The Impact of Laparoscopic Ovarian Cystectomy on Ovarian Reserve in Cases of Endometrioma

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Abstract
Background: An endometrioma is one of the most common manifestations of endometriosis. Laparoscopic cystectomy is the preferred approach to managing bengin ovarian cysts in adolescents and adults, but unfortunately it affects the ovarian reserve.
Aim of the work: This study was aimed to evaluate the effects of laparoscopic cystectomy on ovarian reserve in patients with endometriomas.
Patients and methods: This prospective study was conducted on 44 cases suffering from ovarian endometriomas and subjected to laparoscopic cystectomy. The patients in the study were selected from the Outpatient Clinic in Sayed Galal University Hospital and EL-Gala Maternity Teaching Hospital. This study was conducted between April 2017and March 2018. Serum anti-mullerian hormone (AMH), FSH and E2, as well as the antral follicle count (AFC) were measured preoperatively and 3 months postoperatively.
Main outcome measures: Ovarian reserve based on the comparison of AMH alterations. The secondary end points are changes in FSH, E2 and AFC.
Results: There was a statistically significant reduction in postoperative median, values of AFC, serum, AMH, serum E2 and serum E2: FSH ratio, and a statistically significant rise in postoperative median serum FSH, when compared to preoperative measurements in included women.
Conclusion: The AMH level decreased and the FSH level increased after laparoscopic cystectomy for endometriomas, especially in older patients and those with bilateral cysts.
Keywords: Laparoscopic cystectomy, endometrioma, ovarian reserve.

Introduction:

Endometriosis is an estrogen-dependent, chronic, inflammatory disease prevalent worldwide in 10–30% of women of reproductive age and beyond. Characterized by the growth of endometrium-like tissue in aberrant locations outside of the uterus, it is responsible for symptoms including chronic pelvic pain, inflammation, dysmenorrhea, dyspareunia, and subfertility that degrade quality of life of women significantly [(1)]. Endometriosis lesions in the pelvis can be categorized as superficial peritoneal, ovarian, and deeply infiltrating. Similar to eutopic endometrial tissue, endometriosis lesions contain endometrial glands and stroma. [(2)].Patients with minimal to mild endometriosis are likely to have normal tubal-ovarian anatomical relationships and no endometriotic cysts involving their ovaries. Follow-up without active intervention is termed 'expectant management'. However, some of these couples will conceive without any treatment [(3)].Medical treatment options include nonsteroidal analgesics, hormonal contraceptives, gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors. As there are no data supporting one treatment or treatment combination over another, the treatment choice is based upon symptom severity, patient preferences, medication side effects, treatment efficacy, contraceptive needs, costs, and availability [(4)]. Endometriomas usually present as a pelvic mass arising from growth of ectopic endometrial tissue within the ovary [(2)].Ovarian reserve refers to the functional potential of the ovary, reflected as the number and quality of the remaining primordial follicles at any given time. There are various tests and markers of ovarian reserve, none of which has as yet been shown to be ideal. Static tests include age, FSH, LH, E2, FSH:LH ratio, antimullerian hormone (AMH), inhibin B, and sonographic variables such as ovarian volume, antral follicle count (AFC), and stromal blood flow. Dynamic tests include clomiphene citrate (CC) challenge test, exogenous FSH ovarian reserve test, and GnRH agonist stimulation test[(5)(6)].Recently, AMH has been suggested as the most reliable and reproducible marker, because it is menstrual

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cycle independent and unaffected by the use of hormonal drugs[7].

The aim of the study was to evaluate the impact of laparoscopic ovarian cystectomy on the ovarian reserve in females with ovarian endometrioma.

Patients and Methods

This prospective study included a total of 44 women presenting with pain or infertility due to ovarian endometriomas and subjected to laparoscopic cystectomy. The patients in the study were selected from the outpatient clinic in Sayed Galal University Hospital and EL-Gala Maternity Teaching Hospital. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between April 2017 and March 2018.

Inclusion criteria:

Patients complaining of infertility or pain due to ovarian endometriosis aging 18-35 years.

Exclusion criteria:

1-Women less than 18 or more than 35 years old.
2-Previous adnexal surgery.
3-Hormonal therapy (HT) or oral contraceptive (OC) for the past 3 cycles.
4- Other endocrine diseases such as thyroid Disease, hyper-prolactinoma, DM or adrenal disorders.
5- Suspected ovarian malignancy.
6-Evidence of premature ovarian failure (POF) or diminished ovarian reserve.

