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THE EFFECT ON OVARIAN RESERVE IN THE EARLY POSTOPERATIVE PERIOD IN HYSTERECTOMY ACCORDING TO THE TYPE OF SURGERY

CERRAHİ METODUN TÜRÜNE GÖRE HİSTEREKTOMİNİN AMELİYAT SONRASI ERKEN DÖNEMDE OVER REZERVİNE ETKİSİ

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ABSTRACT

Objective: The aim of this study was to estimate the possible differential levels of influence of the applied hysterectomy type on ovarian reserve.

Materials and Methods: Our study is a single-center prospective cross-sectional study. We included 82 patients who underwent benign hysterectomies between July 2021 and March 2022. There were two groups, abdominal hysterectomy (n=54) and laparoscopic (L/S) hysterectomy (n=28). Transvaginal ultrasonography and hormone status were evaluated before and after the hysterectomy. Patients with a preoperative anti-Mullerian hormone (AMH) value greater than 0.01 ng/dl and a follicle stimulating hormone (FSH) value less than 15 IU/L were included in the study.

Results: There was a significant difference between the groups regarding age, parity, duration, and bleeding. There was no significant difference in the percent decrease in AMH value between abdominal and laparoscopic hysterectomies. There was no difference in the comparison regarding the amount of decrease in ovarian volume and antral follicle count (AFS) parameters. In the analysis of serum estradiol values, an increase in 33 patients and a decrease in 49 patients were observed. While serum estradiol values decreased in 33 of 54 patients who underwent abdominal hysterectomy, this rate was 67.3% among patients with decreased estradiol. The difference in estradiol values was not statistically significant. There was a difference between the two groups in the comparative analysis regarding the amount and rate of increase in FSH parameters (p=0.03).

ÖZET

Amaç: Bu çalışmada yapılan histerektomi tipine göre over rezervinin ne kadar etkilendiğini tahmin etmeyi amaçladık.

Gereç ve yöntem: Çalışmamız tek merkezli prospektif kesitsel bir çalışmadır. Temmuz 2021 ile Mart 2022 arasında benign histerektomi yapılan 82 hastayı dahil ettik. Abdominal histerektomi (n=54) ve laparoskopik (L/S) histerektomi (n=28) olmak üzere iki grup vardı. Histerektomi öncesi ve sonrası transvajinal ultrasonografi ve hormon durumu değerlendirildi. Ameliyat öncesi anti-Müllerian hormon (AMH) değeri 0,01 ng/dl'nin üzerinde ve folikül uyarıcı hormon (FSH) değeri 15 IU/L'nin altında olan hastalar çalışmaya alındı.

Bulgular: Gruplar arasında yaş, parite, süre ve kanama açısından anlamlı fark vardı. Abdominal ve laparoskopik histerektomiler arasında AMH değerindeki azalma yüzdesi açısından anlamlı bir fark yoktu. Over hacmindeki azalma miktarı ve antral folikül sayısı (AFS) parametreleri açısından karşılaştırmada fark yoktu. Serum estradiol değerlerinin analizinde 33 hastada artış, 49 hastada düşüş gözlendi. Artanların %63,7'si, azalanların ise %67,3'ü abdominal histerektomi geçirenlerdi. Estradiol değerleri arasındaki fark istatistiksel olarak anlamlı değildi. FSH parametrelerindeki artış miktarı ve hızı açısından karşılaştırmalı analizde iki grup arasında fark vardı (p=0,03).

Sonuç: Her iki grupta da ameliyat öncesi ve sonrası over rezervinde azalma gözlendi. Aralarında yapılan analizlerde anlamlı bir fark gözlenmedi. FSH düzeylerindeki artış L/S lehine daha anlamlıydı. Elektrotermal enerji kullanımına bağlı olarak over foliküllerinde inhibin-B düzeylerinin araştırılması da dahil olmak

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Conclusion: In both groups a decrease in ovarian reserve before and after surgery was observed. No significant difference was observed in the analyses performed between them. The increase in FSH levels was more significantly in favor of L/S. Prospective large-scale studies are needed to investigate the effect of L/S hysterectomy on ovarian reserve compared to abdominal surgery, including investigating inhibin-B levels in ovarian follicles due to electrothermal energy use.

