

Postoperative Pregnancy Outcomes Following Laparoscopic Surgical Management in Women with Stage III/IV Endometriosis: A Single-Center Follow-Up Study

Maya Fujii, Akemi Koshiba*, Fumitake Ito, Izumi Kusuki, Jo Kitawaki, Taisuke Mori

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

Abstract

Objectives: The effects of laparoscopic surgical management in women with stage III/IV endometriosis remain controversial. The standard extent of resection for stage III/IV endometriosis with deep endometriosis to treat endometriosis-associated infertility is debatable. This study aimed to assess the postoperative pregnancy outcomes following a routine surgical intervention for stage III/IV endometriosis patients.

Materials and Methods: Patients with stage III/IV endometriosis who underwent conservative laparoscopic surgery at our hospital between January 2010 and December 2018 were retrospectively analyzed. Statistical analyses were performed to determine the correlations between endometriosis features and postoperative pregnancy outcomes.

Results: Of 256 patients enrolled, 94 wished to conceive. Exclusion criteria: ≥ 40 years, adenomyosis, partners with infertility issues. Finally, 71 women were included. The overall postoperative pregnancy rate was 76.1% ($n = 54$): 49 and five from non-assisted reproductive technology (ART) and ART, respectively. The postoperative pregnancy rate in patients diagnosed with infertility presurgery (40/71) was 70.0% ($n = 28$): 24 (non-ART) and four (ART). The endometriosis fertility index (EFI) score was higher in the pregnant than in the nonpregnant group ($P = 0.03$). The EFI score and surgical score of EFI were higher in the non-ART than in the ART group ($P = 0.04$; $P = 0.02$); in the infertile group, they were higher in the pregnant than in the nonpregnant group ($P = 0.018$; $P = 0.027$).

Conclusion: Our postoperative pregnancy rate after conservative laparoscopic surgery for patients with stage III/IV endometriosis compared favorably with previous reports. EFI was a significant predictor of postoperative pregnancy. Our surgical approach to maintain a high surgical score of EFI might help treat endometriosis-associated infertility.

Keywords: Deep endometriosis, endometriosis, laparoscopic surgery, pregnancy rate

INTRODUCTION

Endometriosis is a common disease that occurs in 5%–10% of reproductive-age women. It is defined as the presence of endometrial tissue outside the uterus, predominantly within the peritoneal cavity, and causes symptoms such as pelvic pain, dysmenorrhea, dyspareunia, and infertility.^[1] Endometriosis is detected in 25%–40% of women with infertility, and up to 50% of women with endometriosis are infertile.^[2-4]

Nevertheless, it remains controversial as to which assisted reproductive technology (ART), or surgical intervention should be primarily used for women diagnosed with endometriosis who wish to conceive. Alternatively, for patients diagnosed with endometriosis (e.g., ovarian endometrioma), conservative laparoscopic surgery to correct the anatomical position of the uterus, ovaries, and fallopian tubes to improve immunological

Article History:

Submitted: 21-Nov-2022

Revised: 08-Dec-2022

Accepted: 22-Dec-2022

Published: 13-Jun-2023

Video Available on: <https://journals.lww.com/gmit>

Access this article online

Quick Response Code:



Website:
<https://journals.lww.com/gmit>

DOI:
10.4103/gmit.gmit_132_22

Address for correspondence:

Dr. Akemi Koshiba,
Department of Obstetrics and Gynecology, Kyoto Prefectural University of
Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kamigyo-ku,
Kyoto 602-8566, Japan.
E-mail: koshiba-a@koto.kpu-m.ac.jp

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Fujii M, Koshiba A, Ito F, Kusuki I, Kitawaki J, Mori T. Postoperative pregnancy outcomes following laparoscopic surgical management in women with stage III/IV endometriosis: A single-center follow-up study. *Gynecol Minim Invasive Ther* 2023;12:153-60.

abnormalities in the pelvis may positively affect postoperative pregnancy outcomes.^[5-8] Furthermore, surgical treatment may improve the symptoms experienced due to endometriosis.^[9] However, some studies have reported a reduction in ovarian reserve due to cystectomy for endometrioma.^[10-13]

The European Society of Human Reproduction and Embryology (ESHRE) guideline recommends hormonal therapy or surgical intervention for endometriosis patients who experience pain.^[9] Furthermore, the ESHRE guideline states that irrespective of surgical intervention, moderate-to-severe endometriosis negatively affects ART outcomes.^[14-16] Conversely, very recently, the first meta-analysis of the effect of surgical interventions for endometriosis, especially deep endometriosis (DE), was published and this revealed a significant benefit of surgery for DE before undergoing ART.^[17] In essence, postoperative fertility outcomes might be greatly influenced by surgical procedures, which should be systematic and standardized. However, surgery performed for endometriosis varies greatly and depends on the severity of endometriosis in each patient, the range of excision in each facility, and/or the skill of the performing surgeon. Accordingly, it is difficult to precisely evaluate the benefits of the surgical procedures.

