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HOT FLUSHES: ARE BLACK SOUTH AFRICAN WOMEN ANY DIFFERENT?
Lineo Matsela (PhD), Department of Obstetrics & Gynaecology, School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, South Africa P.O. Box 149, Sefako Makgatho Health Sciences University, Pretoria, 0204. A. Towobola (PhD) Department of Internal Medicine, School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, P.O. Box 149, Sefako Makgatho Health Sciences University, Pretoria, 0204, South Africa. Ephraim T. Mokgokong (MD) Department of Obstetrics & Gynaecology, School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, South Africa, P.O. Box 149, Sefako Makgatho Health Sciences University, Pretoria, 0204.

Corresponding author: Professor Lineo Matsela, Department of Obstetrics & Gynaecology School of Medicine, Sefako Makgatho Health Sciences University, Pretoria, South Africa. E-mail: lineomatsela@yahoo.com

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L. Matsela, A. Towobola and E. T. Mokgokong

ABSTRACT

Objectives: **This study evaluated hormonal changes in black South African women at transition to menopause and examined their understanding of "hot flushes" and its remedial medication.**

Methods: **Black South African women stratified by their menstrual history into pre-; peri- and post-menopause were enrolled for the study. A total of 165 women (55 women in each of the three groups), were enrolled for this study. Timed blood samples were taken based on the menstrual history of each of the women and the samples were analysed for follicle stimulating hormone, dehydroepiandrosterone-sulphate and oestradiol. Each woman was interviewed for awareness and knowledge of symptoms of "hot flushes" and its' remedial medication. Data from the study were analysed for variance (ANOVA) and Student t – test. Significant differences in mean values and the strength of the significant difference (*p-value*) in any of the factors determined were carried out using the Duncan Multiple Range test for the mean.**

Results: **Serum FSH, DHEAS and E_2 levels were characteristic of women during transition to menopause. Endocrinopathy was evident among perimenopausal women and became worse in postmenopausal women. The women demonstrated sufficient knowledge about "hot flushes", the use of hormone replacement therapy, yet, only 20% of them had ever sought for remedial measures for "hot flushes".**

Conclusions: **Hormonal changes in black South African women as they transit to menopause are similar to levels reported for this group of women. However, there is a need to fully explore the reluctance of these women to seek remedial medication for hot flushes.**

INTRODUCTION

Ovarian aging is marked by changes in the duration and frequency of menstrual cycles which reflect the hormonal fluctuations that occur with the decline in quality and quantity of the ovarian follicles. The process of declining quality accelerates in women around 35 years of age and continues through a long transition of 2 to 8 years which ends at menopause. This is the point at which bleeding stops, as determined after one year without menstruation [1]. There is increasing evidence that the rates of acute menopausal symptoms, including vasomotor symptoms and sleep disturbances, are higher in the early menopausal transition period when compared to pre-menopausal status [2].

It is important to understand the transition period in ovarian aging, to improve healthcare and optimise treatments for women who experience acute menopausal symptoms or who are at risk of developing chronic diseases such as osteoporosis in the post-menopausal years [2]. Chronological age is always used as a marker of the menopausal transition, but it is a less sensitive indicator of the reproductive aging because of the relatively wide range of 42 – 58 years [3].

The absence of menstrual episodes for 3 to 11 months is an observable indicator of menopausal transition, but clinical symptoms may occur prior to the observed menopausal amenorrhoea [4]. The hormonal levels of Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH) and inhibin have been found to change from the late pre-menopausal stage to the late transition period [5] during which there is a decrease in inhibin and increases in both FSH and LH. The levels of oestradiol (E_2) and LH in the transition period are lower in Afro-Americans when compared with Caucasians, signifying the importance and an evidence that women of African descent are not spared from the physiological changes at menopause [5, 6]. The significance of body mass index (BMI) is that women with a high index have lower levels of inhibin, LH as well as E_2 when compared with their counterparts with normal BMI in the pre-menopausal stage [6]. The explanation, therefore, is that adipose tissue produces oestrone through peripheral conversion, thus resulting in high levels of E_2. Adipose tissue produces other hormones, including leptin and tumour necrosis factor alpha (TNF-A) that can suppress ovarian steroid production in pre-menopausal women [7]. Moreover, the low levels of sex hormone-binding globulin in obese pre-menopausal women [8] result in greater clearance and subsequently lower levels of oestradiol.

