ASSOCIATION OF INFLAMMATORY MARKERS WITH DEPRESSION IN PERI MENOPAUSAL WOMEN IN A TERTIARY CARE CENTER IN NORTHERN KARNATAKA - A CROSS-SECTIONAL STUDY

Dissertation submitted to

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In partial fulfilment of requirements for

MASTER OF SURGERY

OBSTETRICS AND GYNAECOLOGY

Under the guidance of

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I hereby declare that this dissertation entitled **"ASSOCIATION OF INFLAMMATORY MARKERS WITH DEPRESSION IN PERI MENOPAUSAL WOMEN IN A TERTIARY CARE CENTER IN NORTHERN KARNATAKA - A CROSS SECTIONAL STUDY"** is a genuine research work carried out by me under the support and guidance of DR.(prof.) NEELAMMA PATIL, M.D, DNB, Professor, Department of Obstetrics and Gynaecology, B.L.D.E (Deemed to be University) Shri. B.M. Patil Medical College and Research Centre, Vijayapura.

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ABBREVIATIONS

FMP - Final Menstrual Period

MRS - Menopause Rating Scale

PHQ-9 - Patient Health Questionnaire-9

TLC - Total Leucocyte Count

CRP - C Reactive Protein

IL-6 - Interleukin 6

ABSTRACT

BACKGROUND: Menopause is an essential phase in the physiological life cycle of women, associated with changes in the biochemical factors such as decreasing Estrogen level. 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. [1] 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.[43] 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 possibility of use of Anti-Inflammatory agents as an adjuvant to treatment in mood disorders and Major Depressive Disorder can also be explored, on understanding the etio-pathology of the same in Peri Menopausal Women.

OBJECTIVES OF THE STUDY: To study the association between Inflammatory markers such as CRP, IL-6, D-Dimer, Total WBC Count and Neutrophil-Lymphocyte Ratio and depression in Peri Menopausal and Menopausal Women between 40 to 55 years.

MATERIALS AND METHODS: A cross-sectional study was conducted in BLDE (DU) Department of Obstetrics and Gynaecology and Department of Psychiatry of 110 patients. All patients fitting the inclusion criteria will be included in the study. After obtaining Informed and written consent, the patients were first be screened for depression using the PHQ-9 questionnaire and will be divided into depressed (cases = 55) and non-depressed (controls = 55) patients. Depressed patients will further be categorised based on the severity of depression using PHQ-9 questionnaire. They were asked to rate their menopausal symptoms based on the MRS. Blood Sample were drawn for both the control and test group and sent for CRP, IL-6, D-Dimer, Total Leucocyte Count and Neutrophil-Lymphocyte Ratio.

RESULTS: A total of 110 patients were included into the study. Cases were those patients who, according to the PHQ–9 questionnaire, were classified as depressed and controls were those patients who were not depressed. 87.2% of the cases were found to be mildly depressed and 12.8% were moderately 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%). The least reported symptom was bladder problems. No association was noted between any of the inflammatory markers and depression.

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.

KEYWORDS: Menopause, Depression, Inflammatory Markers, PHQ-9, MRS

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1. INTRODUCTION

Menopause is defined as the permanent cessation of menses. It is an essential phase in the reproductive aging and health of women. The depletion of ovarian follicles with the progression of age results in a reduced ovarian hormone production. Lowering of estrogen and progesterone hormone levels result in menopause.[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]

Climacteric is the term that is used to define the period of falling ovarian function; it is usually associated with irregular menstrual cycles and vasomotor symptoms.[1] This period usually starts around 1 to 2 years prior to the last menstrual period.[2] The term is now used infrequently.

Perimenopause is thought to be the time between the onset of the climacteric and the year after the last menstrual period. Pre-menopause is the entire reproductive span before the onset of menopausal symptoms. Post-menopause is the lifespan after menopause. WHO defines post-menopause as the time from the last

menstrual period, irrespective of whether the menopause was achieved spontaneously or was induced.[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]

Senescence is termed as the phase of life after 60 to 65 years of age.

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. Several agencies have held workshops to address this gap and reach a consensus regarding the terminologies and operational definitions.

WHO (1981 – 1999)

World Health Organisation's "Scientific Group on Research in the Menopause" has defined natural menopause as the loss of ovarian follicular activity resulting in a permanent cessation of menopause.[3-4] The group also deemed that for it to be known as natural menopause, the process should occur after 12 months of amenorrhoea, with no determined physiological or pathological cause for the amenorrhoea. It is diagnosed retrospectively as the menopause occurs 12 months after the final menstrual period (FMP).

Menopause that occurs following either surgical elimination of bilateral ovaries, as in oophorectomy, or due to ablation of ovarian function, such as due to irradiation or chemotherapy, is termed Induced Menopause.

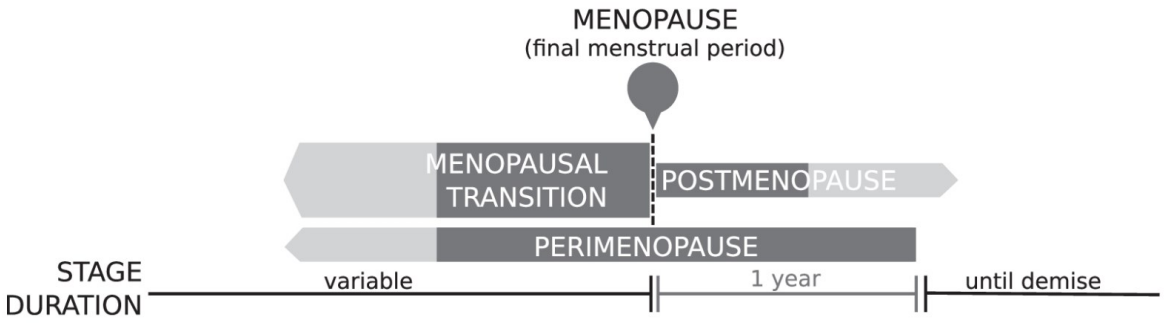

Fig 1 – Time periods of menopause as per WHO's Scientific Group on Research in the Menopause

The term pre-menopause was initially recommended to include the entire period of reproductive age up to the FMP. However, in 1996, WHO concluded that researchers often used the term pre-menopause alternatively only to include the 1 to 2 years before menopause. They also determined that the term perimenopause was being used to define the period immediately before menopause wherein the clinical, biological and endocrinological features of the forthcoming menopause were noticed.

A recommendation was also made to avoid the previously popular term Climacteric. However, due to the wide use of the word, in 1999, The Council of Affiliated Menopause Societies (CAMS) reinstated the term; it now included the phase of perimenopause but also extended to incorporate the period after menopause. The transition in a woman's life from reproductive to non-reproductive phase is hence termed as Climacteric. [5]

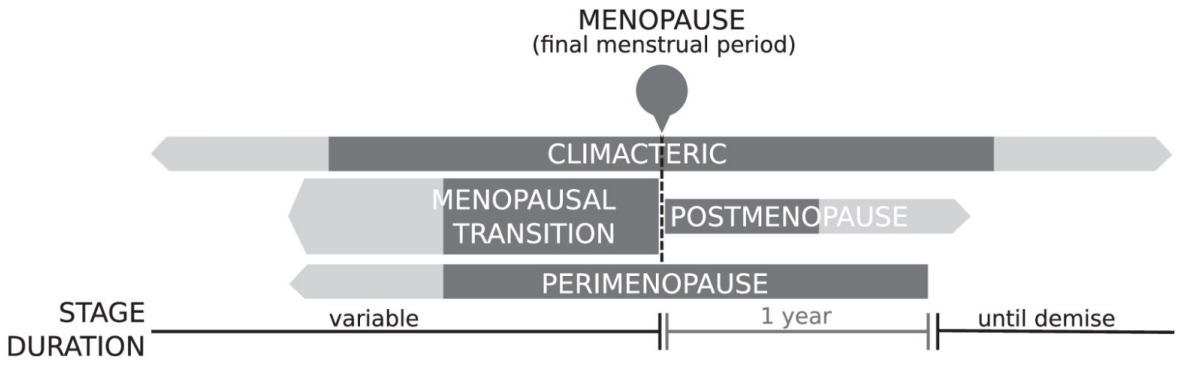

Fig 2 – Time periods of Menopause, including the term Climacteric

While the above-established nomenclature by WHO and CAMS defined the phases of female reproductive aging, there was no clear starting and ending point. The overlapping time periods and the lack of objective and clear criteria were a point of confusion among academicians and clinicians alike. This led to the Stages of Reproductive Ageing Workshop (STRAW) in 2001.

STRAW (2001)

The following STRAW Criteria segregated female reproductive aging into seven clearly defined categories. The focal point was natural menopause as experienced by healthy women. Definitions of the stages were based on menstrual cycles, measurable biochemical parameters, anatomy of both the uterus and ovaries and changes seen in other organ systems.[6]

The STRAW criteria places menopause at the core of the staging system, designating it as zero (0) point. Five stages are noted before the final menstrual period (−5 to −1) and two stages are seen following it (+1 to +2). The stages are categorized as follows: stages −5 to −3 cover the Reproductive Interval, stages −2 to −1 represent the Menopausal Transition, and stages +1 to +2 define Post-menopause. The Menopausal Transition (−2 to −1) begins with changes in

menstrual cycle length and increased follicle-stimulating hormone (FSH) levels, ending with the FMP.[7,8]

Early post-menopause (+1) refers to the first five years after the final menstrual period and is further divided into two phases: 'a,' the initial twelve months following the FMP, and 'b,' the subsequent four years. Late post-menopause (+2) has no fixed endpoint, continuing for the remainder of a woman's life.

Perimenopause is defined as the period spanning from stage −2 to +1a, ending 12 months after the FMP. Additionally, the STRAW criteria recommend that the terms' perimenopause' and 'climacteric' be used interchangeably when communicating with patients or the public. However, they should be avoided in scientific literature, in line with WHO guidance.

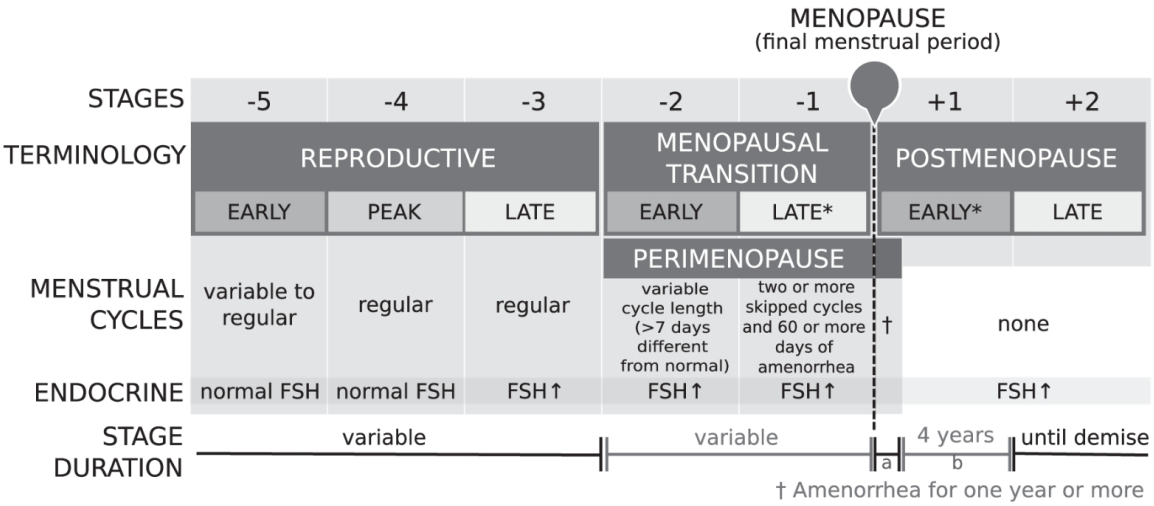

Fig 3 – STRAW Staging System

A key limitation of the original STRAW criteria was the absence of multiethnic cohort studies at the time of development, which restricted the applicability of the staging system to general population with racial and ethnic diversity. The original criteria also relied solely on follicle-stimulating hormone (FSH) as a biomarker. Still, they lacked detailed information about the timing of FSH changes or specific threshold values due to limited data. Therefore, the staging system primarily concentrated on patterns of menstruation and qualitative FSH levels.[9]

Other drawbacks included that the STRAW criteria were designed exclusively for healthy women. They were not recommended for women

(i) who have a history of smoking,

(ii) with extremes of BMI, over 30 or under 18,

(iii) who are involved in intense aerobic exercise (over 10 hours per week),

(iv) who have chronic menstrual irregularities,

(v) who have undergone a hysterectomy,

(vi) who have altered uterine anatomy (e.g., fibroids), or

(vii) who have altered ovarian anatomy (e.g., endometrioma).

