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Original Research Article

Association of Inflammatory Markers with Depression in Peri Menopausal Women in a Tertiary Care Center in Northern Karnataka - A Cross-Sectional Study

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Abstract

Introduction: Menopause is well established to be associated with decreasing estrogen level. Declining estrogen levels contributes to inflammation and can explain the onset of mood disorders in women in the peri-menopausal age, particularly depression. This study aims to examine the association between inflammatory markers and depression in perimenopausal women.

M**ethods:** A cross-sectional study of 110 perimenopausal women were conducted, and they were divided into 55 depressed (cases) and 55 non-depressed (control) groups based on the PHQ – 9 questionnaire. Both groups rated their menopausal symptoms using MRS. All 110 women were tested for Total Leucocyte count, N-L Ratio, CRP, IL-6 and Serum Estrogen levels.

Results: No statistically significant association was found between any of the inflammatory markers and the severity of depression amongst both the groups or between Serum estrogen levels and depression.

Conclusion: The negative result could either suggest that such an association does not exist or that the relationship between inflammation and subthreshold, mild and moderate depression is more complex than previously understood and requires a deeper exploration between the interplay of hormones, inflammation, and depression.

Keywords: Depression, Menopausal Women, Inflammatory Markers.

Introduction

Menopause is an essential phase in the physiological life cycle of women, associated with changes in the biochemical factors such as decreasing estrogen level. Menopause is defined as the permanent cessation of menses. [1] Clinically, it is a retrospective diagnosis, determined as the time after 12 months of amenorrhoea. The average at menopause is usually around 51 years. [2] Perimenopause is thought to be the time between the onset of the climacteric and the year after the last menstrual period. [1] The term Menopausal Transition has replaced the terminologies, 'perimenopause' and 'climacteric.' It is now the preferred term to describe the period of physiological changes that occur around the cessation of the menstrual cycle and, therefore, the end of ovarian reproductive function. It is thought to start prior to menopause and ranges from 0 to 10 years, with an average duration of around four years. [1] While the term menopause is widely used in literature, and while the underlying physiology is well explored in research, there is a critical

challenge in the operationalization of the nomenclature. There is substantial variation in the standards of definition of various phases of reproductive aging across publications. WHO and STRAW have delved further into menopause to categorise the different phases of reproductive ageing, to better understand the biochemical and endocrinological aspects of Menopausal transition. [3-6] Better understanding of the menopausal transition and the association of specific symptom with each stage of the process has been possible because of several longitudinal follow up studies that were conducted in the early 2000s. [7-9] The peri-menopause is a systemic inflammatory phase that increases a woman's risk of cerebral ischemia and Alzheimer's disease.10 It is associated with a rise in chronic low-grade inflammation, which accelerates ovarian failure and makes the brain more susceptible to ischemic damage. [11,12]

Estrogen plays a crucial role in Menopause, with declining estrogen levels contributing to increased inflammation and immune disorders. It is also associated with increased inflammatory markers, including higher circulating interleukins (ILs) and tumor necrosis factor (TNF). [11]

Estrogen is known to have a mood-elevating effect, and the decrease in levels can explain the onset of mood disorders in women in the peri-menopausal age, particularly depression. [12] However, menopause-associated depression is still a much-debated topic. While there have been significant advances made to prove the prevalence of depression in perimenopausal women, there is still much that needs to be understood.

Identifying the biological markers that reflect the disease pathology is necessary. Major Depressive Disorder has been hypothesized to be an inflammatory process, showing an increase in inflammatory markers such as CRP, IL-6, D-Dimer, Total WBC count and Neutrophil-Lymphocyte Ratio in depression. [13] Correlating the same in perimenopausal women between the ages of 45 to 60 years can help in early identification and possibly predicting post-menopausal women at higher risk of developing Depression at a later stage in life. The model of reproductive senescence as a systemic inflammatory phase of life is crucial to understanding neurological changes that can occur in menopausal women and to the development of novel therapeutic targets to mitigate morbidities associated with age and reproductive senescence. [14]

This study was hence conducted to study the a such as CRP, IL-6, D-Dimer, Total WBC Count and Neutrophil-Lymphocyte Ratio.