There is the possibility that obesity has a negative effect on the granulosa cell function and therefore decreases inhibin-B levels. This explains the negative association between inhibin-B and Body Mass Index (BMI), which becomes less evident as the follicles become depleted with advancing menopausal state [7]. There is an increase in cortisol levels in women in menopausal transition [9] - an increase which reflects a function of the biological milieu. The increasing level of FSH in women in the menopausal transition stimulates ovarian follicles to produce oestrogen, and in response to FSH stimulation, hyper-oestrogenism may occur. Oestrogen seems to regulate human corticotropin-releasing hormone gene expression, resulting in elevated cortisol levels. Cortisol is not only produced by the adrenal glands, but it is also generated in adipose tissue by the conversion of inactive cortisone by 11β-hydroxysteroid type-1, and oestrogen has the capacity to up-regulate 11β-hydroxysteroid dehydrogenase type-1 mRNA expression in pre-adipocytes from women [10].

In the study of hormones approaching transition to menopause, by Dennerstein and Co-workers [11], an age-related decline in DHEAS levels was observed in African-Americans but not in Caucasians. DHEAS serves as a precursor of oestradiol (DHEAS →androstenedione→oestrone →oestradiol). The decline in DHEAS and E2 levels, which is similar to the decline in E2 in African-

Americans, may point to the importance of race in the menopausal transition.

The insensitivity of age as a marker of the menopausal transition has been further questioned by the development of the new definition to identify the early changes of the menopausal transition. It is for this reason that we have seen the rebirth of the stages of reproductive aging workshop (STRAW) - 2001which was subsequently revised in 2011 as [STRAW + 10] [12].

It becomes important from the clinical standpoint to be aware that even a single change in cycle length in late reproductive aged women can herald the onset of menopausal transition and should alert clinicians to begin counselling their patients about possible symptoms and available treatment options. Great strides have been made in the understanding of ovarian aging, and its endocrine and clinical correlates, which are providing a comprehensive understanding of changes that occur during reproductive aging before and after the cessation of monthly menstruation.

The role of anti-Mullerian inhibiting hormone (AMH), Inhibin-B as well as the status of the antral follicle count are currently better understood as the markers of declining fertility and ovarian aging. This provides additional information to the existing knowledge of FSH and oestradiol hormones that reflect ovarian aging [12]

From the work of Santoro [13] menopausal transition has been subdivided into early and late phases. The early menopause transition is characterised by a marked increase in variability of menstrual cycle duration, defined as a persistent difference of 7 days or more in length of consecutive cycle. There is an elevated but variable FSH level during the early follicular phase and a low AMH level and Antral follicle count (AFC) due to a decline in granulosa cells. Further decline in Inhibin-B leads to increase in FSH. These early changes lead falls in luteal phase progesterone levels and variable luteal phase oestradiol which will result in cycle irregularity. The presence of E2 secretion during the luteal phase is regarded as an aberrant and it is referred to as luteal out of phase event and is similar to luteal phase oestrogen excretion found in prolonged ovulatory cycles. The late menopause transition is marked by the occurrence of amenorrhea of 60 days or longer. Menstrual cycles in this stage are characterised by increased variability in cycle length, fluctuations in hormonal levels and increased prevalence of ovulation.

