

# A prospective cohort study to assess the change in ovarian reserve after laparoscopic surgery in patients with endometriosis

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## SUMMARY

**AUTHORS' CONTRIBUTION:** (A) Study Design · (B) Data Collection · (C) Statistical Analysis · (D) Data Interpretation · (E) Manuscript Preparation · (F) Literature Search · (G) No Fund Collection

**Introduction:** Endometriosis results in impairment of the physiological mechanisms of ovulation, with fewer follicles found in ovaries. The current study aims to assess ovarian reserve (FSH, E2, AMH, and AFC) in infertile patients with endometriosis after laparoscopy

**Methodology:** This prospective cohort study was done in a private hospital in Saudi Arabia from January 2022 to June 2022. Sixty cases were divided equally into three groups, each 20 patients (after laparoscopy was done): Group 1: Patients with severe endometriosis (stage 3 or 4) as proven by laparoscopy, while Group 2: Patients with minimal or mild endometriosis (stage 1 or 2) as proven by laparoscopy Group 3: Patients with tubal obstruction without endometriosis. Ovarian reserve markers (FSH, E2, AMH, and AFC) were measured pre-operative in all groups and three months post-operative in the group of severe endometriosis. ANOVA and the Post Hoc Turkey test were used to compare the three groups.

**Results:** Preoperatively, cases of severe endometriosis had significantly lower ovarian reserve than cases with mild endometriosis and no endometriosis regarding AMH ( $6.5 \pm 1.5$ ,  $10.75 \pm 1.0$ ,  $11.15 \pm 2.25$  with  $P < 0.001$ ) and regarding AMH ( $1.94 \pm 1.06$ ,  $1.51 \pm 0.86$ ,  $2.3 \pm 1.0$ ,  $P = 0.048$ ). Surgery further reduced ovarian reserve in the group of severe endometriosis regarding FSH ( $8.89 \pm 2.8$ ,  $9.78 \pm 2.78$ ,  $P = 0.015$ ), AMH ( $1.85 \pm 1.12$ ,  $1.36 \pm 0.82$ ,  $P < 0.001$ ), and AFC ( $6.53 \pm 1.62$ ,  $7.65 \pm 1.37$ ,  $P < 0.001$ ).

**Conclusion:** Severe endometriosis decreases ovarian reserve, with a further decrease after surgery.

**Keywords:** Severe endometriosis; Surgery; Ovarian reserve

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## INTRODUCTION

Endometriosis is the presence of endometrial glands and stroma outside the uterine cavity. The prevalence of endometriosis is rising to 10% in women of reproductive age. Endometriosis can affect fertility in 30% of women [1]. The pathology can be pelvic and extra pelvic endometriosis. The most common sites affected by pelvic endometriosis are the ovary and pelvic peritoneum. It may result in ovarian chocolate cysts (endometrioma) and pelvic adhesions [2].

Endometriosis affects ovarian function and causes a decrease in the number of ovarian follicles [3]. Also, the spontaneous ovulation rate is lower in endometriotic patients when compared to age-matched control [4]. Laparoscopy is considered the gold standard modality in diagnosing and treating pelvic endometriosis. Several studies proved the decrease in ovarian reserve after laparoscopic treatment [5]. Best predictors for ovarian reserve are Antral Follicular Count (AFC), Anti Mullerian hormone, serum E2 and FSH [6].

## AIM

The current study aims to assess ovarian reserve (FSH, E2, AMH, and AFC) in infertile patients with endometriosis and to assess if there is a post-laparoscopic decrease in ovarian reserve in cases of severe endometriosis.

**Design:** This prospective cohort study was done in a private hospital in Saudi Arabia from January 2022 to December 2022.

## PATIENTS AND METHODS

All women attending the infertility clinics in our hospital and scheduled for laparoscopy and fulfilling the inclusion criteria, which are age 18-35 years, regular menses, normal TSH level, BMI  $< 30$  kg/m<sup>2</sup>, and normal semen analysis of their husband, while those with endocrine disorders, previous surgery for endometriosis, or those with a cause of infertility other than endometriosis (except for those with tubal factors of infertility who served as a control group) were excluded from the study. Women who agreed to participate in the study signed informed consent and were recruited for this study.

The studied cases were sixty cases divided into three groups (after laparoscopy was done):

**Group 1:** Patients with severe endometriosis (stage 3 or 4) as proven by laparoscopy according to American Society for reproductive medicine classification [7].

