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Pattern of Anovulatory Infertility in The University of Port Harcourt Teaching Hospitalin South-South Nigeria

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Abstract:
Background:Anovulation *is one of the causes of female factor infertility. In sub-Saharan Africa, anovulation has received minimal attention as a cause of infertility due to the very high prevalence of tubal factor infertility. Management of anovulatory infertility requires understanding of the classes of anovulation and available treatment options.Some classes of anovulatory infertility are easily treated with pharmacologic agents, others may require assisted conception techniques involving ovum donation. There is need to identify the different types of the disease as first step towards appropriate effortsin helping couples with anovulation.*
Objective: *To determine the incidence and prevailing classes (using WHO classification) of anovulatory infertility amongst women with infertility presenting to the gynaecology clinic of the University of Port Harcourt teaching Hospital.*
Materials and Methods:*A cross sectional study was conducted at the University of Port Harcourt Teaching Hospital (UPTH) between January and June 2014. All (261) patientsdiagnosed with infertility were made to undergo serum analysis to determine their gonadotropins, progesterone, oestrogen and prolactin serum levels as part of theirinfertility evaluation. The data generated was collected and analysed using SPSS version 19.0. The results are shown as figures and tables using percentages.*
Results: *Anovulatory infertility was found in 44.3% of patients. No patient was identified as having WHO type 1(hypogonadotrophic,hypo-oestrogenic, normoprolactinaemic) anovulation. The WHO type 2 (normogonadotrophic, normo-oestrogenic, normoprolactinaemic) was the commonest form of anovulation at 66.4%,WHO type 3 (hypergonadotrophic, hypo-oestrogenic, normoprolactinaemic) was responsible for 12.2% of cases and hyperprolactinaemia accounted for 21.4% of patients with anovulation.*
Conclusion*: Anovulation is also a common cause of infertility in south-south Nigeria, contributing about 44% of female infertility. The WHO type 2 is the most preponderant and responsible for 66.4% of anovulation.Endocrine factors resulting in anovulation are likely to be the major challenges in management of infertility in the future for reproductive physicians in this region as uptake of reproductive health services improves.*

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I. Introduction

The World Health Organisation (WHO) defines infertility as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse[2].

Nigeria is a society with serious emphasis on child bearing and rearing, infertility is abhorred in the Nigerian society. The extent to which Nigerians will go to have a child is demonstrated by the illicit commercialisation of adoption of babies in the baby factory menace.[1]Infertility has been recognised as a public health issue in Nigeria with far reaching medical and psychological implications.[3, 4]At the same time the country is plagued with the problem of maternal mortality being the second largest contributor to maternal deaths globally. This understandably attracts funding above other pressing health issues such as infertility.

The female partner has traditionally borne the blame when a couple is adjudged to be infertile and it is not unusual to see the female being the one to seek help[5]. Female factors are thought to be responsible for about 31% of cases of infertility[6]. Other contributors to the burden of infertility are male factor 29%, combined male and female factors 30% and unexplained infertility 10%[6]. Inassessing female factor infertility, tubal occlusion has been identified as the predominant problem in sub Saharan African. It is said to be responsible for the majority of female infertility and this has been attributed to the high prevalence of sexually transmitted infections, unsafe abortions and post partum infections within the region[5, 6, 7]. Anovulatory disorders leading to

infertility have not received enough attention due to the high prevalence of tubal factor infertility.There is misconception that anovulatory infertility is not prevalent in our environment and this misconception is compounded by the lack of facilities for making diagnosis[8].

The World Health Organisation(WHO) in classifyingdisorders of ovulation[9], as known causesto female factor infertility,took into consideration the site of endocrine dysfunction and grouped disorders of ovulation into the following: Hypogonadotrophic hypo-oestrogenic normoprolactinaemic (WHO type1),

Normogonadotrophicnormo-oestrogenic normoprolactinaemic (WHO type 2), Hypergonadotrophic hypo-oestrogenic normoprolactinaemic (WHO type 3) and hyperprolactinaemic. The ability to recognise thesetypes of ovulation disorders and the manipulation of the Hypothalamo-Pituitary-Ovarian (HPO) axis using pharmacological agents in specific cases, has brought some succour to women with anovulatory infertility.

