The peri-menopause is a critical period for women

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Introduction

The peri-menopause or menopausal transition is an unrecognized conundrum for most women because it can be a confusing and difficult time. The concept of the critical window crystalizes on women aged between 45-63years. This age range coincides with the peak age of breast cancer, the peak age of diagnosis of ovarian cancer, the peak age of depression in women, the peak age of migraines in women, the age range when Alzheimer's dementia can be prevented and the peak age of divorces in the United Kingdom.

This concept of the critical window for women was propelled more than twenty years ago but focused on Alzheimer's Dementia.[1–3] This dimension is now being expanded to include the relationship between unopposed Estrogen replacement therapy (ERT) or more widely called Hormone Replacement therapy (HRT) and two special conditions that are the causes of significant mortality in women, namely Breast cancer[4] and Alzheimer's Dementia.[5]

Most women and their families will have a natural fear of breast cancer if their relative has to use HRT. The prayer is that while HRT makes their relative well and happy, they pray that she does not develop breast cancer.

Secondly, they will have no idea that there is a cogent relationship between ERT/HRT and Alzheimer's Dementia (AD). Most people are too afraid to think of AD because they have heard that there is no treatment or cure for AD. However, that worry should not arise if the woman needs to use Estrogen Replacement therapy alone (unopposed ERT) which is the hormone that needs to be replaced, and not the additional Progestogens for the protection of the uterus against cancer of the endometrium. The concern about the risk of endometrial cancer has not been supported with appropriate evidence.[6]

The critical window coincides with when women have common symptoms of the peri-menopause including depression, anxiety, accomplishing less, impatience, feeling tired and worn out, avoiding intimacy, aching in muscle and joints, difficulty sleeping, decrease in physical strength, decrease in stamina, lacking energy, frequent urination and avoiding intimacy. While these would be easily recognized in women who have stopped menstruating as menopausal, women in the peri-menopause might still be menstruating and the diagnosis is not considered.

The peri-menopause is associated with other conditions which affect women cogently such as migraines, depression and even divorces.

This article reports on the association between ERT and breast cancer, Alzheimer's Dementia, Ovarian cancer and Depression. It shows, cogently, that ERT does not harm the breasts. There is some logical evidence that it might protect the breasts against cancer. This is important because it is very different from the widely held belief, worldwide, that Estrogen replacement can cause breast cancer and confirms that peri-menopausal Estrogen replacement can prevent against AD.

Breast cancer

Breast cancer is rare before puberty.[7] The incidences of breast cancer by age increases in the general population from 30/100,000 for 30-34year women who are likely to be using the pill to 41/100,000 in women who are likely to be using the contraceptive pill aged 15-44years. It rises dramatically to 424/100,000 in women aged 70-74years who are unlikely to be using the pill. The incidence of Breast cancer associated with pregnancy in women aged 15-44years in the general population is 55/100,000.

It takes 5-7 years before on abnormal single breast cancer cell reaches a pea-sized lump. So if you might not feel it during a breast examination, a breast examination might not be adequate enough when the incidences dramatically increase in the peri-menopause. A mammogram identifies areas of calcium spill and therefore areas of small early cancer can be seen which translates into better choice of earlier treatment.

For the peri-menopausal woman, serial screening for breast cancer by mammography is an appropriate test to start in the critical window. Women in the United Kingdom who are aged from 50years to their 71st birthday and registered with a General Practitioner doctor are automatically invited for mammographic screening every 3years. But the National Health Service (NHS) is in the process of extending the programme as a trial, offering screening to some women aged 47 to 73years.

In a systematic review, Onwude JL (2021)[5] showed that the majority of studies that had examined the relationship between unopposed Estrogen-only HRT and Breast cancer have been retrospective studies. There were a few prospective cohort studies. However, all the studies were methodologically flawed either in their study direction – exposure to disease outcome in prospective studies and in retrospective studies, from disease outcome to exposure. In addition the flaws include the use of wrong measures of effect such as odds ratio, incidence rate or ratio or relative risks. In effect, they did

not survive the critical evaluation to assess the validity of a cause and effect relationship.[8,9]

The two Women's Health Initiative trials included women without a uterus who were randomized to unopposed Conjugated Equine Estrogen (CEE) versus placebo and secondly, Conjugated Equine Estrogen (CEE) plus Progestogen (Medroxyprogesterone acetate (MPA) versus placebo in women with an intact uterus.

Between 5-10years follow-up, it was concluded that there was a causal link between use of unopposed Estrogens and reduced risk of Breast cancer.[10] For CEE plus MPA, there was a causal link with higher risk of Breast cancer.[11]

When these studies were subjected to a critical 'cause and effect' analysis, Shapiro et al.[12] and Shapiro et al.[13] stated that these WHI studies largely met the criteria for successful cause and effect, lower[12] or higher[13] Breast cancer risk, respectively.

