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"HORMONAL HARMONY: INVESTIGATING THE RELATIONSHIP BETWEEN SERUM ESTROGEN, PROLACTIN, AND HAEMOGLOBIN LEVELS IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN "

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ABSTRACT:

Background: Menopause is the cessation of menstruation for a year due to reduced ovarian follicular activity. This results in decreased estrogen secretion and affects haemoglobin and prolactin levels. Haemoglobin levels increase due to decreased estrogen-induced erythropoiesis inhibition. Prolactin levels decrease due to estrogen inhibition of hypothalamic Prolactin Inhibitory Factor (PIF). Estrogen deficiency after menopause causes osteoporosis, increased cholesterol levels, and risk of coronary artery disease. The impact of estrogen deficiency on haemoglobin and prolactin levels is not well studied, but it may affect these hormones in postmenopausal women. **Materials and Methods**: The study was conducted on women in Guwahati, aged between 35-44 and 45-75 years, who provided informed consent. Those with tuberculosis, malignancy, diabetes, anaemia, thyroid disorders, renal diseases, rheumatoid arthritis, or on hormone replacement therapy were excluded. Blood samples were collected after fasting for 12 hours and stored for estrogen and prolactin estimation using the Enzyme Linked Fluorescent Assay (ELFA) technique. Haemoglobin was estimated using a digital photo colorimeter. Data analysis was done using Microsoft Excel, with mean, standard deviation, ANOVA, and Pearson's correlation coefficient. **Results:** The study aimed to compare the levels of serum estrogen (17β-estradiol), serum prolactin, and haemoglobin in premenopausal and postmenopausal women in Guwahati. The study population consisted of 100 women, with 50% in the premenopausal group (35-44 years) and 50% in the postmenopausal group (45-75 years). The study found that premenopausal women had higher levels of serum estrogen and serum prolactin, while postmenopausal women had lower levels of both. Haemoglobin levels were higher in postmenopausal women compared to premenopausal women. The study also found a

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

positive correlation between serum estrogen and serum prolactin in both premenopausal and postmenopausal women, but a negative correlation between serum estrogen and haemoglobin in premenopausal women. **Discussion:** Postmenopausal women experience decreased serum estradiol, leading to symptoms like hot flashes and increased risks of heart disease, osteoporosis, and fractures. Elevated haemoglobin levels post-menopause suggest a link between estrogen and erythropoiesis. Lower estrogen levels are associated with decreased prolactin, impacting health and necessitating hormone replacement therapy monitoring. **Conclusion:** This study compares estrogen, prolactin, and haemoglobin levels in premenopausal and postmenopausal Guwahati women, revealing significant changes with menopause. Higher estrogen correlates with lower haemoglobin and higher prolactin, while hormone replacement therapy may correct postmenopausal deficiencies. Follow-up studies are warranted.

Key words: Estrogen, Prolactin, Premenopausal, Post-menopausal, Hormones.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

INTRODUCTION:

Menopause, characterized by a year-long cessation of menstruation, stems from diminished ovarian follicular activity, resulting in reduced estrogen secretion and typical menopausal symptoms. Haemoglobin, an oxygen-binding protein within erythrocytes, undergoes variations with age and sex, notably increasing in women from the fifth decade to age 65, largely influenced by hormonal changes associated with menopause1. Studies, such as one by S. Kotwaney in 2011, have highlighted menstrual blood loss's negative impact on iron stores, raising the risk of iron deficiency anaemia2. Additionally, estrogen fluctuations are known to influence haematopoiesis, with estrogen's decline post-menopause contributing to increased erythropoiesis and subsequently elevated haemoglobin levels.

Prolactin, a single-chain peptide secreted by the anterior pituitary glands acidophilic cells, exhibits pulsatile secretion, reaching peak levels during pregnancy and lactation. Its secretion is closely linked with estrogen levels, with estrogen inhibiting hypothalamic Prolactin Inhibitory Factor (PIF). Studies, like the one conducted by Balint-Peric LA and Prelevic GM, have demonstrated a significant decrease in prolactin levels post-menopause, unaffected by estrogen therapy3. Prolactin plays multifaceted roles beyond lactation, impacting haematopoiesis, blood clotting regulation, and immune function, with prolactin deficiency potentially predisposing individuals to infections.

Estrogens, a class of C-18 steroids, including estradiol, estrone, and estriol, exert diverse physiological effects, with estradiol being the most potent and predominant form. Predominantly synthesized by ovarian follicular cells premenopause, estrogen levels plummet

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

post-menopause, primarily produced in peripheral tissues. Estrogen's decline post-menopause contributes to osteoporosis, cardiovascular risks, cognitive impairments, and altered lipid metabolism4.While estrogen's influence on haemoglobin and prolactin levels remains underexplored, the observed rise in haemoglobin and decline in prolactin post-menopause may correlate with estrogen reduction5.

Examining haemoglobin, prolactin, and estrogen levels in Guwahati women can unveil potential correlations, shedding light on the interplay between these hormones and their implications for women's health post-menopause6. Such insights could guide targeted interventions and therapeutic strategies to mitigate menopause-related complications and enhance women's well-being.

MATERIALS AND METHODS:

The study was carried out on adult women in Guwahati, who were aged between 35-44 years of age. Postmenopausal women with permanent cessation of menstruation for more than one year in the age group of 45-75 years of age. Prior to participation in the study, each patient provided informed written consent. A proforma containing the necessary queries regarding the subject of the present study was given to each subject to fill up. The patients who were suffering from tuberculosis, malignancy, diabetic women, anaemic women, those suffering from thyroid disorders, renal diseases, rheumatoid arthritis were not included. Those patients who were on hormone replacement therapy (HRT) were excluded. Participants who refused to participate were excluded from the study. Additionally, women who had undergone hysterectomy were excluded from the study. The institutional ethical permission was obtained for carrying out the experiment.

