ng/mL, Group 1: 4 ng/mL $>$ AMH $\leq$ 6 ng/mL, and Group 2: AMH $>$6 ng/mL. Based on women's age: $>$32 years or $\leq$32 years, they were classified as Group 0 and Group 1.

Data were analyzed using R software package version 3.4.4 (https://cran.r-hub.io/bin/windows/base/old/3.4.4/). We used package "rms" for nomogram and "pROC" for ROC plots. Student's *t*-tests were used for continuous values and 83 Chi-square tests were used to compare categorical values. Moreover, a generalized linear 84 model was made. AMH levels were projected to interact with age in the generalized linear model. A nomogram was constructed to visualize the results of the generalized linear model.

3. Results

The demographics of 220 patients are shown in Table 1, including their age, previous pregnancy history, duration of infertility, serum AMH levels, intraoperative finding as LF score, revised American Fertility Society (rAFS) score, and existence of endometrial polyps which located in the middle and upper part of the uterine cavity, with a number of 1–6 and a diameter of 2–10 mm, most of them present with tongue-like or inflammatory protrusions. The mean duration of follow-up was 14.7 months (10–22 months). There were 123 spontaneous pregnancies (55.90%, 123/220) noted during follow-up with 4 being ectopic pregnancies. There were 101 full term deliveries and 6 preterm births secondary to of twin pregnancy or premature rupture of membrane.

In women $>$32 years, AMH Group 2 showed statistical significance in improving the probability of spontaneous pregnancy (Table 2 and Fig. 1). In women $\leq$32 years,

Table 1. Patient characteristics, medical history, and intraoperative findings.

Variable	Pregnant (n = 123)	Non-pregnant (n = 97)
Basic information		
Age (years), mean ± SD	29.39 ± 3.46	30.79 ± 4.54
≤32 years	101	61
>32 years	22	36
Serum AMH levels (ng/mL), mean ± SD	6.20 ± 4.20	5.55 ± 4.10
≤4	46	45
4–6	24	21
>6	53	31
Medical history		
Duration of infertility (years), mean ± SD	2.22 ± 1.80	2.88 ± 2.05
≤3 years	107	72
>3 years	16	25
Previous pregnancy history		
Yes	66	48
No	57	49
Intraoperative findings		
Endometrial polyps		
Yes	40	30
No	83	67
LF-Score (mean ± SD)	5.16 ± 1.16	5.24 ± 1.09
rAFS-Score (mean ± SD)	4.91 ± 2.05	4.99 ± 2.45

Note: Values are expressed as mean ± standard deviation (SD) or (%). The data were analyzed by Student *t* test and Chi-square test. AMH, antimüllerian hormone; LF, least function; rAFS, revised American Fertility Society.

AMH Group 2 had lower probability of spontaneous conception. Duration of infertility, previous pregnancy history, rAFS score, and endometrial polyps were included in the construction of the predictive model for to determine their clinical relevance, although they were not significantly associated with spontaneous pregnancy. The values for each of the model covariates were mapped to points on a scale ranging from 0 to 100 (Fig. 1). Total points were calculated to predict the probability of spontaneous pregnancy in infertile women with minimal to mild endometriosis. The area under the curve (AUC) for prediction model for spontaneous pregnancy was 0.697 (95% confidence interval (95% CI): 0.626–0.768). The best cut-off point was 0.629 (sensitivity: 78.4%; specificity: 54.5%) (Fig. 2). The distribution of patients according to their EFI score is shown in Fig. 3. The AUC for EFI as a spontaneous pregnancy predictor was 0.573 (95% CI: 0.498–0.648). The best cut-off point was 7.5 (sensitivity: 42.3%; specificity: 74.8%) (Fig. 4).

The probability of spontaneous pregnancy after surgery is calculated by drawing a line to the point on the axis for each of the following variables: duration of infertility, previous pregnancy history, LF score, rAFS score, endometrial polyps and age interacting with AMH. First, the points for each variable are summed and located on the total points line. Next, a vertical line is projected from the total points line to the predicted probability bottom scale to obtain the individual probability of spontaneous pregnancy.

