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ROLE OF ANTI-MULLERIAN HORMONE IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME ON METFORMIN THERAPY.

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ABSTRACT
Background: AMH production by granulosa cells in the polycystic ovary is 2-3 fold increase compared to healthy women. **Purpose of the study:** Anti-Mullerian hormone (AMH) is produced by the granulosa cells surrounding prenatal and antral follicles and has an important role in the development and maturation of follicles. Several studies have suggested that AMH serum levels may be a marker for polycystic ovary syndrome (PCOS). **Methods:** Prospective study was conducted in the Department of Obstetrics and Gynaecology, Owaisi Hospital and Research Centre and Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad from March 2014- April 2015. **Results:** A total of 34 patients diagnosed cases of PCOS. Mean serum Anti Mullerian hormone levels were significantly decreased in PCOS population on metformin therapy as compared to PCOS population not on metformin therapy. **Conclusion** : Serum AMH is a useful prognostic biochemical marker for metformin therapy in PCOS .

KEY WORDS: granulosa, Anti-Mullerian, antral follicles.

INTRODUCTION
Anti-Mullerian hormone (AMH) is produced by the granulosa cells surrounding preantral and antral follicles and has an important role in the development and maturation of follicles . Several studies have suggested that AMH serum levels may be a marker for polycystic ovary syndrome (PCOS). The level of AMH is not affected by the menstrual cycle or altered by use of oral contraceptives, therefore it can be used as a biological marker for PCOS. AMH expression occurs after deployment of the follicle and continues through the antral phase of follicle development. It suppresses follicle-stimulating hormone (FSH) production and affects follicular growth. AMH produced in the polycystic ovary is 75 times higher when compared to healthy women. AMH levels in the plasma of PCOS patients are two or three times higher than average and begin to fall five years later than healthy women. In PCOS, follicle do not become the dominant follicle. There is low levels of FSH, high levels of AMH which decrease the sensitivity of follicles to FSH. Thus, follicles cannot develop into a dominant follicle, which leads to an accumulation of small antral follicles. AMH also inhibit the aromatase enzyme activity, suggesting that AMH contributes to the severity of PCOS. Metformin is an oral antidiabetic drug in the biguanide class, for the treatment of type 2 diabetes mellitus. Primary clinical action is to inhibit hepatic glucose production and also decreases intestinal glucose uptake, and increases insulin sensitivity in peripheral tissues. Metformin has antilipolytic effects, lowers circulating free fatty acid, which leads to reduction in gluconeogenesis. The use of metformin in PCOS is associated with increased menstrual cyclicity, improved ovulation, and a reduction in androgen levels. Metabolic benefits are achieved with weight loss. Metformin is available in 500, 850, and 1000 mg tablets with a target dose of 1500-2550 mg per day.

MATERIALS AND METHODS

This prospective study is conducted at Owaisi Hospital and Research Centre and Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad. Patients were selected from the outpatient department of Obstetrics and Gynaecology for a period of one year March 2014 - April 2015.

Informed consent was obtained after explaining about the nature and purpose of the study, a total of 34 patients were enrolled age ranging from 18-36 years, mean age

calculated as 28.6 years. These patients were allocated into 3 groups: Group I consisted of 20 women diagnosed to have PCOS who were studied on Day 2 of cycle ; Group II which included the 20 women in group I, treated with metformin hydrochloride tablet 500 mg 3 times daily for 3 months and followed up and were studied on a Day 2 of cycle ; and Group III consisted of 14 women diagnosed PCOS and already on metformin treatment 500 mg tablet 3 times daily for 6 months to 1 year , and this group was also studied on Day 2 of cycle. Pregnant women and diabetic patients were excluded from the study. Ethical approval was obtained. Diagnosis of PCOS was based on the Rotterdam Criteria, presence of at least 2 of the following 3 criteria: 1. oligo-ovulation and/or anovulation; 2.hyperandrogenism; and 3. polycystic ovaries on ultrasound defined as the presence of 12, or more follicles in either ovary measuring 2-9 mm in diameter, and/or increased ovarian volume greater than 10 ml.The ultrasound was done at Owaisi hospital , Ovarian morphology was assessed by transvaginal ultrasound on the same machine . Blood samples of patients in Group I, Group II, and Group III on Day 2 of the cycle. Serum measurements of AMH were measured using enzyme linked immunosorbent assay (ELISA).Anthropometric measurements taken.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel 2010 and analysis was done using SPSS version 20.Descriptive statistical analysis was done. Results on continuous measurements are presented as **Mean & Standard Error Mean**. Linear regression was utilized to test for correlation between different studied parameters, and the significance of the R-value was assessed by related Student's t-test. $P<0.05$, $P<0.01$ was considered statistically significant.