All patients were subjected to:

- Complete history taking including previous adnexal surgeries, present history of pain, menstrual irregularity, discharge "leucorrhea" due to pelvic congestion and obstetric history.
- **Examination included:**
- General examination, abdominal examination and gynecological examination:
- Investigations included "All at the day 3 of the cycle" (All pre-operative and 3 months post-operative)
    - Laboratory investigation; Serum E2, FSH and AMH.
    - Transvaginal ultrasound.
- **Procedures of laparoscopic ovarian cystectomy:**

It was done by the same group of surgeons to avoid bias.

The operation was done under general anesthesia with endotracheal intubation with no need for prophylactic antibiotics. Three puncture sites were incised one paraumbilical and two suprapubic lateral to rectus muscles, then the abdomen is inflated by C02.

After inserting the laparoscope with 5mm ports, evaluation of peritoneal surfaces, diaphragm and liver done and presence of ovarian endometrioma was confirmed. All adhesions removed by sharp dissection and deep infiltrative endometriosis lesions resected to the extent that restore normal anatomical relations. Then initial ovarian incision was done by electrocautery(22 cases unipolar electrocautery and 22 cases bipolar electrocautery) and cyst was separated from the ovary using traction and blunt dissection, after the cyst became free from the ovary it was opened by electrocautery and contents aspirated in order to reduce the mass size, then it was removed through one of the ports.located ringer was used to irrigate the pelvis and to allow inspection for any bleeding site.

B-Statistical Method

Statistical analysis was performed using Microsoft Excel version 2010 and SPSS for Windows version 20.0. Data was described as range, mean and standard deviation (for numeric parametric variables), range, median and interquartile range (for numeric non-parametric variables), or number and percentage (for categorical variables). Difference between two related groups was analyzed using paired student's t-test (for numeric parametric variables), Wilcoxon rank signed test (for numeric non-parametric variables), or McNemar's test (for categorical variables). Correlation between two metric variables was estimated using Pearson's correlation coefficient (for numeric parametric variables) or Spearman's rank correlation coefficient (for numeric non-parametric variables).Significance level is set at 0.05.

Results:

Table (1) Kolmogorov- Smirnov test of normality was applied to all measured variables (Table -1),

Table (1): Kolmogorov- Smirnov Test of Normality for measured Variables

	Test Statistic	**P**	**Distribution**
Age (years)	**0.124**	**0.090**	**Parametric**
Weight (kg)	**0.127**	**0.073**	**Parametric**
BMI (kg/㎡)	**0.159**	**0.077**	**Parametric**
Preoperative AFC	**0.181**	**0.001**	**Non- Parametric**
Preoperative Serum AMH (ng/ml)	**0.135**	**0.042**	**Non- Parametric**
Preoperative Serum FSH (mIU/ml)	**0.139**	**0.039**	**Non- Parametric**
Preoperative Serum E2 (pg/ml)	**0.243**	**0.000**	**Non- Parametric**
Preoperative SerumE2: FSH Ratio	**0.147**	**0.018**	**Non- Parametric**
Preoperative AFC	**0.149**	**0.015**	**Non- Parametric**
Preoperative Serum AMH	**0.132**	**0.043**	**Non- Parametric**
Preoperative Serum FSH	**0.180**	**0.002**	**Non- Parametric**
Preoperative Serum E2	**0.171**	**0.003**	**Non- Parametric**
Preoperative serum E2: FSH Ratio	**0.202**	**<0.001**	**Non- Parametric**

BMI body mass index(calculated as weigh (Kg) divided by squared height (㎡))
AFC antral follicle count
AMH anti-mullerian hormone, FSh follicle - stimulating hormone, E2 estradiol.

Table (2): Preoperative Measurements of Ovarian Reserve in included Women.

