Thieme

Laparoscopic Endometriosis Surgery in Patients with Infertility: Identifying Surgical and Non-Surgical Variables Affecting Postoperative Pregnancy. Long-term Follow-up in a University Endometriosis Center

Laparoskopische Endometriose-Chirurgie bei Patientinnen mit Infertilität: chirurgische und nicht chirurgische Variablen, die sich auf eine postoperative Schwangerschaft auswirken. Langzeit-Nachbeobachtung in einem universitären Endometriose-Zentrum

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ABSTRACT

Background
Endometriosis is a disease which affects the quality of life and fertility of many young women. Choosing the right time for surgery is important for the outcome of patients. We evaluated the surgical variables affecting postoperative pregnancy rates.

Method
This study is a retrospective analysis of women treated for endometriosis in Frankfurt University Hospital between 2007 and 2017. A total of 695 patients underwent laparoscopic surgery, of whom 125 patients fulfilled the inclusion criteria of wanting to have a child for more than one year. Finally, 102 patients (82%) with surgery and infertility were followed up for 70 months.

Results
We found a cumulative pregnancy rate of 69.6% after 38 months in our patients. The duration of infertility before surgery had a significant effect on postoperative pregnancy rates. There was no significant difference between the different kinds of surgical techniques, but complete treatment of all visible lesions significantly increased the chance of pregnancy (hazard ratio 2.2). Repeated abdominal operations reduced the chance of postoperative pregnancy and prolonged the time to pregnancy.

Conclusions
In patients with endometriosis and infertility, both laparoscopic surgery with complete resection of all visible lesions and the timing of surgery are important to achieve pregnancy. Early intervention with careful planning of the

operation is critical. It is important to avoid repeated operations to achieve the best results regarding pregnancy.

ZUSAMMENFASSUNG

Hintergrund
Endometriose ist eine Krankheit, die sich auf die Lebensqualität und Fertilität vieler junger Frauen auswirkt. Die Wahl des richtigen Zeitpunkts für den chirurgischen Eingriff ist wichtig für das Outcome. Wir haben die chirurgischen Variablen, die sich auf eine postoperative Schwangerschaft auswirken, evaluiert.

Methode
Es handelt sich bei dieser Studie um eine retrospektive Analyse von Patientinnen, die im Universitätskrankenhaus Frankfurt am Main zwischen 2007 und 2017 behandelt wurden. Insgesamt haben sich 695 Patientinnen einer laparoskopischen Operation unterzogen. Das Einschlusskriterium, ein unerfüllter Kinderwunsch seit mehr als einem Jahr, wurde von 125 Patientinnen erfüllt. Schließlich wurden 102 operierten Patientinnen (82 %) mit Infertilität über 70 Monate nachbeobachtet.

Ergebnisse
In unserer Patientinnenkohorte betrug die kumulative Schwangerschaftsrate 69,6 % nach 38 Monaten. Die Dauer der Infertilität vor dem operativen Eingriff hatte eine signifikante Auswirkung auf eine postoperative Schwangerschaft. Es gab keine signifikanten Unterschiede zwischen den verschiedenen chirurgischen Techniken, aber eine vollständige Resektion aller sichtbaren Endometrioseläsionen hatte eine signifikante Auswirkung auf die Wahrscheinlichkeit einer Schwangerschaft (Risikoquotient 2,2). Wiederholte abdominale Operationen reduzierten die Chance einer postoperativen Schwangerschaft und verlängerten die Zeit bis zum Eintritt einer Schwangerschaft.

Schlussfolgerungen
Bei Patientinnen mit Endometriose und Infertilität sind sowohl ein laparoskopischer Eingriff mit vollständiger Resektion aller sichtbaren Läsionen als auch der Zeitpunkt des Eingriffs wichtig für den Eintritt einer Schwangerschaft. Eine frühe Intervention mit sorgfältiger Planung der Operation ist unerlässlich. Um die besten Ergebnisse für eine Schwangerschaft zu erzielen, ist es wichtig, dass wiederholte chirurgische Eingriffe vermieden werden.

Introduction

Endometriosis is defined by the presence of endometrial glands and stroma outside the uterus, which lead to chronic inflammation [1]. Despite extensive basic and clinical research, the exact pathogenesis of the disease remains controversial [2]. Although in recent years there has been less emphasis on the surgical diagnosis of endometriosis, laparoscopic surgery is still the most effective intervention, especially in patients with endometriosis and infertility [3]. As a surgical intervention is required to obtain the histological evidence to confirm disease, the true prevalence of endometriosis remains uncertain. The prevalence is believed to range from 2 % to 11 % in asymptomatic women and 5 %–50 % in infertile women [4].