In this study, we aimed to evaluate the postoperative pregnancy rate following a routine surgical procedure performed at a single facility to determine the efficacy of surgical interventions in severe endometriosis patients experiencing pain and/or infertility due to endometriosis. Herein, we reported the postoperative pregnancy outcomes after conservative laparoscopic surgery for the revised American Society for Reproductive Medicine (r-ASRM)^[18] stage III/IV endometriosis combined with endometrioma cystectomy and DE excision performed by a surgical team at our facility.

MATERIALS AND METHODS

Ethics

This study was reviewed and approved by the Institutional Review Board of our hospital (approval no. ERB-C-1915; approval date: January 7, 2021). Informed consent was obtained through an opt-out method on our hospital’s website. Patients who declined participation were excluded. The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013.^[19]

Study design

Medical records of 256 consecutive women with the American Society for Reproductive Medicine (ASRM) stage III/IV endometriosis who underwent conservative laparoscopic surgery between January 2010 and December 2018 at our hospital were retrospectively reviewed [Figure 1]. To

accurately reflect our institution’s postoperative pregnancy results, this study included patients with common benign comorbidities (e.g., hypertension, autoimmune disease, and thyroid function disorders) and malignant cancers (e.g., breast cancer) before and after laparoscopic surgery. We evaluated the pregnancy rate in all patients who wished to conceive. We excluded three women aged ≥ 40 years and eight women whose male partners were infertile, defined as sperm abnormalities based on seminal analysis according to the World Health Organization (Geneva) criteria.^[20] In addition, we excluded 12 patients who had adenomyosis or a history of adenomyosis excision as it might be an independent factor associated with infertility.^[21,22] As a subsequent analysis, we evaluated postoperative pregnancy outcomes only in patients who were diagnosed with infertility before surgery [Figure 2]. We defined patients who failed to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse as infertile. Furthermore, at the time of surgery, we evaluated age, body mass index (BMI), gravidity and parity, and surgical findings, including the r-ASRM score, endometriosis fertility index (EFI), size of the ovarian endometrioma, existence of bilateral ovarian endometriomas, *cul-de-sac* obliteration (CDSO), and DE. We simultaneously evaluated our surgical intervention based on DE excision. DE excision was defined as follows: complete opening of the *cul-de-sac*, excision of the thickened parts of the uterosacral ligament (USL), detachment of all adhesions due to DE, excision of all visible DE lesions, and visualization of the hinge of a uterine manipulator. Cases that did not meet the criteria mentioned above were defined as cases of residual DE.

All pregnant patients were classified into two groups based on the treatment type: non-ART group, which included those

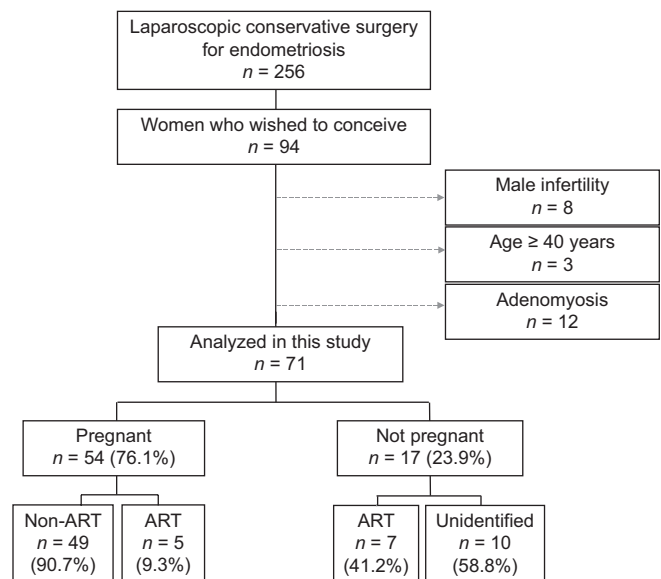


Figure 1: Flow chart of the study

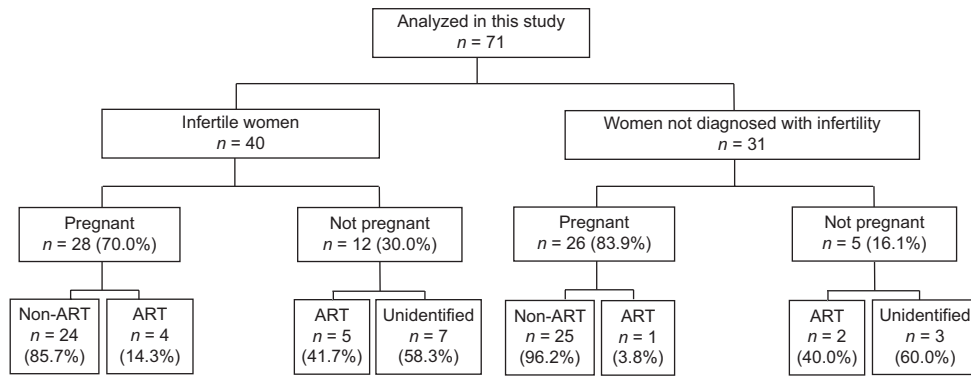


Figure 2: Flow chart of infertile patients

who had natural pregnancy and/or intrauterine insemination, and ART group, which included cases in which standard techniques of *in vitro* fertilization and intracytoplasmic sperm injection followed by fresh or frozen-thawed embryo-transfer were performed. None of the patients used donated gametes.

