CHAPTER 2

Review of Literature
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The term ‘perimenopause’ refers to the phase of the aging process of women preceding the menopause. During this period ovarian function changes, fluctuates and diminishes resulting in a variety of clinical consequences. A number of terms ‘climacteric’, ‘menopausal transition’, ‘menopause’ and ‘postmenopause’ have been used to refer to the stages of this reproductive aging surrounding the final menstrual period (FMP). The term ‘menopausal transition’ and ‘perimenopause’ were recommended for use in place of the term ‘climacteric’ in 1996 with release of the definition by the World Health Organization (WHO). Although the term ‘menopausal transition’ is now used in favor of both ‘perimenopause’ and ‘climacteric’ when referring to the stages of reproductive age in scientific context,[22] normally menopausal transition and perimenopause are used interchangeably.

The term perimenopause was first officially referred to by WHO in 1996 as that period of time immediately before menopause when the endocrinological, biological and clinical features of approaching menopause commences.[23] Based on this definition, many investigators have proposed their own classification criteria to categorize study subjects for research purposes.[24, 25, 26] In a longitudinal study of the experience of menopause, Burger et al[27] and Dennerstein et al[28] used self-reported new onset cycle irregularity as the marker of entry into the early menopause and absence of menses between three and eleven months for entry into the late perimenopause.
The five year longitudinal Massachusetts Women’s Health Study (MWHS) of 2570 women aged 45-55 years produced important information on the mean length of time that women usually spend passing through the menopausal transition. [29] This study reported a median age at inception of perimenopause of 47.5 years and a mean duration of the perimenopausal transition of approximately four years. The natural menopause occurred at the mean age of 51.3 years.

The first standardized classification guidelines for female reproductive aging were prepared in 2001 at the Stages of Reproductive Aging Workshop (STRAW). [22] Then guidelines were proposed in order to develop a relevant and useful staging system (Table 1). The stages were nominated using the final menstrual period (FMP) as a reference point and were based on changes in the pattern of menstrual cycle levels of follicle-stimulating-hormone (FSH).

The STRAW classification system includes five stages (-5 to -1) prior to the FMP (stage 0) and two stages (stage +1 and +2) after FMP (Table 1). The stages are primarily based on the characteristics of the menstrual cycle and secondarily on follicular phase FSH levels. Stages -5 and - 4 (early reproductive age) cover the reproductive years and are characterized by regular menstrual cycle and normal follicular phase FSH levels. Stage -3 (late reproductive age) is characterized by regular menstrual cycle and elevated follicular phase FSH levels. Stages -2 and -1 are the early and late menopausal transitions and +1 and +2 are early and late menopause.
The staging criteria are intended to be guidelines rather than strictly applied ‘diagnoses’, and it is understood that every stage may not occur in individuals and if they do occur in any one individual, they may not occur in the exact sequence provided.

**Table 1: The Stages of Reproductive Aging Workshop (STRAW) criteria**[^22]

<table>
<thead>
<tr>
<th>Stages</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>Reproductive</td>
<td>Menopausal transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Duration of stage</td>
<td>Variable</td>
<td>Variable</td>
<td>a 1 year.</td>
<td>b 4 yrs.</td>
<td>Until demise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual cycles</td>
<td>Variable to Regular</td>
<td>Regular</td>
<td>≥2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Normal FSH</td>
<td>Increased FSH</td>
<td>Increased FSH</td>
<td>Increased FSH</td>
<td>Increased FSH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pathophysiology of menopause:**

The perimenopause is a transition phase from fertile ovulatory cycles with well-characterized hormonal profiles to the postmenopause with low estrogen and progesterone and high gonadotropin (FSH and LH) levels. In order to understand the pathophysiological changes seen at the time of menopause, it is necessary to know the normal function of the hypothalamic-pituitary-ovarian axis in premenopausal women.
The hypothalamus secretes gonadotropin releasing hormone (GnRH) in a pulsatile manner, which in turn regulates the pituitary gland. The stimulated pituitary produces FSH and luteinizing hormone (LH) which function as regulators of ovarian function.

The ovary consists of three main components: granulosa cells, theca cells and the ovarian stroma. Granulosa cells have FSH receptors \[^{30}\] and therefore, under the influence of FSH, convert androgen into estrogen. Theca cells have LH receptors and they under the influence of LH produce androgens and some estrogens. The ovarian stroma produces all three classes of sex steroids: estrogen, androgen, and progesterone. The number of oocytes produced is finite and maximal at 20 weeks of gestational age (7 million). From this time, the number and quality of oocytes decline throughout life, with an exponential decrease from the age of about 37 years, until the ovary is unable to sustain its normal function in the neuroendocrine axis.\[^{31}\] FSH and LH concentrations are controlled by negative feedback from the ovarian hormones, estrogen and progesterone. FSH is also affected by inhibitors which regulate the ovaries and have a negative feedback effect on FSH at the level of pituitary with concentration that are inversely related with FSH.\[^{32, 33}\]

In normal menstrual cycle, the human ovaries regulate the production of a single dominant follicle (DF). After the egg cumulus complex is secreted, the follicle wall transforms into an endocrine gland, the corpus luteum. The corpus luteum secretes estradiol and progesterone in considerable quantities that promote and support pregnancy. FSH is the primary regulator of DF and increase in plasma FSH that occurs during late luteal and early follicular phases of the menstrual cycle, is the basis of DF selection. Activation of LH receptors by LH and human chorionic gonadotropin levels directly to the stimulation of high
levels of androstenedione production which is further metabolized to estradiol. Numerous growth factors produced by follicle can also act via an autocrine or paracrine mechanism to modulate FSH action.\textsuperscript{[34]}

The menopause occurs when the pool of ovarian follicles become depleted. In the years leading up to the menopause, there can be variability in the length of the menstrual cycle, frequency of ovulation and concentration of reproductive hormones.\textsuperscript{[35]} With ovarian aging, the concentration of FSH increases in the early follicular phase leading to estradiol elevation resulting in a shortened follicular phase with earlier or faster growth of follicles.\textsuperscript{[36]} In contrast, the length of the luteal phase and level of progesterone remain the same until very late in the ageing process, which in turn leads to shorter cycles. The concentrations of inhibins are also affected by ovarian ageing.\textsuperscript{[37]} Since DF produces most of the circulating estradiol, its concentration fall dramatically after the menopause, resulting in the increased secretion of FSH and LH from anterior pituitary due to the lack of negative feedback. This gives rise to the postmenopausal state of hyper gonadotrophic hypogondism.\textsuperscript{[38]}

The next section describes in detail the hormonal changes associated with perimenopause which is central to understand the clinical and metabolic consequences and also to plan the effective management.

\textbf{Hormonal changes with advancing female reproductive age:}

One of the earliest descriptions of the hormonal changes occurring with advancing reproductive age was by Sherman and Korenman.\textsuperscript{[39]} The major feature of reproductive aging in this first description were a monotropic rise in FSH secretion, folliculogenesis with variable evidence of ovulation and periods of hypo-estrogenemia associated with substantial
elevation of FSH but little change in LH. In the second study by the same authors, of eight regulatory cycling women aged 46-56 years and two women with cycles of variable length, the authors observed normal follicular maturation and corpus luteal function in the presence of high menopausal levels of LH and FSH and diminished levels of estradiol and progesterone. They hypothesized that the variability in cycle length during the perimenopause was due to either irregular maturation of residual follicles with diminished gonadotropin stimulation or anovulatory vaginal bleeding that may follow estrogen withdrawal evidence of corpus luteal function.[40]

Metcaff and Colleagues conducted an extensive longitudinal study of weekly urinary hormone excretion in 308 women aged > 40 years.[41-44] In these studies, irregular cycles were characterized by marked variations in estrogen excretion with both persistently decreased and persistently increased excretion. They were associated with increased FSH and LH excretion. Based on these results, Metcalf stated that ‘there is no evidence for a gradual decline in ovarian function during the transition. The only generalization which can be safely made about menstrual cycles in perimenopausal women is that they are richly varied. Unpredictability is the norm, and is in marked contrast to the regular succession of ovulatory cycles observed in premenopausal women.’[44] It was further concluded that anovulatory cycles and cycles with elevated levels of FSH and LH are common in perimenopause.

The possible relationship between perimenopausal hyper-estrogenism with elevated FSH levels is a matter of concern among some researchers.[45, 46] Naturally elevated estrogen levels have been associated with thickening[47] and even cystic glandular hyperplasia of the
endometrium. [48] Given the characteristics of the elongated cycles, it is paramount to determine the real impact on health of this hormonal imbalance, particularly because nearly 47% of women experience at least five years of menopausal transition. [49] One of the suggested causes for this elongation is the delay in the onset of ovarian response which seems to be due to a temporary lack of ovarian responsiveness to FSH. [50] 

In the British longitudinal FREEDOM study, which is a cohort study designed to determine the endocrine changes, the authors ascertained the different endocrine patterns in a representative population and developed a staging system. [51] In these study, 112 women aged 30 to 58 years collected daily urine samples over a 6 to 8 months period and recorded their menstrual periods. A total of 36,786 samples were analyzed for FSH, LH, estrone-3-glucuronide and pregnanediol 3-glucuronide. Based on the results, a classification of five sequential endocrine stages of reproductive aging was developed: stage 1, regular menstrual cycles with mean initial (day 1-5) FSH less than 5 IU/L; stage 2, regular cycles with FSH greater than 5 IU/L; stage 3, menstrual irregularity (with the appearance of delayed-response cycles); stage 4, acyclical ovarian activity with no evidence of ovulation and luteinization; and stage 5, ovarian quiescence and persistently raised gonadotropins.

The second stage [51] was associated with a rise in early-cycle FSH levels and a decrease in follicular phase length, a finding noted by other authors [52, 53] and suggested to be the first indicator of reproductive aging. Shideler et al [54] observed low urinary estrogen and high urinary FSH during the follicular phase of the elongated cycles, followed by an increase in estrogen excretion (Fig 1). Late reproductive age featured shortened follicular phase associated with increase in estrogen excretion. [55]
Fig 1: Estrogen (E$_1$ Conju) and pregnanediol gluconate (PDG) excretion in a single subject spanning two ovulatory cycle shows a biphoric estrogen curve, a normal PDG risk, and a simultaneous fall in estrogen and PDG at the end of the cycle. In the second cycle, there is a 20 day interval between the menses and follicular phase rise in estrogen excretion, which appear to be normal. During the luteal phase, however, estrogen rises again forming a peak that is almost twice as high as the prior follicular phase.[54]

Luteal out-of-phase (Loop) event:

Hale et al,[56] recently have reported increased ovulatory cycle estradiol and decreased luteal-phase progesterone with progression of STRAW stage (-4 to -1). The estradiol levels were particularly variable (normal to high) during the menstrual and luteal phase of the cycles. In individual ovulatory cycles, these high menstrual and luteal-phase estradiol levels were all found to be associated with a common aberrant estradiol secretion pattern. This aberrant estradiol secretion pattern was termed a ‘luteal out-of-phase (Loop)
and was similar to the rise in luteal-phase estrogen excretion described during elongated ovulatory cycles in the FREEDOM study \[50\] and in a single subject illustrated by Shideler et al. \[54\] The Loop events occurred in six subjects (three STRAW stage-2 and three STRAW stage -1) and were all characterized by a second high peak in estradiol at the mid-luteal point, causing markedly elevated estradiol levels during the luteal phase of current ovulatory cycle and the menstrual phase of the subsequent cycle (Fig 2). The US Study of Women’s health Across the Nation (SWAN) \[58\] reported within-cycle hormone excretion pattern consistent with LOOP events.

