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Anti-Mullerian Hormone (AMH) Level in Presence of Ovarian Endometrioma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: The effect of endometriomas itself on the ovarian responsiveness that relate to ovarian reserve had been reported with several inconsistent results. In one study evaluated women with unilateral endometriomas, ovaries with disease showed lower response to ovarian stimulation than contralateral healthy ovaries .However, recent study on infertile women with un-operated unilateral small endometriomas did not support difference in ovarian responsiveness. The aim was to evaluate the impact of presence of endometriomas on ovarian reserve as measured by circulating AMH.
Methods: This retrospective study was carried out on 80 female patients in childbearing period attending outpatient clinic and/or inpatient department of obstetrics and gynecology at Tanat University Hospital and the study was conducted directly after approval in the period from Apri, 2019 till April 2020.
Group (A): Study group: 60 female patients aged between 20 to 30 years old
GROUP (B): Control group: 20 age matched female with healthy ovaries.
Results: there is no statistical significant difference between groups as regard Menarche (years), Regularity and Amount of menstrual blood flow. There is statistical significant difference between groups as regard fixed tender Right Ventricular Failure. But there are no statistical significant

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differences between groups as regard nodule in rectovaginal septum, fixed tender adnexal masses, association with adenomyosis and infertility. There is highly statistical significant difference between case and control groups as regard AMH levels. there are highly statistical significant positive correlation between duration of endometriosis and each of presence of pelvic pain, cyst diameter and Visual Analogue Scale.

Conclusions: Women with endometrioma have significantly lower serum AMH levels and seem to experience a more rapid decline in serum AMH levels than age matched counterparts, suggesting a harmful effect of endometrioma per se on ovarian reserve.

Keywords: Anti-mullerian hormone (AMH); ovarian; endometrioma.

1. INTRODUCTION

Ovarian endometriomas are found in 20% of patients with endometriosis [1] and are associated with a more severe form of the disease. There is a general consensus that endometriomas require surgical treatment due to ineffectiveness of medical therapies [2]. However, surgery carries a potential risk of significant damage to ovarian reserve [3].

Recently, Kitajima et al. [4] evaluated the histologic features of ovarian cortical tissue in endometriomas and found significantly lower follicular density than that for contralateral normal ovaries; they also found a presence of fibrosis and a loss of cortex-specific stroma in tissues from endometriomas. They demonstrated an association between tissue alteration in endometriomas and reduced ovarian reserve. This finding indicated that endometriosis itself could reduce ovarian reserves. Furthermore, several studies have shown a significant difference in ovarian reserve according to endometriosis severity [5].

The term ovarian reserve is defined as the number and quality of the follicles left in the ovary. Clinical tests to estimate ovarian reserve had been proposed. Endocrinological, ultra-sonographic, and histological methods had been implicated; however, the accuracy of ovarian reserve testing to measure quality and quantity of remaining primordial follicles is still unclear. Serum follicle stimulating hormone (FSH) and estradiol (E2) levels in early follicular phase (i.e. cycle day 2-4) had long been utilized as markers for ovarian reserve classically.

The effect of endometriomas itself on the ovarian responsiveness that relate to ovarian reserve had been reported with several inconsistent results. In one study evaluated women with unilateral endometriomas, ovaries with disease showed lower response to ovarian stimulation than contralateral healthy ovaries .However, recent study on infertile women with un-operated unilateral small endometriomas did not support difference in ovarian responsiveness. Some women with untreated endometriomas showed decreased pre-surgical AMH levels, especially those with bilateral Endometrioma, compared to control women without endometriosis or with other benign ovarian cysts.

Two main surgical methods are widely used for endometriomas including cystectomy and cyst ablation. Cystectomy seems to be the favored modality by many authors as it is associated with less recurrence of the disease [6]. However, cystectomy has been associated with concomitant excision of normal ovarian tissue resulting in significant follicle loss with possible subsequent reduction in ovarian reserve [7,8].

AMH a member of the transforming growth factor-β (TGF-β) family, was identified as a factor that causes regression of the Müllerian ducts during male fetal development [9]. In females, AMH, also known as Müllerian inhibiting substance, is produced in the granulosa cells of ovarian follicles [10]. Human female serum contains measurable amounts of AMH during the reproductive life span [11].

Serum anti-Müllerian hormone (AMH) is a relatively new marker of ovarian reserve, which has gained wide popularity because it offers several advantages over other tests. It has been shown to be remarkably stable throughout the menstrual cycle [12,13] and it is not affected by the use of hormones [14]. In addition, it is very sensitive to changes in ovarian reserve with advancing age and correlates well with antral follicle count [15].

The aim was to evaluate the impact of presence of endometriomas on ovarian reserve as measured by circulating AMH.

2. PATIENTS AND METHODS

This retrospective study was carried out on 80 female patients in childbearing period attending outpatient clinic and/or inpatient department of obstetrics and gynecology at Tanat University Hospital and the study was conducted directly after approval in the period from Apri, 2019 till April 2020.

Oral information and written consent was taken and sighed from all the subjects after ethical committee approval from Research Center in Tanta University.

The patients were identified by coded number to maintain privacy.

All patients submitted to the study were counseled thoroughly about the procedure including its value and hazards, and the aim of the study

The study was approved by ethics, committee of faculty of medicine, Tanta University Patients:

Divided into two groups:

Group (A): Study group: 60 female patients aged between 20 to 30 years old

Group (B): Control group: 20 age matched female with healthy ovaries .

All women will undergo the following:

1. Complete history taking with special attention to symptoms suggestive of endometriosis like infertility, dysmenorrhea, dyspareunia and pelvic pain
2. General examination, cardiovascular system and respiratory system were examined, genitourinary, endocrine system, gastrointestinal system.
3. With special attention to clinical findings suggestive of endometriosis like fixed tender RVF uterus, fixed tender adenexal mass, nodule in rectovaginal septum or Douglas pouch.
4. Ultrasound examination with presence of ground glass appearance of the ovarian cyst.
5. Taking blood samples to determine baseline level of anti- Mullerian hormone(AMH).

3. MEASUREMENT OF AMH

3.1 Principle of the Assay

This assay employs the quantitative sandwich enzyme immunoassay technique. Antibody specific for AMH has been precoated onto a microplate. Standards and samples are pipetted into the wells and any AMH present is bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for AMH is added to the wells. After washing, avidin conjugated Horseradish Peroxidase (HRP) is added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of AMH bound in the initial step. The color development is stopped and the intensity of the color is measured

3.2 Sensitivity

The minimum detectable dose of human AMH is typically less than 15.6 pg/ml. The sensitivity of this assay, or Lower Limit of Detection (LLD) was defined as the lowest protein concentration that could be differentiated from zero. It was determined the mean optical density value of 20 replicates of the zero standard added by their three standard deviations.