Though hormone profile assessments are routine investigations in the assessment of women presenting to the gynaecology clinic with complaints of infertility, studies in this regard are lacking. There has been recognised epidemiological shift in various areas of health care delivery, with non-communicable diseases becoming more prevalent than in the past, there is a need to reviewthe contribution of non-communicable diseases as causes of infertility in this sub-region as well. The recipe for this epidemiological shift in the direction of non-communicable factors, such as anovulation, as a significant cause of infertilityis already present and includes increasing female education, increasing obesity amongst young women, eating disorders/ food fads amongst women of reproductive age groups. In addition to these, the increasing campaign for safe sexual practices will eventually lead to reduction in unwanted pregnancy rates as well as sexually transmitted infections. These put together have the ability to reduce pelvic infections and put the burden of anovulatorydisorders on the same pedestal or even surpass the current burden of pelvic infections, which is presently the leading cause of infertility amongst women in Nigeria.

II. Materials And Methods.

This was a cross sectional study carried out over a six-month period between January and June, 2014. It included the womendiagnosed with infertility at the gynaecology clinic within this period. Socio-demographic data and anthropometric measurements were obtained from the case notes of the women who participated in the study after theywere diagnosed with infertility by the attending gynaecologist. The patients were asked carry out early follicular phase serum levels of follicle stimulating hormone, luteinizing hormone, and prolactin as well as mid-luteal phase progesterone amongst other investigations during their evaluation for treatment. The results of these investigations were entered into the spreadsheet at their follow up visit.

Hormone profile results were categorized using the ranges obtained from the reference laboratory of UPTH where the tests were conducted. Progesterone values of 14ng/ml or more were taken as values indicative of ovulation for this study, as this progesterone value has been found to be compatible with conception[10]while values less than 10ng/dl was consistent with anovulation. Data was analysed using SPSS version 17.0. The results are shown as figures and tables.

III. Results.

Three hundred and sixteen women with infertility, constituting 32% of all gynaecologic consultations,were seen in the gynaecology clinic during the period under review. Of these three hundred and sixty one women with infertility,one hundred and forty (40.3%) were found to have anovulation (day 21 serum progesterone values less than 14ng/ml) and classified as having anovulatory cycles. The other two hundred and eight (57.6%) in the cohort had day 21serum progesterone values above 14ng/dl consistent with ovulatory cycles.

The mean age of women with anovulatory cycles was 33.3 ± 5.0 years, and most of them (61.4%)were in the 25-34 year age group. All the women surveyed were married and Christians. The age at menarche ranged between 11 and 19 years. The mean age at menarche was 14.2 ± 1.6 years. Majority of these women wereself employed (47.9%) withpost secondary education (73.6%). Majority of these women were nulliparous (80%) and pre-obese (45.7%). Oligomenorrhea occurred commonly in these women with anovulation as 51.4% of the women had prolonged menstrual cycles of 35 days or more.

Using the World Health Classification of ovulation disoders[9], it was found that most (66.4%) of the patients had Type 2 (normogonadotrophicnormo-oestrogenic normoprolactinaemic) ovulatory disorder.

Cross tabulations between the WHO classesof ovulatory disorders with the length of the menstrual cycle and the body mass index showed that 50% of the WHO type 2 ovulatory disorder occurred in those with BMI between 25-34 (the pre-obesity and class one obesity groups). Majority of these women with WHO type 2 ovulatory disorder (68 out of 93) had normal cycle lengths as opposed to WHO type 3 and 4 (hyper-prolactinaemia) ovulatory disorder, whichare usually associated with oligomenorrhea.

TABLE 1: SOCIAL AND CLINICAL CHARACTERISTICS OF PATIENTS

CHARACTERISTIC	FREQUENCY (X/140)	PERCENTAGE
AGE GROUP		
18-24	1	0.7
25-34	86	61.4
34-45	53	37.9
TOTAL	140	100
PARITY		
0	112	80
1	8	5.7
≥2	20	14.3
TOTAL	140	100
BODY MASS INDEX (BMI)		
19-24 (Normal)	37	26.4
25-29 (Pre-obese)	64	45.7
30-34 (Obesity class 1)	29	20.7
35-39 (Obesity class 2)	9	6.4
3≥40 (Obesity class)	1	0.4
TOTAL	140	100
LENGHT OF MENSTRUAL CYCLE		
<21 DAYS	0	0
21-35 DAYS	68	48.6
>35 DAYS	72	51.4
TOTAL	140	100