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### Fig 2: Estradiol (●), progesterone (○) and FSH (△) profiles in four menopausal transitional subjects.\[57\]
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The LOOP phenomenon is likely to represent one of the phases in the normal progression of reproductive aging and may be a common endocrinological event that heralds the onset of irregular menstrual cycles and the early menopausal transition. The markedly high FSH levels which cause the LOOP event are most likely the result of low or absent levels of inhibin B, which in turn are due to the diminishing number of ovarian follicles, which is accelerated dramatically to the last decade of menstrual life.

Role of inhibins and anti-mullerian hormone (AMH) in the hormonal changes associated with advancing female reproductive age:

Women with irregular menstrual cycles in menopausal transition have highly complex and variable endocrine and metabolic events. There are substantial elevation in FSH, elevation in LH, unpredictable changes in estradiol (higher or lower than normal), fall in progesterone and irregular menstrual cycles. Studies on inhibin and anti-Mullerian hormone (AMH) have helped in understanding the mechanisms of these reproductive hormone changes.

The Inhibins:

The inhibins are part of the complex hypothalamic-pituitary-ovarian axis that is a closed loop negative feedback system. Inhibins along with ovarian steroid regulate the secretion of pituitary gonadotropins. Inhibin B is a product of central follicle granulosa cells and levels fall with the decline in follicle numbers with reproductive aging. The fall in inhibin B in late reproductive age has been shown to trigger the monotropic rise in follicular phase FSH. The elevation in FSH, in turn, maintain and sometimes increase the productions of estradiol from granulosa cells.
Although both isoforms of inhibin seem to have similar biological properties, their synthesis is regulated differently during the follicular and luteal phase. Under the influence of FSH, inhibin B is secreted mainly during the early follicular phase, with level decreasing in mid-follicular phase and becoming undetectable after the LH surge. LH-induced inhibin A levels, however, are low during the first half of the follicular phase but increase gradually during the mid-follicular phase with a peak during the luteal phase.\textsuperscript{[66]}

Several clinical studies have helped to understand role of inhibins in reproductive endocrinology. The Melbourne Women Midlife Health Project\textsuperscript{[67]} showed that an increase in serum FSH and a decrease in estradiol and inhibin were the major endocrine changes associated with menopausal transition. Klein et al\textsuperscript{[68]} showed monotropic FSH rise only affects levels of inhibin B but not inhibin A and later studies proposed that loss of inhibin B negative feedback on FSH as the most important factor in the increase in FSH with advancing reproductive age.\textsuperscript{[69]}

The Anti-Mullerian Hormone (AMH):

AMH is a dimeric glycoprotein and member of the family of growth and differentiation factors that are best known for their effects on sexual differentiation.\textsuperscript{[70]} Under the influence of AMH, the gonads differentiate into testis; AMH is not expressed during female sexual differentiation. After development of the testes and ovaries, AMH is produced by Sertoli cells in the male or granulosa cells in the female. It is produced steadily by primary follicles until they grow to approximately 8mm in diameter.\textsuperscript{[71]} Most AMH is seen in the granulosa cells of the pre-antral and small antral follicles (<4 mm) with almost no expression in follicles with a diameter of >8mm.\textsuperscript{[72]} AMH inhibits FSH-dependent
follicle growth in a time-dependent manner, mainly as a result of reduced granulosa cell proliferation, and may play a role in follicle recruitment and selection.\textsuperscript{[73]} Unlike the gonadotropins and inhibins, AMH does not appear to vary throughout the menstrual cycle or through pregnancy.\textsuperscript{[74]}

Few studies on the changes in AMH with reproductive aging showed, AMH levels on day 3-5 to be stable between ages of 18-29 years, then fell more than 10-to 20- folds across the 29-37 year age groups with minimal change in FSH.\textsuperscript{[70, 75]} In subjects aged >45 years (including STRAW stage -3 and -2 and -1 group), the FSH: inhibin B ratio rather than the individual’s age was invariably correlated with AMH. No change in AMH was observed throughout the individual menstrual cycles, and AMH did not appear to be influenced by the ovulatory status of a cycle.\textsuperscript{[75]}

\textbf{Classification of the endocrine changes from late reproductive age to menopause:}

On the basis of AMH, inhibin and secretion pattern data, Robertson et al\textsuperscript{[75]} proposed a classification system based on four cycle types. This system builds on stages 1-4 proposed by Miro et al\textsuperscript{[51]} based on FREEDOM urinary data, and includes the serum inhibin and AMH data. Type 1 was characterized by an isolated and age-related decrease in AMH (no elevation in FSH); Type 2 by low inhibin levels, elevated early cycle FSH and further fall in AMH; Type 3 by fall in progesterone, further elevations in FSH and elevation in LH, and Type 4 by anovulation, undetectable inhibin A and B levels, and further marked elevations in FSH and LH.\textsuperscript{[75]}

Although the type number tends to increase through the four STRAW stages, no cycle type is strictly associated with any one STRAW stage. It is likely that individuals
progress through the cycle type in a mostly forward and occasionally back-and-forward fashion, or may even skip a stage or more altogether. These hormonal and menstrual features of each stage during the perimenopause are summarized in the Table 2.

Table 2: The hormone and menstrual features of each stage during perimenopause.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid to late reproductive age; STRAW-4</td>
<td>- Regular menstrual cycles</td>
</tr>
<tr>
<td></td>
<td>- Decreased AMH</td>
</tr>
<tr>
<td></td>
<td>- Normal FSH</td>
</tr>
<tr>
<td>Late reproductive age; STRAW-3</td>
<td>- Regular menstrual cycles</td>
</tr>
<tr>
<td></td>
<td>- Further fall in AMH</td>
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<tr>
<td></td>
<td>- Elevation in early FSH</td>
</tr>
<tr>
<td></td>
<td>- Falls in early-cycle inhibin B</td>
</tr>
<tr>
<td>Early menopausal transition; STRAW-2</td>
<td>- Further fall in AMH and inhibin B</td>
</tr>
<tr>
<td></td>
<td>- Further elevations in FSH and first observable elevation in LH</td>
</tr>
<tr>
<td></td>
<td>- Fall in luteal-phase progesterone levels</td>
</tr>
<tr>
<td></td>
<td>- Initial appearance of LOOP cycles associated with more marked falls in luteal-phase progesterone, and variable to high menstrual- and/or luteal phase estradiol, cycle irregularity with a predominance of short and normal length cycles</td>
</tr>
</tbody>
</table>
Late menopausal transition; STRAW-1

- Further elevation in FSH and LH
- Continuing LOOP events but more with increasing ‘lag phase’ and less frequent high peaks in estradiol
- Cycle irregularity with a predominance of elongated menstrual cycles

Menopause; STRAW +1

- Anovulatory cycles and increase in mean cycle length
- Further elevation in FSH and LH
- Undetectable inhibins
- Variable to low estradiol

Other hormonal changes associated with perimenopause:

Apart from the reproductive hormone changes discussed above, metabolism of several other hormones seems to be affected by menopause.\(^{[77]}\) (Fig 3)
Apart from elevations in FSH and LH, other pituitary hormones are not affected. Growth hormone, thyroid-stimulating-hormone (TSH), and adrenocortico-tropic hormone (ACTH) levels are normal. Serum prolactin levels may be very slightly decreased because prolactin levels are influenced by estrogen status.
Both the postmenopausal ovaries and the adrenal gland continue to produce androgen. The ovary continues to produce androstenedione and testosterone but not estradiol and this has been shown to be at least partially dependent on LH. The adrenal gland also continues to produce androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS); primarily as a function of aging, these values decrease somewhat, although cortisol secretion remains unaffected. It also appears that much “ovarian” testosterone production may actually arise from the adrenal. Most likely, this production is by indirect mechanisms due to the adrenal supplying precursor substrate (DHEA and androstenedione).

Although DHEAS levels decrease with age (20% per year), recent data have suggested that levels transiently rise in perimenopause before the continuous decline thereafter.

Testosterone levels also decline as a function of age, which is best demonstrated by the reduction in 24-hour mean levels. Because of the role of the adrenal in determining levels of testosterone after menopause, adrenalectomy or dexamethasone treatment results in undetectable levels of serum testosterone. Compared with total testosterone, ‘free’ testosterone levels seem to be relatively higher in menopausal women.

**Thyroid dysfunction:**

Many of the menopausal manifestations are similar to those accredited to thyroid dysfunction. Common menopausal complaints of lethargy, tiredness, and weight gain are often blamed on thyroid hormone dysfunction. Similarly, hyperthyroidism can result in general exhaustion following the over activity that become evident. Hence in caring for peri-
and postmenopausal women, full thyroid evaluation and function tests are strongly recommended. It is important to evaluate the thyroid function with increasing age, since postmenopausal women are at increased risk of both osteoporosis and cardiovascular disease, and untreated thyroid disease may exacerbate these risks. A significant decrease of FSH levels was also observed in hyper and hypo thyroid (-52% and -43% respectively) in postmenopausal women. Under this circumstance an altered thyroid functions affects serum inhibin B levels. Early thyroid problems in perimenopausal can be easily treated and the quality of life is greatly improved and conditions such as elevated cholesterol, apathy and anxiety can be relieved.

Adipose tissue and body composition:

Menopause may cause alterations in adipose tissue and fat mass. In a study by Douchi and associates, 365 pre and postmenopausal women were analyzed for lean body and fat mass. With advancing age and postmenopausal status, lean mass significantly decreased, whereas the percentage of body and trunk fat increased, suggesting menopause may be responsible for the decrease in the trunk and total body lean mass.

Another study by Ferrara and colleagues analyzed adipose tissues of perimenopausal and postmenopausal women to determine if there are differences in metabolism. Using an in vitro model, these investigators compared adipose tissue in the abdominal and gluteal subcutaneous regions in women who were matched for race, body mass index (BMI) and percentage of body fat. The two groups of women had similar fat cell size. The postmenopausal women had significantly lower lipolysis in the gluteal fat cells and significantly higher lipoprotein lipase activity in both the abdominal and gluteal regions,
indicating slower adipose tissue metabolism when compared with younger women. These metabolic changes may be related to various hormonal changes associated with perimenopause.

However, other studies have also demonstrated that advancing age is responsible for the weight gain in women, not the menopausal transition. Davies [89] investigated two cohorts of women through the menopausal transition. Weight rose linearly as a function of age in both patient groups and menopausal status did not had any effect on weight gain.

