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Hormonal Reassessment of Iraqi Hirsute Women Searching For Sources of Hyperandrogenism

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ABSTRACT

Background: Hirsutism is an excess of terminal hair growth in women in a pattern more typical of men. Terminal hair growth in a male pattern is undoubtedly due to the effect to androgens, and reflects the conversion of vellus hair to terminal hair follicles .Androgens are produced by the adrenals and ovaries. The four primary circulating androgenic steroids in women are dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S), androstenedione and testosterone. The objective of this study is to reassess the hormonal status of Iraqi hirsute women searching mainly for sources of hyperandrogenism.
Methods: In this cross-sectional study, 98 Iraqi hirsute females patients aged between 14 and 55 years, and aged matched with 50 Iraqi females (the control),who referred themselves to the Dermatology Clinic of AL-Saddar teaching hospital and two private dermatology clinics between February2013 and December 2014, were investigated. A personal history was obtained from each patient. Body mass index (BMI; weight/height^2) was also measured. A trans abdominal ultrasonography and hormonal profile was conducted for all patients with hirsutism regardless of the degree of hirsutism or regularity of menses.
Results: The degree of hirsutism was assessed according to the Ferriman-Gallwey score. Fifty-three patients had a score of more than 7 (54%), 41 of them had a score of more than 10 (41.8%), and only 4patients presented with a score of more than25 (4%). Overall, 58 patients(59.1%) had a positive family history of hirsutism. The hormonal workup revealed that the total serum level of testosterone was elevated in 30 patients (33.7%), while the serum level of free testosterone was elevated in 55 patients (56.1%). Sex hormone-binding globulin as the main transporter for androgens was significantly decreased in 25 patients (25.5%).The dehydroepiandrosterone sulphate (DHEA-S) serum level was elevated in 24 patients (24.4%). The insulin level was above the normal range in only 6 patients (6.1%) and all of them had PCOS. Hyperprolactinemia was present in 37 patients (37.7%). An abnormal lipids profile was seen in 79 women(80.6%),all of whom either overweight or obese.
Conclusion: Nearly all of the Iraqi hirsute premenopausal women had an abnormal hormonal profile. The sources of hyperandrogenism were PCOS in one third of patients, followed by an adrenal source in a quarter of them as a mild elevation in DHEA-S. Another important source was the low level of SHBG, while idiopathicity did not register as a factor, according to this study. Good advice regarding the results of the lipids profiles and body mass index measurements for all hirsute women is to lose weight.

Keywords :*Hirsutism,Hyperandrogenism,Hormonal Reassessment*

1. INTRODUCTION

Hirsutism is an excess of terminal hair growth in women in a pattern more typical of men. Androgen-dependent growth areas affected include the upper lip, cheeks, chin, central chest, breasts, lower abdomen and groin.[1]

What constitutes significant hirsutism is difficult to define, as it depends on a variety of cultural and racial factors, media-driven perceptions of normality, and the perceptions of the individual physician and patient. Not surprisingly, therefore, estimates of the frequency of hirsutism in the female populations have varied widely.Terminal hair growth in a male pattern is undoubtedly due to the effect of androgens, and reflects the conversion of vellus to terminal hair follicles. In many women, hirsutism is associated with raised levels of circulating androgens (54 percent in one series).However in some, androgen levels are within the normal range, suggesting in these individuals that hair growth is especially sensitive to androgen stimulation. Other clinical features of hyperandrogenism include oligo- or amenorrhea, sub- or infertility, acne, acanthosis nigricans, and female pattem hair loss to frank virilization with male patternbalding and clitoromegaly.[2]Hirsutism may be associated with obesity, insulin resistance, diabetes, polycystic ovary syndrome (PCOS), hypertension, infertility, and menstrual irregularities.[3,4]

Androgens are produced by the adrenals and ovaries. The four primary circulating androgenic steroids in women are dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S), androstenedione and testosterone. Approximately 50% of the testosterone is secreted from the ovaries and adrenal glands.