Surgical indication policy

We proposed conservative laparoscopic surgery for patients with pain symptoms (e.g., dysmenorrhea, chronic pelvic pain, and dyspareunia) due to endometriosis (endometrioma). In addition, we suggested surgical interventions to patients who had an endometrioma that appeared to be enlarging in size. For patients with endometriomas not associated with pain who wished to conceive, we recommended non-ART treatment for 6 months before suggesting surgery or ART treatment; if a patient did not conceive through non-ART treatment in 6 months, we subsequently recommended surgery or ART treatment. The above policy was applied to women in their 20s and 30s, but we recommended ART treatment immediately for women in their forties, except for those who refused ART treatment.

Surgical procedures

Before study initiation, the following standard procedures of conservative laparoscopic surgery for endometriosis were prepared [Figure 3 and Supplementary Video 1]. All surgeries were performed using the standard operative method for excision of endometriosis lesions, including DE. First, all laparoscopic findings were evaluated and recorded preoperatively [Figure 3a]. Chromotubation using indigo carmine was performed to evaluate tubal patency. The adhesions between the posterior surface of the ovary, posterior surface of the broad ligament of the uterus, and pelvic organs were completely detached [Figure 3b]. Afterward, the retroperitoneum at the ovarian fossa was opened, the ureter and hypogastric nerves in the broad ligament of the uterus were separated from the lesions and fibrotic tissues to avoid damaging them, and the pararectal space between the USL and rectum was opened [Figure 3c]. Subsequently, we proceeded to the caudal side and opened the rectovaginal space [Figure 3d].

The thickened DE of the rectovaginal septum and USL was excised [Figure 3e]. Furthermore, the DE was excised to expose the hinge of the uterine manipulator that served as an indicator of the posterior vaginal fornix [Figure 3f-h]. With this method, the posterior cervical region and USL were separated from the rectum [Figure 3h], CDSO was completely and safely opened, and DE was excised firmly, thus avoiding ureteral and hypogastric nerve damage [Figure 3i]. In addition, DE lesions in other organs, such as the intestinal bowel, bladder, and ureter, were excised. Severe DE lesions that caused ileus, hydronephrosis, and ureteral obstruction were also noted. However, DE resection was not performed in cases with invasion of other organs requiring bowel resection or urinary tract alteration. In this study, all surgeries were performed by a single surgical team that followed the same procedure described above at a single facility.

Statistical analysis

Statistical analyses were performed using JMP software version 7.0 (SAS Institute Inc., Cary, NC, USA). Categorical variables were compared using Student's *t*-test and the χ^2 test to determine the correlations between factors and infertility treatment outcomes. Cumulative pregnancy rate analyses were performed using Graphpad Prism software version 5.04 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com) according to the Kaplan–Meier method. Multivariate analysis was performed using EZR, which is a graphical user interface for R software. More precisely, it is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics, according to the cox proportional hazards analysis. A $P < 0.05$ was considered statistically significant.

RESULTS

Pregnancy rates and patterns

Of the 256 patients enrolled, 94 women wished to conceive [Figure 1]. Patients whose male partners had infertility issues ($n = 8$), those aged ≥ 40 years ($n = 3$), and those who had adenomyosis or a history of adenomyosis

