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Endocrine assessment of non-obese infertile females in a developing economy

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ABSTRACT

Infertility remains a major cause of marital disharmony in our environment. We conducted a cross sectional study of 408 women being managed for infertility between February 2005 and January 2007 in Enugu, Nigeria. The objective was to determine prevalence and pattern of abnormalities in secretion of some reproductive hormones for possible correlation.

Our results show 27.3% had primary infertility while 72.7% had secondary infertility. Also, 55.1% had abnormal FSH levels while abnormal luteinizing hormone (LH) levels occurred in 49.8%. FSH/LH ratio was also elevated in 73.5% of subjects, 41.9% had Hyperprolactinaemia and 37.8% had low progesterone levels.

These findings suggest a correlation of infertility in our environment with anovulation from polycystic ovarian syndrome, hyperprolactinaemia and defective luteal function. We thus propose routine endocrine evaluation of infertile women in Nigeria despite its cost ineffectiveness.

Key words: Infertility, Hormone profile, anovulation, developing economy.

INTRODUCTION

Infertility remains one of the most pressing gynaecological problems in Nigeria .It has attracted considerable attention because of its impact on reproductive health and the great importance attached to child bearing. The occurrence worldwide has been reported to vary form region to region. This may be attributed to societal awareness, literacy level, and socio-economic status as well as the medical bias of the particular society[1].

Worldwide, infertility occurs in about 1 in every 10 couples[2]. The prevalence is particularly high in sub-Saharan Africa, ranging from 20-40% in some parts of West Africa[2] and between 36.7% and 63.3% in Nigeria[3].

Globally, female factors account for between 30% and 48%, male factors account for between 20% and 30%, both factors account for between 17% and 30%, while the aetiology is unknown in about 10% of cases [4,5].

The aetiology of female factor infertility could be due to ovulatory dysfunction, tubal factors, uterine factors and cervical factors [6,7]. The scope of this study was however, limited to ovulatory (hormonal) dysfunction. Approximately 20% of infertile women have ovulatory dysfunction in the Western countries [8] while it is approximately 25% in most centers in sub-Saharan Africa [5]. The common causes are polycystic ovarian syndrome (PCOS) accounting for 70% of cases. Other causes include, hypogonadotropic

hypogonadism, hyperprolactinaemia and premature ovarian failure (hypergonadotropic hypogonadism) each accounting for approximately 10% of cases [8].Prior to the introduction of hormone assay facilities in our environment, diagnosis of ovulatory dysfunction was made by histological examination of a 21 day endometrial biopsy. Currently this has largely been replaced by assay of reproductive hormones whose cost can hardly be afforded by an average Nigerian.

The serum levels of the reproductive hormones determine the ovulatory functions and thus cyclical changes that occur in the endometrium. This plays a significant role on fertility profile of any woman within the reproductive age group.

This study examined the prevalence of abnormal serum levels of pituitary gonadotropins, prolactin, and progesterone among infertile women in Enugu, South Eastern Nigeria.

METHODS

Patient characteristics

This is a cross sectional study of 408 apparently healthy women being managed for infertility between February 2005 and January 2007.This study had ethical approval from the relevant local authority and oral consent was also obtained from the subjects.The subjects were drawn from Enugu state university Teaching Hospital Enugu, University of Nigeria Teaching Hospital, Enugu and some private hospitals in Enugu and environs. The investigations were done at Amblin laboratories Enugu. Amblin was chosen because the laboratory was one of the first that started hormone assay in South East Nigeria; no doubt many gynaecologists in the region patronize them. They have good quality control with the production of standardized results. Consecutive, consenting infertile female patients referred for hormone assay were interviewed to obtain detailed infertility history. Detailed physical examination was also carried out. Subjects with medical disorders example diabetes mellitus, hypertension, thyroid abnormalities or indeed any chronic debilitating disease were excluded from the study. Also excluded were those with BMI more than 30 kg/m^2. All the women studied were within the age group of 20-40years.They were offered 50% discount on the actual cost of the investigation.

Laboratory methods

Fasting blood samples were taken at the mid follicular phase for FSH, LH, and prolactin levels while the samples for progesterone were taken at the midluteal phase. For all the cases, fasting venous blood was collected from the antecubital vein into sterile plain bottles. Samples were allowed to stand for about 30 minutes to clot and then centrifuged at 3,500 rpm for ten minutes. Serum samples were analyzed within three days of sample collection using the Microwell immunoassay kit, SYNTRON Bioresearch incorporated USA.Samples analyzed immediately were refrigerated at a temperature of 2-8 degrees centigrade.

FSH assay

For precision, the intra-assay coefficient of variation (C.V) was 7.5 % while the inter-assay C.V was 5.6% .The sensitivity was less than 1.95mIU/ml. The non-midcycle reference range used was 3-20 mIU/ml standardized against World Health Organization 2nd international reference preparation (IRP) 94/632(78/549).

