Clinical and Biochemical Characteristics of Polycystic Ovary Syndrome in Benghazi, Libya: A Retrospective study

Najem FI, Elmehdawi RR and Swalem AM

Department of Medicine, 7th of October Hospital, Faculty of Medicine, Garyounis University, Libya

Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine condition affecting women of reproductive age and characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries. There are no published data on this syndrome in Libyan patients. Aims and objectives: To assess the frequency of clinical and biochemical features of PCOS in our patient population, and to compare this with data collected in other parts of the world. Subjects and methods: A retrospective analysis of patient records at the endocrine clinic in Benghazi was undertaken. Patient inclusion was according to Rotterdam ESHRE/ASRM criteria. Clinical features, associated diseases, family history, hormone levels, and ultrasonography results were analyzed. Results: The mean age of the 318 PCOS patients at presentation was 25.8 years (range 15-44 years), and the majority (67%) were 20-29 years old at presentation. Of all patients, 57% were obese (BMI ≥ 30), 93% had oligo-amenorrhea, 91% were hirsute, and 74% had ultrasound features of polycystic ovaries. Diabetes mellitus was diagnosed in 9% of all PCOS patients and hypertension in 4%. Total serum testosterone was elevated in 26% of the patients, and serum prolactin was elevated in 31%. Thyroid disease was noted among 5.3% of the patients, and a history of diabetes or hypertension among first-degree relatives was seen in (16%) and (8%) of the patients respectively. Conclusion: Chronic anovulation and hirsutism are the dominant features of PCOS in our patient population. More than half were obese, and the prevalence of diabetes, hypertension and thyroid disease in our patients seemed to be underestimated in comparison to other parts of the world.

Key words: polycystic, ovary, hirsutism, diabetes, obesity.

Introduction

Polycystic ovarian syndrome (PCOS) affects 4-12% of women of reproductive age [1]. It is characterized by chronic anovulation and hyperandrogenism with variable clinical manifestations that include oligomenorrhea, infertility, hirsutism, and acne. Until recently, there was no universally accepted clinical definition for PCOS. The 2003 Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group concluded that no single diagnostic criterion was sufficient for a clinical diagnosis of PCOS. Two out of three criteria have to be met to fit the definition: chronic anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries [2]. However, ethnicity influences the extent of these signs and symptoms, especially with regard to hirsutism and obesity [3]. Therefore, the frequency of symptoms varies between different countries and ethnic groups. The prevalence of this syndrome in Libya is unknown, and its clinical and biochemical characteristics have not been reported so far.

Aims and objectives

This investigation aimed to assess the frequency of different clinical and biochemical features of PCOS among Libyan patients and to compare these frequencies with those reported in different parts of the world.

Subjects and methods

The records of 318 patients diagnosed with polycystic ovary syndrome and under regular follow up at the endocrine clinic in Benghazi-Libya were analyzed. Patients were included according to the Rotterdam ESHRE/ASRM criteria [2]: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasound (PCO). If the patient met two of these criteria, she was included in the study after other etiologies were ruled out. Trans-abdominal ultrasound scanning (US) was performed by expert ultrasonographers. PCO was defined as the presence of 12 or more follicles measuring 2-9 mm in diameter in each ovary and/or ovarian volume > 10ml. Other possible causes of the symptoms were excluded. Cushing’s syndrome was excluded by a low-dose (1 mg) overnight dexamethasone suppression test whenever the syndrome was clinically suspected. Non-classical congenital adrenal hyperplasia (NCAH) is excluded by measuring the morning level of 17-hydroxyprogesterone in the serum; levels < 2 ng/ml are considered low enough to exclude NCAH. Androgen-secreting tumors were excluded by clinical evaluation, total testosterone level, and DHEA-S level. Clinical features, associated diseases, family history, hormonal levels, and ultrasonography results were all analyzed. Total testosterone was measured by immunoassay using the Elecsys Testosterone reagent kit from Roche (USA) (normal range 0.06–0.82 ng/ml). Prolactin was measured by immunoassay using the Elecsys reagent kit from Roche (USA) (normal range 6–29.9 ng/ml). Luteinizing hormone (LH) was measured by immunoassay using the Elecsys LH reagent kit from Roche (normal range 2.4–12.6 mIU/ml). Follicular stimulating hormone (FSH) was measured by immunoassay using the Elecsys FSH reagent kit from Roche, (normal range 3.5–12.5 mIU/ml). Thyroid stimulating hormone (TSH) was measured by immunoassay using the Elecsys TSH reagent kit from Roche, (normal range 0.27–4.2 μU/ml).

