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Polycystic ovary syndrome: Impact of obesity and aging on the profile of gonadotrophin and adrenal hormones

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Many studies have been conducted to understand thoroughly the mechanism of polycystic ovaries syndrome (PCOS), but very few of them came from Africa. The aim of this study, was firstly to make a diagnostic of this syndrome, according to Rotterdam criteria, and secondly to assess the correlation of obesity and age on this pathology. The study was conducted at Bouaké, within the medical School and Hospital, during the period, September 2014 to January 2016. All participants have been diagnosed with PCOS on the basis of the Rotterdam criteria. The mean age was 25.37 ± 5.47 and the mean body mass index (BMI) was 28.82 ± 8.51 kg/m^2. There were either significant or no significant statistical differences about parameters value concerning age or BMI into the population. There was no significant statistical difference between age and BMI. Otherwise the overweight and obese patients were both present in the group under 25 years old and in the group having above 25 years old. The differences related to the mean value of hormonal parameters were observed in the two populations according to the BMI range. The mean value of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) has increased according to the augmentation of BMI and age. Contrary to this trend, the mean value of estradiol and sex hormone binding globulin (SHBG) has decreased in the same conditions. The data suggest that in everyday practice, the collaboration between clinician and biologist must be built up in order to make early the diagnosis of PCOS among infertile women.

Key words: Polycystic ovaries syndrome, obesity, age, gonadotrophin, adrenal hormones.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders among adolescent girls and women of reproductive age. PCOS is the leading cause of female infertility (Ehrmann, 2005). Menstrual irregularity, chronic anovulation, hyperandrogenism, and multiple small sub-capsular cystic follicles in the ovary on ultrasonography characterize the syndrome. Obesity, mainly central obesity, is present in

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varying degrees (30-70%) in women with PCOS. An ethnic variation of the metabolic and endocrine pattern in PCOS was also reported (Ramanand et al., 2012). All features of this syndrome may not be present in an individual patient. Depending on the interactions of different hormones in PCOS patients, the pathogenesis, clinical presentation, and biochemical profile varies in an individual. Hence biochemical parameters and the hormone profile become important in understanding the pathogenesis of PCOS.

Obese women with PCOS are more prone to dyslipidaemia, particularly elevated triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) (Bickerton et al., 2005) .However, in other investigations, no difference was observed in lipid profile between PCOS women and control participants. A study (Ehrmann et al., 2006) showed that metabolic syndrome and its components are common in PCOS, especially among women with the highest BMI and insulin levels. Obesity is regarded one of the putative factors leading to metabolic syndrome (MetS); it seems to contribute mainly to the link between PCOS and MetS (Grundy et al., 2007).

During aging in normal subjects of either sex, a gradual increase in body weight is observed, which is associated with an unfavorable impact on metabolic profile and insulin resistance (IR) has been considered as the main pathophysiological link between obesity and metabolic disturbances (Karakelides et al., 2010).

Many other studies have been conducted in order to understand thoroughly its mechanism, but very few of them coming from Africa in general and particularly in the undeveloped countries.

The mean goal of this study, realized in Cote d'Ivoire (West Africa), was on the one hand to make a diagnostic of this syndrome, according to Rotterdam criteria, and on the other hand to assess the correlation of obesity and age on the disturbances of the value of hormonal parameters.

MATERIALS AND METHODS

This study was conducted at Bouaké, within the medical school and hospital (Côte d'Ivoire), during the period of September 2014 to January 2016. The study comprised 71 newly diagnosed PCOS women. All participants were in the age group of 15 to 41 years. Patients have been diagnosed with PCOS on the basis of the Rotterdam criteria (Fr and Tarlatzis, 2004); which state that, two out of three of the following are required for diagnosis: Oligo- and/or anovulation (defined by the presence of oligomenorrhea or amenorrhea); clinical and/or biochemical signs of hyperandrogenism [defined by presence of hirsutism (Ferriman-Gallwey score ≥ 6), acne or alopecia, and/or elevated androgen levels]; and polycystic ovaries by gynecological ultrasound. During investigation, patients with congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, and those who were under any medication that affected endocrinal parameters were excluded.

Height and weight were obtained from each subject. The BMI was calculated as the weight in kilograms divided by the square of height in meters.

