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Research article

COMPARATIVE STUDY OF GONADOTROPIN LEVELS AND CLINICAL PRESENTATION IN SURGICAL AND NATURAL MENOPAUSE

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ABSTRACT

Introduction: Menopause means complete stoppage of menses for last one year due to failure of follicular activities of the ovaries. This can be determined by the various hormones secreted by ovary such as LH and FSH. As these hormones are responsible for normal maintenance of basic ovarian function in reproductive life; there occurs considerable alteration in their levels in menopause. **Aims and Objectives :-** 1] To study and compare ovarian function by determining levels of LH and FSH in Surgical and Natural menopause. 2] To study and compare ovarian function in Surgical and Natural menopause. **Brief Methodology:** - Case study: - 50 women with surgical menopause between 45 – 50 years of age. Control study: - 50 women with natural menopause between 45 – 50 years of age. **Material & Methodology :-** Fasting serum samples of all women with surgical and natural menopause were analysed for LH and FSH on Immulite 1000 chemiluminescence based analyser in special investigation lab. **Summary of the Results :-** Mean levels of LH and FSH were higher in surgical menopausal women as compared to natural menopausal women. Women in surgical menopause suffered from more vasomotor symptoms and cognitive decline as compared to women in natural menopause group

Keywords: Surgical menopause, Natural menopause, LH, FSH, Chemiluminescence

INTRODUCTION

Follicle stimulating hormone (FSH) and Luteinizing Hormone (LH) is secreted by beta cells of the adenohypophysis. FSH controls the ripening of primordial follicles and in conjugation with LH activates secretion of estrogen. FSH is suppressed by estrogen secretion through a negative feedback mechanism.¹ In conjugation with FSH, LH activates secretion of estrogen, brings about the maturation of the ovum and causes ovulation. Following ovulation LH produces luteinization of granulosa and theca cells and initiate progesterone secretion. LH also stimulates the secretion of testosterone and androstenedione in ovarian stroma which

diffuses into follicular fluid and are aromatized into estradiol.¹ Menopause is defined as that point in time when permanent cessation of menstruation occurs following loss of ovarian activity.² It takes 12 months of amenorrhoea to confirm menopause. Sixty million women in India are above the age of 55 years. It is therefore important to address all these menopause related impairment and apply prophylactic measures so that these women can have an enjoyable and healthy life.³ Menopause normally occurs between the ages of 45 and 55 years; the average being 47 years.³ *Surgical menopause* is the cessation of menses resulting

from surgical removal of the uterus, leaving one or both ovaries, or the removal of both ovaries.⁴ Women who have undergone hysterectomy with ovaries preserved will experience menopausal symptoms because of hypoestrogenism caused by depletion of oocytes. Hysterectomy is surgery to remove a woman's uterus. In physiological or natural menopause, the ovaries gradually lose function, secreting less hormones over time. With surgical menopause, the loss of ovarian hormones happens instantly with no adaptation time. The onset of menopausal symptoms is therefore much quicker and symptoms are usually more severe.⁶ Symptoms associated with surgical menopause are often more severe than with natural menopause, particularly the vasomotor symptoms of hot flushes and night sweats.⁶ Hot flushes are the most common symptom of the climacteric and occur in 75% of postmenopausal women in whom it is more common after Hysterectomy.⁷ Hot flushes tend to last longer and be more severe in women who have had a surgically induced menopause.⁸ It is recognized that hot flushes occur with the pulsatile release of LH.⁹ The symptoms are characteristic of a heat dissipation response, and consist of sweating on the face, neck and chest as well as peripheral vasodilation.¹⁰ There is an acute rise in the skin temperature of several degrees centigrade,¹¹ a transient increase in heart rate, fluctuations in the electrocardiographic baseline and a pronounced decrease in skin resistance.¹² Tataryn IV et al¹³ conducted a study on LH, FSH and skin temperature during the menopausal hot flush and found positive correlation of simultaneous skin temperature and circulating LH levels. These data suggest that LH or the factors that trigger its pulsatile release are related to the mechanism responsible for the initiation of hot flushes. Depressed mood is more common after a hysterectomy, as it results in a greater frequency and severity of vasomotor symptoms.¹⁴ It could be a 'domino effect' of vasomotor symptoms, causing sleep disturbance and tiredness, which in turn precipitate depression.¹⁵ Cognitive decline is directly related to hot flushes in women who have undergone hysterectomy, but natural menopause itself does not necessarily result in significant cognitive dysfunction.¹⁶ During a hot flush, blood flow decreases in the hippocampus, possibly impairing

memory and cognition.¹⁶ Such reductions in blood flow may contribute to the decreased mental clarity and short-term verbal memory problems experienced by postmenopausal women.¹⁶ Symptoms of menopause are irritability, mood swings, sudden tears, anxiety, depression, memory lapses, headaches, vaginal tissue atrophy that can lead to more urinary tract or vaginal infections and urinary incontinence, loss of skin tone and osteoporosis. Other symptoms include heart palpitations, insomnia, loss of libido, vaginal dryness and painful intercourse, fatigue, weight changes and difficulty in losing weight, itchy skin and difficulty in concentrating.⁶

Aims & Objectives

1. To study and compare hormonal levels of LH, FSH in Surgical and Natural menopause.
2. To compare the symptoms like hot flushes and cognitive decline in Surgical and Natural menopause.