STRAW +10 (2011)

The STRAW + 10 criteria were introduced in 2011 to incorporate important advancements in the understanding of reproductive aging of a woman and to offer updated recommendations that addressed some of the shortcomings in the original staging system. [9]

The STRAW + 10 staging system proposed dividing the late reproductive stage (−3) into two sub-stages (−3b and −3a) based on menstrual cycle patterns and FSH levels. This adjustment aimed to reflect minor changes in menstruation and smaller cycle lengths in stage −3a, along with increased variability in FSH levels.

The updated criteria also incorporated recommendations from the ReSTAGE Collaboration[8]. The recommendations called for criteria that was based on menstrual cycle variation to define the early (−2) and late (−1) menopausal transition stages, including quantifying FSH levels in the late transition. The early menopausal transition (−2) was distinguished from the late reproductive stage (−3a) by greater variation in menstrual cycles, defined as a cycle length difference of 7 days or more that recurs within 10 cycles. The late menopausal transition

(−1) was identified by an absence of menstruation lasting 60 days or more and an elevated FSH level exceeding 25 IU/L.

Additionally, early postmenopause (+1) was sub-categorised as +1a, +1b and +1c to reflect ongoing rise in FSH and decline in estradiol over the two years following the final menstrual period (FMP). Stage +1a represented the first 12 months after the Final menstrual period (marking the end of peri-menopause), +1b covered the following year, and +1c referred to the period before FSH and estradiol levels stabilized.

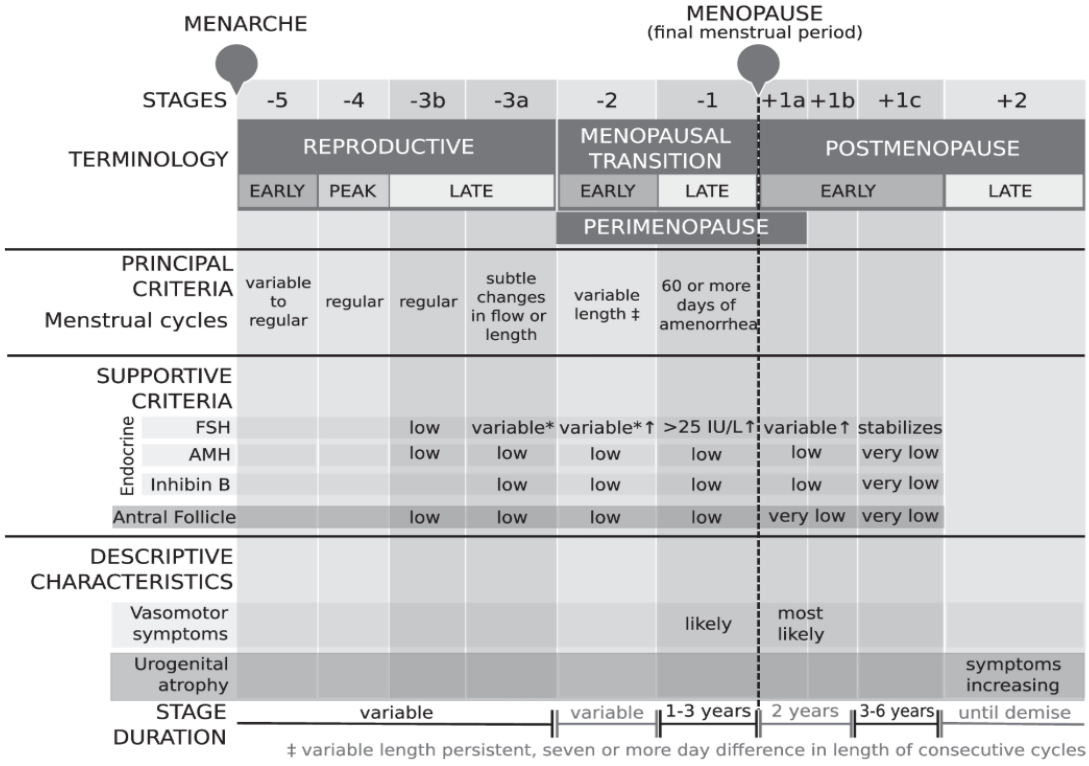

Fig 4 – STRAW +10 Staging System

The STRAW + 10 staging system is adaptable to almost all women, irrespective of their age, demography, body mass index, or lifestyle.[9] Nevertheless, several important research areas remain necessary to refine future criteria. These include (i) adopting standardized analysis for key biomarkers such as Anti-Müllerian Hormone (AMH), (ii) conducting further verifiable studies across diverse groups to clarify menstrual flow patterns in the late reproductive stage, and (iii) improving understanding of reproductive aging in women with specific health conditions, such as those who have had a single ovary removed, undergone a hysterectomy, or have chronic illnesses like HIV, cancer treatments, PCOS, or premature ovarian failure.

A significant drawback of the STRAW + 10 criteria is that it does not include women using exogenous hormones like hormone replacement therapy.[10] A woman using HRT cannot be accurately classified into reproductive stages. This creates a challenge for literature and studies that explore different outcomes through the various stages of reproductive aging.

Although the STRAW Criteria has several shortcomings, it has significantly broadened the understanding of female reproductive health. It is widely accepted as the gold standard definition of female reproductive aging.

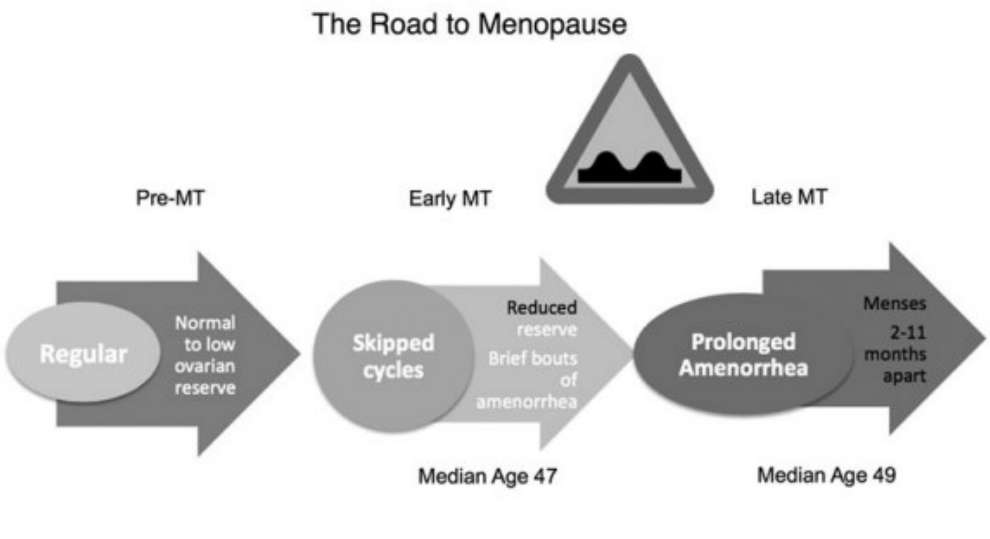

Fig 5 – Road to Menopause, based on STRAW, showing the stages preceding final menstrual period

SYMPTOMATOLOGY OF MENOPAUSAL TRANSITION

Since the 1980s, several Longitudinal studies have been conducted to understand the symptomatology of menopause better.[11-15] The studies conducted earlier during the 1980s and 1990s were of cohorts of 400 to 500 women and were targeted toward identifying the menstrual milestones that occurred during the transition and the associated cardiovascular risk factors.

The second generation of studies included the Melbourne Healthy Women's Study[16]; SWAN, the Study of Women's Health Across the Nation[17]; and the Penn

Ovarian Aging Study[18]. A better understanding of the menopausal transition and the association of the specific symptom with each stage of the process has been possible because of these studies. These studies had long-term follow-up periods of 9 to 20 years. This proved helpful in gathering extensive information on various aspects such as quality of life and sexual function, reproductive endocrinology and bone density.

Irregular bleeding patterns are considered to be one of the earliest signs of menopause. Anovulation causes changes in the frequency and duration of menstrual cycles.[19]

Vasomotor symptoms

Hot flushes, also known as vasomotor symptoms (VMS), affect most women during the menopausal transition. It is a reason for a significant reduction in quality of life. The pathophysiology behind vasomotor symptoms can be explained by reducing estrogen levels in the menopausal transition, causing the narrowing of the thermoregulatory system, which is known to control the core body temperature.[20-21] A rapid increase in body temperature and vasodilation causes a sensation of warmth to spread through the upper body, usually lasting

for a few minutes. Typically, these symptoms can last for up to 4 to 5 years, with around 25% of women experiencing them for up to 10 years. Several factors, such as race and ethnicity, affect the severity and duration of hot flashes. African American women experience the most intense and prolonged symptoms.[12] While VMS is usually benign, they are associated with higher cardiovascular risk in the future.[22] Loss of estrogen is related to the loss of endothelial function in menopause.[23]

Genitourinary

Estrogen deficiency in menopause causes changes in the lower genital tract, such as vulvar and vaginal atrophy, vaginal dryness, shortening and narrowing of the vagina, uterine prolapse and urinary incontinence. These symptoms are known as Genitourinary symptoms of menopause (GSM).[24] These changes can lead to discomfort during intercourse (dyspareunia), irritation, and a higher risk of urinary tract infections. Reduced estrogen leads to a decrease in vaginal blood flow, leading to decreased vaginal secretions, increased vaginal pH, thinning of the surface epithelium, and a rise in parabasal cells. Vulvar atrophy is thought to be caused by structural narrowing of the of the vagina and vestibule due to dehydration of connective tissue.[25]

Mood

The menopausal transition is characterized by mood disturbances such as an increased chance of depression and anxiety. The SWAN study followed perimenopausal women for five years and found that depressive symptoms were most severe during late peri-menopause.[26] Women with previous history of depression are at a higher risk of experiencing future episodes. Still, even those without a prior history have a 16% risk of developing new-onset depression or anxiety during menopause.[27] Longitudinal studies suggest that a longer menopausal transition may increase the likelihood of depression, likely due to more severe symptoms.[28] Additional risk factors during the menopausal transition include nulliparity, separation from a partner, premenstrual symptoms, and smoking.[29]

Sleep

While natural aging is linked to declining sleep quality, research indicates that the menopausal transition worsens sleep problems. A SWAN survey of over 12,000 women revealed that nearly 40% reported sleep difficulties that were linked to the timing of the menopausal transition rather than age alone.

Sleep disturbances have been associated with hot flashes. The more severe the hot flashes, the more likely it was for a woman to report insomnia.[30] However, it is not completely described by increased nocturnal vasomotor symptoms, as a SWAN sub-analysis showed substandard sleep even in women without VMS. Sleeping disturbances start at early menopausal transition and peak in the late transition. It persists at similar levels through postmenopause.[31]

Libido

Reduced sexual desire is common during the menopausal transition, affecting up to ten percent of women.[32] The PRESIDE study[33] found that women aged 45 to 64 reported more issues with sexual desire compared to both younger and older women. Fewer than half of these women also experience depression. The decreasing estrogen and testosterone in menopause is thought to be the cause of these symptoms.

Bone

Estrogen acts as a potent inhibitor of bone resorption. Hence, the decline in estrogen levels during menopause causes an increasing bone loss rate. Fractures

caused by osteoporosis affect about fifty percent of women over the age of 50.[34] Estrogen stimulates osteoblast activity and enhances calcium absorption from the intestines. When estrogen levels drop, calcium absorption decreases, increasing bone resorption through osteoclasts' activation by elevated PTH. Highest bone mineral density is reached around thirty years of age and gradually drops by about 0.7% annually. However, the rate of bone loss increases sharply about a year before the final menstrual period (FMP). It continues for up to three years, reaching rates as high as 5% per year before slowing to premenopausal levels.

INFLAMMATION AND MENOPAUSE

The peri-menopause is a systemic inflammatory phase that increases a woman's chance of developing of cerebral ischemia and Alzheimer's disease.[35] It is associated with a rise in chronic low-grade inflammation, which accelerates ovarian failure and makes the brain more susceptible to ischemic damage. [36-37]

The inflammasome is an important aspect of innate immunity and is activated during the menopausal transition, leading to a pro-inflammatory state. Estrogen receptor-beta regulates the inflammasome. It is also responsible for regulation of neuronal mitochondrial function. [38-39]

The decreasing estrogen level causes a pro-inflammatory state. Inflammasomes might be a key indicator of the menopausal effect on the immune system. Estrogen decline leads to chronic inflammation, and can potentiate dysfunctional immune and metabolic state and neurodegenerative disease, posing significant health challenges for women.