Clinical symptoms of the Menopause:

Many symptoms are associated with menopause and seem to be directly related to a decrease in estrogen levels (Table 3) and are experienced by over 70% of women. Most menopausal symptoms can be classified into either psychological or physical in nature, the physical including vasomotor and sexual symptoms.
Table 3: Disorders related to hypoestrinism

<table>
<thead>
<tr>
<th>Directly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic vulvovaginitis</td>
</tr>
<tr>
<td>Urethral syndrome</td>
</tr>
<tr>
<td>Skin, hair, and breast changes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirectly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Psychosexual problems</td>
</tr>
<tr>
<td>Functional cardiac diseases</td>
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</table>

<table>
<thead>
<tr>
<th>Probably</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological conditions</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
</tr>
<tr>
<td>Lipid metabolism</td>
</tr>
</tbody>
</table>

Physical:

The menopause is classically associated with the onset of vasomotor symptoms, which include hot flushes and night sweats. Other physical symptoms include palpitations, headaches, bone and joint pain, asthenia, tiredness, lower back ache, feeling bloated, flatulence, lack of energy, decrease in physical strength, frequent urination, skin changes and increased facial hair. The determinants of experiencing menopausal symptoms are complex, including biological, psychological and social factors. Polymorphism in the estrogen synthesis and metabolic pathways are also seems to be associated with the symptoms experienced during the menopausal transition.\[^{90, 91}\]
Hot flushes:

Hot flushes are the most common symptoms of the perimenopause and occur in 75% of perimenopausal women, although only 30% of women seek medical help.\[38\] The hot flash usually refers to the acute sensation of heat, while the flush or vascular episode includes changes in the early perception of this event and other skin changes (including diaphoresis). Frequent vasomotor symptom can be disabling, affecting a woman’s social life, psychological health, sense of well-being and ability to work. Women with hot flushes are more likely to experience disturbed sleep, depressive symptoms and significant reduction in quality of life compared with asymptomatic women.\[92\] They typically last for 0.5-5 years after the natural menopause, but may present for as long as 15 years in a small percentage of women and they also tend to be more severe in women with surgical induced menopause.\[93\] They tend to occur most often in the first year after the final period, and can occur at any time during day or night.

Despite multiple theories, the exact pathophysiology of hot flush is not yet known. It is postulated that they are a result of a central disorder of temperature regulation, and that the hypothalamus is pivotal as hot flushes have been recorded in patients with pituitary insufficiency.\[94\] It is recognized that hot flushes occur with the pulsatile release of LH.\[95\] Increase in plasma levels of proopiomelanocortin peptides (ACTH, β-endorphin) at the time of flush has been reported.\[96\] But these occurrences are thought to be epiphenomena that result as a consequences of the flush and are not related to its etiology. The flush has been well characterized physiologically. It results in heat dissipation as witnessed by an increase in peripheral temperature (finger, toe); a decrease in skin resistance, associated with diaphoresis; and a reduction in core temperature (Fig 4).\[97\] There is peripheral
vasodilatation,\textsuperscript{98} acute rise in the skin temperature of several degree centigrade,\textsuperscript{99} a transient increase in heart rate associated with fluctuations in the electro-cardio-graphic base line.\textsuperscript{100} The symptom usually last for 4-5 minutes. Estrogen significantly eliminates hot flushes but its mechanism of action is unknown.\textsuperscript{98}

\textbf{Fig 4: Temperature responses to two spontaneous flashes (–) and evoked flashes (\textasciitilde).}

One of the primary complaints of women with hot flushes is sleep disruption. They may awaken several times during night and require changes of bedding and clothes because of diaphoresis. Nocturnal sleep disruption in postmenopausal women with hot flushes has been well documented by electroencephalographic (EEG) recordings.\textsuperscript{101} Sleep efficiency is
lower, and the latency to rapid eye movement (REM) sleep is longer in women with hot flushes compared to asymptomatic women.\textsuperscript{[102, 103]} This disturbed sleep often leads to fatigue and irritability during the day.

Numerous factors are associated with the frequency and intensity of vasomotor symptoms, including race. African-American women tend to have a higher frequency of hot flushes compared to white American women.\textsuperscript{[104]} In United States the incidence of these episodes varies in different ethnic groups. Symptoms are greatest in Hispanic and African American women, intermediate in white women, and lowest among Asian women (Fig 5).\textsuperscript{[105]} Asian women again widely differ in presentation of vasomotor episodes.\textsuperscript{[106-114]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Study of Women’s Health across the Nation (SWAN): Symptom severity\textsuperscript{[105]}}
\end{figure}
It has also been hypothesized that increased adiposity in a woman could be associated with decreased vasomotor symptom during menopause because of conversion of androgens to estrogens in body fat. However, recent thermoregulatory models have postulated that increased adipose tissue would actually be associated with greater likelihood of vasomotor symptoms. [115] These hypotheses were evaluated in the study of women’s health across the nation; a multi-ethnic, community based observational study of 1776 US women aged 47-59 years transition through the menopause. Their findings supported the thermoregulatory model of vasomotor symptoms. [115]

**Palpitations:**

Palpitations can be caused by a variety of cardiac disorders, such as valvular heart disease, cardiomyopathy and coronary artery disease, but the most common cause is primary cardiac arrhythmias. Several non-cardiac diseases may affect cardiac rhythm resulting in palpitations. Palpitations are common in women at all ages, especially during the luteal phase of the menstrual cycle, during pregnancy, and during the perimenopausal period. [116] Palpitations occur frequently in perimenopausal women, are usually benign and seem to be related to the increased sympathetic activity caused by menopause. [117] Palpitation can lead to a poorer quality of life. [118] The reasons and mechanisms of palpitation in perimenopause are unclear but it has been shown that 17-β-estradiol has a significant effect on electrophysiological parameters, thereby suggesting that it may play a role in the development of palpitations in women. [117]
Headaches:

Incidence of migraine headaches is more in women than in men. Menses, pregnancy and menopause affect the frequency and treatment of headaches.\[119\] The mechanisms that underline the sex-related differences in the prevalence of these conditions remain not clear and may involve both physiological and psychosocial factors. Several pain conditions localized to the craniofacial region show a remarkable sex-related difference in their prevalence and their presentation. In terms of physiological factors relevant to the origin of headaches, direct evidence of sex-related differences in the properties of dual afferent fibers or durally activated second order trigeminal sensory neurons has yet to be provided. However, there is some evidence, which shows sex-related difference to occur in the response properties of afferent fibers and second order trigeminal neurons in various chronic pain conditions. The sex related differences in the trigeminal nociceptive processing primarily seem to be affected by estrogens which appear to alter the excitability of trigeminal afferent fibers and sensory neurons to noxious stimulation of craniofacial tissues.\[120\]

Estrogen and progesterone seems to have paradoxical effects on incidence of migraine. Estrogen withdrawal can trigger migraine headaches, while administration of estrogen and progesterone also can exacerbate migraine. Women’s Health Study \[121\] showed the use of hormone therapy to be associated with higher incidence of migraines than non-users. The Head HUNT study \[122\] also revealed similar results and concluded that it is difficult to know whether hormone therapy actually precipitates headaches or whether hormone therapy was used partly because of headaches.
Bone and joint pain:

Complaints of musculoskeletal pain are more common than vasomotor complaints amongst perimenopausal women. Sievert and Goode-Null, in a recent study, [123] examined musculoskeletal pain among women of menopausal age in the city of Puebla, Mexico. Symptoms frequencies were collected by open-ended interviews and with structured symptom list that questioned the symptom experience during the two weeks prior to interview. In response, bone pain was volunteered by 47% of respondents as a symptom associated with perimenopause. From the structured symptom list, 55.8% and 55.6% reported back pain and joint stiffness during the two weeks prior to interview. Women with back pain and joint stiffness reported reduced quality of life and were less active during their leisure time. These authors concluded that: ‘while the menopause is not necessarily a risk factor for musculoskeletal pain, it is important to recognize the pervasiveness of this complaint among women of menopausal age’.

Restless leg syndrome:

Restless leg syndrome is a common symptom mainly presenting at night. Female sex hormone may be responsible for the high prevalence of this syndrome in women and may influence the severity during female reproductive life. The severity seems to increase with the onset of perimenopause with almost 69% of patients reporting worsening of the symptoms.[124]

Asthenia and tiredness:

Compared to men, women seems to have better sleep quality, with longer sleep times, shorter sleep-onset latency and overall higher sleep efficiency. However, women have
more sleep-related complaints than men. Normal physiological periods including puberty, menstruation, pregnancy and menopause, are associated with alterations in sleep patterns. Gender differences in normal sleep may contribute to the sleep disorders. Studies of insomnia indicate a female predominance, with increased divergence of prevalence between men and women as they grow older.\[125\] The cause for this disorder may be directly due to hormonal changes associated with advancing reproductive age or may be secondary to depression, stress and other behavioral factors, night time hot flushes, sweats or restless legs causing disturbed sleep patterns resulting in weakness and tiredness. In addition, several life factors like financial, family, mental, relationship or work related issues can all effect sleep quality. Reducing the hot flushes may be some extent improve the sleep quality but may not alleviate the associated primary sleep disorders.\[126\]

**Urogenital symptoms:**

Urogenital symptoms are the most prevalent consequences of the perimenopause, and affects large number of women.\[127\] It can lead to numerous symptoms, and in turn, can have an adverse effect on quality of life.\[128\] Initially symptoms of dryness and atrophic changes occur in 21% to 15% of women respectively. However, these findings increase with time, and by four years these incidence are 47% and 55% respectively.\[129, 130\]

Estrogen and progesterone receptors are found throughout the urogenital tract and are sensitive to any hormonal changes that occur during perimenopause.\[131\] Menopause causes characteristic changes in the vaginal area including decreased blood flow, epithelial thinning, reduced elasticity and distensibility of the vaginal walls, which collectively can result in dyspareunia.\[132\] The epithelium becomes less cellular, susceptible for injury thus
resulting in vaginal bleeding. The loss of cellular glycogen causes reduced lactic acid which in turn increases the vaginal pH to 6-8 compared to more acidic pH of 4-5 in the premenopausal state. The relative alkalinity increases the susceptibility of infections.[133] All these local changes cause vaginal irritation, dryness, burning and itching.[133, 134]

Estrogen receptors are present in the bladder, urethra and pelvic floor and sex steroid are important for normal physiologic functions of lower urinary tract during adult life.[135] The estrogen decrease associated with perimenopause also alters the quality of connective tissue[136] and this overall changes in the physiological environment has been implicated in the development of numerous urogenital symptoms like dysuria, frequency, nocturia, urgency and recurrent bladder infections, which can compromise bladder function leading to urinary incontinence,[132, 135, 137] further affecting the quality of life.

Irregular vaginal bleeding and menorrhagia are often present during menopause. These symptoms are due to the depletion of the ovarian follicle pool leading to an increase in the number of anovulatory cycles. This menstrual blood loss may increase with menopausal age.[138]

**Breast tenderness:**

Breast tenderness tends to occur primarily at the early stages of the perimenopause, and the frequency of symptom severity reduces with age. This symptom can also occur as a result of taking hormone replacement therapy, and may occur either as a result of the progesterone or if there is a sudden increase in the circulating levels of hormone. A significant reduction in the area and percentage of breast tissue on mammography is also noted in longitudinal studies of perimenopausal women.[139]
Sexuality:

Women are often reluctant to discuss their sexual attitudes and experiences surrounding sexuality at the menopause as this is a sensitive and personal area. A woman’s ethnic and cultural background shapes her attitude to the menopause, as well as her expectations regarding sexuality and intimate relationships. It is difficult to disentangle the effects of aging and the hormonal changes of the menopausal transition, but recent longitudinal studies have been helpful. There are number of factors that can impinge on sexuality, making it difficult to evaluate. These include hormones, ageing itself, length of a relationship, declining physical health, education and mental health. The midlife may produce considerable psychosocial stress for women who are confronted with loss of youth and reproductive function, which may negatively affect the attitude to the menopause in the West than in traditional Far-Eastern societies. Coming to terms with children leaving home may leave less of an adverse impact than was previously thought, particularly if it is for a positive reason, e.g. marriage or for education, then caring for elderly relatives. A partner’s ill health, losing a partner, divorce or redundancy also affects the sexual life. Career changes for the women who may feel vulnerable going back to work after a long period of time out may increase these stressors and affects sexual function.