The remainder is produced from metabolism in the liver, fat and skin of the pre-hormones androstenedione, DHEA and DHEA-S. Androstenedione is produced from both the ovaries and adrenal glands. DHEA-S originates in the adrenal glands. The liver is the major site of testosterone metabolism. Testosterone overproduction overwhelms the liver's clear ancecapabilities and excessive testosterone appears in the circulation. The hair follicle then becomes a site to metabolize the excess testosterone. Androgens are transported in the blood by sex hormone-binding globulin (SHBG) to the hair follicle, where they are converted and bind to androgen receptors. Serum levels of testosterone are regulated by SHBG. SHBG levels increase with higher oestrogen levels, such as with oral contraceptive therapy. Lower levels of SHBG increase the availability of free testosterone. SHBG levels decrease in response to hyperinsulinemia, hyperprolactinemia, obesity, polycystic ovary syndrome, exogenous androgens and Cushing syndrome.[5] Women with hyperprolactinemia may have anincrease in functional androgens throughadrenal overproduction and through adecrease in sex hormone-binding globulin caused by a diminution of ovarianestrogen production.[2] Prolactin elevations may be seen in patients with PCOS.[6]

Studies of the psychological burden of hirsutism among women seeking medical treatment suggest that it has a significant effect on them, adversely affecting quality of life.[7,8]The objective of this study was to reassess the hormonal status of Iraqi hirsute women searching mainly for sources of hyperandrogenism.

2. PATIENTS AND METHODS

In this cross-sectional study, 98Iraqifemaleshirsute patient aged between 14 and 55, and aged matched with 50 Iraqi females (the control),who referred themselves to the Dermatology Clinic of AL-Saddar Teaching Hospital and two private dermatology clinics between February2013 and August 2015, were investigated. Exclusion criteria include pregnant or lactating women, those who had received oral contraceptive pills or other drugs that could interfere with the hormonal assays and postmenopausal women. Informed consent was obtained from each patient.

A personal history was obtained from each patient using a questionnaire, including age, marital status, parity and duration of hirsutism. Questions on their medical history included ones about diabetes, hypertension and history of drug use or any kind of hormonal treatment. The menstrual cycle history of the preceding two years was recorded in order to detect the presence of menstrual irregularities. The menstrual patterns were defined as regular cycles if the length of the cycle was between 22 and 40 days. The cycle was considered irregular if the patient had either oligomenorrhea (bleeding at intervals of greater than 40 days), polymenorrhea (bleeding at intervals of less than 22 days) or amenorrhea (absence of menstruation for 12 months or more).[9]A careful family history of hirsutism was obtained.

Hirsutism in women is measured by the degree of hair growth in nine body regions, using the Ferriman-Gallwey score, in the chin, upper lip, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms and thighs. The maximal hair score is 36. A score of more than 6 in a white woman indicates an abnormal hair distribution. The score in all of the affected parts was assessed for all patients.

Body mass index (BMI; weight/height^2) was also measured. A BMI of less than 18.5 is regarded as underweight, while a BMI greater than 25 is considered overweight, and above 30 is consideredobesein three classes.[10]

A transabdominal ultrasonography was done onall patients in the early follicular phase (5th–9thday of the menstrual cycle) and PCO was defined as the presence of bilaterally normal or enlarged ovaries contain in gat least 10 microcysts (2mm–8mm in diameter) onultrasonography.[11]A hormonal profile was done for all patients with hirsutism regardless of the degree of hirsutism and regularity of menses.

Blood Samples

5mlof blood from each of 98 Iraqi female hirsute patients was transferred into a plain tube without anticoagulant and left at room temperature for 20 minutes for clotting, and then centrifuged at 3000 rpm for 10 minutes. Serum was then taken and used to measure the serum levels of total testosterone (T), free testosterone (FT), sex hormone-binding globulin (SHBG), prolactin (PRL) and dehydroepiandrosterone sulfate (DHEA-S). Insulin assays were performed with commercial radioimmunoassaykits. All of the performedassays were based on the standard operating procedures using kits supplied by Bio labo/France.

Data management and statistical analysis

Data were double entered into a Microsoft Excel database, compared and corrected for data entry errors, and then imported into the Statistical Package for Social Sciences (SPSS) software program. The data was visually inspected for extreme values, and 10values for single parameters that appeared physiologically impossible were removed.