3.3 Specificity

This assay has high sensitivity and excellent specificity for detection of human AMH. No significant cross-reactivity or interference between human AMH and analogues was observed
Note: Limited by current skills and knowledge, it is impossible for us to complete the cross-reactivity detection between human AMH and all the analogues, therefore, cross reaction may still exist.

Collect plasma using EDTA, or heparin as an anticoagulant. Centrifuge for 15 minutes at 1000 x g at 2-8°C within 30 minutes of collection. Assay immediately or aliquot and store samples al -20°C or -80°C. Avoid repeated freeze-thaw cycles. Centrifuge the sample again after thawing before the assay.

3.4 Tissue Homogenates

100mg tissue was rinsed with 1X PBS homogenized in 1 ml of 1X PBS and stored

overnight at -20°C. After two freeze-thaw cycles were performed to break the cell membranes, the homogenates were centrifuged for S minutes at 5000 x g, 2-8°C. The supernate was removed and assayed immediately. Alternatively, aliquot and store samples at -20°C or -80°C. Centrifuge the sample again after thawing before the assay. Avoid repeated freeze-thaw cycles.

3.5 Reagent Preparation

- Kindly use graduated containers to prepare the reagent. Please don't prepare the reagent directly in the Diluent vials provided in the kit.
- Bring all reagents to room temperature (18-25°C) before use for 30min.
- Prepare fresh standard for each assay. Use within 4 hours and discard after use.
- Making serial dilution in the wells directly is not permitted.
- Please carefully reconstitute Standards according to the instruction, and avoid foaming and mix gently until the crystals have completely dissolved. To minimize imprecision caused by pipetting, use small volumes and ensure that pipettors are calibrated. It is recommended to suck more than 10ul for once pipetting.
- Distilled water is recommended to be used to make the preparation for reagents. Contaminated water or container for reagent preparation will influence the detection result.

3.6 Calculation of Results

Average the duplicate readings for each standard and sample and subtract the average zero standard optical density.

Create a standard curve by reducing the data using computer software capable of generating a four parameter logistic (4-PL) curve-fit.

As an alternative, construct a standard curve by plotting the mean absorbance for each standard on the x-axis against the concentration on the y-axis and draw a best fit curve through the points on the graph. The data may be linearized by plotting the log of the AMH concentrations versus the log of the O.D. and the best fit line can be determined by regression analysis. This procedure will produce an adequate but less precise fit of the data.

If samples have been diluted, the concentration read from the standard curve must be multiplied by the dilution factor

3.7 Statistical Analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>33) were 95% confidence limit, 80% power of the study, expected outcome in in treatment group 90% compared to 60% for control groups.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). They were compared between the two groups by unpaired student's t- test and within the same group by paired T test. Quantitative non-parametric variables (e.g. VAS) were presented as median and range and compared between the two groups by Mann Whitney (U) test and within the same group by Wilcoxon test. P value < 0.05 was considered significant.

within the same group by Wilcoxon test. P value < 0.05 was considered significant.

4. RESULTS

This study was conducted on 80 patients divided as 60 Study group and 20 Control group presented in (Table 1). Mean ±SD of Age at Study group was 24.95 ± 3.078. But at Control group was 26.20 ± 2.526.

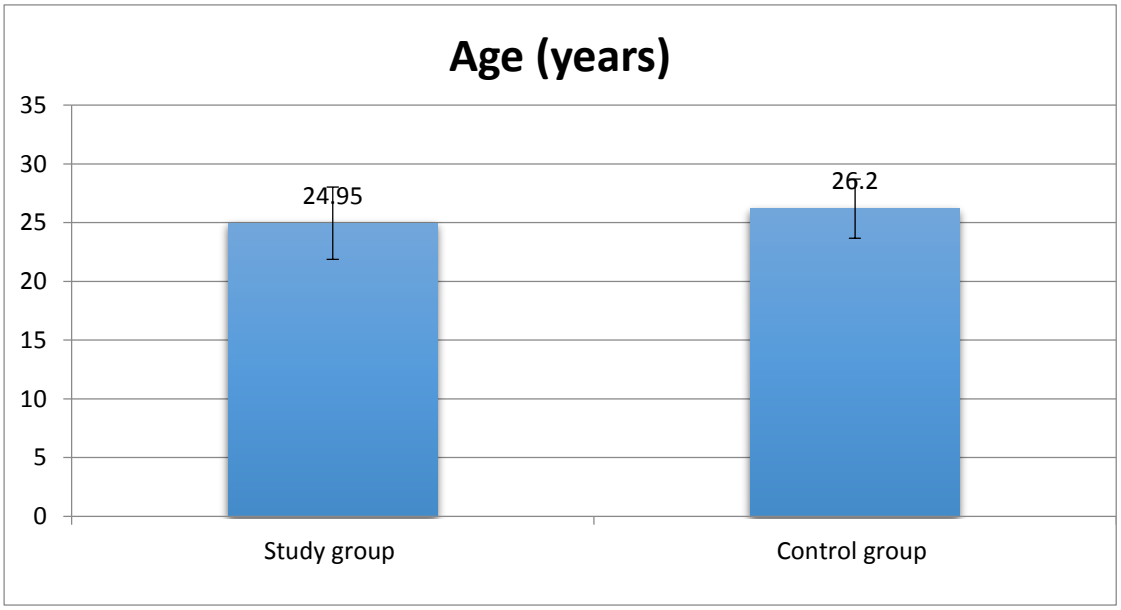
This table shows that there was high statistical significant difference between groups as regard the occurrence of symptoms of pelvic pain. There was statistical significant difference between groups as regard the occurrence of symptoms of (Dysmenorrhea, Dyspareunia), and Marital status. But there was no statistical significant difference between groups as regard Age (years).

This table shows that there is no statistical significant difference between groups as regard Menarche (years), Regularity and Amount of menstrual blood flow.