A reproducible and well-organized classification for this disease is an issue of concern, not only to clarify communications among physicians but also to standardize the optimal treatment strategy. The revised American Society for Reproductive Medicine classification (rASRM) is a numerical severity score, based on the visual findings at laparoscopy [5]. Despite some disadvantages, the rASRM classification is easy to use, is accepted globally, and has been widely used in recent years and in different studies [6].

Endometriosis is a disease that not only causes pelvic pain due to chronic inflammation and decreases quality of life but also negatively impacts fertility. It significantly lowers the chance of spontaneous conception as well as conception after assisted reproductive treatment (ART) [7]. Mechanisms that affect fertility in patients with endometriosis are multifactorial: possible pathophysiological factors leading to infertility are inflammatory changes of the peritoneal fluid, reduced functional ovarian tissue, and endometrial changes [8].

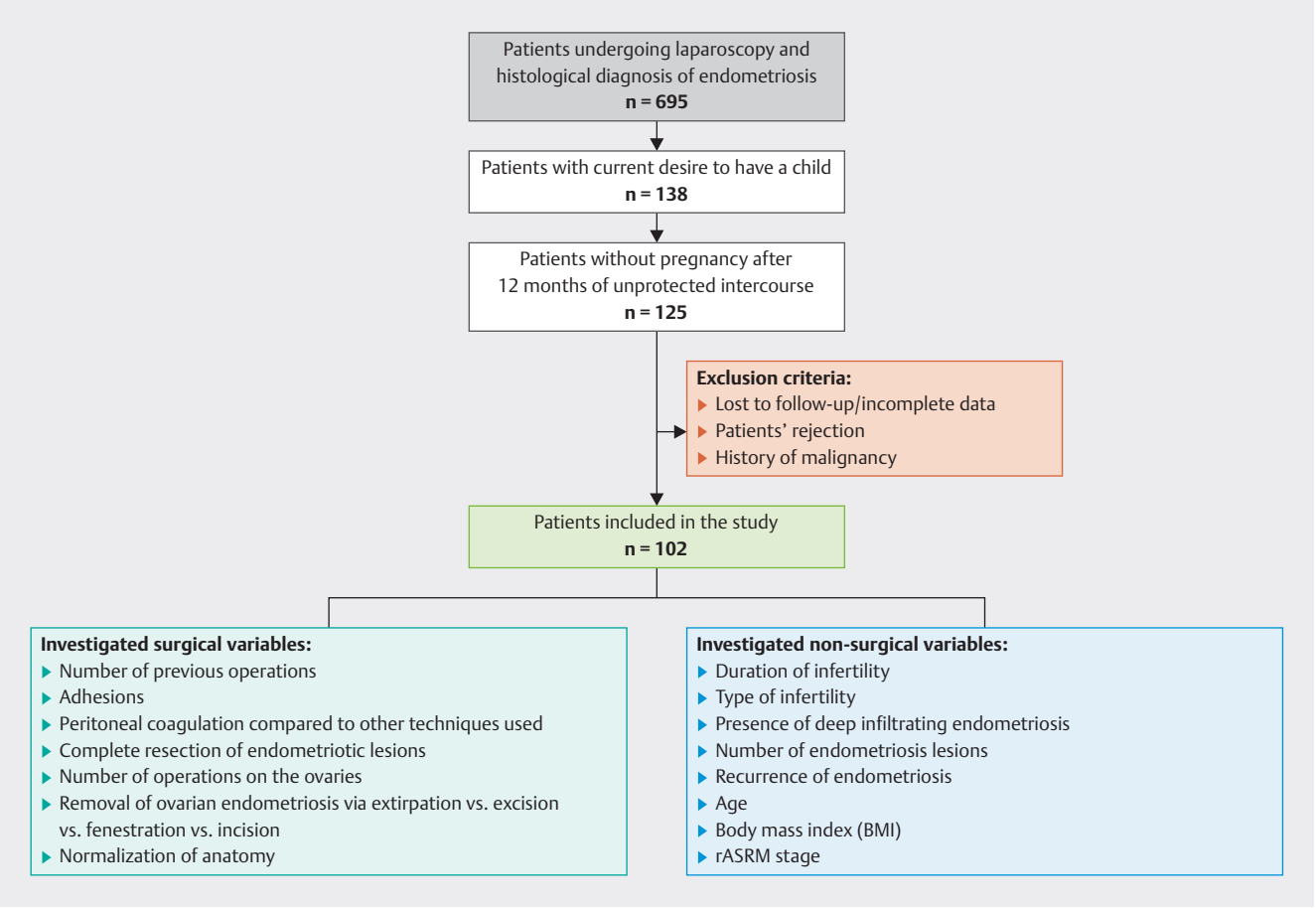
The role of laparoscopic surgery and the surgical variables influencing fertility outcomes in women who wish to have a child are still the subject of research [2]. Surgical methods are mostly based on expert consensus [3]. Laparoscopic surgery aims to destroy or remove all visible lesions, repair the damage to organs, and restore the normal anatomy. However, these interventions do not always improve fertility. Therefore, the timing of surgery and the right choice of surgical method can be very important [9].