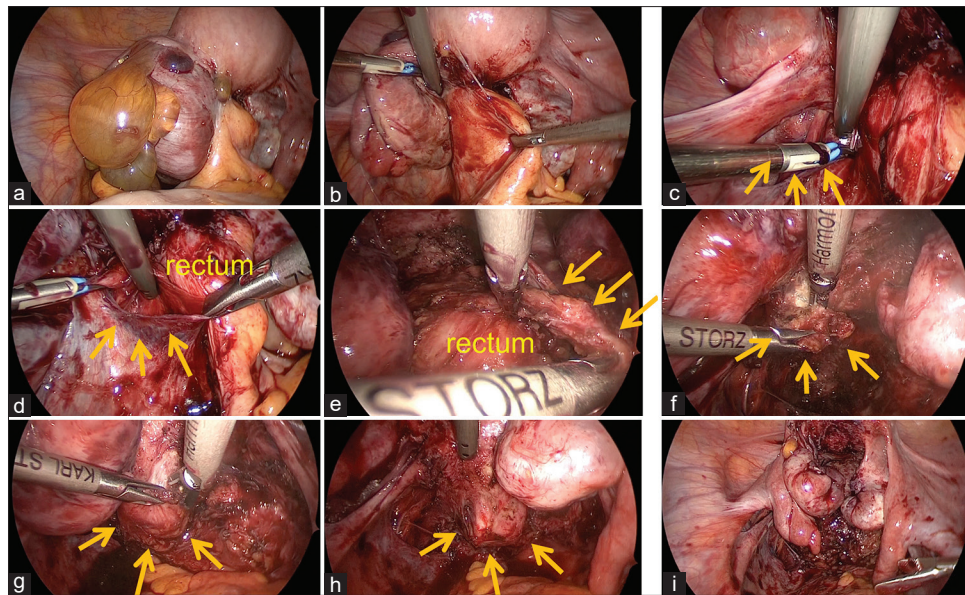


Figure 3: Our conservative laparoscopic surgical procedure for endometriosis. (a) Observation and recording of surgical findings under a laparoscope. (b) Complete detachment of adhesion between the posterior surface of the ovary and the posterior broad ligament of the uterus/pelvic organs. (c) Opening of the retroperitoneum between the ligamentum infundibulum pelvicum and the USL and visual recognition of the ureter (arrow) and hypogastric nerve. (d) Opening of the retroperitoneum of the pararectal space (arrow) between the USL and the rectum. (e) Excision of the thickened DE of the rectovaginal septum (arrow) using a rectal probe to identify the contour of the rectum. (f) Excision of the thickened USL (arrow) with DE. (g) Additional DE excision to make the hinge of a uterine manipulator (arrow) visible as an indicator for the posterior vaginal fornix. (h) Complete opening of the CDSO (arrow). (i) Normalization of the anatomical positional relationship of the uterus, ovaries, and fallopian tubes. USL: Uterosacral ligament, DE: Deep endometriosis, CDSO: *Cul-de-sac* obliteration. <http://www.apagemit.com/page/video/show.aspx?num=>

excision ($n = 12$) were excluded. Finally, 71 women were included in the analysis. The overall postoperative pregnancy rate for these 71 patients was 76.1% ($n = 54$). Of the 54 pregnant patients, 49 (90.7%) conceived through non-ART interventions, whereas five (9.3%) conceived through ART treatment. Overall, 17 (23.9%) patients did not conceive, seven of whom underwent ART treatment. Ten patients who could not be followed up were regarded as not pregnant.

Characteristics and surgical findings of all patients

Patient characteristics are presented in Table 1. The mean age at surgery was 30.4 years and 31.5 years in the pregnant and nonpregnant groups, respectively. No significant differences in age, BMI, or pregnancy history were identified between the two groups. The EFI score was significantly higher in the pregnant group than in the nonpregnant group ($P = 0.03$). There were no significant differences in other operative findings (i.e., r-ASRM score, size of the ovarian endometrioma, existence of bilateral ovarian endometrioma, CDSO, DE, or residual DE) between the two groups. No severe complications such as intraoperative or postoperative massive bleeding that required blood transfusion and abscess formation that required re-operation were observed in any of the eligible cases.

Pregnancy patterns and surgical findings in all pregnant patients

Of the 54 pregnant patients, 49 (90.7%) conceived through non-ART interventions, whereas five patients (9.3%) conceived

through ART treatment [Table 1]. The two groups did not significantly differ with respect to age, BMI, or pregnancy history. The EFI score and the surgical score of EFI were significantly higher in the non-ART group than in the ART group ($P = 0.04$ and $P = 0.02$). There were no significant differences in the ASRM score, size of the ovarian endometrioma, existence of bilateral ovarian endometriomas, CDSO, or DE between the two groups. DE lesions were observed in 23/49 (46.9%) patients of the non-ART group and 4/5 (80.0%) patients of the ART group. There were seven (30.4%) residual DE cases in the non-ART group and four (100%) in the ART group, which was a significant difference ($P = 0.008$).

Pregnancy rates and patterns of infertile patients

Of the 71 patients, 40 (56.3%) women experienced infertility and the postoperative pregnancy rate was 70.0% ($n = 28$) [Figure 2]. Of the 28 pregnant patients, 24 (85.7%) conceived through non-ART interventions, whereas four (14.3%) conceived through ART treatment. Twelve (30.0%) patients did not conceive, five of whom underwent ART treatment. Seven patients who could not be followed up were regarded as not pregnant.

