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Original Article

Polycystic Ovarian Syndrome: Analysis of Management Outcomes Among Infertile Women at a Public Health Institution in Nigeria

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Abstract

Background: Infertility remains an issue of concern especially to the female partner who bears the brunt of the stigma attributed to the disease in this environment. Among the identified etiological factors for infertility, polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age that impact on ovulation and conception. **Aims and Objectives:** The objective of this study was to determine pregnancy outcome following the various modalities of management of PCOS at the University of Ilorin Teaching Hospital (UITH). **Materials and Methods:** This is a nonrandomized (nonblinded) clinical trial of five therapeutic options for infertile women with PCOS from the Assisted Reproductive Technology (ART) Clinic and Gynaecology Clinic of UITH between January 1, 2011 and December 31, 2013. **Results:** Of 624 infertile women who presented at ART and general gynecology clinic of UITH, 76 met the Rotterdam criteria for PCOS, giving a prevalence rate of 12.2%. The patients aged 20–44 years with a mean age of 31.5 years. Most 49 (64.5%) of the patients were nulliparous, and more than half (56.6%) belong to the middle social class. Thirty-four (44.8%) were obese while 22 (28.9%) were overweight. Of the various management options, 48.7% had laparoscopic ovarian drilling; other treatment options offered were the use of clomiphene citrate (CC) alone, CC with metformin, weight reduction, and gonadotropin. Patients were followed-up within 6–12 months (mean 5.5 ± 1.2 months) following the initial treatment for evidence of laboratory/clinical pregnancy. An overall pregnancy rate of 46.0% was recorded. However, a total of 13 (17.1%) were lost to follow-up. The highest pregnancy rate (75%) was reported in women managed with CC alone ($P = 0.229$). **Conclusion:** PCOS occurs commonly in reproductive age and management outcomes are promising in Nigeria. CC, metformin, and laparoscopic ovarian drilling are of great benefit. Further studies on PCOS in low resource countries are needed.

Key words: Clomiphene citrate, infertility, polycystic ovarian syndrome, University of Ilorin Teaching Hospital

Introduction

The polycystic ovarian syndrome (PCOS) also known as Stein-Leventhal syndrome was first described, in 1935, by Stein and Leventhal.[1] This syndrome is characterized by oligo-amenorrhea, obesity, infertility, and hirsutism. It is undoubtedly associated with long-term health sequelae such as diabetes mellitus, endometrial cancer, and cardiovascular disease among others.[1,2]

PCOS has a prevalence of 5–10% with variance among races and ethnicities.[3] The highest reported prevalence has been 52% among South Asian immigrants in Britain of whom 49.1% had menstrual irregularity.[4] Up to 10% of women are diagnosed with PCOS during gynecologic visits.[2] Approximately 50% of patients are hirsute, and 30–75% are obese.[3] The prevalence rate of 18.1% has been reported by Ugwu *et al*. in south eastern, Nigeria with the majority having infertility and oligo-menorrhea.[2] PCOS accounts for 75% of anovulatory infertility in childbearing women.[5]

PCOS affects premenopausal women, and the age of onset is most often perimenarchal (before bone age reaches 16 years).[2]

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In lean women with a genetic predisposition to PCOS, the syndrome may be unmasked when they subsequently gain weight.[2]

The exact underlying defect in PCOS is unknown, a genetic component is likely as PCOS tend to run in families, and the pattern of inheritance is X-linked dominance.[6] Family studies have shown that about 50% of first degree relatives have PCOS.[7] A presumptive diagnosis of PCOS often can be made based on the history and examination findings. According to an international consensus, the syndrome can be diagnosed using the Rotterdam criteria (presence of at least two of the following conditions): Oligo-menorrhea or amenorrhea, hyperandrogenism, and polycystic ovaries on ultrasound. The morphology of polycystic ovaries has been defined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and increased ovarian volume (>10 cm^3) on transvaginal ultrasound (TVS).[8]

Management of PCOS is symptom oriented. The objectives are to restore normal menstruation; ovulatory cycles and fertility; prevent endometrial hyperplasia/cancer and to treat acne; and infertility. This study aimed at determining the prevalence, sociodemographic characteristics, and outcomes of management modalities of PCOS in women with infertility. It is hoped that the findings from this study will enable us identify the most effective therapeutic option for anovulatory PCOS in our locality since there is a paucity of knowledge in the provision of such care in our environment.