As the options to carry out randomized controlled trials are limited due to ethical considerations, the surgical variables influencing the outcomes of endometriosis patients with infertility are still being evaluated. Even though collaboration between reproductive medicine centers and endometriosis centers is important [10], it is still difficult to predict potential fertility and pregnancy rates of infertile endometriosis patients. In this retrospective study with a long-term follow-up of 70 months we aimed to evaluate surgical and non-surgical variables which may affect pregnancy rates after surgery.

Material and Methods

Ethical approval and informed consent for the study

This study was approved by the Ethics Committee of Frankfurt am Main University Hospital, (approval no. 19–487). Informed verbal consent was obtained from all patients at their follow-up interviews.



▶ **Fig. 1** Patient selection process and investigated surgical and non-surgical variables.

Subject selection and variables

The data of 695 patients who underwent laparoscopic surgery for endometriosis between January 2007 and December 2017 at Frankfurt am Main University Hospital in Germany were reviewed. Laparoscopic interventions consisted of visual inspection of lesions and histological confirmation of endometriosis (according to a prospectively updated database of patients with endometriosis). 102 patients with infertility (no pregnancy after 12 months of regular unprotected intercourse) who wished to conceive directly after surgery were registered and followed up for a mean of 70 months (range 36–197 months). The exclusion criteria were:

1. previous or current malignancies;
2. concomitant benign diseases which could affect fertility such as premature ovarian failure, uterine fibroids, and reproductive malformations;
3. current infections such as chlamydia and/or
4. any incomplete clinical or follow-up data.

The following variables were collected and analyzed to obtain the patient's history and intraoperative endometriosis status: type of endometriosis (external genital endometriosis and extragenital endometriosis), presence of deep infiltrating endometriosis (defined as one or more endometriotic lesions infiltrating deeper than 5 mm as described in the surgical report or revealed on ultrasound/MRI), rASRM stage, location of endometriosis/involved pelvic organs (one or both ovaries, fallopian tubes, uterus, bowel), adhesion situation (extensive and/or non-extensive), number of previous operations in general and due to endometriosis. It is important to mention that adhesions with clear vascularization or strongly attached organs, where lysis was only possible by sharp dissection, were defined as extensive adhesions. Filmy adhesions or adhesions where blunt dissection could be carried out easily were defined as non-extensive adhesions. With regards to the surgical intervention, the following variables were considered and evaluated: type of surgical treatment of the ovaries including cyst extirpation (complete removal), cyst excision (partly removal), fenestration, and coagulation, and surgical treatment of other endometriotic lesions (resection, partial peritonectomy, coagulation). The follow-up data was collected using questionnaires which were completed during consultation interviews. In these interviews we also collected patients' data including age, BMI, duration of infertility, primary vs. secondary infertility, symptoms of endometriosis, deliveries and live births, and treatment with ART. The patient selection process and the analyzed surgical variables are shown in ▶ **Fig. 1**.

▶**Table 1** Patient characteristics and their effect on pregnancy rates after surgery.

Variable		Pregnancy	No pregnancy	P value	Hazard ratio	95% CI of the hazard ratio	
						Upper	Lower
Age		32 ± 4 (mean ± SD)	35 ± 5 (mean ± SD)	0.081	0.96	0.91	1.01
BMI		23 ± 4 (mean ± SD)	23 ± 5 (mean ± SD)	0.53	0.98	0.92	1.04
Duration of infertility (years)		2.7 ± 2.1 (mean ± SD)	4.7 ± 3.2 (mean ± SD)	0.007	0.84	0.74	0.954
Number of previous operations		0 ± 1	1 ± 1	0.03	0.75	0.58	0.97
Infertility				0.56	0.84	0.48	1.49
	primary	56 (54.9%)	22 (21.6%)				
	secondary	15 (14.7%)	9 (8.8%)				

The data was analyzed using BiAS 11.10. Correlations between different factors were analyzed using log-rank test and the Kaplan–Meier method. Univariate and multivariate analysis were performed using the Cox regression model. Chi-square test and Fisher's exact test were used for comparisons of categorical variables. The cumulative pregnancy rate was compared with log-rank test and the Kaplan–Meier method. The predictive influence of time until pregnancy was investigated for all variables using univariable and multivariable Cox regression. A p value of less than 0.05 was defined as statistically significant.