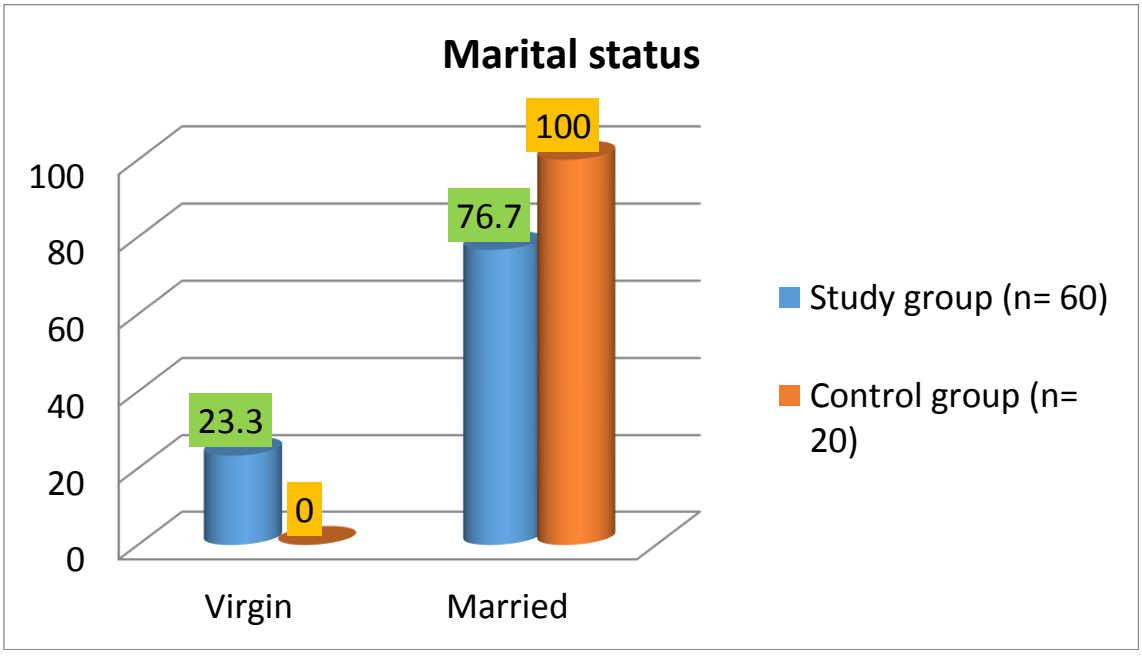
Table 1. Age distribution, Marital status, and Presenting symptoms of the studied groups

		Study group (n= 60)	Control group (n= 20)	95% CI	p
Age (years)		24.95 ± 3.078	26.20 ± 2.526	- 2.77, 0.27	0.105
Marital status	**Virgin**	23.3% (14)	0.0% (0)	-0.34, -0.13	**0.017**
	Married	76.7% (46)	100.0% (20)		
Presenting symptoms	**Pelvic pain**	56.7% (34)	0.0% (0)	-0.69, -0.44	**< 0.001**
	Dysmenorrhea	28.3% (17)	5.0% (1)	-0.38, -0.09	**0.030**
	Dyspareunia	36.7% (22)	5.0% (1)	-0.47, -0.16	**0.007**

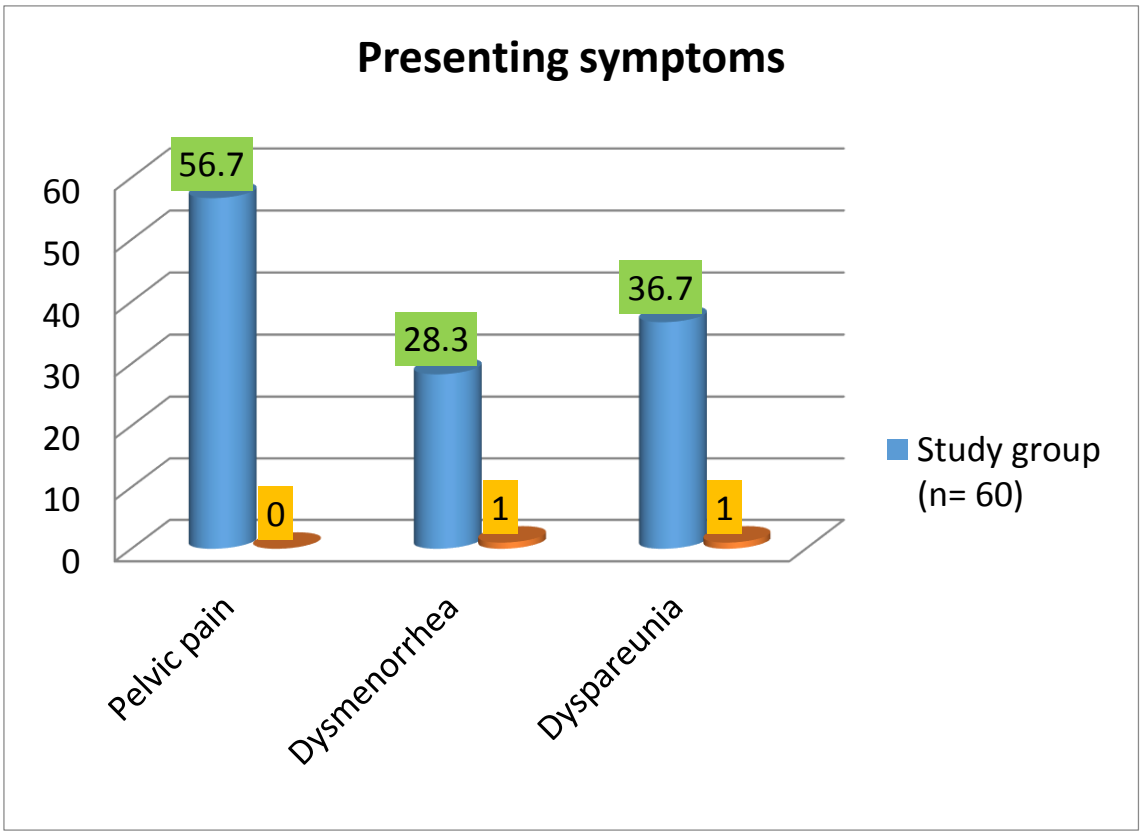
Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05



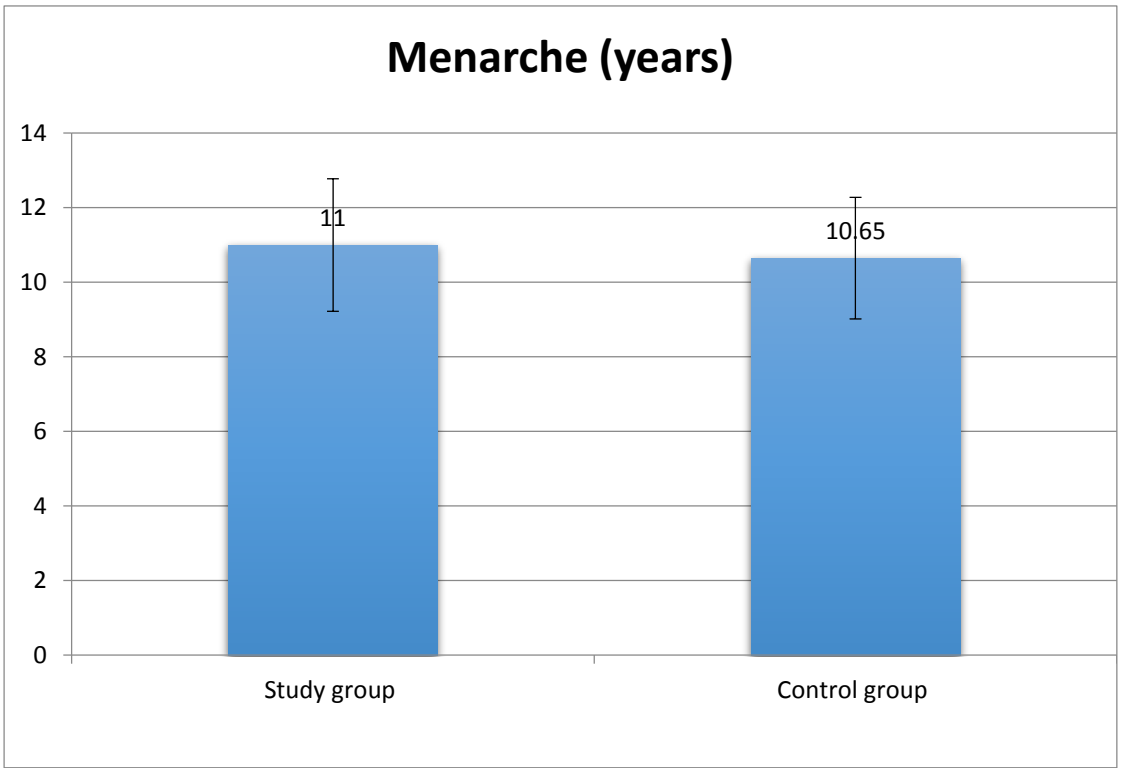
Graph 1. Bar chart shows Age among Study and Control group



