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ARTICLE ORIGINAL/ORIGINAL ARTICLE

The PREVALENCE of ENDOCRINOPATHIES AMONG LEBANESE WOMEN PRESENTING with HIRSUTISM to an ENDOCRINE CLINIC

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Zreik RS, Nasrallah MP. The prevalence of endocrinopathies among Lebanese women presenting with hirsutism to an endocrine clinic. J Med Liban 2014 ; 62 (1) : 27-32.

ABSTRACT : Hirsutism is a common condition in women characterized by excessive growth of terminal hair in a male pattern distribution. It may be a manifestation of underlying pathologies. Since there is no data published about the prevalence of endocrinopathies among hirsute women in Lebanon, this study's aim was to reveal the most common etiologies of hirsutism in this population.

METHODS : The study is a descriptive review of cases of 160 females with hirsutism presenting to a single en- docrinologist clinic. Data about history, physical exam, blood tests and imaging results were collected after review of medical charts.

RESULTS : Out of the 160 cases reviewed, 14 females (8.8%) were left undiagnosed. Out of 146 subjects diag- nosed, 72.6% were found to have polycystic ovary syndrome (PCOS), 18.5% idiopathic hirsutism (IH), 4.6% non-classic congenital adrenal hyperplasia, 2.6% hyperprolactinemia, 0.6% Cushing's syndrome and 0.6% hypothyroidism. A higher percentage of irregular menses and a trend for overweight were found among the PCOS group.

CONCLUSIONS : PCOS remains the most common cause of hirsutism in an endocrine referral clinic, simi- lar to other populations. A low threshold for diagnostic workup is in order, especially when there is associated menstrual irregularity or overweight.

Keywords : hirsutism, polycystic ovary syndrome, endocrinopathies, Lebanon

Zreik RS, Nasrallah MP. La prévalence d'endocrinopathies chez les femmes libanaises hirsutes dans une clinique spécialisée en endocrinologie. J Med Liban 2014 ; 62 (1) : 27-32.

RÉSUMÉ : L'hirsutisme est une manifestation courante chez les femmes, caractérisé par une croissance excessive de poils terminaux répartis selon un modèle anatomique masculin et peut être une manifestation d'une pathologie sous-jacente. L'objectif de cette étude est d'évaluer la prévalence d'endocrinopathies parmi les Libanaises atteintes d'hirsutisme, aucunes données n'ayant été publiées à ce sujet dans la littérature.

MÉTHODES : L'étude est une revue descriptive des dossiers médicaux de 160 femmes ayant consulté une clinique d'endocrinologie à l'AUBMC, Centre médical de l'Université américaine de Beyrouth, pour hirsutisme. L'histoire, l'examen physique, les tests sanguins et l'imagerie radiologique effectués ont été revisités.

RÉSULTATS : Parmi les 160 cas examinés, 14 (8,8%) sont restées sans diagnostic. Les 146 autres sujets se ré- partissent comme suit : syndrome d'ovaires polykys- tiques (PCOS) 72,6% ; hirsutisme idiopathique (IH) 18,5% ; hyperplasie surrénale non classique 4,6% ; hyperprolactinémie 2,6% ; maladie de Cushing 0,6% et 0,6% avaient une hypothyroïdie. La majorité des sujets PCOS avaient des menstruations irrégulières et une tendance à l'excès de poids.

CONCLUSION : Le syndrome d'ovaires polykystiques (PCOS) est la cause la plus prévalente d'hirsutisme dans une clinique endocrinologique. Un minimum d'investigations est indiqué chez les patientes atteintes d'hirsutisme, surtout si elles ont une irrégularité menstruelle ou une tendance à l'excès de poids.

Mots-clés : hirsutisme, syndrome d'ovaires polycystiques, endocrinopathies, Liban

INTRODUCTION

Hirsutism is a common clinical condition in women characterized by excessive growth of terminal hair in a male pattern of distribution. It affects five to fifteen percent of females in the reproductive age group, depending on the population studied. Hirsutism is associated with significant negative impact on psychosocial development [1-3] and may be a manifestation of an underlying pathology. Various studies on women presenting with hirsutism have found a prevalence of endocrinopathies ranging from 60 to 95% [4-8]. Among these, polycystic ovary syndrome (PCOS) was the most common underlying etiology, followed by idiopathic hirsutism. Other less common conditions such as nonclassic adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, and thyroid disease were rare causes of hirsutism, even though their prevalence varied depending on the population studied. There is no data published in the Lebanese population. This paper describes the prevalence of endocrine disorders in women presenting to an endocrine clinic with hirsutism.