Results

Patient characteristics

Between 2007 and 2017, a total of 695 patients, who underwent surgery for endometriosis-related symptoms, received histopathological confirmation of endometriosis. A total of 102 patients with infertility from this group of patients were registered and followed up for a mean of 70 months (range 36–197 months).

The mean age of our patients was 33.3 (SD: 4.6) years. Mean body mass index (BMI) was 22.8 kg/m^2. In this group of patients, the mean duration of infertility was 40 months. The duration of infertility correlated significantly with the time between surgery and pregnancy (p = 0.007). With each year of infertility (without any intervention), the chance of pregnancy was reduced by around 4.6 to 26%. 76.5% of patients (n = 78) were diagnosed with primary infertility and 23.5% (n = 24) had had at least one previous pregnancy (secondary infertility). The type of infertility was not identified as a significant influencing factor (p = 0.56). When the cumulative pregnancy rate was compared, no statistically significant difference was found between patients with primary and patients with secondary infertility (p = 0.55; log-rank test). An overview of patient characteristics comparing the groups with and those without pregnancy is given in ▶ **Table 1**.

Pregnancy and live births after surgery

A total of 26.5% of patients (n = 27) became pregnant in the first 6 months and 48% (n = 49) in the first 12 months after surgery. The cumulative pregnancy rate increased more than 10% from the first to the second postoperative year (cumulative pregnancy rate: 61.8%, n = 63). After the 38 th postoperative month, the cumulative rate of pregnancy remained stable at 69.6%, no other pregnancies were registered (▶ **Fig. 2**). No pregnancy was reported in 30.4% of patients (n = 31). All 102 patients in this study were supported to have live births. The long-term follow-up showed a live birth rate of 58.8% (n = 60), meaning that 41.1% of patients did not have a successful pregnancy and delivery.

Use of assisted reproductive technology (ART)

32.4% of patients (n = 33) became pregnant spontaneously, while 67.6% (n = 69) used ART. This group of patients also included patients who did not achieve spontaneous pregnancy (n = 13, 12.7%) and then turned to reproductive medicine. In 54.6% of patients (n = 56), ART was carried out directly after surgery. There was no significant difference between the different reproduction medicine techniques (p > 0.05, log-rank test).

Surgical findings

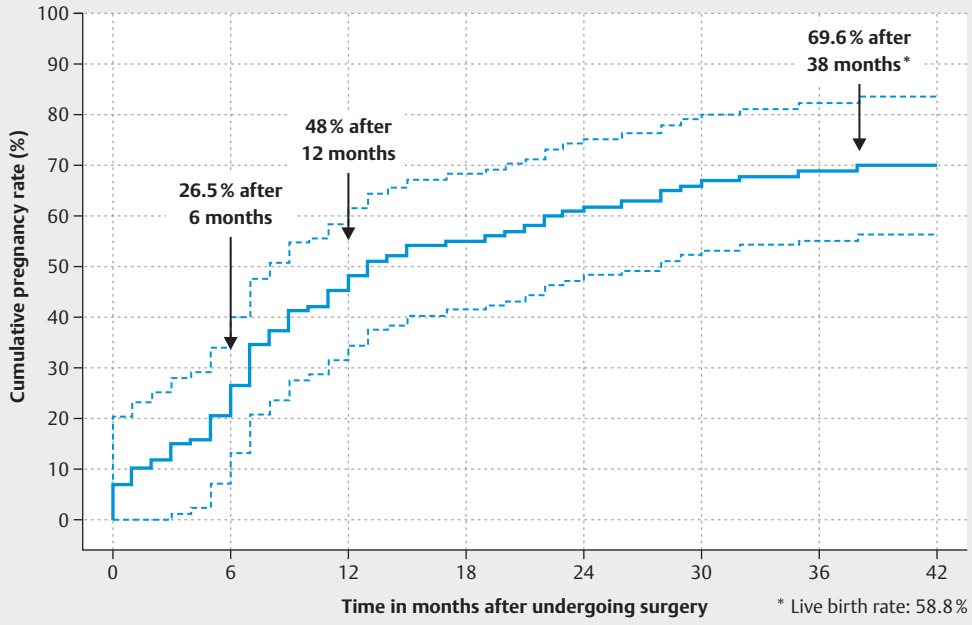
Type and location of endometriosis

The surgical reports were reviewed and the subtypes of endometriosis were recorded: 97% (n = 99) had external genital endometriosis and 15.7% (n = 16) had extragenital endometriosis. A total of 13.7% (n = 14) had deep infiltrating endometriosis. Of the patients with deep infiltrating endometriosis (DIE), only 21.4% of patients (n = 3) became pregnant, and no pregnancy was reported for the other 78.6% (n = 11) after a follow-up of 36 months. 64.2% (n = 9) used ART.

