

Endometrioma is a Responsible Factor for Reduced Ovarian Reserve

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Abstract:

Objective (s): The aim of the study was to assess ovarian reserve (OR) of patients with endometrioma and to explore the differences of ovarian reserve in age matched group of infertile patients without endometrioma.

Materials and methods: This prospective analytic study was done in Infertility Care and Research Center, between January 2013 and December 2015 to assess the ovarian reserve of patients with endometrioma. During this period 105 patients of endometriosis with endometrioma were selected for study. Selection criteria were: no history of previous surgery, <36 years of age, no history of endocrine problems, no history of recent medical treatment for this condition within 6 months and no history of irregular menstruation. For ovarian reserve testing we assessed serum FSH, E2 and AMH. Patient of same age group who had no endometrioma, no history of any surgery, no menstrual irregularity, endocrine disorder or any other medical diseases were taken as control to compare the ovarian reserve between these two groups. For control group also we did the same tests. Data was analyzed by SPSS package. One-way ANOVA test was done for test of significance. A p-value of <0.05 was considered as significant.

Results: There was no difference in characteristics of patients of both groups regarding age, type of infertility and duration of infertility. Size of the endometriotic cysts were variable and average diameter of cyst was 6.2 ± 2.32 cm. Most (58.10%) of the cysts were unilateral. There is a significant difference of FSH and AMH level between the groups. FSH of endometrioma and non-endometrioma group was 7.9 ± 1.17 and 7.1 ± 1.05 mIU/mL respectively with a p value of 0.029. Similar difference was present in AMH level, which was 2.42 ± 0.63 and 2.98 ± 0.88 ng/mL in endometrioma and non-endometrioma group respectively with a p value of 0.020.

Conclusion: This small study shows a reduced ovarian reserve in patients with endometrioma in comparison to patients of same parameters without endometrioma. It suggests that there is an association of presence of ovarian endometrioma and reduced ovarian reserve

Key words: Endometrioma, Ovarian reserve

Introduction:

Female reproductive age is short because over time, oocytes decrease in quantity and quality and do not regenerate¹. In early weeks of intrauterine life 6–7 million oocytes present in the ovary, which undergo continuous and profound apoptosis and atresia during

intrauterine life and approximately 1–2 million oocytes are present at birth. Until puberty only 300,000–500,000 oocytes remain in both ovaries.² Different factors such as lifestyle, environment, genetics and medical issues, including endometriosis, ovarian cystectomy, oophorectomy, pelvic inflammatory

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disease, chemotherapy, and radiotherapy reduce the quantity and quality of oocytes.³ Although this reproductive decline occurs with age, there is significant variation in fertility among women of similar age, which highlights the unpredictability and individuality of the reproductive aging process.⁴

The concept of “ovarian reserve” defines a woman’s reproductive potential as a function of the number and quality of her remaining oocytes.¹ The purpose of ovarian reserve testing is to assess the quality and quantity of the remaining oocytes in an attempt to predict reproductive potential and for discussing prognosis and recommending a treatment plan. When test results suggest decreased or diminished ovarian reserve, it is reasonable to counsel the woman that her window of opportunity to conceive may be shorter than anticipated, and attempting to conceive sooner rather than later is encouraged.

To make decision or planning of treatment in infertility with endometriosis is important in this regard. Endometriosis affects 0.8% -2% of women of reproductive age⁵⁻⁹ and 20-40% women with endometriosis have endometrioma.¹⁰⁻¹² About 30-50% of women with endometriosis experience fertility problems and endometriomas are frequently encountered during infertility work-up.¹³⁻¹⁵ Based on the current evidence, treatment by laparoscopic ovarian cystectomy appears to be the method of choice.¹⁶⁻¹⁸ Despite the improvements in technique of laparoscopy and management of symptomatic patients with endometriomas, there is growing concern about the negative impact on ovarian reserve due to inadvertent removal or destruction of the healthy ovarian tissue adjacent to the pseudocapsule of the cyst.¹⁹⁻²³ Several studies have suggested that ovaries with endometrioma may already have some damage and decreased ovarian reserve preceding surgery²⁴⁻²⁶ Specifically, Kitajima et al.²⁵ showed that the cortex of 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. Undertaking surgery on these ovaries further deteriorates ovarian reserve. So before taking decision of surgery it is important to assess ovarian reserve.

Purpose of this study was to assess ovarian reserve of patients with endometrioma and to explore the differences of ovarian reserve in age matched group of infertile patients without endometrioma.