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METHODS

The study is a descriptive review of the medical charts of 160 consecutive females presenting to a single endocrinologist clinic at the American University of Beirut Medical Center, with the chief complaint of hirsutism. Institutional Review Board (IRB) approval was obtained prior to the review and data collection was done, with appropriate decoding of subjects identifiable information. Patients were either self-referred or referred by their family physician or a dermatologist.

The age, menstrual history, fertility status, hirsutism location and degree, coexisting medical conditions, hyperandrogenic manifestations such as androgenic alopecia and acne, presence of acanthosis nigricans, medication intake, family history of any endocrinopathy, blood pressure (BP) and body mass index (BMI) were retrieved from the charts. Blood tests for the following results, when available, were reviewed: FSH, LH, prolactin, total and free testosterone, androstenedione, DHEAS, 17-hydroxyprogesterone, cortisol, fasting insulin, fasting glucose and lipid profile. Radiologic reports of pelvic ultrasound and MRI sella, when indicated, were recorded. The final diagnosis, treatment offered and duration of follow-up were also retrieved.

Definitions

Subjects who were younger than 20 years of age were considered adolescents and older females were labeled as adults. Irregular menses is defined as a menstrual cycle of less than 21 or more than 35 days. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were considered to be high if equal or greater than 140 and 90 mmHg, respectively. Body mass index (BMI), in kg/m^2, was categorized according to the WHO definition: normal weight 18.5 to 24.9, overweight 25-29.9, and obese 30 and above. The diagnosis of PCOS was made based on the Rotterdam criteria, which require the presence of two out of three of the following: 1) Oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasound. The diagnosis of PCOS requires the exclusion of other causes of hyperandrogenism such as hypothyroidism, hyperprolactinemia, and non-classic congenital adrenal hyperplasia (NCAH) [9]. Biochemical hyperprolactinemia was defined as a prolactin level of more than 24.1 nanogram/mL in the absence of other causes such as hypothyroidism, hyperandrogenism, or medication intake; idiopathic hirsutism (IH) diagnosis was made when no endocrinopathies were found.

Data are reported as means and standard deviation (SD) or absolute numbers and percentages. Comparison between PCOS and idiopathic hirsutism groups was made using Student's t test for continuous variables and Chi^2 for discrete variables, using Statistical Software Package SPSS (version 16.0). Where applicable, Fisher's exact test was used for discrete variables where the number of cases per cell was less than six. Comparison of the prevalence of PCOS in women with hirsutism in our population was made to other populations with a similar setting, using STATA. A p value < 0.05 was considered to be significant.

