Endometriosis Fertility Index for Predicting Pregnancy after Endometriosis Surgery

Xin Li[1], Cheng Zeng[1], Ying-Fang Zhou[1], Hui-Xia Yang[1], Jing Shang[1], Sai-Nan Zhu[2], Qing Xue[1]

[1]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China
[2]Department of Biostatistics, Peking University First Hospital, Beijing 100034, China

Abstract

Background: The endometriosis fertility index (EFI) has a predictive value for pregnancy after surgery. *In vitro* fertilization and embryo transfer (IVF-ET) is a good treatment to infertility. This study aimed to provide external validation of EFI, assess the factors affecting the ability of EFI to predict cumulative spontaneous pregnancy rates (PRs), and propose reasonable advice for treatment by evaluating the effect of infertility management combining surgery and IVF-ET.

Methods: This retrospective study enrolled 345 endometriosis-related infertile women after laparoscopic surgery from January 2012 to January 2016. Among them, 234 patients tried to conceive naturally and were divided into six groups according to their different EFI scores. Of the 345 patients, 307 with an EFI score ≥ 5 were divided into non-IVF-ET group ($n = 209$) and IVE-ET group ($n = 98$) to compare the cumulative PRs. Cumulative PRs' curves were calculated using the Kaplan-Meier product limit estimate and the differences were evaluated by log-rank test. Independent predictive factors for pregnancy were assessed using the Cox regression model.

Results: Significant differences in spontaneous PRs among different EFI scores were identified ($\chi^2 = 29.945$, $P < 0.05$). The least function score was proved to be the most important factor for EFI ($\chi^2 = 6.931$, $P < 0.05$) staging system. In patients with an EFI score ≥ 5 after 12 months from surgery, the cumulative PRs of those who received both surgery and IVF-ET were much higher than the spontaneous PRs of those who received surgery alone ($\chi^2 = 4.160$, $P = 0.041$).

Conclusions: The EFI is a reliable staging system to predict the spontaneous PR of patients. The least function score was the most influential factor to predict the spontaneous PR. Patients with an EFI score ≥ 5 after 12 months from surgery are recommended to receive IVF-ET to achieve a higher PR.

Key words: Endometriosis; Fertilization *In vitro*; Infertility; Pregnancy Rate

Introduction

Endometriosis is an inflammatory condition characterized by lesions of endometrial-like tissue outside the uterus. The primary presenting symptoms of endometriosis are infertility and/or pain. Among infertile women, 25–50% are thought to have endometriosis, and 30–50% of women with endometriosis are infertile.[1] Currently, the most frequently used staging system for endometriosis is the revised American Fertility Society (rAFS) classification system. Unfortunately, this classification system cannot predict the clinical outcomes of treatment effectively, especially the pregnancy rate (PR) in infertile women.[2-4] For this reason, in 2010, Adamson and Pasta[5] proposed the endometriosis fertility index (EFI) as a new scoring system. The EFI staging system includes historical factors (age, length of infertility,

and previous pregnancy) and surgical factors (AFS total score, AFS endometriosis lesions, and the least function score as the anatomical and functional result of the surgery on the reproductive fallopian tubes, fimbriae, and ovaries, bilaterally). This index has been validated as clinically useful among patients with surgically confirmed endometriosis who wish to be pregnant and has been validated externally in populations of infertile patients with endometriosis at 3 years after surgery.[5] The higher a patient's EFI score is,

Address for correspondence: Dr. Qing Xue,
Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China
E-Mail: xueqingqq@hotmail.com

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the higher their chances of spontaneous pregnancy are. On this basis, the first aim of this study was to provide a further external validation of the EFI score to predict spontaneous pregnancy in a population of infertile Chinese patients with endometriosis within 4 years after surgery.

The EFI staging system is a 10-point scale system, which considers historical factors, age and length of infertility, and surgical factors, such as the least function score and the AFS score.[5] The second aim of this study was to identify the most significant influencing factor in the EFI system.