Changing hormonal metabolism associated with menopause affect sexuality and loss of libido. Sexual behavior involves motivational behavior which is related to testosterone and the biological response which is related to estrogen and the interplay between these two responses and the factors is quite complex. A loss of libido, sensitivity and response are all commonly reported following the decreased concentration of estrogen and testosterone. These could be due to a change in self-image at the time of menopausal
transition, a direct result of hormone deficiency or partner associated problems, an direct
effect of aging or a combination of all these. The effect of estrogen deficiency on the
integrity of the sexual tissues may also have a marked effect on sexuality.\textsuperscript{[150]} Lack of
estrogen may result in marked dyspareunia, vaginal infections and vaginal prolapse.\textsuperscript{[149]}
Along with hormonal alterations, the age-related changes may further add to the impact on
sexual behavior. These involve chronic illnesses (e.g. osteoarthritis, COPD), medications
(antidepressants may effect libido), surgical procedures (e.g. mastectomy affecting self-
image, bilateral salpingo-oophorectomy affecting hormone levels) and biological aging
(vaginal dryness).

Dennerstein and Lehert were able to trace out the effects of psychological as well
hormonal factors, ageing and the menopause using techniques of auto-correlation and cross-
correlation together with structured equation modeling.\textsuperscript{[151]} When psychosocial and life style
status was added to the model, mood was found to be the only additional variable affecting
sexual function. Dennerstein et al\textsuperscript{[152]} constructed a reasonable and practical model based on
these factors (Fig 6), where estradiol is seen to affect sexuality indirectly via its
improvement in vasomotor symptoms, sleep etc., which impact on health and ultimately on
mood. Vaginal dryness also improves. The model reflects the circular model of Basson \textsuperscript{[153]}
where intimacy and feelings for the partner are reflected in the sexual response. Daily
hassles and stress feed in via mood. These models provide a much greater understanding and
appreciation of the complexity of female sexuality, with all the factors that can impact on it.
Psychological Symptoms:

Psychological symptoms are frequently reported during perimenopause. These include depression, loss of memory, irritability, poor concentration, tiredness, feeling anxious/nervous, dissociation with personal life, feeling of tiredness and loss of confidence. There is higher incidence of depressive illness in women than in men, and this is exacerbated during the perimenopause. The causes and mechanisms of psychological symptoms in perimenopause seem to be multifactorial with estrogen playing a major role.

The brain is an active site for estrogen action as well as estrogen formation. Estrogen activity in the brain is mediated via ER α and ER β receptors. Figure 7 illustrates the predominance of ER β in the cortex (frontal and parietal) and the cerebellum, based on
the work in the rats. While $17\beta$ estradiol is a specific ligand for both receptors, certain synthetic estrogens (e.g., diethyl-stilbestrol) have greater affinity for ER $\alpha$, while phytoestrogens have a greater affinity for ER $\beta$.

**Fig 7**: ‘A’, shows specific brain functions in different regions and ‘B’ shows distribution of estrogen receptors, ER $\alpha$ and ER $\beta$ in the rat brain. ‘ARC’ arcuate nucleus; ‘POA’ pre optic area; ‘SO’ supra optic nucleus; ‘PVN’ para ventricular nucleus; ‘VMN’ ventra medial nucleus.

There are multiple actions of estrogen on the brain as reviewed by Henderson (Table 4), thus there are important functions linked to estrogen that contribute to well-being in general and, more specifically, to cognition and mood.

Cognitive decline in postmenopausal women is related to ageing as well as to estrogen deficiency. The literature is somewhat mixed in sharing whether there are benefits of estrogen in terms of cognition. In more recent studies, verbal memory appears to be enhanced by estrogen and has been found to be correlates with acute changes in brain imaging signifying brain activation.
Table 4: Effects of estrogen on brain function [158]

<table>
<thead>
<tr>
<th>Organizational actions:</th>
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<tr>
<td>Effects on neuronal number, morphology, and connections occurring during critical stages of development</td>
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<th>Neurotropic actions:</th>
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<tr>
<td>Neuronal differentiation, Nuerite extension, Synapse formation, Interactions with neurotrophins</td>
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<tr>
<th>Neuroprotective actions:</th>
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<tbody>
<tr>
<td>Protection against apoptosis, Antioxidant properties, Anti-inflammatory properties, Augmentation of cerebral blood flow</td>
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<tr>
<td>Enhancement of glucose transport into the brain</td>
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<tr>
<td>Blunting of corticosteroid response to behavioral stress</td>
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<td>Interactions with neurotrophins</td>
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<tr>
<th>Effects on neurotransmitters:</th>
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<tbody>
<tr>
<td>Acetylcholine, Noradrenaline, Serotonin, Dopamine</td>
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<tr>
<td>Glutamate, Gamma and neurobutyric acid, Neuropeptides</td>
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<th>Effects on glial cells</th>
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<table>
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<tr>
<th>Effects on proteins involved in Alzheimer’s disease:</th>
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<tbody>
<tr>
<td>Amyloid precursor protein, Tau protein, Apolipoprotein E</td>
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</table>
In postmenopausal women, estrogen has been found to be improving depressed mood.\cite{154, 162} Blinded studies carried out in asymptomatic women also have shown benefit.\cite{163} In an estrogen deficient state such as occurs after the menopause, a higher incidence of depression and dementia is often manifest.

Dementia increases as women age, and the most common form of dementia is Alzheimer’s disease (AD). The relation between estrogen and several neurotropic and neuroprotective factors (Table 4) may be involved in development of AD. Estrogen has different effects on serotonin,\cite{164} to augment the effect of glutamate, increase sensitivity to catecholamine’s and inhibits glutamate-decarboxylase and thereby reduce the formation of gamma-amino butyric acid\cite{165} which all would affect the brain function. In addition, estrogen has a positive role in enhancing neurotransmitter function, which is deficient in women with AD. This function of estrogen has particular importance and relevance for the cholinergic system that is affected in AD.\cite{166, 167} Estrogen use after menopause appears to decrease the likelihood of developing or delays the onset of AD.\cite{168, 169} However, once a woman is affected by AD, estrogen is unlikely to provide any benefit.\cite{170}

In spite of the strong evidence of estrogen in psychological functions, still this is a very difficult area to assess as there can be numerous interlinking factors influencing the brain function and mood. The perimenopause can be a difficult time for a woman as it not only marks the end of her reproductive capacity, can also be associated with changes in domestic arrangements, feelings of loss of youth and femininity. Therefore, the symptoms experienced may not be entirely related to estrogen metabolism. The majority of studies performed in this area have been observational studies with inherent biases, particularly
considering the enormous placebo effect on psychological symptoms. The main problems with studies in this area are that numerous different HRT preparations have been used. In addition, there is no standard method for assessing each symptom, so a variety of methods have been used. This makes data analysis very difficult. However, one meta-analysis, which included studies that were mostly randomized, double blind and placebo controlled, concluded that HRT appears to be effective in reducing depressed mood among menopausal women \[^{171}\] and there could be also a decreased risk of dementia.\[^{169}\] Assessment techniques that are universally accepted are required for future studies.

**Biochemical and metabolic consequences of perimenopause:**

**Cardiovascular effects and lipid metabolism:**

Cardiovascular disease (CVD) is an important cause of death in women. Women tend to develop this disease about ten years later than men, with a marked increase through the menopausal years.\[^{172}\] Cardiovascular disease is rare among women younger than 45 years, but women older than 55 years are more likely than men to have CVD.\[^{173}\] This has led to the hypothesis that changes during the menopausal transition increase the risk of CVD, independent of normal aging.\[^{174}\] This hypothesis is supported by studies that show that surgically induced menopause increases the CVD \[^{175}\] and by autopsy studies that show minimal vascular disease before but not after menopause.\[^{176}\]

When the possible reasons for the increase CVD are examined, the most prevalent finding seems to be the altered lipid and lipoprotein metabolism associated with perimenopause. Women in menopausal transition have higher total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triacylglycerol (TG), Lipoprotein (a) [Lp-a] levels
and lower high density lipoprotein cholesterol (HDL-C) levels, than premenopausal women.\cite{177, 178, 179} LDL-C levels increases by 10%-20% \cite{180} with menopause, and the greatest change in LDL concentration appears to occur early in the transition from premenopause to postmenopause.\cite{181} The size, density and chemical composition of LDL is also important in deciding the atherogenic potential. A preponderance of small dense LDL is associated with an increase rise of myocardial infarction\cite{182} as well as severity of CVD.\cite{183} These high risk atherogenic LDL particles increases to 30%-49% in postmenopausal women,\cite{184} increase the rise of CVD to three fold higher than in those with large, regular LDL.\cite{182, 185}

Most studies have shown that total HDL levels are reduced slightly with menopause,\cite{186, 187} where as other reveal no changes.\cite{179} Menopausal changes in HDL metabolism are more complex than the simple measurements of HDL reveals, because the more antiatherogenic HDL\textsubscript{2} levels decrease (by 25%), whereas HDL\textsubscript{3} levels increase.\cite{179, 188} The strong inverse relationship between HDL cholesterol and abdominal adiposity appears to be largely dependent on variation in HDL\textsubscript{2} levels.\cite{189}

Lp(a), an LDL like particle with structural homology to plasminogen, has been shown to predict cardiovascular events in women independent of LDL levels.\cite{190} Studies have now shown significant increase in Lp (a) levels (by 25-50%) with menopause \cite{191, 192} which may reflect the fact that Lp (a) levels are sensitive to sex steroid hormones.\cite{192}

Longitudinal studies have shown that triacylglycerol (TG) levels increase with menopausal transition.\cite{177} Although men generally have higher TG levels than women, TG increase in middle age (between 40-60 yr) in women, but not in men,\cite{193} and TG appears to
be a better predictor of CVD risk in women than in men.\textsuperscript{[194]} Increase in TG with menopause may be related to the fact that TG levels are highly correlated with increasing abdominal fat and insulin resistance.