Estrogen's Role In Menopause And Inflammation

Estrogen plays a crucial role in Menopause and inflammation, with declining estrogen levels contributing to increased inflammation and immune disorders. Estrogen decline around peri-menopause may contribute to the accumulation of amyloid-β (Aβ) and the emergence of Alzheimer's disease (AD) endophenotype. It is also associated with increased inflammatory markers, including higher circulating interleukins (ILs) and tumor necrosis factor (TNF). [36]

The idea that reproductive ageing could be a systemic inflammatory physiology is key to understanding the various neurological changes that are seen in menopausal women. It is also important in the development of novel therapeutic targets that alleviates the morbidities that occurs with ageing and reproductive senescence. [40]

Association of IL 6 in Menopause

Interleukin-6 (IL-6) is often called “the cytokine for gerontologists.” It is an acute-phase reactant that is important in regulating metabolic processes and the development of various chronic diseases. It is primarily produced by monocytes and macrophages and has a wide range of effects.[41] While IL-6 levels are typically low in healthy younger individuals, elevated levels in older adults are often linked to higher mortality rates. A meta-analysis by Ng et al revealed that elderly individuals with depression showed elevated levels of IL-6.[42]

Association of CRP in Menopause

C-reactive protein (CRP) is a pentameric acute phase reactant. It is primarily produced by hepatocytes due to the activation of innate humoral immune system. High sensitivity form (hs-CRP) is easily detected in blood. It is widely used in clinical practice as a biomarker for infection, chronic diseases, and low-grade inflammation. Although CRP typically does not cross the blood-brain barrier (BBB) freely, several mechanisms have been proposed to explain how it may interact with the central nervous system (CNS). CRP is also proposed to be

elevated in Menopause, especially in correlation with adverse mood symptomatology of Menopause.[43]

2. NEED FOR STUDY

Menopause is an essential phase in the physiological life cycle of women, associated with changes in the biochemical factors such as decreasing Estrogen level. 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. [1] 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.

Depression is a complex multifactorial disorder, with morbidity seen across physical, emotional, and functional spectrums. [44] The disease doesn't impact the patient alone; it's a vicious cycle that takes an adverse turn on the near and dear ones of the patient. There is an increase in the economic, physical, and psychological burden on the family.

With increasing life expectancy, women worldwide spend almost one-third of their lives in the post-menopausal phase. Many developed countries now have a significant percentage of their population falling in the 65+ demographic, which

indicates the rising dependent population. Presently, in India, 5.62% of the population is in the 65+ demographic.[45] With the increasing life expectancy, and decreasing mortality and fertility rate, India expects an increasing percentage of the above 65+ ages in the coming decade. This further necessitates the need to understand the onset of depression in menopause early and provide necessary intervention.

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.[46] 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 possibility of use of Anti-Inflammatory agents as an adjuvant to treatment in mood disorders and Major Depressive Disorder can also be explored, on understanding the etio-pathology of the same in Peri Menopausal Women.

3. AIMS AND OBJECTIVES

AIMS

To the study the association between Inflammatory Markers and Depression in Peri Menopausal Women

PRIMARY OBJECTIVE

To study the association between Inflammatory markers such as CRP, IL-6, D-Dimer, Total WBC Count and Neutrophil-Lymphocyte Ratio and depression in Peri Menopausal and Menopausal Women between 40 to 55 years.

SECONDARY OBJECTIVE

To study the association between Severity of Depression and Levels of Inflammatory markers in relation to Serum Estrogen levels.

4. SOURCE OF DATA

This study was conducted in the Department of Obstetrics and Gynecology and Department of Psychiatry in BLDEDU's Shri B M Patil Medical College, Hospital and Research Center, Vijayapura.

Method of Collecting Data: All women attending the OPD Clinic in Shri B M Patil Medical College Hospital and Research Center

Study Setup – Tertiary care hospital

Type of Study - Cross-Sectional Study

Study Period – January 2023 – September 2024

5. INCLUSION CRITERIA

1. Age between 40 to 55 years
2. Presenting with Menopausal symptoms according to Menopausal Rating Scale

6. EXCLUSION CRITERIA

1. Patients on Hormone Replacement Therapy
2. Patients with comorbidities such as Liver or Kidney dysfunction
3. Patients with acute febrile illness or autoimmune disorders
4. Patients not consenting

7. SAMPLE SIZE

Using G*Power ver 3.1.9.4 software for sample size calculation, the proportion of depressed female 73.7 and Nondepressed female 47.3, this study requires a total sample size of 110 (for each group 55, assuming equal group sizes), calculated based on **Bremmer A B et al (2007)**[52], so as to achieve a power of 80% for detecting a difference in Proportions: Exact - Proportions: Inequality, two independent groups unconditional) with 5% level of significance.

8. 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. For normally distributed continuous variables between the two groups will be compared using an independent sample t-test. For not normally distributed variables, the Mann-Whitney U test is used. Categorical variables between the two groups are compared using the Chi-square test/Fisher's exact test. If $p<0.05$ will be considered statistically significant. All statistics are performed two-tailed.

9. METHODOLOGY

It was a Cross-Sectional Study.

All patients between the ages 40 to 55 visiting the OPD clinic of Department of Obstetrics and Gynecology and the Department of Psychiatry at Shri B M Patil Medical College, Hospital and Research Center, who fulfilled the inclusion criteria, were included in the study.

Consents of the patients were taken once they were admitted into the study.

Detailed history was taken regarding Menopausal symptoms according to the Menopausal Rating Scale. History of any significant past and present medical conditions were taken to rule out other underlying chronic inflammatory pathology.

Examination was performed to collect weight, height, and other baseline vitals. Systemic Examination was done to rule chronic chest and other inflammatory conditions.

The patients were first screened for depression using the PHQ-9 questionnaire and were divided into depressed and non-depressed patients. Depressed patients were further categorized based on the severity of depression.

Blood Sample was drawn for both the control and test group and sent for CRP, IL-6, D-Dimer, Total Leucocyte Count and Neutrophil-Lymphocyte Ratio, and Serum Oestrogen levels.

The approval of the Institutional Ethical Committee (IEC/899/2022-23) was acquired before the study started.

THE MENOPAUSAL RATING SCALE

The Menopause Rating Scale (MRS) is a standardized tool used to assess the severity of menopausal symptoms and their impact on quality of life. It helps in both clinical practice and research to evaluate the effectiveness of treatments and monitor symptom progression over time.

Structure of the MRS

The MRS consists of 11 items that are further divided into three main symptom domain:

1. Somatic Symptoms
    - Hot flashes, sweating
    - Heart discomfort (unusual awareness of heartbeats, heart skipping, heart racing)
    - Sleep problems (difficulty falling asleep, difficulty sleeping through the night, waking up early)
    - Muscle and joint problems (joint pain, muscle tension)
2. Psychological Symptoms
    - Depressive mood (feeling down, sad, on the verge of tears)

- Irritability (feeling nervous, inner tension)
- Anxiety (inner restlessness, feeling panicky)
- Physical and mental exhaustion (general decrease in performance, forgetfulness, lack of concentration)

3. Urogenital Symptoms
    - Sexual problems (change in sexual desire, activity, and satisfaction)
    - Bladder problems (difficulty in urinating, increased frequency, incontinence)
    - Vaginal dryness (sensation of dryness or burning in the vagina, pain during intercourse)

Scoring System

Each symptom is rated on a 5-point Likert scale:

- 0 = No symptoms
- 1 = Mild symptoms
- 2 = Moderate symptoms
- 3 = Severe symptoms
- 4 = Very severe symptoms

Total Score and Interpretation

- The total score ranges from 0 to 44.
- Higher scores indicate more severe symptoms.

Interpretation of Scores

- 0–4 – No or minimal symptoms
- 5–8 – Mild symptoms
- 9–16 – Moderate symptoms
- ≥17 – Severe symptoms

PHQ – 9 QUESTIONNAIRE

The PHQ-9 (Patient Health Questionnaire-9) is a widely used, standardized tool for screening, diagnosing, monitoring, and measuring the severity of depression. It is based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria for major depressive disorder.

Structure of the PHQ-9

The PHQ-9 consists of 9 questions, each assessing the frequency of the main depressive symptoms over the past two weeks. Each of the questions represent the nine diagnostic criteria for major depressive disorder.

PHQ-9 Questions

Over the last two weeks, how often have you been bothered by the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy

5. Poor appetite or overeating
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed — or the opposite: being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or thoughts of hurting yourself in some way

Scoring System

Each item is rated on a 4-point Likert scale based on how often the symptom was experienced in the last two weeks:

Response Option	**Score**
Not at all	0
Several days	1
More than half the days	2
Nearly every day	3

Total Score and Interpretation

- 0–4 → No or minimal depression
- 5–9 → Mild depression
- 10–14 → Moderate depression
- 15–19 → Moderately severe depression
- 20–27 → Severe depression

10. REVIEW OF LITERATURE

1. **Greendale G et al.**[2] described Menopause as diagnosed to be after 12 months of amenorrhea, typically around age 51, with perimenopause preceding it. They further described perimenopause as a time of altered functioning of the ovaries, preceding the last menses by many years. The article tried to establish the causal associations between menopause and several symptoms and diseases.

2. **Gatenby C et al.**[7] noted in the article titled 'Menopause' that menopause is a natural biological process typically occurring in women between ages 45 and 55, marked by the end of ovarian reproductive function and menstrual bleeding. The transition can be challenging, affecting multiple organ systems and quality of life. The usual symptoms of menopause were vasomotor symptoms like hot flushes and night sweats, which persists for years and, significantly impacts psychological well-being. Other symptoms are low mood, anxiety, cognitive deficits, and vulvovaginal atrophy.

3. **Soules MR et al.**[6] wrote an executive summary to describe the events of The Reproductive Ageing Workshop that was conducted in 2001 to discuss the need for a staging system for women's reproductive years that reflect the physiological changes that occur from years before menopause to post-

menopausal period and to standardize the terminologies used in literature and clinical practice.

4. **Freeman EW et al.**[12] conducted the Penn Ovarian Aging Study of 255 premenopausal women during pre-menopause and who attained natural menopause within 16 years. They concluded that moderate and severe hot flushes continue, for up to five years following menopause and that more than thirty three percent of women observed for more than 10 years following menopause have moderate/severe hot flashes. They also noted that the duration of the hot flashes should be taken into consideration while considering the proposed management plan.

5. **Avis NE et al.**[13] conducted a study to determine the total duration of frequent VMS during the menopausal transition, to quantify how long recurring VMS persists after the FMP and to ennumerate the risk factors for longer total VMS duration and longer post-FMP persistence. They concluded that frequent VMS was noted to last for longer than seven years during the transition for more than fifty percent of the women and lasted for four and half years after the FMP. Individual characteristics (e.g., being premenopausal and having greater negative affective factors when first experiencing VMS) were related to longer-lasting VMS.

6. **McKinlay SM et al.**[14] analyzed the largest and most comprehensive prospective cohort study of middle-aged women — the Massachusetts Women's Health Study (MWHS), to estimate the parameters of normal menopausal transition. The duration of the transition was averaged at almost four years. Symptoms of menopause seem to only be marginally related to the transition, with reported rates rising during the perimenopause and thereby, falling in the post-menopause.

7. **Portman DJ et al.**[24] summarised a terminology consensus conference, which was held in May 2013 by the Board of Directors of the ISSWSH and the Board of Trustees of The NAMS. They came to the consensus that the term genitourinary syndrome of menopause (GSM) is a medically more precise, inclusive, and publicly acceptable term than vulvovaginal atrophy. "GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder.[24]" The syndrome includes genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections.

8. **Bromberger JT et al.**[26] conducted a study to evaluate the relationship between changing menopausal status and the risk of clinically significant depressive symptoms. It also examined whether the relationship differed according to the level of depressive symptom at the beginning. It reported that a woman was more likely to report depressive symptoms when she was early peri-, late peri-, postmenopausal or currently/formerly using hormone therapy (HT) relative to when she was premenopausal.

9. **Cohen L et al.**[47] conducted a study to study the correlation between the menopausal transition and the start of the first ever reported episode of depression amongst women who have no prior history of mood disturbance. They concluded that Premenopausal women with no prior history of major depression, and who entered the transition were two times more likely to develop significant depressive symptoms as compared to women who remained premenopausal after adjusting for age at start of the study and for history of any extreme experiences in life. The increased risk for depression was noted to be marginally more in women who self-reported vasomotor symptoms.

10. **Freeman EW et al.**[48] conducted a study to longitudinally study the associations among reproductive hormones, menopausal status, and other

predictors of depressed mood in midlife women. They described an increased likelihood of depressive symptoms during the transition to menopause and a decreased likelihood after menopause. The possibility of depressive symptoms decreased for individuals with a rapidly increasing follicle-stimulating hormone profile and decreased with age compared with premenopausal women. Participant aggregate profiles with increasing estradiol levels were significantly associated with depressive symptoms in bivariate analysis.

11. **Osimo E F, Pillinger T et al. (2020)**[46] carried out a meta-analysis of 107 studies, including a total of 5166 patients with depression and 5083 controls. Studies that were included in the meta-analysis were those that matched depressed patients to healthy control. The report uniformly showed an increase in CRP and IL-12 in patients with depression, with reduced variability, which suggests that Depression is a pro-inflammatory process. This suggests an inflammatory phenotype in depression.