MATERIAL AND METHODS

Place of study: Special investigation laboratory of Department of Biochemistry, Grant Medical College & Sir JJ group of hospitals. Samples were collected from female patients and staff of the hospital.

Study design: Prospective study. Institutional Ethical Committee clearance was taken.

Study population: Present study includes 50 women (cases) belonging to surgical menopausal group and 50 women (controls) belonging to Natural menopausal group.

Ethics: Institutional Ethical Committee approval, Informed consent were taken from all the women included in the study.

Period of study: July 2011 – September 2013.

Inclusion criteria:

1. Women aging between 44 to 50 years who have undergone Total Hysterectomy in past one to two years.
2. Women aging between 44 to 52 years who were experiencing natural menopause since past one to two years.

Exclusion criteria - women with:

1. Hormonal intake in any form e.g.: Drugs, Soyaflavons.
2. Endocrine disorder. eg: Hyperpituitarism.
3. Ovarian Tumors.

Blood Sample Collection- 5 ml blood sample was collected by venipuncture in plain tube. All blood

samples were centrifuged at 4500 revolutions per minute for 5 minutes to obtain clear serum. Serum samples are then stored between 2-8⁰C before analyzing on Immulite 1000 chemiluminescence machine.

Biochemical Analysis: All the hormonal parameters (LH, FSH) were measured by Solid Phase Competitive Chemiluminescent Enzyme Immunoassay. The solid phase (bead) is coated with rabbit anti-hormonal polyclonal antibody. The reagent contains alkaline phosphatase conjugated to respective hormone. This hormone-enzyme conjugate competes with respective hormone in patients blood sample for limited antibody binding sites on bead. The excess sample and reagent are removed by centrifugal wash. Finally chemiluminescent substrate is added to the bead and the signal is generated in proportion to the bound enzyme. Fully automated enzyme amplified chemiluminescent immunoassay based Immulite 1000 analyzers was used. Measurement of these blood hormonal parameters was done by using commercial kits from Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA.

Statistical analysis: Numerical variables were reported in terms of mean and standard deviation. An independent (unpaired) sample t-test was used to compare the difference of means for independent quantitative variables following normal distribution. Pearson chi-square test was used to test the significance of qualitative variables like symptoms. Variables showing P-value less than 0.05 were considered to be statistically significant and less than 0.01 as very significant. The SPSS software was used for data analysis.

RESULTS

The present study included 50 women with surgical menopause and 50 women with Natural menopause, thus a total of 100 subjects fulfilling the inclusion criteria were enrolled in this study.

Age at Menopause: In this study the mean age at menopause in the study group was 46.76 years \pm 1.43, while that in the control group was 50.9 \pm 0.83 years. On applying independent (Unpaired) sample t – test, the difference in mean age at menopause between two groups was found significantly different at the 0.01 level of significance.

Table:1. Mean Age statistics of surgical and natural menopausal.

Menopause	N	Mean Age at menopause \pm Standard Deviation (Years)
Surgical	50	46.76 \pm 1.437
Natural	50	50.9 \pm 0.839
Mean Difference= -4.14 Years		

Table 2: Serum mean LH level of surgical and natural menopausal females

Menopause	LH[mIU/ml]	FSH [mIU/ml]
Surgical	37.32 \pm 2.924	104.62 \pm 12.952
Natural	22.96 \pm 4.389	66.4 \pm 9.216
P Value	< 0.001	< 0.001

Note: Reference values in Postmenopausal women LH: 11.3 – 39.8 mIU/ml, FSH 21.7 – 153 mIU/ml

LH: In this study the mean level of Luteinizing hormone in study group was found to be 37.32 \pm 2.92 while that in control group was 22.96 \pm 4.38. On applying independent (Unpaired) sample t – test, the difference between mean LH levels in both the groups was found to be very significant with P value < 0.001.