Materials and Methods

Study Subjects and Sample Collection

A cross - sectional study was conducted in the Department of Obstetrics and Gynecology and Department of Psychiatry in BLDE DU's Shri B M Patil Medical College, Hospital and Research Center, Vijayapura, amongst the women attending the OPD Clinic between January 2024 to January 2025. A total of 110 participants were included in the study. Patients were divided into cases (depressed, N=55) and controls (non- depressed, N=55). All women between the ages 40 to 55 years of age, presenting with menopausal symptoms, according to the Menopause Rating Scale were included in the study. The following women were excluded from the study:

1. Patients on HRT,
2. Patients with comorbidities such as a Liver or Kidney dysfunction, and
3. Patients with acute febrile illness or autoimmune disorders.

Methodology

After informed and written consent was obtained from patient, detailed history taking was done. Parameters collected included age, place of residence (urban/rural), presenting complaints, obstetric and menstrual history, and past medical and surgical history.

Menopausal symptoms were rated using the Menopause Rating Scale (MRS). Detailed examination was done including pulse rate, systolic and diastolic blood pressure, weight, height, BMI, cardiovascular and respiratory system, and per abdominal examination. Patients were screened for depression using the PHQ-9 questionnaire and those identified as depressed were categorised based on severity. Blood Sample was drawn for both the control and test group for CRP, IL-6, D-Dimer, Total Leucocyte Count and Neutrophil-Lymphocyte Ratio.

Statistical Analysis: The data obtained was entered in a Microsoft Excel sheet, and statistical analyses are performed using a statistical package for the social sciences (SPSS) (Version 20). Results are presented as Mean, SD, counts and percentages, and diagrams. $p<0.05$ was considered statistically significant.

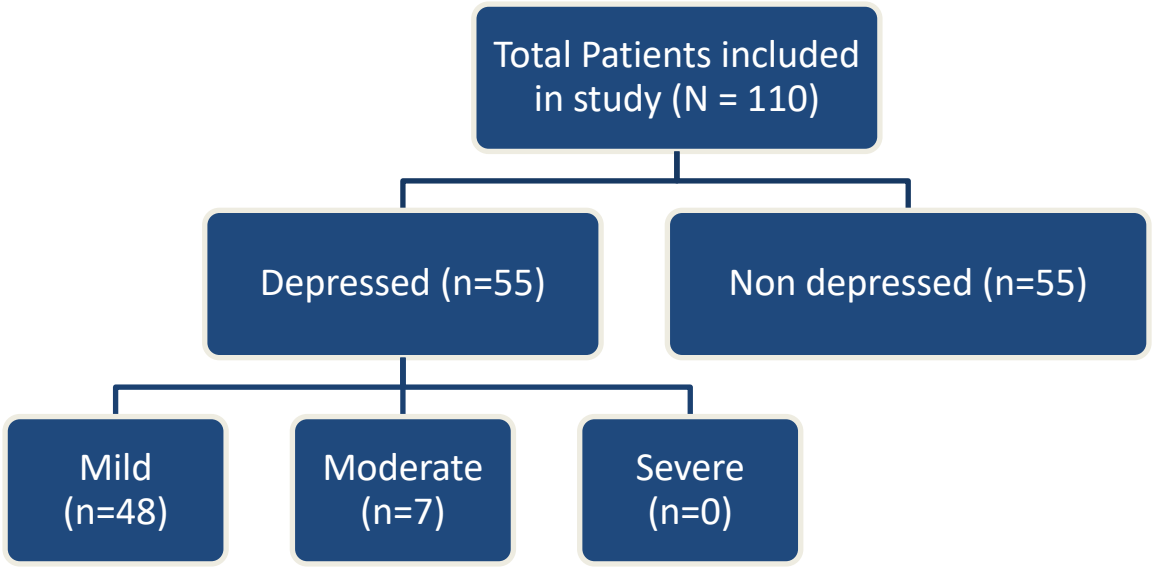

Figure 1: Consort Diagram

Results

In our study, 110 patients were included in the study and were divided into cases (55) and controls (55). Cases were those patients who, according to the PHQ – 9 questionnaire, were classified as depressed and controls were those patients who were not depressed.