4. Discussion

To our knowledge, the prediction model and the nomogram designed in this study has not been previously reported to evaluate individual probability of postoperative pregnancy rate in women with mild/minimal endometriosis. In addition to factors included in commonly used EFI score, our prediction model contains ovarian reserve and endometrial polyps, which have been suggested to have influence on pregnancy. Our results suggest that the individual probability of postoperative spontaneous pregnancy in women with minimal to mild endometriosis can be predicted more accurately by a nomogram than EFI. This is of particular interest for clinicians who are increasingly interested in such tools to support their decision about treatment options and medical advice for the patients. According to the consensus on diagnosis and evaluation of female infertility by ASRM (American Society of Reproductive Medicine), if patients have signs and symptoms of endometriosis or risk factors for tubal obstruction, laparoscopy should be considered [19]. In our study, the surgery for each patient was performed in the same hospital, ensuring that the surgical indications and treatment options are similar. Of the 21 couples who were lost to follow-up, 8 couples divorced, 10 couples lost contact, and 3 couples did not desire for pregnancy for other reasons. The advantages of our study can be presented as follows: accurate clinical data, prospective collection of

Table 2. Estimation of the probability of postoperative spontaneous pregnancy (Logistic regression model).

Variable	Odds ratio	95% CI		*p*
		Lower	Higher	
History of pregnancy	1.370	0.766	2.451	0.289
Duration of infertility	0.873	0.744	1.025	0.096
LF score	0.963	0.743	1.249	0.779
rAFS score	0.977	0.859	1.112	0.727
Endometrial polyps	1.138	0.615	2.106	0.680
Age group (1)	3.984	1.587	10.006	0.003
AMH group				
AMH group (1)	0.672	0.114	3.979	0.661
AMH group (2)	6.011	1.305	27.684	0.021
Age group * AMH group				
Age group (1) by AMH group (1)	1.100	0.150	8.070	0.095
Age group (1) by AMH group (2)	0.138	0.025	0.761	0.023

Note: *Refers to interaction. 95% CI, 95% confidence interval.

Formula = History of pregnancy + Duration of infertility + LF score + rAFS score + Endometrial polyps + Age × Serum AMH.

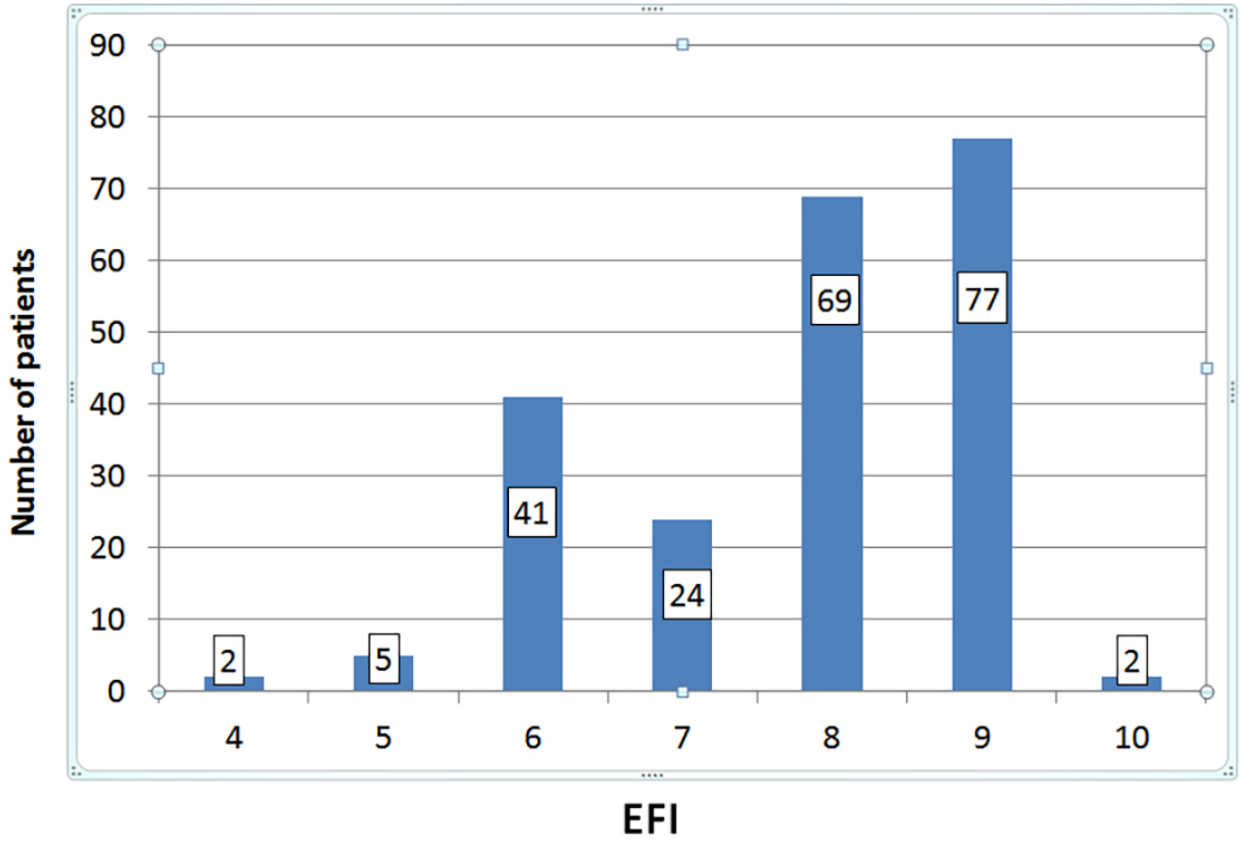

Fig. 3. Distribution of patients according to their endometriosis fertility index (EFI) score. The median EFI score was 8.

