Use of endometriosis fertility index to predict non-ART pregnancy and live birth after endometriosis surgery based on optimal stratification

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Running title: Endometriosis fertility index and pregnancy
Abstract

Background: The EFI, which was previously developed and validated externally, has shown predictive accuracy of non-ART pregnancy following surgery in infertile women with endometriosis. But up to now it was less accurate among the patients with lower scores based on the classification of the original literature. In addition, so far the only study has reported a strong association between the EFI and the live birth. However, the analysis of that study was done in women undergoing surgery rather than in those who had conceived post-operatively.

Methods: 501 infertile women undergoing laparoscopic treatment of endometriosis were recruited and followed up for post-operative pregnancy outcomes. The associations of EFI with non-ART pregnancy and with live birth were investigated with survival analysis and the Cochrane-Armitage test. The optimal cut-offs for EFI were determined using the Maximally Selected Rank Statistics (Maxstat).

Result(s): The follow-up rate was 92.4% with a mean duration of 38.5 months (range: 14.4-67.4 months). A total of 270 women (58.3%) conceived without ART, 187 (69.3%) had a live birth. A statistically significant association of EFI with non-ART pregnancy rate was observed (hazard ratio: 1.29, 95% confidence interval: 1.19-1.36; 95% confidence interval: 0.57-0.65). The Maxstat method suggested optimal EFI strata of 4, 6 and 8. The cumulative non-ART pregnancy rates 3 years after surgery were 15.0%, 47.1%, 67.6% and 73.6% for EFI scores of 0-4, 5-6, 7-8 and 9-10, respectively (Log-rank p < 0.001). No statistical differences were seen in the live birth rates and the time to pregnancy in the four EFI groups.
**Conclusion:** The EFI is predictive of post-operative non-ART pregnancy but not live birth among non-ART pregnancies. ART might be advisable to women with an EFI score <4 immediately after surgery and to women who have not achieved non-ART pregnancy after 12 months despite a high EFI.

**Key words:** Endometriosis fertility index, pregnancy, live birth, time-to-pregnancy, laparoscopy
Introduction

Endometriosis is one of the major causes of infertility, affecting 10% of women in reproductive age and about 50% of women with infertility [1-3]. Surgical treatment of endometriosis via laparoscopy can improve non-assisted reproductive technologies (ART) fecundity overall [4-8], but a more precise estimate of likelihood of post-operative pregnancy would be useful for patient counseling and development of individualized treatment plan. The most frequently used staging system, the American Society for Reproductive Medicine classification of endometriosis (r-ASRM) [9] is not capable of stratifying patients by their chance of post-operative pregnancy, because it does not take into account reproductive factors and surgical findings [10-13]. By adding age, duration of infertility, previous pregnancy, and adenexal function at conclusion of surgery, Adamson and Pasta developed the endometriosis fertility index (EFI) to predict non-ARTR pregnancy rate after surgery [14].

The EFI staging system has consistently shown an acceptable predictive accuracy in different external validations [15-27], with the area under the receiver operating characteristic curve (ROC) ranging from 0.65 to 0.75. However, in these validation studies, the patient classification depending on the cumulative pregnancy rate was less accurate among those with lower EFI scores [16, 20, 22]. Other studies used the ROC to obtain the optimal threshold that maximized the Youden index but ignored the duration between surgery and subsequent pregnancy [20, 23, 25, 26]. Meanwhile, whether the EFI can also be used to predict the rate of live birth remains unclear. So far there is only one study that
has reported a strong association between the EFI and the live birth rate [28]. However, it is notable that the analysis of that study was done in women undergoing resection surgery rather than in those who had conceived post-operatively making their results questionable because it is logical that pregnancy rate and live birth rate are strongly associated. Therefore it is necessary to examine whether that the association between the EFI and the live birth rate was actually driven by the association between the EFI and the pregnancy rate.

In the present study, we aimed to validate the EFI in a Chinese cohort and to identify the optimal classification using the Maximally Selected Rank Statistics (Maxstat) method [29]. We further explored whether the EFI is a good predictor for live birth rate among the women who conceived without ART after surgical treatment of endometriosis and suggested a reasonable amount of time that should be allowed for non-ART conception attempts before staring ART.