The mean age of the cases was 45 years and that of the controls was 42 years. 98 patients (89%) were in the perimenopausal phase while 12 patients (11%) had already attained menopause. Out of these, it was seen that 8 patients (14.5) in the cases were post-menopausal and 4 (7%) of the controls were post-menopausal. 58.2% of patients in the cases group hailed from urban area as compared to 50.9% of the controls. Majority of the patients enrolled in the study were multiparous women (81.8%). 41 patients (74.5%) of cases and 49 patients (89.1%) of controls were multiparous. Only a total of 7 patients (6.4%) in the entire study were nulliparous. There were no clinically significant associations between depression and the obstetric score of the patients. Among the cases (depressed patients), severity of depression was calculated using the PHQ-9 scoring system. 48 (87.2%) out of them were found to be mildly depressed and 7 patients (12.8%) were found to be moderately depressed. No patients were found to be severely depressed. The commonest symptom of menopause reported was vasomotor symptom (98.2%), followed by sleep disturbances (80.1%), physical and mental exhaustion (65.5%), depressive mood (63.6%), irritability (53.7%), and joint and muscular disturbances (32.7%). None of the participants reported bladder problems.

Table 1: Severity of Menopausal Symptoms in cases and controls

Menopausal Symptoms		**Cases**		**Controls**		**P Value**
Symptoms	Scoring	N	%	N	%	
Hot flushes	0	0	0	2	3.6%	0.000
	1	12	21.8%	48	87.3%	
	2	43	78.2%	5	9.1%	
Heart discomfort	0	47	85.5%	55	100%	0.013
	1	4	7.3%	0	0%	
	2	4	7.3%	0	0%	
Sleep disturbances	0	4	7.3%	17	30.9%	0.000
	1	36	65.5%	38	69.1%	
	2	15	27.3%	0	0	
Depressive disorders	0	0	0	40	72.7%	0.000
	1	55	100	15	27.3%	
Irritability	0	2	3.6%	49	89.1%	0.000
	1	45	81.8%	6	10.9%	

	2	8	14.5%	0	0%	
Anxiety	0	15	27.3	51	92.7	0.000
	1	36	65.5	4	7.3	
	2	4	7.3	0	0	
Physical and Mental Exhaustion	0	4	7.3%	34	61.8%	0.000
	1	51	92.7%	21	38.2%	
Sexual Problems	0	43	78.2%	48	87.3%	0.207
	1	12	21.8%	7	12.7%	
Bladder problems	0	51	92.7%	55	100%	0.042
	1	4	7.3%	0	0	
Dryness of vagina	0	17	30.9%	52	94.5%	0.000
	1	38	69.1%	3	5.5%	
Joint and Muscular Discomfort	0	40	72.7%	34	61.8%	0.223
	1	15	27.3%	21	38.2%	

The patients were asked to rate the symptoms of depression based on the PHQ – 9 questionnaire and the severity of each symptom was assessed based on a scoring system from 0 (not at all), 1 (several days), 2 (more than half the days) and 4 (nearly every day).