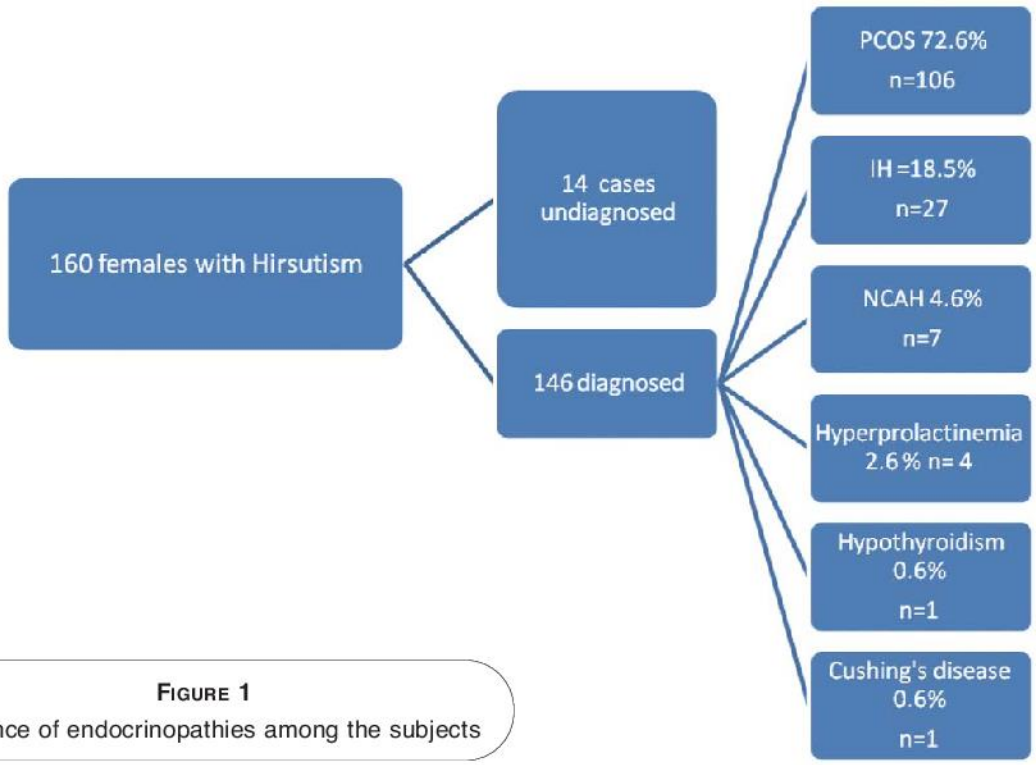

Figure 1
Prevalence of endocrinopathies among the subjects

RESULTS

Out of the 160 cases reviewed, 14 females (8.8%) were left undiagnosed mainly due to loss of follow-up or due to incomplete workup and insufficient data. The mean age of the study population is 22 years (standard deviation = 5). The diagnoses of the other 146 subjects were as follows: 72.6% PCOS, 18.5% had IH, 4.6% NCAH, 2.6% hyperprolactinemia, 0.6% Cushing's syndrome and 0.6 % had hypothyroidism (Figure 1). Out of the four women who had hyperprolactinemia in the absence of other features, three had normal MRI sella; two out of them were on cabergoline therapy. The fourth woman had a borderline prolactin level of 29.5 ng/mL with regular menses, no medication intake, and normal thyroid and androgen profile, and was being monitored only.

Comparison between PCOS and IH groups

Out of the 146 women with a final diagnosis, 106 were found to have PCOS and 27 had IH. A comparison was done among these cases, for baseline characteristics and biochemical measurements (Table I and Table II). The percentages of adolescents at initial presentation in the two subpopulations were similar with 32.1% of PCOS versus 25.9% of IH. The mean age of hirsutism onset reported by the patients was similar in both subgroups. The grading of hirsutism was based on clinician assessment, rather than Ferriman Gallwey, and was labeled as mild-moderate in most cases for both groups. The distribution of hirsutism was most often in the facial areas (chin, temples, and neck), followed evenly by other body parts (linea alba, nipples and chest, upper thighs). The vast majority (72.1%) of PCOS cases had irregular menses and none of the IH cases, by definition. None of the patients, in either subgroup, had a medical history of Type 1 diabetes mellitus (T1DM), only one PCOS patient had Type 2 diabetes. As for the family history, a higher prevalence of PCOS was noted in families of PCOS patients (12.4%) as well as a trend towards a higher prevalence of hirsutism (40.7%) was seen amongst families of females diagnosed with IH. None of the IH patients had an elevated blood pressure whereas eight females diagnosed with PCOS had either an elevated SBP and/or DBP. Half of PCOS subjects were either overweight or obese, whereas only one-third of subjects with idiopathic hirsutism fits in this category.