**Materials and Methods**

**Study design**

We collected data on all infertile patients with endometriosis who underwent laparoscopic fertility-sparing surgery and diagnostic hysteroscopy at our center between 2014 and 2017. Diagnosis of peritoneal endometriosis was established by histopathology or visualization of typical lesions, such as white, red, and black lesions. Diagnosis of ovarian endometrioma and deeply invasive endometriosis (DIE) was based on histopathology.
DIE lesions were classified as ≥ 5mm deep invasive endometriotic lesions or those involving bowel, bladder, ureter or other sites [30-32]. Patients with the following conditions were excluded: 1) Ovulation disorder 2) double tubal obstruction 3) congenital defects 4) intrauterine adhesion 5) endometrial hyperplasia 6) abnormal sexual function 7) abnormal semen analyses of partners according to the WHO criteria [33]. Patients were censored when they were lost follow-up, had a subsequent surgery for recurrent endometriosis, or the initiation of ART, whichever came first.

The post-operative treatments were basing on individual clinical assessment of the patients. Gonadotrophin-releasing hormone agonists (GnRH-a) were used starting 1 to 6 months post-operatively when ovarian reserve function was normal in patients with moderate-severe endometriosis. For patients who received GnRH-a, the calculation of time to post-operative pregnancy started from the date of the last injection. For those who did not, the time started from the date of surgery. ART was recommended to the patients who failed attempt non-ART conception for 12 months. Post-operative pregnancies were ascertained using the WHO-ICMART definitions [34], namely overall pregnancy was defined by a HCG > 25 IU/L, clinical pregnancy was diagnosed based on ultrasound visualization of one or more gestational sacs or definitive clinical signs of pregnancy.

**Surgical procedure**

All patients had laparoscopic and hysteroscopic diagnosis simultaneously. Tubal patency was assessed with methylene blue during the operation. During the laparoscopic surgery,
all visible peritoneal lesions were excised or coagulated. Endometriomas were excised using a careful stripping technique to minimize the loss of the normal ovarian tissue. Deeply invasive endometriosis (DIE) in the cul-de-sac and uterosacral ligament was resected completely and laparoscopic shaving or disc bowel resection was undertaken. Complete adhesiolysis was performed as much as possible to restore normal anatomic structure of pelvic organs, the cul-de-sac and mobilize the tubes, fimbria and ovaries. Endometrial biopsy and hysteroscopic surgery were carried out when endometrial lesions were suspected or diagnosed by hysteroscopy. All patients had a normal uterine cavity. Hysteroscopic proximal tubal cannulation was undertaken to restore the tubal patency when a proximal obstruction was found.

Data collection

Eligible patients were identified using the electronic medical record (EMR) and then contacted via telephone interview for further assessment of eligibility. The demographic data, the reproductive history, the endometriosis type and staging, were derived from the electronic medical record (EMR). The r-ASRM lesion score and the LF score was confirmed from the detailed operative reports and pictures and then the EFI, as previously described in the literature [14], was calculated independently by a researcher blinded to the subsequent pregnancy outcomes.

Subsequent fertility details and pregnancy outcomes of the eligible patients were derived from the EMR. If not, those were ascertained via telephone interview. When patients could
not be reached after two telephone calls, text messages were sent. Women were asked to provide information regarding their pregnancy attempts, pregnancy outcomes and infertility treatment with or without ART.

**Statistical analysis**

The EFI was calculated as described by Adamson and Pasta in their original work [14]. A Cox model including solely the EFI was built to examine the EFI's predictive accuracy for post-operative non-ART pregnancy. The Maxstat method was used to determine the optimal cut-points for the EFI by using a maximally selected log-rank statistic [29]. The cumulative pregnancy rates were estimated with the Kaplan-Meier method for the EFI categories defined first using the original cut-offs and then using the optimal cut-offs derived from the Maxstat statistic. For the survival analyses above, study participants were censored at the time of loss to follow-up, a subsequent surgery, or the initiation of ART, whichever came first.

Whether the EFI was associated with live birth was examined within the women who had conceived without ART after surgery. The Cochrane-Armitage test was conducted to test trend in live birth rates across the EFI categories. Kruskal-Wallis test and pairwise comparison were used to test the differences in the duration between surgery and pregnancy across the EFI categories.

All statistical analyses were conducted with R software, version 3.6.1 (R Foundation for
Statistical Computing, Vienna, Austria). A two-sided P value of less than 0.05 was considered statistically significant.

