

Impact of Surgical Management of Endometrioma on Ovarian Reserve

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Abstract:

Objective: The aim of this study was to explore the outcome of surgical removal of endometriotic cyst on ovarian reserve.

Materials and methods: This prospective observational study was carried out in Infertility Care and Research Centre, Dhaka, Bangladesh between January 2011 and December 2018. One hundred and fifty-five patients, who had an ultrasonographic diagnosis of endometrioma measuring ≥ 3 cm and underwent surgical excision due to subfertility were the candidates for this study. The exclusion criteria were a) previous ovarian cystectomy, b) removal of one ovary, c) irregular menstrual cycle, d) polycystic ovarian syndrome e) endocrine disorder, f) low AMH (< 1 ng/ml), g) history of taking medication for endometriosis that could affect ovarian function, e.g., GnRH analogues or oral contraceptives during the 6 months preceding scheduled surgery. To investigate the effect of surgery on ovarian reserve, their FSH, E2 and AMH were measured before and after surgery. Tests were done before surgery and repeated after 3 months and 6 months of surgery. A value of < 0.05 was considered significant.

Results: Mean age of the patients was 31.72 ± 2.77 years. The baseline FSH, E2 and AMH were within normal limit. In 63.88% of the cases the cysts were unilateral and 83.22% of the cases the size of the cysts were within 10 cm. To assess the change of ovarian reserve FSH, E2 and AMH were measured in 3 and 6 months after surgery. There was marked declining of AMH level from baseline to both 3 months and 6 months after surgery p is < 0.0001 . There was no significant change of FSH and AMH between 3 months and 6 months after surgery.

Conclusion: Cystectomy in ovarian endometrioma significantly reduces ovarian reserve, which is manifested by reduced level of AMH.

Introduction:

Ovarian endometrioma is one of the most frequent manifestations of endometriosis, affecting 17-44% of women with endometriosis^{1,2}. It has been reported that 30-50% of women with endometriosis experience fertility problems and endometriomas are frequently encountered during fertility workup. Recommended treatment is still a subject of debate. There is a general consensus, that laparoscopic cyst excision represents the first line and the best treatment in

women with endometriotic ovarian cysts in terms of lower recurrence and improved fertility. Surgical treatment is effective in the management of pain and fertility. Cystectomy of ovarian endometriomas improves spontaneous pregnancy rates and reduces pain. In addition, it may improve the response to in vitro fertilization (IVF). It has been shown that laparoscopic cystectomy for ovarian endometriomas > 4 cm in diameter improves fertility compared to drainage and coagulation³. Drawbacks of surgery

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include postoperative adhesion formation and incomplete removal of the cyst. Another major concern associated with surgical management of endometriomas in infertile women is the potential detrimental impact of surgical excision on ovarian reserve, which is already diminished in endometriotic women^{4,5}. Biopsy study of healthy cortex from ovaries affected by endometriomas 4 cm and contralateral ovaries without cysts reported that cortex from ovaries with endometriomas contained significantly more morphologically atretic early follicles than cortex from contralateral ovaries without cysts⁴. Different studies have reported that the existence of endometrioma would attenuate preoperative serum antimullerian hormone (AMH)⁶⁻⁸ and the post-operative serum AMH significantly decreased in women with endometrioma surgery⁹⁻¹⁷. Endometriosis is a recurrent disease. If patient does not get pregnant after 1st surgery cyst may recur at any time, which will further reduce AMH level and chance of fertility. Moreover, if patient needs repeat surgery which might destroy total follicular pool and patient may go into ovarian failure.

The purpose of our study is to explore the effect of surgery in our population in terms of reduction of AMH and the extent of reduction of AMH so that gynaecologists can plan the subsequent treatment option according to AMH level.

Materials and Methods:

This prospective observational study was carried out in Infertility Care and Research Centre, Dhaka, Bangladesh between January, 2011 and December, 2018. One hundred and fifty-five patients, who had an ultrasonographic diagnosis of endometrioma measuring ≥ 3 cm and underwent surgical excision due to subfertility, were the candidates for this study. The exclusion criteria were a) previous ovarian cystectomy, b) removal of one ovary, c) irregular menstrual cycle, d) polycystic ovarian syndrome, e) endocrine disorder, f) very low AMH (less than 1 ng/ml), g) history of taking medication for endometriosis that could affect ovarian function, e.g. GnRH analogues or oral contraceptives during the 6 months preceding scheduled surgery. As the aim of the study was to investigate the effect of surgery on ovarian reserve (AMH), pre and postsurgical AMH of the same patient was measured.