Alterations in the coagulation balance associated with perimenopause are also important determinants of cardiovascular effects. Blood flow in all vascular beds decreases after menopause: prostacyclin production decreases, endothelin level increases and vasomotor responses to acetylcholine become constrictive.\textsuperscript{[195, 196]} Some procoagulation factors increase (factor VII, fibrinogen), but so do counterbalancing factors like antithrombin III, plasminogen, protein C and protein S.\textsuperscript{[197]} These changes are associated with increase in plasma nitrites and nitrates and decreased angiotensin- converting enzyme levels.\textsuperscript{[198]}

Another important CVD risk factor frequently coexisting in perimenopausal women is the metabolic syndrome (Met S). This syndrome is evident in 20\% to 30\% of middle aged women and has been linked to the development of CVD and diabetes.\textsuperscript{[199, 200]}

**Metabolic Syndrome:**

Metabolic syndrome (Met S), also referred as insulin resistance syndrome (IRS) or syndrome X, is a cluster of metabolic and hemodynamic abnormalities that both collectively and independently predicts the development of atherosclerosis and CVD.\textsuperscript{[201]} Core factors of the Met S are insulin resistance, glucose intolerance, atherogenic dyslipidemia, high blood pressure and visceral adiposity.\textsuperscript{[202]} Other abnormalities associated with Met S include impaired fibrinolysis, increased coagulability, chronic inflammation, endothelial dysfunction and oxidative stress.\textsuperscript{[201, 203]}
Of the several factors which may be responsible for the development of Met S like increased sympathetic activity, enhanced cardiovascular reactivity and reduced parasympathetic activity, [204, 205] the changing hormonal milieu with declining estrogen and alteration of its ratio with testosterone has been implicated also as a causal factor for the emergence of Met S at menopausal transition. [206, 207]

**Bone Metabolism:**

Menopausal bone loss leading to osteoporosis is a substantial health care problem. 35% of postmenopausal women have been estimated to have osteoporosis based on bone mineral density. [208] Further the life time fracture risk for those women is 40%. [209] The morbidity and economic burden of osteoporosis is well documented. [210]

Estradiol, together with growth hormone and insulin like growth factor-1, act to double bone mass at the time of puberty [211] beginning the process of attaining peak bone mass. Post-pubertal estrogen deficiency substantially jeopardizes peak bone mass. Adequate nutrition and calcium intake are also key determinants. While estrogen is of predominant importance for bone mass in both women and men, testosterone is important in stimulating periosteal opposition. [212]

In women, Riggs has suggested that bone loss occurs in two phases. With estrogen levels declining at the onset of menopause leading to an accelerated phase of bone loss—predominantly cancellous bone loss occurs. Here 20% to 30% of cancellous bone and 5% to 10% of cortical bone can be lost in a span of four to eight years. [213] Thereafter a slower phase of loss (1% to 2% per year) ensues where more cortical bone is lost. This phase is thought to be induced primarily by secondary hyperparathyroidism. [214] The first phase is
also accentuated by the decreased influence of stretching or mechanical factors, which generally promotes bone homeostasis, as a result of estrogen deficiency.\cite{215}

The molecular mechanisms of estrogen action on bone involve the inhibition of production of pro-inflammatory cytokines including interleukin-1, interleukin-6 and tumor necrosis factor - α, colony stimulating factor-1, macrophage colony-stimulating factor, and prostaglandin. Riggs\cite{216} has developed a model to show the interaction of all these factors to regulate the bone marrow microenvironment.

**Dental Changes:**

Dental problems also develop in late menopausal transition. The buccal epithelium undergoes atrophy due to estrogen deprivation, resulting in decreased saliva and sensation. A bad taste in mouth, increased incidence of cavities, and tooth loss also may occur\cite{217} which seems to be strongly correlated with associated osteoporosis.

**Collagen Metabolism:**

Collagen is an important component of bone and skin and serves as a major support tissue for the structures of the pelvis and urinary system. Nearly 30% of skin collagen is lost within the first five years after menopause, and collagen decreases approximately 2% per year for the ten years after menopause.\cite{218} This finding, which is similar to that of bone loss after menopause, strongly suggests a link between skin thickness, bone loss and the risk of osteoporosis.\cite{219}

Reductions in collagen support and atrophy of the vaginal and urethral mucosa have been implicated in a variety of symptoms including prolapse and urinary incontinence.\cite{220}
Symptoms of urinary incontinence and irritative bladder symptoms occur in 20% to 40% of perimenopausal and postmenopausal women.\[221\]

**Dermatologic Changes:**

Skin changes that may occur in the menopausal transition include hyperpigmentation (age spots), wrinkles and itching. These are caused in part from skin aging, which results from the synergistic effects of intrinsic aging and photo aging.\[222\] In addition, hormonal aging of the skin is thought to be responsible for many dermal changes. These changes include reduced collagen content, a decrease in sebaceous gland secretion, a loss of elasticity, diminished blood supply and epidermal changes.\[223\]

**Quality of life assessment in the menopause:**

Condition- Specific quality of life can be defined as the extent that the physical, emotional and social aspects of an individual’s life are intact and not adversely affected by that condition or treatment.\[224\] Only recently have studies considered the effect of a therapeutic or other interventions on the individual’s evaluation of quality of life. Treatments goals may be achieved, but may produce unwanted side effects which can impact negatively on quality of life. It is increasingly recognized that the measurements of quality of life should be an integral part of any attempt to assess disease impact or to assess the effects of a medical or any other type of intervention.\[225-227\]

The firstly widely accepted attempts to document the severity of menopausal complaints and also the quality of life in women was the Kuperman Index,\[228\] a listing of the relevant symptomatology in this age-span. Later more specific symptom lists or other questionnaires as instruments to measure changes, and to validate them in a specific manner
were developed. In recent years, increasing recognition is given by clinicians and researchers for these patient reported data instruments as outcome measures for clinical and drug research. Health authorities are also in support of this growing interest. There have been multiple attempts for a state-of-the-art development of health related QOL scales applicable to women in their perimenopausal transition.

The first properly analyzed climacteric symptom scale was the Greene Climacteric Scale. This 22-item questionnaire with a rating of severity (four rating points) specifies the three domains- vasomotor, somatic and psychological. Its practical application and further validation finally resulted in 21-items scale with four domains (vasomotor, somatic, anxiety and depression).

Factor analysis played a central role in the development of the Menopausal symptom checklist. It consists of 25 items with a six point scale for each item. Three subscales were generated: general somatic, vasomotor, and psychological. This list allows a separate evaluation of both frequency and severity.

Another widely used inventory is the Women’s Health Questionnaire also based on an initial factor analysis. It consists of rather complex scale with 32 items but only two rating points (present or absent). Thus frequency but not severity is evaluated. Eight domains are described (vasomotor, somatic, anxiety, depression, cognitive difficulties, sleep problems, sexual behavior and menstrual symptoms). Norm values have been established for middle-aged women perception of their emotional and physical health.
Chapter 2

Review of Literature

The *QualiFemme Questionnaire* is a health related QOL questionnaire based on factor analysis of 32 selected items. It consists of five relevant dimensions which are defined as general, psychological, vasomotor and urogenital domain plus one additional domain related to skin and hair problems. A 15-item version is also available.

The *QualiPause Inventory* (QPI) is a scale with 20 specific and some general items to evaluate symptoms and undesirable treatment effects with special regard to menopausal complaints. Following factor analysis, six dimensions of the instrument were identified: psychosocial, vasomotor, physical, sexual, menstrual and androgenic. The QPI has favorable psychometric characteristics concerning reliability and validity.

Another validated and short symptom scale used in women of transient menopause age is the *Menopause Rating Scale* (MRS), the first version of which has been used since 1992. It was initially developed to provide the physician with a tool to document specific climacteric symptom and their changes during treatment. The MRS was formally standardized following up-to-date psychometric rules. The revised scale consisted of 11 items to be answered: the respondent has a choice among five categories-no symptom, mild, moderate, marked, or severe complaints/symptoms.

All the above scales seem to have certain disadvantages. Generally, the available instruments are not designed to be responsive to change and responsiveness has rarely been tested. In addition, questionnaires designed to assess emotional and psychological function, i.e. the General-well-being scale, have generally been designed to measure community mental health or individual response to a wide range of problems. Although useful for the purpose for which they are designed, these instruments may not be specific enough to pick
up subtle but important features in any one condition such as the menopause. Also, to cover all relevant aspects of quality of life, many questionnaires must be administered, and for purpose of a clinical trial, the test battery must be administered repeatedly. The time and burden on the individual respondent may be too great for efficient and meaningful response.

To overcome this drawback, a *Menopause specific quality of life* (MENQOL) questionnaire has been developed with documented psychometric properties, based on women’s experience.\textsuperscript{238} The Menqol questionnaire is a self-administered instrument which shows potential both for determining differences in quality of life between menopausal women and measuring changes in their quality of life over time. This instrument contained 29 items questionnaire with four domains vasomotor, psychosocial, physical and sexual and a global quality of life question. A panel of experts was used to confirm content validity. Reliability, responsiveness and content validity were determined within the context of a randomized controlled trial. Construct validation involved comparison with the Neugarten and Kraine’s somatic, psychosomatic and psychological subscales,\textsuperscript{239} the reported intensity of hot flushes, the general wellbeing schedule,\textsuperscript{240} Channon and Ballinger’s vaginal symptoms score and libido index,\textsuperscript{241} and the life satisfaction index.\textsuperscript{242}

In this present study, we used MENQOL questionnaire to record the symptom profile in perimenopausal women and also studied the effect of yoga therapy intervention on quality of life.
Management of menopausal transition and postmenopause:

During the past century, the world population and, more importantly, the elderly population have been increasing at a rapid rate.\[^{243}\] Thus, in 1900, the world population was around 2 billion people, by the year 2020 the United Nations has projected it to be 8 billion.\[^{243}\] The proportion of elderly (above 65 years), will have increased from 5% in 1950 to 9% by the year 2020, and this represents an elderly population of 796 million people. The majority of this elderly population will be postmenopausal women, and addressing their health care problems becomes an important aspect of modern medicine. Since this phase is associated with increasing health problems such as menopausal symptoms, osteoporosis, cardiovascular disease, neurodegenerative disease and cancer. It is very essential to develop preventive, curative and other management strategies that will assist these very large numbers of women to maintain a healthy, symptom free and productive quality of life.

The transition to menopause marks a critical and sensitive time of profound change in a woman’s life. Hormonal, physiologic, and psychosocial factors are in flux. Acute symptom clusters can seriously disrupt her work, family and day-to-day life, thus severely affecting the overall quality of life. Contrary to common beliefs, these symptoms can begin in the early menopausal transition during the early reproductive years, well before menstrual irregularities occur. Hence it is important for health care professionals to understand the complexity of menopausal symptoms and to plan and provide suitable interventional remedies.

Preventive, therapeutic or any other interventions during the perimenopausal years have three major goals. The overall objective is to prolong the period of maximal physical
energy and optimal mental and social activity. More specific goal is to reduce maximally the symptom burden and thereby improve the quality of life. Further aim is to detect as early as possible any of the major chronic diseases, including hypertension, heart disease, diabetes mellitus, and cancer, impairments of vision, hearing and dental problems. Finally, the professional should help perimenopausal women to traverse the menopausal period of life smoothly. It is also important, especially to the semi urban/rural women who have been included in the present study to provide menopausal education and to create the awareness. This educational process helps to build a solid relationship with patients, a relationship they will want to continue as they age. Recommendations to be considered while creating awareness and educational programs are available. The perimenopausal years should serve to remind patient and professionals that this is a time for education. Contrary to popular opinion, the menopause is not a signal of impending decline, but rather a wonderful phenomenon that can signal the start of something positive, a life-long good health care program.

Next section reviews some of the current management options available to manage perimenopausal health issues.

**Hormone Replacement Therapy (HRT):**

Until recently, hormone replacement therapy (HRT) was quite straight forward. Estrogen prevented the symptoms of the climacteric, particularly flushes, sweats, vaginal dryness, depression, loss of energy and loss of libido. Cyclical or continuous progesterone although possible producing PMS-type side effects in woman who were progestogen-intolerant, protected the endometrium. There were also long-term benefits of protection from
osteoporosis, reduction in colon cancer and both primary and secondary prevention of heart attacks.\[245\]

The heart and estrogen/ progestin replacement study (HERS) \[246, 247\] first challenged the optimism that estrogen exerted a protective effect in women with established coronary artery disease and more recently the paper from the Women’s Health Initiative (WHI)\[248\] and the Million Women Study (MWS)\[249\] have caused enormous alarm by reporting that heart attacks, strokes, venous thrombo-embolism and breast cancer are more common in women who are receiving hormone treatment. This whole matter has generated lot of controversy and debate in the scientific circles. Following the North American Menopause Society (NAMS) statement in 2002,\[250\] many proscriptive guidelines from advisory bodies in Europe and North America have appeared, which advise prescribing hormone therapy at the lowest dose principally for menopausal vasomotor symptoms and for the shorter time. It was also recommended that it was not to be used as a primary treatment for low bone-density and that it has no place in the prevention of coronary heart disease. These recommendations though have been challenged. Prof. John Studd in his extensive review of this topic,\[245, 251, 252\] lists the following principles of hormone therapy for the menopausal or perimenopausal women.\[253\] Though these items are not entirely consistent with the current advice of regulatory bodies, they do seems to reflect a studied analysis of the available data as well as long clinical and academic interest in the subjects. Moreover, those recommendations have been supported by the latest publication from WHI reporting the decreased CHD mortality.\[254\] Both the North American Menopause Society (NAMS) and the International Menopause Society have now changed their guidelines in accord with the recommendations in view of long term safety of therapy.\[255, 256\]
These recommendations are as follows: [253]

1. Estrogens are safe when started below the age of 60 years, particularly if progesterone is not required and are positively indicated in women with a premature menopause. It should be used for treatment of specific climacteric symptoms and low bone density and the advice that estrogens should not be first option for the prevention or treatment of osteoporosis in this age group is questioned. The dose and route will depend upon the symptoms and the age of the patient.