Results

Descriptive results and baseline characteristics

Of the 501 eligible women who attempted non-ART pregnancy after surgical treatment of endometriosis, 463 (92.4%) had information on pregnancy outcome, which was obtained either from EMR (45.8%) or via telephone interview (54.2%) (SUPPLEMENTAL FIGURE 1). The time between surgery and the follow-up ranged from 14.4 to 67.4 months (median = 38.5 months). Overall, 270 (58.3%) women became pregnant without ART, including 187 (69.3%) live births, 59 (21.9%) pregnancy losses and 24 (8.9%) unknown pregnancy outcomes. The distribution of their EFI was shown in SUPPLEMENTAL FIGURE 2.

External validation of the EFI

A statistically significant association of EFI with non-ART pregnancy rate was observed (hazard ratio: 1.29, 95% confidence interval: 1.19-1.36, C-index of 0.61, 95% CI: 0.57-0.65). We used the original cut-offs (3, 4, 5, 6 and 8) to divide patients into six EFI groups for external validation, showing that the survival curves of EFI 0-3 group and EFI 4 group were close and crossed, as well the curves of EFI 5 group and EFI 6 group (FIGURE 1a). Thus, we used the Maxstat method to determine the three optimal EFI cut-off points (4, 6, and 8) for categorizing the women into 4 groups. For the women with the EFI score of 5-6 (n=105), 7-8 (n=210), and 9-10 (n=110), the median time to
conception were 41.3 months, 13.0 months, and 8.0 months, respectively (Log rank P < 0.001, FIGURE 1b).

The results of Kaplan-Meier Survival curves and Log-rank test were presented in FIGURE 1b and SUPPLEMENTAL TABLE 1. After stratifying the EFI into four groups, we observed a significant relationship between EFI and non-ART pregnancy (Log-rank P < 0.001, FIGURE 1b). From 0-4 EFI score group to 9-10 EFI score group, the cumulative non-ART pregnancy rate shows an ascending trend and this trend remains at the first, second, and third years of follow-up (SUPPLEMENTAL TABLE 2). The cumulative non-ART pregnancy rate at 3 years after surgery steadily increased from 15.0% to 73.6% in women with an EFI of 0-4 and 9-10, respectively.

**EFI in relation to live birth and time-to-pregnancy**

Among women who conceived without ART, the proportion of women with live birth had achieved non-ART pregnancy after surgery did not significantly differ in the four EFI groups (P for trend = 0.930, TABLE 2). The time to pregnancy among four EFI groups also did not significantly differ (P = 0.23 > 0.05, FIGURE 2). The median of the time to pregnancy in each EFI groups were 4.6, 7.7, 6.1 and 5.6 months for 0-4, 5-6, 7-8 and 9-10 EFI score groups respectively. The 75 percentiles of the time to pregnancy in each EFI groups were 9.9, 12.0, 12.4 and 10.5 months for 0-4, 5-6, 7-8 and 9-10 EFI score groups respectively (SUPPLEMENTAL TABLE 2). That is, for all four EFI groups, the half of pregnancies occurred within 8 months after surgery and 75% of pregnancies occurred
within about 1 year after surgery.

Discussion

In our study, the EFI showed a moderate accuracy in predicting the probability of non-ART pregnancy in infertile women with endometriosis, in line with the results of the previous studies [16, 19, 26]. However, the original EFI cut-offs led to a notably poor classification in the women with the EFI scores below 6, inferior to the cut-offs derived from the Maxstat method. Among women who had successfully conceived without ART, the EFI was not significantly associated with the probability of live birth, and the majority of the pregnancies were achieved in the first 12 months post-operatively.

The moderate predictive performance of the EFI might be due to its exclusion of some important factors affecting postoperative fertility, such as ovarian reserve and co-existence of other conditions including adenomyosis and leiomyomas [35-38]. In addition, the EFI scoring system does not consider lesions present in bowel and urinary tract. Their associations with post-operative pregnancy may warrant further investigation [39, 40].

The EFI in the original work by Adamson Pasta chose 3, 4, 5, 6, and 8 to subdivide the patients into 6 groups and showed a good patient stratification depending on their non-ART pregnancy rates over a time period of 36 months. However, using these original cut-offs, all the external validation studies demonstrated a poor stratification for those with
lower EFI scores ($\leq 6$), where patients with higher EFI scores showing similar or even lower cumulative pregnancy rate [16, 20, 22]. To the best of our knowledge, this is the first external validation using the Maxstat method to identify the optimal grouping cut-offs of EFI. Our data shows that the resulting EFI cut-offs outperformed the original cut-offs with respect to patient stratification according to the estimated probability of non-ART pregnancy.