Under all aseptic and antiseptic precautions,5 ml of venous blood was collected by venepuncture in the cubital fossa between 8 am and 9 am after at least 12 hours of fasting. 3 ml of this blood was then transferred into a vial and kept for 30-45 minutes and allowed to clot. The serum obtained was collected in a centrifuge tube and centrifuged for five minutes at 3000 rpm. The supernatant serum was then transferred to a sterile vial and used immediately for estimation of serum estrogen (17β – estradiol) and serum prolactin or stored at 2-8^0C for a maximum of five days. The estimation of serum estrogen and serum prolactin was done in MINIVIDAS machine. The 2 ml of blood which remained was immediately transferred to a EDTA vial and haemoglobin estimation was done using a digital photo colorimeter. The other apparatuses were estrogen kit was used was estrogen Kit (17β – estradiol), prolactin kit where

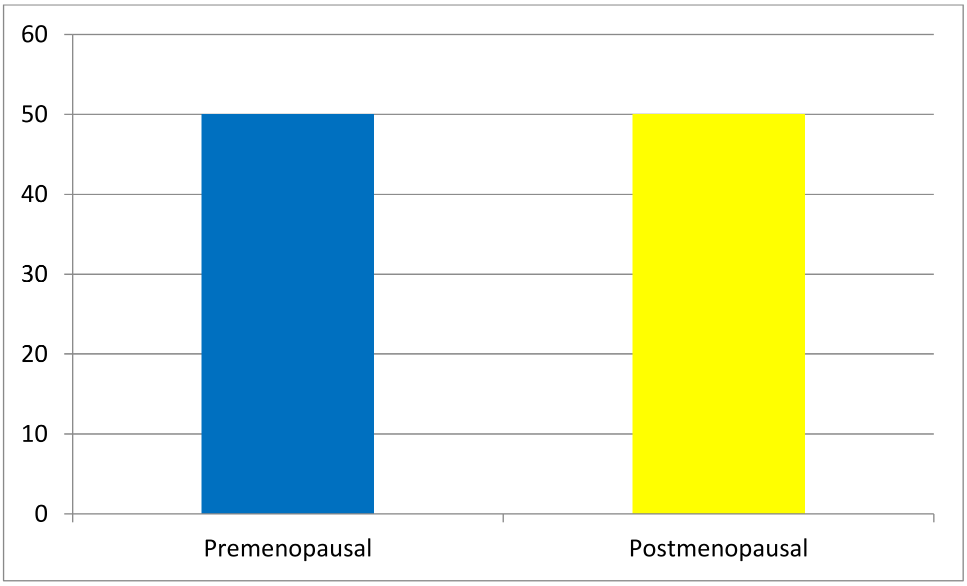
ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

the strip was being stored at 2-8^{0}C. The regents were not freezed, with the exception of calibrators and controls after reconstitution. All unused reagents are stored at 2-8 degree centigrade temperature. The haemoglobin reagent was Hemocor-D (which constituted of ready to use haemoglobin diluting agent). Hemocor – D were stable at room temperature till the expiry date mentioned on the label. Standard solution is stored at 2-8^0 C till expiration. The different apparatuses used were digital photo colorimeter, micropipette, centrifuge machine, mini vidas machine, syringes, test tubes tips, disposable gloves. Serum estrogen (17 β – estradiol) was measured by an automated quantitative test by using the Enzyme Linked Fluorescent Assay (ELFA) technique. The Reference Range of estrogen being premenopausal: 18- 575 pg/ ml and in postmenopausal: <58 pg / ml. Serum prolactin was also measured by an automated quantitative test by minividas machine using the Enzyme Linked Fluorescent Assay (ELFA) technique. The Reference Range of serum prolactin being in premenopausal women: 15-35 ng / ml and in postmenopausal women: 5-15 ng/ ml.

Statistical Analysis: Proper analysis and computation of the data was done by entering the data into the Microsoft excel software. The analysis of the computed data was done using excel and the mean, standard deviation, ANOVA (single arm) was done alongwith determination of Pearson's coefficient of correlation and analysed accordingly.

RESULTS AND OBSERVATIONS

A total of 100 subjects were taken for the study after proper history- taking and clinical examination. The subjects were divided into two broad groups premenopausal women 35-44 years of age, postmenopausal women 45-75 years of age.



ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

Fig1: Bar diagram of study Population

Interpretation: Among the 100 subjects, 50% belonged to the premenopausal and 50% to the postmenopausal group.

Age group in years	No. of subjects
35-39	32
40-44	18
45-49	8
50-54	3
55-59	20
60-64	7
65-69	5
70-75	7