Keywords: Hysterectomy, ovarian reserve, anti-mullerian hormone, follicle stimulating hormone, estradiol

üzere, karın cerrahisine kıyasla L/S histerektominin yumurtalık rezervi üzerindeki etkisini araştırmak için prospektif büyük ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Histerektomi, yumurtalık rezervi, anti-mullerian hormon, folikül uyarıcı hormon, estradiol

INTRODUCTION

Hysterectomy is the second most common type of operation after cesarean section performed by gynecologists in women of reproductive age. Uterine leiomyomas remain the most common indication for hysterectomy. Other benign causes are abnormal bleeding, adenomyosis, endometriosis, pelvic organ prolapse, pelvic inflammatory disease, chronic pelvic pain, and pregnancy-related conditions (1). In the retrospective study of Moawad G. et al. in 2017 on 527,964 women who had undergone hysterectomy for benign reasons, the most common indication for all types of surgery (abdominal, vaginal, laparoscopic, robotic) was fibroids (leiomyoma, benign neoplasms) and the other indications were endometriosis, pelvic prolapse (2).

Today, there are various operative approaches to hysterectomy. The uterus can be removed abdominally, transvaginally, or laparoscopically. However, abdominal hysterectomy is still the most frequently used method for benign reasons; vaginal and laparoscopic operations are considered minimally invasive surgical approaches in terms of short hospital stays and postoperative recovery times (2,3).

The Cochrane Database, which included 47 studies with 5,102 women who had undergone laparoscopic, abdominal, vaginal, and robot-assisted hysterectomy methods, were analyzed comperatively regarding postoperative results. It was stated that a vaginal hysterectomy should be performed as much as possible. In cases where vaginal hysterectomy is not possible, the pros and cons of both laparoscopic and abdominal hysterectomy should be discussed with the patient during the decision-making process (4).

Ovarian reserve represents a woman's reproductive potential as a function of the number and quality of oocytes. Many factors affect ovarian reserves, such as advanced female age (>40 years old is the most critical parameter that determines ovarian reserve), conditions that damage the ovaries, such as endometriosis and pelvic infection, and previous ovarian surgery. In the study of Wang Y. et al., the effects of environmental, social, and surgical factors on ovarian reserve were examined (5). They stated the importance of a significant inverse relationship between early menarche, previous adnexal surgery, intense exercise, alcohol use, sleep quality, and female fertility.

It is known that the use of medical agents, certain radiotherapeutic trials and surgical interventions that damage the ovarian parenchyma significantly damage the ovarian reserve. Surgery that cuts off blood flow to the ovaries or directly damages the ovarian parenchyma can be expected to result in a reduction in the ovarian follicle pool. Many studies have also stated the relationship between surgical interventions and decreased ovarian reserve (6). In the study conducted by Chun S. and Y IJ. in 2020, the ovarian reserve was investigated in short term by evaluating the anti-Mullerian hormone (AMH) levels on preoperative and postoperative 3rd day in women who had undergone laparoscopic and non-laparoscopic hysterectomy. In the results of the research, a significant decrease was observed in both groups. The authors suggested that the electro-thermal energy from laparoscopic surgical devices can cause additional damage to the ovarian reserve. (7).

To our knowledge, there is limited literature comparing the change in ovarian reserve after laparoscopic hysterectomy and non-laparoscopic hysterectomy performed for benign gynecological reasons. In our study, we investigated the early effects on postoperative ovarian reserve in patients undergoing laparoscopic and non-laparoscopic hysterectomy for benign gynecological reasons.