LH assay

The intra-assay coefficient of variation (C.V) was 5.5% and while the inter- assay C.V was 6.3%.The sensitivity was 5.5mIU/ml. The non-midcycle reference range used was 5-20 mIU/ml standardized against World Health Organization 1st international reference preparation (IRP) 68/40.

Prolactin assay

The intra-assay coefficient of variation (C.V) was 5.8% while the inter- assay C.V was 7.5%.The sensitivity was less than 3.0ng/ml. The normal reference range used was 6-24ng/ml standardized against World Health Organization 2nd international reference preparation (IRP) 80/562.

Progesterone assay

The intra-assay coefficient of variation (C.V) was 5.7% while the inter- assay C.V was 6.7% .The sensitivity is 0.1ng/ml. The luteal phase reference range used was 2.5-32ng/ml with a cross-reactivity of less than 0.8% with all major steroid hormones.

Data analysis

The data was analyzed by descriptive and inferential statistics using the statistical package SPSS for windows version 13.

RESULTS

The age range of the patients was 20 to 40 years, with a mean age of 27.9 ±4.6years. 27.3% had primary infertility while 72.7% had secondary infertility. 29(7.1%) had only primary school education, 160 (39.3%) had secondary school education and 219 (53.6%) were undergraduates, graduates or postgraduates.

The minimum (min.) parity was 0 while the maximum (max.) parity was 2.

Table 1 shows the FSH levels. The mean low FSH level was 1.6±0.6miu/ml constituting 154(37.7%) of the cases. The mean normal FSH level was 7.3±3.6miu/ml constituting 183(44.9%) of the cases, while the mean high FSH level was 54.8±21.1 miu/ml constituting 71(17.4%) of the cases.

The mean low LH level was 2.0± 0.9 miu/ml constituting 73(17.9%) of the cases, the mean normal LH level was 10.1±4.6 miu/ml constituting 205(50.2%) of the cases, while the mean high LH level was 49.3±22.8miu/ml constituting 130(31.9%) of the cases. This is shown in table 2.

Table 3 shows the LH/FSH ratio. While 108(26.5%) had normal LH/FSH ratio of 1.0, 97(23.7%) had LH/FSH ratio of 1.1-2.9 and 203(49.8%) had values e" 3. Thus,300 (73.5%) had elevated LH/FSH ratio of more than 1.0. Among those that had elevated LH/FSH ratio, 67.7% had a ratio of e"3,while 32.3% had a ratio of <3.

Prolactin evaluation showed, the mean low of 3.7±1.4ng/ml constituting 14(3.4%) of the cases, a mean normal of 15.2± 4.7 ng/ml constituting 223(54.7%) of the cases and a mean high of 59.0±48.9 ng/ml constituting 171(41.9%) of the cases. This is illustrated in table 4.

The progesterone levels show a mean low value of 1.1± 0.7ng/ml which constituted 154(37.8%) of the cases, a mean normal of 16.3±8.0ng/ml constituting 207(50.7%) of the cases and a mean high of 43.7±7.0ng/ml constituting 47(11.5%) of the cases. This is presented in table 5.

Table 1: Mean FSH levels (miu/ml)

Variable	frequency	Mean(miu/ml)	SD	%
Low	154	1.6	0.6	37.7
Normal	183	7.3	3.6	44.9
High	71	54.8	21.1	17.4
Total	408			100.0

Table 2: Mean LH levels (miu/ml)

Variable	frequency	Mean(miu/ml)	SD	%
Low	73	2.0	0.9	17.9
Normal	205	10.1	4.6	50.2
High	130	49.3	22.8	31.9
Total	408			100.0

Table 3: Fsh/lh ratio

Variable	frequency	percentage (%)
≤1.0	108	26.5
1.1-2.9	97	23.7
≥3.0	203	49.8
Total	408	100

Table 4: Prolactin Levels (ng/ml)

Variable	frequency	Mean(ng/ml)	SD	%
Low	14	3.7	1.4	3.4
Normal	223	15.3	4.7	54.7
High	171	59.0	48.9	41.9
Total	408			100.0

Table 5: Progesterone levels (ng/ml)

Variable	frequency	Mean	SD	%
Low	154	1.1	0.7	37.8
Normal	207	16.3	8.0	50.7
High	47	43.2	7.1	11.5
Total	408			100.0

DISCUSSION

In this study, the mean age of the women was 27.9±4.6 years. This was similar to the mean age of 28.3 years recorded in a study done in northern part of Nigeria in 2003 [2].Majority of the patients studied were attending or had attended tertiary level of education. This could mean that level of education is positively related to hospital attendance or it could have been influenced by the urban setting of the study which harbors more educated people. This could also reflect a comfortable socioeconomic status, hence the ability to pay for the investigations. Nevertheless, further research is required on the correlation between level of education and presentation to hospital for infertility evaluation.