_**Table1: Distribution of subjects according to age groups**

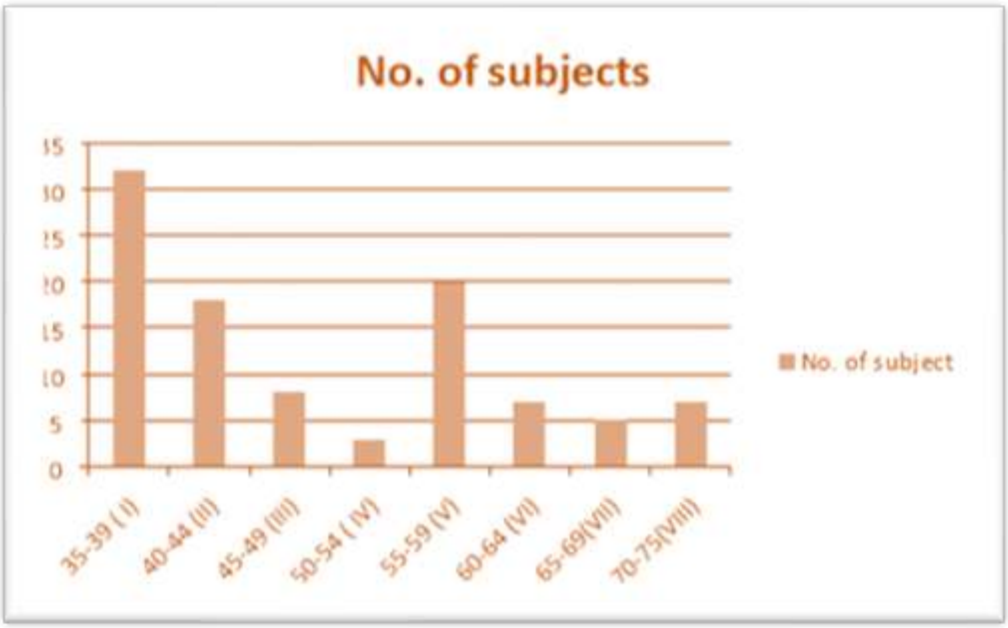


Fig 3: Bar diagram showing distribution of subjects according to age groups

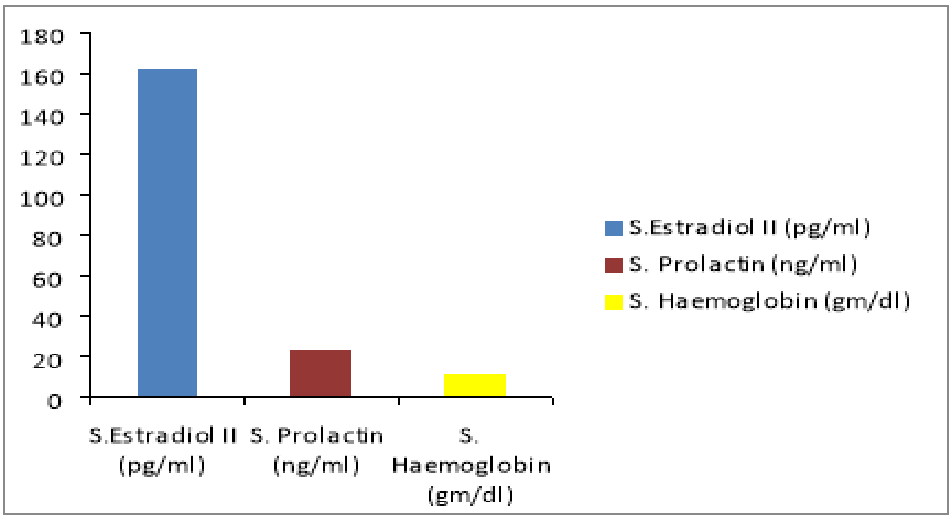
Interpretation: Table1 and the above figure show that the maximum number of premenopausal women were in the 35-39 years' age (64%), while in the postmenopausal group maximum number of subjects belonged to the 55-59 years' age group (40%)

Parameter	**Mean**	**SD**	**Mean± SD**
S. Estradiol II (pg/ ml)	161.94	85.41	161.94 ± 85.41

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

S. Prolactin (ng/ml)	23.35	6.67	23.35+ 6.67
Haemoglobin (gm/dl)	11.51	1.56	11.51+ 1.56

Table 2: Mean distribution of S. Estradiol in Premenopausal group.



<u>Fig 4:</u> Bar diagram showing mean distribution of different parameters in premenopausal age group

<u>Interpretation:</u> From Table 2 we observe that among the 50 premenopausal women, the mean Serum Estradiol was 161.93 pg/ ml with the standard derivation of 85.42 pg/ml, the mean Serum Prolactin was 23.36 ng/ ml with the standard derivation of 6.66ng/ ml and the mean Haemoglobin concentration was 11.52 gm/ dl with the standard derivation of 1.55 gm/dl.

Parameter	**Mean**	**SD**	**Mean + SD**
S. Estradiol (pg/ml)	36.33	18.72	36.33+ 18.72
S. Prolactin (ng /ml)	11.98	4.48	11.98+ 4.48

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

Haemoglobin (gm/dl)	12.13	1.52	12.13± 1.52

_**Table 3: Mean distribution of Serum Estradiol in Postmenopausal group**

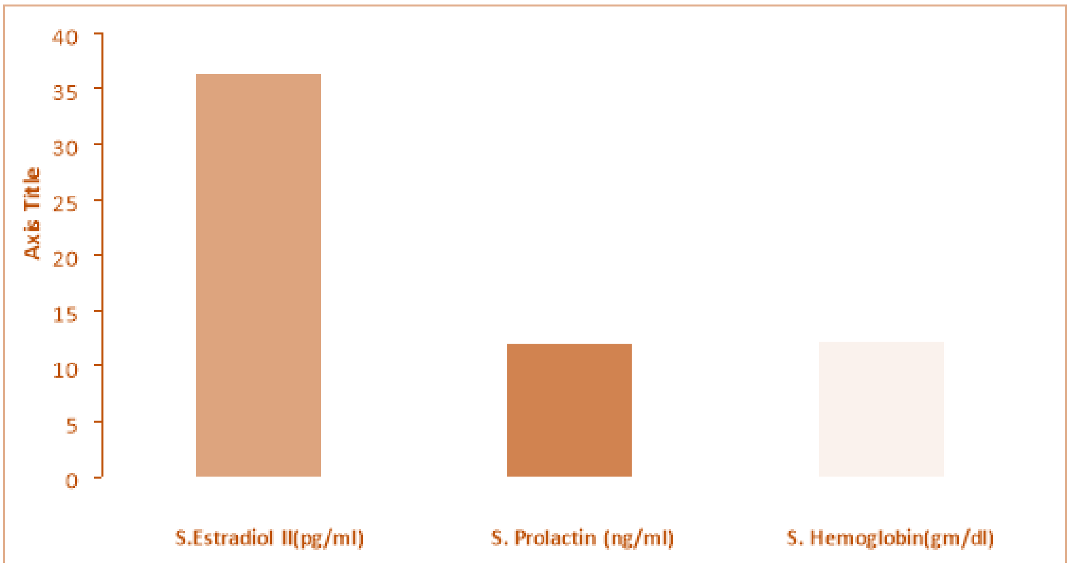


Fig 5: Bar diagram showing mean distribution of different parameters in Postmenopausal group