The FSH levels range between those of women in their early reproductive years, particularly in association with high levels of oestradiol, to levels in their menopausal years. Vasomotor symptoms (hot flushes) are likely to occur at this stage and the FSH levels must be interpreted at this stage with great caution. The levels of Inhibin-B are decreasing further, leading to further increase in FSH. The occurrence of aberrant E2 with less frequent high peaks but increase lag time is observed at this stage. Further falls in luteal phase progesterone still persist. Menstrual cycle irregularity in the form of oligomenorrhea is common during this stage of transition. The deteriorating ovarian function manifests clinically with the occurrence of vasomotor symptoms.

The final menopausal stage is also reported to be of two phases: early and late phases. [11] The early postmenopausal phase indicates that FSH continues to increase while oestradiol continues to decrease for approximately two years after the final menstrual period. This is followed by a period of stabilisation for these hormones. Anti-Mullerian hormone as well antral follicle count would have dropped even further indicating the worsening ovarian function [11]. The late postmenopausal phase is characterised by limited changes in reproductive endocrine function but increased processes of somatic aging. Urogenital symptomatology is the key concern for these women.

The study was conducted to establish the endocrinological profile of black South African women of Odi, Soshanguve and

Garankuwa Districts of Pretoria and to assess the level of understanding of these women about vasomotor symptomatology and the need to seek for remedial medication.

METHODOLOGY

For the purpose of this study, three groups of women were identified: 1) Premenopausal women – these were participants with regular menstruation, not using any exogenous hormone. 2) Perimenopausal women – women who were menstruating with episodes of amenorrhea between 3 months and < 12 months. 3) Menopausal women – those who had not menstruated for ≥12 months. Each of the women provided a signed, written informed consent to participate in this study, following ethics approval by the Research & Ethics Committee of Sefako Makgatho Health Sciences University, Pretoria.

On their first visit, premenopausal participants underwent physical examination. They were instructed to return on day 3 – 7 of the follicular phase of their menstrual cycle, at which visit blood samples were taken for hormonal assays. Perimenopausal and postmenopausal women were evaluated, and blood samples were taken during the same visit. Laboratory assays were carried out for the following steroid and peptide hormones: oestrogen (oestradiol), dehydroepiandrosterone-sulphate (DHEA-S) and follicle-stimulating hormone (FSH). The women who had attained surgical menopause were excluded from the study.

Sample population: The women who participated in this study were those who had previously been interviewed about the psychosomatic and demographic characteristics amongst black South African women. The women were divided into three groups, namely premenopausal, perimenopausal and menopausal women. There were 55 women in each of the three groups, making a total of 165 women who were involved in this study. The premenopausal women had their blood samples taken between days 3 to 7 of their menstrual cycles based on their menstrual history. Perimenopausal and postmenopausal women had their blood samples taken on the day of their visits to the hospital.

Hormone assays: For the purpose of this study, 10 ml of blood was taken from each woman and the sample was allowed to clot completely before being centrifuged. After centrifugation, cell-free serum was separated into a storage tube and kept refrigerated at 2 – 8 ^{0}C until it was assayed. All the hormones were assayed using a Beckman Coulter Instrument (Access® immunoassay system), incorporating internal and external quality assurance programme.

Data Management: The statistical analysis was carried out using the Statistical Package for Social Sciences software for windows (SPSS; version 21.0, IBM, USA). The relationship between FSH, oestradiol and DHEAS levels in all the groups were carried out using analysis of variance (ANOVA) and Student t – test. The significant differences in mean values and the strength of the significant difference (*p-value*) in any of the factors determined were carried out using the Duncan Multiple Range test for the mean.

