Best Marker to Asses Hirsutisim

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ABSRACT---
Aim: To correlate serum levels of Anti Mullerian Hormone and Total Testosterone with severity of hirsutism in females with either polycystic ovarian syndrome or idiopathic hirsutism.
Design: retrospective observational study.
Setting: private sector endocrine clinic.
Patients: eighty- five hirsute patients.
Intervention: female presented for hirsutism management were evaluated physically and biochemically.
Main outcome: Feriman and Gallawy Score for patients and serum levels of Total Testosterone and Anti Mullerian Hormone
Rseults: Eighty- five hirsute women were evaluated for severity of their hirsutism by Ferming-Galawy score, serum Total Testosterone and Anti Mullerian Hormone. Mean age of patients was 27.48 ± 5.6 years. Mean Body Mass Index of the patients were 30. 07±4.93 kg/m2. Mean Total serum testosterone was 51.57±4.93ng/ml and mean serum Anti Mullerian Hormone was 6.72±29.34ng/ml. The patients were divided according to their etiology of hirsutism into Poly Cystic Ovarian Syndrome group and Idiopathic Hirsutism group. There were significant differences in body mass index, serum levels of Total Testosterone, Anti Mullerian Hormone and Feriman and Gallawy score between these two groups. Serum levels of Total Testosterone have significant positive correlation with severity of hirsutism in Poly Cystic Ovarian Syndrome group only, while Anti Mullerian Hormone have no correlation with neither of the two groups.
Conclusion: Serum level of Total Testosterone can serve ideal marker in our study group for hirsute patients with Poly Cystic Ovarian Syndrome.

Keywords---- Hirsutism, idiopathic hirsutisim, polycystic ovarian syndrome, Total testosterone, Anti mullerian hormone.
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1. INTRODUCTION

Hirsutism, the presence of terminal hairs in females in a male-like pattern, is a common endocrine disorder which affects 5–10% of women of reproductive age. Hirsutism is extremely distressing for patients and has a significant negative impact on their psychosocial behavior (1). In these women, the hairiness implies the presence of abnormal androgen action. Pubertal androgens promote the conversion of vellus hairs to coarser, pigmented terminal hairs. The level and duration of exposure to androgens, the local 5-alpha-reductase activity, and the intrinsic sensitivity of the hair follicle to androgen action determine the extent of conversion from vellus to terminal hair.

Hirsutism can be classified broadly into 2 groups androgen induced and non-androgen induced. Androgen induced can either be due to excessive endogenous androgen production (ovarian/adrenal) or exogenous due to drugs. Central over production of androgens, increases peripheral conversion of androgens, decreases metabolism and enhances receptor binding, which are potential causes of hirsutism. Non-androgen induced hirsutism can be idiopathic, familial or drug induced (2, 3).

Polycystic ovary syndrome (PCOS) and idiopathic hirsutism (IH) are the two most common causes of hirsutism. (4).

PCOS is the most common endocrinopathy in women which is characterized by hyperandrogenemia and chronic anovulation. Women with PCOS demonstrate marked clinical heterogeneity; (5); the commonly associated features such as hirsutism, acne, polycystic-appearing ovaries, obesity, and acanthosis nigricans are neither uniform nor universal,(6). HI, the second most common cause of hirsutism is considered when hirsutism is associated with normal ovulatory function and normal circulating serum androgen concentrations. The pathogenesis of IH is still unclear, although increased activity of peripheral 5-alpha reductase enzyme (7), androgen receptor gene polymorphism, and increased sensitivity of hair follicles to androgens have been proposed (8).

The aim of this study is to find weather serum level of TT and AMH could be used as a marker

for the severity of hirsutism in patients with PCOS and IH.

2. PATIENTS AND METHOD:

Medical records of 85 hirsute patients presented to private endocrine clinic in hilla city/ Babylon/ Iraq were analyzed retrospectively. Record only of those who fulfill the criteria of PCOS and IH as will be clarified later had been selected.

Complete history regarding age, marital status, family history of hirsutism, medications and systemic diseases, menstrual and obstetric history, and associated signs of hyperandrogenism were recorded. Demographic data are shown in (tabla1). The female were with mean age of 27.48 ± 5.6 ranging from $17 - 40$ years. Hirsutism was scored according to the Ferriman and Gallwey scoring system.(9). Any woman with a score of 8 or more was considered as hirsute. (10 , 11). Physical examination focused on secondary sexual characteristics, presence of galactorrhea, frontal balding, increase in shoulder girdle muscles, coarsening of voice, acne, loss of female body contours, and clitoromegaly.

