EFFECT OF LAPAROSCOPIC OVARIAN CYSTECTOMY FOR ENDOMETRIOMA ON OVARIAN RESERVE

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ABSTRACT

Background: To assess the effect of laparoscopic ovarian cystectomy for endometrioma on ovarian reserve by markers as Anti-Mullerian Hormone and Follicle Stimulating Hormone.
Subjects: 48 Women of reproductive age who had ultrasonographic diagnosis of endometrioma measuring>3cm whether unilateral or bilateral and subjected to laparoscopic excision.
Methods: From January 2017 to December 2017, Women with endometrioma underwent to laparoscopic excision. Serum AMH and FSH were determined preoperatively and 3months postoperative.
Results: There was a statistically significant reduction in postoperative mean value of AMH (2.04+ 1.69) when compared to the preoperative mean value of AMH (2.59+ 1.85) and a statistically significant rise in postoperative mean value of serum FSH (7.23+ 1.48), when compared to preoperative mean value of FSH (5.50+ 1.85). Post-operative AMH decreases were greater in patients with endometriomas > 5cm in diameter compared with smaller ones and in patients with bilateral endometriomas compared with unilateral ones.
Conclusion: Laparoscopic cystectomy for endometrioma has an adverse impact on ovarian reserve. Bilaterality and size of endometrioma increase the adverse effect of Laparocopic ovarian cystectomy on the ovarian reserve.
Keywords: Endometrioma, Laparoscopic cystectomy, Anti-Mullerian hormone, Follicle stimulating hormone.
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INTRODUCTION

Endometriosis refers to the presence of endometrial glands and stroma outside the normal uterine cavity. It represents 0.8-2% of women of reproductive age [1].

Despite the failure to demonstrate a causal relationship between endometriosis and infertility, over a third of women with endometriosis encounter issues with infertility suggesting an association [2].

Endometrioma is the formation of ovarian cyst lining by endometrial glands and stroma, surrounded by a pseudo capsule adjacent to the healthy ovarian tissue. It is present in 20%-40% of women with endometriosis [3]. It may be associated with infertility, dysmenorrhea and chronic pelvic pain [4].

Endometriomas have a gonadotoxic effect on the surrounding follicles [5] and cause fibrosis, reduced vascularization, loss of cortex-specific stroma and atresia in the recruited follicles resulting in a decline in the antral follicle count [6].

Initial surgery is suggested as the preferred therapeutic approach for women with symptomatic or enlarging endometriomas as medical therapy is unlikely to result in complete regression of endometriomas larger than 1 cm and precludes a definitive histologic diagnosis [7] but evidence exists that supports surgical excision of ovarian endometriomas, as well as evidence that cautious against surgical intervention. Certain factors need to be examined closely before proceeding with surgery or continuing with expectant management. These include the patient's symptoms, age, ovarian reserve, size and laterality of the cyst, prior surgical treatment, and level of suspicion for malignancy [8].

The standard approach to the ovarian endometrioma is laparoscopic excision of the cyst capsule with the stirpping technique (Hart et al., 2008). Evidence-based guidelines suggest surgical excision in case of symptomatic or large (> 3 cm) endometriomas [9]. Surgical excision may affect ovarian reserve due to inadvertent removal or destruction of the

healthy ovarian tissue adjacent to the pseudocapsule of the cyst [10]. Laparoscopic surgery has the advantage of short duration of operation, hospital stay, less blood loss and less adverse effect on ovarian reserve than traditional surgery [11].

Ovarian reserve refers to the functional potential of the ovary, which reflects the number and quality of the follicles left in the ovary [10].

The most reliable measure of ovarian reserve is assessing the Anti-Mullerian Hormone as it is menstrual cycle independent and unaffected by the use of hormonal drugs [12],[10]. AMH is thought to be a reliable measure of the size of ovarian follicle pool [13] so reduction in the number of small growing follicles is followed by reduction in circulating AMH [14].

Another method is basal (day 3) FSH which is the most studied and used endocrine test in determining ovarian reserve [15]. Lower day 3 FSH levels represent satisfactory ovarian reserve and higher levels represent its declining [16].

Another reliable method is ultrasonographic follicle count AFC which is a direct measure of the follicle population and directly correlating with the ovarian reserve of a single ovary unlike AMH which is a systemic serum marker and expresses the ovarian reserve of both ovaries [17]. Ovarian reserve could be underestimated in the presence of endometrioma by AFC so the reduction in ovarian reserve caused by surgery might be compensated for by an improved ability to identify small follicles, once the endometriomas have been removed, when assessing ovarian reserve by AFC [18].

SUBJECTS AND METHODS

Patients;

This prospective interventional study was carried out in the outpatient clinic and Endoscopy Unit in Zagazig University hospital in the period from January 2017 to December 2017.

Sample size: Assuming that the attendance rate of endometrioma case is 2 per week so the total number of cases in 6 monthes (48 cases) were included in the study as a comprehensive sample.