Live birth is ultimately the most important outcome for both patients and gynecologists. The study of Maheux-Lacroix et al. [28] showed that the EFI was positively associated with the live birth, which is contrary to our result when we limited our analysis to women who had conceived without ART. The result is questionable because it is logical that pregnancy rate and live birth rate are strongly associated. In our study, 187 out of the 270 non-ART pregnancies ended up with live birth, suggesting the previously reported positive association of the EFI with the rate of live birth was mainly driven by its association with non-ART pregnancy. Although, age is frequently used to predict the chance of live birth or pregnancy [41, 42], while lower ovarian reserve [43, 44] and severity of the lesion [12, 45] are the factors that might influence fertility outcomes, none of these studies were confined to the pregnancies.

How long women should try to get pregnancy without ART before starting ART is important information for patient counseling and formulation of an individualized treatment strategy after surgical treatment of endometriosis. In one study, approximately 50% of
pregnancies occurred in the 12-18 months following surgery [46]. Hobo et al. suggested that most patients achieved pregnancy without ART treatment within eight months post-operatively, regardless of their EFI [23]. Our study shows similar results in women who had achieved non-ART pregnancy, suggesting that women who have failed to conceive without ART in the first year after surgery should be considered for ART regardless of their EFI score.

This study had several limitations. First, the EFI was calculated retrospectively by reviewing operative reports and pictures. Second, the operation were performed by a number of gynecologists not in the context of a research study, and thus consistency of reporting on key findings that drive the EFI may not have need idea. However, one study has shown a good agreement between gynecologists in calculation of EFI score [47]. Third, this study had a limited number of women with lower EFI and therefore the analysis for this group of women has limited reliability. Finally, we did not exclude patients with adenomyosis, which was diagnosed according to intraoperative or pelvic ultrasound rather than magnetic resonance or histopathology. We did include patients with uterine leiomyoma, but all fibroids were all small (the size less than 3cm) and subserous.

In conclusion, the EFI may be a useful prediction tool for the non-ART pregnancy rate following the laparoscopic surgery but does not appear to predict the rate of live births among women who have conceived successfully without ART. When applied to a specific patient population, the optimal EFI cut-offs should be determined by external validation so
as to improve patient stratification and develop individualized treatment plans. Our data suggest that ART might be recommended to women with an EFI score below 4 immediately after surgery and women who fail to conceive naturally after a 12-month attempt despite high EFI.

**Ethics approval and consent to participate**

This study was approved by the Guangzhou Women and Children’s Medical Center Ethics Committee (No. 2017102709) and oral informed consent was obtained from all patients via telephone interview.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

Q.F. L. is the coordinator of the project. H.S. L., Q.F. L., J.Y. F., K. Q., K.R. L., X.J. L. and H. Y. L. designed the study. J.Y. F., J.Y.X., Y.Y. and Y.S.L. contributed to data collection. K. Q.,
K.R. L. and X. J. L. performed the statistical analyses. J.Y. F., K. Q. and Abraham N. Morse wrote the manuscript. All authors approved the final version of the draft.

**Availability of data and materials**

The datasets analysed during the current study are included in the tables in this published article and are available from the corresponding author on reasonable request.

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Figure legends

FIGURE 1. Kaplan-Meier estimated cumulative non-ART pregnancy rate by the original six EFI groups (a) and the optimal four EFI groups (b). EFI, Endometriosis Fertility Index.

FIGURE 2. Box plot of the time to pregnancy of women with different EFI score. EFI, Endometriosis Fertility Index.

SUPPLEMENTAL FIGURE 1. Flow chart of cases included and excluded from the study.

