

Analysis of factors related to fertility after endometriosis combined with infertility laparoscopic surgery

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Abstract

To investigate the influence factors of laparoscopic postoperative pregnancy of patients with endometriosis and infertility, further validate the application of EFI scoring system in endometriosis, and to improve the pregnancy rate.

A total of 258 patients with endometriosis and infertility who underwent laparoscopic surgery and follow-up treatment at Wuxi Maternal and Child Health Hospital from January 2015 to December 2016 were selected and divided into pregnant and non-pregnant groups according to whether they were pregnant. All patients were divided into 4 groups according to EFI score: group with EFI score ≥ 9 , 7–8, 4–6, and < 4 , and divided into I, II, III, and IV groups according to AFS stages. The uterus-laparoscopic surgery was performed. The patients were followed up for 3 years. The factors affecting the pregnancy rate were analyzed. The pregnancy rate and pregnancy types were calculated at different time points.

Multivariate analysis showed that age < 35 years, infertility time < 5 years, secondary infertility, EFI score, postoperative ART application were protection factors of postoperative pregnancy. The 3-year cumulative postoperative pregnancy rate was 75.6%. The cumulative pregnancy rate was 92.2% in group with EFI score ≥ 9 , 85.9% in group with EFI score 7–8, 62.5% in group with EFI score 4–6 and 5.9% in group with EFI score < 4 , there was significant difference between the 4 groups ($P < .05$). The proportion of pregnancies in 6 months and 12 months was higher in patients with EFI score ≥ 7 , 61.0% in patients with EFI score ≥ 9 and 41.1% in patients with EFI score ≥ 7 . The highest natural pregnancy rate was 83.1% in group with EFI score ≥ 9 , and there was significant difference between the 4 groups ($P < .05$).

Age < 35 years, infertility time < 5 years, secondary infertility, EFI score and ART application were the protective factors of postoperative pregnancy. EFI score had positive significance in predicting and guiding the postoperative pregnancy of patients with endometriosis and infertility. According to EFI score, the pregnancy rate of patients with endometriosis and infertility can be significantly improved by strict management and active pregnancy program.

Abbreviations: ART = Artificial Reproduction Technology, ASRM = American Society of Reproductive Medicine, BMI = body mass index, CMA = Chinese Medical Association, EFI = Endometriosis Fertility Index, GnRHa = Gonadotrophin Releasing Hormone Analogues, IVF = in vitro fertilization, KM = Kaplan–Meier, R-AFS = Retrospective American Fertility Society Score.

Keywords: endometriosis, laparoscopy, pregnancy rate

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1. Introduction

Endometriosis is a common disease in women of childbearing age, which is closely related to infertility.^[1,2] Not only that, it is longstanding recurrent disease and it is distressing women's physical and mental health and social lives.^[3,4]

Hysteroscopic-laparoscopic surgery is currently recognized as the gold standard for the diagnosis of endometriosis with infertility, the removal of lesions, the improvement of pelvic structure, the assessment of the status of the fallopian tubes and ovaries, and improvement of the reproductive status of patients.^[5] However, the role of surgery in the treatment of endometriosis combined with infertility is still controversial. In fact, despite the increasing popularity and wide application of laparoscopic surgery in patients with endometriosis, the current management methods are based on the results of no control studies, especially for moderate and severe endometriosis.^[6,7] Surgical resection (treatment principle) is mostly based on clinical treatment guidelines and expert consensus.^[5] Nevertheless, surgery may not be able to improve the chronic inflammatory changes related to endometriosis and the changes of local tissue molecular biology, besides, surgery may not be able to fully repair the adverse effects of the disease on fertility potential.^[8–10] Laparoscopic surgery to preserve fertility does not improve the

fertility of all patients with endometriosis and infertility.^[11] Therefore, it is an urgent problem to effectively predict the fertility potential, long-term management and prevent the recurrence of endometriosis.

For endometriosis, many scholars have proposed a number of classification systems.^[12–14] The complexity of staging and scoring system in endometriosis is manifested in the pain and fertility of patients due to different ectopic lesions and depth of invasion. The most widely used classification was the revision of the staging system developed by the American Society of Reproductive Medicine (ASRM) in 1985 and 1996.^[15,16] Although widely used, this classification has well-known limitations, which can well express the severity of endometriosis, but can not predict the pregnancy outcome of patients with endometriosis and infertility, deep endometriosis unable to record, staging is not well correlated with fertility potential.