The Student's*t*-test was used for comparison of means between two continuous variables. $P< 0.05$ was considered significant .A comparison of reference ranges for differences within the group was by done using One-Way-ANOVA.

3. RESULTS

The figure shows the results for the 98hirsute patients with a mean age of(24.8±1.2)years studied.(47.9%) of patients were aged 14 to 20 years at the time of the visit,(32.6%) of them were between 21and30 years, and only one patient was aged over45 years .The duration of the hirsutism among Iraqi women involved in this study, as informed, was mostly between 1 and 5 years (67.3%) and between 6 and 10 years (26.5%).There were 53 married patients(approximately 54%), of which 18 were infertile (33.9%), and 35 of the women(66%) had had children.

Overall, 58 patients (59.1%) had a positive family history of hirsutism.

Figure 1 shows the degree of hirsutism as previously mentioned, assessed according to the Ferriman-Gallwey score. Fifty-three patients had a score of more than 7 (54%),41 of them had a score more than 10 (41.8%), and only four patients presented with a score more than25 (4%). The sites affected in the high percentage of patients comprised the chin (which was involved in 100% of patients) and the upper lip,and beard areas came in the second rank. The abdomen, upper back and upper arms were the less frequent sites.

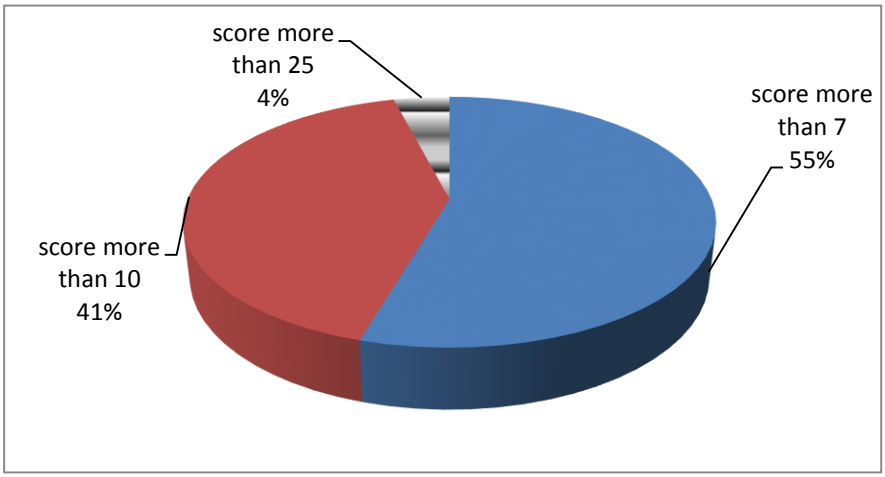

Figure1: Degree of hirsutism according to the Ferriman-Gallwey score

Fourteen patients(14.2%)were considered to be of normal weight according to their BMI measurement .Over weightness as measured was present in 37 patients (37.7%), and approximately half of the patients (47.9%) showed obesity in three classes (Table 1 and Figure 2). This clarifies that the degree of hirsutism correlates directly with weight gain.

Table1:Distribution of Study groups according to age and BMI

Age *Years*	Control		Patients		Total N(%)
	N(%)	BMI(kg/m^2)	N(%)	BMI(kg/m^2)	
14-30	15(30)	24.7±0.1	42(43)	24.7±0.2	57(38)
31-45	18(36)	29.2±0.13	30(31)	30.15±0.4	48(33)
≥46	17(34)	24.4±0.59	26(26)	25.9±0.21	43(29)
Total	50(33)	/	98(67)	/	(148)

Values are expressed as mean ±SE;N=Numbers, BMI=Body mass index(kg/m^2)

