Does IVF-ET Procedure Increase the Pregnancy Rates in Women Underwent Laparoscopic Endometriosis Surgery?

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ABSTRACT

OBJECTIVE: To evaluate pregnancy rates in women who underwent In Vitro Fertilization-Embryo Transfer (IVF-ET) following laparoscopic endometriosis surgery and to assess the success of IVF-ET.

STUDY DESIGN: One hundred forty-one primary infertile patients who underwent laparoscopic endometriosis surgery were included in this retrospective study. After the surgery, the patients were followed up for one to eight years, and 95 patients who did not conceive postoperatively underwent IVF-ET (study group).

RESULTS: The pregnancy rate in the study group was 35.8 % and 32.6% in the laparoscopic surgery only group (p>0.05). The total conception rate (45.4 %) within the first 12 months after laparoscopy with or without IVF was higher than in the other periods (p<0.001). In women with stage III and IV of endometriosis, the pregnancy rate was lower than the stage I and II group. Moreover, the fecundity rate in women older than 35 years was statistically significantly lower than women under the age of 35 years (p=0.003).

CONCLUSIONS: In this study, the pregnancy rate was higher in the laparoscopic endometriosis surgery and IVF-ET group compared with the surgery only group, but difference was not statistically significant. Therefore, after surgery IVF-ET may be recommended to women with endometriosis related infertility.

Keywords: Endometriosis, Laparoscopic surgery, IVF-ET, Infertility

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Introduction

Endometriosis is a complex and clinically progressive disease where endometrial glandular tissue and stroma are located outside the uterus, such as in the ovaries, pelvic peritoneum, rectovaginal septum, and other pelvic regions (fallopian tubes, vagina, cervix, and uterosacral ligaments). Endometriosis can also affect extrapelvic regions (such as pleura and brain) and is usually diagnosed during the reproductive period, affecting 11% of premenopausal women.[1] Although its exact prevalence in the population is not known, endometriosis is one of the most significant causes of infertility and/or pelvic pain, with a prevalence of 6–10% and a frequency of up to 35–60%.[2]

Despite recent developments in understanding of the pathogenesis of the disease and in diagnostic tools, the definitive diagnosis is still made by direct viewing of lesions via invasive methods, such as laparoscopy and laparotomy. Histological confirmation should still be the first step in the laparoscopic diagnosis and treatment of suspected endometriosis.[3]

Various mechanisms could explain the relationship between endometriosis and infertility. Although distortion of pelvic anatomy and pelvic adhesions could explain the infertility in severe endometriosis, high-grade lesions are not observed in all women with endometriosis-related infertility.[4] In patients with minimal endometriosis, peritoneal endometriosis lesions may cause infertility by changing the peritoneal cell population and peritoneal fluid content.[5] The impaired folliculogenesis causes ovulatory dysfunction and the formation of low- quality oocytes, which in turn decreases fertilization and results in abnormal embryogenesis.

Previous studies reported the role of laparoscopic surgery in treating endometriosis before ICSI/IVF procedures.[6,7] Garcia found no significant difference between the pregnancy rate of women who underwent surgery for endometriosis before IVF and who proceeded directly to IVF without prior endometriotic cyst removal.[6] However, Dechaud et al.[5] reported that the laparoscopic approach increases fecundity in infertile endometriotic patients.

In the current study, we aimed to evaluate whether IVF-ET increased pregnancy rates in women who underwent laparoscopic endometriosis surgery.

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Material and Method

This retrospective study was conducted at the Women's Health Training and Research Hospital from January 2001 through December 2008. This is a tertiary hospital at the middle region of Turkey. This institution is a government supported hospital and most of the health services are free of charge. The study was designed according to the Helsinki declaration and was approved by the Ethics committee of the hospital. The ethics committee determined that patient consent was not required because of its retrospective design. A total of 700 patients underwent laparoscopic endometriosis surgery during the study period. Data were collected from surgery reports and patients' files. Patients had been staged according to the revised criteria of the American Society for Reproductive Medicine (ASRM) under guidance of operation records. Two hundred thirty-nine patients having at least one year primary infertility were recorded. Ninety eight of the 239 patients were excluded from the study due to additional infertility factors, and 141 patients who had only endometriosis-related infertility were included to the study.