Obesity and overweight were defined according to WHO criteria as a body mass index (BMI) ≥30 kg/m2 and ≥25 kg/m2 respectively. Amenorrhea was defined as absence of cycles in the past 6 months and oligomenorrhea as menses >35 days. Infertility was assessed only in married patients and was defined as failure of spontaneous pregnancy after one year of marriage in the absence of male infertility. Diabetes mellitus (DM) was defined as...
fasting plasma glucose $\geq 126$ mg/dl. Hypertension (HTN) was defined as blood pressure $\geq 140/90$ mm Hg.

Statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], US). Mean values are reported together with +/- standard deviation (SD). Differences between groups were tested statistically using the Chi square test. Differences were considered statistically significant if the P-value was < 0.05.

Results

Out of the 318 studied patients, 17.3% were married and 82.7% were single. Mean age at presentation was 25.8 $\pm$ 5.3 years, and about 67% of the patients were 20-29 years old. Oligomenorrhea was noted in 85.8%, amenorrhea in 7.5%, while 6.6% had normal menses. Hirsutism was observed in 90.8%, acne in 12%, infertility in 40%, and galactorrhea in 8.8%. Mean BMI was 34.3 $\pm$ 6.6 kg/m2 (Table I); about 57% of patients were obese and nearly 24% were overweight. Acanthosis nigricans (AN) was described in 15.7%, and 6% of these patients were overweight, 94% were obese and 32% were very obese (BMI $\geq 40$ kg/m2).

Table-1: features of PCOS in Benghazi-Libya

| Character          | Mean | Percentage |
|--------------------|------|------------|
| Age                | 25.8 $\pm$ 5.3 yrs | 93%         |
| Hirsutism          | 90.8% | 35%        |
| Oligomenorrhea     | 85.8% | 26%        |
| Amenorrhea         | 7.5%  | 15%        |
| Infertility        | 40%   | 11%        |
| Acne               | 12%   | 23%        |
| Acanthosis nigricans | 15.8% | 11%        |
| Obesity            | 57%   | 6%         |
| BMI                | 34.4 $\pm$ 6.6 kg/m2 | 34%        |
| DM                 | 9%    | 15%        |
| HTN                | 4%    | 16%        |
| Hypothyroidism     | 3%    | 32%        |
| Galactorrhea       | 8.8%  | 6%         |
| Hyperprolactinemia | 31%   | 9%         |
| High Total testosterone | 26.4% | 7%         |
| LH/FSH ratio $\geq$ 3 | 16%  | 16%        |
| USS features of PCOS | 74%  | 16%        |

The mean BMI of those with AN was 38 $\pm$ 6.4 kg/m2, while those without AN had BMI of 30.4 $\pm$ 6.8 kg/m2 (p <0.001). About 9.3% of the patients were diabetic according to fasting plasma glucose levels, and 17% of these were overweight and 83% were obese with mean BMI 38 $\pm$ 7.5 kg/m2. About 3.8% of patients were hypertensive and of these 92.3% were obese with mean BMI 40.95 $\pm$ 6.64 kg/m2. Most of the patients (96.5%) had trans-abdominal ultrasound, whereas only 2.2% and 1.3% had either trans-vaginal or trans-rectal ultrasound, respectively. Ultrasonographic appearance of polycystic ovaries was reported in 73.9% of the patients. These findings were unilateral in two cases. LH was elevated in 16% of patients with a mean value of 12.3 $\pm$ 8.3 mIU/ml and was slightly higher (although non significantly, p >0.05) in non-obese than in obese patients, while the ratio between LH and FSH was >2 in 54.7% and > 3 in only 16% of patients. Total testosterone was elevated in 26.4% and Prolactin in 31.3%. The prolactin elevation was mild (< 50% of upper limit) in 62% of the hyperprolactinemic patients. Thyroid disease was a coexisting diagnosis in 5.34% of the patients; most were hypothyroid (3%).