Laboratory measurements

After a 12-h overnight fasting, 5 mL blood was obtained in the follicular phase of the menstrual cycle (that is, serum progesterone level lower than 2.5 ng/mL). Fasting blood samples were collected in plain and then centrifuged at 3500 rpm for 10 min to separate the serum. The study analyzed either immediately or during the same week after conservation at +4°C.

Hormones, such as, free Testosterone (fT), free estradiol (fE2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), Δ4 androstene-dione (Δ4), dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA) and sex hormone binding globulin (SHBG) were measured by the chemiluminescence immunoassay (CLIA) method using a Beckman Coulter Access fully automated analyzer. The hormone kits used in the Beckman Coulter Access analyzer (USA) were from Beckman Coulter, Ireland.

Hyperandrogenaemia was considered at either serum testosterone level above 2.08 nmol/L and/or serum DHEAS level above 7.80 nmol/L (Noorbala 2010). Increased serum 17-OHP was defined in levels above 4.8 nmol/L to exclude congenital adrenal hyperplasia (Tziomalos et al., 2013).

Statistical analysis

All the results were tabulated as mean and standard deviation. The SPSS 20.0 version for statistical analysis was used. The unpaired student t test was used to determine the statistical significance between the study groups. Pearson correlation was used for correlating different parameters. A P value of <0.05 was considered to be statistically significant.

Ethical considerations

The study was approved by the Institutional Ethics Committee, Medical and Scientific Direction, Medical School, Bouaké, Côte d'Ivoire. Written and informed consent was obtained from the individuals who participated in the study.

RESULTS

There were 71 clinically proved, confirmed PCOS patients in the age range 15n to 41 years chosen for the study (Rotterdam criteria). 34 patients were obese against 37 patients hence 47.88% (Table 1), on the another hand 54.93% patients had above 25 years old. The mean age was 25.37 ± 5.47 and the mean BMI was 28.82 ± 8.51 kg/m^2. There were either significant or no significant statistical differences about parameters value concerning age or BMI in the study population. There was no significant statistical difference between age and BMI. Otherwise the overweight and obese patients were both present in the group under 25 years old and in the group having above 25 years old. The differences related to the mean value of hormonal parameters were observed in the two populations according to the BMI range.

The mean value of testosterone, Δ4 progesterone, FSH, LH and DHEA were more important in the group of overweight/obese patients than in the normal BMI range.

Table 1. General characteristics of PCOS women in the study.

Parameter	Minimum	Mean	S.D	Median	Mode	Maximum
Age (an)	15	25.37	5.47	25	23	41
Weight (Kg)	40.0	77.82	22.24	71.0	60.0	123.0
size (m)	1.26	1.64	0.08	1.65	1.66	1.80
BMI	15.0	28.82	8.51	26.0	25.0	46.68
T (nmol/L)	0.12	0.58	0.26	0.57	0.60	1.50
D4 (nmol/L)	1.70	3.44	1.18	3.30	2.50	5.80
LH (mlU/L)	0.56	8.27	5.07	7.50	12.0	25.0
FSH (mlU/L)	1.30	5.12	1.60	5.20	7.00	8.50
E2 (pg/ml)	12.0	49.90	47.37	35.0	35.0	227.0
DHEAS (nmol/L)	142.0	2272.82	1079.54	2221.0	892.0	5836.0
DHEA (nmol/L)	2.10	9.68	4.61	8.90	12.0	22.0
SHBG (nmol/L)	2.80	37.96	32.27	31.0	33.0	215.0

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; Δ4, Δ4 androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

Amongst all abnormalities observed, SHBG concentration was the only one which had a significant statistical difference; this value was more important for the patients in the normal BMI group than those in overweight and obese group. The mean value of estradiol was more important in the normal-weight PCOS patients group contrary to all others parameters where the concentration were more elevated into the otherwise and obese group (Table 2).

The mean concentration of estradiol, DHEAS, DHEA and SHBG were statistically significant according to the age. The value of estradiol and SHBG increased with age while the DHEAS and the DHEA concentration decreased in the same time. However, overweight and obese proportion was more important amongst the range under 25 years old and then the mean value of testosterone; LH and FSH were more increased into the group above 25 years old (Table 3).

In total, the mean value of testosterone, LH and FSH has increased according to the augmentation of BMI and age. Contrary to this trend, the mean value of estradiol and SHBG has decreased in the same conditions.

