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Prevalence of Polycystic Ovary Syndrome in Nigerian Women with Infertility: A Prospective Study of the Three Assessment Criteria

Chinyere Blessing Akpata[1*], Patrick Ojeifo Uadia[2], Friday Ebhodaghe Okonofua[3]

[1]Chemical Pathology Department, University of Benin Teaching Hospital, Benin, Nigeria
[2]Department of Biochemistry, Faculty of Life Sciences, University of Benin, Benin, Nigeria
[3]Department of Obstetrics and Gynecology, University of Benin Teaching Hospital, Benin, Nigeria
Email: *cbnakpata@gmail.com

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a frequent diagnosis in oligomenorrheic and infertile Nigerian women. However, to date there is a paucity of data on the prevalence of PCOS in Nigerian women. The objective of this study was to investigate the prevalence of PCOS in a cross-section of women attending Infertility Clinics in Benin City, Nigeria using the three assessment criteria namely: the 1990 National Institutes of Health (NIH), the 2003 Rotterdam and 2006 Androgen Excess Society (AES) criteria. **Method:** Four hundred and twenty-one consecutive infertile premenopausal women aged 18 - 45 years were recruited and evaluated with a proforma that elicited information about their maternal and reproductive health history. Blood samples were analyzed for hormone levels using standard immunoassay procedures, while trans-vaginal ultrasound scan was carried out to determine the presence of ultrasonic features of PCOS. The control group comprised of eumenorrheics (n = 180). **Results:** An estimated prevalence of biochemical hyperandrogenism (BHA) was as high as 20.9% (88 women), while 3.6% (15 women) presented with clinical hyperandrogenism (CHA). Also the prevalence of polycystic ovaries (PCO) was 13.8%. The prevalence of PCOS based on NIH, Rotterdam and AES criteria was 16.9% (71 women), 27.6% (116 women) and 20.7% (87 women) respectively. However, women with PCOS were significantly younger and had higher total testosterone levels (p = 0.001) when compared to controls. **Conclusion:** The prevalence of PCOS is as high in the population under study as in other prevalence studies. The hormonal investigations were clinically useful in assessing the prevalence rates. However, the recruitment criteria, together with the regional and racial factors may

have contributed to the estimates obtained, and the high incidence of biochemical hyperandrogenism in this region.

Keywords

Infertility, Nigerian Women, Oligomenorrhea, Polycystic Ovarian Disease

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder, leading to several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome [1]. It appears that several factors may be involved in its development but the pathophysiology remains largely unknown. However many believe that PCOS appears to be familial, with its various aspects differentially inherited from one generation to the next [2]. The three major diagnostic criteria of PCOS widely followed are criteria defined using the recommendation of the National Institutes of Health (NIH) in 1990 [3], 2003 Rotterdam Consensus proposed by European Society of Human Reproduction and Embryology (ESHRE) and American Society of Reproductive Medicine (ASRM) [4] [5], and the criteria proposed in 2006 by the Androgen Excess Society (AES) [6].

The reported prevalence of PCOS ranges from 2.2% to 26% in various countries, depending on the recruitment process of the study population, the criteria used for its definition, and the method used to define each criterion [7] [8] [9]. A systematic review has shown that the prevalence under Rotterdam more than doubles that under the 1990 NIH, with the prevalence under the 2006 AES lying in-between [10]. In a study in the United Kingdom [11] an increase of 8% to 26% was demonstrated when Rotterdam criteria were used instead of the NIH [12]. Another study in the Middle East provided a related data [13] of an increase of 7.1% to 14.6% when Rotterdam criteria were used.

From the reviewed literature, there has been no population-based study that estimated the prevalence, clinical and/or biochemical characteristics of PCOS in Nigeria. In a multi-country study of infertility in both developed and developing countries, the World Health Organization (WHO) had previously shown that the African region has a lower prevalence of anovulatory infertility as compared to more developed parts of the world [14]. There is emerging evidence that ethnicity is closely associated with PCOS phenotype due to different genetic and environmental propensity to metabolic and hormonal aberrations [15] [16].

However two studies in Nigeria [17] [18] reported the prevalence of PCOS as 18.1% and 12.2% respectively, but these studies were based on the Rotterdam criteria. Therefore, given the impact of PCOS on the incidence of many disorders, the current study aims at investigating the prevalence of this syndrome under the NIH, Rotterdam and the AES criteria in a selected population.