MATERIAL and METHODS

Our study is a single-center, prospective cross-sectional study comparing the effects of hysterectomy performed for benign gynecological reasons with the types of operations on early ovarian reserve. We included a total of 82 patients who were scheduled for benign uterine hysterectomy at to the Health Sciences University Bursa Yüksek Ihtisas Training and Research Hospital, Department of Obstetrics and Gynecology, between July 2021 and March 2022. The Clinical Research Ethics Committee

of the University of Health Sciences Bursa Yüksek Ihtisas Training and Research Hospital approved the research (Date: 23.06.2021, No: 2011-KAEK-25 2021/06-10). The patients were given detailed information about our study and the operation, and informed consent was obtained. Preoperative care of each patient and control one month after the operation was planned. Patients who agreed to come for this follow-up and volunteered to participate in the study were included.

Patients' age, height, weight, body mass index, parity, previous operation history, hysterectomy indication, and type of hysterectomy performed were recorded. In addition, ovarian volume, number of antral follicles, AMH, FSH, and estradiol (E2) values were evaluated and recorded by transvaginal ultrasonography performed on the third day of menstruation and in the first month postoperatively.

The same gynecologist also performed a total laparoscopic hysterectomy and bilateral salpingectomy. In this process, round and utero-ovarian ligaments were sealed and cut by Ligature 10 (Covedian 1037 with a blunt tip as a bipolar vessel sealing device, used with a force trial generator to provide a permanent fusion for the vessels up to 7 mm diameter and heat spread depending on the tip and the duration of activation). The uterine artery was sealed (cutting mood, power 40 W) and cut by bipolar cautery (Günter Bissinger Medizintechnik 's Powergrip bipolar), and the bladder was separated by sharp dissection. Finally, the vaginal cuff was cut by monopolar cautery and sutured. During both processes, if present, adhesion of the bowel and omentum to the anterior wall of the abdomen was released.

Patients who had a history of using drugs that would affect ovarian reserve, any surgical procedure to the ovaries during the operation, patients who had no menstrual bleeding in the past year, and patients with malignancy were excluded from the study. Preoperative blood samples were taken from the patients on the third day of their menstruation for the hormone profile. Blood samples were studied in the central laboratory of Bursa Yüksek Ihtisas Training and Research Hospital. AMH was measured by the ELISA method (Beckman Coulter-Inc). Reference ranges were taken for AMH as 0.01-6.2 ng/ml (8). Preoperative transvaginal ultrasonography (TVUSG) (GE Voluson 730 4D MHZ) was used to calculate ovarian volume and antral follicle count. The volume of each ovary was calculated by taking measurements perpendicular to each other (length × width × depth × 0.52 = volume). We measured and averaged the diameters of both ovaries. In TVUSG, follicles with a diameter of 2-10 mm were counted as antral follicles. The antral follicles in both ovaries were counted, and the largest antral follicles were sampled. Ultrasonographic measurements were performed by the same specialist doctor. Patients were called in for follow-up in the first month after surgery, and serum hormone levels were evaluated. The average of both ovarian volumes or the ovarian tissue left in after the operation was measured with TVUSG, and the antral follicle numbers were calculated.

Statistical analysis

The conformity of the data to the normal distribution was examined using the Shapiro Wilk test. Normally distributed continuous data are defined by mean and standard deviation, and non-normally distributed continuous data are defined by median and minimum-maximum values. Normally distributed continuous data between the two groups were compared with the Student's t test and non-normally distributed continuous data were compared with the Mann-Whitney U test. The comparison of categorical data between the two groups was made with chi-square and Fisher's exact chi-square test, and descriptive statistics were given as frequency and percentage. The Fisher-Freeman Halton test was used to compare categorical data for more than two groups. SPSS v23 (SPSS, IBM, USA) package programs were used in the analysis of the data. In the statistical analyses, α=0.05 was taken as the level of significance.

RESULTS

Eighty-two patients were included in the study. Patients were classified into 2 groups abdominal (n=54) and laparoscopic (n=28) hysterectomy. Patients with a preoperative AMH value greater than 0.01 ng/ml and an FSH value less than 15 IU/L were included in the study. After the hysterectomy, two patients whose laboratory derived FSH value could not be measured, six patients whose AMH value could not be measured, and two patients due to the inability to visualize the ovaries on USG were excluded in the comparison according to the types of surgery.

