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Research Article

Diagnostic and Epidemiological Role of Early Follicular Phase FSH in Non-Selected Adults in Eastern Nigeria

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Abstract: Request for FSH measurement is one of the routine investigations in the Clinical or Chemical Pathology laboratory. The clinical utility of the test depends on the understanding of requesting clinician, and in most cases for investigation of primary or secondary infertility. However, since the introduction of reproductive Biotechnology otherwise known as assisted reproductive technology, the clinical utility of FSH measurement has undergone important revolutionary changes. Today, the marker is used in diagnosis, prediction of fecundity, ovarian reserve. Though some of these uses have not been properly validated.This research aimed to explore the diagnostic and predictive values of early follicular phase FSH measurement as an epidemiological tool in screening patients with reproductive diseases including polycystic ovarian syndrome in low resources or low in-come countries, In this study,involved 54 subjects, data showed that 4% had FSH suggestive of POF which is a clear indication of hypergonadotropic hypogonadism. In addition FSH was found to be directly associated with age, this is important in family planning program. Furthermore, for the first time, data showed that length of menstrual flow may be associated with either increased or decreased level of follicular phase FSH. In conclusion, this study shows that, in Eastern Nigeria, 4% of females at early reproductive age who are below the usually age at which POF may be suspected, may be diagnosed of POF. This shows that the signs of hypergonadotrophism are more likely to be seen in studied population at younger age than expected elsewhere. This is important for both scientists and clinicians working at this studied area.
Keywords: Reproductive failures, infertility, premature ovarian failure, folliculogenesis and ovulation.

INTRODUCTION

Approximately 75% of women with PCOS have menstrual irregularities suggestive of anovulation [1], this includes oligomemorrhea and amenorrhea 12]. In an exhaustive literature review found that about half of women with PCOS present with amenorrhea, about 30% with functional bleeding and 12% with cyclic menses. No particular pattern of menstrual bleeding typifies women with PCOS. Although a history of oligomenorrhea is probably most common. Women with PCOS may ovulate spontaneously on occasionally [3].

The ovaries, where a woman's eggs are produced have tinny fluid field sacs called follicles or cysts as the eggs grow, the follicle build up fluid. When the egg matures, the follicle breaks opens, the egg is released and the egg travel through the fallopian tube to the uterus for fertilization, this is called ovulation. In woman with PCOS the ovary doesn't make all the hormones it needs for an egg to fully mature. The follicle may start to grow and build up fluid but ovulation does not occur instead some follicle may remain as cysts for these reasons, ovulation does not occur and the hormone progesterone is not made without ovulation [2].

The measurement of FSH in the circulation is employed in the diagnosis of disorders of reproduction and development. In general the primary use of FSH measurements is for assessment of gonadal function through classical endocrine feedback pathways, an elevated level of FSH indicates reduced gonadal function or gonadal failure, whereas a normal serum concentration of FSH suggests normal gonadal function.

Ovarian reserve or the total number of remaining oocytes within the ovary, declines with ovarian age but this does not always equate with the age of the woman. A baseline measurement of serum FSH concentration, usually on day 3 of the menstrual cycle, is a fairly good predictor of ovarian reserve in women of reproductive years [4]. A fluctuating base line FSH level is indicative of Compromised ovarian function. The picture is further enhanced if measurement of FSH is combined with serum estradiol and inhibition [5]. In an irregular menstrual cycle it can be difficult to time collection of samples correctly, and therefore more ample may have to be taken, often in combination with an ultrasound scan of the ovaries to help determine the stage in the cycle [6]. Measurement of FSH is also helpful in determining the presence of common disorder of reproduction such as polycystic ovary syndrome [7].

Currently, a number of criteria have been proposed for diagnosis of conditions commonly associated with FSH abnormalities. Importantly focus of the role on FSH in predictive, diagnostics and monitoring of patients undergoing a number of treatment protocols especially since the surge on application of reproductive technologies including management of infertility, Assisted Reproductive Technology, has received more attentions in the literature. In fact, FSH values are currently used in determining ovarian reserves, the success of assisted fertility procedures for a woman at certain reproductive age and the onset of menopause among other uses. Here we evaluate the diagnostic role of FSH measurement in relation to days and length of menstrual flow in arriving at informed counseling for women from low resource economies. We hypothesize that early follicular phase FSH can provide vital information useful for management of women with reproductive conditions.