12. **Nobis A, Zalewski D et al. (2020)**[49], in an article published in 2020, described the inflammatory pathogenesis of Major Depressive Disorder. The article described the enhanced inflammatory process of Depression, as suggested by the elevated CRP, IL-6 and TNF-alpha levels in patients with Major Depressive Disorders. The article also indicated that the dysregulated

stress axis, thereby leading to an increased cortisol level, is also characteristic of MDD. It further noted that the increased levels of lipid peroxidation markers are an essential finding in MDD.

13. **Felger J C, Haroon E et al. (2018)**[50] conducted a study on 89 men and women in Atlanta who were diagnosed with Major Depressive Disorder and other mood disorders by Structured Clinical Interview for Diagnostic and Statistical Manual-IV (SCID-IV) and Hamilton Rating Scale for Depression. Plasma and CSF were collected from the study patients and were analyzed for their depressive symptoms. They found a significant positive correlation between Plasma CRP and other plasma inflammatory markers; a similar association was also noted between CSF CRP and other CSF inflammatory markers. They also found that increased CRP, both central and peripheral, was related to specific symptoms of depression, such as anhedonia and also to the severity of depression.

14. **Al-Hakeim HK et al. (2015**)[51] conducted a study of 30 patients between 22 to 61 years diagnosed with MDD and another 30 patients aged 22 – 46 years diagnosed with Schizophrenia, both based on ICD 10, in Iraq. This was compared to 30 healthy control samples. Results showed a significant increase in Serum IL-6, Il-8, TNF-alpha and sIl-2R levels in both the groups

with MDD and Depression, compared to the controls. They also noted that the patients with Schizophrenia showed increased levels of inflammatory markers as compared to the MDD group.

15. **Bremmer A B et al. (2007)**[52] studied the association between Inflammatory markers and depression in late life. A population-based study was conducted on 1285 participants in Longitudinal Aging Study Amsterdam, of 65 years and above. An association was found between higher plasma levels of Il-6 and major depressive disorder, independent of age, chronic disorder, cognitive functioning or antidepressant.

16. **K A Mathews et al. (2007)**[53] did a five-year follow-up study to see the association between Inflammatory markers in perimenopausal women and the severity of depression. After informed consent, 3292 women were enrolled in the Study of Women's Health Across the Nation and were followed up for 5 years. The study revealed that higher depressive symptoms were related to higher fibrinogen, PAI-1, and tPA-ag levels. They concluded that depressive symptoms may, in part, also be related to higher cardiovascular risk in perimenopausal women. This was the first study ever conducted to see the association in Menopausal transition between Depression and Inflammatory markers.

11. 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, as seen in the table below.

GROUP	MEAN	STANDARD DEVIATION
Cases	45.2	4.445
Controls	42.47	2.721

Table 1 – Age of the patients

As shown in the table below, a total of 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.

GROUP	PERIMENOPAUSAL (N,%)	POSTMENOPAUSAL (N,%)
Cases	47 (85.5%)	8 (14.5)
Controls	51 (93%)	4 (7%)

Table 2 – Menopausal Status of patients

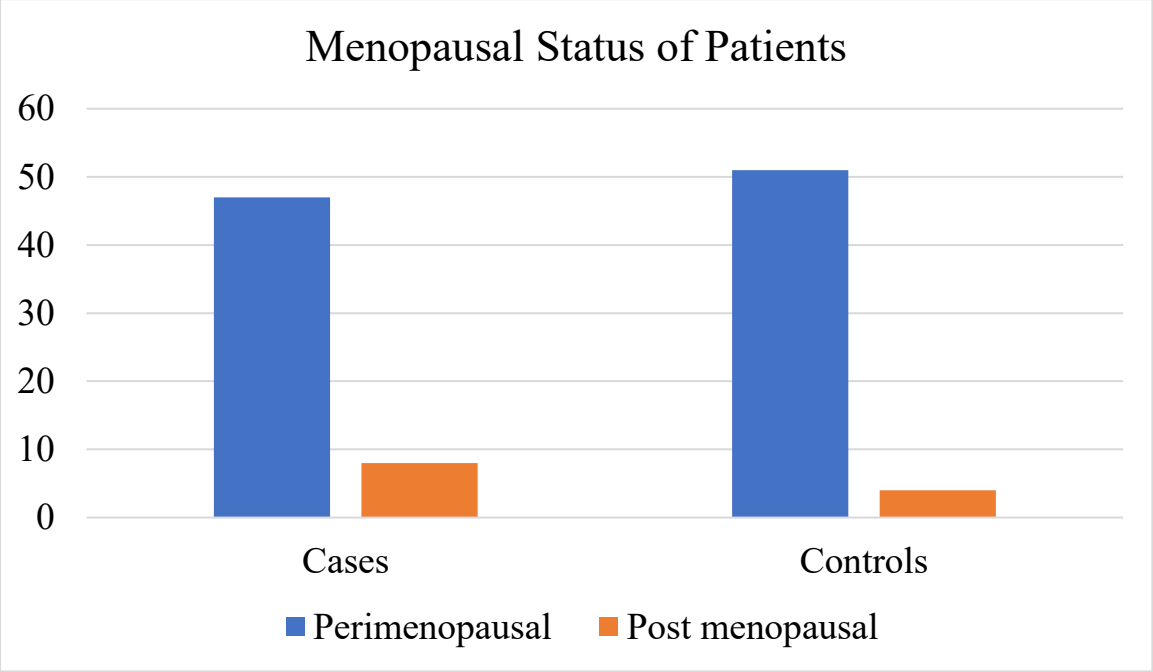

Fig 6 – Bar graph showing the Menopausal Status of patients

PLACE		CASE	CONTROL	TOTAL
URBAN	N	32	28	60
	%	58.2%	50.9%	54.5%
RURAL	N	23	27	50
	%	41.8%	49.1%	45.5%
TOTAL	N	55	55	110
	%	100.0%	100.0%	100.0%

Table 3 – Distribution of patients according to their place of residence

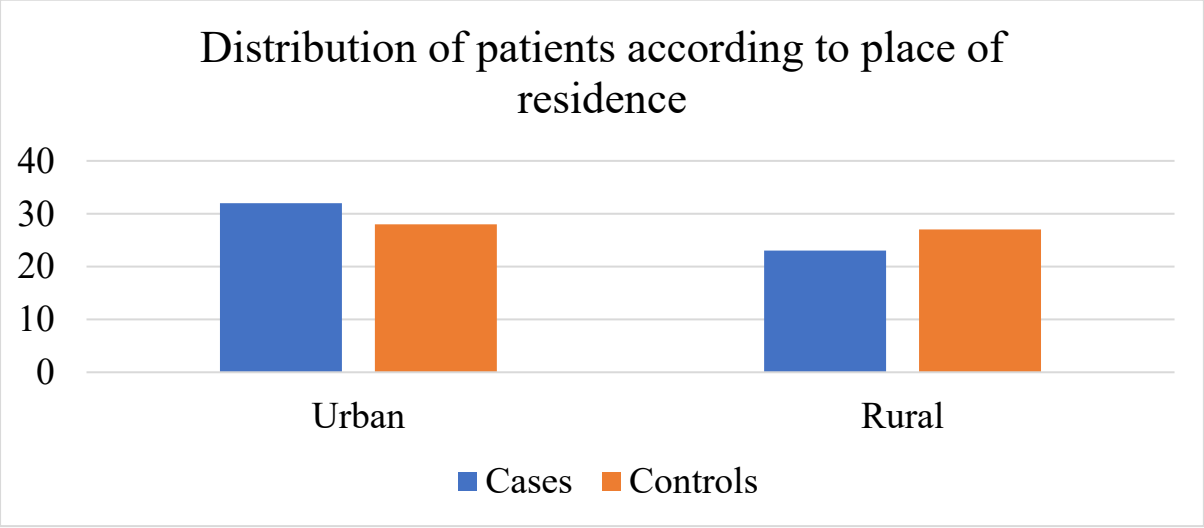

Fig 7 – Bar graph showing patients according to place of residence

According 58.2% of patients in the cases group hailed from urban area as compared to 50.9% of the controls. p value for the same was calculated to be 0.444 and was found to be not significant.

OBSTETRIC SCORE		**CASES**	**CONTROLS**	**TOTAL**
Nulliparous	N	4	3	7
	%	7.3%	5.5%	6.4%
Primiparous	N	10	3	13
	%	18.2%	5.5%	11.8%
Multiparous	N	41	49	90
	%	74.5%	89.1%	81.8%

Table 4 – Obstetric Score of the patients

As shown in the table below, 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 as the p value was calculated to be 0.99.

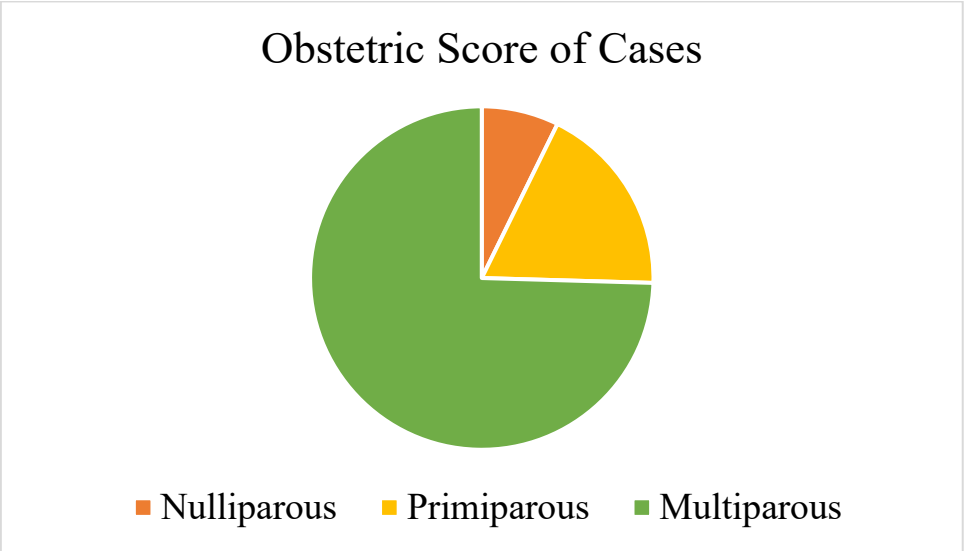

Fig 8 – Pie Diagram showing the Obstetric Score of Cases

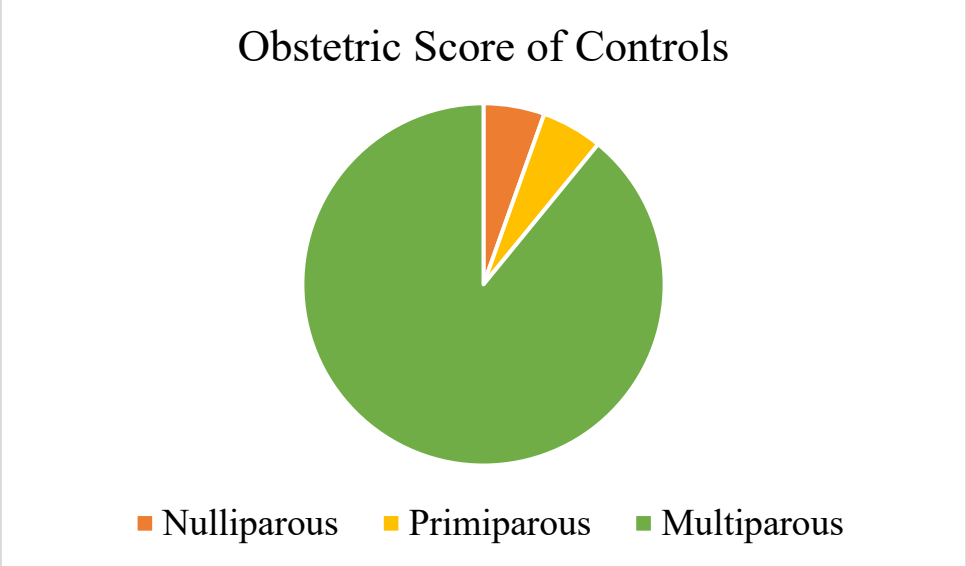

Fig 9 – Pie Diagram showing the Obstetric Score of Controls

SEVERITY OF DEPRESSION	NUMBER (N)	PERCENTAGE (%)
Mild	48	87.2 %
Moderate	7	12.8 %
Severe	0	0
Total	55	100%

Table 5 – Severity of Depression

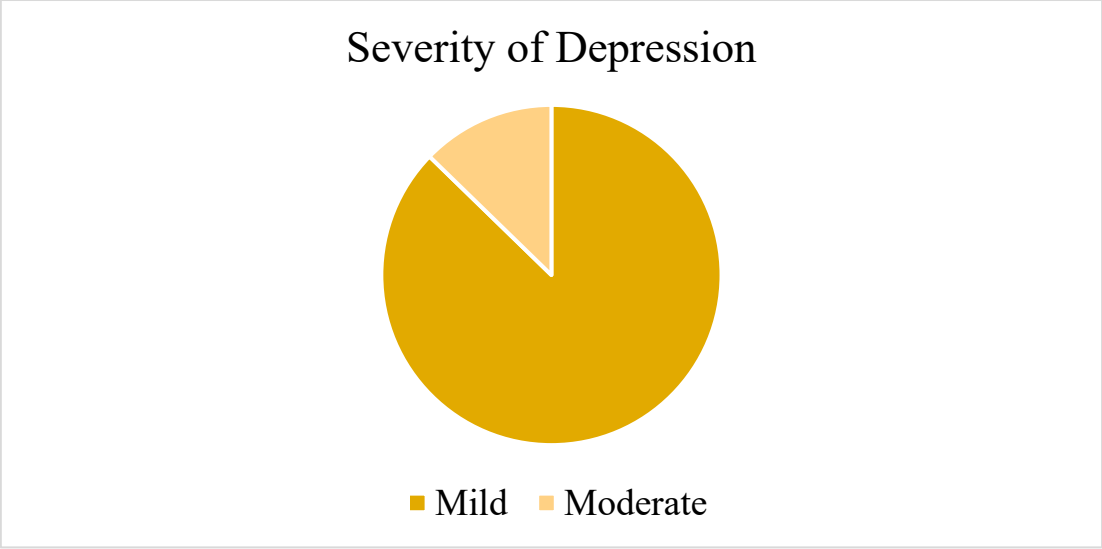

Fig 10 – Pie Diagram showing Severity of Depression

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.