2. Methods

2.1. Settings

The study was carried out with a cross-section of consecutive women attending Infertility Clinics at the University of Benin Teaching Hospital (UBTH) and the Women's Health and Action Research Centre (WHARC) in Benin City, Edo State, Nigeria between April 1, 2009 and November 30, 2010. The Infertility Clinic at UBTH is one of the largest such clinics in Nigeria and attends to a large catchment area spanning 8 contiguous States in the country. WHARC, a leading Nigerian non-governmental organization (NGO), also runs a reproductive health clinic that provides conventional infertility treatment.

2.2. Subjects

A total of 421 women aged 18 - 45 years who gave their consent to participate in the fully informed study, were recruited into the study. The study procedure was explained to the subjects and their consent obtained. Medical, gynecological and obstetrics history were obtained from each patient using a pre-prepared standard proforma. Interviews were conducted by trained nurses. Clinical history included elicitation of menstrual history (using basal body temperature and cervical mucus secretion recorded with a calendar), previous medications and family history of diabetes mellitus. Menstrual cycle history was carefully detected and included a detailed menstrual history of the previous two to three years. This was followed by detailed anthropometry [with emphasis on height, weight and body mass index (BMI; weight/height^2, kg/m^2)]. Using these criteria, normal weight was characterized as BMI ranging between 18.5 - 24.9, overweight between 25 - 29.9, and obesity rising above 30.0 [19]. Blood pressure measurements were undertaken with subjects in the sitting position. The mean arterial blood pressure (MABP) was calculated by adding a third of the difference between the systolic and diastolic blood pressures. Physical examination was performed in each woman by a gynecologist. Hirsutism was classified using the modified Ferriman-Gallwey (mFG) by scoring the presence of terminal hairs over nine body areas (*i.e.* upper lip, chin, chest, upper and lower abdomen, thigh, upper and lower back and upper arms) [20]. An mFG score of ≥6 was considered hirsutism. Presence or absence of acne was recorded by the gynecologist. Clinical hyperandrogenism (CHA) was diagnosed by the presence of hirsutism and/or acne [20]. The transvaginal ultrasound scan was carried out using the Mindray Digital Ultrasonic Diagnostic Imaging System DP-6600 Model, Hamburg, Germany.

2.3. Selection Criteria

Women who completed the proforma and had menstrual dysfunction (chronic oligomenorrhea/ammenorrhea) were further assessed using random blood sample for serum hormonal assays to exclude related or mimicking etiologies which included thyroid dysfunction, hyperprolactinemia, hypergonadotropic hypogo-

nadism, non-classic congenital adrenal hyperplasia (NCAH). Those who completed the proforma and were regular cycling women had day 3 and day 21serum hormonal investigations carried out. The day 21 progesterone (P4) assay levels were used to confirm ovulatory status. Women with P4 levels < 4.0 ng/ml were regarded as indicating ovulatory dysfunction, while P4 levels ≥ 4.0 ng/ml were regarded as confirmed ovulation. All women who met the inclusion criteria and had total testosterone (TT) levels > 1.0 ng/ml were regarded as indicating hyperandrogenemia. All regular cycling women with no polycystic ovarian syndrome features, specifically no clinical and/or biochemical hyperandrogenism and no chronic oligo/anovulation were regarded as eumenorrhea which formed the control group for the study.

2.4. Defining PCOS

Based on the NIH criteria, PCOS was defined as a combination of menstrual disorder (chronic oligo- or anovulation) and clinical and/or biochemical signs of hyperandrogenism, with the exclusion of related disorders. The Rotterdam criteria defined PCOS by the presence of any two of the following three criteria: menstrual disorders, clinical and/or biochemical hyperandrogenism, and polycystic ovaries. For the AES, definition was analogous to the Rotterdam criteria but excluded women with only menstrual dysfunction and polycystic ovaries. Menstrual dysfunction was defined as less than eight cycles per year. Specifically, the individual criteria were: menstrual history of less than eight cycles in a year, or menstrual cycles less than 26 days or more than 35 days in length, or oligo-ovulation which was day 21 - 24 (mid-luteal) progesterone (P4) levels < 4 ng/ml in women with regular menstrual cycles. Eumenorrhea was defined as women with regular menstrual cycle of 26 - 34 days in length, P4 levels ≥ 4.0 ng/ml with no signs of clinical and/or biochemical hyperandrogenism nor polycystic ovaries [7]. The eumenorrheics were taken as control subjects (N = 180). Biochemical hyperandrogenism (BHA) was defined as a TT and/or FT, A4 and/or DHEAS levels above the upper 95th percentile of eumenorrheic women as reported earlier [7]. Specifically, the upper normal limit for TT was 1.0 ng/ml, FT was 4.1 pg/ml, A4 was 2.6 ng/ml, and DHEAS was 2.2 ng/ml. Polycystic ovaries (PCO) was diagnosed by the presence of 12 or more follicles in each ovary measuring 2 - 9 mm in diameter and/or increased ovarian volume greater than 10 ml [21].