Table 2: Severity of depression symptoms as per PHQ-9 questionnaire

PHQ – 9 rating		**Cases**		**Controls**		**P Value**
Questions	**Response**	**N**	**%**	**N**	**%**	
Little interest or pleasure in doing things	Not at all	39	70.9%	55	100%	0.000
	Several days	16	29.1%	0	0	
Feeling down depressed or hopeless	Not at all	12	21.8%	47	53.6%%	0.000
	Several days	40	72.7%	8	14.5%	
	More than half the days	3	5.5%	0	0	
Trouble falling or staying asleep, or sleeping too much	Not at all	0	0%	11	20%	0.000
	Several days	18	32.7%	44	80%	
	More than half the days	37	67.3%	0	0	
Feeling tired or having little energy	Not at all	0	0	16	29.1%	0.000
	Several days	14	25.5%	34	61.8%	
	More than half the days	39	70.9%	5	9.1%	
	Nearly every day	2	3.6%	0	0	
Poor appetite or overeating	Not at all	2	3.6%	42	76.4%	0.000
	Several days	15	27.3%	8	14.5%	
	More than half the days	38	69.1%	5	9.1%	
Feeling bad about yourself or that you are a failure or have let yourself or your family down	Not at all	25	45.5%	53	96.4%	0.000
	Several days	27	49.1%	2	3.6%	
	More than half the days	4	5.5%	0	0	
Trouble concentrating on things, such as reading the newspaper or watching television	Not at all	33	60%	55	100%	0.000
	Several days	22	40%	0	0	

The commonest reported symptom was sleeping disturbance (90%), followed by feeling tired (85.4%), poor appetite (60%) and feeling down and hopeless (46.4%). No patients experienced any thoughts of self-harm or thoughts that they would be better off dead, and of moving or speaking slowly or being so fidgety or restless, that was noticed by others. On analysing the association between depression and each of the inflammatory markers (CRP, IL-6, TLC, and N-L Ratio), p value was noted to be more than 0.05 for all the markers and hence, no clinically significant association was found. However, an average increase in IL-6 was noted among the cases as compared to the controls, with mean value in cases being 6.598 pg/mL and controls being 4.802 pg/mL. Similarly, average N-L Ratio was also noted to be 13.98 among the cases, elevated, as compared to 0 4.52 amongst controls. Average Serum Estrogen levels in both groups were noted to be 66.147 pg/mL and 66.944 pg/mL, suggesting a well-matched control and cases group, endocrinologically.

Table 3: Significance of Inflammatory markers and Serum Estrogen levels amongst Cases and Controls

Parameter	Group	N	Mean	Std. Deviation	P-Value
CRP	Depressed	55	5.705	1.4478	0.51
	Non Depressed	55	7.8	7.7446	
IL-6	Depressed	55	6.598	8.9209	0.147
	Non depressed	55	4.802	1.4649	
TLC	Depressed	55	9699.64	2586.748	0.778
	Non Depressed	55	9548.73	2995.905	
N -L Ratio	Depressed	55	13.9865	36.54744	0.058
	Non Depressed	55	4.5220	3.30200	
Serum Estrogen	Depressed	55	66.147	14.7212	0.765
	Non Depressed	55	66.944	13.1155	

Discussion

Our study involved 110 women, divided between cases (55) and controls (55). The mean age of the cases was 45 years, and that of the controls was 42 years. It could be inferred that perimenopausal symptoms were likely to be experienced at an earlier age in women in our study as compared to that conducted by Li Guo et al. (2018) [15], where the mean age of the controls (depressed group) was found to be 50.78 years, and that of the controls (nondepressed) was found to be 49.01 years.

11% of the participants were post-menopausal. Out of these, eight were found to be among the cases. This is in comparison to a systemic review of 14 studies conducted by Georgakis K. et al. (2016) [16], where an inverse relationship was found between the age at menopause and depressive symptoms. A 2% decrease in the risk of depression in post-menopausal women was noted with increasing age at menopause.

58.2% hailed form urban and 50.9% from rural areas with no significant association with the severity of depression. This contrasts with the study conducted by Sharma S. et al. (2015) [17], where the somatic, psychological, and urogenital symptoms were higher in women from rural parts of the country as compared to the urban.