data, consecutive incorporation of 220 patients and lower loss of patients to follow-up which was only 8.7%.

Currently, other clinical models of predicting pregnancy outcomes have been built. The most commonly used prediction rule for endometriosis-associated infertility is EFI, which includes age, duration of infertility, previous pregnancy history, LF score, rAFS endometriosis lesion score and rAFS endometriosis total score. EFI has been proved to be an efficient way to predict pregnancy rate in various studies [8–10,20,21]. However, ovarian reserve should not be ignored in predicting the pregnancy probability of women with minimal to mild endometriosis. Since intrauterine factors such as endometrial polyps are of high prevalence in endometriosis-associated infertil-

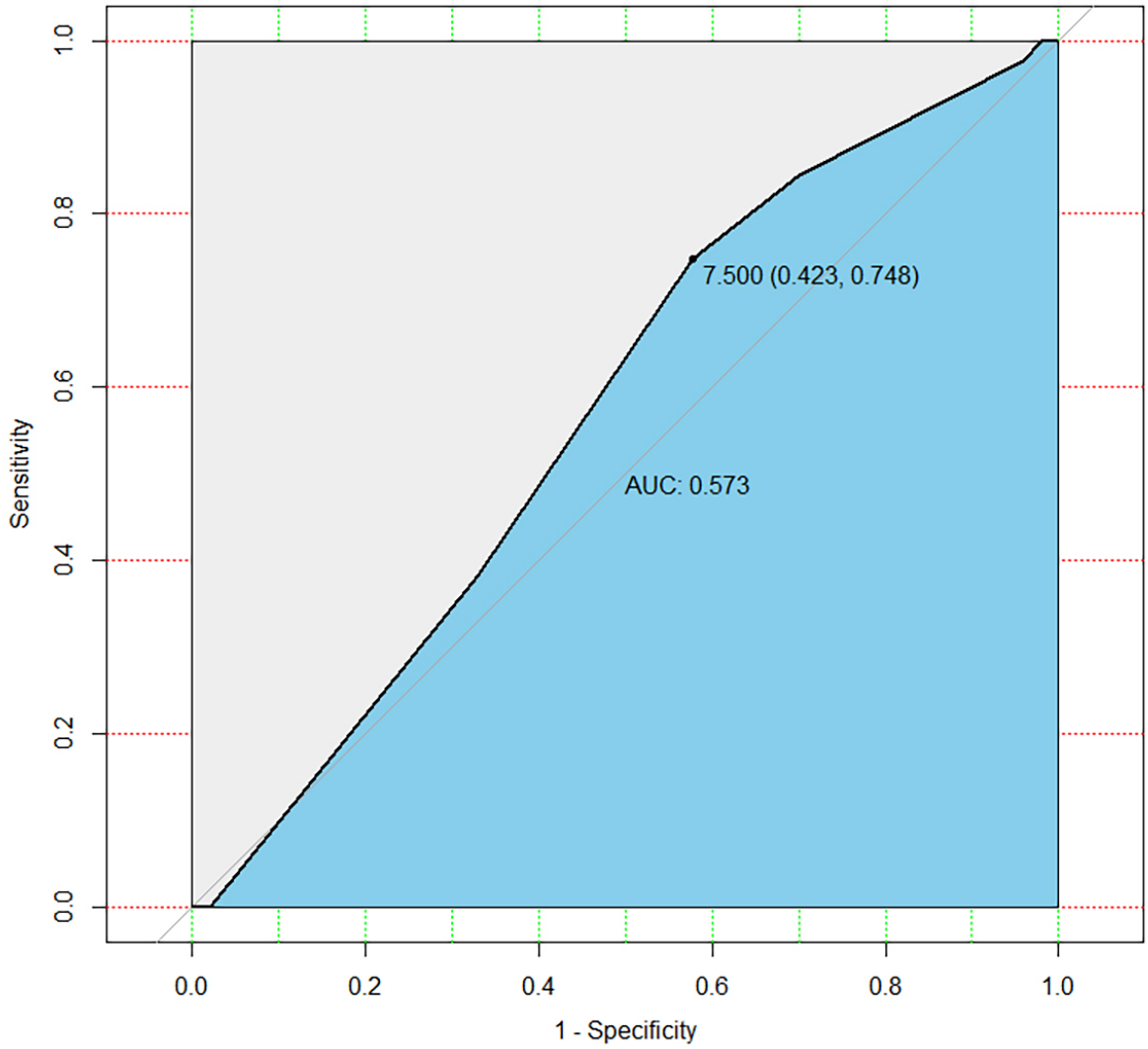

Fig. 4. Receiver operator characteristic curve. The area under the curve for EFI as a spontaneous pregnancy predictor was 0.573 (95% CI: 0.498–0.648). The best cut-off point was 7.5 (sensitivity: 42.3%; specificity: 74.8%).

ity [16], it should be taken into consideration. Our study was focused on the post-operative spontaneous pregnancy rate, and aimed to develop a model including AMH levels and other pregnancy related factors, statistically or clinically, to predict the spontaneous pregnancy rate of women with minimal to mild endometriosis. Previous study suggested that AMH levels were associated with age, and that AMH levels decrease steadily with the increase of age from 24 to 50 years [11]. A recent study has suggested that women in their late thirties experience a significant reduction in fecundity and an increase in the probability of infertility [22]. Our study demonstrated similar results in that inpatients $\leq$32 years the spontaneous pregnancy rate was significantly higher than that in patients $>$32 years ($p < 0.05$). When age was taken into account, AMH levels affected spontaneous pregnancy rate significantly in women $>$32 years ($p < 0.05$), which is consistent with the previous study [23]. Women $>$32 years with higher AMH levels ($>$6 ng/mL) had a better pregnancy rate than those who had lower AMH levels. In women $\leq$32 years, higher AMH levels ($>$6 ng/mL) might have lower probability of spontaneous pregnancy, which may be attributed to the influence of higher AMH levels on ovulation. A previous study has shown that endometrial polyps are safely and effectively diagnosed and treated with hysteroscopy [24]. As can be seen in Table 2 and Fig. 1, endometrial polyps showed a positive role for spontaneous conception, suggesting that endometrial polyps may be a significant factor affecting fertility in patients with minimal to mild endometriosis. Hysteroscopic polypectomy of endometrial polyps could be an effective way to improve spontaneous conception. This interesting result was consistent with previous research of our team [16]. EFI has been an efficient rule in predicting the ability to become pregnant in women suffering from