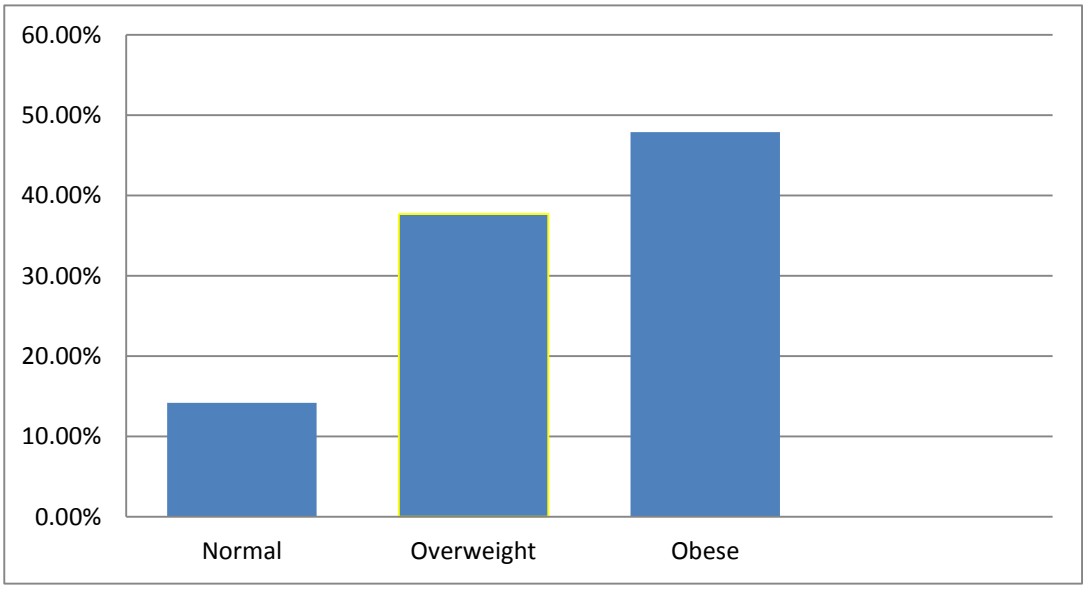

Figure2: Distribution of hirsute patients according to their body mass index

An assessment of menstrual cycles revealed that the menstrual cycle was regular in 47(47.9%) patients, while 51(52.1%) women had irregular menses. Approximately half(49%) of the women(25 patients) with both hirsutism and menstrual irregularity had PCOS; this percentage is lower than to be expected by dermatologists for Iraqi women. Only 12 patients with hirsutism and regular menses presented with a positive diagnosis ofPCOS.

As mentioned, a hormonal workup was done for all study groups included in this study. A normal random plasma testosterone level in a hirsute woman frequently does not accurately reflect the testosterone production rate. The free serum testosterone level is a more sensitive index of increased testosterone production in women with hirsutism than the total testosterone level.[12]So, both the total and free serum level of testosterone was measured .The total serum level of testosterone was elevated in 30 patients (33.7%), in comparison

with elevated levels in six age-matched control women (11.1%), while the serum level of free testosterone was elevated in 55 patients (56.1%) in comparison with only one age-matched control patient.

Sex hormone-binding globulin as the main transporter for androgens was significantly reduced in 25 patients(25.5%), while one age-matched control patient showed a value below the normal range(p = 0.00746). In conjunction with this important finding,20patients showedelevated levels of free testosterone. The dehydroepiandrosterone sulphate (DHEA-S) serum level was elevated in 24 patients (24.4%) in comparison to just three patients in the age-matched control group(p = 0.0018); in addition, 15 age-matched control patients showed a low level of DHEA-S.

The insulin level (2-25 µIU/ml) was above the normal range in only 6 patients(6.1%). All of them had PCOS in comparison with 11 age-matched control patients.

Hyperprolactinemia was present in 37 patients (37.7%). Only 11 patients had PCOS. An abnormal lipids profile was seen in 79 women(80.6%):all of them were either overweight or obese in the three classes.

The mean lipid concentration, SD_s, is shown in Table3; the hirsute patients showed a significant increase in serum total cholesterol (TC), triglycerides and phospholipid (Ph.L) control ($P \leq 0.05$).