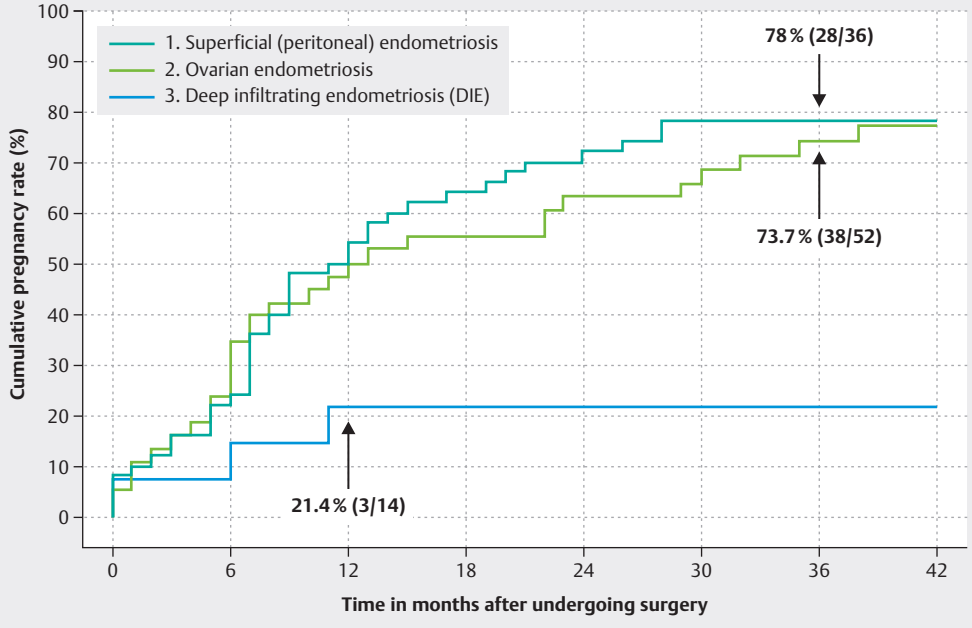
This difference in the cumulative pregnancy rate between patients with peritoneal, ovarian, and DIE was statistically significant using log-rank test (p = 0.0009). In univariate analysis, DIE was a significant unfavorable factor affecting postoperative pregnancy (p = 0.004). Patients with DIE were found to have an 82% reduced chance of postoperative pregnancy compared to patients without DIE (hazard ratio [HR] 0.18; 95% CI of HR: 0.06–0.58) (▶ **Fig. 3**).

Using univariate Cox regression, a reduced possibility (reduction by 74%) of postoperative pregnancy was shown for women with bowel endometriosis or DIE (HR 0.26).

In the group of patients with bowel endometriosis or DIE, 45% had unilateral or bilateral ovarian endometriosis and 17.4% (n = 8) patients had additional DIE. The cumulative pregnancy rate after



▶ **Fig. 2** Cumulative pregnancy rate of our cohort (n = 102) with 95 % confidence intervals.



▶ **Fig. 3** Cumulative pregnancy rate of our cohort (n = 102) according to subgroups 1: superficial (peritoneal) endometriosis, 2: ovarian endometriosis, and 3: deep infiltrating endometriosis (DIE). Patients with DIE were shown to have an 82 % reduced chance of postoperative pregnancy compared to patients without DIE (HR 0.18; 95 % CI of HR: 0.06–0.58).

42 months in the group with only ovarian endometriosis was 76.3 % and therefore higher than in the group of patients with additional DIE (cumulative pregnancy rate of 25 % after 42 months). This difference in cumulative pregnancy rates was statistically significant (p = 0.02, log-rank test).

The number of endometriosis locations was significant for the incidence of pregnancy (p = 0.006). With each additional location the postoperative chance of pregnancy decreased by 6–29 % (95 % CI of HR).

In the first six months after laparoscopy, 38 % of patients with rASRM stage I, 13.3 % of patients with rASRM stage II, 43.8 % of patients with stage III, and 6.9 % of patients with stage IV became pregnant. After 42 months of follow-up, the highest cumulative pregnancy rate was 93.8 % in the group with rASRM stage III, followed by the group of patients with rASRM stage I (83.3 %). The lowest pregnancy rate was found in the group of patients with rASRM stage IV endometriosis (cumulative pregnancy rate of 37.9 %). Log-rank test and Kaplan–Meier analysis found no significant difference between groups with different rASRM stages regarding the cumulative pregnancy rate ($p > 0.05$). Univariate analysis with the Cox regression model showed a significant effect of rASRM stage on the postoperative pregnancy rate ($p = 0.002$). This effect could not be demonstrated in multivariate analysis ($p > 0.05$, Cox regression).