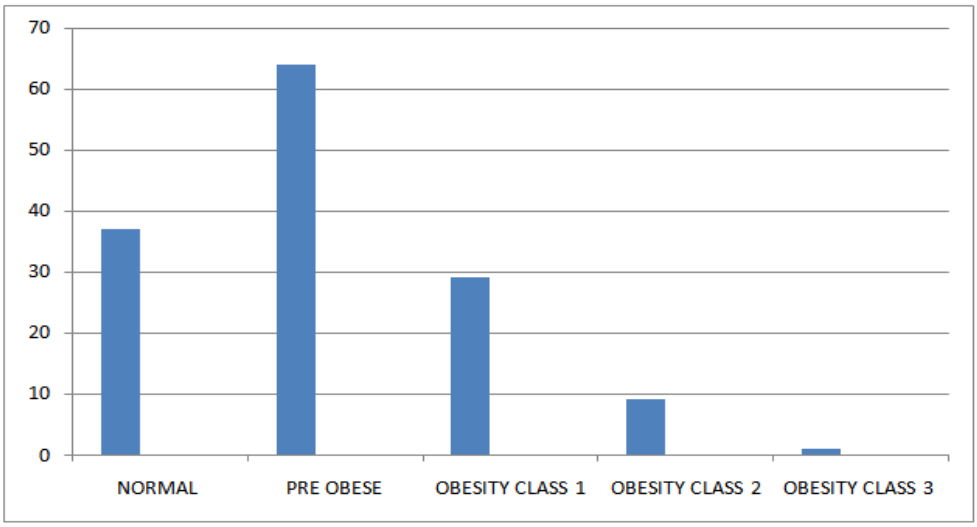

FIGURE 2: CHART SHOWING DISTRIBUTION BY BODY MASS INDEX.

TABLE 2: PATIENTS DISTRIBUTION BASED ON WHO CLASSIFICATION OF OVULATORY DISORDERS.

WHO CLASSIFICATION OF OVULATORY DISORDERS	FREQUENCY	PERCENTAGE
HYPOGONADOTROPHIC HYPO-OESTROGENIC NORMOPROLACTINAEMIC (WHO TYPE1)	0	0
NORMOGONADOTROPHIC NORMO-OESTROGENIC NORMOPROLACTINAEMIC (WHO TYPE 2)	93	66.4
HYPERGONADOTROPHIC HYPO-OESTROGENIC NORMOPROLACTINAEMIC (WHO TYPE 3)	17	12.2
HYPERPROLACTINAEMIC	30	21.4
TOTAL	140	100

Table 3: Cross tabulation between WHO classification and body mass index.

		WHO Classification			
		Type 2	Type 3	Hyper-prolactinemia	Total
Body mass index	Normal	17	8	12	37
	Pre-Obesity	50	6	8	64
	Class 1 Obesity	20	3	6	29
	Class 2 Obesity	5	0	4	9
	Class 3 Obesity	1	0	0	1
Total		93	17	30	140

Table 4: Cross tabulation between WHO classification and length of menstrual cycle

		WHO Classification			
		Type 2	Type 3	Hyper-prolactinemia	Total
Menstrual cycle length	21-35	68	0	0	68
	>35	25	17	30	72
Total		93	17	30	140

IV. Discussion

Ovulation of a mature oocyte from the dominant follicle is a key event in the build up to conception. Anovulatory cycles can occur in the course of a woman's reproductive life and are more common shortly after menarche and in the climacteric period[11].

The occurrence of anovulatory cycles during the reproductive years and in a patient not on hormonal contraceptives could be worrisome. Anovulation could occur due to hypothalalmo-pituitary dysfunction, ovarian disorders or other endocrine disorders[10].

Clinical indicators that suggest the occurrence of cyclical ovulation include regular menstrual cycles, mittelschmercz, ovulation bleeds, watery and stretchable cervical mucus and a small rise in basal body temperature[10]. The occurrence of pregnancy is regarded as a sure sign of ovulation. In assessing infertile women, ovulation could be determined with the assay of serum progesteroneat mid luteal phase of the menstrual cycle and follicular tracking using in the follicular phase withultrasoundscan.