Interpretation: From Table 3 we can conclude that among the 50 post-menopausal women, the Serum Estradiol was 36.33 pg/ ml with the standard derivation of 18.72 pg/ ml; and the mean Serum Prolactin concentration was 11.98 ng/ml with the standard derivation of 4.48 pg/ml; and the mean Haemoglobin concentration was 12.13 gm/ dl with the standard derivation of 1.52 gm/dl.

To make comparisons of Serum Estradiol, Serum Prolactin and Haemoglobin between premenopausal and postmenopausal women was the chief aim of the present study. For this purpose of comparison, the following tables were constructed and unpaired t- test was applied to test the statistical significance of the variables between the two groups.

Group	Me an	SD	Mean ± SD	DF	T value (One- tail)	P value (One- tail)	Remark
Premenopausal	161.93	85.42	161.93± 85.42	53	1.67	<0.001	Highly Significant
Postmenopausal	36.33	18.72	36.33± 18.72				

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

Table 4: Comparison of Serum Estradiol between Premenopausal and Postmenopausal group

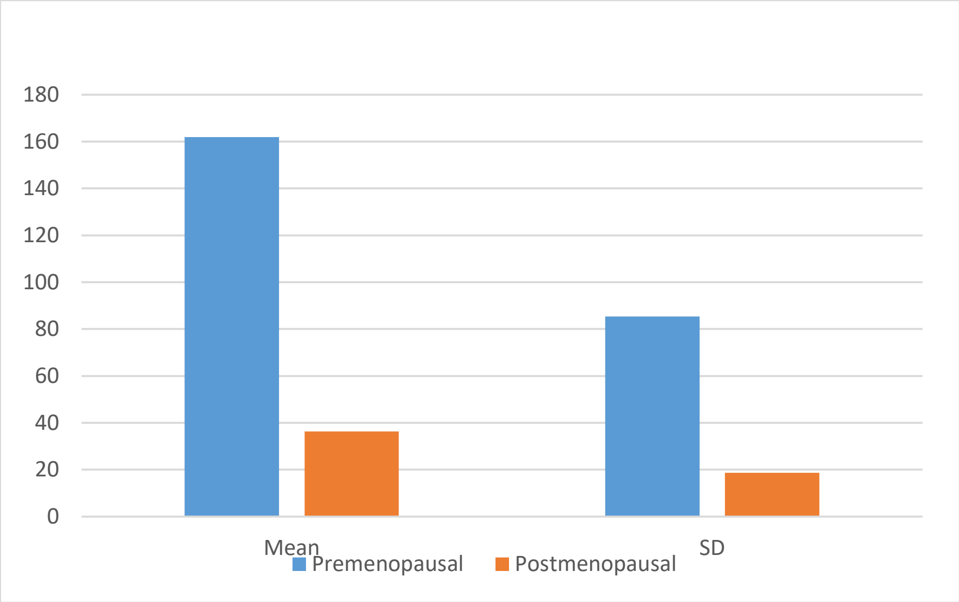


Fig 6: Bar diagram showing comparison of S. Estradiol between premenopausal and postmenopausal group.

Interpretation: From Table 4 it is seen that the mean S. Estradiol in the premenopausal group is much more than in the postmenopausal group. The difference between the two groups is highly significant.

Group	Mean	SD	Mean ± SD	DF	T. value	P-Value	Remark
Premenopausal	23.36	6.66	23.36± 6.66	86	1.66	<0.001	Highly Significant
Postmenopausal	11.98	4.48	11.98± 4.48				

_Table 5: Comparison of Serum Prolactin between premenopausal and postmenopausal group**

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

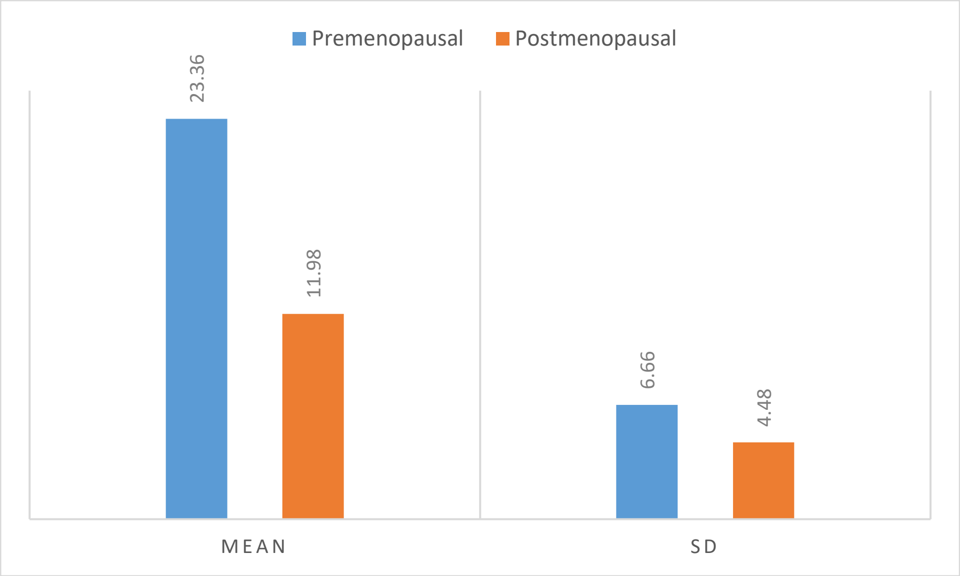


Fig 7: Bar diagram showing comparison of S. Prolactin between premenopausal and postmenopausal group

Interpretation: From Table 5, it is seen that mean S. Prolactin in the premenopausal group is much more than the postmenopausal group. The difference is found to be highly significant.