All females underwent anthropometric measurement to calculate body mass index (BMI). The routine investigations that were performed included detailed hemogram and serum chemistry including liver and kidney function tests. Hormone estimations were performed in the follicular phase (days 3–5) of the menstrual cycle or, when cycle is induced in case of amenorrheic patients. The hormonal estimations were comprised of basal levels of serum cortisol, Luteinizing Hormone, Follicle stimulating Hormone, Prolactin, thyroid hormones, AMH and TT .A pregnancy test was performed on all amenorrheic women and ultrasonography for adrenals and ovaries.

All samples for hormone estimation were stored at $-20°C$ before being analyzed. All hormone estimations were performed by Mini VIDAS technique by commercially available kits. AMH level was measured by Enzymatic Linked Immune Sorbent Assay (ELISA).None of the subjects were premenarchal or postmenopausal, had undergone previous hysterectomy, bilateral oophorectomy, or natural menopause. Menstrual irregularities were defined as a history of intermenstrual intervals of greater than 45 days, or less than 21(12*).*Oligomenorrhea was defined as fewer than nine menses per year (13).

Clinical hyperandrogenism was defined by presence of hirsutism, acne or androgenetic alopecia. (14).

TT serum level > 56 ng/ dl, was considered abnormal according to our lab, reference value.

AMH lower than 1 or above 4 ng/ml considered abnormal according to our laboratory reference value.

Definitions of diagnostic groups:

1. Polycystic ovary syndrome: PCOS patients was diagnosed according to Rotterdam criteria: presence of two of the three elements of: Clinical or biological hyperandrogenism, polycystic ovaries (were diagnosed on pelvic sonography by presence of ≥12 follicles measuring 2-9 mm in diameter and/or ≥10 ml ovarian volume) and chronic anovulation (15).

2. Idiopathic hirsutism: hirsutism in association with regular menstrual cycles and normal hormonal levels (16).

3. STATISTICAL ANALYSIS

The Statistical analysis of the data was performed with Statistical Package for Social Science; version 20 for windows (SPSS, Inc, Chicago, IL). In addition to descriptive statistics, the χ^2 test was used for comparison between categorical variables and the t-test for comparison among continuous variables. A $P<.05$ was considered statistically significant. Pearson's correlation was used to examine the relation between serum levels of TT and AMH with the severity of hirsutism.All the subjects who participated in the study gave informed consent for their participation.

4. RESULTS

A total of 85 patients records were retrospectively analyzed in the study. All were suffering from various grades of hirsutism. The age range was 17-40 years with a mean age of 27.48 ± 5.6 years. Mean BMI of the patients were 30. 07 ± 4.93 which makes them fall in the obese categories. Mean Total serum testosterone was 51.57 ± 4.93ng/ml and mean serum AMH was 6.72 ± 29.34ng/ml.

According to the F-G score their mean score was 9.03 ± 1.17. Menstrual cycle irregularity was found in 56.5% of the cases and Oligomenorrhea in 54.1% of the studied group. (Table 1).

Table 1 : demographic data of the patients. N= 85. Values are mean ± SD or percentages

Parameter	Mean ± SD
Age(year)	27.48 ± 5.63
BMI kg/m2	30. 07 ± 4.93
Total serum testosterone ng/ml	51.57 ± 4.93
AMH ng/dl	6.72 ± 29.34
F-G score	9.03 ± 1.17
Menstrual cycle irregularity %	56.5
Oligomenorrhea %	54.1

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These subjects were divided into two groups according to menstrual cycle rhythm and serum hormonal levels.(Table 2).

Table 2: A comparisim between demographic characteristic of PCOS and IH group.