TABLE I BASELINE CHARACTERISTICS, COMPARISON BETWEEN PCOS AND IH GROUPS*

		Polycystic Ovary Syndrome n¹			Idiopathic Hirsutism n²			*p* value
Adolescents	n (%)	106	34	(32.1%)	27	7	(25.9%)	*0.54*
Irregular menses	n (%)	104	75	(72.1%)	0	0	(0.0%)	*< 0.001*
Mean age of onset & SD	(years)	37	18.7	(5.7)	17	18.7	(3.5)	*0.99*
Presence of acne	n (%)	104	43	(41.3%)	27	10	(37.0%)	*0.68*
Presence of alopecia	n (%)	104	3	(2.9%)	27	0	(0.0%)	*0.50*
T2DM	n (%)	106	1	(0.9%)	27	0	(0.0%)	*0.80*
Family history of hirsutism	n (%)	106	26	(24.5%)	27	11	(40.7%)	*0.09*
Family history of T2DM	n (%)	105	53	(50.5%)	27	11	(40.7%)	*0.37*
Family history of PCOS	n (%)	105	13	(12.4%)	27	0	(0.0%)	*0.04*
Body mass index > 24.9	n (%)	95	53	(55.8%)	24	9	(37.5%)	*0.11*
Mean BMI and SD	(kg/m^2)	95	26.9	(6.5)	24	24.4	(5.1)	*0.07*
Elevated BP	n (%)	101	8	(7.9%)	25	0	(0.0%)	*0.35*

*Due to missing data, the actual sample size (n) is provided for each variable **PCOS**: polycystic ovary syndrome **IH**: idiopathic hirsutim
n¹: number of PCOS patients having valid data **n²**: number of IH patients having valid data **SD**: standard deviation **FH**: family history
T2DM: type 2 diabetes mellitus **BMI**: body mass index **BP**: blood pressure (either systolic and/or diastolic)

TABLE II BIOCHEMICAL VARIABLES, COMPARISON BETWEEN PCOS AND IH GROUPS*

		PCOS (106 patients) n¹			IH (27 patients) n²			*p* value
High free testoterone	n (%)	71	20	(28.2%)	19	0	(0%)	*0.005*
Mean free testoterone & SD	(pg/mL)	71	3.26	(4.32)	19	1.90	(0.74)	*0.17*
High total testoterone	n (%)	49	17	(34.7%)	12	5	(41.7%)	*0.74*
Mean total testoterone & SD	(ng/dL)	49	64	(35)	12	55	(30)	*0.41*
Mean DHEAS & SD	(ng/mL)	85	2767.1	(1267.1)	20	2761.8	(1054.8)	*0.98*
Mean TSH & SD	(uIU/mL)	85	1.93	(1.00)	20	1.62	(0.87)	*0.20*
Mean 17-OH prog & SD	(ng/dL)	76	1.24	(0.74)	17	1.27	(0.64)	*0.84*
High total &/or Free testoterone	n (%)	89	35	(39.3%)	23	5	(21.8%)	*0.12*
Any high androgen	n (%)	96	46	(43.4%)	24	9	(33.3%)	*0.36*
Mean prolactine & SD	(ng/mL)	80	17.57	8.80%)	17	12.89	(3.95)	*0.001*

*Table is limited by a large percentage of data missing; actual n is given for each variable **PCOS**: polycystic ovary syndrome **IH**: idiopathic hirsutim
n¹: number of PCOS patients having valid data **n²**: number of IH patients having valid data **SD**: standard deviation
DHEAS: dehydroepiandrosterone sulfate **TSH**: thyroid stimulating hormone....**17-OH prog:** 17-hydroxy-progesterone

Biochemical hyperandrogenemia was also significantly higher in PCOS with 28.2% of subjects having elevated free testosterone versus none in IH group, by definition. Similarly, mild elevations in prolactin were significantly higher in the PCOS group as may be expected.

Metabolic profile of PCOS subjects (Table III)
Per guidelines, when the diagnosis of PCOS is made, it is recommended to obtain a fasting glucose and lipid profile. Out of the 106 subjects with PCOS, there were 69 who obtained a fasting glucose level, and out of these, four patients (5.7%) had IFG; similarly, 54 females had a lipid profile with six of them (10.9%) having an LDL level of more than 130 mg/dL and 30 (55.5%) having an HDL of less than 55mg/dL. Two of the subjects with IFG had BMI above 30 kg/m^2, one of them being in the morbidly obese range, yet overall, the BMI and standard deviation of those who obtained a metabolic profile was 28 (6) kg/m^2, similar to the BMI of the total PCOS subpopulation.