2. Women with a uterus need endometrial protection with progestogen. The usual duration is 14 days but, if the extra risk to the breasts from progestogen is confirmed, it would be sensible to reduce the duration to 7 days each calendar month. This shortened course is also useful in women with progestogen intolerance and is adequate for endometrial protection. Alternatively, a Mirena IUS can be inserted. The long term value and safety of low-dose, unopposed estrogen is unproven.

3. Estrogen-only therapy commenced before the age of 60 years is associated with a considerable, but non-significant, decrease in CHD, osteoporotic fracture, colon cancer and deaths. These results are consistent with the previous case-control studies. There may also be a decrease in breast cancer in women receiving estrogens without progestogen.

4. Estrogens appear to have no place for the secondary prevention of CVD but there may be a window of opportunity in 45-60 year-old symptomatic women who may show long-term cardiovascular and neurological benefits from early estrogen therapy. Estrogen commenced in older 69-79-year-old women may do ‘early harm’
before any benefit can be achieved and should be avoided if possible or started on very low-dose estrogens.

5. A moderately high dose of transdermal estrogens are useful for perimenopausal depression as well as premenstrual depression.

6. Patient may wish to avoid bleeding by using low-dose estrogen and progestogen, Tibolone or have a Mirena IUS inserted.

7. If loss of libido and loss of energy remains a problem, the addition of testosterone to estrogen should be considered. Androgen as well as estrogen is often necessary after hysterectomy and bilateral oophorectomy. Hysterectomized women do not need progestogen.

8. Five year duration has been recommended but in reality women remain on HRT if they are feeling well with relief of symptoms. It is difficult to persuade these women to stop even after 10 or more years. The need for estrogen should be reviewed each year for long term users with clear discussion of current views on safety.

9. In spite of the reassuring data from estrogens-only studies, the possible increase in breast cancer remains a problem. Until the controversy concerning breast cancer risk is clarified, it is probably advisable that regular mammograms should be performed each year and breast examination every 6 months although it is correct to recognize that many Oncologists would doubt the value of these frequent examinations.

Complementary and alternative therapies for the menopause:

Concerns about the safety of estrogen-based hormone replacement therapy after publications of WHI and MWS studies have led to women turning to alternative therapies. In USA and Australia, more than half of women use some type of complementary and
alternative medicines during midlife.\textsuperscript{[257, 258]} Evidence from randomized trials that alternative and complementary therapies improve menopausal symptoms or have the same benefits on conventional pharmacopoeia is poor.\textsuperscript{[259, 260]}

The evidence regarding various complementary and alternative therapies is summarized in this section:

The definition adopted by the Cochrane Collaboration describes complementary/alternative medicine (CAM) as ‘diagnosis treatment and/or prevention which complements mainstream medicine by contributing to a common whole by satisfying a demand not met by orthodox or by diversifying the conceptual frameworks of medicine’.\textsuperscript{[261]} CAM entails a wide array of therapeutic and diagnostic modalities (Table 5).
Table 5: The most important modalities in CAM \cite{262}

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>Insertion of a needle into the skin and underlying tissues in special sites, known as points.</td>
</tr>
<tr>
<td>Aroma therapy</td>
<td>The controlled use of plant essences for therapeutic purpose.</td>
</tr>
<tr>
<td>Bach flower remedies</td>
<td>Uses specially prepared plant infusions to balance physical and emotional disturbances.</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>Form of psychophysiological self-regulation using of apparatus to monitor, amplify and feedback responses.</td>
</tr>
<tr>
<td>Chelation therapy</td>
<td>Removing toxins, minerals, and metabolic wastes from the blood stream using intravenous EDTA.</td>
</tr>
<tr>
<td>Chiropractic</td>
<td>Based on the belief that nervous system is most important determinants of health and diseases are caused by spinal subluxations which respond to spinal manipulations.</td>
</tr>
<tr>
<td>Cranio-sacral therapy</td>
<td>Proprietary form of therapeutic manipulation which is tissue-, fluid-, membrane-, and energy oriented.</td>
</tr>
<tr>
<td>Herbalism</td>
<td>The medical use of plant materials.</td>
</tr>
<tr>
<td>Homoeopathy</td>
<td>System of using preparation of substances whose effects when administered to healthy subjects correspond to the manifestations of the disorder in the un-well patient.</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>The induction of a trance-like state to facilitate the relation of the conscious mind, to trial psychological, medial conditions, behavioral changes through suggestion.</td>
</tr>
<tr>
<td>Massage</td>
<td>Manipulating the soft tissue of whole body areas using pressure and traction.</td>
</tr>
<tr>
<td>Naturopathy</td>
<td>A health care system, which integrate elements of complementary and conventional medicine to support and enhance self-healing process.</td>
</tr>
<tr>
<td>Name</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Osteopathy</td>
<td>Manual therapy involving massage, mobilization and spinal manipulation.</td>
</tr>
<tr>
<td>Reflexology</td>
<td>Manual pressure applied to specific area or zone in body to relieve stress and treat physical disorders.</td>
</tr>
<tr>
<td>Relaxation therapy</td>
<td>Technique for eliciting the ‘relaxation response’ of the autonomic nervous system.</td>
</tr>
<tr>
<td>Spiritual healing</td>
<td>Interaction between the healer and the sick, with the intention of curing the illness.</td>
</tr>
<tr>
<td>Yoga</td>
<td>A practice of gentle stretching, breath control and meditation as a ‘mind-body’ intervention.</td>
</tr>
</tbody>
</table>

**Botanicals and herbal medicines: [Table 6]**

Varieties of botanicals and herbal medicine are used widely without consulting a health professional. Unfortunately, knowledge about herb-drug interactions amongst health professionals is poor. Some lead to drug interactions with potential fatal consequences.\(^{263}\) Concern also exists about the quality control of production and contamination with chemicals such as arsenic, lead or mercury can occur.\(^{264}\)
Table 6: Botanical and herbal medicines in common use by menopausal women.

<table>
<thead>
<tr>
<th>Name and chemistry</th>
<th>Function/mechanism of action</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soy</strong>&lt;br&gt;(Isoflavones - genistein - diedzein)</td>
<td>Phyto-estrogens have effects similar to estrogens. Isoflavones are metabolized in the gut to more estrogenic equals. [265] Effective against hot flushes.</td>
<td>About 29 RCTs of soy therapies on menopausal symptoms have been published.[266] The results are mixed; some have shown benefits while majority have shown no significant difference.</td>
</tr>
<tr>
<td><strong>Red Clover</strong>&lt;br&gt;Semi purified isoflavone leaf extracts.</td>
<td>Major use to reduce hot flushes. No serious adverse reports. Safety in women with a h/o breast cancer is unknown</td>
<td>Majority of clinical data do not support the efficacy in alleviating hot flushes.[267]</td>
</tr>
<tr>
<td><strong>Black cohosh</strong>&lt;br&gt;(Actaea racemosa)&lt;br&gt;Indigenous North American herb-the root and rhizome are used. Marketed as Remifemin</td>
<td>Against hot flushes, PMS and dysmenorrhea. Seems to act via non-hormonal mechanisms, but also may have estrogenic actions.</td>
<td>Seems to reduce some symptom associated with menopause, however methodological shortcomings and variations in product and dosage limit definitive conclusions.[268]</td>
</tr>
<tr>
<td><strong>Dong quai</strong>&lt;br&gt;(Angelica sinensis)&lt;br&gt;Root used in traditional Chinese Medicine</td>
<td>For hot flushes, dysmenorrhea, PMS, laxative, antispasmodic, insomnia and hypertension. Said to be estrogenic and has uterotrophic effects on ovarietomized rats.</td>
<td>Not superior to placebo, may be effective when combined with other herbs.[269] One branded product, Rejuvex contains bovine brain and spinal cord tissue which may cause a risk for developing mad cow disease.</td>
</tr>
<tr>
<td>Name and chemistry</td>
<td>Function/mechanism of action</td>
<td>Remarks</td>
</tr>
<tr>
<td>--------------------</td>
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<td>---------</td>
</tr>
</tbody>
</table>
| **Evening primrose** (Oenothera biennis)  
A wild flower, native of North America, the oil is extracted from the seeds of evening primrose plant | Used for PMS, mastalgia and mastodynia. Oil is rich source of linoleic and gamma-linolenic acids which are converted in the body to anti-inflammatory prostaglandins which may affect inflammatory and autoimmune processes. | There have been seven studies, which showed no significant effect on menopausal symptoms.\[270\] |
| **Ginseng** (Panax ginseng)  
Ginseng root is commonly used in Asian medicine | Used for menopausal bleeding, mastalgia, aphrodisiac, reduce body weight, stimulant and digestive. Promoted as an anabolic agent and as a health tonic for the elderly. | No effects on FSH and estradiol levels, endometrial thickness, maturity index, vaginal pH and hot flushes.\[271\] |
| **Kava Kava** (Piper methysticum)  
Kava shrub and root grown in Pacific Islands and are used for spiritual and amusement purposes. | For treating anxiety and insomnia. The pharmacological extract known as Kavapyrones as properties similar to benzodiazepines with sites of action on limbic center and GABA receptors. Side effects include disorientation and intoxication. | Data about menopausal symptoms are conflicting.\[272\] Concern about liver damage has led regulatory authorities to withdraw Kava Kava. |
<table>
<thead>
<tr>
<th>Name and chemistry</th>
<th>Function/mechanism of action</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ginkgo</strong> (Ginkgo biloba)</td>
<td>For slow aging, increase memory, headaches. Increases the blood flow and tissue perfusion and stimulates the production of prostaglandins.</td>
<td>Seems to be useful in improving cognitive symptoms of Alzheimer and multi-infarct dementia. No evidence to show improvement of menopausal symptoms.[273]\</td>
</tr>
<tr>
<td>Tree leaf extracts contains a variety of flavonoids and terpenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>St.John’s Wort</strong> (Hypericum perforatum)</td>
<td>Used to treat mild to moderate depression and mood disorders. Several mechanisms have been proposed, inhibition of MAO and catechol methyl transferase. Decreased ACTH and Cortisol Serotonin receptor blockade</td>
<td>Fifteen controlled trial have been reported.[274]\ Combined analysis of 1757 cases found that hypericin in doses less than 1.2mg/d lead to 61% improvement in mild depression; whereas higher doses up to 2.7 mg/d produced 75% improvement.</td>
</tr>
<tr>
<td>Extracts of flower which contain hypericin, pseudo-hypericin, and flavonoids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valerian</strong> (Valeriana officinalis)</td>
<td>Used as a tranquilizer, limited sedative and calming effects. Before the advent of benzodiazepines and barbiturates, many psychiatric disorders were treated with Valerian.</td>
<td>Both St.John’s Wort and Valerian show no good evidence on menopausal symptom.[275]\</td>
</tr>
<tr>
<td>Valerium root seems to contain GABA derivatives</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Herb-drug interactions:

A major concern about herbs is herb-drug interactions which potentially fatal consequences as well as estrogenic effects, which is important in women with hormone-dependent tumors such as breast cancer.\cite{276} The consequences of herb-drug interactions include bleeding when combined with warfarin or aspirin; hypertension, coma and mild serotonin syndrome, and reduced efficiency of anti-epileptics and oral contraceptives. Further work is definitely deserved in this area so that the results of these studies will increase the choices available for all menopausal women.