2.5. Sample Size Calculation

$$n = \frac{Z_{\alpha}^{2} * p * q}{d^{2}}$$

where: p is the proportion of PCOS, 15% used, $q = 1 - p$, d is the tolerance *i.e.* how close the proportion of interest is to desired estimate, 4%.

$$n = \frac{1.96^{2} * 0.15 * 0.85}{0.04^{2}}, \; n = 307$$

The sample size was calculated to find a prevalence of PCOS of 15% with a confidence level of 95% and an accuracy or errors of 4%, which required the total of 307 women—so we decided to include all women that fulfilled the selection criteria during the study period.

2.6. Assays

Between 08:30 - 09:30 hour, an overnight fasting venous blood samples were collected from the oligomenorrheics while an overnight day 3 and day 21 fasting venous blood samples were collected from the regular cycling women. Serum was stored at −20˚C until assayed. The samples were assayed for serum follicle stimulating hormone (FSH; units per L), luteinizing hormone (LH; units per L), progesterone (P4; nanograms per ml), estradiol (E2; picograms per ml), total testosterone (TT; nanograms per ml), free testosterone (FT; picograms per ml), androstenedione (A4; nanograms per ml), dehydroepiandrosterone sulphate (DHEAS; micrograms per ml), prolactin (PRL; nanograms per ml), thyroid stimulating hormone (TSH; microunits per ml) and 17 hydroxyprogesterone (17-OHProg; nanograms per ml) were measured. All hormones were measured by enzyme-linked immunosorbent assay (ELISA) method using DRG kits [22]. Samples were batched at regular intervals for analysis to minimize the impact of inter-assay variability. Confirmed PCOS was established in those subjects whose evaluation was complete and met the criteria described above while the prevalence of PCOS was calculated using the confirmed PCOS and those subjects who met the inclusion criteria. Inclusion criteria were women with ovulatory dysfunction and infertility. Exclusion criteria were women on hormonal therapy or other medical treatments whose medications could influence the hormonal assay results thereby affecting the prevalence estimates.

2.7. Statistical Analysis

All statistical analyses were carried out using SPSS 17.0 version for Windows (SPSS Inc., Chicago, IL, USA). Means, standard deviations and Analysis of Variance (ANOVA) test were calculated. Descriptive statistics were generated to enable comparisons between groups. Duncan multiple range test was used for source of significance. Results were reported as the mean ± SD. *P*-value of <0.05 was considered statistically significant.

2.8. Ethical Consideration

The Ethics and Research Committee of the UBTH approved the study proposal and issued the clearance certificate (ADM/E.22 A/VOL.VII/174). Fully informed consent was obtained from all women who participated in the study.

3. Results

A total of 421 women completed the proforma and the study protocol. The procedure for the selection of these women was illustrated in **Figure 1**. Menstrual