Characteristics and surgical findings of the infertile patients

Patient characteristics are presented in Table 2. The mean age at surgery was 32.3 and 32.6 years in the pregnant and nonpregnant groups, respectively. No significant differences

Table 1: Characteristics and surgical findings of the patients

	Pregnant (n=54)			Not pregnant (n=17)	P (pregnant vs. not pregnant)	P (non-ART vs. ART)
	Total	Non-ART (n=49)	ART (n=5)			
Age at surgery (years) (n)*	30.4±4.3	30.3±4.4	32.2±2.7	31.5±4.3	0.18	0.18
<30	20	19	1	7	-	-
30-35	25	21	4	5	-	-
36-40	9	9	0	5	-	-
BMI (kg/m ²)*	21.5±3.7	21.6±3.8	20.0±2.2	20.3±2.3	0.12	0.19
Multigravida (n)	10	10	0	2	0.51	0.26
Multipara (n)	5	5	0	2	0.76	0.45
r-ASRM*	53.4±30.8	53.3±31.9	54.6±19.8	54.0±28.9	0.47	0.46
EFI (historical/surgical score)*	6.5±0.8 (3.9±0.5/2.6±0.7)	6.7±0.7 (3.9±0.5/2.7±0.6)	6.0±1.0 (4.0±0.2/0±1.0)	5.9±1.5 (3.8±0.5/2.2±1.0)	0.03 (0.28/0.09)	0.04 (0.34/0.02)
Ovarian endometrioma (mm)*	53.5±18.3	53.7±18.4	52.0±19.9	62.7±40.8	0.09	0.42
Bilateral ovarian endometriomas, n (%)	22 (40.7)	19 (38.8)	3 (60.0)	6 (35.3)	0.68	0.35
CDSO, n (%)	19 (35.2)	17 (34.7)	2 (40.0)	7 (41.2)	0.65	0.81
DE, n (%)	27 (50.0)	23 (46.9)	4 (80.0)	11 (64.7)	0.28	0.15
Residual DE, n (%)	11/27 (40.7)	7/23 (30.4)	4/4 (100)	5/11 (45.5)	0.79	0.008

*Mean±SD. r-ASRM: Revised American Society for Reproductive Medicine, EFI: Endometriosis fertility index, CDSO: *Cul-de-sac* obliteration, DE: Deep endometriosis, SD: Standard deviation, ART: Assisted reproductive technology, BMI: Body mass index

in age, BMI, pregnancy history, or preoperative infertility period were identified between the two groups. The EFI score and surgical score of EFI were significantly higher in the pregnant group than in the nonpregnant group ($P = 0.018$ and $P = 0.027$, respectively). The Cox proportional hazards analysis of age, r-ASRM score, EFI score, and the existence of bilateral ovarian endometriomas presented in Table 3 showed that the only variable that achieved statistical significance was the EFI score ($P = 0.012$). Furthermore, there were no significant differences in the other operative findings (i.e., size of the ovarian endometrioma, CDSO, DE, or residual DE) between the two groups.

Pregnancy patterns and surgical findings in infertile patients

Of the 28 pregnant patients, 24 (85.7%) conceived through non-ART treatment, whereas four (14.3%) conceived through ART treatment [Figure 2]. No significant differences in age, BMI, pregnancy history, or preoperative infertility period were identified between the two groups [Table 2]. The r-ASRM score in the ART group was significantly higher than that in the non-ART group ($P = 0.044$). Furthermore, the EFI score and surgical score of EFI were significantly higher in the non-ART group than in the ART group ($P = 0.028$ and $P = 0.005$, respectively). The existence of bilateral ovarian endometriomas in the ART group was significantly higher than in the non-ART group ($P = 0.047$). There were no significant differences in the size of the ovarian endometrioma, existence of CDSO, DE, or residual DE between the two groups. The cumulative probability of

conception in the 40 patients with infertility was 39% and 46%, at 6 and 12 months, respectively [Figure 4], whereas the cumulative probability of 28 patients who were diagnosed with infertility and conceived through non-ART was 50% at 5 months.

DISCUSSION

In this study, of 71 patients with ASRM stage III/IV endometriosis, 54 (76.1%) were conceived after our conservative laparoscopic surgery. When the analysis was limited to infertile patients, 28 (70.0%) conceived after our conservative laparoscopic surgery. The pregnancy rates after laparoscopic surgery for stage III/IV endometriosis have been previously reported, but these outcomes vary with each report. For example, Marrs found that the pregnancy rate was 30%^[23] and Beretta *et al.*, 67%^[24] after laparoscopic surgery for stage III/IV endometriosis. However, these pregnancy rates might be overestimated because of selection and publication bias, and those studies excluded patients who could not be followed up.^[25] Furthermore, Leonardi *et al.* reported that laparoscopic surgery for endometriosis might improve overall pain levels but had little or no effect on fertility-related or adverse outcomes.^[26] The postoperative pregnancy rate in the current study was 76.1%, although we included patients who could not be followed up as not pregnant. Even when the analysis was limited to infertile women, the postoperative pregnancy rate was 70.0%. This finding is quite compatible with pregnancy rates reported previously.^[23-25] In addition, a study by Olive *et al.* indicated that women with stage III endometriosis had a pregnancy