Inclusion criteria were women of reproductive age (21-39 y) who had ultrasonographic diagnosis of endometrioma measuring>3cm whether unilateral or bilateral and subjected to laparoscopic cystectomy.

The exclusion criteria were women >40 years, prior ovarian surgery, pelvic radiotherapy or chemotherapy, irregular menstrual periods, presence of polycystic ovary syndrome and having used any medications that could affect ovarian function, e.g. GnRH analogues or oral contraceptives, during the 3 months preceding scheduled surgery.

Surgery;

The operation was done under general anesthesia with endotracheal intubation with no need for prophylactic antibiotics. The abdomen is inflated by CO2 using a Veress needle that was passed through a 1-cm umbilical incision until the intra-abdominal pressure reached 12 mmHg and a 10-mm main trocar was inserted then two puncture sites were incised suprapubic lateral to rectus muscles for two 5-mm trocars.

After inserting the laparoscope with 5mm ports, evaluation of peritoneal surfaces, diaphragm and liver were done and presence of ovarian endometrioma was confirmed. All adhesions were removed by sharp dissection and deep infiltrative endometriosis lesions were resected to the extent that restore normal anatomical relations. The ovaries were completely freed with obtuse and sharp dissection.

In the stripping of ovaries, the incision must be made on the antimesenteric surface, as far as possible from the ovarian hilus. After a cleavage plane between the cyst wall and ovarian cortex was identified, the ovaries were pulled slowly and gently in opposite directions by means of two atraumatic grasping forceps. After the cyst became free from the ovary, it was opened by electrocautery and contents were aspirated in order to reduce the mass size.

After removing the pseudocapsule from the abdominal cavity, Heparinized located ringer was used to irrigate the pelvis and to allow inspection for any bleeding site and if needed selective minimal (15 watts) bipolar coagulation of bleeding was performed, without excessive coagulation of the surgical defect to avoid damaging the ovary.

Histopathologic Analysis;

All resected cyst walls were sent to the pathology laboratory to confirm endometrioma and exclude any possibility of malignancy.

Hormonal assay;

For (day3) FSH and AMH the cycle immediately pre-operative and 3 months post-operative. Blood samples were obtained by venipuncture and the sera were extracted by centrifuge. Serum FSH assay was done on Roche / Hitachi Elecys 2010 Immunoassay Analyzer using Sandwich immunoassay. For Serum AMH assay, The patients' serum samples were collected and frozen at -20°C until AMH level is assayed by the AMH Gen II ELISA Kit for the quantitative detection of AMH.

Statistical Analysis;

The data were coded, entered and processed on computer using SPSS (version 18). Mean, standard deviation, range, frequency, and percentage were use as descriptive statistics.

The following test was done:

- Chi-Square testX^2 was used to test the association variables for categorical data.
- Student's paired t-test was used to assess the statistical significance of the difference between two population means in a study involving paired samples.

P value was considered significant as the following:

* $P > 0.05$: Non significant
* $P \leq 0.05$: Significant.

RESULTS

Table (I): Baseline characteristics (n=48).

Age(years)	28± 5.53
BMI(Kg\m^2)	27.65± 5.53
Endometrioma size(cm)	(3.50-10) 5.84± 1.60
Endometrioma involvement **Unilateral** **Bilateral**	 22(45.8%) 26(54.2%)
Infertility	40(83.3%)

BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
Values are given as mean±SD, number (percentage) and range.

Table (II): Comparison between preoperative measurement and postoperative measurement among the studied women .

Hormone	Preoperative (Mean ±SD)	Postoperative (Mean ±SD)	Paired t.test	P. value
AMH	2.59± 1.85	2.04± 1.69	13.50	<0.001
FSH	5.50± 1.85	7.23± 1.48	20.97	<0.001

There was statistically significant reduction in postoperative mean value of serum AMH compared to preoperative measurement (2.04, 2.59 respectively) p <0.001 and statistically significant rise in postoperative mean value of serum FSH compared to preoperative measurement (7.23, 5.50 respectively) p <0.001.

Table (III): Comparison between preoperative AMH and postoperative AMH regarding Age, BMI, Size and Laterality of endometrioma.

		Preoperative AMH	Postoperative AMH	Paired t.test	P
		Mean ± SD	Mean ± SD		
Age	Age from 20-25 years	2.68± .571	2.02± .373	11.57	<0.001
	Age 26-31 years	3.49± 2.70	2.85± 2.58	9.89	<0.001
	Age 32-39 years	1.26± 1.02	.993± .877	6.36	<0.001
BMI	average	1.95± .374	1.70± .320	13.22	<0.001
	overweight	2.97± 2.13	2.28± 2	15.55	<0.001
	obese	1.74± .914	1.41± .775	6.71	<0.001
Endometrioma size	<5cm	1.55± .936	1.2± .789	3.6	0.02
	>5cm	2.94± 1.95	2.35± 1.80	13.72	<0.001
Laterality of endometrioma	unilateral	2.69± 2.11	2.33± 1.93	4.1	0.01
	Bilateral	2.30± .596	1.80± .532	10.15	<0.001

There were statistically significant decrease of AMH after laparoscopic cystectomy regarding Age, BMI, Size and Laterality of endometrioma but more decrease in endometrioma >5cm compared to <5cm and more decrease in bilateral endometrioma compared to unilateral endometrioma.