RESULTS

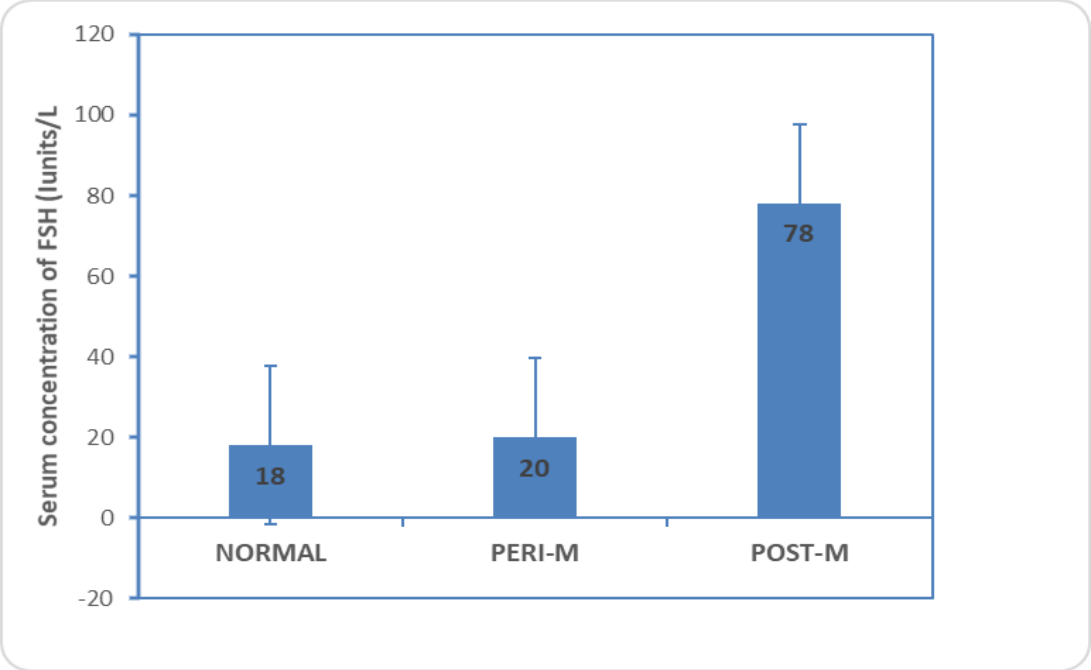
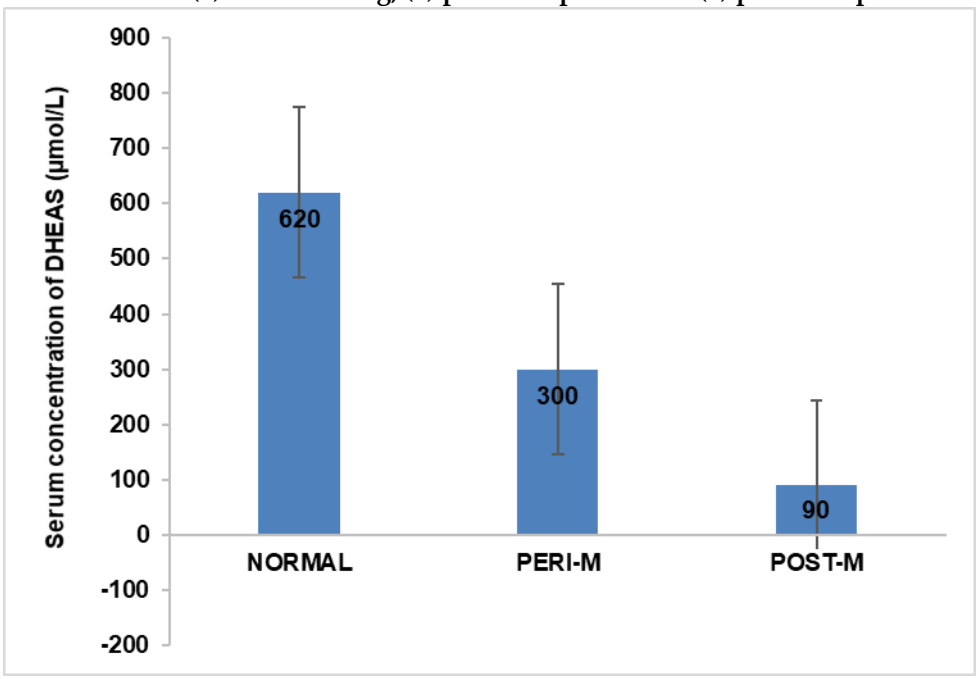