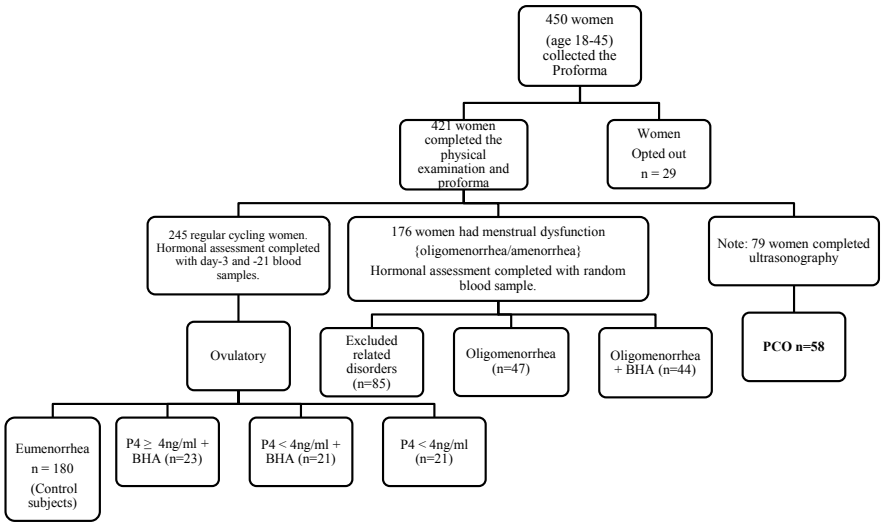

Figure 1. Overview of study participants. Abbreviation: P4, progesterone; BHA, biochemical hyperandrogenism; CHA, clinical hyperandrogenism; PCO, polycystic ovaries.

history revealed that 41.8% (176 women) were oligomenorrheic, while 58.2% (245 women) had regular menstrual cycles. Clinical examination of the women showed that 3.6% (15 women) had CHA (Table 1). Four (1.0%) of the 15 women were hirsute with F-G scores ≥ 6, while 11 (2.6%) of the 15 women had acne. None of the women had androgenic alopecia and none was on oral contraceptive pills. Hormone results obtained from the random blood samples demonstrated that 20.2% (85 women) of the oligomenorrheic women had other related disorders. From the 21.6% (91 women) who were oligomenorrheics with no confounding causes, 47 women were identified as non-hyperandrogenic oligo menorrheics and 44 women as hyperandrogenic oligo menorrheics (Figure 1). The results obtained from the day 21 serum samples of the regular cycling women identified 10% (42 women) as oligo-ovulatory (P4 < 4.0 ng/ml). Twenty one (21) of the 42 oligo-ovulatory women did not show BHA, while the remaining 21 of the 42 women demonstrated BHA (Figure 1). Of the 48.2% (203 women) who were ovulatory (P4 ≥ 4.0 ng/ml), 5.4% (23 women) had BHA and 42.8% (180 women) were eumenorrheics and formed the control subjects (Figure 1). Altogether, 71, 116, and 87 women fulfilled the NIH, Rotterdam, and AES criteria respectively for the diagnosis of PCOS. Therefore, the prevalence of PCOS obtained from population under study was 16.9% (95% CI: 13.4% - 20.8%), 27.6% (95% CI: 23.3% - 32.0%), 20.7% (95% CI: 16.9% - 24.9%) respectively. However, based on NIH criteria, the 23 of the 203 women who were ovulatory (P4 ≥ 4.0 ng/ml) and had hyperandrogenemia (TT > 1.0 ng/ml), were not included in the NIH prevalence estimate. From Table 1, the distributions of the PCOS features (CHA, BHA and PCO) among the oligomenorrheics and the regular cycling women were indicated. From the results of the hormone assay carried out, a total of 88 (20.9%) women had BHA (TT > 1.0 ng/ml). The result of the trans-vaginal ultra-scan (TV-US) assessment of seventy-nine women revealed that 58 (13.8%)

Table 1. The distribution of the phenotypes (clinical hyperandrogenism, biochemical hyperandrogenism and polycystic ovaries) in the two subgroups: oligomenorrheic and regular cycling women.

Subgroup	N (%)	CHA (%)	BHA (%)	PCO (%)
Oligomenorrhea	91 (21.6)	11	44	36
Oligomenorrhea (Related disorder)	85 (20.2)	-	-	-
Regular cycle (ovulatory, P4 ≥ 4 ng/ml)	23 (5.4)	1	23	13
Regular cycle (P4 < 4 ng/ml)	42 (10.0)	3	21	9
Eumenorrhea (**Control**)	180 (42.8)	-	-	-
Total	421	15 (3.6)	88 (20.9)	58 (13.8)

Abbreviation: CHA, clinical hyperandrogenism; BHA, biochemical hyperandrogenism; PCO, polycystic ovaries; P4, progesterone.

women had polycystic ovaries. The ANOVA comparison of the anthropometric and hormonal data of the women with PCOS and the control group using the three assessment criteria are shown in Table 2. When compared with women in the control group, women with PCOS were significantly younger in age (P = 0.001), had significantly higher TT levels and LH:FSH ratio (P = 0.001). Statistically significant differences were observed in the FSH and LH levels between women with PCOS compared to control subjects (P = 0.001). However, there were no statistically significant differences between the groups in mean (± SD) height, weight, BMI, SBP, DBP, MBP and MABP (P > 0.05). All women in the groups were overweight. From the proforma, among the PCOS and control subjects studied, 7.4% (n = 31) and 2.4% (n = 10) had family history of diabetes mellitus (DM) respectively.