Non-botanical complementary and alternative medicine therapies:

Two acupuncture trials have been published. Symptom check list 90 was used as end points and a visual analog scale of ‘general climacteric symptom’ intensity was reduced in both groups with no significant difference between treatment and placebo acupuncture.\cite{277, 278}

Two other studies examined magnetic therapy and reflexology. In the randomized magnetic therapy study, placebo was found to be more effective than magnets in reducing hot flush frequency.\cite{279} An RCT of reflexology for menopausal symptoms were conducted in 76 women.\cite{280} Both reflexology and foot massage found no significant improvement in hot flush frequency or severity.

Studies of homeopathy for menopausal symptoms have been reported. Though small number of these trials are encouraging, more research is clearly needed.\cite{281}
Vitamin Supplements:

Vitamin supplements are very popular, but there are concerns about their efficiency and safety in population where the diet is replete. The WHI study found that calcium and Vitamin D supplements in women at low risk for osteoporosis did not reduce fractures and increased the risk of kidney stones.\cite{282} There is now concern that these supplements can also increase the risk of CVD.\cite{283}

It has been estimated that 10-20% of the adult populations (80-160 million people) in North America and Europe take antioxidants with claims that they improve health with reduced mortality. However, a meta-analysis has shown that while beta-carotene, vitamin A and Vitamin E increased mortality, Vitamin C and selenium did not appear to have any significant effect.\cite{284}

Non-estrogen-based pharmacopoeia for hot flushes:

Various non-estrogen drugs like clonidine, selective serotonin re-uptake inhibitors, gabapentin and progestogens have been used to manage hot flushes. However, they are less effective than estrogens, evidence of efficiency is quite conflicting and the effects are very short lasting. Moreover they have several undesirable side effects including gastrointestinal symptoms, dizziness, nocturnal restlessness, thromboembolism, and sexual dysfunctions.\cite{285}

Yoga:

Yoga is an art, a science and a philosophy. Yoga is a general name for the systems of spiritual and physical culture practiced from ancient times in India. The word Yoga has been applied not only to the central aim of attaining heightened consciousness, but also to the development of every human faculty- physical, emotional and ethical which may conduce to
that end. In fact, the best way to define yoga as a way of integral living including the whole man- material, physical, mental, ethical and spiritual - by which each of the levels of our beings serves all the others in nature and results in complete sanity, harmony and happiness.

The standard and most authoritative work on yoga, the Yoga Sutras of Patanjali, contains 196 aphorisms or sutras covering all aspects of life, beginning with a prescribed code of conduct and ending with man’s vision of his true self. The associated classical works include Hatha yoga pradeepika, the Gheranda Samhita and the Shiva Samhita.

In the Yoga sutras eight limbs or tools or aids are prescribed. These are sometimes spoken as “steps”, because the course of yoga practices is often alluded to as a road or path or way. These eight limbs are: Abstention (Yama); Observances (Niyama); Posture (Asana); Breath Control (Pranayama); Sense withdrawal (Prathyahara); Concentration (Dharana); Meditation (Dhyana); Contemplation (Samadhi). The first two of these are concerned with the aspirant’s attitude towards the outer world and towards himself, in short, to ethics and morality in the widest sense of those terms; the next three have to do with the body and senses (physical); and the last three with the mind (psychological).

Though originally yoga was developed as a spiritual discipline to attain the goal of kaivalya, which may be translated as either ‘state of oneness’ or ‘state of unconditional freedom’; freedom from all bondages and suffering; its practice has great practical relevance to modern medicine with promotion, preventive and curative potential. Especially the three limbs of yoga namely asana, pranayama and dhyana promote positive health, vitality, sense of wellbeing and increased quality of life. They are also effective in
controlling and managing stress related, chronic degenerative, age and life style related disorders.

Asana:

The term ‘asana’ or seat is used to connote a large variety different postures which mostly involve bending and stretching the trunk of the body, and serve to keep it very supple. There is this vast difference between yoga and physical exercises- the later are largely intended to develop muscular strength, the former not at all. The chief aim of asana is to cultivate poise and balance which, whether in sitting or in standing or in walking, will call for the minimum effort and if possible no compensatory effort at all.

Asana-s acts as bridges to unite the body with the mind, and the mind with the spirit. Asana has two facet, pose and repose. Pose is the artistic assumption of a position. ‘Reposing in the pose’ means finding the perfection of a pose and maintaining it, reflecting in it with the penetration of the intelligence with dedication. The conjunction of effort, concentration and balance in asana forces to live intensely in the present moment and being in the present, has both a strengthening and a cleaning effect: physically in the rejection of disease and symptoms, mentally by ridding the mind of stagnated thoughts or prejudices.

The original texts list almost eighty four postures (asana-s) altogether, but many of them are rarely used. Indeed, it is necessary to practice regularly only few asana-s to obtain the health benefits and the desired therapeutic effects [Table 7].
Table 7: Important asana-s for daily practice

<table>
<thead>
<tr>
<th>A. Sitting-down postures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swastikasana, Vajrasana, Suptavajrasana, Pascimottanasana, Poorvatanasana,</td>
</tr>
<tr>
<td>Janusirsasana, Vakrasana</td>
</tr>
<tr>
<td>B. Standing-up postures:</td>
</tr>
<tr>
<td>Tadasana, Trikonasana, Parshvakonasana</td>
</tr>
<tr>
<td>C. Lying on the back postures:</td>
</tr>
<tr>
<td>Pavanamuktasana, Paryankasana, Padottanasana</td>
</tr>
<tr>
<td>D. Lying on the stomach postures:</td>
</tr>
<tr>
<td>Bhujangasana, Shalabhasana, Dhanurasana</td>
</tr>
<tr>
<td>E. Relaxation postures:</td>
</tr>
<tr>
<td>Makarasana (lying on the stomach), Shavasana-1 (lying on the back with left palm</td>
</tr>
<tr>
<td>on the chest and right palm on the stomach), progressive relaxation - Shavasana 2</td>
</tr>
</tbody>
</table>

Pranayama:

Prana means life force and ayama means ascension, expansion and extension. Pranayama is the expansion of the life force through control of the breath. Normal breath flows irregularly, depending on one’s environment and emotional state. In the beginning, this irregular flow of breath is controlled by deliberate process. This control creates ease in the inflow and outflow of the breath. When this ease is attained, the breath must be regulated with attention. This is pranayama.

In pranayama, the spine and spinal muscles are the sources of action and the lungs are the receiving instruments. They must be trained to open and to extend backwards,
forwards, upwards and outwards, and the spinal muscles straightened, cultured and toned to create space and stimulate the spinal nerves to draw energy from the breath.

Pranayama by nature has three components: inhalation, exhalation and retention. They are carefully learned by elongating the breath and prolonging the time of retention according to the elasticity of the torso, the length and depth of breath and precision of movements.

**General effects of pranayama:**

The lungs are directly concerned with disposal of carbon dioxide in the venous blood and preventing various acidic components like ammonia, ketone bodies and aromatic amines wastes from building up to toxic levels. The arterial, capillary, venous and lymphatic circulation is stimulated by the rhythmic contraction and relaxation during pranayama, creating the proper circulation of the body fluids within kidneys, liver, spleen, skin and other organs, thereby improving the function of these organs.

The rhythmic use of the diaphragm and abdominal muscles in pranayama directly stimulates the peristaltic and segmental movement of the intestine, as well as promoting intestinal circulation which in turn helps the intestine in its function of absorbing food and disposing of solid wastes. Pranayama helps to maintain flow of pure blood, which tones the nerves, the brain, the spinal cord and cardiac muscles, thus maintaining their efficiency.

Pranayama increases vigor, perception and memory. It frees the mind from the grasp of the body and sharpens the intellect. Practice of pranayama quietens the upsurge of senses and desires, and mind becomes sacrosanct or free of thoughts. The thoughts and deeds become clean and pure. It helps to maintain the firmness of body and steadiness of the mind.
The practitioner experiences a state of serenity. He no longer thinks of past, nor fears the future, but remains ever in the present. As wind drives away smoke and impurities from the atmosphere, pranayama is a powerful fire which cleanses the organs, senses, mind, intellect and ego. As the rising sun slowly disperse the darkness of light, pranayama removes the impurities and refines the individual by preparing his body and mind to become fit for meditation (Dhyana).

Pranayama should be practiced by sitting in any one of the meditative posture like Swastikasana, Padmasana, Vajrasana or Sukhasana comfortably, keeping the head, neck and back straightly [Table 8].

**Table 8: Important pranayama-s for daily practice:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Ujjayee pranayama (simple deep breathing)</td>
</tr>
<tr>
<td>B.</td>
<td>Anuloma-viloma pranayama (breathing alternatively)</td>
</tr>
<tr>
<td>C.</td>
<td>Bhashrika pranayama (forcible exhalation)</td>
</tr>
<tr>
<td>D.</td>
<td>Suryabhedhana Pranayama (breathing only through the right nostril)</td>
</tr>
<tr>
<td>E.</td>
<td>Sheetali Pranayama (breathing in through the tongue breathing out through the nose)</td>
</tr>
<tr>
<td>F.</td>
<td>Chandrabhedhana pranayama (breathing only through the left nostril)</td>
</tr>
<tr>
<td>G.</td>
<td>Bhamari Pranayama (while breathing out producing the humming sound)</td>
</tr>
</tbody>
</table>

**Dhyana (Meditation):**

There are many misconceptions regarding meditation and what one can achieve through meditation. Actually meditation is neither like a drug experience nor like the contemplative resolution of particular concerns, nor the wandering of a non-directed mind.
Meditation is a method of training a disorderly, disorganized mind to become proficient and creative. In the basic text, sage Patanjali defines meditation as the ‘controlling of the thought waves of the mind’. The accomplishment of this task is the aim of the entire science of yoga.

The science of meditation is as ancient as human existence, through it was developed in a scientific manner some 5000 years ago by wise sages in India. In order to find answers for the basic questions of human life, these sages experimented with various approaches to self-study and discovered certain definite methods of meditation.

By using the tool of observation, they tried to put the whole complex puzzle of life into a meaningful order. They watched the way their feelings and thoughts arose, the way they become interested in certain things, what made them miserable and unhappy, and what made them feel peaceful and joyous. They delved deeper and deeper into the subtle working of the mind and found that the more they explored, the calmer their minds became. As they continued in their self-study, their sensitivity to experiences of body and mind greatly increased. Through this practice of study of the internal states, they became aware and began to understand the working of the mind and the body and how they were controlled.