Parameter	PCOS Group	IH Group	P value
Age(year)	27.03 ± 5.92	28.18 ± 5.07	P> 0.05
BMI(kg/m2)	31.26 ± 4.94	28.07 ± 4.28	P< 0.05**
AMH(ng / dl)	7.53 ± 5.04	5.33 ± 4.38	p>0.05
Serum testosterone(ng/dl)	57.83 ± 29.171	40.52 ± 27.10	P< 0.05**
F-G score	9.46 ± 1.02	8.36 ± 1.11	P<0.05**
Oligomenorrhea%	88.5	none	P< 0.05**
Menstrual irregularities %	92.3	none	P< 0.05**

** Significant difference from corresponding value.

PCOS group: These patients fulfill the Rotterdam criteria defind by Clinical hyperandoginisim (F-G score9.46±1.02) and /or Biochemical hyperandoginisim (TT 57.83±   29.17)   And / or oligomenorrhea and mensural irregularities 88.5 % ,92.3% respectively. IH : the idiopathic hyperandroginisim ,defined by clinical hyperandroginisim (F-G score 8.3636 ± 1.11) and normal level of seum TT levels (40.52 ±27.10 ng/dl) (Table 2).

 The study showed that commonest cause of hirsutism in our population was PCOS in 52 patients (61.17%), followed by idiopathic hirsutism in 33 (38.82℅) patients .

Table 3 illustrate the correlation of serum AMH and TT to the severity of hirsutism , using Pearson correlation to detect the relation between the severities of hirsutism with hormones measured. There were only significant correlation between F-G score of PCOS group with serum TT level (p< .0.05). Otherwise the relations were insignificant with AMH as well as with serum TT in IH group (p> 0.05).Table 3

Table 3: Correlation of serum levels of AMH and Testosterone to F-G score in PCOS group and IH group.

Parameter	PCOS	IH
SerumTotalTestosterone level.ng/ml	0.522*	0.169
AMH serum leveling/dl	0.213	0.33

** Significant difference from corresponding value.

5.   DISCUSSION

 Hirsutism, the presence of terminal (coarse) hairs in females in a male-like pattern. It affects between 5% and 10% of women of reproductive age. (17).Conventionally Hirsutism is divided into two major groups: those with elevation of serum androgens levels having some underlying endocrine disorder (secondary) and those without significant elevation of it and having no underlying disorder often termed as idiopathic. Other less common causes include anorexia nervosa, hypothyroidism and porphyria or could be iatrogenic. Simple obesity may lead to hyperandrogenism and hirsutism without significant metabolic disorder. (18).

The increased levels of androgens may originate from ovaries, adrenals or prolactin-secreting tumours. The commonest causes of ovarian hyperandrogenism are PCOS and virilizing ovarian neoplasia. However, PCOS alone accounts for 75-80% cases of hyperandrogenism.(14,19).Hirsutism is the most common sign of hyperandrogenism in PCOS and it has been estimated that 17% and 83% of PCOS patient have hirsutism ,(2).

 Worldwide the prevalence of hirsutism varies between literature which may be due to variation in the study population regarding the race and ethnicity and acceptance of hirsutism itself.It is very difficult to investigate thoroughly all cases of hirsutism, as it is expensive and fruitless in majority of cases. Only those women who present with severe hirsutism and/or have other manifestations of virilism need elaborate investigation. (20), for rest the serum androgen levels suffice.

There is very sparse literature on the relationship of serum androgens to severity and pattern of hair growth in hirsutism in my country. To fill this gap we decided to undertake this study. We revised medical records of 85 female patients who attend private endocrine clinic because of hirsutisim. Their mean age was age of 27.48 ± 5.6 years ranging from 17-40 years (Table1).

According to WHO criteria our study group fall in obese category, their mean BMI was 30. 07 ± 4.93 kg/m2 (21). The relations between obesity and hirsutism may be modified by racial and ethnic characteristics of different populations. for example in a retrograde2 year cohort study by Khalil et al. of adult Saudi populations the associations between obesity and certain skin diseases such as hirsutism, dry skin, pruritus, and planter keratosis were all nonsignificant .(22) But this fact was not concluded by other research work in this field (23, 24, 25). The increased frequency of hirsutism in overweight and obese women could be explained by increased insulin resistance and more androgen production by adipose tissue.Hirsutism is a common problem of our population. It varies in severity from mild to severe.

Perception and acceptance of hirsutism by women varies considerably between cultures, races and individuals. Therefore a standard tool is essential to properly assess, classify and monitor prognosis in hirsutism. Ferriman and Gallwey designed a nice scoring system for this purpose which has remained gold standard to assess the severity and monitor treatment efficacy and prognosis. (9), when we apply this score to our patients, the mean score found to be 9.03±1.17 which put this group in moderate type of hirsutisim (26).