Adhesions

Adhesions were examined as a factor that could affect pregnancy. Extensive adhesions in the abdomen, pelvis or genital organs were observed in 60.8 % (n = 62) of patients. In this group of patients, 59.7 % (n = 37) became pregnant after surgery during the follow-up period. In patients without adhesions (n = 40, 39.2 %), the pregnancy rate was 85 %, i.e., 20 % higher than in the other group. Univariate analysis found a significant but negative effect of adhesions on the time to pregnancy ($p = 0.001$). Patients with adhesions had a 55 % lower postoperative chance of becoming pregnant (HR 0.45).

Surgical technique

The Kaplan–Meier method and log-rank test were used to compare the cumulative pregnancy rates of patients treated with different surgical techniques.

Coagulation of peritoneal endometriosis was carried out in 36 patients (35.3 %). 86.1 % of these patients (n = 31) subsequently became pregnant after surgery. The p value was statistically significant ($p = 0.002$, log-rank test) in favor of peritoneal coagulation, irrespective of the rASRM stage.

In univariate analysis, peritoneal endometriosis coagulation ($p = 0.003$) and coagulation of ovarian endometriotic lesions ($p = 0.001$) were found to have a significant protective effect on fertility and the time to pregnancy. Univariate analysis found that coagulation of peritoneal endometriosis almost doubled the chance of becoming pregnancy (HR). Forty-six patients with ovarian endometriosis had ovarian surgery, which could consist of extirpation or excision, fenestration, and/or incision. None of these techniques was found to have a statistically significant effect on the incidence of pregnancy ($p > 0.05$).

Postoperative functionality

Endometriotic lesions were completely removed (coagulation or resection) in 52 % of patients (n = 53), but endometriosis lesions could not be completely excised in 48 % of patients (n = 49). Univariate analysis showed that complete resection of endometriosis (irrespective of the technique used) was a protective factor for fertility ($p = 0.001$). The group of patients with complete resection of endometriosis had a 2.2-fold higher chance of conception (hazard ratio). Log-rank test and the Kaplan–Meier method were used to compare the cumulative pregnancy rate and showed a significant difference between patients with complete (cumulative pregnancy rate of 83 % after 24 months) and patients with incomplete (cumulative pregnancy rate of 55.1 % after 42 months) resection of endometriotic lesions ($p = 0.0007$).

In accordance with the Endometriosis Fertility Index (EFI), a score used to predict the spontaneous pregnancy rate after endometriosis surgery [11], the intraoperative situation after laparoscopic intervention was evaluated with regards to normalization of pelvic anatomy and complete resection of endometriosis.

In 90.2 % (n = 92) of cases, the pelvic anatomy was defined as normal at the end of the operation; in 9.8 % (n = 10), normalization of the anatomy was not possible. Of these ten patients, four (cumulative pregnancy rate of 40 %) became pregnant in the follow-up period. The cumulative pregnancy rate after 36 months was considerably higher in patients with normal postoperative pelvic anatomy (72.8 %). The difference in cumulative pregnancy rates between patients with normalization of the pelvic anatomy and patients without normalization was statistically significant ($p = 0.04$, log-rank test), but the favorable effect on the time to pregnancy was not confirmed by univariate analysis ($p = 0.054$).

Prior surgical history

48 % of patients (n = 49) had not previously had abdominal surgery, 35.3 % (n = 36) had one operation, 6.9 % (n = 7) had two, 4.9 % (n = 5) had three and 3.9 % (n = 4) had four previous abdominal operations. The cumulative pregnancy rate after 36 and 42 months for patients with at least one previous abdominal operation was 66 % lower compared to patients with no previous operations (71.4 % and 73.4 % after 36 and 42 months, respectively). Even though the number of previous surgeries was not statistically significant with regards to the cumulative pregnancy rate ($p = 0.4$; log-rank test), univariate analysis showed that any previous abdominal operation reduced the chance of postoperative pregnancy by 25 % hazard ratio 95 % CI of HR: 0.58–0.97, $p = 0.03$).

In univariate analysis, the number of operations on the ovaries also negatively affected the pregnancy rate ($p = 0.022$). Each additional surgical ovarian procedure reduced the chance of pregnancy by 4–39 % (95 % CI of HR). Each surgical intervention to treat endometriosis in any location reduced the chance of pregnancy by 28–66 % (95 % CI of HR); this was found to be statistically significant. No statistically significant effect was found for other surgical techniques such as resection and partial peritonectomy ($p > 0.05$).