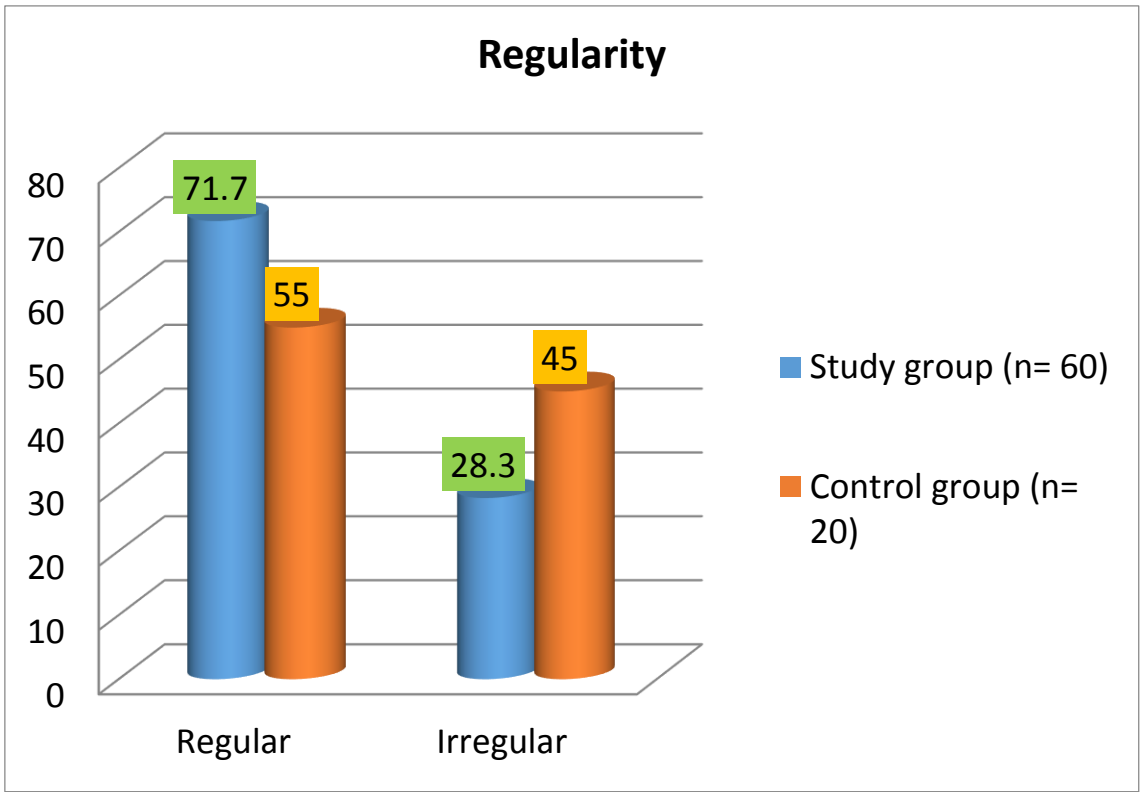
Graph 2. Bar charts showing Marital status among Study and Control group



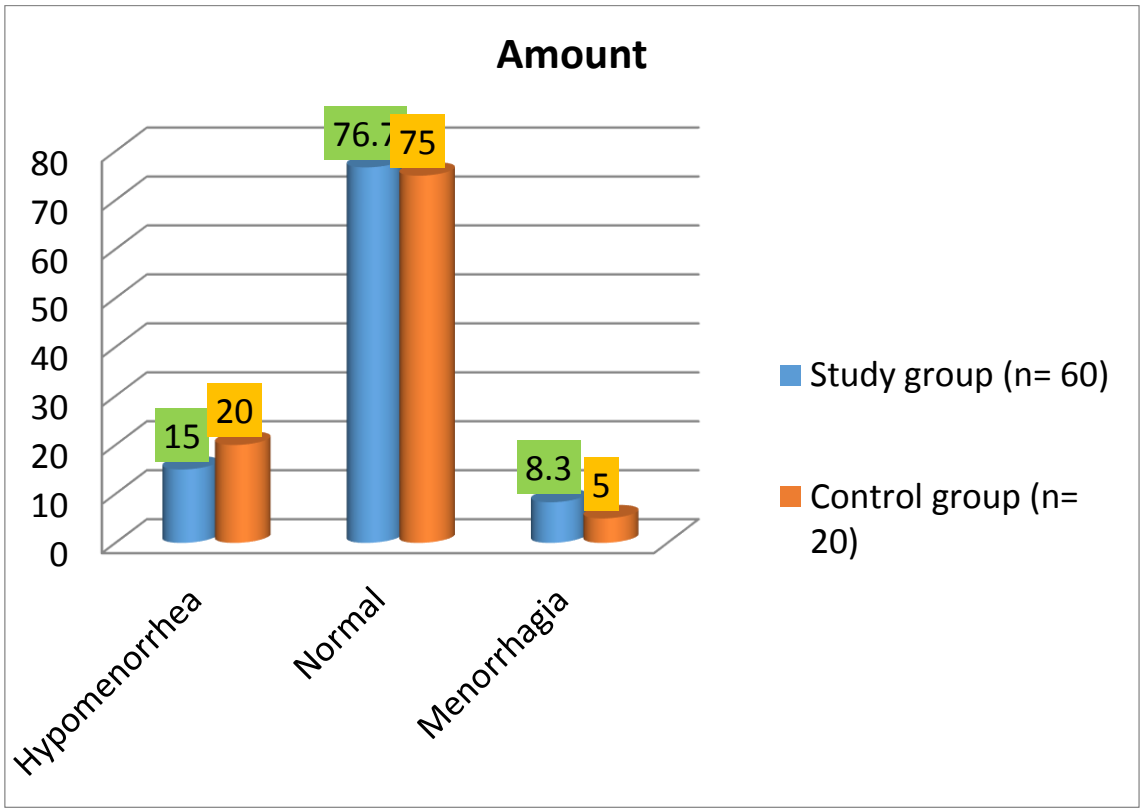
Graph 3. Bar charts showing Presenting symptoms among Study and Control group