DISCUSSION

The aim of the current study was to assess the short-term impact of laparoscopic ovarian cystectomy for endometriomas on certain ovarian reserve markers as serum FSH, serum AMH.

The result of the current study was a statistically significant reduction in postoperative mean value of AMH (2.04+ 1.69) when compared to the preoperative mean value of AMH (2.59+ 1.85) and a statistically significant rise in postoperative mean value of serum FSH (7.23+ 1.48), when compared to preoperative mean value of FSH (5.50+ 1.85).

These results are in agreement with the systematic review and meta-analysis conducted by Somigliana et al[13] 11 articles were included in the meta-analysis. Pooled data showed a significant reduction in serum AMH level after surgical treatment for ovarian endometriomas with the decline being more evident in women operated on for bilateral endometriomas.

Alborzi et al. [11] published a larger follow-up study of 193 women; this showed that AMH levels significantly decreased in the first week (1.66 ± 1.92 ng/mL),, third month (2.06 ± 2.5 ng/mL), and ninth month (1.77 ± 1.76 ng/mL) after operation compared to the preoperative levels (3.86 ± 3.58 ng/mL). In contrast, in a 3 month follow-up, AFC levels were significantly increased from baseline to the third postoperative month as AFC was underestimated in the presence of endometrioma. The FSH levels increased significantly from baseline (6.28 ± 3.79) to 3 months postoperatively (6.99 ± 3.92).

Ergun et al. [19] reported in his study that the serum AMH levels were found to decrease following the laparoscopic ovarian cystectomy and this finding could be accepted as an indicator of diminished ovarian reserve. The statistically-significant decrease in postoperative AMH levels were observed in laparoscopic cystectomy operations performed due to either ovarian endometrioma or ovarian cysts other than endometrioma. The amount of decrease in AMH levels was similar for the two groups. All those findings of diminished ovarian reserve could not be supported by pre and postoperative serum FSH and E2 levels.

Then, Saliholu et al., [20] supported that excision of endometrioma led to a significant decrease in AMH levels ($p<0.001$) but nonsignificant change in FSH levels and his explanation for this finding was that FSH is not relevant to ovarian reserve and the clinical outcomes of fertility but Ercan et al. [21] failed to show the negative effect of surgery on the ovarian reserve and stated that if surgery is carried out by an experienced physician with recognition of the cleavage of the cyst capsule and proper excision of the endometrioma, it is a safe approach and some studies have evaluated the effect of laparoscopic stripping of endometrioma on follicle-stimulating hormone and estradiol, other serum markers of ovarian reserve; these studies reported the ovarian-reserve markers were unaffected by laparoscopic surgery [22].

In the present study, post-operative AMH decreases were greater in patients with endometriomas > 5cm in diameter compared with smaller ones (p value <0.001 , 0.01 respectively) and in patients with bilateral endometriomas compared with unilateral ones (p value <0.001 , 0.02 respectively).

These results are in agreement with Kashi et al[23] who concluded from his study that Laparoscopic cystectomy was associated with post-operative decreases in serum AMH, particularly with bilateral involvement (p value in bilateral = 0.029 and in unilateral = 0.046) and endometriomas at least 50 mm in diameter (p value in ≥ 50mm was < 0.001 and in <50mm was 0.015).

Kwon et al. [24] showed a significant reduction in serum AMH after laparoscopic ovarian cystectomy on 100 women (68 had endometriomas while 32 had other benign cysts). The authors found that bilaterality was the only significant factor that predicted the rate of postoperative decline in AMH levels.

In another previous study, a reduced number of retrieved oocytes and impaired in

vitro fertilization outcomes were recorded among patients who had undergone bilateral cystectomy compared with patients who underwent unilateral cystectomy; a 2.4% ovarian-failure rate was recorded among patients who underwent surgery for bilateral endometriomas [25]

Based on 2013 ESHRE endometriosis guidelines[9], laparoscopic ovarian cystectomy is only recommended in the presence of ovarian endometriomas at least 4 cm in diameter; this could improve access to follicles, and possibly increase ovarian response.

ESHRE guidelines 2013 [9] have also recommended that patients with endometriomas should receive appropriate counseling as ovarian reserve was damaged following endometrioma excision.

In conclusion, the adverse impact of laparoscopic ovarian cystectomy for endometriomas on ovarian reserve as measured by serum AMH is evident from the current study as well as the previously published studies. The effect is more profound on large endometrioma > 5cm and bilateral lesions.

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