Materials and Methods

This is a nonrandomized (nonblinded) clinical trial involving infertile women with PCOS, who had treatment for infertility at the Assisted Reproductive Technology (ART) clinic and Gynaecology Clinic of University of Ilorin Teaching Hospital (UITH) between January 1, 2011 and December 31, 2013.

Information on biosocial data, the mode of treatment and management outcomes were documented using a structured questionnaire. Social classes were determined based on patient's education and her husband's occupation as validated by Olusanya *et al*.[9] Similarly, the contacts (telephone numbers and home address) of the patients were collected. Furthermore, diagnostic workup including hysterosalpingography/saline infusion sonography, transvaginal ultrasonography, and measurement of baseline levels of follicle-stimulating hormone, leutinizing hormone, estradiol, thyroid-stimulating hormone, triiodothyronine (T3), thyroxin (T4), prolactin, and day 21 progesterone were carried out on them prior to commencement of treatments. In addition, the spouse of the clients also had a seminal fluid analysis done. Patients with abnormal serum prolactin levels, bilateral tubal blockade or whose husbands had abnormal semen parameters (sperm count <20 million/mL, motility <50%, morphology <30% [normal: World Health Organization criteria]) were excluded from the study.

The patients were counseled on the five therapeutic options, and they made an informed decision. The treatment modalities employed included: Clomiphene citrate (CC) alone, CC with metformin, weight reduction, gonadotropins, and laparoscopic ovarian drilling (LOD). Patients who received metformin were given the tablets at the initial dose of 500 mg and increased in a stepwise fashion which was individualized during the first 3 weeks to accommodate the side effects until patients were taking a total dose of 1500 mg/day. The patients were then asked to come for follow-up once they had a menstrual period, and a TVS and follicular tracking were done to document evidence of follicular growth and ovulation on days 10 or 12, and 16 of cycle. Patients that received CC only were given CC at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document follicular growth and ovulation on days 10 or 12, and 16 of cycle. If there was the absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis (50 mg incremental dose per cycle) after a progesterone withdrawal bleeds to a maximum of 200 mg. If there was evidence of ovulation, but the patient did not get pregnant, the same dosage was continued for a maximum of six cycles.

In the combination treatment group, metformin was given in a similar manner to the metformin only group. Clomiphene was given at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document evidence of follicular growth and ovulation on days 10 or 12, and 16. If there was the absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a progesterone withdrawal bleeds to a maximum of 200 mg. If there was evidence of ovulation, but the patient did not get pregnant, a similar dosage was continued for a maximum of six cycles.

In the gonadotropin group, intramuscular injection of highly purified human menopausal gonadotropin (Menopur; Ferring Pharmaceuticals, Kiel, Germany) was administered at a dose of 75 IU on day 6, 9, and 12 of cycle. The TVS and follicular tracking were done to document evidence of follicular growth and ovulation on days 10 or 12, and 16. If there was absence of ovulation, the gonadotropin dose was increased stepwise on a treatment cycle basis after a progesterone withdrawal bleed to a maximum of 300 IU. If there was evidence of ovulation but patient did not get pregnant, a similar dosage was continued for a maximum of six cycles. Weight reduction therapy in the form of dieting as recommended by the dietician (this includes eating lots of fruit and vegetables, choosing lean meats and low-fat dairy foods, as well as limiting the amount of fatty, and sugary foods, and drinks) and exercise was sustained for 6 months, and LOD was offered to patients who failed to ovulate after three treatment cycles with gradually increasing doses of CC prior to presentation (clomiphene resistant).

Patients were allocated to the treatment groups purposively and counseled on adequate coital exposure with their spouse during ovulation period between 12 and 15 days of menstrual cycle as determined by ovulation test kit (predict®; Unipath Diagnostics) and or days 12–15 follicular TVS study. Patients were followed-up within 6 to 12 months following

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the initial treatment for the evidence of laboratory/clinical pregnancy.

Ethical approval was obtained from the departmental ethical committee of the ART unit of the hospital. The data retrieved were analyzed using a commercial statistical package (Statistical Package for the Social Sciences [SPSS] version 16.0, SPSS Inc. Chicago, IL, USA). The results are depicted using percentages.