Graph 4. Bar chart shows Menarche (years) among Study and Control group



Graph 5. Bar charts showing Regularity among Study and Control group



Graph 6. Bar charts showing Amount among Study and Control group

Table 2. Menstrual history of the study participants

		Study Group (n= 60)	Control Group (n= 20)	95% CI	p
Menarche (years)		11.00 ± 1.776	10.65 ± 1.631	-0.55, 1.25	0.439
Regularity	**Regular**	71.7% (43)	55.0% (11)	-0.41, 0.08	0.168
	Irregular	28.3% (17)	45.0% (9)		
Amount	**Hypomenorrhea**	15.0% (9)	20.0% (4)	-	0.902
	Normal	76.7% (46)	75.0% (15)		
	Menorrhagia	8.3% (5)	5.0% (1)		

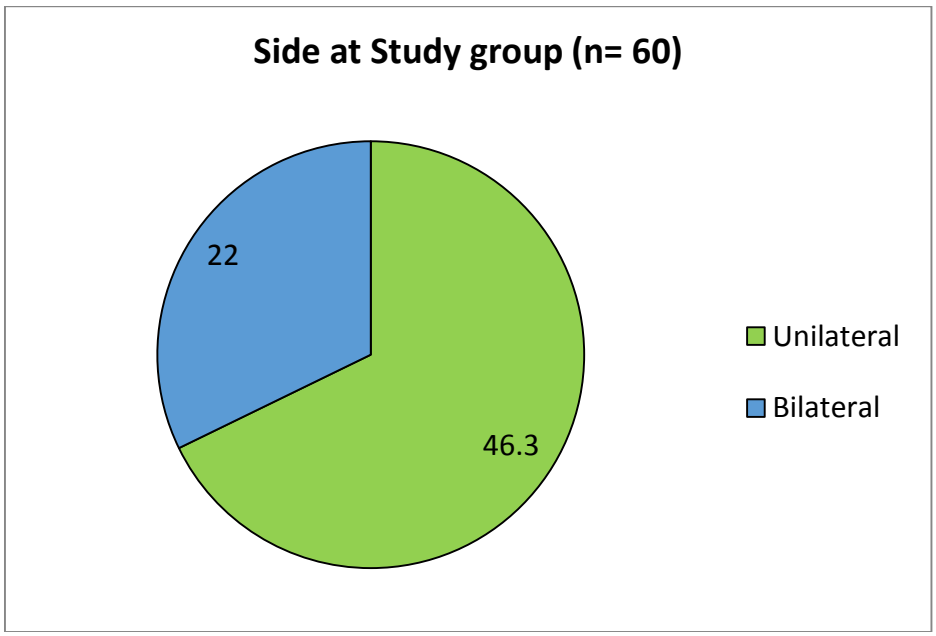
Data is expressed as mean and standard deviation or percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05

Table 3. Signs and symptoms related to endometriosis in the current study

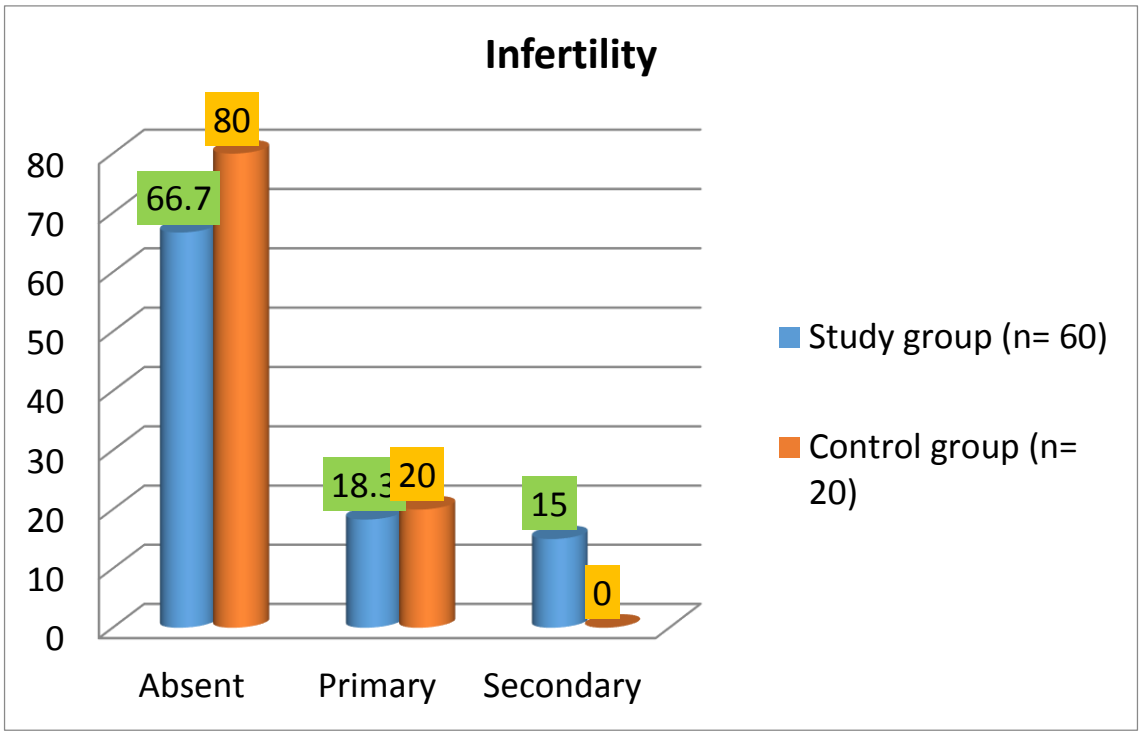
		Study group (n= 60)	Control group (n= 20)	p
Side	**Unilateral**	62.7% (46.3)	-	-
	Bilateral	37.3% (22)	-	
Infertility	**Absent**	66.7% (40)	80.0% (16)	0.212
	Primary	18.3% (11)	20.0% (4)	
	Secondary	15.0% (9)	0.0% (0)	
Fixed tender RVF		25.0%(12)	0.0% (0)	**0.017**
Nodule in rectovaginal septum		1.7% (1)	0.0% (0)	**1**
Fixed tender adnexal masses		13.3% (6)	0.0% (0)	**0.191**
Association with adenomyosis		11.7% (7)	0.0% (0)	0.110