The laparoscopy procedure was performed under general anesthesia by three competent endoscopy specialists, using a standard access technique to reach the pelvic region. Pelvic endometriosis lesions were completely excised using bipolar coagulation and drainage. To restore normal anatomy, tubo-ovarian adhesions were dissected deeply with adhesiolysis. Endometrioma cysts were drained, and cyst capsules were removed completely or as completely as possible considering the need to avoid damage to the ovarian cortex. Methylene blue dye was administered to all the women for evaluating chromopertubation.

All the patients were followed up for at least six to twelve months. During the study period, 46 (32.6%) of the patients conceived spontaneously. In 95 patients, we performed the IVF-ET procedure. The patients were classified according to whether they conceived spontaneously or with the IVF-ET procedure. In addition, the results were analyzed according to the patient's age and endometriosis stage. For IVF-ET, the long-down regulation and controlled ovarian stimulation protocol was used in accordance with the clinical approach of our hospital.

A total of 0.5 mg of leuprolide acetate (Lucrin) was subcutaneously administered on the 21st day of the menstrual cycle. After effective down-regulation (if Estradiol <35 pg/mL, luteinizing hormone (LH) <5 mIU/mL) had been reached, the leuprolide acetate dosage was reduced by half and continued at a dosage of 0.25 mg. At the same time, a daily dosage of 225-300 IU of recombinant follicle stimulating hormone (FSH) was started. Serial ultrasound examinations were performed during controlled ovarian stimulation. When at least two follicles reached a maximum diameter of 17-18 mm, 10000 IU of human chorionic gonadotropin (hCG) (Pregnyl 5000 IU, two ampules) were administered intramuscularly. Oocyte collection was carried out by transvaginal ultrasound after 35-36 hours. All the oocytes collected were inseminated for IVF-ET, and fertilization was assessed by an embryologist the next day. Two days after the collection of the oocytes, a maximum of two embryos was transferred to patients under the age of 35, and a maximum of three embryos was transferred to patients above the age of 35. For luteal phase support, crinone gel (8% progesterone) was administered on the day of oocyte collection.

Pregnancy was determined by positive β-hCG and a visible intrauterine gestational sac. To analyze the data, the day of the laparoscopic surgery was accepted as the participation day of the study. Patients who conceived in the first year after the surgery were accepted as followed for one year. The patients were followed up by phone. The exit day of the study was accepted as the pregnancy date and last telephone conversation day for those who did not conceive.

Statistical Analysis

Descriptive statistics were used to demonstrate the average ± standard deviation (minimum-maximum) for constant variables, whereas nominal variables were expressed as percentages and case number. The Log-Rank test and Kaplan-Meier survival analysis were used to assess whether a significant change occurred in the pregnancy rate according to the stage and age. Pregnancy rates during periods of 6, 12, and 24 months and estimated pregnancy rates for each case were calculated. Nominal variables were analyzed with a chi-square test. Two-sided p values were considered statistically significant at $p<0.05$. Statistical analyses were carried out with statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The demographic features of the patients are shown in Table 1. The mean age of the patients was 27.4±3.6 years in the surgery only group and 30.7±5.0 years in the study group ($p<0.001$). Mean infertility duration in the surgery only group and study group was 4 years and 2,5 years, respectively (p:0.002). The stages of the disease were significantly at earlier periods in the surgery only group ($p<0.001$). All the cases were primary infertile. Endometrioma cysts were detected in 119 (84%) patients, and 24 (17%) of them had bilateral endometriomas. Fifty-nine (41.8%) patients had Stage 1 and Stage 2 endometriosis, and 82 (58.2%) had Stage 3 and Stage 4. According to the records, in 23 (16.3%) patients, at least one of the tubes showed patency after chromoperturbation.

Forty-six (32.6%) of all patients had conceived spontaneously during the postoperative one-year period. Of these, 29 (49.2%) had Stage 1 and Stage 2 endometriosis, and 17 (20.7%) had Stage 3 and Stage 4. The cumulative fecundity rates were also analyzed according to the stage of endometriosis and the age of the patients. The pregnancy rates after laparoscopic surgery and IVF-ET are shown in Table 2.