Table 2: Characteristics and surgical findings of the infertile patients

	Pregnant (n=28)			Not pregnant (n=12)	P (pregnant vs. not pregnant)	P (non-ART vs. ART)
	Total	Non-ART (n=24)	ART (n=4)			
Age at surgery (years) (n)*	32.3±3.1	32.2±3.2	33.0±2.4	32.6±4.4	0.39	0.32
<30	4	4	0	4	-	-
30-35	18	14	4	3	-	-
36-40	6	6	0	5	-	-
BMI (kg/m ²)*	20.9±2.9	21.2±3.0	19.4±2.1	20.6±2.1	0.37	0.14
Multigravida (n)	5	5	0	2	0.92	-
Multipara (n)	3	3	0	2	0.60	-
Preoperative infertility period	17.8±15.7	18.5±16.2	12.0±12.0	21.1±21.8	0.31	0.26
r-ASRM*	48.3±28.1	46.0±29.5	61.8±13.6	53.2±30.9	0.31	0.044
EFI (historical/surgical score)*	6.4±0.8 (3.9±0.6/2.5±0.7)	6.6±0.7 (3.8±0.6/2.8±0.5)	5.7±0.9 (4.0±0/1.7±0.9)	5.4±1.5 (3.8±0.6/1.8±0.9)	0.018 (0.31/0.027)	0.028 (0.31/0.005)
Ovarian endometrioma (mm)*	51.7±19.2	52.2±19.2	49.0±21.7	49.4±20.1	0.37	0.38
Bilateral ovarian endometrioma, n (%)	9 (32.1)	6 (25.0)	3 (75.0)	5 (41.7)	0.56	0.047
CDSO, n (%)	7 (25.0)	5 (17.9)	2 (50.0)	5 (23.8)	0.29	0.21
DE, n (%)	14 (50.0)	10 (41.7)	4 (100)	8 (66.7)	0.33	0.15
Residual DE, n (%)	8/14 (57.1)	4/10 (40.0)	4/4 (100)	3/8 (37.5)	0.38	0.11

*Mean±SD. r-ASRM: Revised American Society for Reproductive Medicine, EFI: endometriosis fertility index, CDSO: *Cul-de-sac* obliteration, DE: Deep endometriosis, SD: Standard deviation, ART: Assisted reproductive technology, BMI: Body mass index

Table 3: Independent predictive factors of postoperative fertility (Cox's model) in the patients with infertility

Risk factor	Pregnant (n=28)	Not pregnant (n=12)	HR	HR 95% CI	P
Age at surgery (years)* (n)	32.3±3.1	32.6±4.4	2.33	1.00-2.32	0.051
<30 (n)	4	4	-	-	-
30-35 (n)	18	3	-	-	-
36-40 (n)	6	5	-	-	-
r-ASRM*	48.3±28.1	53.2±30.9	1.01	0.99-1.03	0.30
EFI*	7.29±1.0	7.08±1.1	2.07	1.17-3.65	0.012
Bilateral ovarian endometrioma, n (%)	9 (32.1)	5 (41.7)	0.51	0.17-1.51	0.22

*Mean±SD. r-ASRM: Revised American Society for Reproductive Medicine, EFI: Endometriosis fertility index, SD: Standard deviation, HR: Hazard ratio, CI: Confidence interval

rate of only 25%, and no pregnancies occurred with stage IV endometriosis on expectant management without surgical intervention.^[27] The discrepancy in pregnancy outcomes after surgical intervention in the previous studies could be caused by differences in the clinical parameters, surgical procedures, and intraoperative status.^[25,28,29] Most of the original research on pregnancy outcomes after surgery for endometriosis has been reported more than 10 years ago. Recent advances in laparoscopic surgical equipment and techniques have made it possible to perform surgery not only merely for endometrioma but also for DE. A strength of this study was that all surgeries were performed by a single surgical team, following a routine protocol. Thus, we consider that our surgical intervention did not negatively influence the postoperative pregnancy outcomes and was helpful for patients experiencing pain due to endometriosis.

According to the ESHRE guidelines, there is no strong evidence to support surgical intervention to improve the spontaneous pregnancy rate in women with DE lesions.