To date, in women suffering from endometriosis-related infertility, it is difficult to decide when to perform surgical excision and/or fertility treatment. Barri *et al.*'s study[6] indicated that the highest PRs for women with endometriosis-related infertility are often achieved using a combination of surgery and assisted reproductive technology (ART). The method of combined surgery and ART can provide significantly higher PRs compared with using either of the two treatments alone.[6] Cook and Adamson[7] claimed that it is preferable to perform surgery first, if clinically indicated, and to perform ART if spontaneous pregnancy does not occur after 9–15 months. In 2010, a study[8] by Dominique also suggested that if couples could not conceive naturally for 6–18 months after surgery, they should undergo *in vitro* fertilization and embryo transfer (IVF-ET). The frequent use of IVF after failure to conceive addresses the issue on the most appropriate individual therapeutic strategy, particularly for couples whose fertility prognosis is radically different. On this basis, the final aim was to investigate the optimal time for IVF-ET after endometriosis surgery.

METHODS

Ethical approval
This retrospective study was conducted in the Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing, China. The subjects of follow-up were patients who received laparoscopic surgery from January 2012 to January 2016. The collected data included age, history of infertility, surgery, and subsequent fertility for all endometriotic and infertile patients. The local ethics committee granted permission to this study. Informed consent was obtained from each of the subjects before the surgery.

Inclusion and exclusion criteria
From 2012 to 2016, 542 infertile women (who failed to conceive for more than 12 months) were diagnosed with endometriosis, by laparoscopy with histological confirmation, in the Peking University First Hospital, Beijing, China. Among them, 469 women were normal ovulation with at least one patent tube according to hysterosalpingography. One hundred and twenty partners of these 469 patients had a normal semen analyses according to the WHO criteria.[9]

The exclusion criteria were as follows: uterine fibroids (24 patients excluded), adenomyosis or uterine malformations (three patients excluded), and reproductive system malformations (one patient excluded). Patients were also excluded from the study if they were lost to follow-up (39 patients excluded). Finally, a total of 345 patients were included in this study, giving a follow-up rate of 89.8%.

Surgical procedure and postoperative management
The patients underwent a standard laparoscopic approach to remove all the visible foci of endometriosis by diathermy or laser vaporization. After surgery, the patients were expected to actively attempt to conceive, either naturally or with IVF-ET treatment, according to their personal decision and financial conditions.

Study participants were contacted by telephone to find out whether the patient had become pregnant or not, and the date of the patient's last menstrual period was recorded. Pregnancy was defined as serum β-human chorionic gonadotropin >25 U/L and ultrasound evidence of a gestational sac.

Endometriosis fertility index calculation
The EFI scores were calculated retrospectively based on the age at surgery, infertility duration in years, prior pregnancy, least function score, rAFS endometriosis score, and rAFS total score for all patients, ranging from 0 for the poorest prognosis to 10 for the best prognosis.[5] Endometriotic implants on the peritoneum or ovaries were scored according to diameter and depth, whereas adhesions were scored according to density and degree of enclosure. The least function score (functional score of fallopian tubes, fimbriae, and ovaries, bilaterally) was performed retrospectively by the operative surgeon using the operative report.

Statistical analysis
Statistical analyses were carried out using Statistical Package for the Social Sciences Version 20.0 (Chicago, IL, USA). Data were presented as the mean ± standard deviation (SD) or median (range), Kaplan-Meier survival analysis was used to calculate the cumulative proportion of spontaneous PRs according to different EFI scores and to predict the cumulative PR after surgery and IVF treatment. The event dates used in the calculation were the time to pregnancy from the date of surgery to the date of the last menstrual period or follow-up visit. The log-rank test was used for the survival analysis. The Cox model was adopted to assess independent predictive factors for pregnancy. Comparisons were performed using the Chi-square test, independent *t*-test, and Mann-Whitney *U*-test. A $P < 0.05$ was considered statistically significant.

