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Anti –Mullerian Hormone is a new Marker for Ovarian function in females with polycystic ovary syndrome

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Abstract:- *Anti-Mullerian Hormone (AMH) is a member of the transforming growth and differentiation factors in the ovary, AMH has an inhibitory effect on primordial follicle recruitment as well as on the responsiveness of growth follicles to follicle stimulating hormone (FSH) 'The ovary-specific expression pattern in granulosa cells of growing non selected follicles makes AMH an ideal marker for the size of the ovarian follicle pool.*
The aims *of the present study were as follows:*
1) to confirm the increase of serum AMH in patients with PCOS ;
2) to search for any relationship of serum AMH to the other hormonal features of PCOS;
3) whether metformin administration affects serum AMH levels..
Design: *case series.*
Setting: *Private clinic of Dr.Luma Al Sarraj and Al Duaa clinical laboratory of Dr.Islam Al Jalili.*
Participants and Methods*: this study was conducted on 75 female subjects aged less than 45 years for the period from March2012-July 2012,infertile women were diagnosed as poly cystic ovary syndrome(PCOS) according Rotterdam Consensus (2004),thirty women were normal (n=30) used as control. Serum AMH hormone was measured using Enzyme Linked Immune Sorbant Assay(ELISA),LH, FSH, Testosterone ,Prolactin were measured by using Enzyme Linked Fluorescent assay(ELFA).*
Results: *There was a significant increase & difference in serum AMH, LH, prolactin while a significant decrease in serum FSH in women with PCOS as compared to control women.*
Concerning testosterone hormone, there was an increase in its level in women with PCOS but not reached significance when compared to its level in control women. Women with PCOS showed a significant decrease in their serum AMH levels after their treatment with Metformin.
The percent improvement rate after treatment with Metformin was 48.12%. There was a significant positive correlation between serum AMH and LH levels in patients with PCOS while no significant correlation was seen between serum AMH and FSH, prolactin and testosterone.
Conclusion: *Serum levels of AMH were increased in women with PCOS and AMH measurement can be used as a marker with high specificity and sensitivity for PCOS.*
KeyWord*: AMH, Female Infertility, PCOS.*

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I. Introduction

Anti-Müllerian hormone (AMH) was initially thought to be produced solely by the fetal male during sexual differentiation to promote regression of the Müllerian ducts. Over the last decade, however, a new and interesting role has emerged for AMH in the ovary. In human ovaries, AMH is produced by granulosa cells from 36 weeks of gestation until menopause [(1)]. Direct measurements of AMH protein production by human GCs and follicular fluid in 2007 confirmed that the highest concentrations were in small antral follicles and became very low or undetectable in follicles ≥10 mm [(2)] , small antral follicles reflected the remaining follicle pool[(3)]. Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-β (TGF-β) super family of glycoprotein's that has been found to play an important role by :1) inhibiting the initial recruitment of primordial follicles[(4,5)] and 2) promoting follicular arrest[(5,6)] .Although the effects of AMH on the ovarian functions are not fully elucidated and even though it is still questioned whether AMH is a marker of primordial development or both[(7)], its serum level appears as a reliable marker of the ovarian follicle pool. It has been shown recently that AMH levels decreased in situations of ovarian aging, along with follicle depletion[(8)] .Women of <25 years of age had higher serum AMH concentrations than those aged 35 years and above[(4)]. DIAGNOSTIC CRITERIA**:-** for polycystic ovary syndrome (PCOS), as suggested in the Rotterdam conference sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) in 2003, include 1) oligo- and/or anovulation (ANOV), 2)

hyperandrogenemia and/or hyperandrogenism (clinical signs of high androgen levels) (HA), and 3) polycystic ovaries (PCO). Diagnosis presupposes the presence of at least two of the three features, after the exclusion of other androgen excess disorders[10,11] .AMH production is reported to increase in women with polycystic ovary syndrome (PCOS) compared to controls[12,13,14]. AMH measurement can offer a high specificity and sensitivity (92% and 67%, respectively) as a marker for PCOS. On this basis it has been proposed that in situations where accurate ultrasonography data are not available, AMH could be used instead of the follicle count as a diagnostic criterion for PCOS [15]. Indeed, AMH levels have been found to be increased in serum [16, 17, 18].Recently studies showed that higher AMH levels in amenorrhoeic than in oligomenorrhoeic women with PCOS, which could indicate a role for AMH in the pathogenesis of PCOS-related anovulation. Alternatively, high AMH values could reflect a more evident impairment in follicular development and granulosa cell function in the ovaries of amenorrhoeic than oligomenorrhoeic PCOS women [19].

The aims of the present study were as follows:1) to confirm the increase of serum AMH in patients with PCOS ; 2) to search for any relationship of serum AMH to the other hormonal features of PCOS;3) whether Metformin administration affects serum AMH levels. **Participants &Methods:-** This study was carried out in the private clinic of Dr. Luma Al-Surraj & Al- Duaa clinical lab for the period between March 2012-July 2012 and informed consent was obtained from patients and controls before entry into the study. Seventy-five women with PCOS were recruited for this study (mean age 31.29 years) and the control population consisted of thirty healthy fertile women (mean age 27.96 years), the exclusion criteria were a history of menstrual diturbances, hirsutism. The diagnosis of PCOS was based on the association of at least two of the three following criteria:

1) hyperandrogenism as defined by hirsutism and or testosterone >0.7ng/ml;

2) menstrual and /or ovulatory disturbances, mainly oligomenorrhea and amenorrhea; 3) U/S criterion of PCO [10, 11]. Serum AMH levels were measured using ELISA (Enzyme Linked Sorbant Assay). Serum concentrations of LH, FSH, prolactin and testosterone were measured using ELFA (Enzyme Linked Fluorscent Assay).