DISCUSSION

Results showed that there is a real difference within hormonal profile within the population. Most of hormonal values were more increasing for overweight and obese PCOS women in contrast to those who had a normal BMI. Amongst the PCOS patients, there were more normal women according to the body mass index than overweight or obese women. This trend could be explained away by the length of the study population and moreover by the bias in the recruitment. Many studies proved that (Moran et al., 2012) obesity is associated mainly to abdominal adiposity in PCOS patients. It is important to recognize the presence of obesity and its upper body distribution or abdominal adiposity, which changes in accordance to race and geographical distribution (Saxena et al., 2012). They reported that obese PCOS patients have a greater prevalence of some clinical manifestations, such as hirsutism and menstrual disorders; however, other studies have not found differences (Saxena et al., 2012). The main pathophysiological components of PCOS are gonadotropic dysfunction and insulin resistance (Dale et al., 1992). It has been found that both of these components are related to BMI.

In this study, only the difference of SHBG between PCOS patients are statistical significant. The mean value is more elevated to normal PCOS than overweight and obese patients. Out of this parameter and estradiol, the value of testosterone, LH, FSH, Δ4 androstenedione, DHEA and DHEA-S were more elevated for overweight and obese patients than the lean. Controversy exists about the effect of obesity on serum androgen concentrations in PCOS. Some investigators have reported that testosterone and androstenedione levels are similar in obese and non obese PCOS patients (Dale et al. 1992). However, it is well known that obesity generates a decrease in the sexual hormone-binding globulin (SHBG), and therefore an increase in the free androgens (Holte et al. 1994). Other studies have found that obesity generates an increase in testosterone levels in PCOS patients (Moran et al., 2008). These findings corroborated the explanations of Bhathena (2011), and Mathur et al., (2008) who stated that hyperinsulinemia probably acts at the level of hypothalamic-pituitary axis and stimulates LH secretion which leads to anovulation with irregular cycles. This hypothesis was, in fact, provided by the Escobar-Morreale group, who reported a significantly higher prevalence of PCOS in overweight and obese women compared with their lean peers (28.3

Table 2. Correlation between body mass index (BMI) and the mean value of hormonal parameters**.**

Parameter		BMI	
		< 25	**≥ 25**
T	Number	37	34
	Mean	0.56	0.61
	Variance	0.06	0.07
	P value	***0.406***	
D4	Number	37	34
	Mean	3.36	3.53
	Variance	1.56	1.23
	P value	***0.541***	
LH	Number	37	34
	Mean	7.60	9.0
	Variance	30.19	2.,62
	P value	***0.249***	
FSH	Number	37	34
	Mean	4.87	5.40
	Variance	3.04	1.96
	P value	***0.167***	
E2	Number	37	34
	Mean	50.05	49.73
	Variance	2595.83	1927.35
	P value	***0.977***	
DHEAS	Number	37	34
	Mean	2309.09	2233.16
	Variance	1065000	1310000
	P value	***0.776***	
DHEA	Number	37	34
	Mean	9.81	9.53
	Variance	21.54	21.56
	P value	***0.813***	
SHBG	Number	37	34
	Mean	51.44	22.99
	Variance	1475.34	155.42
	P value	***0.000***	

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; Δ4, Δ4 androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

vs 5.5% respectively) (Alvarez-Blasco et al., 2006), and this finding has been confirmed by other researchers groups (Liang et al., 2012, Stovall et al.,2011). In the liver, it decreases production of sex hormone-binding protein and IGF-1-binding protein which results in an increase in free androgen in the blood and an increase in free IGF-1 in the ovary.

It is known that androstenedione and testosterone are produced mainly in the ovaries, while dehydroepiandrosterone and dehydroepiandrosterone sulfate are secreted predominantly in the adrenals (Azziz et al., 2009). However, the disturbance of secretion triggers a high production by the ovaries approximated 50% of testosterone and androstenedione while the adrenals 70% of dehydroepiandrosterone and almost all dehydroepiandrosterone sulfate (Miller et al., 2006).

Table 3. Correlation between age and the mean value of hormonal parameters.