RESULTS

Of the 345 patients included in the study, the average age of the patients was 32.2 ± 4.0 years (range: 22.0–45.0 years). The average EFI score of the 345 patients was 6.5 ± 1.9 (range: 0.0–10.0), and the most common EFI score was 7 (68 patients, 19.7%). Among the 345 patients, 111 received IVF treatment, and the average EFI score of these patients was 6.0 ± 1.8 (range: 0.0–10.0). The remaining

234 patients tried to conceive naturally (without using ovulation induction or intrauterine insemination), and their average EFI score was 6.7 ± 1.9. The characteristics of the 345 analyzed patients are shown in Table 1. In this study, the probability of spontaneous conception was 46.5% and that of IVF conception after surgery was 54.6%.

External validation of endometriosis fertility index for predicting spontaneous pregnancy

The cumulative spontaneous clinical PR was calculated using Kaplan-Meier survival analysis estimates for 234 patients. The 234 patients who attempted to conceive spontaneously were divided into six groups according to the EFI score ranges (Group 1: EFI scores 0–3, $n = 14$; Group 2: EFI score 4, $n = 19$; Group 3: EFI score 5, $n = 35$; Group 4: EFI score 6, $n = 35$; Group 5: EFI scores 7–8, $n = 87$; and Group 6: EFI scores 9–10, $n = 44$).[5] The life table analysis showed a significant relationship between EFI score and time to achieve spontaneous pregnancy [Figure 1]. The cumulative PRs of the different EFI groups at different times showed a significant statistical difference (log-rank test: $\chi^2 = 29.945$; $P < 0.001$). Patients with high EFI scores had significantly higher cumulative PRs compared with patients with low EFI scores. For patients with an EFI score of 4 or less, the spontaneous PR was only 13.6% at the 4th year.

Influence of various factors in endometriosis fertility index

To identify the contribution of different factors in the EFI system, we used the Cox regression analysis to assess the constituent variables of EFI in 234 patients who tried to conceive spontaneously. Table 2 shows that the least function score is more important than the other factors in the EFI staging system, as revealed by comparing the P values of the various Cox models ($\chi^2 = 6.931$; $P < 0.05$). The least function score was also significantly positively correlated with the probability of conceiving without IVF (spontaneous pregnancy after surgery: 5.2 vs. no spontaneous pregnancy: 4.5; $P = 0.005$).

Optimal time of *in vitro* fertilization treatment

To evaluate the effect of IVF-ET treatment after surgery, we compared the difference between patients who tried to conceive spontaneously and those who underwent IVF-ET treatment after surgery in terms of the PR. The small sample size ($n = 33$) and low PR (13.6%) of patients who tried to conceived spontaneously and who had an EFI score <5 resulted in their exclusion from the following analysis. For the 307 patients with an EFI score ≥5, we further divided them into the IVF-ET group ($n = 98$) and the non-IVF-ET group ($n = 209$) depending on whether they received IVF-ET treatment or not. The basic characteristics of the patients in the IVF-ET and non-IVF-ET groups were listed in Table 3. We also used Kaplan-Meier survival analysis to estimate the cumulative PRs in these two groups. The cumulative PRs did not show any statistically differences between these two groups within 12 months (from the 1st month to the

Table 1: Characteristics of the women included in the study ($n = 345$)

Characteristics	Values
Age (years)	32.2 ± 4.0*
≤35	287 (83.2)
36–39	42 (12.2)
≥40	16 (4.6)
Infertility length (years)	3.2 ± 2.6*
<3	178 (51.6)
≥3	167 (48.4)
Previous pregnancy	
Yes	121 (35.1)
No	224 (64.9)
Least function score	
7–8	71 (20.6)
4–6	176 (51.0)
1–3	98 (28.4)
AFS endometriosis score index	
<16	180 (52.2)
≥16	165 (47.8)
ASRM total score	
<71	306 (88.7)
≥71	39 (11.3)
IVF treatment	
Yes	111 (32.2)
No	234 (67.8)