Table 1: Demographic and clinical features of the cases

Variables	Total (n=141)	Spontanenous pregnancy group (n=46)	IVF group (n=95)	P value[b]
Age	29,6±4,9 (20-45)	27,4±3,6 (20-36)	30,7±5,0 (21-45)	<0,001
Infertility Duration	4 (1-18)	2,5 (1-9)	4 (1-18)	0,002
Stage				
Stage I-II[a]	59 (41,8)	29 (63,0)	30 (31,6)	<0,001
Stage III-IV*	82 (58,2)	17 (37,0)	65 (68,4)	<0,001

a: Data presented as n (%), b: The differences between groups is statistically significant

Table 2: Pregnancy rates according to all stages and patients

	Stage I-II		Stage III-IV		Total	
	n	%	n	%	n	%
Number of Patients	59	41.8 (59/141)	82	58.2 (82/141)	141	100.0
Spontaneous Pregnancy	29	49.2 (29/59)[a]	17	20.7 (17/82)[a]	46	32.6 (46/141)[b]
IVF Treatment Group	30	31.6 (30/95)[a]	65	68.4 (65/95)[a]	95	100
Pregnancy After IVF	16	53.3 (16/30)[a]	18	27.7 (18/65)[a]	34	35.8 (34/95)[b]
All Pregnancies	45	76.3 (45/59)[a]	35	42.7 (35/82)[a]	80	56.7 (80/141)

a: The differences between stage I-II and stage III-IV is statistically significant p<0.001, b: The differences between the rate of spontaneous pregnancy and pregnancy after IVF is not statistically significant p>0.05

Ninety-five (67.4%) patients who did not conceive spontaneously underwent the IVF/ET procedure. Eighteen (12.7%) of the patients underwent IVF/ET six months after the surgery due to advanced age (≥35 years) and other factors, with a median of one (min-max: 1-2) IVF/ET cycle. Seventy-seven (54.6 %) patients underwent IVF/ET one year after the surgery, with median of two (min-max: 1-4) IVF/ET cycles. Of these 77 patients, 52 underwent IVF/ET at the current clinic, and the other 25 were followed up by a telephone call.

In all patients, the pregnancy rates were 25.5% (n=36) at the end of the sixth month, 45.4% (n=64) at the end of the 12th month, 53.2% (n=75) at the end of the 24th month, and 56.7% (n=80) at the end of 34th month. After the 34th month, the pregnancy rates reached a plateau and remained constant thereafter (Figure 1). In both the Stage 1 and Stage 2 patients, the pregnancy rates were 40.6% at the end of the sixth month and 72.8% at the end of the 24th month. At the end of the 34th month, the pregnancy rate was 76.3% and remained constant thereafter. With regard to the Stage 3 and Stage 4 patients, the pregnancy rate was 14.6% at the end of the sixth month and 39% at the end of the 24th month. At the end of the 29th month, the pregnancy rate was 42.7%, and it remained constant thereafter. The cumulative pregnancy rates of the Stage 1 and Stage 2 (76.3%) patients were significantly higher than the pregnancy rates of the Stage 3 and Stage 4 (42.7%) patients (Figure 2). The pregnancy rates of the Stage 3 and 4 patients were significantly lower than those of the Stage 1 and Stage 2 patients (p<0.001).

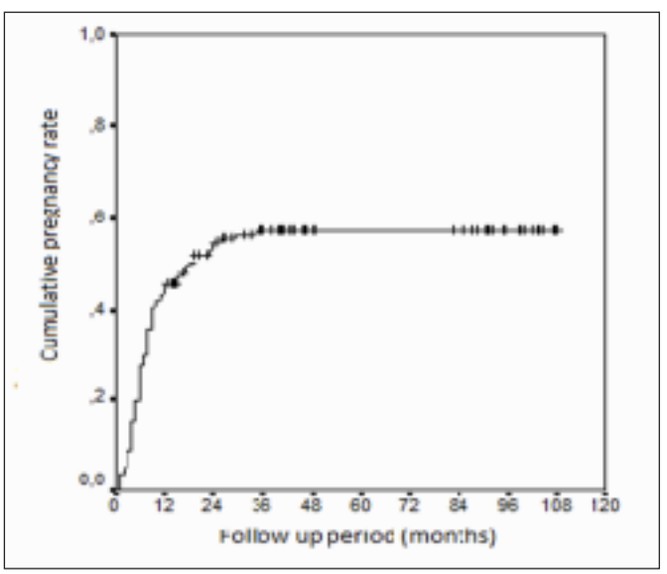

Figure 1: Kaplan-Meier curve showing cumulative pregnancy rates for all patients

The pregnancy rate of the group of patients aged 35 years or below was 31.9% at the end of the sixth month and 51.3% and 60.3% at the end of the 12th and 24th months, respectively. At the end of the 34th month, the pregnancy rate in this group was 62.4%, and it remained constant thereafter. In the group of patients above the age of 35 years, there was no pregnancy at the end of the sixth month. In this group, the pregnancy rate was 10.5% at the end of the 12th month, 16.9% at the end of the 24th month, and 25.3% at the end of 29th month. After the

29th month, the pregnancy rate remained constant (Figure 3). In the group of patients older than 35 years, the pregnancy rate was statistically significantly lower than those aged 35 or below (p=0.003).