**Group 2:** Patients with minimal or mild endometriosis (stage 1 or 2) as proven by laparoscopy.

**Group 3:** Patients with tubal obstruction without endometriosis.

All cases were exposed to detailed medical history and complete clinical examination. An infertility workup was recorded (hormonal profile, pelvic ultrasound, HSG, and semen analysis).

Blood samples were done for day 2 FSH, AMH, and Estradiol, in addition to the transvaginal ultrasound done on the same day to measure the AFC and diameter of all selected follicles. After a few days, laparoscopy was done on all cases, which confirmed cases diagnosed pre-operatively with ovarian endometrioma, inspected the pelvis to determine the stage of endometriosis, adhesiolysis, and ovarian cystectomy by drainage of content, stripping the cyst wall and coagulation of any unremoved endometriotic tissue using bipolar coagulation. All cases were done following the same routine steps. Three months later, on day 2, FSH, AMH, Estradiol, and AFC were done for all the patients.

The primary outcome to evaluate ovarian reserve in cases of severe endometriosis through measuring (FSH, E2, AMH and AFC).

The secondary outcomes to evaluate postoperative ovarian reserve (FSH, E2, AMH and AFC) three months after surgery.

**Sample size calculation:** The study included all women fulfilling the inclusion and exclusion criteria who were admitted between January 2022 to December 2022 at our hospital.

## Statistical analysis

Statistical analysis is performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Numerical data were checked for normal distribution by the Shapiro-Wilk test. The chi-square test was used to compare qualitative parameters. The one-way analysis of variance (ANOVA) was used when comparing more than two means. The Post Hoc Tukey's test was used for multiple comparisons between different variables, and Paired sample t-test of significance was used when comparing related samples.  $P \leq 0.05$  was considered significant.

## RESULTS

There was no significant difference between 3 groups as regard age and BMI. There was a high statistical difference between the three groups as regard period of infertility being highest in the group of severe endometrioses (**Tab. 1.**).

There was a high statistically significant difference between the three groups regarding AFC and AMH, being lowest in the severe endometriosis group. There was no statistically significant difference between the three groups as regards FHS or E2 (**Tab. 2.**).

After laparoscopy, three patients got pregnant in the severe endometriosis group and were excluded from follow-up. **Tab. 3.** compares ovarian reserve markers in 17 patients before and after laparoscopy. There was a significant decrease in the AFC and AMH in the group of severe endometrioses before and after laparoscopy by three months. While there was no statistical difference in serum estradiol before or after laparoscopy. There was a small significant increase in serum FSH after laparoscopy by three months.

## DISCUSSION

Laparoscopy is considered the gold standard modality for excision of ovarian endometriomas. It causes reduction in the recurrence rate and an improvement in the ovation rate [8]. Several studies proved that laparoscopy can negatively affect postoperative ovarian reserve [5].

**Tab. 1.** Comparison between groups as regards patients' characteristics.

Variables	Group 1 Severe Endometriosis (n=20)	Group 2 Mild Endometriosis (n=20)	Group 3 Tubal Obstruction (n=20)	F-test	p-value
Age (years)	25.75 ± 3.88B	29 ± 4.69A	29.2 ± 2.97A	4.906	0.011*
BMI (Kg/m <sup>2</sup> )	25.84 ± 1.57	25.96 ± 1.42	26.2 ± 1.83	0.257	0.774
Infertility duration	3.15 ± 1.59B	1.68 ± 0.78C	4.05 ± 2.78A	7.904	<0.001**

Tests used are ANOVA and post Hoc Tukey's test p-value >0.05 NS; \*p-value <0.05 S; \*\*p-value <0.001 HS

**Tab. 2.** Comparison between groups as regard ovarian reserve markers.

Variables	Group 1 Severe Endometriosis (n=20)	Group 2 Mild Endometriosis (n=20)	Group 3 Tubal Obstruction (n=20)	F-test	p-value
AFC: Total	6.5 ± 1.5B	10.75 ± 1.59A	11.15 ± 2.25A	40.490	<0.001**
E2 (pmol/ml)	132.08 ± 61.77	122.85 ± 58.44	143.65 ± 65.25	0.567	0.570
FSH (miu/ml)	9.02 ± 2.69	8.54 ± 1.63	7.6 ± 2.08	2.201	0.120
AMH (ng/ml)	1.94 ± 1.06	1.51 ± 0.86	2.3 ± 1.03	3.210	0.048*

Tests used are Chi-square test, ANOVA and post-Hoc Tukey's test; Different capital letters indicate significant difference at ( $p < 0.05$ ) among means in the same column; p-value >0.05 NS; \*p-value <0.05 S; \*\*p-value <0.001 HS

**Tab. 3.** Comparison between preoperative and postoperative ovarian reserve markers in the group of severe endometriosis (group 1). (Three cases got pregnant in group 1 before the three months follow-up, so they were excluded from the follow-up).