4. Discussion

The current study was undertaken to estimate the prevalence of PCOS in a cross section of women attending Infertility Clinic in a Southern Nigerian tertiary health institution, using the three assessment criteria. There is no study in the Sub-Saharan region that estimated the prevalence of PCOS in a selected population using the three defined criteria. The prevalence rates obtained based on the 1990 NIH, 2003 Rotterdam and the 2006 AES criteria were 16.9% (95% CI: 13.4% - 20.8%), 27.6% (95% CI: 23.3% - 32.0%) and 20.7% (95% CI: 16.9% - 24.9%) respectively. This outcome was consistent with reports from other studies [8] [11] [13] where the estimates based on the Rotterdam criteria increased by 1.5 - 2 times when compared to 1990 NIH criteria, and when compared with the study of Tehrani *et al.* [13], the prevalence under the 2006 AES laid in-between. Reports by Ding *et al.* [10] and Bozdag *et al.* [23] confirmed that the highest prevalence estimates are obtained for 2003 Rotterdam and the lowest for the 1990 NIH. They found that white and black females have substantially

Table 2. ANOVA comparison of the anthropometric and hormonal characteristics of women in the three assessment criteria with the control group.

Characteristics	Control (n = 180)	NIH (n = 71)	ROT (n = 116)	AES (n = 87)	P-value
Age (years)	$33.58^{a} \pm 4.12$	$30.9^{b} \pm 5.91$	32.05 ± 5.36	$31.57^{b} \pm 5.66$	0.001**
Height (m)	1.61 ± 0.07	1.61 ± 0.06	1.62 ± 0.06	1.62 ± 0.06	0.246^{NS}
Weight (kg)	69.55 ± 11.63	70.19 ± 11.93	70.51 ± 12.0	70.68 ± 11.78	0.863^{NS}
BMI (kg/m^2)	26.90 ± 4.15	26.95 ± 3.82	26.77 ± 3.85	26.89 ± 3.80	0.99^{NS}
SBP (mmHg)	117.72 ± 10.29	118.87 ± 15.08	119.22 ± 13.52	119.43 ± 14.25	0.68^{NS}
DBP (mmHg)	75.22 ± 9.60	77.18 ± 11.36	77.33 ± 11.06	77.47 ± 11.12	0.23^{NS}
MBP (mmHg)	114.52 ± 11.87	116.25 ± 14.82	116.73 ± 14.18	116.82 ± 14.35	0.43^{NS}
MABP (mmHg)	89.39 ± 8.87	91.08 ± 11.68	91.29 ± 10.94	91.46 ± 11.20	0.30^{NS}
TT (ng/ml)	$0.41^{b} \pm 0.23$	$1.57^{a} \pm 1.11$	1.34 ± 1.45	$1.61^{a} \pm 1.57$	0.001**
FSH (U/L)	$9.87^{a} \pm 4.59$	$8.23^{b} \pm 4.34$	7.97 ± 4.20	$8.46^{b} \pm 4.53$	0.001**
LH (U/L)	$9.90^{b} \pm 5.63$	$19.42^{a} \pm 17.74$	19.10 ± 16.11	$18.18^{a} \pm 16.54$	0.001**
LH:FSH	$1.09^{b} \pm 0.66$	$2.94^{a} \pm 3.21$	2.88 ± 2.73	$2.67^{a} \pm 2.97$	0.001**

**P < 0.01 was Highly Significant; *P < 0.05 was Significant; NS, not Significant; ^{NS}: Not significant. Different Superscript letters across the rows showed significant difference between the study cohorts. Values are the mean ± SD. Abbreviations: kg/m^2, kilogram per meter squared; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; MABP, mean arterial blood pressure; LH:FSH, luteinizing hormone to follicle stimulating hormone ratio.