Data was presented as mean ± SD or as n (%). *: mean ± SD. SD: Standard deviation; AFS: American Fertility Society; IVF: *In vitro* fertilization; ASRM: American Society for Reproductive Medicine.
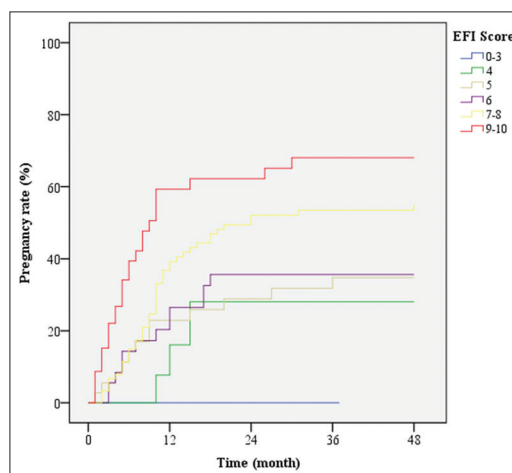
Figure 1: Probability of pregnancy classified by EFI scores during a 48-month follow-up of 234 infertile patients without IVF-ET ($\chi^2 = 29.945$, $P < 0.001$). EFI: Endometriosis fertility index; IVF-ET: *In vitro* fertilization and embryo transfer.

11th month) after surgery. However, the cumulative PR in the IVF-ET group became significantly higher than that in the non-IVF-ET group ($\chi^2 = 4.160$; $P = 0.041$) at 12 months after laparoscopic surgery [Figure 2].

Discussion

Currently, the main choice for the diagnosis and treatment of

Table 2: Overview of the effect of different factors on the spontaneous pregnancy rate according to the EFI staging system (*n* = 234)

Factor in EFI	*B*	SE	χ^2	df	*P*	Exp(B)	95% *CI*
Age	−0.010	0.240	1.870	1	0.665	0.990	0.944–1.038
Previous pregnancy	−0.039	0.182	0.045	1	0.832	0.962	0.674–1.373
Years infertile	0.092	0.049	3.546	1	0.060	1.097	0.996–1.207
Least function score	−0.114	0.043	6.931	1	0.008	0.892	0.819–0.917
rAFS endometriosis score	0.001	0.012	0.011	1	0.915	1.001	0.978–1.025
rAFS total score	−0.005	0.005	1.199	1	0.274	0.995	0.986–1.004

EFI: Endometriosis Fertility Index; SE: Standard error; df: Degrees of freedom; Exp(B): Hazard ratio of parameter B; *CI*: Confidential interval; rAFS: Revised American Fertility Society.

Table 3: Characteristics of patients with an EFI score ≥5 (*n* = 307)

Characteristics	Non-IVF-ET group (*n* = 209)	IVF-ET group (*n* = 98)	Statistics	*P*
Age (years)	31.2 ± 3.5	31.9 ± 3.0	−1.671*	0.094
Previous pregnancy rate	135 (64.6)	58 (59.2)	0.836[†]	0.349
Years infertile (years)	3.0 (1.0–12.0)	4.0 (1.0–10.0)	87,674.000[‡]	0.346
Least function score	5.3 ± 1.8	5.4 ± 2.4	−0.680*	0.498
rAFS total score ≥71	12 (5.7)	8 (8.2)	0.642[†]	0.419
rAFS endometriosis score ≥16	86 (41.2)	51 (52.0)	3.203[†]	0.071
EFI score	7.2 ± 1.5	7.1 ± 1.6	0.537*	0.818