Some prospective studies have introduced the Endometriosis Fertility Index (EFI) score classification system to classify patients with endometriosis and infertility. Which is mainly aimed at the age, infertility time limit, past birth history, fallopian tube, and ovary minimum function of patients with endometriosis and infertility.^[17–19] The functional scores are used to quantify the indicators, and the evaluation of the patients fertility potential provides a reference for postoperative treatment and management. Many studies have verified the application value of the EFI scoring system to predict the fertility after endometriosis combined with infertility.^[15–17,19,20]

In order to explore the related factors of fertility in patients with endometriosis and infertility after laparoscopic surgery, we conducted a prospective study and analyzed the clinical data of 258 patients with endometriosis and infertility, with the aim of improving the pregnancy rate and womens physical and mental health. In addition, we would like further validate the application of EFI score analysis of endometriosis combined with infertile women to try artificial reproduction technology (ART) and non-ART pregnancy after surgery.

2. Materials and methods

2.1. Study patients

A total of 258 patients with endometriosis and infertility diagnosed by laparoscopy in Wuxi Maternal and Child Health Hospital from January 2015 to December 2016 were enrolled in this study. The clinical data such as age, infertility type, infertility time, endometriosis type, Retrospective American Fertility Society Score (R-AFS) stage, ART application, gonadotrophin releasing hormone analogues (GnRHa) medication use, and EFI score were collected. All patients were underwent laparoscopic surgery for the first time and followed-up for 3 years. All patients provided the informed consent. The Ethics Committee at Wuxi Maternal and Child Health Hospital had approved the using clinical information in our study (approval number: 20141228). All procedures and ethical standards were done in accordance with the national research committee and/or institutional.

2.2. Inclusion criteria

Patients were enrolled in this study if they met all the following criteria:

1. patients with endometriosis and infertility diagnosed by laparoscopy;

2. patients aged 22 to 40 years;
3. had a complete and detailed clinical, follow-up data record.

2.3. Exclusion criteria

Patients meeting any of the following criteria were excluded:

1. Non childbearing age patients;
2. infertility caused by male factors;
3. any incomplete clinical or follow-up data.

2.4. Study design

According to the R-AFS revised by the American Society of Fertility (ASF) in 1985,^[21] patients were divided into 4 stages: I, II, III, and IV. On the other hand, patients were divided into 4 groups according to Endometriosis Fertility Index (EFI) score: ≥ 9 ; 7–8; 4–6; < 4 . Endometriosis Collaboration group, Obstetrics and Gynecology branch, Chinese Medical Association (CMA) put forward a classification of endometriosis (peritoneum type, ovarian type, deep infiltration type, and mixed type).^[22]

All patients were underwent laparoscopic surgery on 3 to 7 days after menstruation was over. For patients with R-AFS stage III, IV, and deep infiltrative endometriosis, 3 cycles of GnRHa treatment were carried out. Those who did not accept GnRHa treatment after 12 months were suggested ART application.

2.5. Follow up

The follow-up contents included general information, three-dimensional color ultrasound of pelvic vagina, serum CA125. The natural pregnancy rate within 6 and 12 months after operation was observed. The natural pregnancy of patients without GnRHa treatment was calculate began with the first menstrual tide, patients with GnRHa treatment was calculate began with the menstrual tide after discontinuation of medication. The pregnancy status, pregnancy mode, pregnancy time, and postoperative recurrence were collected and analyzed.

2.6. Statistical analysis

SPSS17.0 software was used for statistical analysis. All continuous measures were analyzed by two-sample t test, graded variables were analyzed with Chi-Squared test and Mann–Whitney test. Univariate and multivariate Cox analyses were used for analysis of pregnancy related factors after laparoscopic treatment of endometriosis. The cumulative pregnancy rate was compared by Kaplan–Meier (KM) method and log rank test. P value $< .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics and postoperative recurrence

Chi-Squared test and Mann–Whitney test showed that age, infertility type, infertility time, ART application and EFI score were significantly different between the pregnancy group and non-pregnancy group ($P < .05$). R-AFS stage, endometriosis type, and GnRHa medication use were not associated with pregnancy (Table 1).

All patients were followed-up for 3 years, among which 10 cases (8.1%) recurred in R-AFS stage I and R-AFS stage II group,

Table 1
Univariate analysis of pregnancy-related factors in patients with endometriosis and infertility.