Menopausal Symptoms		**Cases**		**Controls**	
Symptoms	Scoring	N	%	N	%
Hot flushes	0	0	0	2	3.6%
	1	12	21.8%	48	87.3%
	2	43	78.2%	5	9.1%
Heart discomfort	0	47	85.5%	55	100%
	1	4	7.3%	0	0%
	2	4	7.3%	0	0%
Sleep disturbances	0	4	7.3%	17	30.9%
	1	36	65.5%	38	69.1%
	2	15	27.3%	0	0
Depressive disorders	0	0	0	40	72.7%
	1	55	100	15	27.3%
Irritability	0	2	3.6%	49	89.1%
	1	45	81.8%	6	10.9%
	2	8	14.5%	0	0%
Anxiety	0	15	27.3	51	92.7
	1	36	65.5	4	7.3
	2	4	7.3	0	0
Physical and Mental Exhaustion	0	4	7.3%	34	61.8%
	1	51	92.7%	21	38.2%
Sexual Problems	0	43	78.2%	48	87.3%
	1	12	21.8%	7	12.7%
Bladder problems	0	51	92.7%	55	100%
	1	4	7.3%	0	0
Dryness of vagina	0	17	30.9%	52	94.5%
	1	38	69.1%	3	5.5%
Joint and Muscular Discomfort	0	40	72.7%	34	61.8%
	1	15	27.3%	21	38.2%

Table 6 – Severity of Menopausal Symptoms in cases and controls

Both groups of patients were asked to rate their menopausal symptoms based on the menopausal rating scale. The commonest symptom reported was vasomotor symptom, followed by sleep disturbances, physical and mental exhaustion, depressive mood, irritability, and joint and muscular disturbances. The least reported symptom was bladder problems.

A total of 98.2% of patients experienced hot flushes. Among the cases, 78.2% patients experienced severity scale of 2 and 21.8% reported severity scale of 1. In the controls, most patients (87.3%) reported a severity of 1 while only 9.1% reported a severity of 2.

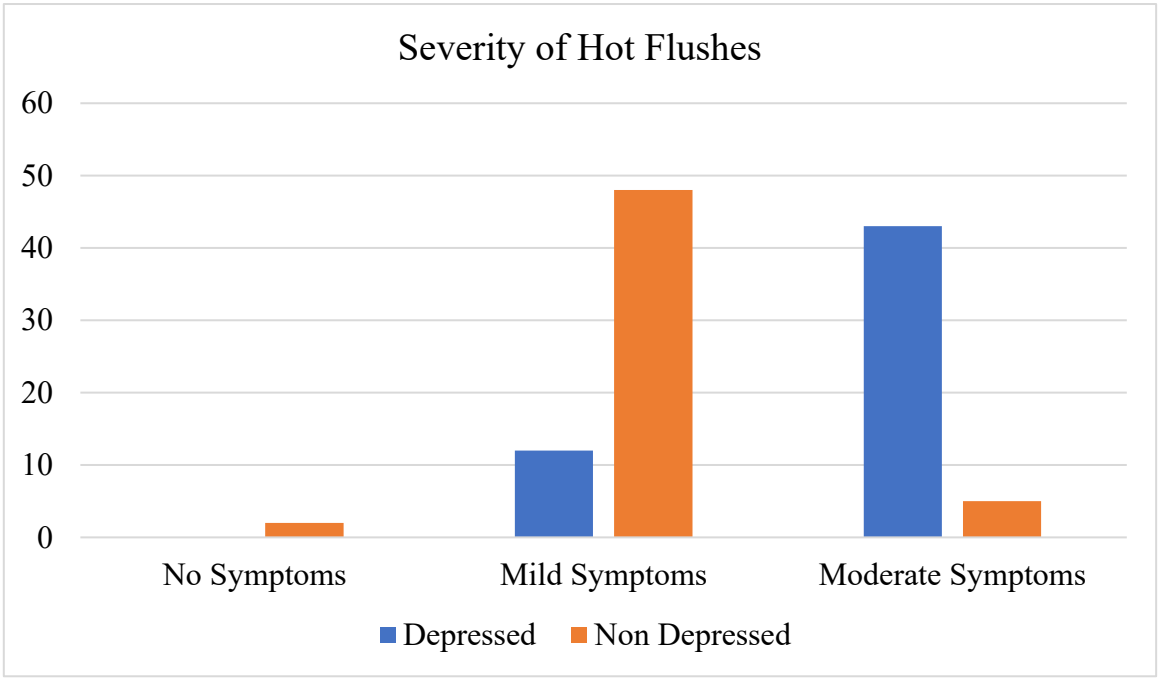

Fig 11 – Bar graph showing Severity of Hot Flushes among both the groups

According to the graph below, sleep disturbances were reported by a total of 89 patients (80.1%). Out of cases, 36 patients (65.5%) experienced mild sleep disturbance and 15 patients (27.3%) experienced moderate disturbance. Amongst the controls, 38 patients (69.1%) reported mild disturbance and 17 patients (30.9%) reported no disturbance.

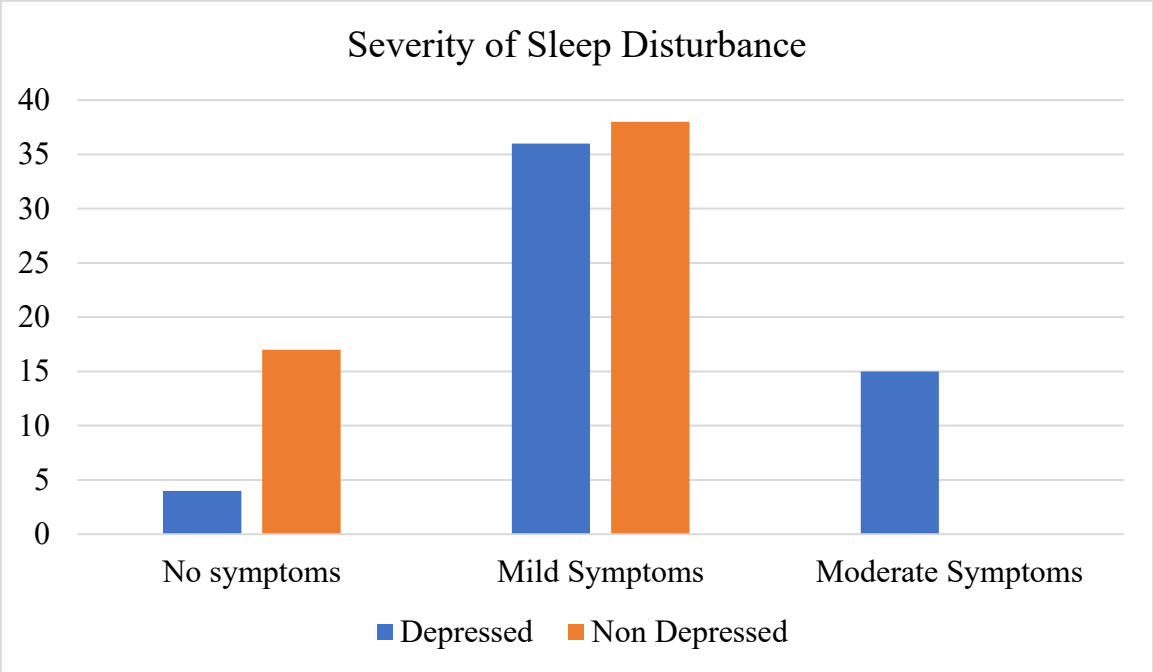

Fig 12 – Bar graph showing Severity of Sleep Disturbance among both cases and controls

As shown in the graph below, physical, and mental exhaustion was the third most reported symptom, with a total of 72 patients (65.5%) experiencing complaint. 51 patients (92.7%) from the case group experienced minimal physical and mental exhaustion as compared to the 21 patients (38.2%) of the control group.

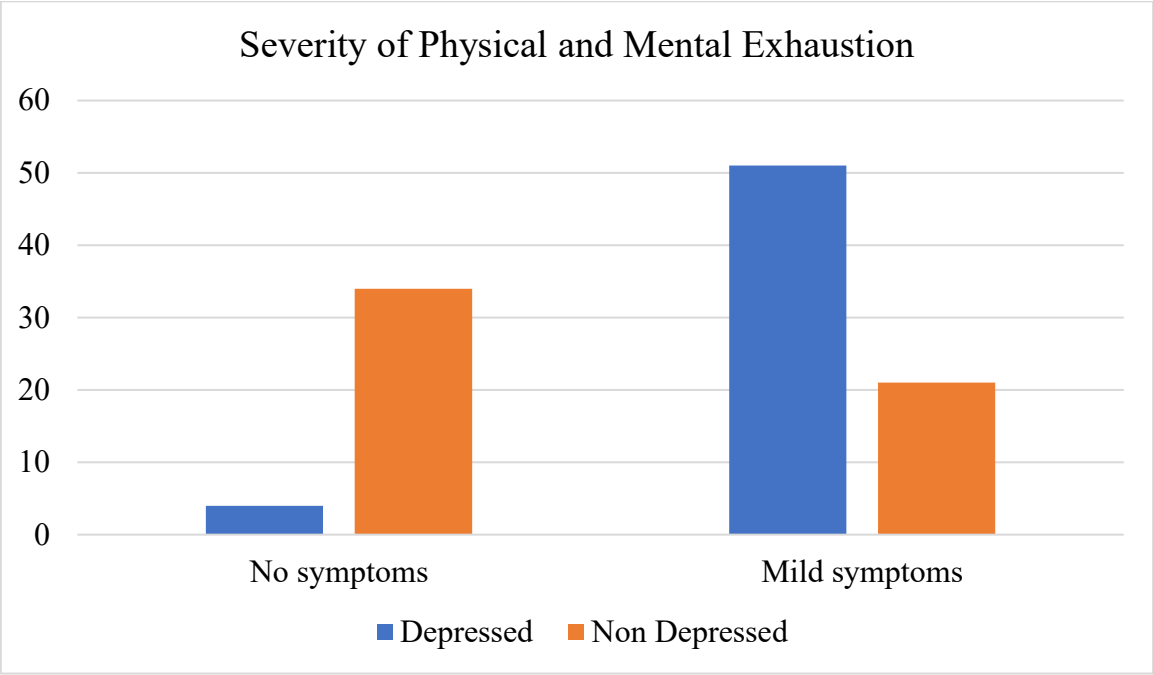

Fig 13 – Bar graph showing Severity of Physical and Mental Exhaustion among cases and controls

Depressive mood was seen in 70 patients (63.6%), as seen in the graph below. Amongst cases, all patients reported to have mild depressive mood. Amongst the controls, only 15 patients (27.3%) reported mild depression. Rest of the patients experienced no depressive symptoms.