Data was presented by mean ± SD, *n* (%), or median (range). *: *t* value; [†]: χ^2 value; [‡]: *U*-value. SD: Standard deviation; EFI: Endometriosis Fertility Index; IVF-ET: *In vitro* fertilization and embryo transfer; rAFS: Revised American Fertility Society.
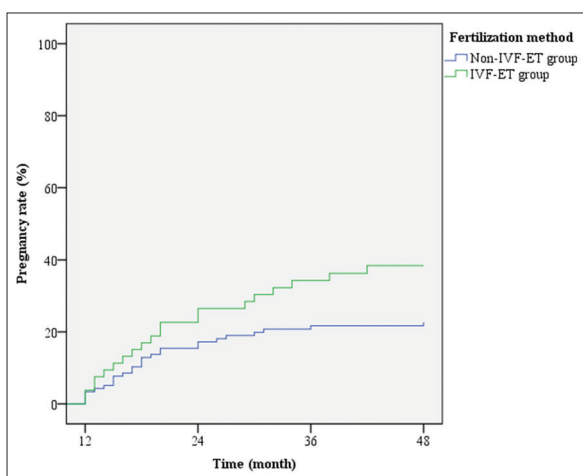
Figure 2: Probability of pregnancy of patients with an EFI score ≥5 beyond 12 months after surgery. Cumulative pregnancy rate in the IVF-ET group (*n* = 209) became significantly higher than that in the non-IVF-ET group (*n* = 98) at 12 months after laparoscopic surgery (χ^2 = 4.160; *P* = 0.041). EFI: Endometriosis fertility index; IVF-ET: *In vitro* fertilization and embryo transfer.

endometriosis is laparoscopic surgery.[10] For infertile women with endometriosis as the only identifiable infertility factor, operative laparoscopy can improve PRs in all stages.[11-13] For women with minimal-to-mild endometriosis, operative laparoscopy is more effective than diagnostic laparoscopy in improving the PR.[11] For women with moderate and severe endometriosis, the spontaneous PR after laparoscopic surgery is much higher compared with those treated by expectant management.[14] In the present study, the probability of spontaneous conception after surgery was 46.5%, which reconfirmed the effectiveness of laparoscopic surgery.

Many endometriosis staging systems have been developed over the last century, and rAFS is the most widespread system in the current clinical practice because of its more comprehensive expression of endometriosis extension. However, some important factors, such as patient age, duration of infertility, and family history, which might influence pregnancy outcomes, are not considered by rAFS. Considering the limitations of the rAFS staging system, for example, being unable to predict patients' probability of conception after laparoscopic surgery, Adamson and Pasta devised the EFI staging system, which is based on both historical and surgical factors to predict the spontaneous PR after surgery for endometriosis. In the original EFI publication, a sensitivity analysis was performed to assess the effect on the EFI of potential differences in the assignment of the least function scores by different surgeons.[5] This analysis showed that the EFI is robust enough to have some predictive capability for the ability to conceive after laparoscopy.

The EFI staging system has been validated externally in previous studies during a 36-month follow-up after surgery.[3,15,16] In the present study, we validated externally the relationship between the EFI score and spontaneous pregnancy up to 48 months after laparoscopy. We found that within 48 months after surgery, the cumulative PR increased with the increment in EFI scores. The higher the EFI score is, the better the chances of spontaneous pregnancy are. In particular, in patients with an EFI score 4 or less, the spontaneous PR was very low.

Nevertheless, using EFI may have some limitations. First, except for very extreme ovarian reserve cases, there is no

test or battery of tests, including EFI, which can predict the PR based on the ovarian reserve. If the score could be used as advice for patients after surgery, patients with decreased ovarian reserve should be advised to undergo IVF treatment more actively. Second, the EFI score does not include severe uterine abnormality and adenomyosis. Fortunately, this condition is uncommon in infertile patients with endometriosis and can be identified easily. When severe uterine abnormality is found, it should be taken into account in predicting the PR, despite being uncommon in infertile endometriosis.

The EFI was developed initially to predict the non-IVF PR and the adoption of IVF largely circumvents the tube and fimbria, which are components of the least function score. On this basis, we used Cox regression analysis to find the most important contributor to the EFI staging system only in the 234 patients who tried to conceive naturally. We observed that the least function score (the sum of those scores determined intraoperatively after surgical intervention that describe the function of the tube, fimbria, and ovary on both sides) is the only significant contributor to the prediction of spontaneous pregnancy among all the factors involved in the EFI score. This result is in line with those reported by Adamson and Pasta[5] and with Tomassetti *et al.*'s[16] research. The least function score is determined intraoperatively after surgical intervention, representing the postoperative functionality of the reproductive organs and is a statistically significant predictor of fertility.