Variables	Pregnancy group	Non-pregnant group	P value
Age (years), n (%)			.003
<35	141 (54.7)	78 (30.2)	
≥35	6 (2.3)	33 (12.8)	
Infertility type, n (%)			.019
Primary	55 (21.3)	65 (25.2)	
Secondary	91 (35.3)	47 (18.2)	
Infertility time (years), n (%)			.008
<5	112 (43.4)	47 (15.2)	
≥5	34 (13.1)	65 (25.2)	
Types of endometriosis, n (%)			.134
Peritoneum type	22 (8.5)	10 (3.9)	
Ovarian type	59 (22.9)	19 (7.4)	
Deep infiltration type	12 (4.7)	40 (15.5)	
Mixed type	50 (19.4)	46 (17.8)	
R-AFS stage, n (%)			.356
I	42 (16.3)	10 (3.9)	
II	57 (22.1)	15 (5.8)	
III	67 (26.0)	19 (7.4)	
IV	29 (11.2)	19 (7.4)	
ART application, n (%)			<.001
Yes	39 (15.1)	54 (21.0)	
No	156 (60.5)	9 (3.5)	
GnRHa medication use, n (%)			.062
Yes	86 (33.3)	23 (8.9)	
No	109 (42.2)	40 (15.5)	
EFI score, n (%)			<.001
≥9	71 (27.5)	1 (0.4)	
7–8	73 (28.3)	12 (4.7)	
4–6	50 (19.4)	30 (11.6)	
0–3	1 (0.4)	16 (6.2)	

16 cases (11.9%) in R-AFS stage III, and R-AFS stage IV group, with an average recurrence time of 30.1 months and 27.8 months, respectively. There was no significant difference between the 2 groups ($P > .05$). Among the 26 recurrent cases, there were 8 cases in group with EFI score ≥ 9 , 9 cases in 7–8, 7 cases in 4–6, and 2 cases in < 4 . There was no significant difference between the groups ($P > .05$).

3.2. Univariate and multivariate Cox analyses of pregnancy-related factors in endometriosis with infertility

All cases were divided into pregnancy group and non-pregnant group. Univariate Cox analysis showed age, infertility type, infertility time, ART application, and EFI score were correlated with pregnancy in the patients with endometriosis and infertility

($P < .05$). R-AFS stage, endometriosis type and GnRHa medication use were not associated with postoperative pregnancy rate ($P > .05$) (Table 2). Multivariate Cox analysis showed only the age, infertility time, ART application, and EFI score were closely related to the cumulative pregnancy ($P < .05$). Among them, age < 35 years old, infertility time < 5 years, EFI score and ART application were the protective factors of pregnancy (Table 2).

3.3. Cumulative pregnancy rate of different groups with R-AFS stage and EFI score

There were no statistically significant differences of cumulative pregnancy rate between different groups with R-AFS stage ($P > .05$) (Table 3). In addition, the cumulative 36-months postoperative pregnancy rate of group with EFI score ≥ 9 was the highest, and that of groups with EFI score ≥ 9 and 7–8 was significantly higher than that of groups with EFI score 4–6 and < 4 ($P < .05$) (Table 3).

3.4. Comparison of cumulative natural pregnancy rates between different EFI score and the time of postoperative pregnancy

There was no significant difference in the cumulative pregnancy rate between the groups with R-AFS stage ($P > .05$), the pregnancy rate of groups with EFI score was shown in Figure 1. The cumulative postoperative natural pregnancy rate calculated by Kaplan–Meier was calculated in 6 months, 12 months, 24 months, and 36 months, respectively.

The difference in the cumulative postoperative natural pregnancy rate of the 4 groups with EFI score was statistically significant ($P < .05$). It was found that the cumulative postoperative pregnancy rate of group with EFI score ≥ 9 was the highest in 36 months, and that of groups with EFI score ≥ 9 and 7–8 was significantly higher than that of groups with EFI score 4–6 and < 4 ($P < .05$). The natural pregnancy occurred from 6 months to 12 months after the operation. The patients who were not pregnant within 2 years after the operation were followed up until 3 years.