Materials and methods:

This prospective analytic study was done in Infertility Care and Research Center a tertiary level infertility care center, between January 2013 and December 2015 to assess the ovarian reserve of patients with endometrioma. During this period 105 patients of endometriosis with endometrioma were selected for study. Only those patients were selected who had no history of previous surgery. Other inclusion criteria were all patients were under the age of 36, there was no history of endocrine problems, no history of recent medical treatment for this condition within 6 months and no history of irregular menstruation. For ovarian reserve testing we assessed serum FSH, E2 and AMH. Ovarian volume measurement was not done as measuring ovarian volume with a cyst is not very informative. Antral follicle count of cystic ovary also was not done to avoid technical error of counting antral follicle with endometrioma. Moreover, it is proved that AMH is a very good predictor of ovarian reserve testing.²⁷⁻³⁰ So we have given emphasis on AMH as indicator of ovarian reserve. Patient of same age group who had no endometrioma, no history of any surgery, no menstrual irregularity, endocrine disorder or any other medical diseases were taken as control to compare ovarian reserve parameters between these two groups. For control group also we did same tests like FSH, E2 and AMH to assess ovarian reserve. AMH was done by a commercial enzyme-linked immunosorbent assay kit (ELISA, Beckman Coulter USA) and FSH, E2 was done by LIAISON automated analyzer. All the serum sample were immediately separated by centrifugation at 4⁰C for 15 minutes and stored at -20⁰ C until assay. Data was analyzed by SPSS package. One-way ANOVA test was done for test of significance. A p-value of <0.05 was considered as significant.

Results:

Characteristics of the patients of both groups are shown in the table I. There was no difference in characteristics regarding age, type of infertility and duration of infertility. Table II shows the characteristics of endometrioma. Size of the endometriotic cysts were varied and average diameter of cyst was 6.2 ±2.32 cm. Most (58.10%) of the cysts were unilaterally distributed. Table III has shown the differences of ovarian reserve parameters between the patients with endometrioma and without endometrioma. There is a significant difference of FSH and AMH level between

Table I
Characteristics of patients of both groups

Characteristics	Endometrioma		No endometrioma		Significance
	Mean	± SD	Mean	± SD	
Age (Years)	28.72	±3.45	29.58	±3.89	NS
<i>Type of infertility</i>	N	%	N	%	
Primary	72	68.58	75	71.42	NS
Secondary	33	31.42	30	28.57	NS
<i>Duration of infertility (Years)</i>	Mean	± SD	Mean	± SD	NS
	4.5	±1.28	5.1	±1.92	

Table-II
Characteristics of endometrioma

Characteristics	Endometrioma	
	Mean	± SD
Size of the cyst (cm)	6.2	2.32
<i>Laterality</i>	N	%
Unilateral	61	58.10
Bilateral	44	41.90

Table-III
Basal hormone of patients with endometrioma and without endometrioma

Hormones	Endometrioma		No-Endometrioma		Significance
	Mean	± SD	Mean	± SD	
FSH mIU/mL	7.9	± 1.17	7.1	±1.05	0.029
E2 pg/mL	48	±20.02	45	±21.22	0.293
AMH ng/mL	2.42	±.63	2.98	±.88	0.020

the groups. FSH of endometrioma and non-endometrioma group was 7.9 ± 1.17 and 7.1 ± 1.05 mIU/mL respectively with a p value of 0.029. Similar difference exists in AMH level, which was $2.42 \pm .63$ and $2.98 \pm .88$ ng/mL in endometrioma and non-endometrioma group respectively with a p value of 0.020. Though there was no statistically significant difference in E2 level of the groups.

Discussion:

This study shows that patients with endometrioma have relatively lower ovarian reserve in comparison to age matched control group. It indicates that endometriosis itself is responsible for reduction of ovarian reserve. AMH which is secreted by preantral

and antral follicle reduces steadily with advancing age as number of follicle reduces by continuous atresia and apoptosis. A number of studies demonstrated that AMH was a steeper marker to predict residual ovarian function.²⁷⁻³⁰ Changes in serum AMH level in patients with endometriosis has been well documented. Remarkable declines in serum AMH were reported in patients with moderate to severe endometriosis, which was more pronounced in those with bilateral endometrioma.^{25,31-36} Ovaries with endometrioma may already have some damage with decreased ovarian reserve.²⁴⁻²⁶ Lower anti-mullerian hormone serum levels and association with the severity of the disease found in women with endometriosis. Till today a number of studies have shown that the presence of

endometriosis has been shown to be associated with a decrease in the follicular ovarian reserve accompanied by a reduction in AMH levels.^{25,31,37}