MATERIAL AND METHODS

Study Subjects

A cohort of 54 randomly selected subjects who consented to participate in the project were enrolled after signing an informed consent form of Ebonyi state University ethical committee. Questionnaires were administered to the subjects, based on the medical and physical sate of the participants; the subjects were either disqualified or were regarded as eligible to be involved in the project. Clearly, those who were on medication, or have been recently hospitalized, or under investigation for unknown ailments were not allowed participating in the project. In addition, only adult females of reproductive age were deemed fit to participate in the project. Women aged 47 and above were also not recruited into the project. The subjects were initially screened for infectious diseases

Sample collection, preparation and storage

Approximately four millititers of blood was collected from the anticubital vein on the (1^{st}-3^{rd}) day of the menstrual cycle. This was done to access the early follicular phase of the cycle. The blood was allowed to clot for 2hours at room temperature. The sera were obtained after centrifugation at 4000rpm for 10minutes. The sera were kept frozen at -20^0c until analyzed.

Immuno-Enzymometric assay

The essential reagents required for an immune-enzymometric assay include high affinity and specificity antibodies (enzyme are immobilized), with different and distinct epitome recognition, in excess and native antigen. In this procedure, the immobilization takes place during the assay at the surface of a microplate well through the interaction of streptavidin coated on the well and exogenously added biotinylated monoclonal anti-FSH antibody. Upon mixing monoclonal biotinylaetd antibody, the enzyme labeled antibody and a serum containing the native antigen and the antibodies without competition or steric hindrance to form a soluble sandwich complex.

Simultaneously, the complex is deposited to the well through the high affinity reaction of strepatividin and biotinylated antibody. After equilibrium is attained, the antibody bound fraction is separated from the unbound antigen by decantation or aspiration. The enzyme activity in the antibody bound fraction is directly proportional to the native antigen concentration. By utilizing several different serum references of known antigen values, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

Procedure

The reagents, serum, references and control were brought to room temperature (25^0). Then the microplate wells were formatted for calibrator, control and specimen to be assayed in duplicate, 50ul of appropriate calibrator were pipetted for references, control serum, and specimen with new disposable tips into assigned wells. The microplate were gently swirled for 20-30 seconds to mix and covered with a protective film. It was incubated for 60 minutes at room temperature, and then the content of microplate was decanted and washed five times with 350µl of working washing solution into each well and tapped firmly against the absorbance paper until completely dried. 100 µl of TMB working substrate were pipetted into each well and incubated for 15 minutes. 50 µl of stopping reagent were pipetted into each well and gently mixed for 15-20 seconds. The absorbance of each well was read at 450nm in a micro plate reader within 30 minutes after addition of the stopping reagent.

RESULTS AND DISCUSSION

Follicle stimulating hormone (FSH) is one of the biochemical indexes for reproductive failure due to ovarian failure. It is significant when the level in serum is high beyond the normal references limit depending on the particular days of menstrual cycle and age of the subject. This study was purely carried to ascertain the FSH level of each individual on the day 1-3 of their menstrual cycle to determine their folliculogenic statue. Early studies showed that high level of the hormone may be associated with impaired the folliculogenesis that may possibly result in impairment of ovulation during menstrual cycle (An ovulation). Data showed that out of 54 subjects that participated in the research exercise 4% had abnormal level of FSH, classed as hypergonadotrophic-hypogonadism an indication of early ovarian failure. 43 subjects (83.34%) had normal level of hormone. The ranges that fell within the normal level have their mean FSH concentration as 2.18, 4.48 and 7.54 while the range that had abnormal hormonal level, had the mean concentration of 10.30 and 12.85 which is beyond the references limit. This finding is in line with [8] which shows that high FSH level indicates poor response by the ovaries.