All women underwent a baseline transvaginal ultrasound examination on D1-D3 to determine the size, number and laterality of the cyst. Before surgery patient's ovarian reserve was assessed by 1) serum

follicle stimulating hormone (FSH), 2) oestradiol (E2) and 3) AMH. Although antral follicle count (AFC) is an important parameter for assessing ovarian reserve we avoided it as the presence of small chocolate cysts may interfere the counting. Moreover, our aim was to assess biochemical marker AMH which is a very good predictor of ovarian reserve. A venous blood sample was taken for serum FSH, E2 and AMH on the same day of transvaginal ultrasonogram. AMH was measured by Beckman Coulter, using commercially available enzyme immunoassay kits following the manufacturer's instructions. FSH and E2 were measured in the same lab using the commercially available kit by Liaison analyzer.

Surgical procedure: During laparoscopy after aspiration of the endometriotic fluid ovary/ovaries were mobilized and freed from adhesion. By saline irrigation cyst cavity was cleaned. After identifying the cleavage between cyst wall and healthy ovarian tissue cyst wall was grasped with forceps. Ovarian wall was also grasped by an atraumatic forceps. By traction and counter traction cyst wall stripped out gradually till hilum. When it was difficult to strip the cyst wall near hilum, it was cut at that point leaving a small portion of cyst wall to avoid destruction of healthy tissue. This small portion was cauterized by bipolar electrocautery. All bleeding points were also cauterized by bipolar electrocautery. Cyst wall was removed through umbilical port and sent for histopathology. The procedure of all patients was performed by the same surgeon.

The tests for ovarian reserve were repeated after 3 months and 6 months of surgery and the values were compared. Ethical approval was not sought for as the results has come out from the rational treatment approach of the patient. Informed written consent for surgery was taken from the patient. Statistical Package for Social Science (SPSS) was used for statistical analysis. Mean SD, students of tests, were done as appropriate. A value of <0.05 was considered significant.

Result:

Table 1 shows the patients' characteristics. Mean age of the patients was 31.72 ± 2.77 years. The baseline FSH, E2 and AMH were within normal limit. In 63.88% of the cases the cysts were unilateral and 83.22% of the cases the size of the cysts were within 10 cm. In 16.78% of the cases cyst size was ≥ 10 cm. To assess the change of ovarian reserve FSH, E2 and AMH were measured 3 and 6 months after surgery. Comparative analysis shows that FSH level was

slightly increased 3 months after surgery, which is statistically insignificant (Table 2) and gradually markedly increased after 6 months of surgery, which shows statistically significant changes, p is <0.001 (Table 3). Changes of AMH level were more marked compared to FSH and was highly significant. There was marked declining of AMH level from baseline to both 3 months and 6 months of surgery p is <0.0001 (Table 2 and 3). There was no significant change of both FSH and AMH between 3 months and 6 months of surgery (Table 4). No effect shown in E2 level before and after surgery regardless of different time frame. (Table 2,3,4).

Table-I
Baseline parameters of the patients (n=155)

Variable	Baseline values before surgery Mean±SD	
Age (Yrs)	31.72±2.77	
Hormone profile before surgery		
FSH (mIU/ml)	8.7±5.25	
E2 (ng/ml)	71±25.35	
AMH (ng/ml)	2.7±1.19	
Laterality of cysts	N	%
Unilateral	99	63.88
Bilateral	56	36.12
Size of the cyst		
<10 cm	129	83.22
≥10 cm	26	16.78

Table-II
Changes of hormones 3 months after surgery (n=155)

Variables	Before surgery Mean±SD	3 months after surgery Mean±SD	P value
FSH (mIU/ml)	8.7±5.25	9.8±4.58	0.0502
AMH (ng/ml)	2.7±1.19	1.92±1.64	<0.0001
E2 (ng/ml)	48±25.35	52±22.54	0.1431

Table-III
Changes of hormones 6 months after surgery (n=155)

Variables	Before surgery Mean±SD	6 months after surgery Mean±SD	P value
FSH (mIU/ml)	8.7±5.25	10. ±5.58	0.0013
AMH (ng/ml)	2.7±1.19	1.82±1.24	<0.001
E2 (ng/ml)	48±25.35	50±21.98	0.4586

Table-IV
Changes of hormones between 3 months and 6 months of surgery

Variables	3 months after surgery Mean±SD	6 months after surgery Mean±SD	Significance
FSH (mIU/ml)	9.8±4.58	10.7±5.58	0.1217
AMH (ng/ml)	1.92±1.64	1.82±1.24	0.54
E2 (ng/ml)	52±22.54	50±21.98	0.4605