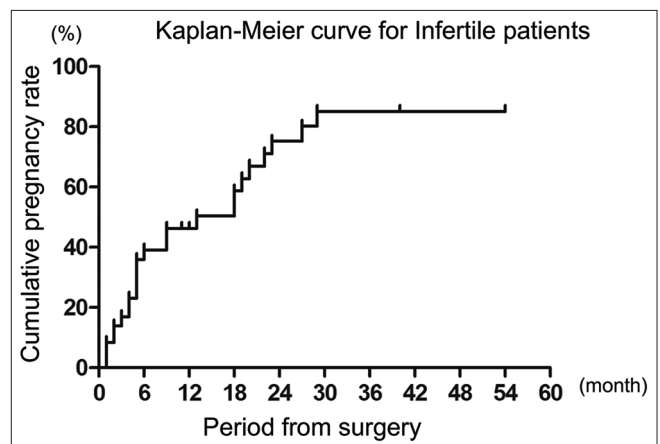


Figure 4: The cumulative pregnancy rate of infertile women by KM analysis. The cumulative probability of conception in the 40 patients who were diagnosed with infertility before surgery was 39% and 46%, at 6 and 12 months, respectively. KM: Kaplan–Meier

Furthermore, the guidelines state that ART should be performed irrespective of the severity of endometriosis,

specifically to shorten the delay in conception.^[30-32] In contrast, some studies have reported that the excision of DE lesions was associated with a higher pregnancy rate after surgery.^[17,28] Furthermore, other studies showed that DE lesions negatively influenced the artificial reproductive outcome in women with infertility.^[29,33] In our study, DE excision was tried in 23/49 patients who conceived through non-ART treatment, but residual DE remained in seven patients (30.4%). Conversely, DE excision was tried in 4/4 of patients who conceived through ART treatment, and residual DE remained in all four cases. These findings suggest that severe endometriosis patients might likely conceive without ART when there is no residual DE after surgery. In addition, infertile women who conceived without ART were pregnant after a median of 5 months following the surgical intervention. Therefore, when patients are unable to conceive early after surgery, it is necessary to consider the transition to ART. We also should promptly explain to the patients that DE lesions might remain.

Alternatively in the analysis limited to infertile patients, there were no significant differences in the r-ASRM score and existence of bilateral endometriomas between the pregnant and nonpregnant groups. Furthermore, we confirmed that EFI is a useful predictor of the establishment of a postoperative pregnancy, particularly in infertile women. Our operative principle is based on the careful dissection of endometriotic adhesions, normalization of the anatomic position of the fallopian tubes, the fimbria, and the ovary, and cystectomy to minimize the damage to the normal ovaries. These procedures contribute to maintaining a high surgical score of EFI. However, it has not been reported whether EFI is determined by the status of endometriosis itself or whether it differs depending on the surgical technique and surgeon. Future studies are needed to address the same. Residual DE seems to be a factor that might make postoperative pregnancy with non-ART difficult, leading to the requirement of ART. However, in this study, the ART group might have been too few in number to obtain a correct analysis, and further evaluation is need on a larger scale in the future.

This study's limitation was the inclusion of a small sample size and single-center setting. In addition, the appropriate DE excision range was not examined. In this study, DE resection was not performed in cases with the invasion of other organs requiring bowel resection or urinary tract alteration. On the other hand, some studies have reported that the excision of endometriosis with bowel resection appeared to offer better results in terms of postoperative fertility.^[29-35] Therefore, the appropriate range of DE excision, as the best surgical procedure, remains controversial; thus, further studies are needed to address this issue.

CONCLUSIONS

The pregnancy rate after our conservative surgical procedure for stage III/IV endometriosis patients was favorable and comparable to those reported by previous studies. EFI was a significant predictor of postoperative pregnancy, particularly in infertile women and our surgical approach to maintain a high surgical score of EFI might help treat endometriosis-associated infertility.

Acknowledgments

The authors would like to thank Editage for providing the English language support and for proofreading this article.

Financial support and sponsorship

The study is supported in part by Grants-in-Aid for Scientific Research (19K18648) from the Ministry of Education, Culture, Sports, Science, and Technology (Japan).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Giudice LC, Kao LC. Endometriosis. *Lancet* 2004;364:1789-99.
- Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, *et al.* A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod* 2016;31:1475-82.
- Lin YH, Chen YH, Chang HY, Au HK, Tzeng CR, Huang YH. Chronic niche inflammation in endometriosis-associated infertility: Current understanding and future therapeutic strategies. *Int J Mol Sci* 2018;19:2385.
- Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: A systematic review and meta-analysis. *Hum Reprod Update* 2015;21:809-25.
- Vallvé-Juanico J, Houshdaran S, Giudice LC. The endometrial immune environment of women with endometriosis. *Hum Reprod Update* 2019;25:564-91.
- Holoch KJ, Lessey BA. Endometriosis and infertility. *Clin Obstet Gynecol* 2010;53:429-38.
- Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, *et al.* Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev* 2014;3:CD011031.
- de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: Pathophysiology and management. *Lancet* 2010;376:730-8.
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, *et al.* ESHRE guideline: Management of women with endometriosis. *Hum Reprod* 2014;29:400-12.
- Kitajima M, Khan KN, Harada A, Taniguchi K, Inoue T, Kaneuchi M, *et al.* Association between ovarian endometrioma and ovarian reserve. *Front Biosci (Elite Ed)* 2018;10:92-102.
- Nirgianakis K, Ma L, McKinnon B, Mueller MD. Recurrence patterns after surgery in patients with different endometriosis subtypes: A long-term hospital-based cohort study. *J Clin Med* 2020;9:496.
- Muzii L, Di Tucci C, Di Felicianantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: A systematic review and meta-analysis. *Hum Reprod* 2014;29:2190-8.
- Younis JS, Shapso N, Fleming R, Ben-Shlomo I, Izhaki I. Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: A systematic review and meta-analysis. *Hum Reprod Update* 2019;25:375-91.
- Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and