Table 1 describes the age distribution of the studied population. Data showed that only 33.3 percent of the subjects are of age > 25 years, up to 48 % of the subjects are within 23-25 years old. This is important to note because people within this age limit are usually suspected to have premature ovarian failure [POF]. The remaining subjects who constitute 18% in the study population are within 18-22 years old. The importance of this observation is that ovarian aging or hypergonadotrophic hypogonadism is commonly seen in aging women. Clearly, the study population comprised the low-risk population.

Table 1: Showing association of age and percentage level at early follicular stage

Sl. No.	Age	Percentage
1	18-20	7.40%
2	21-22	11.11%
3	23-25	48.16%
4	>25	33.33%

Table 2 stratified the mean value of FSH measurement into 5 groups. In this study, values ranging from 12.1 -15.0 IU were regarded as indication of POF or suggests hypogonadism, and the level of FSH 0-3 IU was also regarded as abnormally low value and suggests hypo- pituitaries. Then values ranging from 3-11 IU were considered normal. Data from table 3 demonstrates that 14% of the studied population had values suggestive of hypopituitarism, whereas 81% (37.06% + 31.5% + 13 %) of the studied population had FSH indicating normal early follicular phase response from the hypothalamus and the pituitary. This was what one would expect at this stage of menstrual cycle. It clearly shows that about 81% of women aged 18 and >25 years, < 35 years in Eastern Nigeria may have normal FSH level at early follicular phase stage of their menstrual cycle. However, approximately 4% of the studied population may have early follicular phase FSH indicative of premature ovarian failure (POF) or other associated disease.

Table 2: Showing the mean and the median (±) of standard deviation (SD) of FSH level in the normal population of Ebonyi state who are within reproductive age. The population is grouped into 5 according to their FSH ranges.

Range	0-3	3.1-6.0	6.1-9.0	9.1-12.0	12.1-150
Mean	2.18±4. 29	4.48±4. 29	7.54±4. 29	10.30±4. 29	12.85±4. 29
Median	2.45±4. 29	4.60±4. 29	7.30±4. 29	10.40±4. 29	12.85±4. 29

Table 3: showing percentage number of participants with different ranges of FSH

Sl. No.	FSH(u/l)	Percentage
1	0-3	14.8%
2	3.1-6.0	37.06%
3	6.1-9.0	31.48%
4	9.1-12.0	12.96%
5	12.1-15.0	3.70%

Table 4: Showing length of menstrual flow and percentage level of early follicular stage (FSH) This table shows strong evidence that greater percentage of the studied population had 3-5 days as the length of blood flow.

Sl. No.	Days	Percentage
1	<3	5.56%
2	3-5	70.37%
3	>5	24.07%

The current study investigates the use of early follicular phase FSH measurement as epidemiologic tool in screening women of reproductive age for diseases associated with premature ovarian failure. Here we have shown that in Eastern Nigeria, that 81% of the population may have normal FSH level at early follicular phase stage. From the studied population, data showed that 4% of the studied subjects had POF, or had FSH values indicative of early onset premature ovarian failure. This is important especially for public health intervention and policy development.

In the distribution of the days of menstrual flow those that had menstrual flow within (3-5) days has the highest percentage of (70.37%). This study agrees with the study presented by [9] which demonstrates that abnormality of the hypothalamic-pituitary ovarian axis was implicated in both POF and PCOS, due to disturbances in the plasticity of gonadotrophin releasing hormone (GnRH) and result in the relative increase in FSH release. This study has (4%) of the study population who have elevated level of FSH suggestive of ovarian failure. This study agrees with the study of Mckeinna [10]. That study suggested that abnormal FSH level was due to abnormal feedback mechanism by ovarian estrogen [10].

CONCLUSION

From this study, our data demonstrates that 4% of female at early reproductive age who are below the usual age at which POF may be suspected, may be at

risk or diagnosed of POF. This shows that the signs of hypergonadotrophism are more likely to be seen in those at younger age than expected elsewhere; hence further works may be required to further explore the cause of the observation in this study.

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