Discussion:

Ovarian reserve denotes the presence of ovarian follicular pool at any given time. Though a number of tests can be done to measure this reserve, AMH is the best predictor to measure it¹⁸. Removal of endometrioma either by laparoscopy or by laparotomy removes the healthy ovarian tissue along with cyst wall of endometrioma. This loss of healthy ovarian tissue reduces the healthy follicular pool. A number of studies histologically proved that normal ovarian tissues containing functional follicles can be inadvertently removed in most cases of ovarian cystectomy irrespective of the skill of the surgeon¹⁴⁻¹⁷. Furthermore; electrosurgical coagulation during the procedure causes a serious damage to the ovarian parenchyma and blood supply.

We studied 155 endometriotic patients for AMH before and after surgical removal of endometrioma. In our study we found slow regression of AMH in most of the patients. Decline was more in patients with bigger cysts and with bilateral distribution. Several studies shown that endometrioma itself may damage ovarian follicle and reduces ovarian reserve in different way^{2,13, 19-21}. Kitajima et al⁴ showed that cortex of the ovaries having endometrioma >4 cm have fibrosis and concomitant loss of cortex specific stroma, which leads to significantly lower follicular density compared with contralateral normal ovaries. In our previous study⁵ we also found reduced ovarian reserve in patients with endometrioma comparing patients of the same age group without endometrioma.

Surgical intervention particularly stripping of the cyst wall or ovarian cystectomy further reduces the ovarian reserve due to loss of follicles along with removal of cyst wall. Furthermore, electro-cauterization for haemostasis damages more ovarian tissue. It has been shown that ovarian surgery may cause ovarian

insufficiency²⁴. Women with endometriotic cysts have an increased risk of ovarian insufficiency particularly if cysts are bilaterally removed^{22,25-27}. It became apparent that patients could develop ovarian insufficiency after surgical intervention. In different studies it was shown that cystectomy of endometriotic cysts is the leading cause of ovarian insufficiency^{25,28}. The result of our study demonstrates similar result of AMH reduction after removal of endometriotic cyst. We compared same patient's AMH before and after 3 and 6 months of surgery. Although there was no change of E2 level, there were significant increment of FSH and significant reduction of AMH at 3 months after surgery. There were gradual increment of FSH and reduction of AMH from 3 months to 6 months of surgery, however, the change was not significant. Three studies where two of them were meta-analysis^{17,29,30} showed that there was surgery related decrease of serum AMH but did not mention whether it was progressive or not. Other studies^{10,15,31} shows progressive decline of serum AMH level with passage of time regardless of surgery. They further demonstrated progressive decline, which was more evident at 6 months after surgery than one month after surgery. Our result is consistent with the result of aforementioned studies. In our study we also found progressive decline of AMH though decline between 3 months and 6 months of surgery was not significant.

There is a concern whether removal of multiple, bigger sized and bilateral cysts have any adverse effect than removal of single, smaller and unilateral cyst? The reported investigations shown that cyst diameter was not related to the extent of AMH decline^{7,12,15}. Hirokawa et al¹² showed that bilateral excision of ovarian endometrioma caused a significant decline in serum AMH level than the excision of unilateral endometrioma. The other two studies commented that bilaterality is not an independent factor associated with loss of ovarian reserve^{7,15}. As the number of bilateral and big cysts were not high, we did not analyze them separately in this study. Exception was one patient who underwent ovarian failure after removing 15 and 16 cm of bilateral endometriotic cysts. Two reasons can clarify the outcome. After removing the cyst wall there was a little ovarian tissue left on either side and due to damaging of ovarian circulation the residual tissue became atrophied. Secondly, due to cauterization for haemostasis remaining tissue burned out. There was

no age-related decline of AMH in this series which is consistent with study of Ceilk et al¹⁵.

Modified surgical procedures can be adopted to reduce the loss of follicle. Donez et al³² developed a surgical technique that combines cystectomy and CO2 laser ablation where 80-90% of the cyst wall was removed and remaining 10-20% ablated by laser. This technique reduces the follicular loss associated with cystectomy and recurrence associated with ablation.

In conclusion, it can be said that endometrioma itself reduces ovarian reserve by causing inflammation and atresia of follicles. Surgery further reduces ovarian reserve by inadvertently removing the follicles and unavoidable tissue destruction by bipolar cautery. Modification of surgical procedure and using CO2 laser for coagulation might help to preserve follicular pool to some extent. AMH must be measured in each case of endometrioma. If AMH is already low, surgery should be avoided in favour of long term down regulation and ART.

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