International Journal of Pharmaceutics and Drug Analysis

Available at www.ijpda.com

ISSN: 2348:8948

Understanding menopause-postmenopausal complications, management and quality of life

Timmana V.S. Geethika*, Glory Mattapalli, Emmanuel Gujju, Priyanka Boddu

Department of Pharmacy Practice, Avanthi Institute of Pharmaceutical Sciences, Cherukupally (v), Bhogapuram (m), near Tagarapuvalasa bridge, Vizianagaram district, Andhra Pradesh, India

Received: 04 April 2021 Revised: 13 June 2021 Accepted: 16 June 2021

Abstract

Menopause is a commonly occurring transition that all women go through with advancing age. The permanent cessation of menstruation is defined as natural menopause it happens with the termination of a woman's final menstrual period. Variations in race and ethnicity may be a reason for different menopausal onsets in women which may also be affected by lifestyle and demographic factors. A negative effect on the common health and quality of life (QOL) as well as the contentment of middle-aged women may occur due to Menopause and associated biological changes. From one individual to another, symptoms of menopause and their severity differ due to the effects of different factors such as social status, lifestyle, psychological status, and body composition. QOL in women may be diminished due to Menopausal symptoms, mostly sexual and vasomotor symptoms.

Keywords: Menopause, quality of life, postmenopausal women, postmenopausal complications.

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*Corresponding Author

Timmana V.S. Geethika

Email: geethikatimmana@gmail.comDOI: <https://doi.org/10.47957/ijpda.v9i2.473>

Produced and Published by
South Asian Academic Publications

Introduction

Menopause is a commonly occurring transition that all women go through with advancing age [1]. Menopause is a transformation phase from the reproductive to the non-reproductive period in a woman's living. In the aging population it is nature's defensive event against reproductive morbidity and mortality [2]. The permanent cessation of menstruation is defined as natural menopause it happens with the termination of a woman's final menstrual period [3]. Menopause can be instinctive (natural menopause) or iatrogenic (secondary menopause). The succeeding can be caused earlier by medical interference such as bilateral oophorectomy (surgical menopause) or iatrogenic excision of ovary and its function by radiotherapy, chemotherapy or with treatment of gonadotrophin-releasing hormone

analogues. Induced premature ovarian failure may be permanent or temporary in non-attendance of surgery [4].

When Does Menopause Occur?

Although menopause is a common occurrence among women, the onset time and duration time of the menopausal transition and the timing of the last menstrual period are not same [5]. The cessation of menstruation called the menopause, results in the termination of ovulation leading to the loss of ovarian follicles, which in turn effects in decreased ovarian production of estradiol which is the most biologically active form of estrogen, as well as raised circulating concentrations of follicle-stimulating hormone (FSH) and decreased concentrations of inhibin, that hinders the release of FSH. At the age of menopause woman may be more subtle to different rates of atresia of the ovarian follicles than to the depletion of absolute number of oocytes, but depletion of follicles reduced approximately to 1000 (from a crest of 5 million follicles at mid-gestation and 2 million at birth) when woman reaches menopause. The number of follicles attaining migration to gonadal ridge during gestation, their mitotic abilities until mid-gestation, and the rate of

follicular atresia affects the age where sufficient depletion of follicles occurs. Changes in the regularity, nature and timing of menstrual bleeding may result with the lessening concentration of circulating estrogen amid the menstrual transition. While occurrence of irregular menstrual cycles increases bleeding may occur without ovulation or after a deficient luteal phase or, usually specified by a short luteal phase, are all attribute of women over the age of 40 years. The lower luteal phase oestrogen and progesterone secretion may occur cause of such cycles which are related with insufficient FSH [or insufficient FSH responsiveness of the follicle] in the follicular phase. Profuse bleeding may result in due to absence of a corpus luteum, resulting in oestrogen secretion [even hyper-estrogenicity] unopposed by progesterone [6].

Factors affecting onset of menopause

Variations in race and ethnicity may be a reason for different menopausal onsets in women which may also be affected by lifestyle and demographic factors. Even when few studies have reported no similar relationship, maternal age at menopause being related with age at menopause has been reported in 1 study [7], In a study of twins genetic control of age at menopause has been shown in 1 recent study [8].

1. Demographic factors

In developing countries (including Latin America, Indonesia, Singapore, Pakistan, Chile, and Peru) women experience menopause several years earlier when compared to the women in developed countries and this has been indicated in several studies. It has also been indicated in some work that women living in rural areas have a early natural menopause than women in urban areas. Those women who are living at lower altitudes or in less rural area have 1 to 1.5 years later menopause than those women living at high altitude in the Himalayas or in the Andes of Peru [6].

2. Health related factors

Women at her final natural menstrual period marks for hormonal imbalance or changes earlier in life [9]. Several studies have examined the relation of body mass to age at menopause, with inconsistent findings. The increase in both upper body fat distribution [indicated by waist-to-hip ratio] and BMI (indicated by weight over height squared) were associated with later age at natural menopause and raised sex hormone concentrations were reported by few studies [6].

Earlier natural menopause in women on weight reduction programs or in women who gained more than 26 pounds amid the ages of 20 and 45 years has been reported in one study [10]. Although natural menopause may be associated with body mass and composition and this natural menopause occurrence is also related inversely to physical activity, alcohol consumption, and education, whereas infertility and parity are firmly and positively related [11].