all stages of endometriosis. However, the factors influencing infertility are far more complex than those included in EFI. As shown in Figs. 2,4, our study constructed the receiver operating characteristic (ROC)-area under the ROC curve (ROC-AUC) of two predicting rules. An AUC of 1 implies perfect discrimination, while an AUC of 0.5 implies that the test does not discriminate at all [25]. Our generalized linear model has reached an AUC of 0.697, whereas EFI has reached an AUC of 0.573. The generalized linear model shows a better predictive value than EFI. Meanwhile, the nomogram visualized the points of variate in the generalized linear model, which may provide a simple and convenient method for clinicians in making decisions for individual patients. However, there are limitations of our study. The retrospective design makes it difficult to exclude such confounding factors as different surgeons and different postsurgical medications. We are currently collecting data for external validation, which will be published in a later article.

5. Conclusions

We presented data that combined laparoscopy with hysteroscopy may offer better fertility outcomes to patients with minimal to mild endometriosis-associated infertility. The nomogram visualized the points of variate in the generalized linear model and may provide a simple and convenient method for clinicians in making decisions for individual patients.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

WH and BL designed the research study. BL, TJP and XH performed the research. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of West China Second University Hospital of Sichuan University (approval number: 2019-067).

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Giudice LC, Kao LC. Endometriosis. Lancet (London, England). 2004; 364: 1789–1799.

[2] Revised American Fertility Society classification of endometriosis: 1985. Fertility and Sterility. 1985; 43: 351–352.

[3] Akande VA, Hunt LP, Cahill DJ, Jenkins JM. Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis. Human Reproduction (Oxford, England). 2004; 19: 96–103.

[4] Jacobson TZ, Duffy JM, Barlow D, Farquhar C, Koninckx PR, Olive D. Laparoscopic surgery for subfertility associated with endometriosis. The Cochrane Database of Systematic Reviews. 2010; CD001398.

[5] Leushuis E, van der Steeg JW, Steures P, Bossuyt PMM, Eijkemans MJC, van der Veen F, *et al*. Prediction models in reproductive medicine: a critical appraisal. Human Reproduction Update. 2009; 15: 537–552.