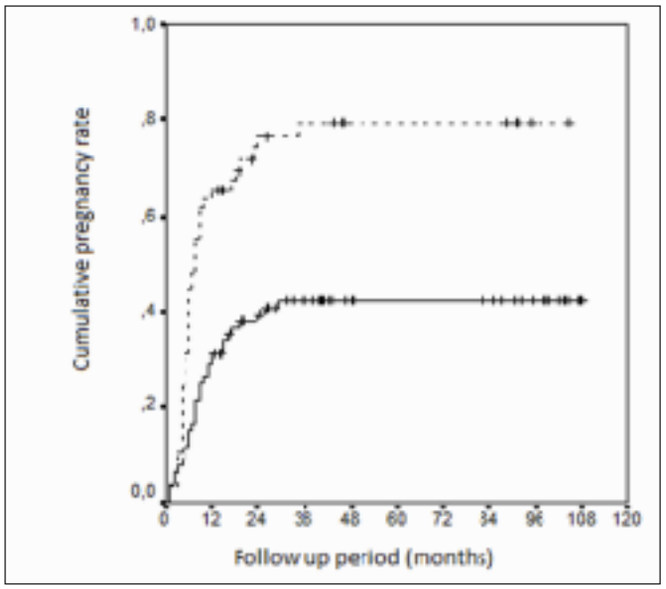

Figure 2: Kaplan-Meier curves showing cumulative pregnancy rates according to stages

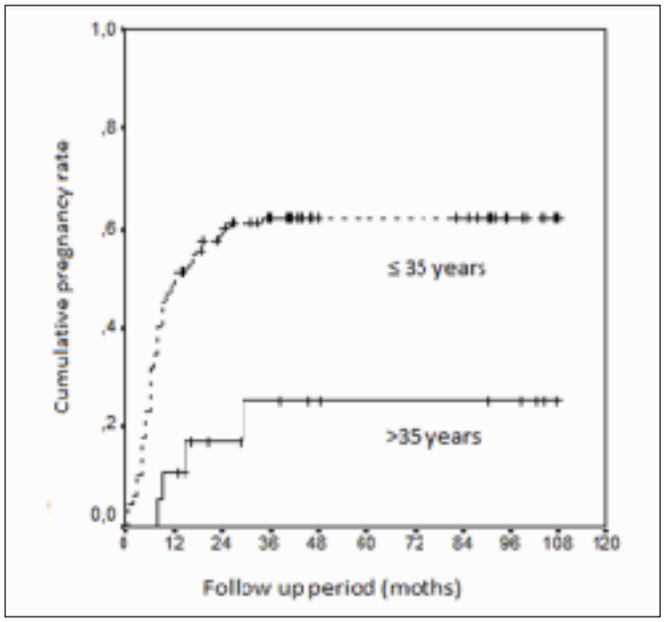

Figure 3: Kaplan-Meier curves showing cumulative pregnancy rates according to age

Thirty-four of 95 patients who had IVF treatment conceived (35.8%). Thirty of 95 patients were Stage 1 and 2 patients (31.6%) and 65 were Stage 3 and 4 patients (68.4%). Sixteen of 34 patients who conceived (53.3%) were Stage 1 and 2 patients, and 18 were Stage 3 and 4 patients (27.7%). The spontaneous pregnancy rate was 32.6% in the surgery only group. After adding IVF-ET to the laparoscopic endometriosis surgery, the total pregnancy rate was 35,8% in the study group. The pregnancy rate was higher in the laparoscopic endometriosis surgery and IVF-ET group compared with the surgery only group, but showed no statistically significantly difference (p>0.05).