Table 2: Hormonal profile among hirsute patients and controls

Parameters (unit)	Results		Normal range
	Patients No.=98	Controls No=50	
Total testosterone	**33.7 %**	**11.1 %**	**0.1 – 0.9 ng/ml**
Free testosterone	**56.1 %**	**1.8%**	**0.3-1.9 ng/dL**
Sex hormone binding globulin	**25.5%**	**1.8%**	**18-144 nmol/L**
Dehydroepiandrosteronesulphate	**24.4 %**	**5.5%**	**14 - 395 (ug/dL)**
Insulin	**6.1 %**	**20.3%**	**Fasting < 25 mIU/L**
Prolactin	**37.7 %**	**0%**	**2-25ng/mL**

Mean lipid concentration, SD_s are presented in table(3), the patients with females hirsute patient shown a significant increased of serum total cholesterol (TC), triglycerides and phospholipid (Ph.L) control ($P \leq 0.05$),

Table(2):Lipid profile levels in sera of three studied groups

Parameters(mg/dl)	Study groups	
	Control	Patients
Total cholesterol	182±3.8	230±7.1*
Triglycerid	115.7±1.3	180±4.7*
Phospholipid	16.2±7.5	17.1±3.1*
HDL-C	41.5±8.7	37±9.1
LDL-C	110±31.1	121±20.2
VLDL-C	22.9±7.71	31±14*
LDL-C/HDL-C	2.7±1.7	3±1.5

Values are expressed as Mean ±SD *($P \leq 0.05$)

4. DISCUSSION

Hirsutism is a common clinical condition that usually follows a benign course. It should be differentiated from hypertrichosis, which is defined as the excessive growth of hair independent of androgens and is usually of a vellus type .Facial and body hair is less commonly seen in oriental people, black people and native Americans than in white people. Even among white people, there are differences: hair growth is heavier in those of Mediterranean than those of Nordic ancestry. The pattern of hair growth in hirsutism within different racial groups is identical. However, different criteria have made the determination of the comparative incidence and severity within these groups difficult to assess.[3]

Most (80%)testosterone is secreted either by the ovaries or adrenals. A small amount of circulating testosterone is derived from the conversion of androgenic precursors, mainly androstenedione (derived from the ovaries and adrenals) and dihydroepiandrosterone (DHEA – derived from the adrenals) in the liver, skin and adipose tissue.[4] However, only between 1% and 2% of testosterone is in free form and is the active androgen. About 98% to 99% is bound to steroid hormone-binding globulin (SHBG), cortisol binding globulin, or, non-specifically, to albumin and other proteins and is biologically inactive. Only free testosterone is converted to dihydrotestosterone (DHT), by the enzyme 5-alpha reductase type 2 isoenzyme present in the outer root sheath of the hair follicles.[13,14]

Approximately 50% of women with even minimal hirsutism have excessive androgen levels. Laboratory studies in hirsutism serve both to confirm the clinical impression of hyperandrogenism and to identify the sources of excess androgens, either adrenal or ovarian.[15]

There are several probable aetiologies for the disease. It can occur idiopathically, be due to ovarian disorders (e.g.PCOS, hyperthecosis and ovarian tumours), have adrenal causes (e.g.classic or late-onset CAH, adrenal tumours, and Cushing syndrome), or be due to prolactinoma, pregnancy or a postmenopausal state. Some cases are iatrogenic. Excessive production of androgens from adrenals or ovaries accounts for between 60% to 80% of cases of hirsutism in different studies.[3]In our study, we found hyperandrogenemia (total serum

testosterone) in 33.7%of the patients, but as we mentioned above, free testosterone is the most sensitive index for hyperandrogenism which is found to be elevated in 56.1% of cases.