3. Familial and genetic factors

With estimation of heritability ranging from 30% to 85% results of family and twin studies recommend that familial and genetic factors will play a dominant role. A strong association found between mothers' and daughters' ages at natural menopause was detailed in 1 relatively large cross-sectional study and 1 large longitudinal British birth cohort study. [6].

Association of polymorphisms of an estrogen receptor gene with earlier natural and surgical menopause has been showed in a Dutch study [12]. Thirteen single nucleotide polymorphisms on 4 chromosomes that were associated with age at menopause was identified by using samples from thousands of women in the Nurses' Health study and the Women's Genome Health study which are of genome-wide association studies [13]. Age at natural menopause have shown having association with 2 single nucleotide polymorphisms of the tumor necrosis factor receptor family [14].

4. Environmental factors

women who do not smoke have a shorter perimenopause when compared to women who smoke and where smoking stopped menstruation 1 to 2 years earlier has been shown as the single most consistent environment effect on age at menopause. [15]. Early natural menopause among smokers is due to the presence of toxic polycyclic aromatic hydrocarbons that exist in the cigarette smoke which are known to be toxic to the ovarian follicles which may ultimately result in premature loss of ovarian follicle. Earlier reduction of estrogen levels in smoker women may be due to the enhanced drug metabolism that also more rapidly metabolises estrogen in the livers of smokers [16].

Both during and after the intense physical activity, number of changes that occur in hormonal parameters [estradiol, progesterone, prolactin, luteinizing hormone (LH), and FSH] show an impact on physical activity. In women who are physically

active these concentrations tend to be lower at rest [17]. Although physical activity has been associated together with reduced concentrations of reproductive hormones and decreased ovulation frequency [10].

Diagnosis of Menopause

Diagnosis of menopause is through retrospective study by history. Preferable restriction of markers for diagnosis of menopause was made to use only in special situations and for fertility issues. Declining ovarian function was indicated by levels of follicle-stimulating hormone [FSH] >10 IU/L. Even in the absence of cessation of menstruation, ovarian insufficiency in the perimenopausal age group with vasomotor symptoms (VMS) are diagnosed with FSH levels >20 IU/L, even in the absence of cessation of menstruation. A reliable marker for menopause or impending menopause and being associated with low levels of estradiol is by detecting FSH level 40 IU/L done atleast 4 weeks apart. At menopause anti-Mullerian hormone becomes imperceptible, levels of inhibin fall, and antral follicular count and ovarian volume also decreases. Menopause transition is defined and established by only objective marker be the menstrual irregularity [2].

In women menstrual cycle length increases to >60 days, anovulation becomes more likely and periods of time with little or no estrogen secretion occur when women progress to the late menopausal transition. All of the commonly observed menopausal symptoms worsen acutely in this late menopausal transition. Women may require treatment as there will be a peak in intensity of many symptoms at this time [18] Women when she is over the age of 45 and has gone at least 12 months without a spontaneous menstrual period is regarded as postmenopausal women. [19].

Menopausal Symptoms

1. Vasomotor symptoms

Hot flushes, cold sweats, and night sweats will be presented as vasomotor symptoms. Menopause transition may report VMS, during the first 2 years of postmenopause, VMS reaches the maximum intensity and then declines over time. Although some may experience for 10 years or longer VMS generally lasts for 6 months to 2 years. [2]. A "hot flush" is referred to as sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest. Lasting for 1 to 5 minutes symptoms like Flushing, chills, clamminess, sweating, anxiety, and

occasionally palpitations may occur. These include night sweats and variations in frequency and duration of these episodes occurs. Daily experience of hot flushes by 87% of women has been reported, with one-third experiencing more than 10 per day has been shown in few studies. With physiologic measures of hot flushes demonstration of sleep disruption is done [20].

In as many as 74% of menopausal women, menopause vasomotor symptoms do occur, and in higher percentages [up to 88./] of perimenopausal women evidence indicates the presence of these symptoms also. For some women, these symptoms may persist for more than 30 years but these symptoms generally subside within 1 year [21]. Menopausal vasomotor symptoms cause cannot be explained alone with the withdrawal of estrogen. The absence of significant correlation between plasma hormone levels and the occurrence of vasomotor symptoms is evidenced by the observation [22]. The physiologic response resulting hot flashes to a marked narrowing of the hypothalamic thermoregulatory neutral zone or set point is the hypothesis. This increase in the chances of sensation of intense heat in response to internal and environmental triggers and ensuing heat loss activation, is due to the change in the set point which involve cutaneous vasodilation and sweating. The change in the hypothalamic function is an assumption that the reduced levels of circulating levels of gonadal hormones may be by menopause association. During menopause the exact trigger that induces a change in thermoregulatory set point or neutral zone activity in the hypothalamus is not fully understood, however the relationship between these events is quite complex [21]. Alterations in the thermoregulation [eg, a reduced neutral zone] and an increased occurrence of hot flashes is due to the instability in CNS concentrations of both norepinephrine and serotonin that may be by reduced levels of gonadal hormones, during menopause [23]. To reduce VMS the risk factors that form basis for certain lifestyle recommendations are obesity, limited physical activity, and cigarette smoking and, along with a variety of known triggers

(alcohol, warm ambient environment, hot drinks). According to ethnicity the prevalence of these symptoms varies. VMS are reported less frequently by Japanese and Chinese women but more frequently by African-American women when compared with the Caucasian women [24].