About 4% of the patients had a family member diagnosed with PCOS and nearly 16% had a family member with a history of hirsutism, irregular menses, or infertility. Diabetes mellitus and hypertension in a first degree relative was reported by 16% and 8% of the patients, respectively. The mother was the affected family member in 82% of the diabetic relatives and in 88% of the hypertensive relatives. A family history of thyroid disease was elicited in nearly 4% of patients. There was no statistically significant difference in the clinical and biochemical features of PCOS between patients with negative (83 patients) or positive (235 patients) ultrasound features for PCO (Table-2).

Table-2: Comparison between patients with positive and negative trans-abdominal ultrasound feature of PCOS.

| Feature                | Patients with PCO(235) | Patients without PCO(83) | P-value | All patients (318) |
|------------------------|------------------------|--------------------------|---------|-------------------|
| Hirsutism              | 88.9% (209)            | 96.3% (80)               | 0.046   | 90.8% (289)       |
| Cycle disturbance      | 91% (214)              | 100% (83)                | 0.003   | 93.3% (297)       |
| Mean BMI               | 34.9 $\pm$ 6 kg/m2     | 33 $\pm$ 7.5kg/m2        | 0.91, ns| 34.4 $\pm$ 6.6kg/m2|
| Obesity                | 56.2% (132)            | 59% (49)                 | 0.72, ns| 56.9% (181)       |
| Overweight             | 23.8% (56)             | 25.3% (21)               | 0.65, ns| 24.2% (77)        |
| High testosterone      | 25.5% (60)             | 28.9% (24)               | 0.46, ns| 26.4% (84)        |
| LH/FSH ratio $\geq$ 3  | 16.2% (38)             | 15.6% (13)               | 0.97, ns| 16% (51)          |

Discussion

To our knowledge, this study is the first report about clinical features of PCOS in Libya. The frequency of ultrasonographic features of polycystic ovaries (PCO) seen in our patients (74%) is much less than that reported by others (96.7%) who used trans-vaginal ultrasound [4,5]. Transabdominal ultrasound is less sensitive and more operator dependant than trans-vaginal ultrasound [6]. Therefore, the 74% rate is probably an underestimate. The underutilization of transvaginal ultrasound is due to cultural and religious restrictions in Muslim societies. The clinical and biochemical features of patients with normal USS did not differ from those with positive USS findings of polycystic ovary morphology (Table 2). The apparent higher rate of hirsutism and cycle disturbance in patients with normal USS findings is an artifact. According to Rotterdam criteria, to diagnose PCOS in the absence of PCO, hyperandrogenism (clinical and/or biochemical) and anovulatory cycle should coexist. Ethnic differences in the phenotypic presentation of PCOS is a well known phenomenon [3,7]. The frequency of Oligo-/ amenorrhea (93%) observed in this cohort was greater than reported in the USA (70%) [3], and the frequency of hirsutism (91%) was much higher than noted in Chinese women (35%) [4]. Only 12% of our patients had acne as compared to 45% in Chinese women [4]. Surprisingly, about 60% of the married patients were fertile without
any medical intervention in contrast to only about 25% reported worldwide [8]. However, the overall prevalence of infertility could be higher because most of our patients were single (83%), married PCOS patients are usually under gynecologist care because of their initial concern of infertility.

This study reports that obesity affects 57% of Libyan PCOS patients. Obesity is less common in PCOS women of Mediterranean descent, but more common in Hispanic, black, and white women with PCOS [3,9]. This high rate of obesity among the Libyan PCOS women may indirectly reflect the high prevalence of obesity in Libyan females in general [10,11]. Obesity in our patients was 2.5 times more common than in the general Libyan female population, which is 22.5% according to the WHO estimation for 2005 and similar to that in Spain [11,12].