Recurrence of endometriosis

22.5 % of patients (n = 23) experienced recurrence in the follow-up period (36 months). Recurrence was diagnosed laparoscopically in all these patients. 47.8 % of patients in this group (n = 11) became pregnant despite recurrence. Compared to the group of patients without recurrence (75.9 %), the cumulative pregnancy rate was significantly lower ($p = 0.003$, log-rank test). In univariate analysis, recurrence was an unfavorable prognostic factor affecting fertility ($p = 0.005$, HR 0.4). The hazard ratio showed that in patients with recurrence, the chance of pregnancy was reduced to 60 %. An

▶**Table 2** Postoperative functionality and the effect on pregnancy rates after surgery during a follow-up period of at least 42 months.

Variable		Pregnancy		No pregnancy	P value	Hazard ratio	95% CI of the hazard ratio	
							Upper	Lower
Complete treatment of endometriosis					0.001	2.2	1.4	3.6
	Yes	44 (43.1%)		9 (8.8%)				
	No	27 (26.5%)		22 (21.6%)				
Tubal patency					0.07	1.7	1.0	2.9
	Yes	42 (50.6%)		12 (14.4%)				
	No	18 (21.7%)		11 (13.3%)				
Normalization of anatomy					0.054	2.7	1.0	7.4
	Yes	67 (65.7%)		25 (24.5%)				
	No	4 (3.9%)		6 (5.9%)				
Recurrence of endometriosis					0.005	0.4	0.21	0.76
	Yes	11 (10.8%)		12 (11.8%)				
	No	60 (58.8%)		19 (18.6%)				
rASRM stage		No ART	ART					
	I 35/42	12 (28.6%)	23 (54.8%)					
	II 10/15	5 (33.3%)	5 (33.3%)					
	III 15/16	3 (18.8%)	12 (75%)					
	IV 11/29	2 (6.9%)	9 (31%)					

▶**Table 3** Overview of influencing ($p < 0.05$) and non-influencing ($p > 0.05$) surgical and non-surgical variables affecting postoperative pregnancy.

	Influencing variables	Non-influencing variables
Surgical	Number of previous operations ($p = 0.03$)	Removal of ovarian endometriosis using extirpation vs. excision vs. fenestration vs. incision ($p > 0.05$)
	Adhesions ($p = 0.001$)	Normalization of anatomy ($p = 0.054$)
	Peritoneal coagulation compared to other techniques ($p = 0.002$)	
	Complete removal of endometriotic lesions ($p = 0.001$)	
	Number of ovarian operations ($p = 0.022$)	
Non-surgical	Duration of infertility ($p = 0.007$)	Age ($p = 0.081$)
	Presence of deep infiltrating endometriosis ($p = 0.004$)	BMI ($p = 0.53$)
	Number of endometriosis locations ($p = 0.006$)	rASRM stage ($p > 0.05$)
	Recurrence of endometriosis ($p = 0.003$)	Type of infertility ($p = 0.56$)

overview of the evaluated variables with regards to postoperative functionality and recurrence of endometriosis is given in ▶ **Table 2**. ▶ **Table 3** shows an overview of all investigated surgical and non-surgical variables.

Multivariate analysis

Multivariate analysis was carried out to evaluate the effect of different factors. All factors identified by univariate analysis (Cox regression) as statistically significant ($p < 0.05$) for the cumulative pregnancy rate were evaluated. The following factors were evaluated: duration of infertility, classification of endometriosis, subtypes of endometriosis (DIE), findings at surgery (bowel endometriosis, number of endometriosis locations, adhesions), surgical technique used (peritoneal endometriosis coagulation, ovarian endometriosis coagulation, complete resection of endometriosis), number of surgical interventions (laparoscopy, surgery for ovarian endometriosis, number of previous operations), and recurrence of endometriosis.

According to multivariate analysis, each year of endometriosis-related infertility without therapy reduced the chance of pregnancy by 2.2 to 27 % (95 % CI of the HR).

Multivariate analysis found that DIE, coagulation of peritoneal endometriosis and complete treatment of endometriotic lesions had no significant effect ($p > 0.05$).

Discussion

Endometriosis can affect the chance of spontaneous conception as well as the probability of becoming pregnancy after ART, due to the associated inflammatory changes and altered immunity [10]. Laparoscopic intervention is considered the standard approach to treat endometriosis-related infertility [12]. For infertile patients with endometriosis, surgical laparoscopy can improve the pregnancy rate of women with all stages and types of endometriosis [12, 13]. In our study we found a cumulative pregnancy rate of 69.6 % over a period of 38 months. Hui et al. [9] reported a rate of 75.6 % over a 3-year follow-up.