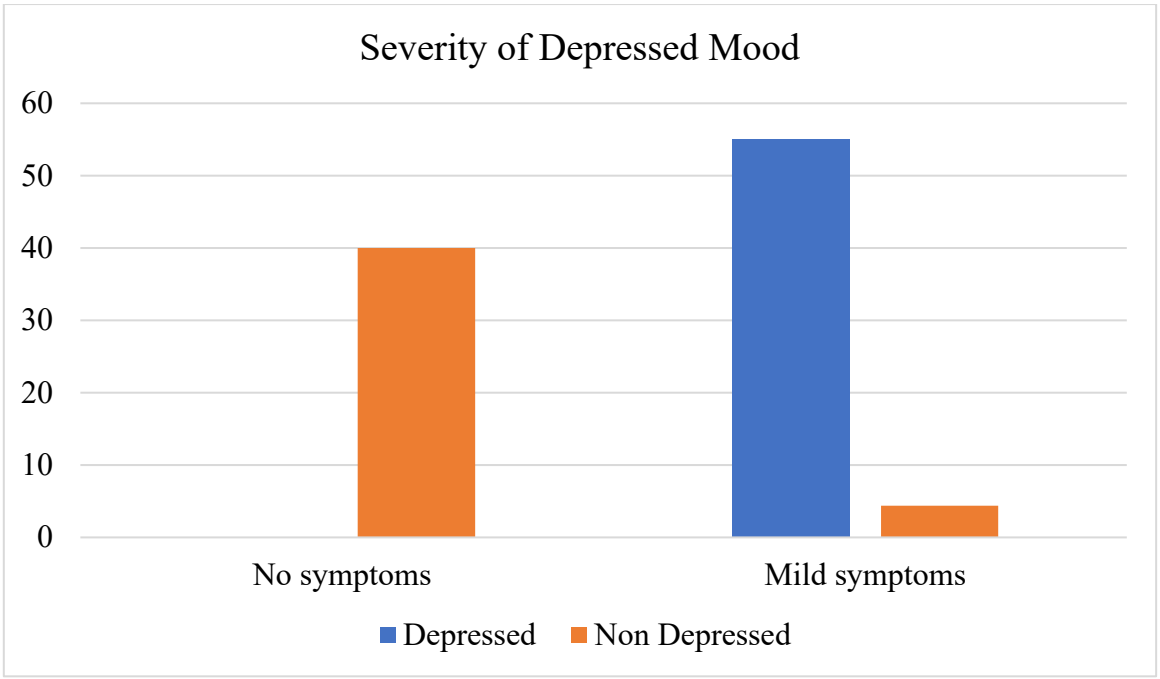

Fig 14 – Bar graph showing the Severity of Depressed Mood among cases and controls

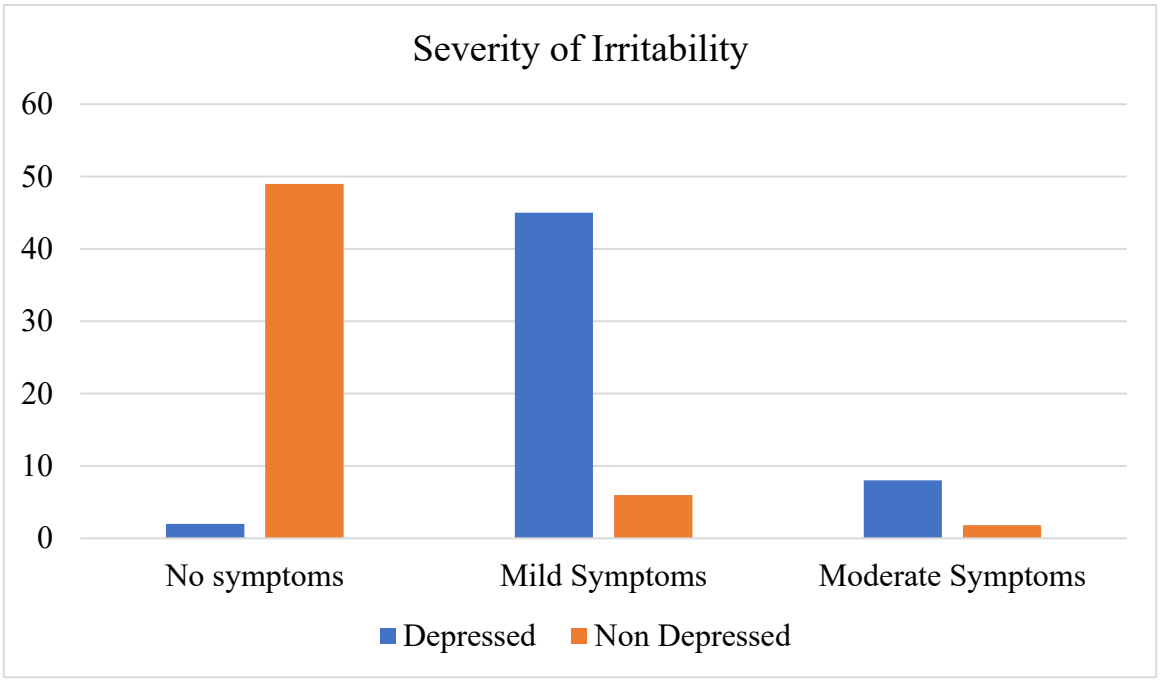

Fig 15 – Bar graph showing Severity of Irritability among cases and controls

As seen in the graph above, irritability was the next most common symptom reported, with 59 patients (53.7%) experiencing the same. 45 patients (81.8%) from the cases reported to have mild irritability and 8 (14.5%) of them reported moderate irritability. Amongst the controls, 6 (10.9%) patients reported mild irritability and no one reported moderate or severe symptoms.

Joint and Muscular discomfort was experienced by a total of 36 patients (32.7%). 15 (27.3%) of the cases and 21 (38.2%) of the controls experienced mild level of symptoms.

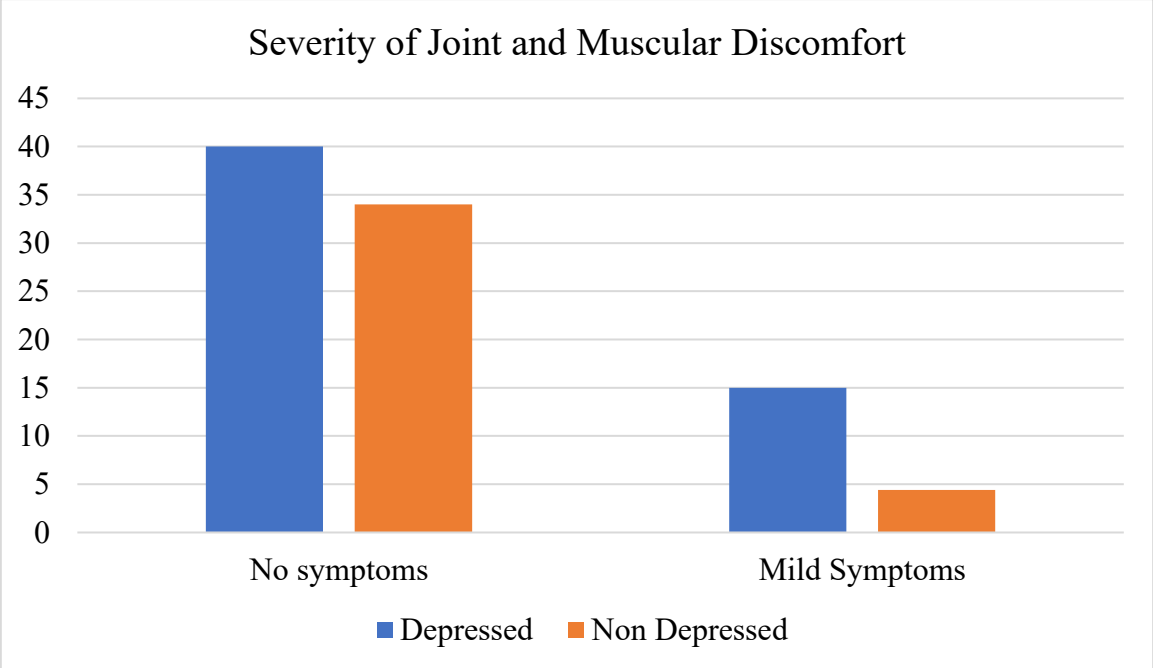

Fig 16 – Bar graph showing Severity of Joint and Muscular Discomfort among cases and controls

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).

PHQ – 9 rating		**Cases**		**Controls**	
Questions	**Response**	**N**	**%**	**N**	**%**
Little interest or pleasure in doing things	Not at all	39	70.9%	55	100%
	Several days	16	29.1%	0	0
Feeling down depressed or hopeless	Not at all	12	21.8%	47	53.6%%
	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%
	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%
	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%
	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%
	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%
	Several days	22	40%	0	0

Table 7 – Severity of depression symptoms as per PHQ-9 questionnaire

The commonest reported symptom was Sleeping disturbance, followed by feeling tired, poor appetite and feeling down and hopeless. No patients experienced any thoughts of self-harm or thoughts that they would be better of dead, and of moving or speaking slowly or being so fidgety or restless, that was noticed by others.

Sleeping difficulties was experienced by a total of 99 patients (90%). 18 patients (32.7%) from the depressed group experienced the same on several days and 37 patients (67.3%) experienced on more than half the days. Amongst the non-depressed patients, 44 patients (80%) experienced the same on several days and 11 patients (20%) reported that they did not experience the symptom at all.

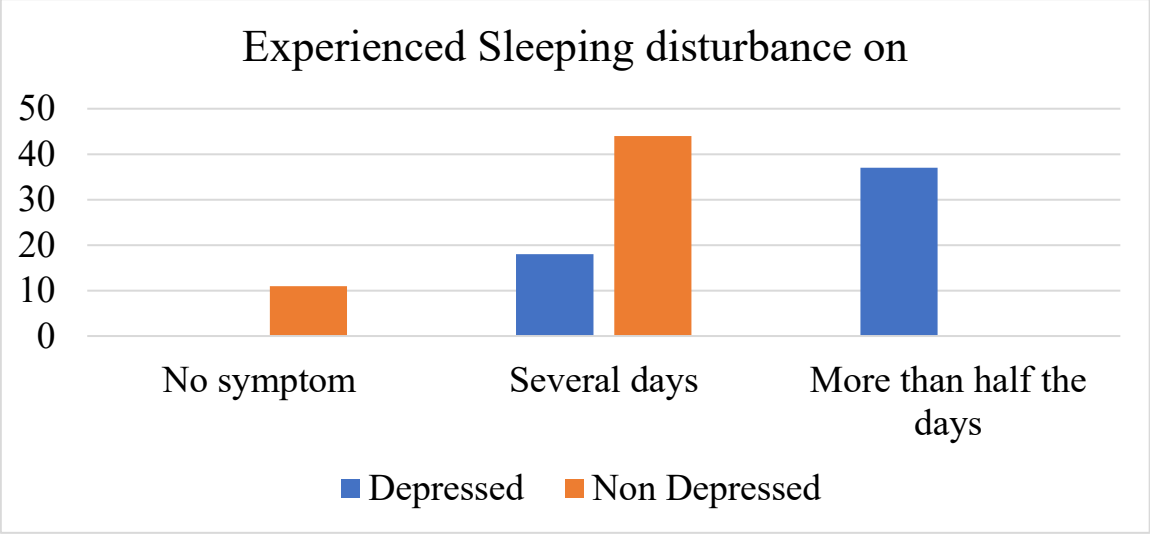

Fig 17 – Bar graph showing distribution of patients experiencing Sleeping Disturbance

A total of 94 patients (85.4%) reported that they felt tired. All patients in the depressed group experienced it at least on several days. Amongst the cases, 14 patients (25.5%) reported that they felt tired on several days, 39 (70.9%) of them felt tired on more than half the days and 2 (3.6%) felt tired on nearly every day. Of the controls, 34 patients (61.8%) felt tired on several days and 5 (9.1%) of them felt tired on more than half the days. 16 (29.1%) of controls did not feel tired at all.