The prevalence of abnormal FSH was 55.1% with the majority having lower values than the higher values of normal. This is quite unlike the LH with a prevalence rate of 49.8% with majority of higher values than the lower values of the normal. These prevalence rates were similar to the one recorded by Kuku SF et al in Lagos, Nigeria with a prevalence of 53% for abnormal serum levels of one or more of the gonadotropins [9]. In view of the above findings, an elevated LH/FSH ratio which is a significant predictor of infertility was found in the majority of the women studied. Among those that had elevated LH/FSH ratio, 67.7% had a ratio of ≥3. This is similar to the 70% recorded in the literature [8] and is known to be suggestive of polycystic ovarian syndrome[10,11,12].The diagnosis of PCOS has been agreed in a recent meeting of European Society of Human Reproduction and Embryology /American Society of reproductive medicine based on the following criteria. The presence of two out of the following,(a) oligomenorrhea and/or anovulation,(b) clinical and /or biochemical hyperandrogenism and (c)polycystic ovaries. However, so far as majority of our patients can not afford further laboratory evaluation like assay of other steroid hormones especially androgens, ultrasonography especially transvaginal, we suggest that treatment for PCOS

in our environment can be instituted in the presence one of the above criteria, in association with an elevated single midfollicular phase LH/FSH ratio of ≥3 with or without abnormal weight gain. Unfortunately we did not relate these variables to abnormal LH/FSH ratio. These shortcomings will be addressed in further studies to enable us evaluate the effectiveness of this suggestion. In this study, 17.4% of the patients had elevated FSH level. This is slightly higher than the value of 10% seen in the previous studies but falls within the range of 4-28% as recorded in some other literature [13]. It has been shown that elevated random FSH level in women with amenorrhoea or severe oligomenorrhoea, or an elevated day-3 FSH level in women with regular menses is highly sensitive and specific for identifying women with a depleted ovarian follicular pool [13].It would have been more appropriate if we had compared hormone profile in women with regular and irregular menstruation. Furthermore, the non exclusion of patiets with premature ovarian failure may have contributed to this value.This will be addressed in further studies.

Hyperprolactinaemia accounted for 41.9%. This was similar to the prevalence rate of 49.5% in the work done by Kuku et al [9]. Reports have also shown that the interpretation of prolactin results in infertile women is not as straight forward as it is the case with some other hormones. This has been attributed to the inter-personal variations that occur in the secretion pattern of prolactin among patients and also the occurrence of different molecular forms which have been found to exert characteristic physiological effects. Since the heterogeneous forms are undifferentiated by the immunoassay technique used, it is therefore possible for a patient's prolactin result to indicate a state of hyperprolactinaemia without any obvious physiological and clinical abnormality [15].It would have been ideal to obtain multiple results at different physical and environmental conditions but our patients cannot afford these complexities.

The prevalence rate of 37.8% for low progesterone level suggests anovulation and luteal phase insufficiency compared unfavorably with a similar study done by Kuku et al which recorded a prevalence rate of 17.4% [9] and Imade et al in Jos that recorded a prevalence rate of 19.2%[15]. However, the 25% rate recorded by Idrisa et al [2], Eskandari and cadieux [17] are similar to the one recorded in this study. Studies have also shown that single progesterone level at the mid-luteal phase was as effective as repeated measurement in predicting ovulation with a sensitivity of 80%, specificity of 71% and accuracy of 79% [18]. The high prevalence rate of low progesterone in this study shows that ovulatory dysfunction and hypothalamo-pituitary-ovarian axis dysfunction are significant contributors to infertility in women of South- Eastern Nigeria. This will definitely pose a serious challenge to our practitioners as the field of reproductive endocrinology is yet to be fully developed in our environment.

The majority of the women investigated had normal hormone levels. This underscores significant contribution of other factors in the aetiology of infertility which should as a matter of fact be fully investigated. Primary infertility was shown to constitute about 27.3% of the cases while secondary infertility was 72.7% of the cases. These were similar to the values recorded in Maiduguri, in Northern Nigeria, where prevalence of primary and secondary infertilities among infertile women was 31.7% and 68.3% respectively [2]. This trend was previously elucidated by the work done by Ulla Larsen where he demonstrated the higher prevalence of secondary infertility than primary infertility in the general population of the different countries of Sub-Saharan Africa[19].

Polycystic ovarian syndrome, hyperprolactinaemia, anovulation and defective luteal function are common endocrine disorders. Hormone assay should thus be a significant tool in contemporary management of infertility. However the unaffordability of these investigative tools by most of our subjects will continue to militate against proper evaluation of infertile couples in our environment. Furthermore, the field of reproductive endocrinology is yet to be fully developed in our environment. And until this is done, diagnosis and treatment of ovulatory dysfunction will continue to be suboptimal but should as a matter of fact involve basic modifications to suite our peculiar circumstances.

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