Table-3: frequency of obesity in PCOS patients

| Weight class by BMI (kg/m²) | Percentage |
|---------------------------|------------|
| Under weight (<18.5)      | ~ 1%       |
| Healthy (18.5-24.99)      | ~ 18%      |
| Overweight (25-29.99)     | ~ 24%      |
| Obese (>30)               | ~ 57%      |
| Class-I obesity (30-34.9) | 23.6%      |
| Class-II obesity (35-39.9)| 18.55%     |
| Class-III obesity (>40)   | 14.6%      |

Diabetes mellitus frequency was 9% in our patients, which is similar to the USA but less than what is noted in Asian women (17%) [13,14]. However, if glucose tolerance tests were to be performed, the prevalence of type-2 DM might turn out to be higher and more patients would likely be found to have impaired glucose tolerance [15]. Hypertension was diagnosed in only 4% of our patients as compared to 12% in Tunisian patients [16]. This is a large difference in the prevalence rate in two population sharing a similar ethnic, and geographical background, however the Tunisian study was a prospective one which is more accurate than retrospective studies. Obesity was clearly over-represented in both hypertensive and diabetic patients. Acanthosis nigricans (AN) was described in 15.8% of patients, which resembles that reported in China [17]. The PCOS women with AN had significantly higher BMI, compared with those without AN, which is similar to observations from Thai study [18]. AN is a marker of insulin resistance, as it is a result of insulin stimulation to the basal layers of the epidermis [3]. The finding of elevated total serum testosterone in 26% of our patients seems to be an underestimate to the actual rate of biochemical hyperandrogenism because we depend on total serum testosterone assays rather than free testosterone assays (due to availability issues), and different commercial kits have different cut off values [19]. In the literature, about 30% of women with PCOS had LH to FSH ratio > 3:1 and many researchers consider this ratio diagnostic for the syndrome [3,5]. However, only 16% of our patients had LH:FSH ratio > 3, indicating the low sensitivity of this test as a diagnostic tool in Libyan patients with PCOS. Clinical studies have repeatedly shown that obese PCOS women have significantly lower LH concentrations than their normal-weight counterparts, which we also observed in our patients [20]. The high frequency of hyperprolactinemia (31%) observed in our patients is worth investigating by using multiple measurements at different time points. However, Prolactin was only mildly elevated (<50% of the upper limit of normal) in most patients (62%). Family history of diabetes in a first degree relative was observed in 16% of the patients; the mother was diabetic in 82% of the cases. This high prevalence of diabetes in mothers of PCOS patients was reported in other studies and may indirectly highlight the role of insulin resistance in the pathogenesis of PCOS [21]. Thyroid disease was reported in 5% of the patients, of which 3% had autoimmune hypothyroidism. In the literature, the prevalence of anti-thyroid antibodies and elevated TSH in PCOS patients was reported to be 27% and 11%, respectively [22]. A screening for subclinical thyroid disease and for anti-thyroid antibodies is needed to define more accurately the prevalence of thyroid diseases in PCOS patients. Finally, despite the limitations of a retrospective review, this study might serve as a preliminary assessment of the disease profile in Libya. Community based studies are needed to define the prevalence of the syndrome and prospective well organized investigations are needed to define the frequency of each clinical and biochemical feature of the syndrome, particularly dysglycemia and other metabolic derangements.

Conclusions and recommendations

Hirsutism and cycle disturbances are the major clinical features of PCOS patients in Benghazi (> 90%). Obesity seems to be more prevalent in Libyan PCOS patients than reported worldwide [8]. However, the overall prevalence of infertility could be higher because most of our patients were single (83%), married PCOS patients are usually under gynecologist care because of their initial concern of infertility.