3.5. Comparison of postoperative pregnancy patterns in groups with EFI score

The higher the EFI score, the higher the natural pregnancy rate within 6 and 12 months after operation ($P < .05$). The natural pregnancy rate was the highest in 12 months after operation in group with EFI score ≥ 9 , and increased by 20% in group with EFI score 7–8 and 4–6 from 12 months to 24 months after operation in combination with ART. The difference was statistically

Table 2
Univariate and multivariate cox analysis of pregnancy related factors after operation.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age/years (<35 vs ≥ 35)	1.952	1.580–2.436	.014	1.674	1.369–1.982	.015
Infertility type (Primary vs ≥ Secondary)	1.011	0.972–1.581	.192	–	–	–
Infertility time/years (<5 vs ≥ 5)	2.870	1.647–4.059	.006	2.234	1.085–2.736	.008
EFI score	2.367	1.833–3.952	.004	1.944	1.562–3.812	.016
ART application (no/yes)	1.846	1.365–3.178	.022	1.357	1.027–1.904	.037

Table 3
Cumulative pregnancy rate of different groups with R-AFS stage and EFI score. [n (%)].

Variables	Cases	6 months	12 months	24 months	36 months	χ^2 value	P value
R-AFS stage						1.34	.248
I	52	23 (44.2)	35 (67.3)	42 (80.8)	42 (80.8)		
II	72	37 (51.3)	50 (69.4)	57 (79.1)	57 (79.1)		
III	86	19 (22.1)	51 (59.3)	67 (77.9)	67 (77.9)		
IV	48	5 (10.4)	20 (41.7)	29 (60.4)	29 (60.4)		
χ^2 value		1.94	1.72	1.38			
P value		.573	.633	.241			
EFI score						11.30	<.001
≥ 9	77	47 (61.0)	64 (83.1)	71 (92.2)	71 (92.2)		
7–8	85	35 (41.2)	55 (64.7)	73 (85.9)	73 (85.9)		
4–6	80	17 (21.3)	37 (46.3)	50 (62.5)	50 (62.5)		
0–3	17	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)		
χ^2 value		10.29	8.12	4.98			
P value		.006	.017	.026			

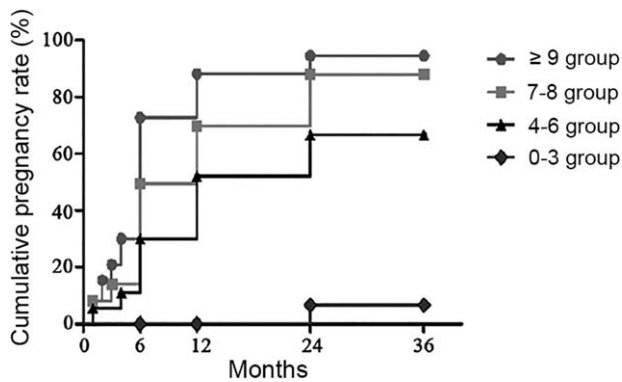


Figure 1. Cumulative pregnancy rate of EFI score groups. All of them were natural pregnancies before 24 months and new ART pregnancies after 24 months.

significant compared with <4 group ($P < .05$), while the natural pregnancy in patients with EFI score <4 was 0 (Table 4).

4. Discussion

This study indicated that the total 3 years-pregnancy rate was 75.6% (195/258) of patients with endometriosis and infertility after laparoscopic surgery, which strongly verified the laparoscopic surgery could improve the fertility. The age, infertility time, infertility type, EFI score, postoperative ART application were closely related to postoperative cumulative pregnancy

($P < .05$). Treatment with GnRHa was not associated with postoperative pregnancy rate ($P > .05$), which is consistent with most previous relevant studies.^[15,16,19,20]

Our study showed that there was no significant difference in the cumulative pregnancy rate between the groups in the traditional R-AFS score group, so this staging method could not predict the fertility after endometriosis. The higher EFI score, the higher the postoperative 3-year cumulative pregnancy rate. The highest postoperative natural pregnancy rate within 12 months was the group with EFI score ≥ 9 , but no postoperative 3-year natural pregnancy was observed of patients with a EFI score of <4. It is consistent with previous studies,^[17,18] thus verifying that EFI is an effective indicator for predicting postoperative fertility in endometriosis.

In the first year after surgery, the natural pregnancy of most patients with endometriosis and infertility occurred during this period. Patients may benefit from one-time uterine-laparoscopic surgery, laparoscopic surgery improved the irregular pelvic anatomy due to endometriosis lesions: removal of adhesions, removal of cysts, and removal of pelvic endometriotic lesions.^[15,23,24] In the second year after surgery, patients who were not pregnant in the first year were advised to actively ART.