II. Stastical Analysis

It was carried out by using the statistical Package for the Social Science (SPSS Inc, Chicago, version 11.5). A descriptive statistics, mean and standard deviation (SD) were given for the data A P- value <o.o5 was considered significant .Unpaired t- test was used to compare means of serum level of hormones in women with PCOS and controls. Paired t-test was used to compare mean of serum AMH level in patients before and after treatment with Metformin.

Relationships between AMH and various hormones were evaluated by nonparametric Spearman correlation coefficient. Analysis of variance (ANOVA) was used to show the difference in AMH levels in different age groups [20].

III. Results

Table 1 shows that women with PCOS had higher levels of serum AMH when compared with control women and it was statistically significant, the 95% confidence for difference :(5.23; 7.95). Concerning serum LH levels, also there was a significant difference between women with PCOS & controls. 95% confidence for difference :(1.81; 3.00). Serum FSH levels in women with PCOS was significantly different from that in control. 95% confidence for difference:(-2.92;-1.64).

Serum prolactin level was higher in women with PCOS as compared to control women. & there was a significant difference. 95% confidence :(9.04; 21.28). Although serum testosterone level was higher in women with PCOS but there was no significant difference .95% confidence for difference :(0.09; 1.40).

Table1: Comparison between mean serum hormonal levels in control & PCOS women.

Parameter	PCOS women(n=75)	Control women(n=30)	p-value
AMH ng/ml	10.38±3.70	3.79±0.85	0.000
LH mIU/ml	5.95±1.56	3.54±0.82	0.000
FSH mIU/ml	4.34±1.67	6.62±0.93	0.000
PRLmIU/ml	26.3±16.6	11.1±4.86	0.000
Testosterone ng/ml	1.21±1.81	0.45±0.17	0.02(NS)

*Unpaired t-test was used

Table 2 depicts a significant decrease in serum AMH levels after treatment with Metformin. 95% confidence for difference :(3.95; 6.42) The percent improvement rate after treatment with metformin was 48.12%.

Table2: Comparison of mean serum AMH levels in women with PCOS before and after treatment with metformin.

Before treatment	After treatment	p- value
11.22±4.04	6.03±2.31	o.ooo

*Paired t-test was used.

Table 3 indicates no significant difference in the mean serum AMH levels between age groups and there was no effect of age on serum AMH levels.

Table3: Serum AMH level in different age groups in PCOS women.

20-29 years(n=34)	30-39 years(n=29)	40+ years(n=12)	p-value
10.25±3.81	9.67±4.01	11.33±3.43	N.S

*Analysis of variance was used.

Table 4 demonstrates a significant positive correlation between serum AMH and LH levels in patient with PCOS while no significant correlation was seen between serum AMH and FSH, prolactin and testosterone.

Table4: Correlation between serum AMH, LH, FSH and testosterone in PCOS women.

Parameter	r-value	p-value
AMH,LH	0.222	0.05
AMH,FSH	-0.035	0.76(NS)
AMH,PRL	0.039	0.73(NS)
AMH,testosterone	-0.002	0.98(NS)

*Pearson correlation coefficient was used.

IV. Discussion

In the current study, the significant difference in serum FSH level between women with PCOS and control was in agreement with the finding of Josso et al [(21)] Durlinger et al (2001) [(22)] that AMH cause inhibition of aromatase activity in granulose cells, thus reducing the production of estradiol E2 and this effect combined with the fact that AMH could reduce the follicle sensitivity to FSH. The present study showed an increased serum AMH levels in women with PCOS this in agreement with other authors [(23, 24, 25)] and this may be the result of aberrant activities of the granulose cells in the polycystic ovaries. Women with PCOS had a significant increase in serum LH as compared to control women & this in agreement with (Lockwood et a1998)[(26)] who found that anovulation in PCOS could be the result of excessive pituitary LH secretion. It has been shown that metformin administration in women with PCOS is associated with reduction in serum AMH levels suggesting that , the measurement of AMH could be used to evaluate treatment efficacy & this in agreement with Piltonin et al 2005[(4)]. For women with PCOS there was no effect of age on serum AMH level and there was no significant difference in serum AMH between age groups this disagrees with the finding of Mulders et al 2004[(27)] who found a decline in serum AMH level with age but it agrees with the finding of Piltonin et al 2005([(4)]) this suggest that the ovarian aging in PCOS women may have been slowed down, possibly due to suppressed primordial follicle outgrowth by the high levels of AMH observed in these women. There was negative correlation between serum FSH & serum AMH although not reached significant level this agrees with the finding of Tomers et al 2009[(28)] but it disagrees with the finding of Pigney et al 2003[(29)]. Because the patient population analyzed in this study was selected for patients with polycystic ovary. The results reported here may therefore not apply to other female populations and future studies of the correlation between FSH and AMH should be conducted using normally fertile women and large sample size. There was no correlation between serum AMH, and testosterone and this disagrees with the finding of Pigney et al 2003 [(29)]Laven et al [2004(23)].

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