Results

Of 624 infertile women who had infertility consultation during the period under review at the ART and general gynecology clinics of UITH, 76 met the Rotterdam criteria for PCOS, giving a prevalence rate of 12.2%. Of 76, a total of 57 (75.0%) patients were recruited from ART unit while 19 (25.0%) were from gynecology clinic. However, a total of 13 (17.1%) were lost to follow-up. In addition, a total pregnancy rate of 46.0% was recorded as 35 out of the 76 patients' recruited attained pregnancy in 12 months. The patients aged 20–44 years with a mean of 31.5 years. The modal age group was 25–29 years. Forty-nine (64.5%) were nulliparous while 18 (23.7%) were primiparous, and the remaining nine (11.8%) were multiparous. Forty-three of them (56.6%) belong to the middle social class. Thirty-four (44.8%) were obese while 22 (28.9%) were overweight [Table 1].

The various treatment options offered to infertile women with PCOS and pregnancy rates is shown in Table 2. Most 37 (49%) had LOD. Sixteen (21%) were administered CC alone. Twelve (16%) received gonadotropins. Seven (9%) received a combination of CC and metformin. Only four (5%) were offered weight reduction. The patients were followed up within 6–12 months (mean 5.5 ± 1.2 months). However, a total of 13 (17.1%) were lost to follow-up and majority 10 (77%) belong to LOD treatment group. Among those that were compliant to follow-up, the highest pregnancy rate was recorded among patients that received CC alone, where pregnancy rate of 75% was recorded.

The odds of pregnancy occurring is highest for CC and lowest for weight reduction and CC + metformin. However, odds ratio across the treatment groups involving comparing odds of weight reduction and CC (0.33/3.00 = 0.11) revealed that the odds of pregnancy occurring with weight reduction is lower than that of CC. Similarly, the odds of pregnancy occurring with CC seem two times higher than with Laparoscopic drilling (3.00/1.25 = 2.4). Comparing the odds of weight reduction and CC + Metformin (0.33/0.33 = 1.00) showed that there is no difference in pregnancy outcome between the two groups. However, there was no statistically significant difference in the pregnancy outcome across the various treatment modalities ($\chi^2 = 5.63$; $P = 0.229$) [Table 3].

Table 1: Sociodemographic characteristics of infertile women with PCOS ($n=76$)

Variables	Frequency	Percentage
Age		
20-24	11	14.5
25-29	21	27.6
30-34	18	23.7
35-39	16	21.1
40-44	10	13.1
Parity		
Nullipara	49	64.5
Primipara	18	23.7
Multipara	9	11.8
Social class		
Low	24	31.6
Middle	43	56.6
High	9	11.8
BMI (kg/m^2)		
18-24.9	20	26.3
25-29.9	22	28.9
>30	34	44.8

BMI: Body mass index, PCOS: Polycystic ovarian syndrome

Table 2: Treatments offered and pregnancy rates among infertile women with PCOS ($n=76$)

Variables	Frequency (%)	Pregnancy rate (%)
Weight reduction	4 (5)	1/4 (25)
Clomiphene citrate alone	16 (21)	12/16 (75)
Clomiphene citrate+metformin	7 (9)	1/4 (25)*
Gonadotropins	12 (16)	6/12 (50)
Laparoscopic ovarian drilling	37 (49)	15/27 (55.6)*

*Number of infertile women lost to follow-up. PCOS: Polycystic ovarian syndrome

Table 3: Modalities of treatment and pregnancy outcome among subjects ($n=63$)

Treatment offered	Pregnancy outcome (%)		OR	χ^2	*P*
	Positive	Negative			
Weight reduction	1 (25.0)	3 (75.0)	0.33	5.63	0.229
Clomiphene citrate alone	12 (75.0)	4 (25.0)	3.00		
Clomiphene citrate+metformin	1 (25.0)	3 (75.0)	0.33		
Gonadotropins	6 (50.0)	6 (50.0)	1.00		
Laparoscopic ovarian drilling	15 (55.6)	12 (43.4)	1.25		

OR: Odds ratio

Discussion

In this study, the prevalence rate of PCOS was estimated to be 12.2%. This compares favorably with a similar study carried out in Niger-Delta University Teaching Hospital in southern Nigeria (12.2%),[10] but lower than the 32% reported by Pembe *et al*. in Tanzania, in 2009.[11] A higher prevalence rate of 18.1% was also reported in Enugu by Ugwu *et al*.[1] A lower prevalence rate of 2.2% was reported by Igwegbe *et al*. in Nnewi.[12] The differing prevalence rates may be attributed to differences in the prevalence rates of the genetic and environmental determinants of PCOS in the various populations or differences in the study populations.