Variables	Pre-operative Group 1 (n=17)	Postoperative Group 1 (n=17)	p-value
E2	125.1 ± 51.93	126.66 ± 52.04	0.517
FSH	8.89 ± 2.8	9.78 ± 2.78	0.015*
MFD	6.49 ± 0.75	6.33 ± 0.69	0.052
AMH	1.85 ± 1.12	1.36 ± 0.82	<0.001**
AFC	6.53 ± 1.62	7.65 ± 1.37	<0.001**

### The results of the present study and their interpretation

In the present study, patients' age was not statistically significant between the groups, with ranges of 25.75 ± 3.88, 29 ± 4.69 and 29.2 ± 2.97, respectively. The results of the present study showed a highly significant difference between the three groups regarding infertility, AMH, and AFC, as it was worst in the severe endometriosis group.

These ovarian reserve markers have worsened significantly after laparoscopy by 3months. So, the current study confirmed that cases of severe endometriosis had significantly lower ovarian reserve than cases with mild endometriosis and no endometriosis (the group with the tubal factor of infertility) and that surgery to cases with severe endometriosis lower further the ovarian reserve as evident in the comparison between ovarian reserve parameters both pre and postoperative. These results can be interpreted that endometriosis may affect almost any step of reproduction, including altered folliculogenesis, ovulatory dysfunction [9], reduced preovulatory steroidogenesis of granulosa cells [10]. The ovarian reserve is related to the number of primordial follicles present in the cortex, so in inadvertent removal of the cortex and the damage caused by the surgery causes loss of good numerous follicles to be lost, and so affects AMH production to be significantly downregulated.

### Comparison of the results of the present study to similar studies

In the study of Song T, et al. there was a significant the decrease in AMH and AFC (the ovarian reserve) after laparoscopic excision of endometriomas. They excluded the cause of this decrease attributed to surgical techniques used in laparoscopy or to laparoscopists [11].

In the study conducted by Uncu G, et al. [5], they studied the correlation between baseline preoperative (baseline) AMH states and postoperative AMH decline; they found a significant decrease in AMH after laparoscopic surgery. Notably, although patients with high baseline AMH concentrations (high ovarian reserves) may lose a higher proportion of this reserve, they may still have a higher residual reserve than those with low AMH levels preoperatively [5].

Goodman LR, et al. suggested that bilateral endometriomas surgery has a higher impairment on the

ovarian reserve [12]. Although the influence of surgery appears lesser when only one ovary is involved, Ferrero S, et al. [12] addressed a higher risk of ovarian failure during laparoscopic surgery for recurrent unilateral endometrioma compared to unilateral cases. The severity of endometrioma, based on the revised American Society for Reproductive Medicine scoring, is likely to predict the decline of post-operative serum AMH levels [13] Wang Y, et al. [13], in their study, found that the decline in the levels of AMH following cystectomy was a short-term effect and the recovery was observed within one year. AMH concentrations decreased significantly after one year in patients with bilateral endometriomas, in patients with cyst size >7 cm, and in stage IV endometriosis [13]. In a great number of cases, the effect of the excision of endometrioma on the ovarian reserve is unpredictable. The long-term effect of surgical excision of endometriomas on AMH levels requires in-depth studies.

### CLINICAL IMPLICATIONS FOR FURTHER STUDIES

Recurrent surgeries for endometriosis cause a decrease in ovarian reserve, so either postoperative medical treatment should be applied and to fasten the step of ART to perverse the ovarian reserve.

### STRENGTH AND LIMITATIONS OF CURRENT STUDY

The current study has the advantage of pre-operative comparison between mild and severe endometriosis and cases with no endometriosis; however, the current study's limitations include the relatively small sample size.

### RECOMMENDATIONS FOR FURTHER STUDIES

Larger numbers of patients are needed to determine the optimum surgical management of ovarian endometriosis without much affection of ovarian reserve.

### CONCLUSION

Severe endometriosis decreases ovarian reserve, with further decrease occurring after surgery.

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