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Evaluating the Age Variations in Follicle-Stimulating Hormone (FSH) Levels among Menopausal Women Attending University of Port Harcourt Teaching Hospital (UPTH)

Ben-Chioma Adline E[1], Omah Isaac J[1], Moore-Igwe, Beatrice W[2]

[1]*Department of Clinical Chemistry, Faculty of Medical of Med. Lab. Science, Rivers State University, Port Harcourt, Nigeria.*

[2]*Department of Haematology & Blood Transfusion Science, Faculty of Medical Lab. Science, Rivers State University, Port Harcourt, Nigeria.*

Corresponding Author:** ***Ben-Chioma Adline E*, Department of Clinical Chemistry, Faculty of Medical of Med. Lab. Science, Rivers State University, Port Harcourt, Nigeria.*

Abstract

Menopause is the irreversible cessation of menstruation due to the decline of ovarian follicular function. This study is a cross-sectional study aimed at evaluating the variations in Follicle-Stimulating Hormone (FSH) levels among menopausal women attending University of Port Harcourt Teaching Hospital (UPTH) in relation to different age groups. The study population comprised apparently healthy forty (40) premenopausal and forty (40) menopausal women. The concentration of Follicle stimulating hormone was determined using Enzyme linked immunosorbent assay (ELISA) kit. The data generated from this study was analyzed using SPSS (Statistical Package for Social Science) version 23 and statistical significance was defined as a p-value less than or equal to 0.05 at 95% confidence interval. The mean concentration of FSH in premenopausal women (6.07±5.38 mIU/ml) was significantly lower (p=0.0001) than that of menopausal women (29.16±32.09 mIU/ml). Women within the ages of 40-50 had the lowest concentration of FSH (17.96±25.02 mIU/ml), while the women within the ages of 51-60 had the highest concentration of FSH (63.52±33.91 mIU/ml), and there was a significant difference (p=0.001) between the FSH levels among the different age groups. Given the age-related variations of FSH, regular monitoring of FSH levels in menopausal women may be particularly informative for assessing reproductive health. Also, healthcare professionals should consider age-specific variations when interpreting FSH levels.

Keywords: *Menopause, FSH, Oesstrogen, Menstraution*

1. INTRODUCTION

Follicle-stimulating hormone (FSH) is a hormone produced by the anterior pituitary in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus (Stamatiades & Kaiser, 2018). FSH plays a role in sexual development and reproduction in both males and females (Orlowski & Sarao, 2023).

The term “menopause” originates from the Greek words’ “men” (month or monthly cycle) and “pausis” (end, stop), signifying the cessation of monthly cycles. The World Health Organization (WHO) characterizes menopause as the irreversible cessation of menstruation due to the decline of ovarian follicular function.

Menopause typically takes place after 12 months of amenorrhea during late reproductive life, and denotes the nearly complete cessation of ovarian hormone secretion. The average age of menopause has been reported as 54 in Europe, 51.4 in North America, 48.6 in Latin America, 51.1 in Asia and 47.5 in Africa (Muka, 2015). Menopausal transition pertains to the period preceding the final menstrual cycle in a woman's reproductive life and is marked by alterations in bleeding patterns and hormone profiles. These changes are triggered by the depletion of ovarian follicles. Women typically spend four years in the menopausal transition, but the duration varies considerably.

Menopause is a natural biological process that denotes the conclusion of a woman's reproductive years. It marks a significant milestone in a woman's existence, indicating the termination of menstrual cycles and the reduction in hormone production by the ovaries. Menopause is usually observed in women between the ages of 45 and 55, with an average age of onset at 51 years.

Nevertheless, the onset and experience of menopause may vary considerably among individuals.

During the period of menopause, the production of the hormones oestrogen and progesterone is gradually reduced by the ovaries, which are crucial in regulating the menstrual cycle and maintaining reproductive health.

The decline in hormone levels can lead to a range of physical and emotional symptoms, including hot flashes, night sweats, vaginal dryness, mood swings, sleep disturbances, and changes in sexual function.

Additionally, the hormonal changes associated with menopause can have long-term effects on a woman's health, particularly in maintaining bone density and cardiovascular health, which can increase the risk of developing osteoporosis and cardiovascular diseases, respectively.

Although menopause is a natural process of aging, it can still pose challenges for women as they cope with this transition. The physical and emotional symptoms can be disruptive and distressing, affecting different aspects of a woman's life, such as her relationships, work, and overall well-being. It is essential for women to comprehend the changes in their bodies and seek appropriate healthcare to manage the symptoms and reduce the long-term health risks associated with menopause.

Recently, there has been an increasing focus on improving the understanding of menopause and providing effective treatment options and support for women during and after this life stage. Healthcare professionals and researchers are working to develop evidence-based interventions and therapies to alleviate menopausal symptoms and promote women's health. Furthermore, education and awareness campaigns are being conducted to reduce the stigma and promote open discussions about menopause, enabling women to seek the support they require.