2. Somatic symptoms

An increasing prevalence of somatic symptoms is noticed especially as midlife characterisation. Low backpain, headaches, joint pain and stiffness, neck pain and stiffness, shortness of breath, numbness and dizziness are all a wide category of complaints that are included in a somatic symptom. Physical function if being interfered by any symptom or complaint can be referred as somatic symptom [25]. Skin changes with the deficiency of oestrogen leads to the decreased collagen content of the skin and bones. Increased aging and wrinkling of the skin, frontal balding, and hirsutism are all due to this reduced collagen content [26]. Body composition – It do not appear to be due to menopausal status or age, although women typically gain weight amidst midlife. Besides loosing lean body mass, women typically gain abdominal fat mass in the early postmenopausal years [2] A rise in the total body fat and increase in the abdominal fat is associated with the change in the hormonal environment of a person at menopause and weight gain per se cannot be attributed to the menopause transition. There is not only a chance of high risk of cardiovascular and metabolic disease, but also on health-related quality of life and sexual function of the individual, when gained excess weight at midlife. [27].

3. genitourinary symptoms

An increasing incidence of lower urinary tract disorders are noticed in post-menopausal women. Major role of vaginal and urethral epithelium normal maintenance is played by oestrogen. These epithelial tissues are receptive to the reduced levels of oestrogen that are circulating. The combination of physiological ageing and hypo-oestrogenism are responsible for the particular urogenital changes which occur during the menopause, but the true contribution of each of the one in above

combination is hard to discover and is more likely to vary inter-individually [28]. Other aspects of oestrogen deficiency; namely atrophy of the lower urinary tract and the resulting symptoms of urinary incontinence, urgency, frequency, dysuria and, recurrent urinary tract infections are paid a less attention. Evidence exists that the tissues of the lower urinary tract are sensitive to the influence of oestrogens. The urethral mucosa atrophies, decrease in the collagen content of the connective tissue, decline in the vascular pulsations of the urethra and decrease in the urethral smooth muscle sensitivity to alpha adrenergic stimulation occurs after the menopause. Oestrogen substitution therapy can reverse all the above effects which may be responsible for the onset of lower urinary tract disorders [29].

4. Sleep disturbances

A health problem reported annually by millions of adults and frequently by many women with symptoms like insomnia, sleep disturbances, and restless sleep, that are included in poor sleep. Few difficulties with sleep disturbance or insomnia is noticed amidst of 40% and 60% of women reaching menopause [30]. It has been hypothesized that menopause-associated sleep disturbance is a primary source for nocturnal hot flashes. However, during midlife women who are reporting sleep problems, other contributors to sleep disruption must also be taken into consideration. In this population, the common causes of determined sleep disturbances include hot flashes, age-related factors, psychiatric illness and primary sleep disorders [31]. Assessment for sleep disturbance should be done in all women who are in period of menopausal transition. Experiencing sleep disturbances or poor sleep amidst one menopausal stage does not essentially determine poor sleep during succeeding stages. woman's health, daily living activities, and quality of life can be influenced by a poor sleep. As depression being a symptom is associated by insomnia, assessment for depression is mandatory in women with poor sleep [32].

5. Psychological symptoms

During menopausal transition an increase in the emotional distress makes it of particular importance. In women during the menstrual transition both symptoms such as depression and anxiety are shown to be more common in some studies, and these symptoms both depression and anxiety are less in men when compared with women and said to be about twice prevalent in women. Variance in the risk of the depression and anxiety is by difference in race with few social and demographic factors (including socioeconomic status and level of education) and is considered as another important issue that requires attention [33]. During the menopausal transition and in early postmenopause, anxiety is more prevalent and this was shown by the results of the community-based study of ovarian aging by a Study of Women's Health Across the Nation (SWAN), that is a large longitudinal, multiethnic study [34].

Postmenopausal Complications

1. Postmenopausal bleeding

Recurrence of vaginal bleeding at least 1 year after cessation of cycles in a menopausal woman is referred to as postmenopausal bleeding (PMB). In women this may also take place on Hormone replacement therapy as unscheduled bleeding. Endometrial or cervical polyps, Tamoxifen therapy and Other (anticoagulation, trauma, other gynecologic neoplasms) Atrophic endometrium, Hormone replacement therapy, Endometrial carcinoma, Endometrial hyperplasia, Uterine leiomyomas, do all involve in the sources of postmenopausal bleeding [35]. Atrophy, either of the endometrium or the vaginal mucosa is the major reason for postmenopausal bleeding. Postmenopausal bleeding will be secondary to endometrial cancer in nearly 1 to 14% of women [37].

Rigorous evaluation by a gynecologist is required to rule out the primary cause of PMB. Cause of PMB will be the exact option for deciding the treatment. The foremost evaluation involves examination of pelvic and the history, and also a Pap smear if appropriate, to look for vaginal or vulvar lesions, any trauma signs, and polyps or

dysplasia in the cervical area. In postmenopausal patients malignancy must be excluded as a reason of bleeding. The chief presenting symptom responsible for endometrial cancer is the postmenopausal bleeding. There may be a need of Investigational studies, like the endometrial biopsy, ultrasound, hysteroscopy, or dilatation and curettage (D&C) [38].