Meditation is an exact science. The science of meditation is an experimental study of inner process comparable to the modern science, which primarily studies the outer processes and events. Although there are several different forms of meditation, at the deepest level, all these methods involves the same principle and the same process of centering the mind on a particular thought or object, and all meditational forms come from the same historical source.
The fact that meditation has been allied with various spiritual traditions does not necessarily mean that its practice involves following the dogma or rituals of a particular religion. Meditation is a universal experimental discipline for the development of one’s consciousness, and has been experienced by the people of all religions. While it can enhance one’s understanding of one’s faith, it can also be practiced without involvement in any religion.

Meditation is thus a universal method for transform the ordinary, restless, disturbed mind which in a state of unrest, confusion and disharmony into a state of equilibrium, harmony, peace and joyfulness.

**Therapeutic effects and benefits of yoga therapy:**

Yoga therapy (asana, pranayama and dhyana) is an economical and non-invasive, safe practice. It is becoming increasingly popular in the modern world as a means of potentially relieving stress, enhancing health, improving fitness and managing the various symptoms associated with chronic diseases.\(^{286, 287}\) Most importantly, there is a growing body of research suggesting that practice of yoga may reduce risk factors for chronic disorders, and may attenuate symptoms, reduce complications, and improve the prognosis and thus contribute significantly to the overall enhancement of quality of life.\(^{288-291}\)

The following section briefly summarizes the research evidence of effect of yoga therapy in managing the various clinical disorders. Though, the studies on effect of yoga therapy on perimenopausal women are very few, the observational findings in these other studies indirectly helps to understand and plan, yoga therapy for the management of perimenopausal symptoms and quality of life which was the objective of this research study.
Body weight and composition:

Several clinical trials have examined the effects of yoga on anthropometric indices. They have reported improvement in body weight and composition after yoga-based interventions ranging from 4 weeks to 12 months.\[290, 292, 293\] Likewise, RCTS have demonstrated improvement in body weight and/or composition relative to usual care, diet and exercise.\[294, 295\]

Blood pressure:

Blood pressure is the endpoint that has been most extensively studied with respect to the influence of yoga-based interventions. Of the 37 such studies, 75% reported improvement in blood pressure with yoga or yoga-based interventions.\[291\] In a study of 95 Japanese females, Cusumano and colleagues demonstrated comparable, significant reduction over time in blood pressure among women receiving 3 weekly training session in either Hatha yoga or progressive muscle relaxation.\[296\] Over all, these studies demonstrated a 4.9% to 24.2% decline in diastolic blood pressure and 2.6% to 21.3% decline in systolic blood pressure with yoga, with the magnitude of change varying with the study design and sample population.

Nervous system:

Scientific evidence shows that practice of yoga including meditation has significant impact on the functioning of nervous system. Yoga promotes relaxation in the practitioners but at the same time help them in increasing their attention and other cognitive abilities.

Yoga techniques cause improvement in all aspects of cognitive function like perception, thinking, reasoning, memory and attention, resulting in the significant decrease
in visual and auditory reaction times. A decrease in reaction time indicates an improved sensory-motor performance and enhanced processing ability of central nervous system. Yoga has also been shown to enhance cognitive processes like letter cancellation task, reduction in peak latencies of P 300, increase in spatial cognitive task, mirror tracing task, decrease in degree of optical illusion and increase in critical flicker fusion frequency.

Several studies have shown that the practice of yoga can produce significant decrease in the basal anxiety scores. Yoga meditation by patients of depression who were on anti-depressant medicine led to higher rates of remission, reduction in Hamilton depression and anxiety scores as compared to those patients who were only on anti-depressant medication. Apart from improvement in perceived stress, state and traits anxiety, yoga practice resulted in improvement of various quality of life parameters like sense of well-being, feeling of relaxation, improved concentration, self-confidence, improved efficiency, good inter-personal relations, lower irritability levels, and on positive outlook in life. Yoga also improved the quality of sleep. Physical well-being was improved with decreased fatigue and relief from headache or back pain in women.

Recent studies have shown that yoga and meditation practices have benefit not only on higher-order cognitive function but they also alter brain structures and therefore, brain activity. Significantly larger gray matter volumes were found in meditators, in the right orbito-frontal cortex, right thalamus, left inferior temporal gyrus and right hippocampus which may account for positive emotions, emotional stability and mindful behavior. Regular practice of yoga and meditation also alters brain blood flow and levels of various neurotransmitters.


**Cardio-Respiratory System:**

Yoga improves cardio-respiratory efficiency resulting in significant increase in maximum expiratory and inspiratory pressure, breathe holding time after expiration and inspiration, increase in forced vital capacity, maximum voluntary ventilation and peak expiratory flow rate.\[^{315}\] Improvement in these parameters indicates that yoga training improves the strength of expiratory as well as inspiratory muscles. Yoga training also results in significant improvement in cardio-vascular endurance and anaerobic threshold,\[^{316}\] with overall strengthening of various cardiac functions. Bharshankar et al\[^{317}\] examined the effects of yoga training for more than five years on cardiovascular function in subjects above 40 years of age. They found significant reduction in resting pulse rate, systolic blood pressure, diastolic blood pressure and Valsalva ratio indicating increase in baroreflex sensitivity and concluded that yoga reduces the age related deterioration in cardiovascular functions.

Several studies have investigated the effects of yoga on markers of sympathetic/parasympathetic activation and cardio-vagal function. Although some studies have yielded inconsistent results, over 85% offer some evidence that yoga promotes a reduction in sympathetic activation, enhancement of cardio-vagal function, and a shift in autonomic nervous system balance from primarily sympathetic to parasympathetic.\[^{318}\] Key changes, include significant reduction in respiratory and heart rate, in cortisol concentrations, catecholamine levels, and renin activity, in skin conductance, and in cardiovascular response to stress, as well as significant increase in heart rate variability and baroreflex sensitivity.\[^{291}\]
Endocrine and Reproductive System:

Studies have shown that practice of yoga fine tunes and modulates neuro-endocrine axis which results in beneficial endocrine and metabolic changes. Long term yoga practice is associated with increased insulin sensitivity and attenuation of the negative relationship between body weight or waist circumference.\footnote{Schmidt et al} Schmidt et al\footnote{292} found a reduction in urinary excretion of adrenaline, noradrenaline, dopamine and aldosterone, a decrease in serum testosterone and LH levels and an increase in cortisol excretion, indicating optimal changes in hormones. Yoga with meditation resulted in higher plasma melatonin levels.\footnote{320,\,321} Whether this increase was due to the decreased hepatic metabolism or a direct effect on pineal physiology is not clear. The maximum night time melatonin levels in yoga group showed a significant correlation with the well-being score. Yoga also showed beneficial effect on pregnant women during the process of delivery with significant reduction in physical pain from base line to post intervention.\footnote{322,\,323}

Musculoskeletal System:

Scientific studies on yoga demonstrated that yoga improves dexterity, strength and musculoskeletal coordination of practitioners. Series of asana-s brings steadiness, strength, stamina, flexibility, endurance, anaerobic power, better neuro-muscular coordination and improved orthostatic tolerance.\footnote{316,\,324} Ray et al\footnote{325} studied the effect of training in hatha yogic exercises on aerobic capacity and observed decreased perceived exertion scores indicating that yoga helps to improve aerobic capacity. Yoga practices also resulted in lower basal metabolic rate which may be the result of reduced arousal.\footnote{326} Further it resulted in the improved hip extension, increase stride length, and decrease anterior pelvic tilt in healthy elders.\footnote{327} Even brief interventions can make appreciable contribution to the overall
performance, work capacity and physical fitness.\textsuperscript{[328]} Oken et al.\textsuperscript{[329]} found that hatha yoga practices by elderly (65-85 years) resulted in significant improvement in quality of life and physical measures compared to walking exercise control group.

**Effect of yoga on cardiovascular disease (CVD) and other core indices of insulin resistance syndrome (IRS):**

Several studies in Indian, European and American populations have suggested that yoga also be helped in the management of CVD and other IRS related chronic conditions. Controlled studies of adults with hypertension,\textsuperscript{[330, 331]} risk factors for CVD\textsuperscript{[332]} and diabetes mellitus\textsuperscript{[333]} showed decline in need for drug therapy among those enrolled in a yoga-based interaction compared with controls receiving usual care. Controlled studies in Indian,\textsuperscript{[334]} British\textsuperscript{[333]} and American\textsuperscript{[335]} population also suggest that yoga based programs may attenuate signs, reduce complications, and improve the prognosis of those with frank or underlying disease. There was retardation of coronary atherosclerosis, increased regression and reduced progression of vascular lesion, and reduced angina episodes.\textsuperscript{[334]}

Researchers have investigated the potential influence of yoga and yoga-based programs on one or more core indices of the IRS, including measures of insulin resistance, lipid profiles, body weight and composition and blood pressure. Patient with type II diabetes mellitus\textsuperscript{[336, 337]} or hypertension\textsuperscript{[338]} reported reduction in fasting\textsuperscript{[336, 337, 319, 340]} and postprandial glucose\textsuperscript{[339-341]} and in fasting glycohemoglobin.\textsuperscript{[335-337]} Overall, yoga practice was associated with a 5.4 to 33.4\% reduction in fasting glucose, 24.5 to 27.0\% reduction in postprandial glucose, and 13.3 to 27.3\% reduction in glycohemoglobin, with the percentage varying by study population and design.
Studies that examined the potential effects of yoga on blood lipid concentrations, most offered evidence suggesting that yoga may improve lipid profiles. These studies included investigation of both healthy adult and patients with hypertension or CVD. Observed changes included reductions in cholesterol and low-density lipoprotein (LDL) cholesterol [341-344] and increase in high density lipoprotein (HDL) cholesterol levels [338] relative to baseline levels and/or controls values. Of those studies demonstrating positive effects, yoga practice was associated with a 5.8% to 25.2% decrease in total cholesterol, 22.0% to 28.5% reduction in triglycerides, and 12.8% to 26.0% reduction in LDL-C, with the observed magnitude of the effect again differing by study population and design.

Procoagulant change and damage caused by oxidative stress are thought to mediate many of the atherosclerotic and thrombotic changes that are associated with IRS and to play a pivotal role in the development and progression of CVD [345-347] and diabetes. [348] Yoga based interventions have demonstrated a significant decline in fibrinogen and a significant increase in fibrinolytic activity, in addition to a pronounced, although non-significant decrease in platelet aggregation and activated partial thromboplastin time and a rise in blood platelets. [349] Studies have also shown significant reduction in malonyldialdehyde (MDA) a circulatory product of lipid peroxidation in following yoga lifestyle intervention. [336, 338] Observed changes in other oxidative stress indices included increase in antioxidants, and antioxidative enzymes, [350] and reduction in free radicals. [351]

Collectively, these studies clearly establish that yoga therapy is the most promising among all the complementary and alternative methods available to effectively manage various clinical disorders. Although there have been no major studies to evaluate the effect
of yoga therapy on perimenopausal symptoms, the findings of the above studies on the various systems like musculoskeletal, cardio-respiratory, nervous and endocrine are very encouraging because all the major perimenopausal symptoms originated from these four systems. Hence yoga therapy may prove beneficial in effective symptom control. More importantly, the therapeutic effect of yoga on CVD, metabolic syndrome and other long term complications is highly relevant because these are the same major complications affecting the perimenopausal women also. Moreover, our own experience during last twenty five years in dealing effectively with the menopausal symptoms through yoga intervention motivated us to conduct the present research study which we expect to reach the women population resulting in the improved quality of life. Providing positive, good health care to women in the society is very important because women take care of our homes, they take care of our lives.