The number of patients who underwent abdominal hysterectomy was 54, and the mean age was 44. The body mass index (BMI) median value was 28.3; parity was calculated as 2. The mean surgical time was 119 minutes (95% confidence level, mean between 108.80 and 129.60 minutes), and the mean amount of bleeding was 206 ml (95% confidence level, mean between 161.72 and 250.28 ml). The number of patients who underwent L/S hysterectomy was 28. The average age was also 46. Median values were calculated as BMI 28.8, parity 3. The mean operative time was 122 minutes (95% confidence level, mean between 105.54 and 139.66 minutes), and the mean amount of bleeding was 134 ml (95% confidence level, mean between 70.03 and 198.77 ml) in this group. When the two groups were compared statistically, there was no difference in terms of BMI. Age, parity, amount of bleeding, and mean operative time values were found to be statistically significant. The sociodemographic and operative data of the patients are summarized in Table 1.

Table 1: Comparison of demographic characteristics, surgical findings and preoperative and postoperative AMH and FSH values of the study groups

	Abdominal hysterectomy (n=54)	Laparoscopic hysterectomy (n=28)	p-value
	Mean±SD; Median (Min-Max)	Mean±SD; Median (Min-Max)	
Age (years) β	44 (21-49)	46 (38-49)	0.025
Body Mass Index (kg/m2) β	28.3 (18.3-48.9)	28.8 (23.4-37.1)	0.89
Parity β	2 (0-7)	3 (2-9)	0.01
Duration (min) *	119.2±3.9	122.6±4.4	0.01
Bleeding (ml) *	206±16.6	134.4±16.6	0.01
Preoperative AMHβ (ng/ml)	0.37 (0.02-3.48)	0.11 (0.02-2.45)	0.021
Preoperative FSH (IU/l) β	4.9 (0.14-14.5)	9 (1.28-15)	0.013
Postoperative AMHβ (ng/ml)	0.14 (0.01-1.5)	0.01 (0.01-2.2)	0.02
Postoperative FSH (IU/l)β	**10.1 (3-89)**	**20 (5-87)**	**0.013**

AMH: Anti Mullerian Hormone, FSH: Follicle Stimulating Hormone, SD: Standard deviation, Min: Minimum, Max: Maximum, *: Student t test, β: Mann Whitney U test

The hormone profile data of the patients were compared according to the type of operation. When the pre- and post-operative values were compared, it was observed that the AMH value decreased in both operation types, and the FSH value increased in both operation types. Table 1 presents the analysis of the data.

In the analysis comparing E2 values in both hysterectomy types, it was found that the E2 value of 21 patients who underwent abdominal hysterectomy and 12 patients who underwent L/S hysterectomy was increased; E2 values of 33 patients who underwent abdominal hysterectomy and 16 patients who underwent L/S hysterectomy were decreased. When the data of both groups were compared, no significant difference was found (p=0.72). Statistical data comparing E2 values are given in Table 2.

The percentage of reduction in AMH levels between the two types of hysterectomy performed was evaluated (Table 3). Six laboratory-derived patients were not included in the evaluation. In the assessment made on 76 patients, the median percent decrease in AMH was 49.4±28.7; in L/S hysterectomy, it was calculated as 37.5±34.4. When the two groups were compared with each other, no significant difference was found (p=0.13).

Preoperative and postoperative 1st-month FSH was measured in each patient. However, two patients of laboratory origin could not be included. In the FSH samples taken

Table 2: Analysis table of serum estradiol values according to hysterectomy types

	Abdominal hysterectomy n (%)	Laparoscopic hysterectomy n (%)	n (%)	X^2	p*
Increased E2	**21 (63.6%)**	**12 (36.4%)**	**33 (100%)**	**0.121**	0.72
Decreased E2	**33 (67,3%)**	**16 (32,7%)**	**49 (100%)**		

E2: Estradiol, *: Pearson Chi-Square, p<0.05 was considered significant

Table 3: Comparative analysis of percent decrease in anti-mullerian hormone parameters between groups

	Abdominal hysterectomy (n=49)	Laparoscopic hysterectomy (n=27)	p-value*
	Mean±SD	Mean±SD	
Anti-müllerian hormone reduction percentage	49.4±28.7	37.5±34.4	0.13

SD: Standard deviation, * Student-t test, p<0.05 was considered significant

from 80 patients, an increase was observed in both types of operation compared to the preoperative period. In the statistical evaluation based on the FSH change value and increase rate between the groups, a significant increase was observed in the L/S type compared to the abdominal type (FSH change value p:0.03 and FSH increase rate p=0.03) (Table 4).