RESULTS

Table (i) Mean values standard error mean of Age, Anti-Mullerian Hormone (AMH) ,Body mass index (BMI), Number of ovarian follicles and Ovarian volume in different groups of women with Polycystic ovary syndrome

Parameters	Group I (n=20)	GROUP II (n=20)	GROUP III (n=14)
Age,years.	29.8± 0.65	28.9 ± 0.57	27.35 ± 0.67
AMH (ng/ml)	4.55 ± 0.17	2.96± 0.10	4.75 ± 0.19
BMI(kg/m^2)	31.9 ± 0.48	29.4 ± 0.42	33.74 ± 0.27
No.of ovarian follicles	10.2± 0.33	8.81± 0.35	10.4 ± 0.43
Ovarian volume	8.61± 0.35	6.78± 0.29	9.50 ± 0.41

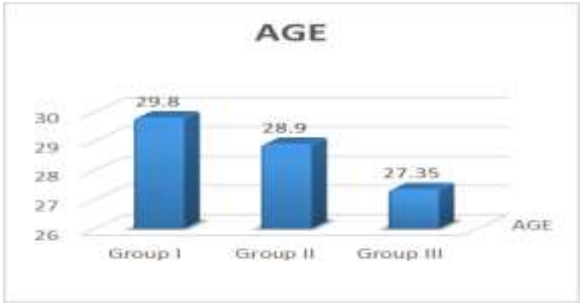
Mean±standard error of mean (SEM) values of serum AMH levels was 4.55±0.17 ng/ml in Group I, 2.96±0.10 ng/ml in Group II, and 4.75±0.19 ng/ml in Group III with a significant decrease in Group II compared with Group I ($p<0.00001$), and Group III ($p=0.22$ NS). However, the PCOS women in Group III did not show a significant difference from those women in Group I.

Mean ±SEM values of age and body mass index (BMI) of Group I, Group II, and Group III. There was no difference in age among the groups. The mean value of BMI of Group II was significantly decreased in comparison with that of Group III ($p<0.00001$), but with a insignificant decrease compared to Group I (31.9±0.48 Kg/m^2) . The women of Group III were the more obese one.

Mean ±SEM values of the ovarian follicles number and ovarian volume of women of Group II were significantly decreased when compared with those of Group I ($p=0.0024$, $p=0.0001$), and Group III ($p=0.0033$, $p< 0.00001$).

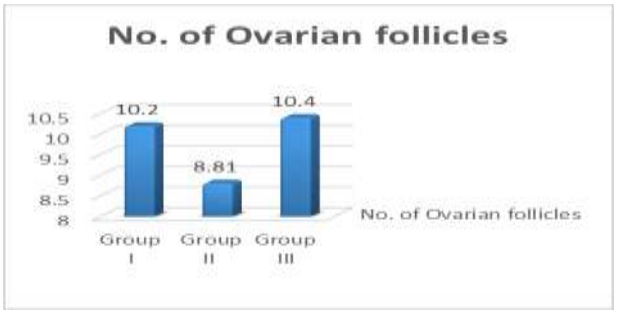
The study also revealed significant positive correlation between serum levels of AMH and the values of ovarian volume (r=0.3, $p=0.05$).