different risks of developing PCOS. They further suggested that under the same diagnostic criterion of PCOS, Chinese and Caucasian females are less likely to develop PCOS compared with females residing in the Middle East, whereas Black females majorly African-Americans and Afro-Brazilians tend to have the highest risks of developing PCOS. Therefore, this study is advantageous in terms of providing ethnicity-specific estimates. The estimates of PCOS from database studies and community based studies [10] are lower than those reported in this study which underlies Bozdag *et al.* [10] observation that PCOS is a syndrome without much public awareness and PCOS patients often do not seek care. However, most of the studies involving selected female population [24] [25] [26] [27] reported high PCOS prevalence which demonstrated the outcome regarding the types of recruitment.

The distribution pattern associated with specific PCOS phenotypes outlined in Table 2, has shown the prevalence rates in the present study in ascending order as CHA 3.6% (n = 15), polycystic ovaries 13.8% (n = 58), BHA 20.9% (n = 88) and oligomenorrhea 21.6% (n = 91). Hirsutism contributed 1% to the CHA in this study and is comparable to the 2.8% identified by Knochenhauer *et al.* [28] but lower than the estimates obtained by Asuncion *et al.* [29], Diamanti-Kandarakis *et al.* [30] and March *et al.* [8]. Hsu *et al.* [31] had reported that 28% - 35% of Asian women with PCOS present with hirsutism, an estimate much higher than demonstrated in this study. Hsu [32] suggested that hirsutism is not only a function of circulating androgen levels but can be determined by

genetic factors. Whereas this study reported a prevalence rate as high as 20.9% for BHA and Yang *et al.* [33] reported 33%, in contrast Hussein and Alalaf [27] reported a lower rate of BHA about 7.5% in Kurdish women. Regarding clinical presentation, excess androgen has been suggested to have a principal role in diagnostic criteria. The estimate (21.6%) of oligomenorrhea in this study is comparable with the 23.8% reported by March *et al.* [8] among Australian women. The present study had oligomenorrhea and BHA as the most common PCOS component while Hsu [32] identified PCO morphology as the most common PCOS component in Taiwanese women. Taken together the implications of ethnic variation on screening and diagnosis, management priorities and response to treatment should be taken into account, when managing women from distinct ethnic background, as well as in developing management guidelines of PCOS [10].

PCOS women were also younger in age ($p = 0.001$) with elevated TT levels ($p = 0.001$) compared to control. Other reports have revealed that PCOS women were significantly younger ($p = 0.00061$) [27]. This study has demonstrated that LH:FSH ratio is a valuable diagnostic tool in evaluating Nigerian women with PCOS. Alnakash and Al-Taee [34] reported that not all women with PCOS possess hormonal and biochemical changes suggestive of the disease. However, the finding of elevated LH:FSH ratio was not included as part of the recommendation for PCOS.

This study has important strengths and weaknesses. The strength lies in the authors' study of consecutive women attending Infertility Clinics in a large urban city in Nigeria. Only a few women attending the clinics during the period opted out of the study, indicating that the results are externally valid for populations of infertile women in the region. Additionally, the use of robust clinical and hormonal parameters in line with international recommendations indicates that not only are the results internally valid, but that they can be compared with results obtained from other populations. The major limitation of this study was that only a few proportion of women in this population actually present in hospital for investigation and treatment. Therefore, the extent of under-representation of actual infertile women becomes apparent. Another limitation was the lack of funding which did not allow for the estimation of free testosterone for all the women in the study. Likewise trans-vaginal ultrasound was not conducted for all the women with PCOS features. Hormone assays are often not available or affordable to many clinics in Africa, and the use of ultrasongraphy for the assessment of ovulation in Africa is limited by the high cost of ultrasound equipment [35].

5. Conclusion

In conclusion, the economic burden of PCOS is significantly huge. Therefore accurate and early diagnosis and intervention of the disease is necessary not only to prevent future health comorbidities, but also to reduce financial cost and

burden, thereby ensuring good health and well-being. This study has provided insights into the contribution of PCOS to the high burden of infertility in the Sub-Saharan region; and showed that the prevalence of PCOS is high in infertile Nigerian women. Clinical approaches and hormonal investigations for managing PCOS as part of the treatment of infertility are imperative.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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