Evaluation of ovarian reserve was performed ultrasonographically in all patients. Still, one patient who had undergone an abdominal hysterectomy and another who had undergone an L/S hysterectomy were excluded for reasons such as postoperative mobility of the ovaries and obesity. By taking the width, height, and depth measurements of both ovaries in three dimensions, volume calculations were made with the formula D1xD2xD3x0.523, and the average of the sum of the volumes of both ovaries was taken. Follicles between 2-10 mm in the ovaries were accepted as antral follicles, and AFS was examined. The change in preoperative and postoperative ovarian volume and AFS were inspected. When the changes in preoperative and postoperative ovarian volume and AFS were examined in both types of operation, both types of ovarian volume and AFS were decreased. When the two operation types were compared, no significant difference was observed (p=0.59, p=0.57, respectively). Ovarian volume and AFS of both types of hysterectomy are evaluated in Table 5.

DISCUSSION

Hysterectomy is the second most common type of surgery performed by gynecologists after cesarean section in the reproductive age. The total number of hysterectomies performed for benign reasons in our gynecology clinic last year was 470; 260 were done abdominally, 136 laparoscopically, and 74 vaginally. In 103 abdominal cases and 42 laparoscopic cases, only hysterectomy was performed, while oophorectomy was not performed. The abdominal/laparoscopic hysterectomy rate in our study was consistent with the annual total abdominal/laparoscopic hysterectomy rates in our department. Salpingoopherectomy was performed in 53% of these hysterectomies. Salpingoopherectomy was performed in 53% of these hysterectomies. The number of patients in the study was also distributed into groups in proportion to the number of surgeries in our department, following the literature examples (9).

This study aimed to evaluate the early period ovarian reserve according to the operation type of hysterectomy performed for benign reasons. As a result, AMH levels, ovarian volume, and the number of antral follicles decreased significantly in the first month postoperatively for all participants when compared before and after surgery; it was observed that FSH levels increased significantly. There was no significant variation in E2 levels. The second aim of our study was to evaluate whether the early postoperative changes of ovarian reserve differ according to the type of surgery. As a result of the study, we observed a decrease in serum AMH values in the early period in both types of operation. The percentage of reduction in AMH parameters was not significant in both types of operation. Also, the decrease in mean ovarian volume and AFS in the ultrasonographic examination

Table 4: Comparison analysis table in terms of the amount and rate of increase in FSH parameters between groups

	Abdominal hysterectomy (n=52)	Laparoscopic hysterectomy (n=28)	p-value *
	Mean±SD; Median (Min-max)	Mean±SD; Median (Min-max)	
FSH exchange value (IU/L)	3.9 (0.2-85.3)	12.3 (0.4-72.8)	**0.03**
FSH increase rate (%)	1.8 (0.3-24.4)	3.2 (1.1-10)	**0.03**

FSH: Follicle Stimulating Hormone, SD: Standard deviation, *: Mann Whitney-U test, p<0.05 was considered significant

Table 5: Comparison analysis table in terms of decrease in Ovarian Volume and Antral Follicle Count parameters between the groups

	Abdominal hysterectomy (n=52)	Laparoscopic hysterectomy (n=28)	p-value*
	Mean±SD; Median (Min-max)	Mean±SD; Median (Min-max)	
Ovarian volume change (ml)	2.5 (0.5-10.7)	3.2 (0.0-7.5)	0.59
Change in the number of antral follicles	2 (0.0-6)	2 (0-7)	0.57

SD: Standard deviation, *: Mann Whitney-U test, p<0.05 was considered significant

were insignificant in both operation types. We found that serum FSH values after surgery increased significantly in the L/S type compared to the abdominal type.