Figure 1: FSH estimation in (1) normal menstruating, (2) perimenopausal and (3) postmenopausal women

FSH: The serum concentration of FSH among normal menstruating women ranged from 5 – 22 mIu/mL (mean = 18 mIu/Ml; ± 2.62). These values became much higher among perimenopausal women with serum concentrations ranging from 7 – 34 mIu/Ml (mean = 20 mIu/Ml; ± 0.66). Among postmenopausal women, FSH assumed the greatest values with serum concentration reaching between 46 and 100 mIu/mL (mean = 78 mIu/Ml; ± 0.69). The increase in the mean value recorded for either post-menopausal and peri menopausal over the pre-menopausal women were statistically significant ($p<0.05$).

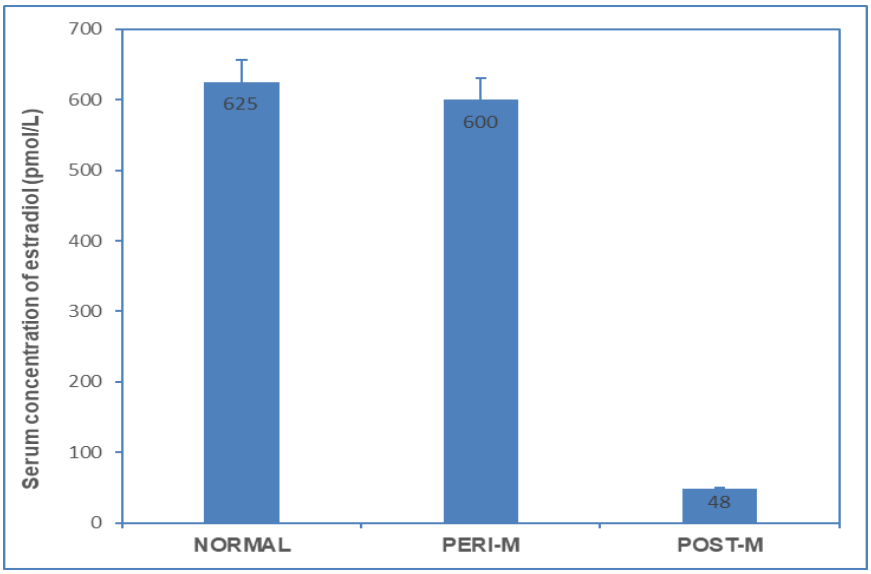
Steroid hormone concentrations: [Figure 2] followed the same pattern of gradual reduction in serum levels as women transited from their normal reproductive period to the perimenopausal and postmenopausal periods. DHEAS concentrations declined from a mean serum level of 620 µmol/L (± 10.3µmol/L) among menstruating women to a mean of 300 µmol/L (± 69 µmol/L) among perimenopausal women and a mean of 90µmol/L (± 65 µmol/L) among postmenopausal women. The results recorded for DHEAS showed that there was a reduction in the value recorded for premenopause over perimenopause and these values were statistically significant using the Student t – test ($p<0.05$).

Figure 2: DHEAS levels in (1) menstruating, (2) perimenopausal and (3) postmenopausal women



OESTRADIOL [Figure 3]: Serum concentrations of oestradiol displayed similar patterns to DHEAS in terms of discrepant values between women who were still menstruating (premenopausal); perimenopausal and postmenopausal women. Among menstruating women, oestradiol serum concentrations ranged between 280 - 1,000 pmol/L (mean = 625 pmol/L; ± 20.0), and it remained fairly stable at 150 - 1,250 pmol/L (mean = 600 pmol/L; ± 8.1) for perimenopausal women. Serum oestradiol concentrations were at their lowest levels among postmenopausal women, with a mean serum concentration of 48.0 (± 7.1). Analysis of oestradiol values using ANOVA showed a significant difference in the declining values obtained for all the three groups of women with a declining pattern from premenopause < perimenopause < postmenopause.