Preoperative AFC Range Median (IQR)	 5-16 9(6-9)
Preoperative serum AMH (ng/ml) Range Median(IQR	 0.1-4.8 1.45(0.63-3.03)
Preoperative Serum FSH (mIU/ml) Range Median(IQR)	 0.1-4.2 1.1(0.33-1.78
Preoperative Serum E2 (Pg/ml) Range Median (IQR)	 8-60 26(22-28)
Preoperative Serum E2:FSH Ratio Range Median (IQR)	 6.19-180 25.13(13.62-72.5)

IQR interquartile range (median 50% of ascendingly- ordered set of data
AFC antral follicle count, AMH anti mullerian hormone, FSH follicle hormone,
E2 estradiol.

Table (3): Dimensions, literally of endometriomas and ASRM class of included women

Average Dimension of Endometrioma (cm) Range Median (IQR)	 3-13 6.5(5-9)
Laterality of ovarian Endometrioma Unilateral Bilateral	 32(72.7%) 12(27.3%)
ASRM Class I II III IV	 0(0%) 24(54.5%) 13(29.5%) 7(15.9%)

IQR interquartile range (central 50%) of ascendingly- ordered set of data
Data presented as range, Median(IQR); or number (percentage)
ASRM American Society of reproductive Medicine.

Table (4): Postoperative Measurements of ovarian Reserve in included Women.

Postoperative AFC Range Median (IQR)	2-9 5.5 (3.3-8)
Postoperative Serum AMH (ng/ml) Median (IQR)	0.1-3.6 1 (0.4-1.9)
Postoperative Serum FSH mIU/mI Range Median (IQR)	1.8-5.2 2.85(2.2-3.55)
Postoperative Serum E2 (pg/ml) Range Median (IQR)	3-52 17(12.3-22)
Postoperative Serum E2:FSH Ratio Range Median (IQR)	0.58-18.57 5.98(4.12-8.42)

IQR interquartile range (median 50%) of ascendingly- ordered set of data
AFC antral follicle count
AMH anti- mullerian hormone
FSH follicle – stimulating hormone
E2 estradoil.

Table (5): Difference between Pre- and post-operative Measurements of Ovarian Reserve in Included Women.

	Preoperative Measurements	Postoperative Measurements	P*
AFC Range Median (IQR)	5-16 9(6-9)	2-9 5.5(3.3-8)	<0.001 HS
Serum AMH (ng/ml) Range Median (IQR)	0.1-4.8 1.45(0.63-3.03)	0.1-3.6 1(0.4-1.9	<0.001 HS
Serum AMH (ng/ml) Range Median (IQR)	0.1-4.2 1.1(0.33-1.78)	1.8-52 2.85(2.2-3.55)	<0.001 HS
Serum AMH (ng/ml) Range Median (IQR)	8-60 26(22-28)	3-52 17(12.3-22)	<0.001 HS
Serum AMH (ng/ml) Range Median (IQR)	6.19-180 25.13(13.62-72.5	0.58-18.57 5.98(4.12-8.42	<0.001

Discussion:

The standard management for ovarian endometriomas in one of the largest tertiary maternity centers in Egypt and the Middle East, namely Sayed Galal University Hospital, is laparoscopic derooting or cystectomy using electrosurgery.

The aim of the current study was to assess the short-term impact of such an intervention on certain ovarian reserve markers namely, serum FSH, serum E2, serum AMH and the AFC.

A total of 44 women presenting with pain or infertility due to ovarian endometrioma

were included in the study. The mean age of included women was 30.11 _+ 4.23 years (range: 21-37 years). The mean BMI was 31.33 _+ 4.05 kg/m2 (range: 26.56 -45.78 kg/m). Preoperative measurements of the mentioned ovarian reserve markers were noted. Recruited women were subjected to laparoscopic ovarian cystectomy using sharp dissection and electrocoagulation for hemostasis. Removed specimens were sent for histopathological confirmation of the diagnosis of endometriosis. Only women with histopathological diagnosis were included in the analysis.

Three-months postoperatively, the same ovarian reserve markers were re-measured.

There was a statistically significant reduction in postoperative median values of AFC, serum AMH, serum E2 and serum E2: FSH ratio, and a statistically significant rise in postoperative median serum FSH, when compared to preoperative measurements. Among them all, only two parameters that had postoperative values of clinically significant diminished ovarian reserve (DOR) in a number of included patients, namely: the AFC (with a cutoff < 4) [11 (25° 0) vs. 0 (0° 0), p=0.001] and the serum AMH concentration (with a cutoff < 1 ng/ml) [21 (47.70 0) vs. 17 (38.600), p=0.125]; with the former being a statistically significant change, while latter being a statistically non significant change.