The main difference between laparoscopic hysterectomy and non-laparoscopic hysterectomy is that electrothermal vessel ligation is used more frequently in laparoscopy. Usually, vessel sealing is accomplished with sutures using Vicryl or Silk during vaginal or abdominal hysterectomy. Electrothermal vessel ligation may damage ovarian flows, thereby accelerating follicular depletion and premature menopause (10). However, to our knowledge, there is limited literature comparing changes in ovarian reserve after laparoscopic and abdominal hysterectomy. In the results of a study conducted with the participation of 50 patients examining the change in ovarian reserve markers after laparoscopic ovarian cystectomy (LOC), it was found that ovarian reserve decreased after LOC, independent of the presence of endometrioma, which can be distinguished by serum AMH levels (11). In another study examining the effects of total salpingectomy performed during abdominal hysterectomy on ovarian reserve and ovarian stromal blood flow, it has been reported that mean FSH, LH, estradiol values and ovarian volume did not change, but mean pulsatility index, resistance index and systole/diastole (S/D) ratio decreased significantly compared to the initial values (12). In another study on 30 premenopausal women evaluating the short-term effects of salpingectomy performed during laparoscopic hysterectomy on ovarian reserve, in which the ovaries were planned to be preserved, the mean serum AMH values measured before and after the operation were compared; it was reported that salpingectomy does not have short-term harmful effects on ovarian reserve (13).

In our study, FSH values increased more significantly in L/S type hysterectomies in the early postoperative period compared to the abdominal method. We think that the negative feedback effect on FSH disappears due to the decrease in inhibin-B secreted from the granulosa cells, which is caused by the destruction of the granulosa cells in the follicles, in addition to the thermal heat used in L/S surgery, and this is the reason for the early increase in FSH. In a study in which ovarian reserve tests were evaluated to determine the histologically defined follicle pool, a post-oophorectomy specimen and serum ovarian reserve tests were compared, and it was mentioned that the first change in the early perimenopausal period was the suppression of serum E2 values with the increase in FSH due to the decrease in inhibin-B (14). The decrease in ovarian volume and the decrease in AFS, which we analyzed in our study's early postoperative ultrasonographic examination, are other reasons for the increased FSH levels.

It is controversial that only the infundibulopelvic ligament can provide perfusion of the ovaries in a hysterectomy performed as an ovarian-sparing surgery. In the literature, various studies compare ischemia due to perfusion damage in the ovaries between cutting and burning the uterine artery with electrothermal effect and ligating it with sutures. In our study, we observed that ovarian volume was higher in the L/S type between the two groups in which ovarian volume and AFS decreased in all patient groups in the early postoperative ultrasonographic imaging.

The critical aspect of our study is that in the early postoperative period, serum AMH, FSH, and E2 values should be evaluated together with inhibin-B, and the correlation of high FSH and variable E2 values with inhibin-B might be necessary. There need to be more studies on inhibin-B in the literature. In addition, increasing the total number of volunteers and working with different populations are other study limitations.

It is obvious that the ovarian reserve decreases after ovarian-sparing hysterectomy. Our study also supports this. There was no significant difference in AMH levels, ovarian volume and AFS reduction levels when compared according to hysterectomy types.

CONCLUSION

As a result, there is evidence in the literature that ovarian-sparing surgery when performed in women who do not carry the risk of ovarian cancer is life-long. It is still discussed whether L/S type hysterectomy causes more damage to the ovary with electrothermal effect. With the development of new surgical devices and techniques, minimally invasive surgery indications are expanding. Electrothermal devices with the least power should be used whenever possible. Electrothermal energy used in laparoscopic hysterectomy may cause additional damage to ovarian reserve. Prospective large-scale studies are needed to investigate its effect on ovarian reserve compared to abdominal surgery.

Ethics Committee Approval: This study was approved by University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Date: 23.06.2021, No: 2011-KAEK-25 2021/06-10).

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