Graph i: (Mean Values of AMH Group I Group II Group III)

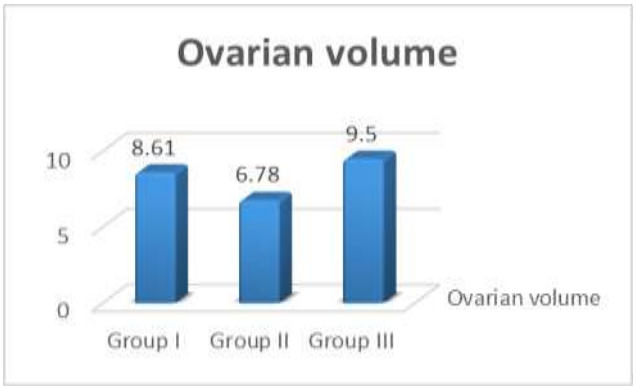


Graph ii : (Mean Age in GroupI Group II Group III)

Graph iii : (Mean BMI in Group I Group II Group III)



Graph iv : (Mean of Ovarian follicles in Group I Group II Group III)



Graph v: (Mean Ovarian Volume in Group I Group II Group III)

Data entered in Microsoft excel 2010 was analysed using SPSS version 20. Descriptive statistical analysis was done and results on continuous measurements were presented as **Mean & Standard Error Mean**. Linear regression was utilized to test for correlation between different studied parameters, and the significance of the R-value was assessed by related Student's t-test. $P<0.05$, $P<0.01$ was statistically significant.

DISCUSSION

The AMH is secreted by the granulosa cells of small antral and pre-antral follicles in the ovary. It inhibits recruitment of primordial follicles.[1]Several studies have reported higher levels of AMH in women with PCOS than in controls. [2,3] An increased production of AMH induces a decrease in the sensitivity of follicles to FSH at receptor level, which leads to an increase in number of antral follicles on the detriment of their size: the number of small antral follicles 2-5 mm in size increases, restraining, thus the selection of the dominant follicle. Such a situation is clinically characterized by anovulation cycles, manifesting themselves as oligo- or amenorrhea.[4] The present study showed positive effect of ovarian volume on AMH levels in Group I, and obesity as an important factors tightly bound with AMH regulation. [5] The results of the present study are consistent with previous studies, in which the patients on metformin therapy reduction in Serum AMH levels.[6,7] Obese PCOS patients responded well to metformin therapy when compared to the patients with low body mass index.[8] However, other studies also did not find significant changes in serum AMH after metformin therapy in PCOS[9], to a low dose for 6 months. The reason for reduction in AMH levels after metformin therapy remains controversial. Metformin suppresses the hepatic gluconeogenesis, improves peripheral resistance to insulin, consumption of glucose in skeletal muscles is increased, there is decrease in intestinal glucose absorption. Metformin enhances insulin action at cell levels by enhancing the caption of glucose in adipose and muscular cells, and by increasing the ligation to the insulin receptors. Metformin helps to induce regular menstrual cycles, increase ovulation, and some weight loss.[9]Six months of androgen suppression by metformin treatment did not influence AMH levels and metformin treatment of PCOS patients results in significant reduction in AMH levels.[10]

The present study showed a decrease in the BMI of Group II patients compared with those of Group III patients . However, the patients in Group II and Group III have a significant increase in BMI. The sustained elevated BMI in both groups (Group II and Group III) after short and long metformin treatment of the present study may highlight the role of lifestyle habits in improving obesity, and efficacy of metformin therapy [11] The present study showed decrease in the number of ovarian follicles in PCOS on metformin therapy for 3 months compared to the same patients before treatment, and to PCOS women treated from 6 months-1 year. The mean ovarian volume in Group II patients was significantly decreased when compared to Group I and Group III**.**

The present study showed positive correlation between BMI and ovarian volume in Group III patients, which

may explain the increased ovarian volume of those women since they were obese, and demonstrate the significant association of lifestyle habit in improvement of PCOS on metformin therapy.

Our study concludes that serum AMH is a better prognostic biochemical marker for metformin treatment in PCOS. Metformin has beneficial effects on follicle growth in women with PCOS. Metformin therapy for more than 3 months is not advised, as there was no improvement in biochemical and clinical features of PCOS.

Limitations: The limitation of the study was inability to collect and store follicular fluid for measurement of AMH and other hormones, and compare their values with blood serum.

DISCLOSURE OF INTERESTS

The authors have no conflicts of interest to declare. All authors participated and approved the article for publication.

Ethics approval

Ethics committee approval was obtained from the IRB Board, Owaisi Group of Hospitals to conduct the study and a written informed consent was taken from the study participants.

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