Figure 3: Oestradiol levels in (1) normal menstruating, (2) perimenopausal and (3) postmenopausal women



The social characteristics of the women are illustrated in Table 1, which provides information on age, marital status, educational levels and employment status. Perimenopausal women were aged between 42.5 and 50.8 years with a mean age (± standard deviation) of 44.6 (± 3.6) and postmenopausal women were aged between were aged between 51.5 and 68.4 years with a mean age (± standard deviation) of 63.4 years (± 7.2).

Table 1

Social characteristics of participants in the study (250 perimenopausal and 200 postmenopausal women)

Social characteristics	**Range**		**Mean (± SD)**	
Age (yrs): Perimenopausal women	42.5 - 50.8		44.6 ± (3.6)	
Postmenopausal women	51.5 – 68.4		63.4 ± (7.2)	
Marital status	**Married**	**Divorced**	**Widowed**	**Never married**
Perimenopausal women	74%	21%	28%	5%
Postmenopausal women	62%	36%	37%	2%
Parity:	**Perimenopausal**		**Postmenopausal**	
0	18 (7.2%)		12 (5.8%)	
1 – 2	125 (50.0%)		48 (23.9%)	
3 – 4	71 (28.3%)		65 (32.6%)	
≥ 5	36 (14.5%)		75 (37.7%)	
Educational:	**Percentage**			
No Education	20%		-	
< 12 yrs.	33%		-	
≥ 12 yrs.	47%		-	
Employment:			-	
Employed	78%		-	
Unemployed	22%			

Majority of the women were married (74%; perimenopausal, 62%; postmenopausal) at the time of their interviews. Only 20% of the perimenopausal women interviewed had no formal education and close to 50% of the women had ≥12 years of education. Most of the women (78%) were still gainfully employed at the time of participating in this study.

Table 2

Symptoms of menopause: comparison between peri- & post-menopausal women

Menopausal Symptoms	**Peri-Menopausal women**	**Post-Menopausal women**
Hot Flushes	5%	52.5%
Mood Irritability	15%	43%
Insomnia	10%	48.5%
Decrease in libido	23%	60%
Problem of passing urine	3%	39.5%

Table 2 above shows that a disproportionate percentage of the women experienced mood changes as a result of having attained menopause, with a higher percentage (43%) among the postmenopausal women as against 15% among perimenopausal women. Insomnia (sleep disturbance) was more prevalent among postmenopausal women (48.5%) in comparison with perimenopausal women (10%). Similar pattern of

deterioration in other indices of menopausal symptoms (hot flushes, decrease in libido and problem of passing urine) was reported by postmenopausal women.

In Table 3, all the four ethnic groups show high levels of good health as reflected by low rates of fracture as well as a low number of hip and spinal effects. The majority of the women were being treated for hypertension and diabetes. The women in the four groups were aware of the existence of hormone replacement therapy and the possible alleviation of psychosomatic symptoms with the therapy. However, between 77% and 86% of the women had never sought medical help to cope with the symptomatology of peri- and post menopause.