One of the most common sources of excess androgen is the ovaries (PCOS), as understoodby Iraqi dermatologists. PCOS is the most common endocrine abnormality affecting women in the reproductive age group with an estimated prevalence of 5% to 10%.[16]In our study, we found that PCOS was present in 37 patients (37.7%)This result should motivate the dermatologist to search for sources of hyperandrogenism other than PCOS.Lamees Mahmood Malik*et al.*, in a study of74 patients ,found 33of them(44.6%)to be diagnosed with polycystic ovary syndrome.[17]In the study by Ansarin H.*et al.* of Iranian premenopausalwomen, a diagnosis of PCOS was positive in 62.5% of them.[18]Gatee *et al.* reported the presence of PCO in 91% of 102 hirsute patients in the United Arab Emirates.[19] In a study of 60 hirsute patients in India by Mithal *et al.*,PCO was found in 75% of the cases.[20]In similar studies, Zargar *et al.* found an incidence PCO in 37.3% of150 patients in Kashmir, India.[21] In our study, we found that irregularity of menses does not rule out the diagnosis of PCOS, as this study reveals that 12 patients with a positive diagnosis of the syndrome had regular menses. No other abnormalities or tumours (benign or malignant)were found in the ovaries as all patients were checked with transabdominal ultrasonography. Hyperinsulinemia as a possible cause of elevated androgens levels, either as a part of PCOS or by lowering the serum level of SHBG, was found only in 6 patients, all of them with positive diagnosis of polycystic ovary syndrome. In a previous study done by Khawla A. Shemran in Iraq, looking at the level of serum insulin among hirsute women, the results were the opposite to ours, as she found a significant elevation of the serum insulin.[22]

Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone. The bulk of DHEA is secreted as a 3-sulfoconjugate (DHEA-S). Both hormones are bound to SHBG, but binding of DHEA-S is much tighter. Elevated DHEA-S levels can cause symptoms or signs of hyperandrogenism in women. Most mild to moderate elevations of DHEA-S levels are idiopathic. However, pronounced elevations of DHEA-S may be indicative of androgen-producing adrenal tumors.[23]

In this hormonal reassessment of hirsute women in our society, we found what we considered to be a mild elevation of DHEA-S in about a quarter of patients as compared to only three control subjects. No obvious lesion or tumour could be detected with transabdominal ultrasonography. Only 6patients presented at the same time with PCOS, leading to the consideration that the adrenals are nearly equal to the ovaries as an important source of hyperandrogenism.

Sex hormone-binding globulin (SHBG) and sex steroid-binding globulin(SSBG)are glycoproteinsthat bind to the sex hormones,androgenandoestrogen.[24] Testosterone and estradiol circulate in the bloodstream, bound mostly to SHBG and, to a lesser extent, serum albumin and corticosteroid-binding globulin(CBG) (AKA transcortin). Only a very small fraction of about 1% to 2% is unbound, or 'free', and thus biologically active and able to enter a cell and activate its receptor. SHBG inhibits the function of these hormones. Thus, the bioavailability of sex hormones is influenced by the level of SHBG.DHEA is weakly bound to SHBG as well, but DHEA-Sis not.[25]Androstenedioneis not bound to SHBG either, and is instead bound solely to albumin.[26]In this study, 20 patients of those presenting with low levels of SHBG (25 hirsute women) had an elevated value of free testosterone.

SHBG levels are decreased by androgens, the administration ofanabolic steroids,[27]polycystic ovary syndrome ,hypothyroidism ,obesity, Cushing syndrome, andacromegaly.[28]As we correlated the decrement in the measurement of SHBG with PCOS, we found that only 8 patients presented with a positive relation. Regarding the obesity, as it may lead to lowering the level of SHBG, all patients wereobese in the first and second class in relation to body mass index.

SHBG levels increase with oestrogenic states (oral contraceptives),pregnancy, hyperthyroidism, cirrhosis, anorexia nervosa and certain drugs. A long-term calorie restriction of more than 50% increases SHBG, while lowering free and total testosterone and estradiol. DHEA-S, which lacks an affinity for SHBG, is not affected by calorie restriction.[29] Polycystic Ovarian Syndrome is associated with insulin resistance, and excess insulin lowers SHBG, which increases free testosterone levels.[30]This not compatible with our result, as we described earlier that only 6patients had elevated serum insulin. Obese girls are more likely to have an early menarche due to lower levels of SHBG. Anorexia or a lean physique in women leads to higher SHBG levels, which in turn can lead toamenorrhea.[31]As an explanation for obesity-related reductions in SHBG, recent evidence suggests sugar or monosaccharide-induced hepaticlipogenesis, hepatic lipids in general, and cytokines like TNF-alpha and Interleukin reduce SHBG, whereas insulin does not.[32] We agree with this, as about 80.9% of our hirsute patients had an abnormal lipid profile and all of them were either overweight or obese. With regard to this, we would advise obese girls or women with hirsutism to lose weight as a part of their management of the problem.