Several mechanisms by which the endometrioma progressively affects the ovarian tissue have been identified. Colour Doppler transvaginal ultrasonography shows interstitial devascularization in the ovarian endometrioma bed and confirmed that fibrosis and microvascular injury were a potential cause of reduced follicle reserve.³⁸ Kitajima et al in a recent study took biopsy of healthy cortex from ovaries affected by endometriomas ≥ 4 cm and contralateral ovaries without cysts and reported that cortex from ovaries with endometriomas contained significantly more morphologically atretic early follicle than cortex from contralateral ovaries without cysts.²⁵ The content of cystic fluid has deleterious effect on the adjacent ovarian cortical tissue. Sanchez et al reported increased free iron level in endometriotic cystic fluid than normal serum iron level and iron level of other ovarian cyst.³⁹ They concluded that sufficient evidences support the adverse effect of endometrial cystic fluid on the adjacent ovarian cortical tissue independent of the mere mechanical stretching owing to its fluid content.

In our study we found increased FSH and lowered AMH in endometrioma group, which is consistent with other studies.^{22 40-45} It has been known that elevated serum oestradiol in early follicular phase predicts poor ovarian reserve when undergoing in vitro fertilization.⁴⁶⁻⁴⁸ Chiang et al found significantly highest oestradiol level in endometriosis group without previous surgery and concluded that patients with endometriosis would have poor ovarian reserve.⁴⁹ In our study we did not find any difference of E2 level between two groups. As AMH is the best predictor of ovarian reserve we focused on AMH level rather than FSH and E2. Increased E2 level suppress FSH level. So both E2 and FSH can't be increased simultaneously. We found significance difference in FSH level.

Now question arises that should we measure ovarian reserve in women with endometriotic cyst irrespective of the age of the patient? If so, why? Biochemical testing of ovarian reserve is expensive in the context of Bangladesh. So for young patients below the age of 30 years most of the gynaecologists of our country do not recommend to do the biochemical tests for ovarian reserve. We know standard treatment of endometrioma in infertility is surgical removal of the

cyst and laparoscopy is the best option. But it has been documented that ovarian surgery may causes *ovarian insufficiency*.⁵⁰ and it is well known that women with endometriotic cysts have an increased risk of ovarian insufficiency, particularly if bilateral cysts have been removed.^{37, 51-53} Several mechanisms have been described to explain the quantitative alteration of ovarian reserve after cystectomy for endometrioma; accidental removal of healthy ovarian tissue during cystectomy, vascular compromise due to electrocoagulation, local inflammation and autoimmune reaction, expertise of the surgeon, extent of the disease and number of surgical interventions may have impact on ovarian reserve. Even at the hand of skilled surgeon there is a progressive decline of AMH after endometriotic cystectomy.⁵⁴ Cyst drainage and coagulation cause less harm than cystectomy, but recurrence rate is higher than cystectomy.^{16,17} Recently surgeons are trying to modify the surgical technique to protect the ovarian reserve. Modified combined surgical technique for ovarian cystectomy in endometrioma is an approach to remove the endometrioma without increasing the recurrence rate and ovarian tissue damage.⁵⁵

Considering these facts it is very important to take the decision of modalities of treatment with endometrioma with already poor ovarian reserve. Whatever may be the age of the patient, reproductive life will go to an end if ovarian follicles are exhausted by one or more surgery. For infertile patients mode of treatment should be individualized according to the patients' status. So depending upon the ovarian reserve of the patient surgical removal of the cyst, aspiration of the cyst followed by down-regulation and ART or long down-regulation and ART should be offered. Pacchiarotti et al. concluded in their study that damage of endometriosis on ovarian reserve, leading to a form of incipient ovarian failure, which is considered as an early sign of advanced ovarian depletion in young women. So AMH could be used in the follow-up of patients with endometriosis, in order to assess promptly the decrease of ovarian reserve.³⁴

In conclusion from findings of this small study it can be said that endometrioma itself might be associated with poor ovarian reserve of this population. So care should be taken for subsequent treatment plan and approach of surgery so that fertility prospect is not lost by treatment itself. It may be prudent to measure AMH levels preoperatively and delay/avoid surgical

excision as far as possible if subsequent fertility is a concern. Further large scale studies are required to investigate whether the endometrioma related decline in ovarian reserve per se is progressive in nature and needs active treatment of infertility.

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