2. Osteoporosis

Weakening of the bone and increase in the risk of its fracture along with reduction in the bone structure is characterized in a common bone disease known as osteoporosis [39]. Acceleration of bone remodeling is done with estrogen withdrawal which results in net increase in bone resorption, which can finally lead to bone loss and even osteoporosis at menopause [40]. Reduced bone mineral density (BMD), disintegration of skeletal microstructure, increased bone fragility and susceptibility to fractures are the common characteristics of postmenopausal osteoporosis (PMOP) which is a most common type of osteoporosis [41]. The occurrence of hip fracture, which is associated with disability, mortality and substantial financial burdens are all put together as complications of PMOP and these fragility fractures are most prevalent [42]. Osteoclastogenesis is inhibited by estrogen through down-regulation of inflammatory cytokines from T lymphocytes and other cells. Up-regulation of some inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-17, tumor necrosis factor alpha (TNF- α) and increase in the activity of T cells is caused by deficiency of estrogen. Osteoclastogenesis and bone resorption are enhanced by such inflammatory conditions [40].

3. Osteoarthritis

Mechanical factors, genetic, hormonal, and metabolic bone, which lead to an imbalance between the synthesis and degradation of joint cartilage and subchondral bone leads to failure of joint cartilage known as osteoarthritis. Softening, fibrillation, ulceration and loss of the cartilage to articulate, sclerosis of the subchondral bone, osteophyte formation and subchondral cysts are the conditions of osteoarthritis [43]. Acceptance of the

relationship between hormonal changes and OA is done long back. A form of "menopausal arthritis" was first described by Kellgren and Moore in 1952 in a group of women with Heberden's nodes and they were characterized by multiple joint involvement (knees, hands, spine) and quick start of symptoms which they renamed as "primary generalized osteoarthritis" [44]. Endogenous estrogens, having nil effects of exposure duration are measured by the age at menarche, menopause, and parity, has been accordantly linked with the increased OA occurrence [45]. Estrogen loss has been strongly implicated in risk of diseases such as heart disease, gout, and osteoporosis as same as in osteoarthritis, where women have a great risk of disease which can increase dramatically after the menopause. The elevation of biomechanical stress on cartilage in women with high bone mass could be due to direct adverse effect of oestrogen or greater oestrogen exposure on cartilage which can be impacted due to the interrelation between high bone density and osteoarthritis. On the other hand, osteophyte formation might be, primarily related with high bone mass and the covariance of these two features in "bone formers" may be explained by cartilage growth factor or elevated bone levels. Higher levels of endogenous oestrogen in postmenopausal women is also been associated with obesity [46].

4. Diabetes mellitus and insulin resistance

A major public health problem now-a-days is type 2 diabetes mellitus (T2DM). It is present quite often in postmenopausal women as it is affected by both chronological and ovarian ageing [47]. Due to the imbalance of endogenous sex hormone levels in that the plasma estrogen is significantly reduced when menopausal period is arrived in women results in high incidence of diabetes [48]. The plasma concentration of estrogen is been closely related with insulin sensitivity. Earlier it is reported that when examined on a pregnancy rat model diminishing insulin sensitivity at high concentrations although estrogen *per se* augmented insulin sensitivity at low concentrations [49]. Postmenopausal women who are at a risk of increased CV may result in circulating estrogen reduction and with

associated risk of increased body weight, where it results in the initiation of insulin resistance. Significant hypersecretion of insulin can be caused by beta cells due to insulin resistance. Deleterious effects can occur on the vasculature, such as sodium and liquid retention, proliferation of smooth muscle cells, vasoconstriction, and proinflammatory activity, which induces hypertension as well as atherosclerosis development due to increased circulating insulin concentrations. The predominant risk factors for CVDs are represented by high blood sugar, hypertension, and atherosclerosis and therefore a significant risk is posed in postmenopausal women [50].

5. Anaemia:

For all the women who are enduring post menopause good nutrition is a paramount, because metabolism of a women tends to slow during this time. In most of the developing countries the serious public health concern is the deficiency of adult micronutrients. Chronic gastrointestinal bleeding and malabsorption is seen in postmenopausal women due to iron deficiency anaemia (IDA). According to a study, poor nutrient intake, anaemia, menopausal symptoms and other disorders are seen in postmenopausal women. To maintain normal health and to prevent osteoporosis and other menopausal symptoms adequate iron, protein, calcium, vitamin D and functional foods should be provided [51].

6. Hyperandrogenism

In the incidence of osteoarthritis the main contributors of menopause *per se* are age, female sex, overloading of the knee joint, weight, quadriceps weakness. On a priority basis these contributing factors should be addressed. The imbalance of rapidly decreasing ovarian estrogen results in excess occurrence of postmenopausal androgen with a relatively gradual decrease in androgen secretion. Increase in hirsutism or changes in hair patterns are the symptoms of postmenopausal androgen which are common and mild. Because these changes are attributed to the subsequent increase in free androgen index and natural aging process which declines in sex-hormone binding globulin (SHBG) and clinicians often do not consider

further biochemical or clinical evaluation [52]. The ovary remains hormonally active, secreting significant amounts of estrogens and androgens even though many years after menopause in postmenopausal women. After menopause the levels of estrogen drop abruptly and secretion of androgen moderately declines during the reproductive years. During menopause, the subsequent imbalance among estrogens and androgens are amplified by a decrease in concentrations of SHBG, which may result in hyperandrogenic symptoms [53]. The normal menopausal process considers the menopause that can go along with the appearance of less terminal hairs in the face and by a decrease in body and scalp hair [54].

7. Thyroid disorders

Mild autoimmune thyroid disease that often only elevates the serum TSH concentration results in thyroid dysfunction which is highly noticed in women >60 years of age. The serum tri-iodothyronine levels are abnormally low in feeble elderly women or women who are ill from various disorders. Contrarily, suppressed serum TSH levels that mimic thyrotoxicosis are noticeable in 2% of seemingly healthy older persons [55].