Our study also evaluated the association between the severity of depression in perimenopause and the parity score of the patients and found no clinical significance. A study conducted in Gansu, China, by Sun X. et al. [18] in 2016 (published in 2020) also found no significant association between parity and age at menopause. However, women who were nulliparous and multiparous (3 and ≥ four births) were seen to be at a higher risk for developing moderate and severe menopausal syndrome.

87.2% of the cases reported mild depression, 12.8% moderate and no severer depression was reported. Comparing our study to one conducted in Saudi Arabia in 2024 by Kandasamy G. et al., [19] 13.38% reported no depression; 21.46% reported mild depression; 23.23% reported moderate depression; 32.83% reported moderately severe depression; and 9.09% reported severe depression.

The most frequent symptoms of the 11 composing the MRS (N = 110) in our study were vasomotor symptoms such as hot flushes (98.2%), sleep disturbances (80.1%), physical and mental exhaustion (65.5%), depressive mood (63.6%), and irritability (53.7%). Chedraui P et al. (2007) [20] conducted a study to evaluate the symptoms of menopause using The Menopause Rating Scale. They found that muscle and joint problems were reported the most, with 77% of patients experiencing it, followed by depressive mood (74.6%), sexual problems (69.6%), hot flushes (65.5%) and sleeping disorders (45.6%). However, in another study conducted by Khatoon A. et al. [21] in Pakistan, most women (75%) in the age group 45 to 50 years reported having hot flushes as the commonest symptom, as was in our study. The study conducted by Kandasamy et al. [19] also revealed that the commonest symptoms of menopause experienced were hot flushes, night sweats and sleep issues.

It was also found that while the prevalence of the reported symptoms was high, only mild to moderate symptoms were noted by patients. This is in concordance with literature such as that by Khatoon A et al., [21] where only mild and moderate symptoms were reported, and by Nisar et al., [22] where most women reported mild symptoms.

In our study, sleeping disturbance was the most reported symptom in the PHQ–9 questionnaire; as is noted in several other studies, such as that conducted by Joffe H et al. (2009), [23] where it was found that women with vasomotor symptoms such as hot flushes and night sweats had poorer quality of sleep, shorter total sleep time, longer sleep-onset latency, and lower sleep efficiency.

While comparing the association of inflammatory markers with depression in the perimenopausal age, no significant association was found between any markers, including CRP, IL 6, Total Leukocyte Count and Neutrophil-Lymphocyte Ratio. These

results concord with the study by Bremmer et al., [24] where no significant rise in CRP levels was noted for subthreshold or major depression. However, the same study also concluded that a substantial increase in IL-6 was indicated in patients with major depression, which contrasts with the results of our research. A survey conducted by Cushman et al. [25] concluded that hormone replacement therapy in menopausal women significantly decreased the levels of CRP and other inflammatory markers. However, in contrast, a study conducted by Stork S. et al. (2002) [26] concluded that no effect was on CRP levels after estrogen therapy for 48 weeks.

The main strength of this study was that included patients between the ages of 40 to 60 years, belonging to the premenopausal phase, the menopausal transition, and the postmenopausal groups with both test and control groups matched well with respect to the endocrinological factor (serum Estrogen). The study was also done using standardised measuring tools.

However, a major limitation of study was that the participants of the study only belonged to mild and modrate severity of depression. This could explain the lack of association with inflammatory markers as mild and moderate symptoms are not noted to cause chronic inflammatory state. Another possible limitation of the study is the stigma associated with psychiatric disorders in rural areas of the country and hence, the hesitation of women to be forthcoming with the symptoms of depression or menopause was noted, with possible biased results.

Conclusion

In conclusion, a lack of association was noted between the acute phase reactants or inflammatory markers and depressive mood amongst the perimenopausal age group of women. This negative result could either suggest that such an association does not exist or that the relationship between inflammation and subthreshold, mild and moderate depression is more complex than previously understood and requires a deeper exploration between the interplay of hormones, inflammation, and depression.

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