The ART pregnancy rate was 21.1% of group with EFI score 7–8 and 16.3% of group with EFI score 4–6. Almost no pregnant occurred in the third year. In patients who were followed up for 3 years, most of the postoperative endometriosis recurrence occurred in the second year after surgery, which indicated that it is effective to improve fertility by surgery for pelvic lesions caused by endometriosis. But for the mechanisms were such as some defects in reproductive function: low ovarian reserve, severe damage to the fallopian tube function, low quality of gametes,

Table 4
Comparison of postoperative pregnancy patterns in EFI score groups. [n (%)].

EFI score	Cases	Pregnancy	ART	Non-ART	χ^2 value	P value
≥ 9	77	71	64 (83.1)	7 (9.1)	4.55	.033
7–8	85	73	55 (64.7)	18 (21.1)		
4–6	80	50	37 (46.3)	13 (16.3)		
0–3	17	1	0 (0.0)	1 (5.9)		
χ^2 value			4.98	8.72		
P value			.026	.017		

and excessive age may affect fertility, it cannot be improved by surgical intervention.

Recently, Wang et al^[25] studied 199 patients with endometriosis who underwent in vitro fertilization (IVF) after surgery and found the EFI score was a predictive tool for IVF results. Specifically, the probability of EFI score ≥ 6 is significantly higher than EFI score ≤ 5 , which is associated with a higher number of sinus follicles and eggs obtained. The results in our study displayed ART pregnancy rate was 21.1% in the group with EFI score 7–8 and 16.3% in the group with EFI score 4–6, which was significantly higher than the group with EFI score < 4 . The EFI score could be used to predict the endometriosis and the possibility of post-ART pregnancy. The ART pregnancy rate was relatively low in this study. It should be considered that ART was only available after the expected natural gestation time in the first year. It is expected that endometriosis may also progress, which may affect the pregnancy rate of ART.

Due to endometriosis occurs in fertility age and affects fertility, we used EFI scoring system in this study. The 1-year pregnancy rate of group with EFI score ≥ 9 was 83.1%, and the 36 months cumulative pregnancy rate was the highest. The cumulative pregnancy rate of group with EFI score ≥ 9 and 7–8 was significantly higher than that of group with EFI score 4–6, and the cumulative pregnancy rate of group with EFI score < 4 was the lowest. Therefore, for the long-term management of postoperative fertility guidance as well as the postoperative recurrence prevention of disease in patients with endometriosis and infertility, pregnancy can be considered for patients with higher EFI scores, but the expected time is no more than 1 year. For patients with lower EFI scores, it is suggested that ART should be used as early as possible to avoid recurrence of postoperative endometriosis. Patients with poor ovarian storage, severe fallopian tube function damage or older, years of infertility are recommended to directly assist fertility after surgery rather than pregnancy.

Unavoidable, some limitations in this study need to state. This study is a single center study, and there are inevitably biases, such as selection bias. Besides, the size of the study sample is small and it is subject to further study by expanding the sample. Moreover, due to lack of body mass index (BMI) data, this study was unable to include BMI as the variable to analyze. But some studies have reported the effect of BMI on in vitro fertilization in patients with endometriosis, Ferrero et al demonstrate lower BMI is a risk factor for development of endometriosis,^[26] nevertheless, Garalejic et al indicated increase in BMI did not adversely affect the outcome of IVF in non-obese endometriosis patients.^[27] Prospective studies with large number of patients with endometriosis or prospective case-control studies should address these issues and provide more comprehensive counseling of infertile endometriosis patients regarding achievement of optimal BMI prior to IVF with the intention of achievement higher pregnancy rates.

5. Conclusion

Age < 35 years, infertility time < 5 years, secondary infertility, EFI score and ART application were the protective factors of postoperative pregnancy. EFI score had positive significance in predicting and guiding the postoperative pregnancy of patients with endometriosis and infertility. According to EFI score, the pregnancy rate of patients with endometriosis and infertility can

be significantly improved by strict management and active pregnancy program.

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Author contributions

Z. conceived and designed the study, Y. H. and J. G. performed the analysis procedures, Y. H. and C. H. analyzed the results, J. G. contributed analysis tools, Y. H. and S. Z. contributed to the writing of the manuscript. All authors reviewed the manuscript.

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