Discussion

Endometriosis is a common benign gynecologic disorder in patients with infertility. The answer to the question ‘‘Does surgery improve fertility?’’ is still controversial. In the current study, we evaluated the effect of IVF-ET on pregnancy rates in women who underwent laparoscopic endometriosis surgery due to infertility and compared these with pregnancy rates of women who conceived spontaneously after surgery. The majority of our patients had endometrioma in different sizes. Forty-six of 141 patients conceived spontaneously after laparoscopic surgery. Of these, 95 formed the IVF-ET group after at least one year of follow up (range; one to eight years). The pregnancy rate in the group who conceived spontaneously was 32.6%, and it was 35.8% in the IVF-ET group.

Laparoscopy is the gold standard in the diagnosis and treatment of endometriosis-related infertility. Although the use of laparoscopy surgery for endometriosis and related infertility has become widespread, there is no consensus in the literature on whether surgery increases pregnancy rates in women who have endometriosis-related infertility.

The management of endometriosis-related infertility is rather difficult, as there are no well designed prospective randomized studies comparing endometriosis surgery with artificial reproductive techniques. Some researchers suggested that surgery increases the pregnancy rates.[8] A meta-analysis of two studies found that surgery increased fecundity in infertile endometriotic patients.[3] They concluded that restoration of tubo-ovarian anatomy might be increased conception rates. Cirpan et al reported that spontaneous pregnancy rate was 44%, after surgical treatment of endometriosis related infertility in their retrospective study.[9] Donnez et al indicated that the pregnancy rate after two IVF cycles was 61%.[10]

On the other hand, other researchers claimed that surgical removal of endometriomas is not required before IVF-ET but that cyst aspiration may be beneficial after failed IVF attempts.[11] In a review, the authors concluded that the absolute benefit of surgery for endometriosis-related infertility seems smaller than believed.[12] There are few studies focused on postoperative treatment methods for patients who fail to respond to surgery.[13] Similarly, there is limited study of whether the addition of IVF-ET to surgery could affect pregnancy rates in patients with endometriosis-related infertility. Somigliana et al evaluated IVF outcome in patients underwent laporoscopic bilateral endometrioma surgery.[14] They found that IVF outcome is significantly impaired in women operated on for bilateral ovarian endometriomas. In our study, bilaterality was only 17%, this is the why our study population has a better pregnancy rates after surgery. Maybe we have done less damage,

but we could not evaluate the extent of ovarian damage such as using ovarian reserve tests after surgery.

The surgical technique performed during operation is also important which determines the possibility of fertility. There are two main points that should be considered; one of them is preventing the injury to the follicular reserve that follows surgical excision of ovarian endometriomas, and the second one is preventing post-surgical formation and re-formation of adhesions.[15] Randomized controlled trials showed that the excision technique is associated with a higher pregnancy rate and a lower recurrence rate, although it may cause severe injury to the ovarian reserve than the coagulation technique.[16] As a clinical approach, we performed a mixed technique that combines maximum excision and minimum ablation to remove endometrioma cysts.

When we carefully analyze the cumulative pregnancy rates, the postoperative period seems to be particularly suitable for conception. The fecundity rates within the 12 months after the surgery were significantly higher than the other six-month periods. Additionally, we found out that there was a significant negative correlation between the severity of the disease and spontaneous pregnancy rates. This highlights the fact that endometriosis is a progressive disease, which lowers fecundity rates over time due to the damaging effect of the disease on ovarian reserve. Given the adverse effect of endometriosis on fecundity, patients should be advised to conceive as soon as possible after laparoscopic surgery.

We also analyzed the IVF-ET treatment group who could not conceive spontaneously after laparoscopic surgery. A literature search showed that there are limited data on the management of patients who are still unable to conceive after laparoscopic surgery. It was shown that IVF-ET resulted in high pregnancy rates in patients with endometriosis-related infertility who had unsuccessful surgery and the average time between surgery and pregnancy was calculated as less than two years in this population.[17] Studies have attributed endometriosis-related infertility to negative effects of the peritoneal environment, abnormal sperm transportation mechanisms, and ovulatory dysfunction corrected by IVF-ET.[12]

However, a meta-analysis of two randomized studies revealed that endometriosis reduced all markers of the reproductive process and that this, in turn, caused the pregnancy rates of patients who had IVF-ET treatment due to endometriosis to decrease by half, whereas the pregnancy rates of those who had IVF-ET treatment due to tubal factors decreased only by 70-75%.[18]

According to our study, patients with endometriosis-related infertility may have a slightly increased chance of becoming pregnant with a laparoscopic surgery-IVF combined approach. Coccia et al found that pregnancy rate was higher in surgery-IVF combined group than surgery-only group and this result was similar to our study.[19] The laparoscopic surgery-IVF combined approach might result in significantly higher pregnancy rates compared to laparoscopic-only endometriosis surgery.