Table 3

Participants' knowledge of the effects of menopause and hormone replacement therapy (HRT)

	Ethnic Groups			
Questions	**Tswana**	**Zulu**	**N. Sotho**	**Tsonga**
Do you experience any pain in your hip or spine? (NO)	84%	86%	79%	87%
Have you ever had a bone fracture? (NO)	97%	98%	99%	96%
Have you ever been treated for hypertension or diabetes? (YES)	78%	82%	86%	79%
Do you know anything about HRT? (YES)	82%	85%	80%	84%
Do you know that HRT can reduce symptoms of menopause? (YES)	78%	76%	81%	80%
Have you ever sought help to cope with the symptoms of menopause? (NO)	81%	84%	77%	86%
Are you afraid of using HRT? (YES)	3%	6%	4%	1%

DISCUSSION

The mean age at onset of menopause among women in this study, using retrospective data, was 51.6 years, which is comparable to that of other local researchers [(14)]. It is equally comparable to the data of other developing countries in Africa, such as Nigeria [(15)] and Ghana [(16)]. The accuracy of calculating the age at menopause is generally affected by differences in methodology, sample sizes, race/ethnicity as well as the accuracy of recall by the participants in the study. The accuracy of the information provided is dependent on the duration since the final episode of menstrual period, the level of motivation and the level of education of the participants in the study. 80% of the participants in this study were literate, hence the reliability of their information. The remaining 20% of the women in the study depended on milestones of important national even.

Menopause is associated with the presence of vasomotor symptoms. This occurrence is as result of oestrogen deficiency that takes place during the late menopausal transition. There is an increase in the level of follicle stimulating hormone (FSH) as a result of decreasing levels of Inhibin; a peptide that is secreted by the granulosa cells in an ovary. [(11)]

The new markers of ovarian staging namely Inhibin; Anti Mullerian hormone as well as Antral follicle count have assisted to improve our knowledge of menopausal transition as

the decrease of their levels reflect the loss of the follicular activity hence the existence of vasomotor symptoms [17].

The incidence of hot flushes in the present study was 52.5 %, which is comparable to the mid-life health study [18] which had a 56.9% incidence of hot flushes. In the study of Women's Health Across the Nation, the incidence of hot flushes among the African-American women was 45.6%, compared to 31.2% of Caucasian Americans, and only 20.5% of Chinese Americans [18].

In spite of the high incidence of hot flushes amongst the black South African women, the need to seek medical assistance is lacking. This peculiar behaviour is observed in other populations, such as among the Malaysian women, who also lacked the tendency in seeking treatment for menopausal treatment [19].

The table on knowledge of osteoporosis and hormone replacement indicates that majority of the women in this study have adequate knowledge about the use of hormone replacement therapy and its benefits, however, there is great reluctance for these women to seek medical help. A study conducted in Nigeria, shows similar pattern of knowledge and reluctance to seek medical help for vasomotor symptoms [15]. These two studies follow the Women's Health Initiative study, which, while well randomized had a short fall of not initially stratifying the participants and hence succeeded to scare the women from the usage of hormone replacement therapy [15, 19].

The pattern of hormonal changes that are presented in this study reflected the transition from premenopause to menopause and it is indicative of the worsening endocrinopathy. The perimenopausal period which takes 2-8 years, is definitely a window of opportunity. The hormonal changes that in a woman, if attended to at this stage; would prophylactically prevent or reduce the long-term consequences of menopause.

The provision of health education on physiological changes of the transition to menopause cannot be over-emphasised. The majority of black African women need appropriate knowledge about hormone replacement therapy, its alleviation of the climacteric symptoms and long term benefits. The high percentage of women who are aware of hormone therapy and are reluctant to use it is a poor reflection on the health education. There is a need to incorporate in the curricula of both medical and nursing colleges the importance of early screening for menopausal symptoms and the effect of menopausal changes on women's health.

There is no knowledge gap among the participants as is reflected by the high percentage (80%) of the women who are literate. The Women's Health Initiative study [20], a randomised controlled study, initially failed to emphasize the importance of stratification of participants based on their ages hence lack of knowledge and creation of fear among the health providers. The stratification of the participants subsequently led to the knowledge and understanding of the window of opportunity. Menopause hormone therapy has now been found to be beneficial in women less than 60 years of age. This golden rule of window of opportunity has not been widely disseminated to women hence the reluctance to use hormone therapy to alleviate the vasomotor symptoms and consequences of long term oestrogen deficiency.

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