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This study showed that, the majority of the women were within the age group 25–29 years, with a mean age of 31.5 years. This is similar to the findings in Enugu, Nigeria with a mean age of 30 years),[1] though slightly higher than the mean age of 27 years recorded in Nnewi, Nigeria.[12] However, this is not surprising as the PCOS is a complex endocrine disorder affecting women in their reproductive years.[1,12] Furthermore, the majority of the women (64.5%) were nulliparous. This is inconsonance with the findings in Nnewi, Nigeria where 70% of the study population were nulliparous.[12] The association of PCOS and its components with socioeconomic status (SES) might shed light on the role of the environment in the development of this condition. Research has shown that individuals with lower SES are more at risk for engaging in adverse health behaviors including smoking, lack of physical activity, and poor nutritional diet[13,14] among women, obesity is associated with low SES.[15,16] Studies have also shown that smoking and obesity can exacerbate insulin resistance,[17] which is a condition highly correlated with and part of the pathogenesis of PCOS. On the contrary, less than one-third (31.6%) of the study population belong to lower SES in this study.

Approximately 75% of women with PCOS are overweight.[6] This finding also agrees with the present study where 73.7% of women were either overweight and or obese. Improvement in lifestyle with a combination of exercise and diet to achieve weight reduction is important to enhance the prospects of both spontaneous and drug induced ovulation.[7] In this study, four women were offered weight reduction. Lifestyle modification and weight loss improves ovulation rate, fertility, and decrease in testosterone levels.[7] It is generally accepted that more than 5–10% weight loss improves fertility and menstrual cycles in women with PCOS.[18]

CC, an ovulation induction drug was administered to 16 patients in this study, and a pregnancy rate of 75% was achieved within 6 months to 12 months of initiation of treatment. This result is far higher as compared to a pregnancy rate of 40% reported in Nnewi[12] and 38% in Enugu, Nigeria.[1] This could be attributed to the smaller sample size in this study as compared to Nnewi and Enugu studies. It has been recommended that when an ovulatory dose of any agent has been found, the patient should continue on it for 6 months.[19] There is presently no consensus on the definition of clomiphene resistance, but most clinicians would define it as a failure to ovulate after three treatment cycles with gradually increasing doses of CC.[12]

A Cochrane review has confirmed a beneficial effect of metformin in increasing rates of ovulation when combined with placebo and also improving both rates of ovulation and pregnancy when used with CC compared with CC alone.[20] This is however, differ from findings in this study, where the highest pregnancy rate (75%) was reported in women managed with CC alone as against 25% in CC and metformin group possibly due to limited sample size in this study.

Parenteral gonadotropin therapy, for example, human menopausal gonadotropin has been used. The drawback with this medication is ovarian hyperstimulation syndrome and multiple pregnancies. Though an expensive medication, only 12 patients were able to purchase it and 6 out of the 12 (50%) conceived.

LOD or diathermy is a one-off therapeutic option for women with clomiphene resistant PCOS.[7,21] This procedure is free of complications such as multiple pregnancy and ovarian hyperstimulation. It also does not require intensive ultrasound monitoring. It has also taken the place of wedge resection of the ovaries which resulted in extensive peri-ovarian and tubal adhesion. Thirty-seven women had LOD, 10 out of these defaulted and a pregnancy rate of 55.6% was reported in those monitored.

One major limitation of this study was the small number of patients used in the study. Another constraint was the limited laboratory resources in the study center; hence, we were not able to measure other blood parameters that would have been useful in the evaluation of PCOS such as dehydroepiandrosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin (SHBG), and fasting insulin. Another limitation was that the pelvic ultrasound examinations were not done by same investigators using a vaginal endoprobe, and so there are chances of intra-observer bias. The baseline hormonal profiles were not repeated following medications, and so we could not assess the effects of medication on the hormonal profile. In addition, pregnant patients were not followed up until an ultrasound could document the viability of pregnancy and copies of patients' obstetric records including delivery records were not reviewed by the investigators to obtain birth outcomes.

Conclusion

PCOS is a common heterogeneous endocrine disorder occurring in one in eight infertile women in our locality. It occurs more often in nulliparous women. The diagnosis requires a high index of suspicion and management outcomes are promising in Nigeria. CC and insulin sensitizing agent (metformin) are of great benefit. However, when resistance to clomiphene is demonstrated, LOD offers hope. There is, therefore, need for further studies on PCOS in developing countries so as to X-ray the effects of various treatment modalities on improvement of pregnancy rates.

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Conflicts of interest

There are no conflicts of interest.

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