In another study, the researchers reported that surgery should not be the first step in the treatment of Stage 4 endometriosis for infertile patients. They proposed that IVF-ET should be the first-line treatment in Stage 4 endometriosis because of the severe inflammation that occurs in Stage 4 disease. They argued that surgery could increase this inflammation and could reduce fecundity rates, in addition to damaging the ovaries and diminishing the ovarian reserve. This effect was seen in Stage 4 endometriosis patients whose pregnancy rates were very low after a surgery-IVF combined approach because of tubal factors compared with the same patient group who had IVF treatment.[20] Afterwards in a similar study it was shown that advanced stage endometriosis following surgery had worse prognosis for IVF-ICSI treatment compared milder stages and tubal factors.[21] According to a study on the surgical management of endometriomas, surgical treatment of endometriomas has no significant effect on either IVF pregnancy rates or the ovarian response to stimulation compared to the case of no treatment.[22] In contrast to this study, we found increased pregnancy rates, but we did not evaluate ovarian reserve and response to the stimulation in the current study.

Although the mean age of the patients was significantly lower in spontaneous pregnancy group, and these patients were in early stage, the pregnancy rates were found higher in patients who underwent surgery and IVF-ET combined approach. The strengths of our study are its follow-up period (eight years) and the number of patients. The limitations are its retrospective design, the customization of the IVF, the lack of ovarian reserve indicators and response to the stimulation in IVF-ET group and also the absence of pregnancy outcomes.

In conclusion, after surgical treatment of endometriosis related infertility, the pregnancy rates seem to be improved slightly. Surely treatment of the patients with endometriosis related infertility should be individualized. However, as a first step in treatment, surgery might be offered to the patients who want to conceive and IVF might be selected as a second-line treatment after endometriosis surgery. We propose that IVF-ET may contribute to the treatment of patients with severe endometriosis and in those who cannot conceive after surgery. A combined approach may produce the best pregnancy rates in endometriosis patients. We think that further randomized, well designed, controlled studies with more participants may be strengthening evidence of the role of surgery and IVF-ET combined approach.

Laparoskopik Endometriozis Cerrahisi Yapılan Kadınlarda İVF-ET Prosedürü Gebelik Oranlarını Arttırır mı?

ÖZET

AMAÇ: Laparoskopik endometriozis cerrahisi sonrası İn Vitro

Fertilizasyon-Embriyo Transferi (İVF-ET) yapılan kadınlarda gebelik oranlarını araştırmak ve İVF-ET'nin başarısını değerlendirmektir.

GEREÇ VE YÖNTEM: Bu retrospektif çalışmaya, laparoskopik endometriozis opreasyonu yapılan 141 primer infertil kadın dahil edilmiştir. Cerrahi sonrası hastalar 1 yıldan 8 yıla kadar takip edilmiş ve operasyon sonrası gebe kalamayan 95 hastaya İVF-ET (çalışma grubu) yapılmıştır.

BULGULAR: Gebelik oranı çalışma grubunda %35,8 ve sadece laparoskopik cerrahi yapılan grupta %32,6 idi (p>0,05). Laparoskopik cerrahi sonrası, İVF ile veya İVF'siz, toplam gebelik oranı ilk 12 ayda %45,4 olup diğer dönemlerden daha yüksekti (p<0,001). Evre 3-4 endometriozisi olan kadınlarda gebelik oranı evre 1-2 olanlardan daha düşüktü. Dahası, fekundite oranı 35 yaşından büyüklerde 35 yaşından küçüklere göre istatistiksel olarak anlamlı düzeyde düşüktü (p=0,003).

SONUÇ: Bu çalışmada laparoskopik endometriozis cerrahisi ve İVF-ET'de gebelik oranları sadece cerrahi yapılanlarla karşılaştırıldığında daha yüksekti fakat bu fark istatistiksel olarak anlamlı değildi. Bu nedenle, cerrahi sonrası gebe kalamayan endometriozis ile ilişkili infertilitesi olan kadınlara İVF-ET önerilebilir.

Anahtar Kelimeler: Endometriozis, Laparoskopik cerrahi, İVF-ET, İnfertilite

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