TABLE III
SUBSET of SUBJECTS with PCOS and METABOLIC PROFILE*

	PCOS			Normal range
	n			
Mean BMI & SD (kg/m^2)	57	28.1	(6.5)	18.5-24.9
Mean FBS & SD (mg/dL)	69	87.3	(8.0)	76-110
High fasting insulin n (%)	61	26	(23.6%)	Not applicable
Mean fasting insulin & SD (µIU/mL)	61	21.62	(13.33)	2-19
Mean LDL & SD (mg/dL)	54	98.94	(34.97)	Desirable 60-130
Mean HDL & SD (mg/dL)	54	55.68	(14.85)	Desirable > 55
Mean TG & SD (mg/dL)	59	82.36	(45.05)	30-200
Low HDL n (%)	54	30	(55.5%)	Not applicable
Mean total cholesterol & SD (mg/dL)	57	169	(38.35)	Desirable 120-200

*Table is limited by a large percentage of data missing; actual n is given for each variable.
PCOS: polycystic ovary syndrome **BMI**: body mass index
SD: standard deviation **FBS**: fasting blood sugar **LDL**: low density lipoprotein
HDL: high density lipoprotein **TG**: triglycerides

DISCUSSION

This study found that PCOS was the most common underlying etiology of hirsutism in women presenting to an endocrine clinic in Lebanon.

Comparison to similar studies
A comparison of proportion of subjects with PCOS was made to studies with a similar setup of women presenting to a referral clinic for hirsutism. In all of these, PCOS (using the same diagnostic criteria) was the most common underlying etiology, varying from 58.2 to 82.0%, whereas idiopathic hirsutism accounted for 4.7 to 39.7% (Table IV). Our population was intermediate with PCOS prevalence being more common than Turkey and Iran, less common than the US and similar to Saudi Arabia.

In a retrospective review held for the US population, 873 patients presenting to an endocrine clinic were evaluated for androgen excess: 82% were found to have polycystic ovarian syndrome (PCOS), 4.7% had idiopathic hirsutism (IH), 3.1% had hyperandrogenic insulin resistant acanthosis nigricans (HAIRAN), 1.6% had non classic adrenal hyperplasia (NCAH), 0.6% had classic adrenal hyperplasia (CAH) and 0.2% had androgen secreting neoplasms [5]. In a prospective study of 101 hirsute females in Saudi Arabia presenting to an endocrine clinic, PCOS was the diagnosis in 82% of the study population, IH was found in 11%, 4% NCAH, 2% microprolactinoma and 1% Cushing's [6]. In a review of 285 hirsute Turkish women presenting to an endocrine clinic, 58.2% were found to have PCOS, 39.7% had IH and 2.1% had NCAH [7]. In a cross-sectional study, 790 Iranian premenopausal females presenting to a dermatology clinic were investigated for hirsutism, 62.5% had PCOS, 35.2% had IH, 0.13% had prolactinomas and 0.38% had CAH [8].

Therefore hirsutism is androgen-dependent in 70% to 80% of cases and like acne and anovulation, is a cutaneous manifestation of an underlying pathology [1-4]. Androgen-dependent hirsutism may be caused by abnormalities in the ovaries (most commonly) or the adrenal glands and/or by exogenous androgen administration [4].

TABLE IV
COMPARISON of a POPULATION of PREMENOPAUSAL WOMEN PRESENTING with HIRSUTISM to an ENDOCRINE CLINIC in LEBANON versus OTHER POPULATIONS
Data using STATA. $p < 0.05$ significantly different proportion of PCOS compared to our population.

	This study	USA [5]	Saudi Arabia [6]	Turkey [7]	Iran [8]
N	160	873	101	285	790
Setting	Endocrinology clinic	Endocrinology clinic	Endocrinology clinic	Endocrinology clinic	Dermatology clinic
PCOS criteria	Rotterdam	Rotterdam	Rotterdam	Rotterdam	Rotterdam
PCOS (%)	72.6	82.0	82.0	58.2	62.5
IH (%)	18.5	4.7	11.0	39.7	35.2
p-value	*Reference*	*0.007*	*0.08*	*0.003*	*0.01*

PCOS: polycystic ovary syndrome **IH**: idiopathic hirsutism

The question remains which patients need to be screened for an underlying disorder? The Endocrine Society Clinical Practice guidelines for hirsutism recommend that patients presenting with isolated mild hirsutism need not to be investigated with androgen levels because *'the likelihood of identifying a medical disorder that would change management or outcome is low'* [10]. It also states that patients with moderate or severe hirsutism, or hirsutism of sudden onset, of rapid progression, or hirsutism associated with any of the following: menstrual irregularity or infertility or central obesity or acanthosis nigricans, need to be tested for elevated androgen levels [10]. These guidelines seem applicable to our study population based on our findings.