Anti-Müllerian hormone also known as mullerian inhibiting substance (MIS) is a member of the large transforming growth factor-p (TGFP) multigene family of glycoproteins that is involved in the regulation of growth and differentiation. In the ovary, AMH is produced by the granulosa cells of early developing follicles and seems to be able to inhibit the initiation of primordial and FSH-induced follicle growth. Interestingly, AMH is expressed in human follicles from the primary follicular stage towards the antral stage, immediately after recruitment right up to the selection stage (4-6 mm diameter) (27).

There is a debate on the association of androgen and AMH serum levels in women with polycystic ovary syndrome (PCOS). It has been demonstrated that androgens promote both theca interna cells and granulose cells proliferation. (28 , 29).This effect on folliculogenesis predominates in small follicles, probably, due to their richness in androgen receptors as it has been reported that the androgen receptor gene expression is the highest in granulosa cells of preantral and antral follicles.(30).

AMH, could be implicated in the hyperandrogenism of PCOS as the detection of AMH type II receptor (AMHRII) in theca interna cells of maturing follicles; by in situ hybridization, that could lend support to a paracrine effect of AMH on these cells.(31). Mean AMH serum levels in our study was 6.72±29.34 ng/ml, this elevated level mostly due to PCOS group.

Menstrual irregularities and Oligomenorrhea were noticed in 56.5 % and 54.1 % respectively   in the studied population which were all in PCOS group , this may be attributed to the fact that AMH play role in follicular growth and have potential value as a marker for the type and extent of ovarian dysfunction in anovulatory women with PCOS.

Mean serum level of TT was 51.57±4.93 ng /ml, this normal level of TT, with the hirsutisim of our patients could be explained by that sex steroids may act on the hair follicle independently of their circulating levels. This local or intracrine effect is extremely important and may prove to play a significant role in the development of androgen excess disorders, particularly IH. **(32).**Sixty-one percent of our patients had PCOS according to Rotterdam criteria, while 38.9% have

IH proved by normal serum TT level, and normal regular cycle , (33), (Table 2). Since a history of "regular menses" does not accurately reflect ovulatory status in the hirsute patient (34) ovulation must be confirmed by using a daily basal body temperature (BBT) charting .These percentages show that PCOS is more common than IH, which match well well with those observed by Farid and colloquies with who reported idiopathic hirsutism as second most common cause after PCOS. (35) but contrast with the study by Malik and colloquies (36) . When we use t- test to compare the demographic data of the two groups we find significant difference regarding BMI TT F-G score is significantly higher in PCOS group. This is attributed to the fact that PCOS is associated with obesity higher serum TT levels and insulin resistance and so more prone to higher F-G score. (37, 38, 39).While in IH the sensitivity of the hair follicle to androgens is largely governed by the alpha reductase activity in the skin, which is responsible for the conversion of testosterone to dihydrotestosterone. So the severity of hirsutism does not correlate well with the level of androgens, and the response of the androgen dependent hair follicle varies considerably within and between individuals.

Pearson correlation was used to find the correlation of severity of hirsutism reflected by F-G score with serum TT and AMH in both groups.

In IH group there was no significant correlation between TT and AMH serum levels with the severity of hirsutism. This could be explained by the normal hormonal milieu of this group, and the cause is idiopathic which explain it self. The hirsutism in this group may be attributed to increase sensitivity of the hair follicles to normal androgen levels or to increase activity of alpha reductase enzyme in the skin of these individuals.

PCOS was the most common cause of hirsutism found in the instant study. Further, there was positive correlation between severity of hirsutism and total testosterone levels.(Table 3).These findings match well with that of Chhabra et al and Cebeci et al. (40,22).Serum AMH found to have no correlation with the severity of hirsutism reflected by F-G score in this study. This in contrast to the study done in turkey Sahmay and team work were they found significant correlation in this regard in PCOS sample(41).A study done in Norway by Eilertsenand co-workers where they concluded that AMH have significant weak correlation with the severity of hirsutism(42) . In both studies the sample size were larger than ours, and they constructed their study group according to ovarian morphology , which was not done in our study .

6. CONCLUSION

Serum total testosterone correlates with the severity of hirsutism in PCOS, but not in IH. AMH have no correlation in this regard in both groups.

7. ETHICAL APPROVAL

The author hereby declare that this work had been approved by the ethical and scientificCommittee of Medical College / Babylon University.

8. COMPETING INTERESTS

Author have declared that no competing interests exist.

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