The patient characteristics "age" and "BMI" appeared to have no significant effect on pregnancy in our group of patients. The duration of infertility had a significant effect on the probability of postoperative pregnancy ($p = 0.007$) (▶ **Table 1**). Hui et al. [9] demonstrated the same effect, while other studies, despite noting the same trend, were unable to show statistical significance [12, 13]. We found that longer duration of endometriosis without therapy can influence the pregnancy rate because of the resultant damage to organs or tissues. Although previous pregnancy is one part of the EFI (Endometriosis Fertility Index) score and different studies have investigated its effect on pregnancy rates after endometriosis operations [14, 15, 16], our study showed no significant difference between the group of patients with primary and secondary infertility.

The current study included patients with different stages of endometriosis. In the final analysis, the rASRM stage had a significant effect on the pregnancy rate in univariate analysis but not in log-rank test or Kaplan–Meier analysis. The highest pregnancy rate was recorded in the group of patients with rASRM stage III endometriosis. As reported by other studies [5, 17], multivariate analysis in our study also found no significant effect for the rASRM stage.

When we looked at the type and location of endometriosis, DIE was found to have a negative effect on the pregnancy rate compared to patients with superficial endometriosis. Although a significant effect was shown in univariate analysis ($p = 0.004$, HR 0.18), multivariate analysis did not show significance ($p > 0.05$). However, this effect has also been confirmed in other studies [18, 19, 20]. In our study, the pregnancy rate for the group of patients with DIE was only 21.4 %, despite the use of ART by 64.2 % of patients in this subgroup. In our study, patients with bowel (colorectal) endometriosis had a lower chance of postoperative pregnancy. It should be mentioned that 50 % of this group had DIE. Other authors have also demonstrated a negative impact of colorectal endometriosis on fertility outcomes [21]. The number of endometriosis locations significantly affected infertility and the results after surgery ($p = 0.006$, HR 0.82). This was also shown by Vercellini et al. in 2006 [22].

We investigated different surgical techniques used to treat endometriosis in different locations. Our data showed that the only effective method was complete resection of lesions. While our data showed that peritoneal coagulation doubles the chance of pregnancy compared to other techniques, we also found that no technique took priority in other locations such as the ovaries. We suggest that an effective use of coagulation, resection, or other techniques with the aim of complete resection of lesions and simultaneous protection of the organ functionality is key to managing these patients. In a recent study, Chen et al. [23] showed that both cystectomy and ovarian coagulation reduced AMH levels, but that the effect of coagulation on ovarian reserve was probably less severe than after cystectomy. On the other hand, a meta-analysis published in 2018 discouraged the use of coagulation [24]. The meta-analysis included 210 patients, but the authors confirmed that probable bias could lead to an overestimation of the negative impact of bipolar hemostasis.

The analysis in our study showed that complete resection of all visible lesions can increase the chance of pregnancy 2.2-fold. Although the normalization of anatomy showed a positive effect on pregnancy rates, it was not statistically significant according to our data (▶ **Table 2**). Pliszkiewicz et al. [25] supported the use of radical conservative laparoscopic surgery in a follow-up study, while another study [26] opposed extensive surgical intervention because of the higher complication rates. Complete resection not only improves fertility outcomes, it also lowers the recurrence rate and thus improves the quality of life of patients [27]. It should be mentioned, however that in endometriosis complete removal of lesions does not have the same value as in cancer. The aim of surgery in our study population was to improve the situation. In our center, all surgeons tried to avoid any damage to organs that could delay pregnancy.

Both adhesions and previous surgical interventions (operations before infertility surgery) reduced the chance of postoperative pregnancy. Repeat surgery must be avoided in this group of patients. The number of laparoscopic operations for endometriosis ($p = 0.03$, HR 0.63), especially ovarian surgery ($p = 0.02$, HR 0.77), will affect the pregnancy rate. Our findings corresponded to the results found in previous studies [28, 29]. Endometriosis recurrence is a complex situation which is difficult to manage. Our group of patients who underwent surgery for recurrent disease had a reduced pregnancy rate of 50 % after a 38-month follow-up. Similar rates have also been reported in other studies [30], which indicates the necessity of an effective therapy which will reduce the recurrence rate.

Based on our findings and analysis, it is not only important to carry out laparoscopic surgery in patients with infertility, the timing of surgery is also important. In infertile patients, surgery should be carried out as soon as possible. Careful planning of the operation is very important. Irrespective of the surgical technique, the aim must be to treat the lesion completely while simultaneously avoiding complications, recurrence, and the necessity of repeat surgeries.

Although we report the results of a long-term follow-up in a European center, our study is a retrospective study which makes it susceptible to bias as well as unmeasured confounders. Further

prospective studies with larger sample sizes are required to draw further conclusions.

No animal research was carried out.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflict of interest.

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