Thus, in our population, the majority of subjects with PCOS had irregular menses. For the remainder, either a tendency for excess weight or other associated hyperandrogenic findings would have warranted further workup. Using this approach, none of the patients with other endocrinopathies and only a minority of cases with PCOS may have been missed, and should they manifest at a later stage with other abnormalities, they would then be worked up. However, it is worthy of noting that the definition of hirsutism as a Ferriman-Gallwey score of more than 8 is likely too stringent and the majority of our population would not have fit into the hirsutism category. In support of our findings, subjects with a Ferriman-Gallwey score of 3 and above, not undergoing cosmetic hair removal, were investigated and concluded that the cutoff of 3 in a mixed population of Caucasian and African-American healthy premenopausal women was a more sensitive cutoff for the definition of hirsutism [11]. The authors go further to use subjective hirsutism, or that which is significantly bothersome to the patient, as an additional guide for further workup.

Having clarified whom needs further screening, which tests are necessary? The Endocrine Society guidelines recommend screening with androgen levels; they suggest total testosterone level and if methodology is available, a free testosterone level in the above cited patients [10]. Taken in isolation, this screening test is likely of poor sensitivity given that the former is sex hormone binding globulins-dependent and the latter is assay-dependent, and was elevated in only a minority of our subjects with PCOS. Similarly to our findings, in a study which investigated women with minimal hirsutism (Ferriman-Gallwey of 5 or more), half the subjects had an underlying hyperandrogenic disorder, and out of these, 20-40% had normal androgen levels [12]. Therefore, a screening panel in women who qualify should provide sufficient information to rule in or out the diagnosis of PCOS. This workup should include serum levels for androgens, TSH, prolactin, 17-hydroxyprogesterone in a follicular phase, and an ultrasound of pelvis looking for cysts [13-14]. Escobar-Morreale goes further in his recommendations to include basal body temperature or day 21 progesterone level to document the presence of ovulation, even in the presence of regular menses [14]. Although the actual prevalence of PCOS at a population level has not been studied in Lebanon, it is likely to be common, as this is the most prevalent endocrinopathy in premenopausal women and since the overweight and obesity epidemic also affects the Lebanese population [15]. Using hirsutism as a surrogate marker to screen for and detect PCOS will allow prompt recognition of the metabolic morbidity associated with this syndrome. In support of this, more than half of the subjects with PCOS in this study had less than ideal lipid profiles.

Our study has the following limitations: firstly, subjects were pooled out of an endocrine clinic population, thus a referral clinic, making the results a possible overestimation of the general female population endocrinopathies. However, our findings were comparable to the international populations which were also pooled from referral clinics. Secondly, rather than using Ferriman-Gallway score, in this study hirsutism was defined and graded based on the endocrinologist's clinical impression and the patient's subjective complaint. However, this is more reflective of real life practice rendering the study findings more applicable. Thirdly, laboratory studies were not performed in the same standardized laboratory; however values were considered to be normal based on the respective laboratories' reference values. A fourth limitation to the study was that some subjects did not perform the full panel of blood tests and radiologic imaging requested. Nevertheless, diagnosis was based on the clinical impression of the physician based on hyperandrogenism and either oligomenorrhea or pelvic ultrasound, according to the Rotterdam guidelines [9]. In cases where clinical diagnosis could not be reached, subjects were classified as 'undiagnosed'.

CONCLUSION

Polycystic ovary syndrome is the underlying disorder in the majority of women presenting with hirsutism to a specialty clinic. We recommend further workup in line with the Endocrine Society guidelines; however, workup should be comprehensive enough to establish the diagnosis.

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