This study reports that obesity affects 57% of Libyan PCOS patients. Obesity is less common in PCOS women of Mediterranean descent, but more common in Hispanic, black, and white women with PCOS [3,9]. This high rate of obesity among the Libyan PCOS women may indirectly reflect the high prevalence of obesity in Libyan females in general [10,11]. Obesity in our patients was 2.5 times more common than in the general Libyan female population, which is 22.5% according to the WHO estimation for 2005 and similar to that in Spain [11,12].

Table-3: frequency of obesity in PCOS patients

| Weight class by BMI (kg/m²) | Percentage |
|---------------------------|------------|
| Under weight (<18.5)      | ~ 1%       |
| Healthy (18.5-24.99)      | ~ 18%      |
| Overweight (25-29.99)     | ~ 24%      |
| Obese (>30)               | ~ 57%      |
| Class-I obesity (30-34.9) | 23.6%      |
| Class-II obesity (35-39.9)| 18.55%     |
| Class-III obesity (>40)   | 14.6%      |

Diabetes mellitus frequency was 9% in our patients, which is similar to the USA but less than what is noted in Asian women (17%) [13,14]. However, if glucose tolerance tests were to be performed, the prevalence of type-2 DM might turn out to be higher and more patients would likely be found to have impaired glucose tolerance [15]. Hypertension was diagnosed in only 4% of our patients as compared to 12% in Tunisian patients [16]. This is a large difference in the prevalence rate in two population sharing a similar ethnic, and geographical background, however the Tunisian study was a prospective one which is more accurate than retrospective studies. Obesity was clearly over-represented in both hypertensive and diabetic patients. Acanthosis nigricans (AN) was described in 15.8% of patients, which resembles that reported in China [17]. The PCOS women with AN had significantly higher BMI, compared with those without AN, which is similar to observations from Thai study [18]. AN is a marker of insulin resistance, as it is a result of insulin stimulation to the basal layers of the epidermis [3]. The finding of elevated total serum testosterone in 26% of our patients seems to be an underestimate to the actual rate of biochemical hyperandrogenism because we depend on total serum testosterone assays rather than free testosterone assays (due to availability issues), and different commercial kits have different cut off values [19]. In the literature, about 30% of women with PCOS had LH to FSH ratio > 3:1 and many researchers consider this ratio diagnostic for the syndrome [3,5]. However, only 16% of our patients had LH:FSH ratio > 3, indicating the low sensitivity of this test as a diagnostic tool in Libyan patients with PCOS. Clinical studies have repeatedly shown that obese PCOS women have significantly lower LH concentrations than their normal-weight counterparts, which we also observed in our patients [20]. The high frequency of hyperprolactinemia (31%) observed in our patients is worth investigating by using multiple measurements at different time points. However, Prolactin was only mildly elevated (<50% of the upper limit of normal) in most patients (62%). Family history of diabetes in a first degree relative was observed in 16% of the patients; the mother was diabetic in 82% of the cases. This high prevalence of diabetes in mothers of PCOS patients was reported in other studies and may indirectly highlight the role of insulin resistance in the pathogenesis of PCOS [21]. Thyroid disease was reported in 5% of the patients, of which 3% had autoimmune hypothyroidism. In the literature, the prevalence of anti-thyroid antibodies and elevated TSH in PCOS patients was reported to be 27% and 11%, respectively [22]. A screening for subclinical thyroid disease and for anti-thyroid antibodies is needed to define more accurately the prevalence of thyroid diseases in PCOS patients. Finally, despite the limitations of a retrospective review, this study might serve as a preliminary assessment of the disease profile in Libya. Community based studies are needed to define the prevalence of the syndrome and prospective well organized investigations are needed to define the frequency of each clinical and biochemical feature of the syndrome, particularly dysglycemia and other metabolic derangements.

Conclusions and recommendations

Hirsutism and cycle disturbances are the major clinical features of PCOS patients in Benghazi (> 90%). Obesity seems to be more prevalent in Libyan PCOS patients than
in other Mediterranean countries. The ratio between LH and FSH as a diagnostic tool had low sensitivity in the Libyan patients. Prevalence rates of DM, HTN, and hypothyroidism seem to be underestimated in our patients.