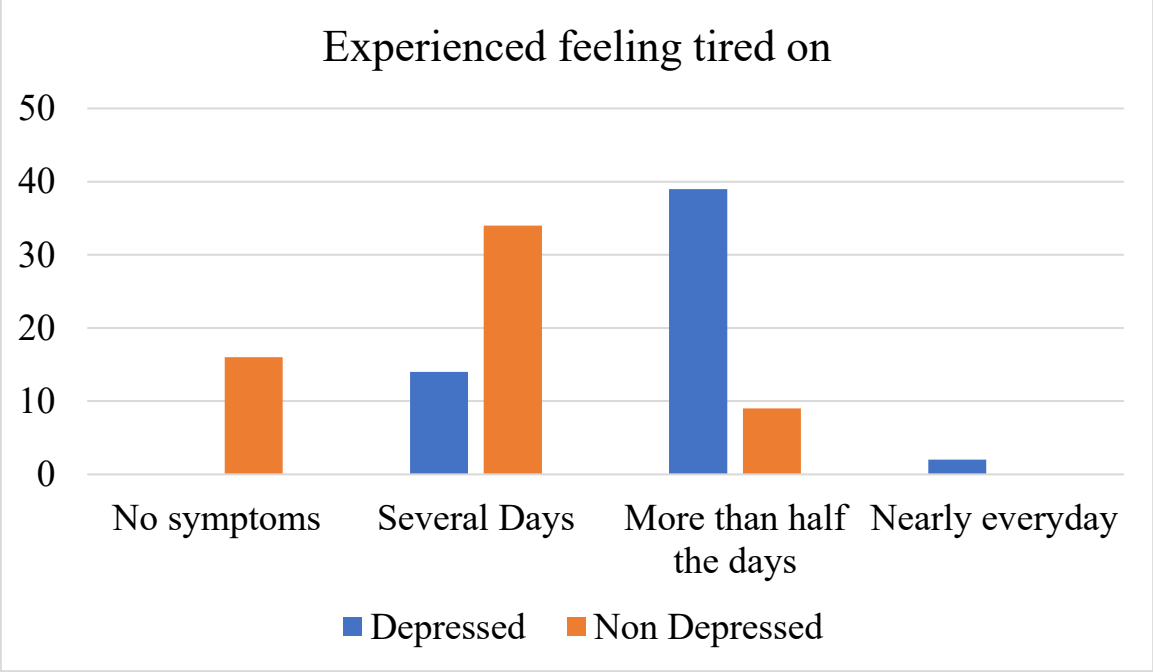

Fig 18 – Bar graph showing distribution of patients experiencing Tiredness

66 patients (60%), in total, reported that they had poor appetite or overeating habits. Amongst cases, 15 (27.3%) patients reported poor eating habits on several

days, 38 patients (69.1%) reported the same on more than half the days and 2 (3.6%) of them reported that they did not have poor eating habits. Of the controls, 8 patients (14.5%) reported poor eating habits on several days, 5 (14.5%) of them reported the same on more than half the days whereas 42 (76.4%) of them reported no symptoms.

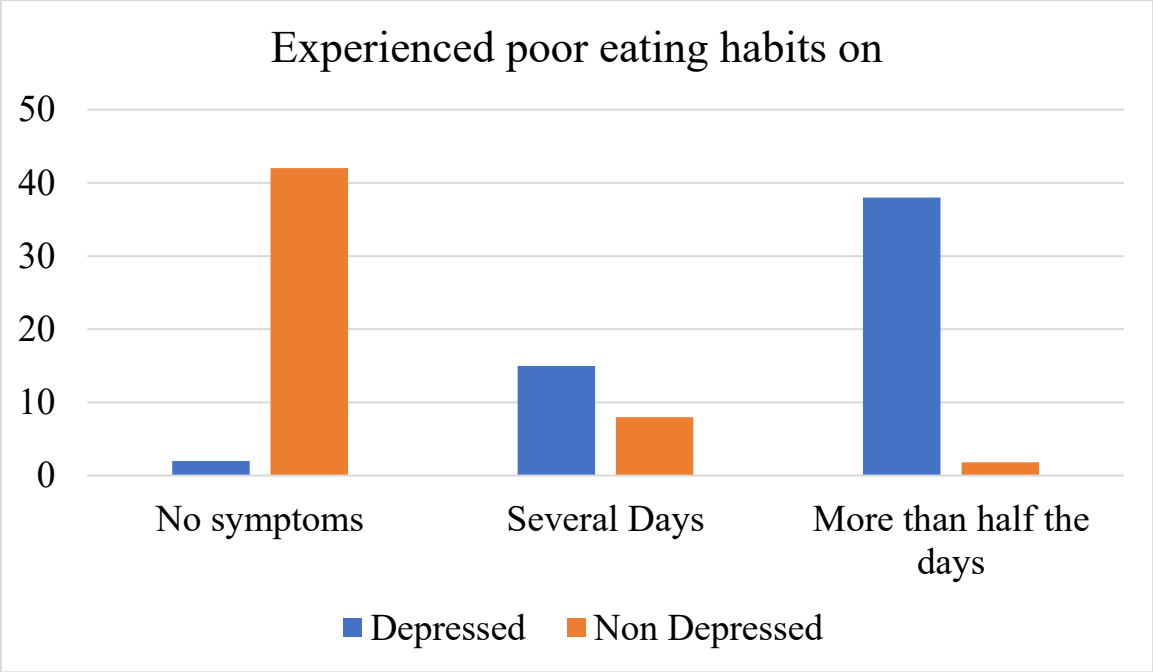

Fig 19 – Bar graph showing distribution of patients experiencing Poor eating habits

A total of 51 (46.4%) patients experienced feeling down, depressed or hopeless. 40 patients (72.7%) of the cases experienced it on several days, and 3 (5.5%) of them experienced it on more than half the days whereas 12 (21.8%) of them did

not report the symptom. 47 patients (85.5%) of the controls experienced no symptoms, and 8 (14.5%) of them experienced the same on several days.

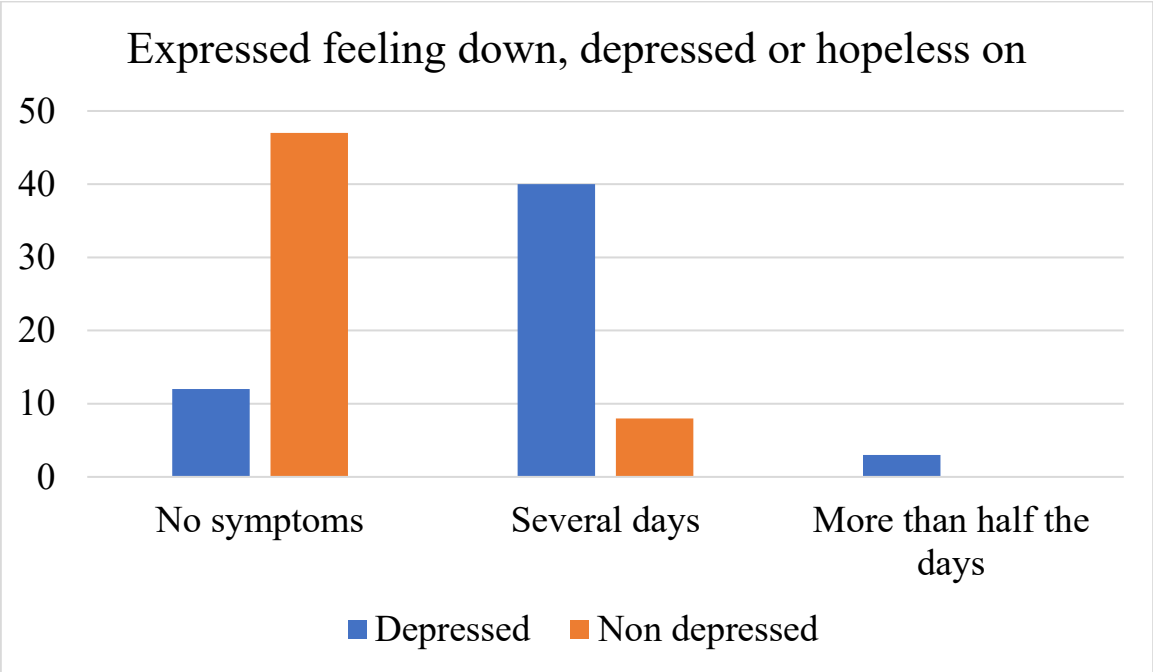

Fig 20 – Bar graph showing distribution of patients feeling down, depressed or hopeless

The least experienced symptom was little interest or pleasure in doing things. Only 16 (29.1%) patients in total reported the same. All of them belonged to the cases group. None of patients in the controls experienced the symptom.

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	0.58
	Non Depressed	55	4.5220	3.30200	
Serum Estrogen	Depressed	55	66.147	14.7212	0.765
	Non Depressed	55	66.944	13.1155	

Table 8 – Significance of Inflammatory markers and Serum Estrogen levels amongst Cases and Controls

CRP values were noted to range from <5 (lowest measurable value) to 34.8 with the mean value of 5.705 in cases and 7.8 in controls. No significant association was noted with p value calculated as 0.51.

IL – 6 values ranged from 2.3 pg/mL to 9.3 pg/mL. The mean value pf the cases was noted to be 6.598 pg/mL, elevated as compared to the controls with 4.802 pg/mL. pg/mL There was no significant association noted, with p value being 0.147.

Total Leukocyte Count was found to be between 5600 to 16200, with the mean value 9699.64 amongst the cases and 9548.73 amongst the controls. p value was 0.778 and no significant association was found.

N-L Ratio ranged between 1.29 to 143 with the mean value of 13.98 amongst the cases and was increased as compared to 4.52 amongst the controls. p value of 0.58 was calculated, suggesting no significant clinical association.

Serum Estrogen values ranged between 40.3 pg/mL and 106.8 pg/mL. Mean value in the depressed group was 66.147 pg/mL and amongst the controls, it was

66.944 pg/mL, implying that both the cases and controls were well matched endocrinologically. No significant association was noted with p value of 0.765.

PARAMETER	CASES	CONTROLS
CRP	0.781	0.525
IL-6	0.537	0.06
TLC	0.286	0.097
N-L Ratio	0.913	0.481

Table 9 – Association of Serum Estrogen with Inflammatory markers

From the above table, it was noted that while correlating Serum Estrogen with each of the inflammatory markers, no association was noted and all p values was found to be above 0.05.

12. 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) [54], 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.

12 (11%) post-menopausal women were included in our study. 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)[55], where a converse proportionality was seen between the age at menopause and depressive symptoms. A 2% decrease in the chance of developing depression in post-menopausal women was noted with increasing menopausal age.

In our study, 58.2% of patients in the cases group hailed from urban areas compared to 50.9% of the controls. There was no significant association noted

between where the patients hailed from and the severity of depression. This contrasts with the study conducted by Sharma S. et al. (2015)[56], where the somatic, psychological, and urogenital symptoms were higher in women from rural parts of the country as compared to the urban. Depressive mood score was observed to be 1.57 ± 1.25 amongst the rural women compared to urban women with a score of 1.33 ± 1.16.

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.[57] 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.

On analyzing the severity of depression among cases (55 patients), we found that 87.2% reported mild depression, and 12.8% reported moderate depression. None of them reported severe depression. Comparing our study to one conducted in Saudi Arabia in 2024 by Kandasamy G. et al.,[58] 13.38% said they experienced no depression; 21.46% said they experienced mild depression; 23.23% said they

experienced moderate depression; 32.83% said they experienced moderately severe depression; and 9.09% said they experienced severe depression.

The commonest of the 11 symptoms 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)[59] 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.[60] 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.[58] also revealed that the commonest symptoms of menopause experienced were hot flushes, night sweats and sleep issues.

In our study, while the prevalence of the reported symptoms was high, all patients only reported mild to moderate symptoms, and severe symptoms were not experienced by any of the patients. This agrees with a study conducted by

Khatoon A et al., [60] where only mild and moderate symptoms were reported, and by Nisar et al., [61] where most women reported mild symptoms.

In our study, sleeping disturbance was the most reported symptom in the PHQ–9 questionnaire. This is noted in several other studies in literature, such as that conducted by Joffe H et al. (2009),[62] where it was found that women with VMS like that of hot flashes 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.[52], 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.[63] 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)[64] concluded that no effect was on CRP levels after estrogen therapy for 48 weeks.

In our study, correlating Serum Estrogen with each inflammatory marker, no association was noted, and all p-values were found to be above 0.05. Serum oestradiol levels were found to be conversely proportional with CRP levels in premenopausal women in a study conducted by Park J M et al. (2020).[65] Estrogen deprivation after menopause was found to enhance IL-6 production in a study conducted by Rachon D et al. (2002).[66] Both the above studies are in contrast to the results of our research.

Strengths of the Study

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. All the patients had several menopausal symptoms according to the menopause rating scale. Thus, the study encompassed an age range of 20 years. The mean of Serum Estrogen in both the groups were comparable, thus, implying a well-matched group.

The patients hailed from both rural and urban areas and hence, a variety of socio-economic strata were involved in the study.

Standard rating scales for both the severity of menopausal symptoms and depression was used in the study.

Limitations of the Study

One of the major drawbacks of the study was the smaller sample size. A greater sample size is needed to generalise the results of the study to the general population.

Most of the patient in the study only belonged to mild or moderate severity of depression. No patients reported severe depression. Hence, the inflammatory markers could not be assessed in patients with major depressive disorder. 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.

13. SUMMARY

A cross-sectional study was conducted in the Department of Obstetrics and Gynaecology and Department of Psychiatry in BLDE (Deemed to be University) Shri B M Patil Medical College, Hospital and Research Centre, Vijayapura on 110 women, presenting to the Out-patient Department, who belonged to the perimenopausal age group on the association of inflammatory markers with depression in perimenopausal women. It was found that the commonest menopausal symptom that patients presented with was Vasomotor symptoms. However, no significant association was noted between depression and any of inflammatory markers included in the study.

14. 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.