SUPPLEMENTAL FIGURE 2. Distribution of EFI score in the study cohort. EFI, Endometriosis Fertility Index.
**TABLE 1**

Characteristics of the study population

| Variables                                      | N = 463 |
|------------------------------------------------|---------|
| BMI (kg/m²)                                    | 21.1±2.9 (15.2-36.2) |
| Age (years)                                    | 31.9±4.6 (20-46) |
| ≤35                                            | 369 (79.7) |
| 36-39                                          | 64 (13.8) |
| ≥40                                            | 30 (6.5) |
| Duration of infertility (month)                |         |
| ≤36                                            | 348 (75.2) |
| >36                                            | 115 (24.8) |
| Previous pregnancy                             | 227 (49.0) |
| LF                                             |         |
| 7-8                                            | 97 (21.0) |
| 4-6                                            | 305 (65.9) |
| 1-3                                            | 61 (13.2) |
| r-ASRM endometriosis score                     |         |
| <16                                            | 279 (60.3) |
| ≥16                                            | 184 (39.7) |
| r-ASRM total score                             |         |
| <71                                            | 402 (86.8) |
| ≥71                                            | 61 (13.2) |
| EFI                                            | 7.1±1.8 (0-10) |
| 0-4                                            | 38 (8.2) |
| 5-6                                            | 105 (22.7) |
| 7-8                                            | 210 (45.4) |
| 9-10                                           | 110 (23.8) |
| Superficial peritoneal endometriosis           | 339 (73.2) |
| Uterosacral endometriosis                      | 59 (12.7) |
| Cul-de-sac endometriosis                       | 139 (30.0) |
| Endometrioma                                   | 202 (43.6) |
| Digestive endometriosis                        | 6 (1.3)  |
| r-ASRM                                         |         |
| I                                               | 199 (43.0) |
| II                                              | 41 (8.9)  |
| III                                             | 112 (24.2) |
| IV                                              | 111 (24.0) |
| Adenomyosis                                    | 49 (10.6) |
| Uterine leiomyoma                              | 88 (19.0) |

EFI, Endometriosis Fertility Index; LF, least function score; DIE, deep infiltrating endometriosis; r-ASRM, revised American Society for Reproductive Medicine; ART, assisted reproductive technology.
## TABLE 2
Live birth rate among women achieving non-ART pregnancy stratified by EFI score

| EFI   | n   | Non-ART live birth rate (%) | P for Trend* |
|-------|-----|------------------------------|--------------|
| 9-10  | 75  | 56(74.7)                     | 0.930        |
| 7-8   | 120 | 94(78.3)                     |              |
| 5-6   | 46  | 32(69.6)                     |              |
| 0-4   | 5   | 5(100)                       |              |

EFI, Endometriosis Fertility Index.

*The P value was calculated by the cochrane-armitage test.

Of the 270 natural pregnancies, 24 had unknown pregnancy outcomes.

## SUPPLEMENTAL TABLE 1
Kaplan-Meier estimated cumulative natural pregnancy rate at 1 to 3 years by EFI

| EFI   | No. of women | 1 year       | 2 years      | 3 years      |
|-------|--------------|--------------|--------------|--------------|
| 9-10  | 110          | 59.0±11.6    | 68.6±14.7    | 73.6±17.8    |
| 7-8   | 210          | 46.2±6.4     | 62.3±9.3     | 67.6±11.3    |
| 5-6   | 105          | 35.7±7.3     | 43.4±8.8     | 47.1±10.0    |
| 0-4   | 38           | 10.8±5.7     | 10.8±5.7     | 15.0±7.5     |

EFI, Endometriosis Fertility Index.

*Log-rank test, P < 0.001

## SUPPLEMENTAL TABLE 2
Summary of the time to pregnancy of women with different EFI score

| EFI   | No. of pregnancy | Time to pregnancy (months) |
|-------|------------------|----------------------------|
|       | median | mean | min | 25th percentile | 75th percentile | max |
| 9-10  | 82     | 5.6  | 9.4 | 0.3 | 2.3 | 10.5 | 49.3 |
| 7-8   | 133    | 6.1  | 8.7 | 0.4 | 2.6 | 12.4 | 46.2 |
| 5-6   | 50     | 7.7  | 12.1| 0.8 | 3.9 | 12.0 | 62.2 |
| 0-4   | 5      | 4.6  | 9.0 | 1.0 | 3.0 | 9.9  | 26.3 |

EFI, Endometriosis Fertility Index.
FIGURE 1. Kaplan-Meier estimated cumulative non-ART pregnancy rate by the original six EFI groups (a) and the optimal four EFI groups (b). EFI, Endometriosis Fertility Index.
FIGURE 2. Box plot of the time to pregnancy of women with different EFI score. EFI, Endometriosis Fertility Index.
SUPPLEMENTAL FIGURE 1. Flow chart of cases included and excluded from the study.
SUPPLEMENTAL FIGURE 2. Distribution of EFI score in the study cohort. EFI, Endometriosis Fertility Index.