Hyperprolactinaemia can be a part of normal body changes during pregnancy and breastfeeding. It can also be caused by diseases affecting the hypothalamus and pituitary gland. It can also be caused by disruption of the normal regulation of prolactin levels by drugs, medicinal herbs and heavy metals. Hyperprolactinaemia may also be the result of disease in other organs, such as the liver, kidneys, ovaries and thyroid .In our study, we searched for the value of prolactin in the serum of all hirsute women to link the elevations in the prolactin level and, being a source of hyperandrogenism, either as a part of polycystic ovary syndrome or by decreasing the level of sex hormone-binding globulin.[33]A high serum level of prolactin was present in 37 hirsute women. Eleven of them had a positive diagnosis of PCOS and only 10 patients presented with low level of SHBG. These findings are in agreement with some suggestions that there are other causes of hyperprolactinemia that may be related to a disorder in the pituitary gland or using certain drugs.

A family history present in more than half of the collected sample in our study correlates to the hirsutism itself rather than its underlying causes. So, a family history should be included in future studies. a detailed family history of the first degree relative and a some necessary investigations if possible to link the familial clustering of some etiological conditions in Iraqi hirsute women.

A complete normal hormonal profile was present in four patients, and we considered them as idiopathic hirsutism as these hirsute women had no underlying PCOS or adrenal disorder. This result was incompatible with the result of the Iranian study done by Ansarin H.*et al.*, which reveals that idiopathic hirsutism was the final diagnosis in 35.2% of cases.[18]In astudy by Lamees Mahmood Malik *et al.*on74 patients, idiopathic hirsutism waspresent in 47.3% of them.[17] These figures reflect the individual variety between societies and confirms for us that nearly all Iraqi hirsutism has underlying hormonal abnormalities.

In conclusion, nearly all of the Iraqi hirsute premenopausal women studied had an abnormal hormonal profile. The source of hyperandrogenism was PCOS in one third of patients, followed by an adrenal source in a quarter of them, revealed as a mild elevation in DHEA-S. Another important source is the low level of SHBG, while idiopathicity was not a factor, according to this study. Good advice regarding the results of the lipids profile and the body mass index measurement of all hirsute women is to seek to lose weight.

REFERENCES

William D James, Dirk M Elston,Timothy G Berger. Andrew's diseases of the skin clinical dermatology, Diseases of the skin appendages. Eleventh Edition 2011, Elsevier.Vol.2;33:761-763.

Klaus Wolff, Lowell A. Goldsmith, Stephen I. Katz, et al.Fitzpatrick's Dermatology in General Medicine. Hair growth disorders.Seventh edition. Mc Grawhill.2008;86:774-776.

de Berker DAR, Messenger AG, Sinclair RD. Disorders of hair. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's Textbook of Dermatology. 7th ed. Oxford: Blackwell Science; 2004.

.Hunter MH, Carek PJ. Evaluation and treatment of women with hirsutism. Am Fam Physician. 2003; **67:** 2565 – 2572.

Thomas P Habif MD . Clinical Dermatology, A Color Guide to Diagnosis and Therapy. Hair diseases. 4th ed.Mosby;2004:24:846-854.

Rosenfield RL: What every physician should know about polycystic ovary syndrome. DermatolTher 2008 Sep-Oct; 21 (5):354-361.

Lipton MG, Sherr L, Elford J et al.Women living with facial hair: the psychologi-cal and behavioral burden. J Psychosom Res 2006; 61: 161–8.

Coffey S, Mason H. The effect of polycystic ovary syndrome on health-related quality of life.GynecolEndocrinol 2003; 17: 379–86.

Hammond CB, Riddick DH. Menstruation and disorders of menstrual function. In: Scott JR, Di Saia PJ, Hammond CB, Spellacy WN, eds. Danforth's Obstetrics and Gynecology. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 1999: 601 – 615.