[6] McLernon DJ, te Velde ER, Steyerberg EW, Mol BWJ, Bhattacharya S. Clinical prediction models to inform individualized decision-making in subfertile couples: a stratified medicine approach. Human Reproduction (Oxford, England). 2014; 29: 1851–1858.

[7] Incognito GG, Di Guardo F, Gulino FA, Genovese F, Benvenuto D, Lello C, *et al*. Interleukin-6 as A Useful Predictor of Endometriosis-Associated Infertility: A Systematic Review. International Journal of Fertility & Sterility. 2023; 17: 226–230.

[8] Zhang X, Liu D, Huang W, Wang Q, Feng X, Tan J. Prediction of Endometriosis Fertility Index in patients with endometriosis-associated infertility after laparoscopic treatment. Reproductive Biomedicine Online. 2018; 37: 53–59.

[9] Maheux-Lacroix S, Nesbitt-Hawes E, Deans R, Won H, Budden A, Adamson D, *et al*. Endometriosis fertility index predicts live births following surgical resection of moderate and severe endometriosis. Human Reproduction (Oxford, England). 2017; 32: 2243–2249.

[10] Li X, Zeng C, Zhou YF, Yang HX, Shang J, Zhu SN, *et al*. Endometriosis Fertility Index for Predicting Pregnancy after Endometriosis Surgery. Chinese Medical Journal. 2017; 130: 1932–1937.

[11] Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertility and Sterility. 2011; 95: 747–750.

[12] Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Human Reproduction Update. 2006; 12: 685–718.

[13] Hagen CP, Vestergaard S, Juul A, Skakkebæk NE, Andersson AM, Main KM, *et al*. Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study. Fertility and Sterility. 2012; 98: 1602–1608.e2.

[14] Sahmay S, Oncul M, Tuten A, Tok A, Acıkgoz AS, Cepni I. Anti-müllerian hormone levels as a predictor of the pregnancy rate in women of advanced reproductive age. Journal of Assisted Reproduction and Genetics. 2014; 31: 1469–1474.

[15] Zarek SM, Mitchell EM, Sjaarda LA, Mumford SL, Silver RM, Stanford JB, *et al*. Is Anti-Müllerian Hormone Associated With Fecundability? Findings From the EAGeR Trial. The Journal

of Clinical Endocrinology and Metabolism. 2015; 100: 4215–4221.

[16] Shen L, Wang Q, Huang W, Wang Q, Yuan Q, Huang Y, *et al*. High prevalence of endometrial polyps in endometriosis-associated infertility. Fertility and Sterility. 2011; 95: 2722–2724.e1.

[17] Zhang YN, Zhang YS, Yu Q, Guo ZZ, Ma JL, Yan L. Higher Prevalence of Endometrial Polyps in Infertile Patients with Endometriosis. Gynecologic and Obstetric Investigation. 2018; 83: 558–563.

[18] Zheng QM, Mao HI, Zhao YJ, Zhao J, Wei X, Liu PS. Risk of endometrial polyps in women with endometriosis: a meta-analysis. Reproductive Biology and Endocrinology: RB&E. 2015; 13: 103.

[19] Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility. 2015; 103: e18–25.

[20] Kim JS, Lee CW, Yun J, Lee JH, Yun BH, Park JH, *et al*. Use of the Endometriosis Fertility Index to Predict Natural Pregnancy after Endometriosis Surgery: A Single-Center Study. Gynecologic and Obstetric Investigation. 2019; 84: 86–93.

[21] Tomassetti C, Geysenbergh B, Meuleman C, Timmerman D, Fieuws S, D'Hooghe T. External validation of the endometriosis fertility index (EFI) staging system for predicting non-ART pregnancy after endometriosis surgery. Human Reproduction (Oxford, England). 2013; 28: 1280–1288.

[22] Steiner AZ, Jukic AMZ. Impact of female age and nulligravidity on fecundity in an older reproductive age cohort. Fertility and Sterility. 2016; 105: 1584–1588.e1.

[23] Steiner AZ, Herring AH, Kesner JS, Meadows JW, Stanczyk FZ, Hoberman S, *et al*. Antimüllerian hormone as a predictor of natural fecundability in women aged 30-42 years. Obstetrics and Gynecology. 2011; 117: 798–804.

[24] Raz N, Feinmesser L, Moore O, Haimovich S. Endometrial polyps: diagnosis and treatment options - a review of literature. Minimally Invasive Therapy & Allied Technologies: MITAT: Official Journal of the Society for Minimally Invasive Therapy. 2021; 30: 278–287.

[25] Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982; 143: 29–36.