- intrauterine insemination. *Fertil Steril* 2006;86:566-71.
15. Bourdon M, Raad J, Dahan Y, Marcellin L, Maignien C, Even M, *et al.* Endometriosis and ART: A prior history of surgery for OMA is associated with a poor ovarian response to hyperstimulation. *PLoS One* 2018;13:e0202399.
 16. Prefumo F, Rossi AC. Endometriosis, endometrioma, and ART results: Current understanding and recommended practices. *Best Pract Res Clin Obstet Gynaecol* 2018;51:34-40.
 17. Casals G, Carrera M, Domínguez JA, Abrão MS, Carmona F. Impact of surgery for deep infiltrative endometriosis before *in vitro* fertilization: A systematic review and meta-analysis. *J Minim Invasive Gynecol* 2021;28:1303-12.e5.
 18. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67:817-21.
 19. World Medical Association. World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
 20. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, *et al.* World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 2010;16:231-45.
 21. Bourdon M, Santulli P, Oliveira J, Marcellin L, Maignien C, Melka L, *et al.* Focal adenomyosis is associated with primary infertility. *Fertil Steril* 2020;114:1271-7.
 22. Vercellini P, Consonni D, Barbara G, Buggio L, Frattaruolo MP, Somigliana E. Adenomyosis and reproductive performance after surgery for rectovaginal and colorectal endometriosis: A systematic review and meta-analysis. *Reprod Biomed Online* 2014;28:704-13.
 23. Marrs RP. The use of potassium-titanyl-phosphate laser for laparoscopic removal of ovarian endometrioma. *Am J Obstet Gynecol* 1991;164:1622-6.
 24. Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: Cystectomy versus drainage and coagulation. *Fertil Steril* 1998;70:1176-80.
 25. Vercellini P, Somigliana E, Viganò P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility: A pragmatic approach. *Hum Reprod* 2009;24:254-69.
 26. Leonardi M, Gibbons T, Armour M, Wang R, Glanville E, Hodgson R, *et al.* When to do surgery and when not to do surgery for endometriosis: A systematic review and meta-analysis. *J Minim Invasive Gynecol* 2020;27:390-407.e3.
 27. Olive DL, Stohs GF, Metzger DA, Franklin RR. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. *Fertil Steril* 1985;44:35-41.
 28. Centini G, Afors K, Murtada R, Argay IM, Lazzeri L, Akladios CY, *et al.* Impact of laparoscopic surgical management of deep endometriosis on pregnancy rate. *J Minim Invasive Gynecol* 2016;23:113-9.
 29. Stepniewska A, Pomini P, Bruni F, Mereu L, Ruffo G, Ceccaroni M, *et al.* Laparoscopic treatment of bowel endometriosis in infertile women. *Hum Reprod* 2009;24:1619-25.
 30. Bendifallah S, Roman H, Mathieu d'Argent E, Touleimat S, Cohen J, Darai E, *et al.* Colorectal endometriosis-associated infertility: Should surgery precede ART? *Fertil Steril* 2017;108:525-31.e4.
 31. Bendifallah S, Roman H, Rubod C, Leguevaque P, Watrelot A, Bourdel N, *et al.* Impact of hospital and surgeon case volume on morbidity in colorectal endometriosis management: A plea to define criteria for expert centers. *Surg Endosc* 2018;32:2003-11.
 32. Roman H. Endometriosis surgery and preservation of fertility, what surgeons should know. *J Visc Surg* 2018;155 Suppl 1:S31-6.
 33. Khan S, Lee CL. Treating Deep Endometriosis in Infertile Patients before Assisted Reproductive Technology. *Gynecol Minim Invasive Ther*. 2021;10:197-202. doi: 10.4103/GMIT.GMIT_154_20. PMID: 34909375; PMCID: PMC8613499.
 34. Khan S, Lee CL. Treating deep endometriosis in infertile patients before assisted reproductive technology. *Gynecol Minim Invasive Ther* 2021;10:197-202.
 35. Roman H, Chanavaz-Lacheray I, Ballester M, Bendifallah S, Touleimat S, Tuech JJ, *et al.* High postoperative fertility rate following surgical management of colorectal endometriosis. *Hum Reprod* 2018;33:1669-76.