"BMI Classification". Global Database on Body Mass Index.World Health Organization. 2006. Retrieved July 27, 2012.

The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19: 41 – 47.

.Leshin M:Southwestern internal medicine conference:hirsutism,Am J Med Sci 1987;294:369.

Rittmaster RS. Hirsutism [review] Lancet. 1997;349:191–5.

Rosenfield RL. Clinical practice.Hirsutism. N Engl J Med. 2005;353:2578–88.

Mueller A, Cupisti S, Binder H, Hoffmann I, Kiesewetter F, Beckmann MW, et al. Endocrinological markers for assessment of hyperandrogenemia in hirsute women. Horm Res. 2007;67(1):35-41.

Archer JS, Chang RJ. Hirsutism and acne in polycystic ovary syndrome. Best Pract Res ClinObstetGynaecol. 2004; 18: 737 – 754.

Lamees Mahmood Malik, KhawarKhursheed,Tahir Saeed Haroon, Mahmood Ali Malik.An aetiological study of moderate to severe hirsutism. Pak J Med Sci April 2007 Vol. 23 No. 2 167-171.

Ansarin H, Aziz-Jalali MH, Rasi A, Soltani-Arabshahi R. Clinical presentation and etiologic factors of hirsutism in premenopausal Iranian women.Arch Iran Med. 2007 Jan;10(1):7-13.

Gatee OB, al Attia HM, Salama IA. Hirsutism in the United Arab Emirates: a hospital study. Postgrad Med J. 1996; 72: 168 – 171.

Mithal A, Ammini AC, Godbole MM, Khurana ML, Raj D, Karmarkar MG, et al. Late-onset adrenal hyperplasia in North Indian hirsute women. Horm Res. 1988; 30: 1 – 4.

Zargar AH, Wani AI, Masoodi SR, Laway BA, Bashir MI, Salahuddin M. Epidemiologic and etiologic aspects of hirsutism in Kashmiri women in the Indian subcontinent. FertilSteril. 2002; 77: 674 – 678.

KhawlaAbed Al-HemzaShemran. Total , Free Testosterone and Insulin Hormone Levels in Patients with Hirsutism. Medical Journal of Babylon-Vol. 9- No. 2 -2012.

Ibanez L, DiMartino-Nardi J, Potau N, Saenger P: Premature adrenarche-normal variant or forerunner of adult disease? Endocrine Reviews 2001;40:1-16.

Hammond GL (2011). "Diverse Roles for Sex Hormone-Binding Globulin in Reproduction". Biology of Reproduction 85 (3): 431–441.

25.Somboonporn W, Davis SR (June 2004). "Testosterone effects on the breast: implications for testosterone therapy for women". Endocrine Reviews 25 (3): 374–88.

26.Principles and Practice of Endocrinology and Metabolism. Lippincott Williams & Wilkins. 24 April 2001.

Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S (2009). "Sex Hormone–Binding Globulin and Risk of Type 2 Diabetes in Women and Men". New England Journal of Medicine 361 (12): 1152–1163.

Selva DM, Hammond GL (July 2009). "Thyroid hormones act indirectly to increase sex hormone-binding globulin production by liver via hepatocyte nuclear factor-4alpha". J. Mol. Endocrinol. 43 (1): 19–27.

Cangemi R, Friedmann AJ, Holloszy JO, Fontana L (April 2010). "Long-term effects of calorie restriction on serum sex-hormone concentrations in men". Aging Cell 9 (2): 236–42.

Manni A, Pardridge WM, Cefalu W, et al: Bioavailability of albumin-bound testosterone. J ClinEndocrinolMetab 1985;61:705.

Hammond GL (2011). "Diverse Roles for Sex Hormone-Binding Globulin in Reproduction". Biology of Reproduction 85 (3): 431–441.

Selva DM, Hogeveen KN, Innis SM, Hammond GL (2007). "Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone–binding globulin gene". J. Clin. Invest. 117 (12): 3979–87.

Mancini, T.; Casanueva, FF; Giustina, A (2008). "Hyperprolactinemia and Prolactinomas". Endocrinology & Metabolism Clinics of North America 37 (1): 67.