Hypothyroidism is more frequently noticed in postmenopausal woman and actually when compared in men and women is more common fourfold disorder in woman than men. Hashimoto's thyroiditis is reason for half of the cases and most the others (40%) outcomes are from treatment of Graves' disease. Elevated serum TSH level with serum free thyroxine concentration being normal known as the subclinical hypothyroidism and having no symptoms, occurs in 10% of >60 years older women. Fatigue, being the most common complaint, cold intolerance, dry skin, and constipation are noticed in women with mild hypothyroidism having mildly elevated serum TSH levels.

Thyrotoxicosis

In about 1% of elderly persons, and mostly in women who are with multinodular goiter or Graves' disease occurrence of symptomatic thyrotoxicosis is noticed. Either or both serum free triiodothyronine and thyroxine are elevation and serum TSH suppression occurs

by thyrotoxicosis. Severe weight loss, myopathy, or cardiac symptoms (atrial arrhythmias or heart failure) frequently occur as primary manifestations in women >70 years having thyrotoxicosis.

Thyroid nodules in about 5% of women >50 years old have palpable thyroid nodules, where most of them are benign. Thyroidectomy should be undergone by those with malignant or suspicious cytologic study results, but in patients with benign nodules medical management with thyroid hormone is done or simply followed up [56].

In postmenopausal women particular aggression of well-differentiated papillary and follicular carcinoma are seen [57].

8. Uterine Fibroids

Benign tumors under the influence of gonadal hormones that come up from a single genetically altered mesenchymal stem cell are called as uterine fibroids (UFs). Malignant transformation into sarcoma is attainable but extremely rare. providentially, regression of size of the fibroid and symptoms is one of some benefits of menopause [58]. Menopause does not prevent the occurrence of UFs although it helps to relieve the symptoms of UFs. Irrespective of HT use, a study showed that obesity (specified by the (WHO) World Health Organization as a body mass index [BMI] >30 kg/m²) doubled the risk of uterine fibroids. [59]. In postmenopausal women it is found that with increasing body mass index (BMI) increase in the average oestrogen levels also occur [60]. Even after menopause in obese women by the increased adiposity a higher estrogenic environment is created from the peripheral conversion of oestrogen predisposing them for Uterine fibroids development as uterine fibroids are known to be oestrogen responsive [61].

In menopausal women with asymptomatic fibroid variable effects on the volume and size of uterine fibroids are demonstrated by various hormonal therapies [62].

9. Cancers

• Breast

In many parts of the world classification of breast cancer as a multifactorial disease in pre and post-menopausal women amid the

major sources of morbidity and mortality is done [63]. In patients at premenopausal and postmenopausal ages, definite causes, outcomes, and prognosis and effects are noticed in breast cancer. By menopausal status, the burden of breast cancer distinguishing is important for many causes. Distinct molecular features are present in the mammary gland with hormonal cancer and this causes at premenopausal and postmenopausal stages; for example, With some research suggesting an inverse association, the women with postmenopausal breast cancer have excess bodyweight as a risk factor while the relation with premenopausal cancer is compared less. Secondly, At the time of menopause, the subtypes of breast cancer (prognosis, therapeutic management and distinct in risk factors) also have separate age-incidence profiles. Thirdly, depending on population age structures, the proportion of female populations having risk of premenopausal versus postmenopausal breast cancers vary greatly according to the perspective of both patient and public health. Fourthly, because of breast density and with cancers which are mostly identified at later stages, the early identification of breast cancer is most difficult in premenopausal women [64].

Influence of breast carcinogenesis by oestrogen through molecular studies on possible mechanisms proposes that oestrogen receptor gets acted upon by oestrogen where, the formed oestrogen-oestrogen receptor (dimer) binds to the oestrogen responsive element and activator protein-1 (AP-1), a transcription factor gets activated along with stimulating protein-1 (SP-1) which finally results in spread of cancerous cells by stimulating cell proliferation [65]. The risk of postmenopausal osteoporosis increases with women who develop oestrogen receptor positive-breast cancer at a relatively younger age, and treated with anti-oestrogen drugs like tamoxifen and the effect of oestrogen in breast cancer and

osteoporosis in these women become evident through observation [66].

- **Cervix**

Among the women worldwide, the second most cancer is the cervical cancer. Human papillomavirus (HPV) infection is the cause for cervical cancer. Nearly in all 99 % of the cervical tumours HPV is detected, particularly in HPV 16 and HPV 18 which are oncogenic subtypes and they account mostly in 70% of all cervical tumours. Comparing with the HPV derived cancers (anal, laryngeal, vulva, vagina, and penile) the most common occurring cancer is the cervical cancer and this is because of the cervix transformation zone. The cervix transformation zone is the region where the external surface of the cervix is being exposed to the columnar cells and transform into squamous cells by undergoing a process called squamous metaplasia. The effects of oncogenic HPV are mainly susceptible to this region [67].