Xu *et al.*[17] have found that 516 proteins were modified at phosphorylation level during endometriosis and the study of Zhao *et al.*[18] indicated that ATP1B4 and FGA were associated with endometriosis pathogenesis. Although a lot of progresses on endometriosis have been made in recent studies, the molecular mechanisms underlying the endometriosis are still not completely revealed. Laparoscopic surgery can improve fertility by removing adhesions, cul-de-sac obliteration, and endometriosis.[5,15] However, simultaneous disease progression might also exist. Previous studies have reported that a combination treatment comprising IVF and surgery can result in higher fecundity compared with surgery alone.[16,19,20] According to the European Society of Human Reproduction and Embryology guidelines published in 2014, IVF-ET is an effective alternative, especially in women with endometriosis who fail to conceive following other treatments.[13] Moreover, cumulative endometriosis recurrence rates do not increase after controlled ovarian stimulation for IVF-ET; therefore, clinicians may offer IVF-ET following endometriosis surgery to infertile women.[21,22] Whether and when to provide IVF to infertile patients with endometriosis who have undergone surgery remain to be determined.

A French retrospective study[23] suggested that patients with moderate and severe endometriosis should attempt to conceive naturally for 8–12 and 6–8 months, respectively, before opting for ART. Slabuszewska-Józwiak *et al.*'s[24] study reported that operative laparoscopy is an efficient method to treat infertility related to endometriosis and that the period for expectant management after a surgical procedure should last for 6 months. The Chinese guidelines for the diagnosis and treatment of endometriosis-related infertility allow couples to have a period of about 12 months for potential spontaneously conception after surgery, before being offered IVF-ET, especially in younger women with minimal or mild endometriosis.[25] In the present study, a statistically difference in the PRs between the IVF-ET group and non-IVF-ET group appeared at 12 months after laparoscopy surgery in patients whose EFI scores ≥5, which indicated that the 12th month after surgery is the optimal period to maximize the benefits of surgery for patients whose EFI scores are higher than 5. This result allows the possibility of providing more complete counseling at the time of decision-making in the postoperative fertility management of patients with endometriosis.

Based on the statistical analysis in our study, first, we demonstrated that the EFI staging system is very effective to predict reproductive performance after laparoscopic endometriosis surgery. Second, we proved that the least function score offers the greatest contribution to predict the PR in patients who are attempting to conceive spontaneously. Finally, we suggested that patients with an EFI score ≥5 should be allowed to attempt conception naturally for at least 12 months after surgery. If the attempt fails, IVF-ET should be considered for these patients.

There remain some limitations of our work that should be mentioned and investigated in future works. This was a retrospective study, in which the EFI score was graded by the operative surgeon with the use of the operative report, which could potentially reduce the accuracy of the EFI calculations. A prospective study is required to evaluate the validity of EFI scoring system to predict the spontaneous PR following endometriosis surgery. Moreover, we used the Kaplan-Meier survival analysis to estimate the crude PR, which might overestimate the cumulative PR.[26] The number of patients was limited; therefore, our study could only evaluate the optimal time to propose IVF treatment after surgery in patients with EFI scores ≥5. The purpose of the EFI classification is to provide valid clinical information on the PR over time after surgery. Given any time point after surgery, the EFI would give a validated estimate on the PR with continuation of non-ART treatment. This information can be used by patients and physicians as a reference to determine when to adopt IVF-ET. On the basis of the EFI score, patients could be advised to attempt spontaneous pregnancy before considering IVF-ET or, conversely, patients with a low EFI score (indicating a poor prognosis for spontaneous pregnancy) could opt for IVF-ET earlier to prevent wasting time. Theoretically, a lower EFI score is predictive of a lower PR, and such patients would obtain more benefits from IVF-ET.[19] According to the newly published (2015) guidelines from the Chinese Medical Association, Obstetrics and Gynecology branch, endometriosis cooperation group, women with an EFI score

of 4 or lower should undergo IVF-ET treatment directly after surgery.[25] Thus, the EFI score enables targeted and individualized infertility treatment. Further research should be performed to define the optimal timing for IVF in patients with different EFI scores.

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Conflicts of interest

There are no conflicts of interest.

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