Data is expressed as percentage and frequency. P is significant when < 0.05

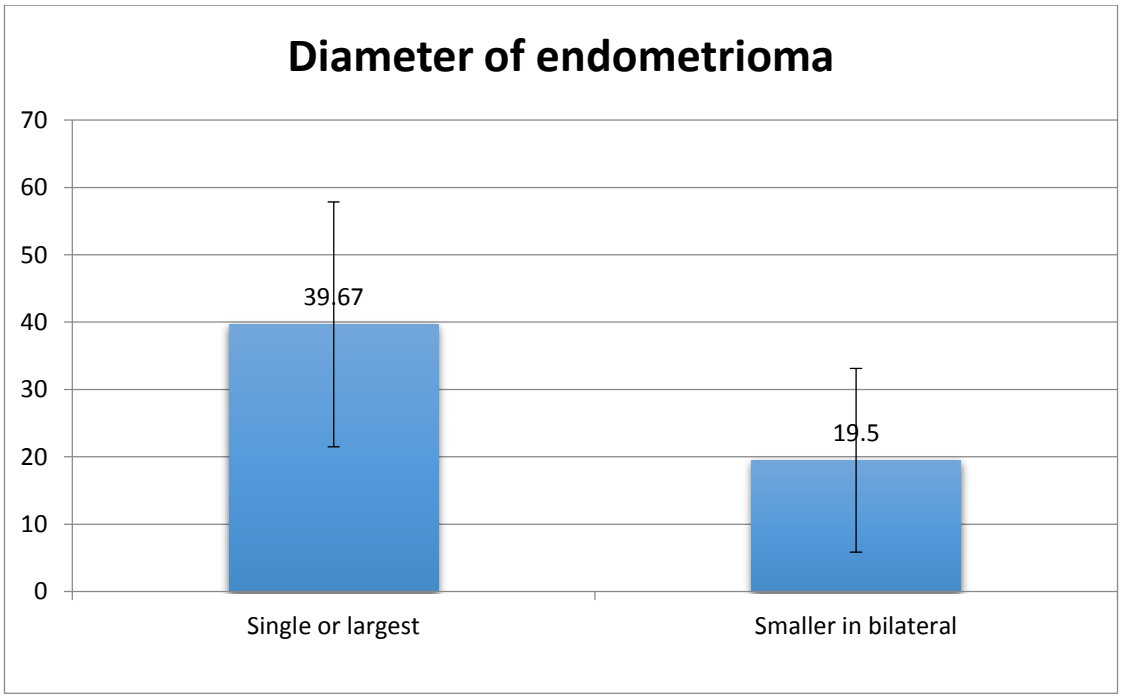
This table show that 62.7% has unilateral endometriosis, 37.3% has bilateral endometriosis there is statistical significant difference between groups as regard fixed tender RVF. But there are no statistical significant differences between groups as regard Nodule in rectovaginal septum, fixed tender adnexal masses, Association with adenomyosis and Infertility.



Graph 7. Pie charts showing Side at Study group



Graph 8. Bar charts showing Infertility among Study and Control group



Graph 9. Bar chart shows Diameter of endometrioma among Study and Control group

Table 4. Duration of endometriosis in the current study

	Mean & SD	Median	Range	IQR
Duration (months)	7.95 ± 3.515	8.0	2, 16	5, 11

Data is expressed as mean and standard deviation, median, range and inter-quartile range
This table shows that Mean ±SD of Duration of endometriosis in the current study is 7.95 ± 3.515

Table 5. Diameter of endometrioma in the current study

	Mean & SD	Median	Range	IQR
Single or largest	39.67 ± 18.192	39.5	7, 76	26, 53
Smaller in bilateral	19.50 ± 13.644	16.0	3, 50	9, 31.25

Data is expressed as mean and standard deviation, median, range and inter-quartile range.
This table shows that mean ±SD of Single or largest endometrioma in the current study is 39.67 ± 18.192, and mean ±SD of Smaller in bilateral endometrioma is 19.50 ± 13.644

Table 6. Grading of pain in the study group by VAS score

	Mean & SD	Median	Range	IQR
Visual analogue scale score	2.91 ± 1.288	3	1, 6	2, 4

Data is expressed as mean and standard deviation, median, range and inter-quartile range
This table shows that mean ±SD of VAS score in study group is 2.91 ± 1.288.

Table 7. Comparison of AMH levels of the studied groups

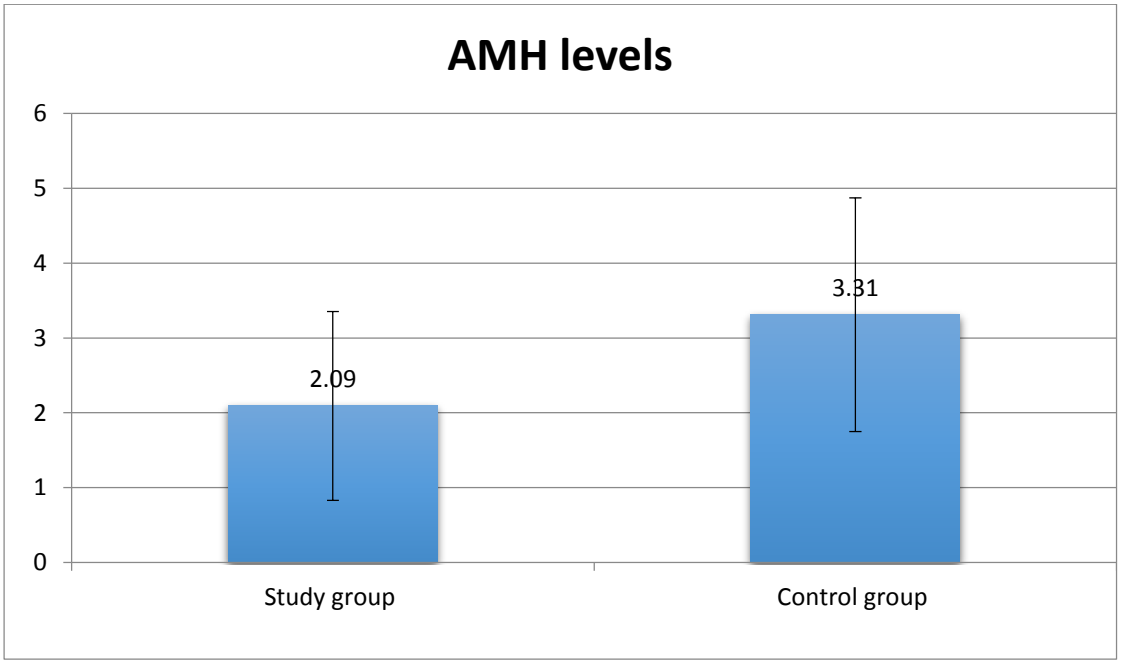
	Study group (n= 60)	Control group (n= 20)	95% CI	p
AMH	2.09 ± 1.262	3.31 ± 1.561	-1.92, -0.54	**0.001**

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05
This table shows that mean ±SD of AMH in study group is 2.09 ± 1.262, and is 3.31 ± 1.561 in control group; there is highly statistical significant difference between case and control groups as regard AMH levels