- **Endometrial**

At present, in UK the most usual gynaecological malignancy is endometrial cancer, which principally affects the postmenopausal women. Over 90% of the women who are postmenopausal and initially present with abnormal vaginal bleeding are suffering with endometrial cancer. Ten percent of the women who are postmenopausal suffer with postmenopausal bleeding and endometrial cancer can ultimately be present in another 10% [68]. Avoidance of giving oestrogen after endometrial cancers are treated seemed reasonable as it is known that oestrogen plays an important role in the carcinogenesis of large part of endometrial cancers [69]. Proliferative endometrium had been present in 16% of the postmenopausal women who undergone endometrial sampling. Apart from age, high estrogenic states such as nulliparity, anovulation, obesity and diabetes are the risk factors which are incorporated. The risk of developing endometrial hyperplasia and cancer and a four-fold increase is great in

women with proliferative endometrium, when differentiated with atrophic endometrium in postmenopausal women [70]. Endometrial cancer can be divided into two major types. Cancers accounted for 80-90%, are commonly oestrogen dependent endometrioid adenocarcinomas on oestrogen, which are type 1 among endometrial cancers and these can generally have a greater prognosis. Tumours which act more aggressively and are generally present late are the type 2 among endometrial cancers and they bring a poor development. The risk of metastasis and relapse is great as they are not oestrogen driven [71].

- **Ovary**

More than 90% of ovarian malignancies are being accounted with epithelial ovarian cancers with the worst prognosis for gynaecological malignancy, in part because advanced stage of disease conditioned cases were detected over more than 70%. Most of the tumours expressing high levels of androgen receptor concentrations are present in epithelial ovarian carcinogenesis in which steroid hormones, specifically androgens are implicated [69]. From the coelomic epithelium, the origination of majority of malignant neoplasms of the ovary takes place, less regularly, from the follicular cells (granulosa cell tumours) and the germ cells (teratomas and dysgerminomas) tumours arise. Ovarian cancer can have a risk factor when females achieve menarche at early stages, but its effect is moderate on ovarian cancer occurrence and its bit part in pre-menopause is evidently stronger. The increased risk of ovarian cancer is related to usage of hormone replacement therapy (HRT) in menopause, by nearly 50% for 5 years of usage [72].

Accumulation of fluid or a large ovarian mass leads to expansion of the abdomen making it a most common sign of ovarian cancer. However, making this sign unconfined many women complain of having bloating or weight gain in the abdominal region.

- **Vulvular**

A rare disease that considers for approximately 5% of cancers in gynaecology is vulvar cancer. In case of invasive cancer the median onset age is around 65-70 years and for carcinoma in situ the onset age is approximately 45-50 years. vulvar cancer includes risk factors such as HPV, obesity, chronic vulvar pruritus, previous genital warts, greater number of sexual partners, current smoking, PAP smear abnormality, diabetes, and having poor personal hygiene have also been suggested as contributing to risk. Protection against vulvar cancer can be promoted by monogamy, protected intercourse, and sufficient hygiene of the external genitalia [2].

Having long record of pruritus is the most commonly described symptom of vulvar cancer. vulvar bleeding, discharge, dysuria, and pain are all the symptoms that are less often recorded. Vulvar lump or mass, which may be presented as ulcerated, leukoplakic, fleshy, or warty is the most obvious manifestation of vulvar cancer [73].

10. PCOS

A common disorder of the endocrine with heterogeneous clinical manifestations is Polycystic ovary syndrome (PCOS). Polycystic ovary syndrome association with long-term health risks including, glucose intolerance and type 2 diabetes, hypertension (HTN), dyslipidemia, metabolic syndrome, obstructive sleep apnea (OSA), endometrial cancer, obesity, depression and anxiety is indicated in the evidence. With increase in age PCOS phenotype increases, with an indication by the rise in regular menstrual cycles, fall in follicle number and ovarian volume, and also decrease in levels of serum androgen [74]. Women who are diagnosed with PCOS before menopause will experience a drop in circulating androgens during menopause although rest are higher than those of non-PCOS post-menopausal women (at least during the years of early post-menopause). In post-menopausal PCOS women stromal and thecal androgen production might still be seemingly responsive for some time to the enhanced luteinizing

hormone (LH) levels. non-tumorous (functional) or tumorous adrenal or ovarian origin (adenomas and carcinomas) could be a reason for post-menopausal women hyperandrogenism. Obesity being cause for non-tumorous PCOS, is associated with conditions like insulin resistance, endocrinopathies (acromegaly, Cushing disease, hyperprolactinemia, and hyperthyroidism), conditions that are abuse linked or pharmaceutical use; while the tumorous are related to origin of adrenal or ovarian tumors [75]. postmenopausal period besides from bringing sterility would also bring a number of risks and long-term complications to health like breast cancer, osteoporosis and, increased cardiovascular risk mainly in conditions of PCOS. In woman at the phase of postmenopause an increasing incidence of cardiovascular disease is associated with the decline of Estrogens wherein they act as cardioprotective at the phase of premenopause and so in later life these give rise to an increased risk of cardiovascular disease [76].

11. CNS disorders

• Dementia

Dementia includes factors such as age, sex, genetic factors, inflammation, comorbidity, environmental factors, and lifestyle. High education level, average consumption of alcohol, use of hormone replacement therapy (HRT) for women, use of anti-inflammatory drugs, and diet will all fall into factors for protection from dementia [77]. In women after the menopause there has been a potential to impact other forms of dementia and Alzheimer's disease due to the reduction in circulating oestrogen concentrations. [78]. Decline in estrogen levels also have been speculated to be associated with higher chances for dementia risk. The relation between dementia and estrogen levels is credible, and if present, might show crucial inference for anticipation or delay of onset of dementia [79]. Recommendations in post-menopausal women regarding the retardation of Alzheimer's disease progression or for reducing risk of

dementia are not presently made. Counselling on significance of good overall health, good vascular and cardiac health, exercise, nurturing of active mind, avoidance of immoderate consumption of alcohol, and planning to decrease risk of HTN and diabetes and should be done in women in order to achieve best safeguarding of memory at cognition. Now-a-days Menopausal Hormone Treatment (MHT) is not suggested for neuroprotection [2].