Group	Mean	SD	Mean± SD	DF	T-Value (One Fail)	P-Value (One fail)	Remark
Premenopausal	11.52	1.55	11.52± 1.55	98	1.66	0.02	Significant
Postmenopausal	12.13	1.52	12.13± 1.52				

Table 6: Comparison of Haemoglobin between premenopausal and postmenopausal group

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

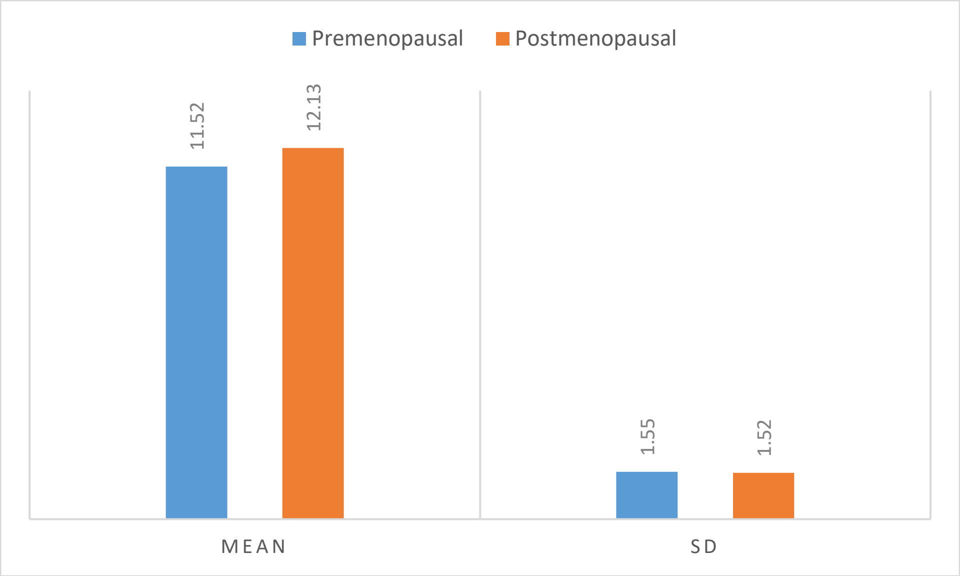


Fig 8: Bar diagram showing comparison of Haemoglobin between premenopausal and postmenopausal group

Interpretation: From Table 6 it is seen that the mean Haemoglobin in the premenopausal group is less than that in the postmenopausal group.

The difference is found to be significant.

CORRELATION BETWEEN S. ESTRADIOL AND THE OTHER PARAMETERS IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN:

To correlate Serum Estradiol with the other parameters namely Serum Prolactin and Haemoglobin in the premenopausal and postmenopausal women, Pearson's Correlation Coefficient (r) has been applied.

The range of the correlation coefficient is $\pm$ I, i.e. $-1 \leq r \leq +1$.

Following table shows the co- efficient of correlation 'r' between Serum Estradiol and all the other parameters.

Parameter	R
Prolactin	0.47
Haemoglobin	-0.44

Table 7: Table showing correlation between Serum Estradiol and other parameters – Serum Prolactin and Haemoglobin in premenopausal women.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

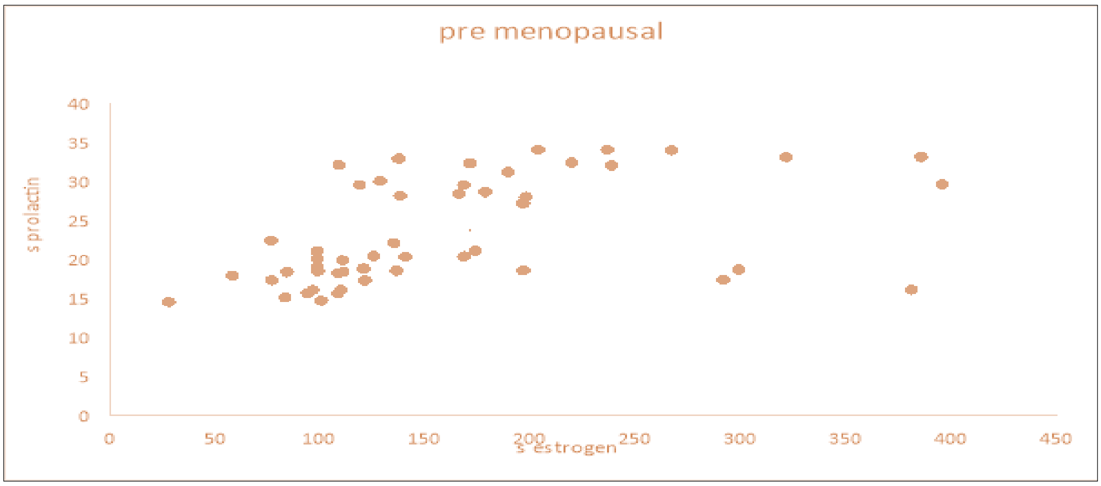


Fig 9: Scatter diagram showing correlation between Serum Estradiol and Serum Prolactin in premenopausal women (n=50)

<u>Interpretation</u>: The calculated value of the correlation coefficient 'r' has been found to be 0.47. The scatter diagram has shown a positive linear correlation between the two variables. Therefore, there is a positive correlation between the two variables Serum Estradiol and Serum Prolactin in premenopausal women.