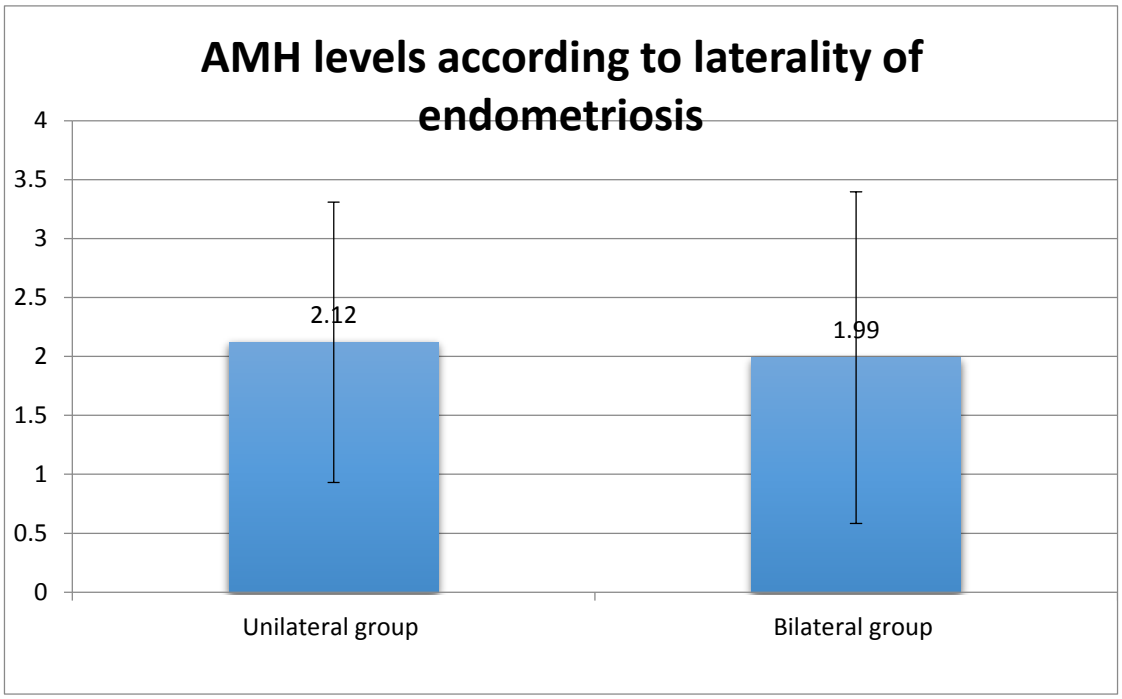
Table 8. Comparison of AMH levels according to laterality of endometriosis

	Unilateral group (n= 37)	Bilateral group (n= 23)	95% CI	p
AMH(ng/ml)	2.12 ± 1.190	1.99 ± 1.407	-0.56, 0.81	0.721

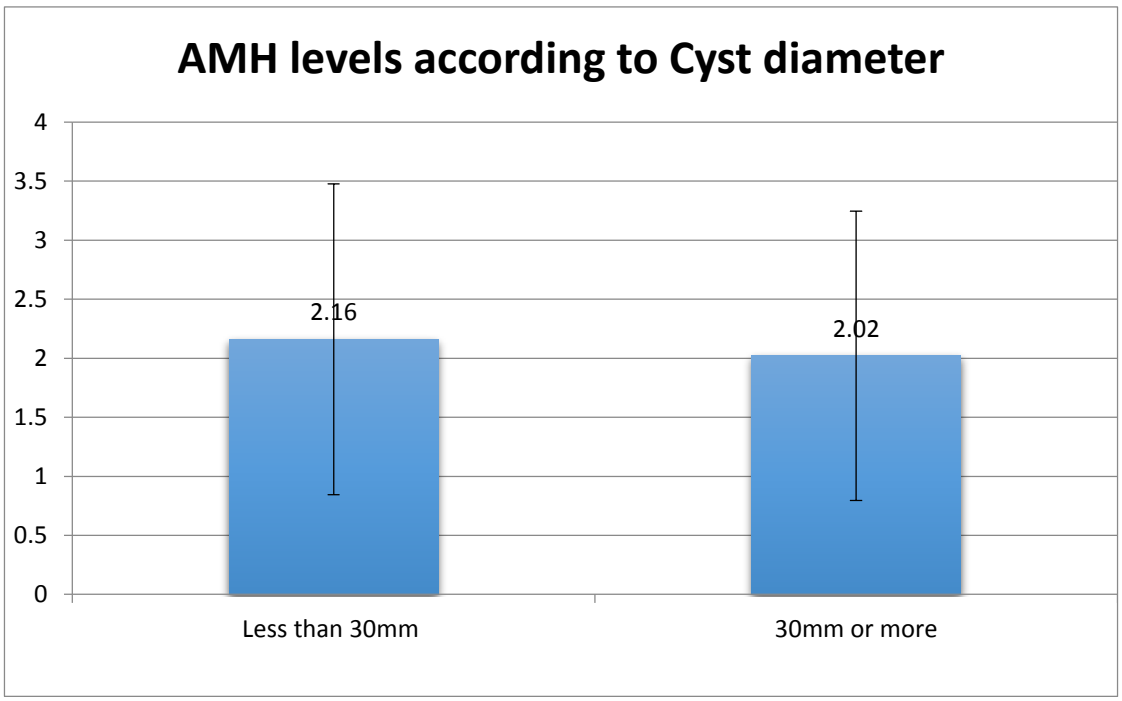
Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05
This table shows that mean ±SD of AMH in Unilateral endometriosis is 2.12 ± 1.190, and mean ±SD of AMH in Bilateral endometriosis is 1.99 ± 1.407, and there are non- statistical differences between the laterality of endometriosis as regard AMH levels



Graph 10. Bar chart shows AMH levels among Study and Control group



Graph 11. Bar chart shows Comparison of AMH levels according to laterality of endometriosis



Graph 12. Bar chart shows Comparison of AMH levels according to Cyst diameter

5. DISCUSSION

Endometriosis is defined as the presence of endometrial tissue (gland and stroma) outside the uterus. It is estimated to occur in 10% of reproductive aged women and is associated with pelvic pain and infertility. The overall prevalence of endometriosis is greater in infertile women than in fertile women. The etiology of endometriosis is not exactly known, however, polymorphism studies on estrogen receptor (ER) associated with the risk of endometriosis in

different countries showed that the risk of endometriosis varies and it is associated with genetic, environmental, and other numerous factors [16].

There are many studies suggesting the causal relationship between the presence of endometriosis and subfertility, but the exact mechanism is still unclear. However, it is evident that when endometriosis is moderate to severe, involving the ovaries and causing adhesions that block tubo-ovarian motility and ovum pickup, it is associated with subfertility. Because benign ovarian cysts including endometrioma are frequently encountered in women of reproductive age, fertility preservation is important in-patient management [17].