References
1. Sheehan MT. Polycystic Ovarian Syndrome: Diagnosis and Management. Clin Med Res. 2004, 2 (1):13–27.
2. 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. Fertil Steril. 2004, 81(1):19-25.
3. Richardson MR. Current Perspectives in Polycystic Ovary Syndrome. Am Fam Physician. 2003, 68(4):697-704.
4. Li L, Yang D, Chen X, Chen Y, Feng S, Wang L. Clinical and metabolic features of polycystic ovary syndrome. Int J Gynaecol Obstet 2007; 97(2):129-134.
5. Hunter MH, Sterrett JJ. Polycystic Ovary Syndrome: It's Not Just Infertility. Am Fam Physician. 2000, 62(5):1079-1088.
6. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update. 2003, 9(6):505-514.
7. Williamson K, Gunn AJ, Johnson N, Milsom SR. The impact of ethnicity on the presentation of polycystic ovarian syndrome. Aust N Z J Obstet Gynaecol. 2001; 41(2):202-206.
8. Lakhani K, Seifalian AM, Atiomo WU, Hardiman P. Polycystic ovaries. Br J Radiol. 2002; 75(889):9-16.
9. Carmina E, Legro RS, Stamets K, Lowell J, Lobo RA. Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. Hum Reprod, 2003; 18(11):2289-2293.
10. Bakoush O, Elgzyri T. Do we have a diabetes epidemic in Libya? Libyan J Med 2006, 1(2):AOP: 061016.
11. WHO Global Infobase. [Online] Available. http://www.who.int/ncd_surveillance/infobase/web/InfoBasePolicyMaker/ reports/Reporter.aspx, February 16, 2007.
12. Quinonez Zarza C, Silva Ruiz R, Torres Juarez JM. Obesity, arterial hypertension, metabolic disorders, and polycystic ovary syndrome. Ginecol Obstet Mex. 2000; 68:317-322.
13. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and Characteristics of the Metabolic Syndrome in Women with Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2005; 90(4):1929–1935.
14. Weerakiet S, Srismutb C, Bunnag P, Sangtong S, Chuangsoongnern R, Rojanasakul A. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in Asian women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2001; 75(2):177-184.
15. Elgzyri. Basic Management of Diabetes Mellitus: Practical guidelines. Libyan J Med 2006, 1 (2):AOP: 060813.
16. Ben Salem Hachmi L, Ben Salem Hachmi S, Bouzid C, Younsi N, Smida H, Bouguerra R, Ben Slama C. Hypertension in polycystic ovary syndrome. Arch Mal Coeur Vaiss. 2006; 99(78):687-690.
17. Li X, Lin JF. Clinical features, hormonal profile, and metabolic abnormalities of obese women with obese polycystic ovary syndrome. Zhonghua Yi Xue Za Zhi. 2005; 85(46):3266-3271.
18. Charvises K, Weerakiet S, Tingthanatikul Y, Wansumrith S, Chanprasertyothin S, Rojanasakul A. Acanthosis nigricans: clinical predictor of abnormal glucose tolerance in Asian women with polycystic ovary syndrome. Gynecol Endocrinol. 2005; 21(3):161-164.
19. Iwasa T, Matsuzaki T, Minakuchi M, Tanaka N, Shimizu F, Hirata Y, et al. Diagnostic performance of serum total testosterone for Japanese patients with polycystic ovary syndrome. Endocr J. 2007; 54(2):233-238.
20. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes. 2002, 26(7):883–896.
21. Yilmaz M, Bukan N, Ersoy R, Karakoc A, Yetkin I, Ayvaz G, et al. Glucose intolerance, insulin resistance and cardiovascular risk factors in first degree relatives of women with polycystic ovary syndrome. Hum Reprod. 2005; 20(9):2414-2420.
22. Janssen OE, Mehmimauer N, Hahn S, Offner AB, Gartner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol. 2004; 150(3):363–369.