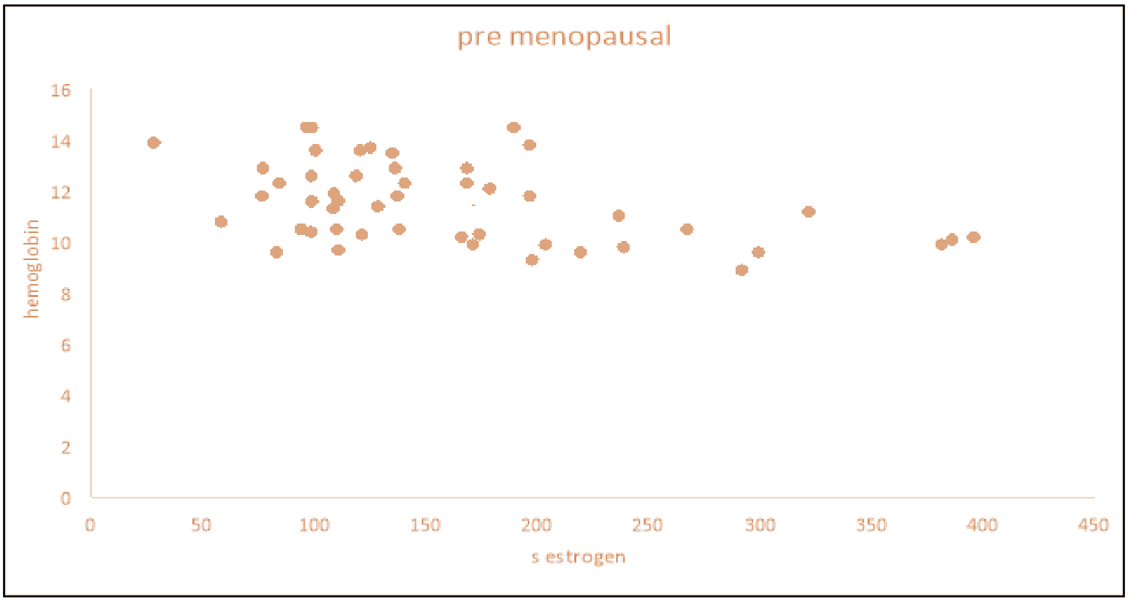


Fig 10: Scatter diagram showing correlation between Serum Estradiol and Haemoglobin in premenopausal women (n=50)

<u>Interpretation</u>: The calculated value of the correlation coefficient 'r' has been found to be -0.44. The scatter diagram has shown a negative relation between the two parameters. Hence, it can be commented that there is a negative correlation between the parameters Serum Estradiol and Haemoglobin in premenopausal women.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

Parameter	"r'
S. Prolactin	0.50
Hemoglobin	0.03

Table 8: Table showing the correlation coefficient 'r' between Serum Estradiol and the other parameters- Serum Prolactin and Haemoglobin in postmenopausal women (n=50).

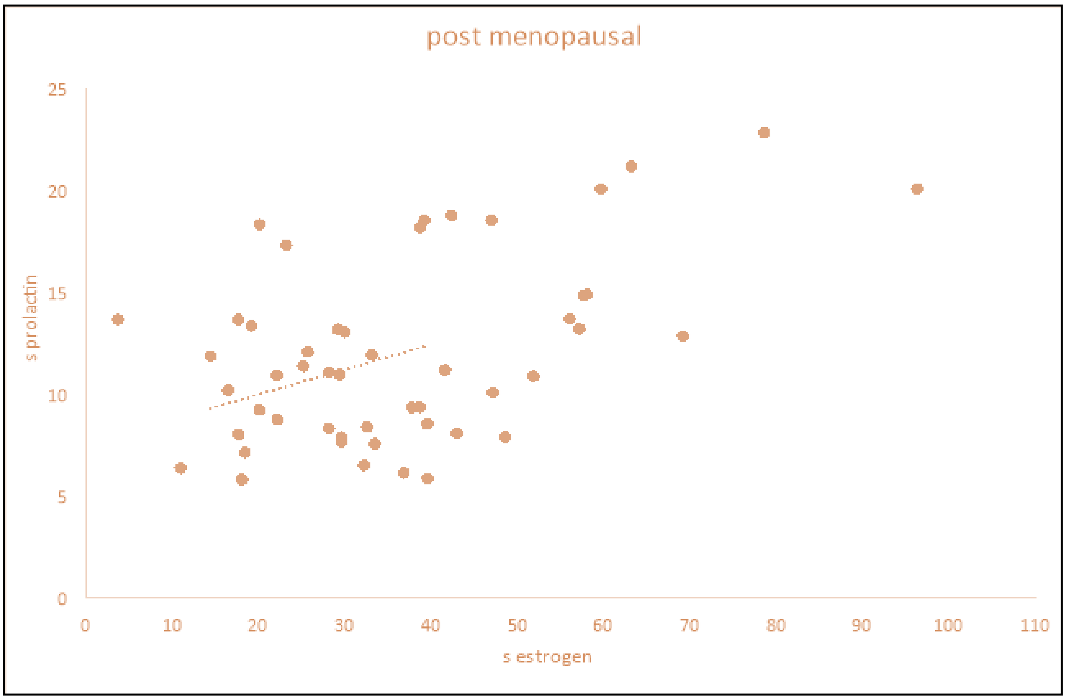


Fig 11: Scatter diagram showing correlation between Serum Estradiol and Serum Prolactin in Postmenopausal women (n=50)

Interpretation: The calculated value of the correlation coefficient 'r' has been found to be 0.50. The scatter diagram has shown a positive relationship between the two variables. Hence it can be commented that there is a positive correlation between the parameter Serum Estradiol and Serum Prolactin in postmenopausal women.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