FSH: In this study the mean level of Follicle stimulating hormone in the study group was 104.62 \pm 12.95 while that in the control group was 66.4 \pm 9.21. On applying independent (Unpaired) sample t – test, the difference in mean FSH level in both the groups was found to be very significant with P value < 0.001. (Independent Sample t test:- t value 17, df-88.49, P value <0.001)

Table 3: Clinical feature of surgical and Natural menopause

	Surgical menopause	Natural menopause
Mood Swings	32 (64%)	20 (40%)
Osteoporosis	35 (70%)	27 (54%)
Hot Flushes	44 (88%)	28 (56%)
Irritability	44 (88%)	28 (56%)
headache	30 (60%)	18 (36%)
Memory lapses	33 (66%)	18 (36%)
anxiety	34 (68%)	20 (40%)
depression	30 (60%)	20 (40%)
Sudden tears	31 (62%)	15 (30%)
Vaginal tissue atrophy	35 (70%)	16 (32%)

Hot flushes: In the present study 88% of the women in surgical menopausal group had hot flushes as compared to only 56% of women in natural menopausal group. On applying Pearson Chi-square test, the frequency of hot flushes in surgical menopause was significantly higher than that in natural menopause with $P < 0.001$.

Mood Swings : In the present study 64% of the women in surgical menopausal group had mood swings as compared to only 40% of women in natural menopausal group. On applying Pearson Chi-square test, the frequency of mood swings in surgical menopause was significantly higher than that in natural menopause with $P < 0.05$. Women with hot flushes are more likely to experience disturbed sleep, depressive symptoms and significant reductions in quality of life. Women in surgical menopause suffer more from hot flushes thus are more affected by mood swings. LH and FSH levels were found to be significantly increased in surgical menopause as compared to natural menopause. Women belonging to surgical menopause group suffer more from hot flushes and mood swings as compared to women in the natural menopause group.

DISCUSSION

In the present study the mean age of the surgical menopausal group was significantly lesser than that of the natural menopausal group; which was well supported by another study done by Ozdemir S et al.¹⁷ Ovarian function was indeed depressed in the natural menopausal women but was still preserved for 1 to 2 years after menopause.¹⁸

In the present study, serum LH and FSH levels in the group of women within 2 years after surgical menopause were significantly higher than those in the group of natural menopausal women at a comparable period after menopause. Similar finding were suggested by Nobuaki Furuhashi et al¹⁸ who reported significantly increased levels of LH and FSH within 2 years after surgical menopause as compared to their levels in natural menopause. Similarly Edward.E et al¹⁹ also found a significant increase in LH and FSH levels in surgical menopause. Carina C.W. Chan et al²⁰ found that women with hysterectomy had significantly elevated serum FSH level and lower stromal blood flow indices as compared to healthy natural menopausal women. S.Muttukrishna et al²¹ reported

that ovarian inhibin A & B were cleared from circulation within short period of surgical menopause which was responsible for early rise of FSH in surgical menopause.

The ovaries are the predominant source of Inhibin A and B²² which are characterized for their inhibitory effect on pituitary follicle-stimulating hormone (FSH) secretion²³, by a negative feedback regulation^{24,25}. It has been speculated that after surgical menopause and the fall in inhibins ; estradiol and progesterone stimulates increase in the synthesis as well as secretion of FSH and LH.²¹ It is well established fact that estradiol demonstrate a direct pituitary site of estrogen negative feedback on LH and FSH responsiveness to GnRH but the effect of estradiol on FSH responsiveness is greater than that on LH and this effect is attenuated with aging and menopause.²⁶ This negative feedback is disrupted in surgical menopause because of abrupt deficiency of estradiol which may also contribute to more increase in levels of LH and FSH when compared with natural menopause.²⁷ In the present study the percentage of surgical menopausal women experiencing hot flushes , mood swings was significantly higher than that of natural menopausal women. Pearce J et al²⁸ and Bachmann GA et al²⁹ reported similar significant difference in hot flushes percentage between two menopausal groups and concluded that hot flushes tends to last longer and be more severe in women who have had a surgically induced menopause. Nachtigall et al³⁰ reported that 100% of surgically menopausal women had vasomotor symptoms, and 90% had severe symptoms which lasted an average of 8.5 years after menopause. Another study done by Tataryn IV et al¹³ found a positive correlation of simultaneous skin temperature and circulating LH levels. So it may suggest that LH or the factors that trigger its pulsatile release relate to the mechanism responsible for the initiation of hot flushes.¹³ Depressed mood is more common after surgical menopause, as it results in a greater frequency and severity of vasomotor symptoms.³¹ So it could be a 'domino effect' of vasomotor symptoms, causing sleep disturbance and tiredness, which in turn precipitate depression.¹⁵

CONCLUSION

LH and FSH levels were found to be significantly increased in surgical menopause as compared to natural menopause. Significant increases in the levels of these hormones are seen in surgical menopause due to sudden decline in the function of ovarian activity. These women suffer more from hot flushes, cognitive decline and mood swings as compared to women in the natural menopause group.

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