1.1. Oestrogen Production

Follicle-stimulating hormone stimulates granulosa cells in the ovarian follicles to synthesize aromatase, which converts androgens produced by the thecal cells to estradiol (Orlowski & Sarao, 2023). FSH acts on the granulosa cells to initiate and regulate various processes, including the synthesis of aromatase. Aromatase is an enzyme produced by granulosa cells that plays a pivotal role in the conversion of androgens into estradiol. Androgens, which are predominantly produced by the thecal cells surrounding the ovarian follicles, serve as precursor molecules. Thecal cells respond to luteinizing hormone (LH) by producing androgens such as testosterone.

The interaction between FSH, granulosa cells, and aromatase is essential for the production of estradiol, a potent estrogen. This estrogen is crucial for the maturation of the ovarian follicles, regulation of the menstrual cycle, and preparation of the endometrium for possible implantation of a fertilized egg. As FSH stimulates granulosa cells, these cells respond by increasing the expression and activity of aromatase. Aromatase then facilitates the conversion of androgens into estradiol within the granulosa cells (Orlowski & Sarao, 2023).

1.2. Follicular Development and the Menstrual Cycle

During the follicular phase of the menstrual cycle, FSH stimulates the maturation of ovarian follicles. As a dominant follicle takes over and secretes estradiol and inhibin, FSH secretion is suppressed (Simoni *et al*., 2020). When the dominant follicle produces enough estradiol to maintain levels of 200 to 300 pg/ml for 48 hours, the hypothalamus responds with a surge of GnRH which stimulates the secretion of gonadotropic hormones instead inhibiting them. FSH peaks at the same time as the LH surge that causes ovulation. FSH then remains low throughout the luteal phase, preventing the development of new follicles (Barbier, 2014).

Functions of Follicle Stimulating Hormone in Males

Follicle Stimulating Hormone, along with testosterone, is necessary for maintaining normal sperm count and function. Studies have shown that FSH deprivation not only lowers sperm count but also affects the quality of the remaining sperm (Krishnan & Muthusami, 2017). FSH affects independently and in concert with testosterone, the proliferation, maturation and function of the supporting Sertoli cells that produce regulatory signals and nutrients for the maintenance of developing germ cells (Santi *et al*., 2020).

1.3. Excretion of Follicle Stimulating Hormone

The half-life of FSH is about 3 to 4 hours (Sembulingam & Sembulingam, 2012). Follicle-stimulating hormone is cleared from the circulation by the kidneys and liver. In premenopausal women there is a rapid clearance of the FSH molecule, thus achieving a shorter half-life, compared with post-menopausal

women in whom the rise in FSH concentration is due to a decrease in clearance as well as to an increased secretion of a more glycosylated form (Simoni *et al*., 2020)

1.4. Regulation of Follicle Stimulating Hormone

Gonadotropin-releasing hormone stimulates FSH release. The hypothalamus produces GnRH, and it is released into the hypophyseal portal circulation to act on G-protein-coupled receptors at gonadotropic cells of the anterior pituitary. Those gonadotropic cells produce FSH and luteinizing hormone (LH) and release them into the peripheral circulation (Orlowski & Sarao, 2023).

Gonadotropin-releasing hormone (GnRH) release occurs in a pulsatile manner, with low pulse frequencies stimulating more FSH production and high pulse frequencies stimulating more LH production (Stamatiades & Kaiser, 2018). Continuous use of GnRH suppresses the release of FSH and LH from the anterior pituitary which inhibits ovulation and estrogen production in women. Clinically, GnRH agonists like leuprolide work via this mechanism.

In women, negative feedback from oestrogen levels inhibits FSH secretion (Shaw *et al.*, 2010). In men, levels of inhibin B, secreted by the Sertoli cells in response to FSH, inhibit FSH secretion via negative feedback (Boepple *et al.*, 2018). Also, the testosterone secreted by the testes in response to LH has the reciprocal effect of inhibiting anterior pituitary secretion of both FSH and LH.

2. STATEMENT OF PROBLEM/JUSTIFICATION OF THE PROBLEM

Despite the well-established role of FSH in the menopausal transition, there is a need to explore how FSH levels fluctuate in correlation with specific age brackets within this demographic. This research seeks to fill this gap in knowledge and provide understanding into the dynamic interaction between age and FSH levels among menopausal women, potentially contributing to improved healthcare strategies and quality of life for this population. This research can provide valuable understanding into the Follicle stimulating hormonal changes that occur during menopause, which can help in understanding the biological and physiological processes associated with aging in women. Additionally, the findings could contribute to improving healthcare and personalized treatments for women in these age groups. By investigating into the complex connection between FSH levels and menopause onset, this research can yield valuable understanding that empower women to navigate this life phase with greater awareness and informed decision-making.