Parameter		Age (years)	
		< 25	**≥ 25**
BMI	Number	32	39
	Mean	30.43	27.49
	Variance	84.62	60.27
	P value	***0.150***	
T	Number	32	39
	Mean	0.55	0.61
	Variance	0.08	0.06
	P value	***0.296***	
D4	Number	32	39
	Mean	3.59	3.32
	Variance	1.63	1.20
	P value	***0.331***	
LH	Number	32	39
	Mean	7.71	8.73
	Variance	27.79	24.28
	P value	***0.406***	
FSH	Number	32	39
	Mean	4.99	5.27
	Variance	2.71	2.45
	P value	***0.404***	
E2	Number	32	39
	Mean	41.63	56.69
	Variance	1849.60	2519.15
	P value	***0.008***	
DHEAS	Number	32	39
	Mean	2606.93	2001.92
	Variance	1681000	613775
	P value	***0.021***	
DHEA	Number	32	39
	Mean	11.83	7.79
	Variance	19153	15.78
	P value	***0.000***	
SHBG	Number	32	39
	Mean	32.62	42.78
	Variance	1565.66	557.10
	P value	***0.016***	

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; Δ4, Δ4 androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

According to age, it was found that the PCOS was more present among patients in the range above 25 years old. This trend may be justified through the occurrence of disturbance in the regulation of hormonal secretion related to age. Aging arouses alterations of many functions and make several diseases such as PCOS appear. Although, there were more overweight/obese PCOS patients in the range under 25

years old and amongst them, the level of E_2, DHEA-S and DHEA were statistical significant contrary to SHBG. These results are in accordance with evidence given by previous studies (Herter et al., 2002; Carmina et al., 2010). Additionally, it has been demonstrated that in patients younger than 24 years of age, age is negatively correlated with homeostasis model assessment of insulin resistance (HOMA-IR) and only in patients older than 28 years of age there was a weak-positive association between age and HOMA-IR (Livadas et al., 2014). Accordingly, in this age group, HOMA-IR is strongly correlated with BMI and this positive association should be attributed mainly to BMI increment. There are data suggesting that women with PCOS display a higher degree of intrinsic insulin resistance compared with age and BMI-matched peers (Moran et al., 2010; Palmert, 2002). Additionally, in their study, women with PCOS displayed higher HOMA-IR values compared with their control peers, even in those older than 30 years of age, irrespective of the BMI. Nevertheless, these authors for the first time provided ample evidence that in women with PCOS through time IR is not increased, but rather ameliorated, in non-obese women with PCOS.

The mean value of testosterone, LH, FSH and estradiol are more elevated in the range of PCOS patients above 25 years old in this study. This trend may be due to the number of patients in this proportion; because, age has an adverse impact on this augmentation up to pre- or postmenopausal normal women. In their report, Corbould (2008), notified that androgen action declining with aging. In their report for women with PCOS, but also in controls, androgen levels gradually decrease through time, as has been shown in several studies (Spencer et al., 2007; Panidis et al., 2012). However, it should be emphasized that androgens decreased irrespective of the BMI, implying that the association of androgens with age is direct and not through obesity. Tsikouras et al. (2015) reported that over the past few decades, there has been a striking increase in the prevalence of obesity among adolescents. This obesity is the primum movens of this pathology and predisposes to the development of insulin resistance, hyperinsulinemia and PCOS. Due to an increasingly unhealthy lifestyle, growing numbers of adolescent girls are at risk of becoming obese and thus develop a metabolic syndrome. Obesity is found in 50% of the patients with PCOS and is linked to insulin resistance, the metabolic syndrome and cardiovascular complications. It is notable that a large number of young girls with PCOS have a normal body weight and will not develop clinical symptoms of the syndrome until they become overweight. According to Leibel et al. (2006), the frequency of the metabolic syndrome in PCOS patients is approximately 25%.

Conclusion

Based on the results, it can be concluded that PCOS is independent of age and BMI. Many over hormonal disturbances could arise according to IR resulted from central obesity. The recommendations match what previous authors said about this pathology. Whether this trend should be attributed to the resolution of ovulation, as has been recently suggested, to decrease in androgens, to prevention of obesity, or to a combination of these interrelated factors remains to be further elucidated. However, the data suggest that in everyday practice, the collaboration between clinician and biologist must be built up in order to make early the diagnosis of PCOS among infertile women. The clinician should encourage lean women to maintain their body weight and insist on obese women to reduce their body weight.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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