Several serologic tests, such as basal follicle stimulating hormone (FSH), estrogen, and inhibin B and ultrasonographic findings, such as ovarian volume and antral follicle count can be used to predict ovarian reserve, however, there are several limitations. Serum anti-Müllerian hormone (AMH) is a dimeric glycoprotein within the transforming growth factor-beta superfamily, and is produced by the granulosa cells of primary to small antral follicles to prevent depletion of the primordial follicle pool. AMH levels are independent of the menstrual cycle and are not affected by the use of gonadotropin-releasing hormone (GnRH) agonists or oral contraceptives. Hence, serum AMH measurement has been widely used in clinical practice for assessment of ovarian reserve and is currently measured frequently during the initial work-up for infertility [18].

Endometriosis is related to subfertility and many studies have shown corresponding results. Shebl et al. demonstrated the association between low serum AMH levels and severity of women with endometriosis [18]. Pacchiarotti et al. [19] reported that serum AMH levels are reduced in women with endometriosis who have never undergone ovarian surgery, suggesting a state of poor ovarian reserve. However, it is unclear whether patients with endometriosis have a real decrease in ovarian reserve, furthermore, what causes the decreased ovarian reserve is unknown [19].

Our results were supported by study of Suardi et al. [20] as they reported that there were no significant differences in the characteristics of the two study groups. These characteristics include age (P=0.678) and body mass index (P=0.351). The mean patient age was 31 (20–35) years in the endometrioma group and 30 (21–35) years in the control group. However, most of the endometrioma subjects presented with chief complaints of an abdominal mass (45.5%), while lower abdominal pain and infertility were the second and third most common complaints, with percentages of 31.8% and 22.7%, respectively.

Table 9. Comparison of AMH levels according to Cyst diameter

	Less than 30mm (n= 36)	30mm or more (n= 24)	95% CI	p
AMH(ng/ml)	2.16 ± 1.315	2.02 ± 1.225	-0.52, 0.8	0.672

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05

This table shows that mean ±SD of AMH in cyst Less than 30mm is 2.16 ± 1.315, and mean ±SD of AMH in cyst30mm or more is 2.02 ± 1.225, and there are non- statistical differences between the different cyst diameters as regard AMH levels

Table 10. Correlation between duration of endometriosis and other studied parameters

	Correlation coefficient	p
Dysmenorrhea	-0.171	0.190
Dyspareunia	-0.217	0.095
Presence of pelvic pain	0.808	**< 0.001**
Association with adenomyosis	0.154	0.240
Cyst diameter	0.462	**< 0.001**
VAS	0.953	**< 0.001**
AMH	0.072	0.586

P is significant when < 0.05

This table shows that there are highly statistical significant positive correlation between duration of endometriosis and each of Presence of pelvic pain, Cyst diameter and VAS

However, in the study of Nezhat et al. [21] 97 patients were divided to 2 groups by pathologic confirmation. Sixty-five patients were diagnosed with ovarian endometrioma and 32 patients had other benign ovarian cysts. The mean age of endometrioma group was 30.3 ± 4.4 years and 27.6 ± 4.2 years in other benign ovarian cysts group. Mean age was significantly older in the endometrioma group than another ovarian cyst group.

However, in the study of Jeon et al. [22] mean diameter of endometrioma group was 67.26 ± 56.41 mm, and 76.03 ± 39.25 mm in another benign cyst group. The difference was not statistically significant. Among the 65 patients with endometrioma, 34 patients had unilateral endometrioma and 31 patients had bilateral endometriomas. Grouping by bilaterality and multiplicity, single unilateral (group 1) were 17, single bilateral (group 2) were 5, multiple unilateral (group 3) were 17, and multiple bilateral (group 4) were 26. In all patients with ovarian endometrioma, advanced endometriosis (stage III and IV) was diagnosed by laparoscopy.

In the study of 23. Czernobilsky et al. [23] the distribution of the diameter of right ovary endometriomas was: 4 cm: n = 14; 5–6 cm: n = 8; and ≥7 cm: n = 5. The distribution of the diameter of left ovary endometriomas was: 4 cm: n = 20; 5–6 cm: n = 18; and ≥7 cm; n = 7.

Our results were supported by study of Suardi et al. [24] as they indicate that serum AMH levels significantly lower in endometrioma than non-endometrioma, with the lowest level found in the bilateral endometrioma group. For the correlation between serum AMH levels and ovarian volume in women with endometrioma, we found a non-statistically significant correlation.

An earlier study carried out by Donnez.et al. [25] also observed that the group of women with endometrioma experienced more rapid reduction in serum AMH levels compared to the control group, but this was also strongly influenced by the therapy that had been undertaken by the subjects. The study also showed a decrease in serum AMH levels, resulting in earlier menopause onset in women with endometriosis, and led to an increase in morbidity.

Nezhat et al. [26] compared the longitudinal decline of AMH levels over six months, between 40 women with endometriomas and similarly aged 40 healthy women. None of the women were on any medication that could affect AMH levels. AMH levels were found to decline faster in the endometrioma group (median decline: -26.4% (25th and 75th percentile -11.36% to -55.41%) vs. -7.4% (25th and 75th percentile: 11.98%, to -29.33%), in the endometrioma and control groups, respectively). The increased rate of decline can be an explanation for the lower AMH levels observed in women with endometrioma in previous cross-sectional studies [27].

Raffi et al. [28] in a metanalysis of eight studies and 237 patients, reported a statistically significant decline in AMH levels following endometrioma surgery (1.13 ng/ml, CI; 0.37 - 1.88). The decline in AMH levels was significant even after unilateral cystectomy (30% decline, SMD: -0,96 ng/mL; CI: -0,22, -1,70). The decline is reported to be 44% after bilateral endometrioma excision. Somigliana et al. [29] published a similar systematic review with 11 studies in the same year, but did not pool the data due to the heterogeneity of original studies. Nine of the eleven studies reported a decrease in AMH levels after surgery, while only two studies reported otherwise. The authors concluded that endometrioma excision leads to a decline in AMH levels.

Also, Padilla et al. [30] prospectively compared 58 patients with endometrioma with 29 women without endometriosis; preoperatively, AMH levels were significantly lower in the presence of an endometrioma (1.8 ng/mL; CI, 1.2 - 2.4, vs. 3.2 ng/mL; CI: 2.0 – 4.4). One month after endometrioma excision AMH levels were significantly lower than preoperative levels (decline by -48%; CI; -54%, -18%; P<0.01, mean AMH decreased from 1.77 ng/ml to 1.12 ng/ml). At the sixth month after surgery, despite some increase over the values at the first month, AMH levels were still lower than the preoperative levels, albeit short of statistical significance (1.41 ng/ml, CI: 0.97 -1.85, compared to preoperative levels p=0.22).

6. CONCLUSIONS

Women with endometrioma have significantly lower serum AMH levels and seem to experience a more rapid decline in serum AMH levels than age matched counterparts, suggesting a harmful effect of endometrioma per se on ovarian reserve.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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