Anovulatory disorders accounted for 44% of infertility cases in this study. This confirms the findings in similar studies in the western andsouthern regions of Nigeriawith the incidence of anovulation at 40.9 and 42.2% respectively.[12, 13] In these studies, aetiology of infertility was differentiated into tubal factors, cervico-uterine and ovulatory factors with no consideration for women with more than one factor responsible for their infertility. Similarly, some of the patients in our study may have had more than a single aetiology to their infertility. This was not ascertained since this study was focused on incidence and classification of anovulation.

Majority of the patients in our study (66.4%)are type 2 of the WHO classification of anovulatory disorders see table 2. These patients may pose a diagnostic dilemma as the gonadotrophic hormones and oestrogen levels are within normal limits and 68% of these women in our study having normal menstrual cycle length and BMI less than 30 tables 3 and 4. Studies show that up to 70% of patients in this category have polycystic ovarian syndrome.[9, 14] Other conditions that may be implicated in WHO type 2 anovulation, though less commonly, include congenital adrenal hyperplasia, adrenal tumours and androgen producing ovarian tumors.[9] An assay of the serum androgens such as testosterone, dehydroepiandrostenedione sulphate (DHEAS) and 17-hydroxyl progesterone may assist in determining the underlying cause of anovulation in patients with WHO type 2 anovulation without polycystic ovary disease.

Irradiation, chemotherapy or autoimmune disorders may be responsible for WHO type 3 anovulation. Patients in this class may benefit from ovum donation, as there is exhaustion of ovarian reserve in these patients. In our study about 12% of the infertile population had type 3 anovulation and they all had oligomenorrhea and were all none obese as in tables 1,3,4. The importance of these findings is that obesity is not a common feature in types 2 and 3 anovulatory infertility in this environment.

Hyperprolactinaemia was responsible for 21.4% of anovulation in this study. This was higher than the 5% obtained in western Nigeria[13] and lower than the 55% found in southern Nigeria, in an earlier study from this region[12]. In the earlier study, the incidence of hyperprolactinemia obtained was for all infertile patients

regardless of their ovulatory status and notably higher. Some factors known to cause hypeprolactinaemia include sleep abnormalities, post-prandial states, nipple stimulation and chest surgery. Chemotherapeutic agents such asDopamine agonists,in the absence of hypothyroidism, chronic renal failure and drugs which deplete serum dopamine levels or block its receptors, have been effective in treating hyperprolactinemia and inducungovulation in cases of anovulation. Imaging studies are indicated to rule out a pituitary macrodaenoma at very high serum prolactin values of 100ng/ml and above.In this study, patients with hyperprolactinemia (30/140) were all found to have abnormal oligomenorrhea as well, as cycle lengths exceeded 35 days see table 4. Elevated prolactin levels cause hormonal disturbances at the hypothalamus, pituitary and ovary.[6]These disturbances prevent the formation of a secretory endometrium and hence oligomenorrhea.

Majority of patients (73.6%) in this study were found to have body mass index values in the pre-obesity and obesity level.Obesity is a known risk factor for anovulation and polycystic ovary syndrome andit is generally recommended that all obese women regardless of their cycle characteristics should be informed that it is likely that they would take a longer time to achieve conceptionand thatweight loss programs should form a part of the care for infertile obese women who are desirous of pregnancy[15, 16]

V. Conclusion And Recommendations.

Anovulation is a common cause of infertility in our environment and should not be overlooked due to the high prevalence of infertility due to pelvic infections.

Obesity is known determinant of many gynaecologic variables including fertility and it is culturally encouraged in our environment. The high incidence of women with a higher than normal body mass index indicates that studies correlating obesity to gynaecologic outcomes need to receive more attention.

Seeing that majority of women with anovulatory infertility in this study were classified as having type 2 anovulation using the WHO criteria and hyperprolactinaemia, it may serve as a source of encouragement to the women as pharmacological methods may be used to achieve pregnancy.

A prospective study to determine the underlying causes of WHO type 2 anovulation and the success of different treatment regimens for women with anovulatoryinfertilitymay help to improve the management of infertile patients with anovulation

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