3. MATERIALS & METHODS

3.1. Study Population/Design

The study comprised of randomly recruited forty (40) premenopausal and forty (40) menopausal women aged 40 years and above who were apparently healthy and attended University of Port Harcourt Teaching Hospital for health checks. It is designed to be a cross-sectional study with randomized sampling. The subjects were assigned into two groups using pre-defined criteria. Group1: This group comprised of 40 premenopausal women. Group 2: This group comprised of 40 menopausal women above 40 years

3.2. Study Area

This study was carried out at the University of Port Harcourt Teaching Hospital (UPTH), located on East-West Road, opposite Alakahia Junction, Rivers State. Its GPS coordinates are 4°53′58″N 6°55′43″E. The University of Port Harcourt Teaching Hospital is managed through a three-tier managerial system consisting of the Board of Management, Hospital Management Committee (HMC), and the Departments. Nearly 200,000 patients are seen annually in both outpatient and inpatient settings, with over 3,000 surgical operations performed each year. The average bed occupancy rate in 12 months has risen to above 80%. In addition to providing medical services, the hospital also offers clinical education and training to students, and other healthcare professionals. Over the years, many research activities and results from its organized units have been published in several major national and international medical and scientific journals.

3.3. Criteria for Selection

The 80 subjects that were recruited for this study where screen based on their age and menopausal status.

Inclusion Criteria

- Only those willing to provide at least oral consent were included in the study.
- Only premenopausal and menopausal women were included in this study
- Only premenopausal and menopausal women above 40 years
- Absence of any medical conditions or treatments that could significantly affect FSH levels

Exclusion Criteria

- Individuals who did not consent to the study were excluded.
- Post-menopausal women
- Presence of medical conditions or treatments that could significantly affect FSH levels

3.4. Ethical Approval

Ethical approval was obtained from the Health Research Ethics Committee of the University of Port Harcourt Teaching Hospital.

Blood Sample Collection and Storage

A structured questionnaire was distributed to all participants to collect their information. The laboratory test results for participants were connected to their questionnaire data using a unique identifier. Blood samples were obtained by venipuncture as described by Chesbrough, (2010) drawing 3mL of blood from each participant's cubital vein using sterile disposable syringes. These samples were then placed in plain bottles and left to clot at room temperature for an hour. Thereafter, separated by centrifugation at 3500 rpm for 5 minutes using a TDA4 Tabletop Low-Speed Centrifuge, and the serum was collected into plain bottles. The sera were stored at 4-8˚C until the analysis. Before the assay, frozen samples were thawed and centrifuged to remove all precipitates. The serum samples were analyzed for Follicle Stimulating Hormone using the Diasino FSH assay kit, following the manufacturer's instructions.

3.5. Methods of Assay

Quantitative determination of Follicle Stimulating Hormone in Serum

Method: Enzyme-Linked Immunosorbent Assay

Remove

Sample, Anti-FSH coated microwells and enzyme labeled Anti-FSH are combined. During incubation, FSH present in the sample is allowed to react simultaneously with the two antibodies, resulting in the FSH molecules being sandwiched between the solid phase and enzyme-linked antibodies. After washing, a complex is generated between the solid phase, the FSH within the sample and enzyme-linked antibodies by immunological reactions. Substrate solutions then added and catalyzed by this complex, resulting in a chromogenic reaction. The resulting chromogenic reaction is measured as absorbance. The absorbance is proportional to the amount of FSH in the sample.

3.6. Data Analysis

The data generated from this study was analyzed using SPSS (Statistical Package for Social Science) version 23 and statistical significance was defined as a p-value less than or equal to 0.05 at 95% confidence interval.

4. RESULTS

Eighty (80) apparently health female subjects were recruited for this study. The subjects were divided into 2 groups based on their menopausal status. Group 1 consisted of 40 premenopausal women and Group 2 comprised of 40 menopausal women.

For the premenopausal women, 16 (40%) subjects were within the ages of 21-30 and 24 (60%) subjects were within the age range of 31-40. For menopausal women, 25 (62.5%) subjects were within the age range of 40-50, 8 (20%) subjects were within the age of 51-60, 3 (7.5%) subjects were within the age range of 61-70 and 4 (10%) subjects were within the age range of 71-80.