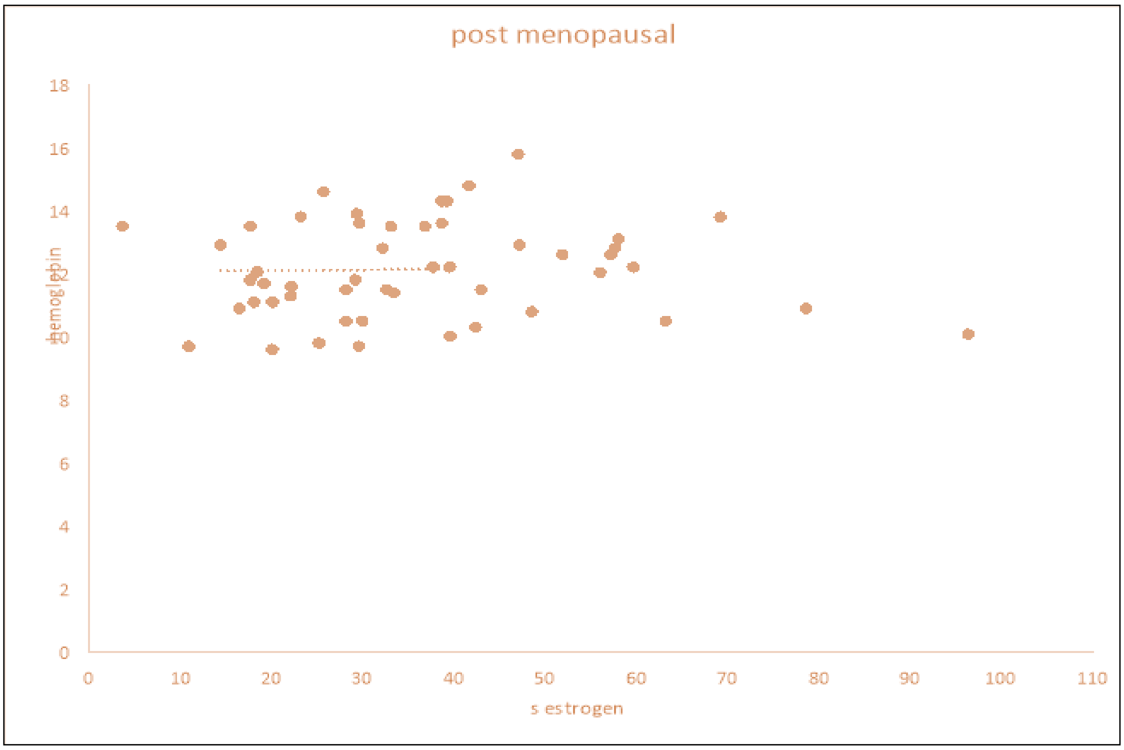


Fig 12: Scatter diagram showing correlation between Serum Estradiol and Haemoglobin in postmenopausal women.

Interpretation: The computed correlation coefficient 'r' was determined to be 0.03.The scatter diagram also shows a negligible or too small relationship between the two variables. Therefore, it can be concluded that there is a negligible correlation between Serum Estradiol and haemoglobin in postmenopausal women.

DISCUSSION

Low serum estradiol levels occur as a result of the cessation of ovarian estradiol secretion during menopause.[73]

A number of symptoms occur with menopause, beginning in the transition period ‘perimenopause’ and continuing 3-5 years postmenopausal. The most prevalent perceivable and physiologically detectable symptoms associated with the onset of menopause include hot flashes and night sweats. Postmenopausal coronary heart diseases rise in women, as also does increased osteoporosis and incidence of fractures. Decreased estrogen also results in genitourinary diseases and deterioration of CNS functions. Postmenopausal hormone replacement therapy is associated with increased incidences of venous thrombosis and breast carcinoma.[74]

The results of the present study indicated that the level of serum estradiol II was significantly less in postmenopausal women. The mean serum estradiol II was 36.33 pg/ml in

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

postmenopausal women. The difference between postmenopausal (36.33 pg/ml) and premenopausal (161.93 pg/ml) mean serum estradiol was statistically highly significant. Similar results have been found in many others studies. [8, 9, 10, 13, 75-79, 93.]

Repeated observations have demonstrated that adult men have higher values than women of red blood cell count, haemoglobin and hematocrit. Recent studies have demonstrated that the total red cell volume in males surpasses that of females. These differences are not solely attributable to iron deficiency, pregnancy, or menstrual blood loss. These statistically significant sexual differences, most pronounced during periods of peak sexual activity, indicate that erythropoiesis and the production of sex hormones are closely intertwined.[80]

In a 2009 study conducted by Vincenzo Rochira et al., the impact of high-dose testosterone and physiological doses of estradiol administration on erythropoiesis was observed. It was seen that while testosterone administration increased haemoglobin, haematocrit and red cell count, administration of estradiol had the opposite effects. [81]Similar results have been seen in many other studies [82-92,103] In our study, it was seen that haemoglobin levels in premenopausal women was less as compared to postmenopausal women. Mean haemoglobin levels in premenopausal women (11.52 gm /dl) were lower than of post-menopausal women (12.13 gm/dl). The difference was statistically significant.