15. PROFORMA

ASSOCIATION OF INFLAMMATORY MARKERS WITH DEPRESSION IN PERI MENOPAUSAL WOMEN IN A TERTIARY CARE CENTER IN NORTHERN KARNATAKA - A CROSS-SECTIONAL STUDY

CASE/CONTROL - _____

NAME: AGE:

UH ID OF THE PATIENT: DATE OF STUDY:

ADDRESS AND PHONE NUMBER:

PRESENTING COMPLAINTS:

OBSTETRIC HISTORY: PAST HISTORY:

MENSTRUAL HISTORY: PERSONAL HISTORY:

GPE: PULSE: BLOOD PRESSURE: TEMPERATURE:

WEIGHT: HEIGHT: BMI:

CVS: RS: PE:

MENOPAUSAL RATING SCALE

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply. please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficully in falling asleep, diffcully in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irrtabilty (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restessness, feelling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burrning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

PATIENT HEALTH QUESTIONNAIRE - 9

Over the last 2 *weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite —being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

TOTAL SCORE:

DEPRESSED: YES / NO

SEVERITY OF DEPRESSION:

INVESTIGATION REPORTS:

S. NO	**INFLAMMATORY MARKERS**	**REPORT**
1	CRP	
2	D-DIMER	
3	IL-6	
4	TOTAL WBC COUNT	
5	NEUTROPHIL-LYMPHOCYTE RATIO	
6	SERUM OESTROGEN LEVEL	

16. CONSENT FORM

B.L.D.E. (DEEMED TO BE UNIVERSITY)

SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPURA-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned, _____, D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that Dr Nirupa Nemmara Ramachandran of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am _____ disease (condition). Further, Dr Nirupa Nemmara Ramachandran informed me that he/she is conducting dissertation/research titled "Inflammatory Markers and Association with Depression in Peri Menopausal Symptoms - a cross-sectional study" under the guidance of Dr. Neelamma Patil requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative, and follow-up observations and investigations will be utilized for the study as reference data. Further Doctor has informed me that my participation in this study would help in evaluation of the

results of the study which is useful reference to treatment of other similar cases in near future, and, I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made photographs video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes. The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time, I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged. After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient: Signature of doctor:

Date:

Place:

17. REFERENCES

1. Malhotra N, Malhotra J, Saxena R, Bora NM. Jeffcoate's principles of gynaecology. JP Medical Ltd; 2018 Aug 16.
2. Greendale G., Lee N., & Arriola E.. The menopause. The Lancet 1999;353(9152):571-580. https://doi.org/10.1016/s0140-6736(98)05352-5
3. Who SG. Research on the Menopause in the 1990's: A Report of the WHO Scientific Group. Geneva: World Health Organization. 1996;1:07.
4. Barrett-Connor BH, Collins P, Coope P, Coope J, Dennerstein L. World Health Organization research on menopause: report of a WHO scientific group. WHO Technol. Rep. 1996;866:1-16.
5. Utian WH. The International Menopause menopause-related terminology definitions. Climacteric. 1999 Jan 1;2(4):284-6.
6. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: stages of reproductive aging workshop (STRAW). Climacteric. 2001 Jan 1;4(4):267-72.
7. Gatenby C, Simpson P. Menopause: Physiology, definitions, and symptoms. Best Practice & Research Clinical Endocrinology & Metabolism. 2024 Jan 1;38(1):101855.
8. Harlow SD, Crawford S, Dennerstein L, Burger HG, Mitchell ES, Sowers MF, ReSTAGE Collaboration. Recommendations from a multi-study evaluation of

proposed criteria for staging reproductive aging. Climacteric. 2007 Jan 1;10(2):112-9.

9. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, De Villiers TJ, STRAW+ 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop+ 10: addressing the unfinished agenda of staging reproductive aging. Climacteric. 2012 Apr 1;15(2):105-14.
10. Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. Reproductive health. 2022 Jan 31;19(1):29.
11. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstetrics & Gynecology. 2000 Aug 23;96(3):351-8.
12. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. Menopause. 2014 Sep 1;21(9):924-32.
13. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, Hess R, Joffe H, Kravitz HM, Tepper PG, Thurston RC. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA internal medicine. 2015 Apr 1;175(4):531-9.
14. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas. 1992 Jan 1;14(2):103-15.
15. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Plantinga P. Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-

aged healthy women. Archives of internal medicine. 1994 Oct 24;154(20):2349-55.

16. Guthrie JR, Dennerstein L, Taffe JR, Lehert P, Burger HG. The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. Climacteric. 2004 Dec 1;7(4):375-89.

17. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Waetjen LE, Matthews K. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause. 2019 Oct 1;26(10):1213-27.

18. Freeman EW, Sammel MD. Methods in a longitudinal cohort study of late reproductive age women: the Penn Ovarian Aging Study (POAS). Women's Midlife Health. 2016 Dec;2:1-1.

19. Van Voorhis BJ, Santoro N, Harlow S, Crawford SL, Randolph J. The relationship of bleeding patterns to daily reproductive hormones in women approaching menopause. Obstetrics & Gynecology. 2008 Jul 1;112(1):101-8.

20. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. The Journal of steroid biochemistry and molecular biology. 2014 Jul 1;142:115-20.

21. Berendsen HH. The role of serotonin in hot flushes. Maturitas. 2000 Oct 31;36(3):155-64.

22. El Khoudary SR, Thurston RC. Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. Obstetrics and Gynecology Clinics. 2018 Dec 1;45(4):641-61.
23. Moreau KL, Hildreth KL, Meditz AL, Deane KD, Kohrt WM. Endothelial function is impaired across the stages of the menopause transition in healthy women. The Journal of Clinical Endocrinology & Metabolism. 2012 Dec 1;97(12):4692-700.
24. Portman DJ, Gass ML. Genitourinary syndrome of menopause. Menopause. 2014;21(10):1063-8.
25. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause. 2008 Jul 1;15(4):661-6.
26. Bromberger JT, Kravitz HM, Chang YF, Cyranowski JM, Brown C, Matthews KA. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). Psychological medicine. 2011 Sep;41(9):1879-88.
27. Soares CN. Depression in peri-and postmenopausal women: prevalence, pathophysiology and pharmacological management. Drugs & aging. 2013 Sep;30(9):677-85.
28. Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. Climacteric. 2001 Jan 1;4(3):243-9.

29. Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Prevalence and predictors of depressive symptoms in older premenopausal women: the Harvard Study of Moods and Cycles. Archives of General Psychiatry. 1999 May 1;56(5):418-24.
30. Santoro N. Perimenopause: from research to practice. Journal of women's health. 2016 Apr 1;25(4):332-9.
31. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause. 2003 Jan 1;10(1):19-28.
32. Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). Menopause. 2006 Jan 1;13(1):46-56.
33. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. Obstetrics & gynecology. 2008 Nov 1;112(5):970-8.
34. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician’s guide to prevention and treatment of osteoporosis. Osteoporosis international. 2014 Oct;25:2359-81.
35. Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Rees M. Menopause Nat Rev Dis Primers. 2015; 1: 15004 [Internet]. 2015

36. Yasui T, Maegawa M, Tomita J, Miyatani Y, Yamada M, Uemura H, Matsuzaki T, Kuwahara A, Kamada M, Tsuchiya N, Yuzurihara M. Changes in serum cytokine concentrations during the menopausal transition. Maturitas. 2007 Apr 20;56(4):396-403.
37. Dalal PK, Agarwal M. Postmenopausal syndrome. Indian journal of psychiatry. 2015 Jul 1;57(Suppl 2):S222-32.
38. Tomura S, de Rivero Vaccari JP, Keane RW, Bramlett HM, Dietrich WD. Effects of therapeutic hypothermia on inflammasome signaling after traumatic brain injury. Journal of Cerebral Blood Flow & Metabolism. 2012 Oct;32(10):1939-47.
39. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, Sakkinen PA, Tracy RP. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation. 1999 Aug 17;100(7):717-22.
40. McCarthy M, Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. Journal of neuroinflammation. 2020 Dec;17:1-4.
41. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annual review of medicine. 2000 Feb;51(1):245-70.
42. Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC. IL-1β, IL-6, TNF-α and CRP in elderly patients with depression or Alzheimer's

disease: systematic review and meta-analysis. Scientific reports. 2018 Aug 13;8(1):12050.

43. Orsolini L, Pompili S, Tempia Valenta S, Salvi V, Volpe U. C-reactive protein as a biomarker for major depressive disorder?. International journal of molecular sciences. 2022 Jan 30;23(3):1616.

44. Belmaker RH, Agam G. Major depressive disorder. New England Journal of Medicine. 2008 Jan 3;358(1):55-68.

45. Kulkarni PM. Demographic transition in India. Office of Registrar General of India and CSRD, SSN, JN University, Government of India, New Delhi. 2014 Dec 4

46. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain, behavior, and immunity. 2020 Jul 1;87:901-9.

47. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Archives of general psychiatry. 2006 Apr 1;63(4):385-90.

48. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in womenin

transition to menopause. Archives of general psychiatry. 2004 Jan 1;61(1):62-70.

49. Nobis A, Zalewski D, Waszkiewicz N. Peripheral markers of depression. Journal of clinical medicine. 2020 Nov 24;9(12):3793.

50. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, Le NA, Feinberg R, Tansey MG, Miller AH. What does plasma CRP tell us about peripheral and central inflammation in depression?. Molecular psychiatry. 2020 Jun;25(6):1301-11.

51. Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH. IL-6, IL-18, sIL-2R, and TNFα proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation. Journal of affective disorders. 2015 Aug 15;182:106-14.

52. Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, Hoogendijk WJ. Inflammatory markers in late-life depression: results from a population-based study. Journal of affective disorders. 2008 Mar 1;106(3):249-55.

53. Matthews KA, Schott LL, Bromberger J, Cyranowski J, Everson-Rose SA, Sowers MF. Associations between depressive symptoms and inflammatory/hemostatic markers in women during the menopausal transition. Psychosomatic medicine. 2007 Feb 1;69(2):124-30.

54. Guo L, Ren L, Zhang C. Relationship between depression and inflammatory factors and brain-derived neurotrophic factor in patients with perimenopause syndrome. Experimental and therapeutic medicine. 2018 May 1;15(5):4436-40.

55. Georgakis MK, Thomopoulos TP, Diamantaras AA, Kalogirou EI, Skalkidou A, Daskalopoulou SS, Petridou ET. Association of age at menopause and duration of reproductive period with depression after menopause: a systematic review and meta-analysis. JAMA psychiatry. 2016 Feb 1;73(2):139-49.

56. Sharma S, Mahajan N. Menopausal symptoms and its effect on quality of life in urban versus rural women: A cross-sectional study. Journal of mid-life health. 2015 Jan 1;6(1):16-20.

57. Sun X, Li W, Zhang R, Wang L, Shen X, Lu Y, An J, Wang L, Wang Y, Luo X, Zhu H. Effects of parity on the age at menopause and menopausal syndrome: A cross-sectional study in Northwest China. medRxiv. 2020 Apr 23:2020-04.

58. Kandasamy G, Almaghaslah D, Almanasef M. A study on anxiety and depression symptoms among menopausal women: a web based cross sectional survey. Frontiers in Public Health. 2024 Dec 16;12:1467731.

59. Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle aged women with the Menopause Rating Scale. Maturitas. 2007 Jul 20;57(3):271-8.

60. Khatoon A, Husain S, Husain S, Hussain S. An overview of menopausal symptoms using the menopause rating scale in a tertiary care center. Journal of mid-life health. 2018 Jul 1;9(3):150-4.

61. Nisar N, Sohoo NA, Sikandar R. Menopausal symptoms: prevalence, severity and correlation with sociodemographic and reproductive characteristics. A cross sectional community based survey from rural Sindh Pakistan. Education. 2015 Apr 1;60(222):3-7.

62. Joffe H, Soares CN, Thurston RC, White DP, Cohen LS, Hall JE. Depression is associated with worse objectively and subjectively measured sleep, but not more frequent awakenings, in women with vasomotor symptoms. Menopause. 2009 Jul-Aug;16(4):671-9.

63. Cushman M. Effects of hormone replacement therapy and estrogen receptor modulators on markers of inflammation and coagulation. Am J Cardiol. 2002 Jul 3;90(1A):7F-10F.

64. Störk S, von Schacky C, Angerer P. The effect of 17β-estradiol on endothelial and inflammatory markers in postmenopausal women: a randomized, controlled trial. Atherosclerosis. 2002 Dec 1;165(2):301-7.

65. Park JM, Lee YJ. Serum oestradiol levels are inversely associated with C-reactive protein levels in premenopausal women, but not postmenopausal women. Journal of International Medical Research. 2020 Oct;48(10):0300060520961228.

66. Rachon D, Mysliwska J, Suchecka-Rachon K, Wieckiewicz J, Mysliwski A. Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women. Journal of Endocrinology. 2002 Feb 1;172(2):387-96.

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