Table 4.1. *Demographic Characteristics of the Pre-menopausal Population*

Age Range	Number of Participants	Percentage of the Population
21-30	16	40
31-40	24	60

Table 4.2. *Demographic Characteristics of the Menopausal Population*

Age Range	Number of Participants	Percentage of the Population (%)
40-50	25	62.5
51-60	8	20
61-70	3	7.5
71-80	4	10

Table 4.3. *Comparison of the Levels of Follicle Stimulating Hormone in Premenopausal and Menopausal Women*

	Follicle Stimulating Hormone (mIU/ml)
Pre-menopausal women	6.07 ±5.38
Menopausal women (Menopausal women)	29.16±32.09
p-value	0.0001
t-value	-4.49
Inference	Significant

The mean concentration of FSH in premenopausal women (6.07 ±5.38 mIU/ml) was significantly lower (p=0.0001) than that of menopausal women (29.16±32.09 mIU/ml)

4.4. *Comparison of the Levels of Follicle Stimulating Hormone in Different Age Range of Menopausal Women*

Age Range	Follicle Stimulating Hormone (mIU/ml)
41-50	17.96 ± 25.02^{a}
51-60	63.52 ± 33.91^{b}
61-70	46.65 ± 3.75^{c}
71-80	32.2 ± 34.96^{d}
p-value	0.001
F-value	6.6

Values with different superscripts are significantly different ($p<0.05$)

Women within the ages of 40-50 had the lowest concentration of FSH (17.96±25.02 mIU/ml), while the women within the ages of 51-60 had the highest concentration of FSH (63.52±33.91 mIU/ml).

5. DISCUSSION

This study aimed at evaluating the variations in Follicle-Stimulating Hormone (FSH) levels among menopausal subjects attending the University of Port Harcourt Teaching Hospital (UPTH) in relation to different age groups.

According to the results of our study, the mean concentration of FSH in premenopausal women was significantly lower (p=0.0001) than that of menopausal women (29.16 ± 32.09 mIU/ml). Thus, menopausal women have higher levels of FSH than pre-menopausal women. This result is supported by who stated that as women grow older, their ovarian follicles diminish in number. There is a decline in granulosa cells of the ovary, which were the main producers of estradiol and inhibin. With the lack of inhibition from Oestrogen and Inhibin on gonadotropins during menopause, follicle-stimulating hormone (FSH) production increases. Also, Hall (2010) stated that the half-life of FSH disappearance is prolonged in menopausal women. Sembulingam and Sembulingam (2012) stated that Oestrogen and Inhibin inhibit the release of Gonadotropin releasing hormone (GnRH), which in turn causes decreased production of FSH. Low levels of oestrogen seen in menopausal women lead to reduced inhibition of GnRH, which in turn causes increased stimulation of the gonadotrophs to release FSH.

The results of our study also showed that women within the ages of 40-50 had the lowest concentration of while the women within the ages of 51-60 had the highest concentration and there was a significant difference (p=0.001) between the FSH levels among the different age groups. Several studies in younger and older postmenopausal women suggest that there are effects of aging on the hypothalamus and pituitary that are independent of the loss of Oestrogen and Inhibin feedback. Hall (2015) stated that after menopause, there is a 30–40% decrease in FSH between the ages of 50 and 75. He also stated that

these gonadotropin changes are complex effects of aging on GnRH secretion with a 22% decrease in GnRH pulse frequency. Shaw et al. (2010) stated that there are also age-related effects at the pituitary with a 30% decrease in both LH and FSH responses to GnRH in older compared to younger menopausal women. Thus, the marked decline in the levels of FSH from 60-80 years may result from decreased GnRH pulse frequency and decreased responses of the gonadotrophs of the anterior pituitary to GnRH.

6. Conclusion

The study reveals significant variations in Follicle-Stimulating Hormone (FSH) levels among menopausal women attending University of Port Harcourt Teaching Hospital, emphasizing the impact of age on hormonal dynamics. Menopausal women exhibit higher FSH levels compared to premenopausal counterparts which highlights age-related changes in ovarian function. Age-stratified analysis of menopausal women underscores distinct FSH concentration differences, with the highest levels in women aged 51-60 and the lowest in those aged 40-50. This research indicates that aging influences hypothalamic-pituitary function independently of estrogen loss, leading to complex changes in gonadotropin secretion. The observed decline in FSH levels in individuals aged 60-80 may be attributed to reduced GnRH pulse frequency and diminished gonadotroph responses to GnRH. Overall, these findings contribute valuable insights into the nuanced hormonal dynamics of menopause, with implications for future research and clinical considerations in women's health.

7. Recommendations

- Monitoring FSH levels in menopausal women can provide valuable insights into their reproductive health and hormonal balance. Thus, there should be routine monitoring of FSH levels in menopausal women
- Healthcare professionals should consider age-specific variations when interpreting FSH levels in menopausal women.
- Insights from the study and supporting literature suggest that decreased GnRH pulse frequency contributes to the rise in FSH levels during menopause. Researchers should explore interventions targeting GnRH regulation to potentially modulate FSH levels in menopausal women.
- Further studies should investigate the mechanisms underlying age-related effects on the hypothalamus, pituitary, and gonadotropin responses, contributing to a more comprehensive understanding of hormonal changes during menopause.

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