The results of the current study are in agreement with **Chang *et al.*** [8] and **Iwase *et a1*.** [9] who first describes the adverse impact of cystectomy for ovarian endometrioma on the ovarian reserve.

Subsequently, several studies by **Raffi *et al.*** [10] and **Somigliana *et al.*** [11] addressed similar conclusions, the results of which were revised in two meta-analyses and showed a significant adverse impact of surgical treatment of endometriomas on ovarian reserve.

In the systematic review and meta-analysis conducted by **Raffi *et al.*** [10] 21 studies were reviewed; of them 8 were included in the meta-analysis. Pooled analysis of 237 patients showed a significant reduction in the serum AMH concentration following cystectomy for ovarian endometrioma [weighed mean difference -1.13 ng/ml, 95% CI (-0.37 to -O.188).

In the systematic review and meta-analysis conducted by **Somigliana *et al.*** [11] 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.

The results of **Muzzi *et al.*** [12] in a more recent systematic review and meta-analysis conducted on 13 studies (including 597 patients) showed that the AFC was significantly lower in the surgically-treated ovary when compared to the contralateral ovary [mean difference = 1.4, 95% CI (-2.27 to -0.52), p=0.002].

While the disagreement to our results based on revising the literatures which documented that the more presence of benign ovarian cysts was already shown to be associated with low serum AMH levels from the start, particularly with endometriomas.

In a study conducted 102 women with ovarian endometriomas and 48 women with mature cystic teratorna, **Kim *et al.*** [13] showed that preoperative serum AMH levels were significantly low in such two groups of women, when compared to age-and BMI-matched control group of women.

In a second study conducted 172 women with benign ovarian cysts (122 with endometriomas and 50 with non endometriotic cysts), **Somigliana *et al.*** [14] showed that serum AMH was significantly low in bilateral ovarian cysts regardless of the histology.

In contrast, **Streuli *et al.*** [15] showed, in a study conducted 313 women with endometriosis, that serum AMH was decreased only in women who had previous endometrioma surgery; thus negating the possible impact of the endometrioma per se on the ovarian reserve.

The advantage of AFC as a marker of ovarian reserve, is its ability to assess the impact of treatment on one ovary [16].

In addition, **Muzii *et al.*** [12] proposed the AFC as a more reliable marker than serum AMH, due to the inconsistent results and the methodological flaws in the studies assessing the value of the latter marker in assessing ovarian reserve.

In the prospective study conducted by **Wahd *et al.* [17],** AFC was the best predictor (when compared to serum FSH, serum AMH and serum E2) for ART outcomes in women with ovarian endometriomas whether previously treated surgically or not.

The pathogenesis underlying the adverse impact of surgical management of ovarian endometrioma has been a matter of research. The most accepted explanation by **Matallotakis *et al.*** [18] and **Bongioanni *et al.*** [19] is the use of electrocoagulation for hemostasis after ovarian cystectomy.

In conclusion,the adverse impact of laparoscopic ovarian cystectomy for endometriomas on ovarian reserve as measured by serum AMH and AFC is evident from the current study as well as the previously published studies.The effect is more profound on obese women and those with bilateral lesions.

Conclusion: It could be concluded that Anti-mullerian hormone decrease significantly after Laparoscopic ovarian cystectomy, the FSH level increased significantly after Laparoscopic ovarian cystectomy, AFC decreased significantly after Laparoscopic ovarian cystectomy and bilaterality and obesity increase the adverse effect of Laparoscopic ovarian cystectomy on the ovarian reserve.

Recommendations

- Further analytical studies have to be done on a larger number of patients to prove the current results on a wider scale.
- Other studies have to be done to include follow up periods to determine the effect of laparoscopic ovarian cystectomy in patients with endometriosis on the pregnancy rate and the role of AMH in this setting.
- In non-fertility complain, Give the patient the chance of being pregnant with traditional methods even we know the success rate of pregnancy with endometriosis is low.
- If you decide on laparoscopic cystectomy be careful of the use of the cautery by decreasing the energy to minimum coagulation to preserve the ovarian function and decrease the destruction of the ovarian tissue.
- It's better to use bipolar electrocautery than unipolar electrocautery to reduce the area of ovarian tissue damage.

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