• Depression

A incapacitate situation, which frequently leads to exceptional personal, societal, and economical values is named as depression. Women experience depression two times greater when compared to men. This high risk in women may be caused by hormonal changes that occur in women mainly in situations like puberty, pregnancy, and menopausal transition will all contribute for high risk of dementia [80]. Though depression frequently coexists with menopausal transition, mood disorder as well as depression is not regular in symptoms of menopause. In menopausal transition insufficiency of estrogen is the cause of speculation of depression. Reduction in activities of serotonin in brain might be due to estrogen insufficiency. Conversion of mood namely depression is due to the decline in serotonin levels [81].

In menopausal transition many factors might be responsible to depression. Many features involving unfavourable or stressful events in life, menopause that is surgically brought up, having a history of depressive mood disorder and symptoms of menopause itself like the vasomotor symptoms may all increase the chance of getting depression. Apart from the above, menopausal transition symptoms are also associated with sleeping problem. Those symptoms caused by depression and vasomotor symptoms linking via biological mechanisms, psychological and social impact of vasomotor symptoms, or depression is not clear till now. This relationship due to "domino effect" in

which sleeping problems may be caused by vasomotor symptoms therefore developing the probability to advance into depression was stated in the earlier study [82].

Quality of life in postmenopausal women

"An individual's insight of their position in conditions such as the value and culture systems in which they survive and in relation to their goals, expectations, standards and concerns" in life is defined as QOL [83]. QOL is a crucial outcome measure of complete health. Consequently, in the present-day health care system understanding the effect of menopause on the QOL in middle-aged women is critically needed [84].

A negative effect on the common health and quality of life (QOL) as well as the contentment of middle-aged women may occur due to Menopause and associated biological changes. From one individual to another symptoms of menopause and their severity differs due to the effects of different factors such as social status, lifestyle, psychological status and body composition. QOL in women may be diminished due to Menopausal symptoms, mostly the sexual and vasomotor symptoms [85].

No linear relation exists between health status and quality of life. There has been an increasing perception of the view of aging and quality of life in modern years. QOL can be said as a subjective parameter. Hence, to know information about how patients feel and function, direct questioning is the ultimate easiest and suitable way. QOL measures that exist aims to measure the effect ill health has over a number of psychological, physical and social parameters. chief motive of health promotion is development of quality of life. With higher effect on morbidity rather than mortality quality of life can be attained by preventive health programs [86].

The consequences of an individual's physical condition on all features of psychosocial functioning known as (HRQoL) Health-related quality of life. HRQoL is the only universal basis that concludes the daily well-being for postmenopausal women. In postmenopausal women Quality of life is affected by the menopausal symptoms and sociodemographic attributes. HRQoL may be remarkably declined in symptomatic, younger postmenopausal women. In whatever way, several additional, non-menopausal factors also influence quality of life after menopause. Main factors influencing quality of life after menopause are-

- General health
- Lifestyle

- Physical functioning and integrity
- Mental health (also before menopause)
- Psychological and emotional stability (also before menopause)
- Positive former and actual partnership (including satisfactory sexual life)
- Education, professional activity
- Religion
- Cultural environment
- Social integration (also before menopause)

Health-related quality of life (HRQoL) – issues in menopause and aging

- Vasomotor symptoms
- Cognitive functioning
- Vaginal dryness
- Mood symptoms
- Urinary complaints
- Uterine bleeding
- Sleep
- Attractiveness
- Sexual activity
- Anxiety
- Depression
- HRQoL associated with chronic conditions [87]

Various instruments used to assess the quality of life of postmenopausal women include:

1. Greene Climacteric Scale
2. Women's Health Questionnaire (WHQ)
3. Qualifemme
4. The Menopause-Specific QOL Questionnaire (MENQOL)
5. Menopausal Symptom List (MSL)
6. Menopause Rating Scale (MRS)
7. Menopausal Quality of Life Scale (MQOL)
8. Utian Quality of Life Scale (UQoL)

1. Greene Climacteric Scale

In 1998, Greene developed a standard climacteric scale which is now named as Greene climacteric scale (GCS), where this is non-dependent and can estimate somatic, vasomotor and psychological symptoms. Nearly 21 symptoms can be measured by Greene climacteric scale. With the help of a four point rating scale which shows: extremely (3); quite a bit (2); a little (1); not at all (0) a woman can rate a symptom by her own relating to symptom present severity. Association of the symptoms is done to somatic, vasomotor function in the climacteric and psychological (depression and anxiety)

[88]. Psychological symptoms are addressed in symptoms 1-11 where they are divided to depression (a sum of 7-11 symptoms) and anxiety (a sum of 1-6 symptoms). Addressing of somatic aspects is done in symptoms 12-18 and vasomotor symptoms in 19-20 items. Malfunction of sexuality is explored in symptom 21. The sum of all 21 scores of the given subject is the total Greene Climacteric Score. Adding all individuals scores by dividing them with number of subjects for each symptom calculates the mean score. The score of the clusters and the total score are given as the sum of the symptoms with mean scores in the cluster within and the addition of the mean scores of all symptoms are been given, approximately as the cluster score and the total score [89].