In our study, there is a negative correlation between serum estradiol and haemoglobin in premenopausal women according to the Pearson's correlation coefficient (r), with the 'r' value being -0.44(fig 10). In postmenopausal women, there is a negligible or too small positive correlation between the two variables, with the 'r' value being 0.03 (fig. 12). Estrogen hormone has been implicated in several studies as an inhibitor of erythropoiesis [23,24,32,91,92]. A diminished level of this hormone in menopause is associated with increased haemoglobin levels as stated by Bodies et al in a study in 2003.[94] It is also suggested that estrogen has a possible suppressive effect on erythropoiesis induction.[52] Several studies have found higher haemoglobin values in postmenopausal women.[22,25]

In 2009, Vazquez et al found no significant differences in the haematocrit and haemoglobin between premenopausal and postmenopausal women. [98]

In 2006, Bain indicated that the increase in red cell indices with menopause is usually noticed in women who were at least 10 years postmenopausal.[99]

In our study the mean age at menopause was 47.3 years, and the peak level of haemoglobin was found in the 50-54 years' age group. Haemoglobin levels in our study started decreasing after 60 years of age, which was similar to a study in 2011 by L.N. Achie et al who attributed the cause to nutritional deficiency.[100]

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

This is further corroborated by the higher MCV in women who were more than 10 years postmenopausal, in a study of elderly Nigerians by Olayiwola and Ketiku in 2006.[101]The mechanism of estrogen action in erythropoiesis has been widely studied. Study done in 1966 by Edwin A. Mir and Albert S. Gordon came to the conclusion that estrogen suppresses the production of erythropoiesis-stimulating factor (ESF). It was suggested that estrogen inhibits erythropoiesis by suppressing the production of an extra renal precursor of ESF which requires activation by a kidney mechanism for elaboration of the functional circulating ESF.[24]

In a study in 2014 by Nakada D et al in mice, it was concluded that estrogen increases haematopoietic stem cell self- renewal in females during pregnancy. Estrogen signalling through Estrogen receptor-α promotes the self-renewal of hematopoietic stem cells, leading to an expansion of splenic hematopoietic stem cells and increased erythropoiesis during pregnancy.[102]

In a study conducted by Yokomizo et al. in 2002, it was proposed that ovarian steroids stimulate the production of erythropoietin in human endometrial glandular epithelial cells.[104]

In a study by GA Blobel et al, it was shown that estrogen also reduces the number of erythroid progenitor cells in primary human bone marrow cultures in addition to delaying their maturation. [105]

In humans, prolactin is produced in the anterior pituitary, decidua, myometrium, breast, lymphocytes, leucocytes and prostate[106,107]. A key regulator of prolactin production is estrogen that enhances growth of prolactin – producing cells and stimulates prolactin production directly by acting on lactotropes, as well as by suppressing dopamine.

In a study by Balint Peric LA et al, it was seen that mean prolactin concentrations decrease significantly during the second menopausal year, when compared to the premenopausal or the beginning of menopause. [51] Another study in 2014 by Tikk K et al also concluded that prolactin levels were significantly higher in premenopausal women and among postmenopausal women using hormone therapy compared to nonusers. [71]

In our study also, the level of serum prolactin was significantly less in postmenopausal women as compared to premenopausal women. The mean serum Prolactin was 11.98 ng/ml in postmenopausal women. The difference between postmenopausal (11.98 ng/ml) and premenopausal (23.36 ng/ml) Serum Prolactin was statistically highly significant. Similar results were seen in many others studies [66-69, 72,73,77] In a study by Reyes F1 et al, a significant linear correlation was seen between prolactin and estradiol concentrations in premenopausal and postmenopausal women. [54] Another study by S.S. Yen et al in their study came to the conclusion that prolactin secretion is increased by estrogen in hypogonadal women.[55]

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

Robyn C et al in a study demonstrated the effect of estradiol administration in postmenopausal women aged 52-78 years. Mean prolactin level increased significantly after 10 days of estradiol administration. [72]

In our study also a positive correlation between Serum Prolactin and Serum Estradiol in postmenopausal women was seen according to the Pearson's correlation coefficient (r), with the 'r' value being 0.50 (fig 11). In premenopausal women, there is a positive linear correlation between the two variables, with the 'r' value being 0.47(fig 9). From the above discussions, it can be said that the findings of this study is consistent with many previous studies. Menopause does away with the inhibitory effects of estrogen on erythropoiesis, thus increasing serum haemoglobin. As age advances there is again a fall in haemoglobin levels which needs to be monitored and corrected.

However, low serum estrogen in postmenopausal women results in a number of systemic disorders, notably coronary artery disease and increased incidence of osteoporosis and bone fractures. Hormone replacement therapy in these women while averting such risks, results in decreased haemoglobin levels and may sometimes result in venous thrombosis and breast carcinoma and therefore needs regular monitoring. Rise in prolactin levels in both premenopausal and postmenopausal women leads to increased incidence of breast carcinoma. The long term impact of the above mentioned disturbances and its effect on health has brought in considerable interest on follow-up studies.

CONCLUSION

The current study aimed to analyse and compare serum levels of estrogen, prolactin, and hemoglobin in premenopausal and postmenopausal women from Guwahati, examining changes associated with menopause Another objective of this study was to analyse the independent association of serum estrogen with haemoglobin and serum prolactin in pre and postmenopausal women. The study reveals that there are significant changes in these parameters with menopause. The mean serum estrogen and serum prolactin levels were lower in the postmenopausal group and was statistically highly significant. The mean haemoglobin was lower in the premenopausal group as compared to the postmenopausal group. The difference was statistically significant. The findings confirm that a higher level of serum estrogen in premenopausal women is associated with a decreased haemoglobin level and a high prolactin level, while a fall in serum estrogen in postmenopausal women raises the haemoglobin levels and decreases the serum prolactin levels. However, our study had some limitation, as because we have used cross -sectional analysis to compare premenopausal

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 07, 2024

women with postmenopausal women. Confounding factors such as age, ethnicity, nutritional status, parity, geographical location etc. have to be adjusted for statistical procedures to find out the changes in the variables independent of these factors. The estimation of these simple parameters may help in detection and correction of anemia in premenopausal women, while lower levels estrogen in postmenopausal women leading to osteoporosis, cardiovascular disease etc. can be corrected with hormone replacement therapy. Higher levels of estradiol and prolactin in postmenopausal women may help to identify women at risk of venous thrombosis and breast carcinoma. The long term impact of the above mentioned disturbances and its effect on health has brought a considerable interest on follow-up studies.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest with any person or organisation.

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