2. Women's Health Questionnaire (WHQ)

The 6 domains: memory/concentration, sleep problem, vasomotor symptoms, anxiety/depressed mood, somatic symptoms, and wellbeing are investigated and QoL in women is measured by 23 item WHQ. Menstrual manifestations and sexual behaviour are assessed by two optional modules. For each optional module and each domain calculation of score is done. Using this new scoring, adding up of scores are being done. By the usage of psychometric properties of translated versions were tested. Firstly, distribution of correlation of scores according to clinical criteria to assess discriminative power of the questionnaire, Secondly, multitrait analysis (MA) to prove the construct justifiability of the proposed model and thirdly, Cronbachalpha's coefficient to estimate inner constancy reliability are covered in the analyses that were used [90].

3. Qualifemme

To estimate the effect of hormone deficiency in the menopause basing on quality of life of a woman, an instrument was invented in France which is known as Qualifemme. The number of 32 items were contained in the first version. By the usage of visual analogue scale the scoring of qualifemme instrument is done. By a group of experts of menopause and by the contribution of their clinical experience, the achievement of item weighting is finished. Investigation is done to a subject pool of 351 women ages 51 to 68. The five domains: urogenital (6), vasomotor (2), psychologic (12), general (9), and the last domain covering pain and problems with hair and skin (3) with 32 items are identified in the analysis result of a principal component [91].

4. The Menopause Specific QOL Questionnaire

Evaluating the consequences of the items which are parted into 4 domains, sexual (3 items), physical (16

items), psychosocial (7 items), vasomotor (3 items) basing on the life standards in women of postmenopausal stage is done by a 29 item validated instrument which is a Menopause-Specific Quality of Life (MENQOL) questionnaire. Hot flushes, sweating, night sweats are estimated by vasomotor domain. The psychosocial wellbeing of a person is assessed by psychosocial domain which comprise items excepting feeling "blue", anxiousness and memory. Sleeping, flatulence, weight gain, tiredness, bloating, energy, pain are the things which are evaluated by physical domain. Modifications in vaginal dryness, intimacy, sexual desire are enquired by the sexual domain. For all four of MENQOL domains, the systematic scoring is same. Along the management of the MENQOL conversion the 7- point Likert scale is used for data analysis and scoring [92].

5. Menopausal Symptom List (MSL)

The development of Menopause Symptom List (MSL) in 1997 is done for evaluating the symptoms seriousness which are generally related with menopause. Nearly, to 40 women, living in Australia, aged between 45 to 55 years, a theoretical symptom checklist was dispatched. 25 remarkable items were emerged in three domains, such as labelled psychologic, general somatic, and vasosomatic, following two main component analysis fulfilment [93].

6. Menopause Rating Scale (MRS)

In 1990s in Germany creation of earliest version of menopause rating scale questionnaire took place. In 2014 printed and electronic forms of the Czech version of MRS came into light. The Czech version of MRS in both type of forms is same but it varies only in form and design of the graphic. [94]. 3 domains such as somatic-vegetative (MRS-S), psychological (MRS-P) and urogenital (MRS-U) with 11 symptoms are covered in this MRS questionnaire. Assessment of intensity of different symptoms is done by the respondents using a five-point Likert scale 0-4 (0 - none; 1 - minor; 2 - medium; 3 - major; 4 - unbearable difficulties). Depending on the values of score in the various domains and on the total score (MRS-T), information on the intensity of the various symptoms is obtained by the assessment of MRS questionnaire. Higher level of difficulty is marked by the woman's higher scores in various domains. By representing the relevant area, the evaluation of every one of the three areas consisting in adding up the scores for entire items is made. The abstract of scores of all three areas decides the total assessment of difficulties ranging from points 0 to 44 [95].

7. Menopausal Quality of Life (MQOL)

In 2000 development of MQOL scale took place. To examine the effects of menopause on HRQoL, as well as the effects of employment, age, and medical history a condition-specific questionnaire was intended. In addition to this, in women of community-based sample ensuing to a self-rated change in menopausal phase a cross-sectional information on differences in HRQoL was derived. This consists of 48 questions. These questions generally include topics such as sleep, energy, appetite, feelings, and cognition, interactions, and impact of symptoms. A six-point Likert scale is used to describe each of the above topics [91].

8. Utian quality of life questionnaire (UQOL)

Modified form of original Utian questionnaire from the 1970s is the (UQOL) Utian quality of life questionnaire Score. UQOL was a systematic improvement from the old type of questionnaire in which evaluation of the sense of participants well-being in a treatment study differentiating estrogen to placebo is designed [96]. UQOL was greatly improved with factor analysis having two stage application. This instrument comprises of 23-item along with five-point rating scale in which each item involves four subscales such as occupational, sexual, health, emotional.

Conclusion

In this review article, we had an overall outline on the concept of menopause and the postmenopausal symptoms experienced by the postmenopausal women. The post menopausal women experience many vasomotor, psychological, physical and sexual symptoms. Most of the postmenopausal women also experience few post menopausal complications such as heavy postmenopausal bleeding, uterine prolapsed, ovarian cysts, uterine fibroids, cervical hyperplasia and several other gynaecological cancers. Due to the wide range of symptoms and complications, the quality of life in postmenopausal women is greatly declined. There are various scales to measure the quality of life of postmenopausal women which are also discussed in this article.

Author contributions

all authors contributed equally to this work

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