The combined trials comprised 27,347 post-menopausal women with a baseline mean [SD] age of 63.4years [7.2years]. After more than 20 years of median cumulative follow-up, mortality information was available for more than 98%. Unopposed Estrogen (CEE) compared with placebo among 10,739 women with a prior hysterectomy was associated with statistically significantly lower breast cancer incidence with 238 cases (annualized rate, 0.30%) vs 296 cases (annualized rate, 0.37%; hazard ratio [HR], 0.78; 95% CI, 0.65-0.93; P= .005). It was also associated with statistically significantly lower breast cancer mortality with 30 deaths (annualized mortality rate, 0.031%) vs 46 deaths (annualized mortality rate, 0.046%; HR, 0.60; 95% CI, 0.37-0.97; P= .04). In contrast, CEE plus MPA compared with placebo among 16,608 women with a uterus was associated with statistically significantly higher breast cancer incidence with 584 cases (annualized rate, 0.45%) vs 447 cases (annualized rate, 0.36%; HR, 1.28; 95% CI, 1.13-1.45; P < 0.001) but no significant difference in breast cancer mortality with 71 deaths (annualized mortality rate, 0.045%) vs 53 deaths (annualized mortality rate, HR, 1.35; 95% CI, 0.94-1.95; P= 0.11).[14]

There are two substantive observational trials that have confused the scenario of the relationship between Estrogen and Progestogens in HRT and the risk of Breast cancer. The notable studies are the Collaborative Re-analysis (CR Study)[15] and the Million Women's Study (MWS).[16]

The CR study[15] was not suitable to assess the prospective relationship of use of hormones and subsequent Breast cancer using individual data from 51 studies from combined retrospective and prospective studies. This unusual mixed observational study contributed little. Indeed, Shapiro et al.,[8] critically summarised that the findings in the CR Study did not adequately satisfy the criteria of time order, bias, confounding, statistical stability and strength of association, dose/duration response, internal and external consistency and biologic plausibility. It concluded that the causality link was unreliable because of defects in quality of design, execution, analysis and interpretation.

In the Million Women's Study (MWS),[16] which recruited 1,084,110 UK women aged 50-64 years, half the women had used HRT. 9364 incident invasive breast cancers and 637 breast cancer deaths were registered after an average of 2.6 and 4.1 years follow-up, respectively. Current users of HRT at recruitment were more likely than never users to develop breast cancer (adjusted relative risk (RR) 1.66 [95% CI 1.58-1.75], p<0.0001) and die from it (1.22 [1.00-1.48], p=0.05). Past users of HRT were however not at an increased risk of incident or fatal disease (1.01 [0.94-1.09] and 1.05 [0.82-1.34], respectively).

The MWS concluded that current use of HRT was associated with an increased risk of incident and fatal breast cancer and the effect is substantially greater for Estrogen-Progestogen combinations than for other types of HRT.

In a critical cause and effect analysis, Shapiro (2012)[9] commented that based on the MWS findings, it was not possible to distinguish between bias and causation as alternative explanations for the observed associations, and the conclusion that it has been established that HRT increases the risk of breast cancer was not justified. Similarly, Farmer R[17] criticised the MWS on the basis of methodological flaws citing the most obvious flaw as the time of collection of the exposure data, at the beginning because their exposure could have changed by the end of the study. Indeed it did. The results of the breast cancer study are not based on the Million Women recruited into the MWS but on 1.12% of this. The 12,221 women were analysed part way through the years. Of the baseline never-users, 11% had become users, 22% of baseline users had become non-users.

Summary

The risk of breast cancer associated with Estrogen-only HRT is lower when the women have had a hysterectomy because they do not require additional oral progestogens to protect their uterus from uterine cancer. When a woman has not had a hysterectomy, the alternative protection can be the use of an intrauterine device loaded with a Progestogen.

The combined CEE and MPA, an oral Progestogen, seems to be the problem with the risk of Breast cancer.

Ovarian cancer

The starting point is to estimate the prevalence of early ovarian cancer in peri-menopausal women. As a disease of menopausal women, ovarian cancer rates are highest in women aged 55-64years. The median age at which women are diagnosed in the UK is 63years, meaning that half of women are younger than 63years when diagnosed with ovarian cancer and half are older. As 70% of ovarian cancer is diagnosed in late stages, and morbidity and mortality are worst at these stages, it is a plausible hypothesis that an earlier diagnosis at stage 1 or stage 2 ovarian cancer and minimal comparative treatment will be beneficial. In the Netherlands where women have to have regular tests to maintain their insurance cover, most ovarian cancer is diagnosed in stages 1 and 2. Indeed it is current practice to remove the ovaries in women who have a strong family history of ovarian cancer after childbearing. My hypothesis is that ovarian cancer is difficult to diagnose in peri-menopausal or menopausal women because these women are not likely to feel a cancerous mass which can be accommodated within the pelvis. Even when a mass is felt it can often be ignored as low abdominal weight gain. As there is no coordinated screening for ovarian cancer in the UK, there is a financial drain on the whole health system and the family of the affected because of later diagnosis in advanced disease which is associated with higher morbidity and multiple treatments including chemotherapy and/ or other therapies. Ovarian cancer must start at an earlier stage. It is incontestable that when an ovarian cancer is found in the earlier stages (stages 1 and 2) treatment is easier, morbidity is easier and there might be no requirement for expensive chemotherapy. Ideally therefore, screening for ovarian cancer should aim to pick up early ovarian cancer in asymptomatic women.

The diagnosis of Ovarian cancer involves women who are either symptomatic or have pelvic masses or suspicious pelvic lumps.

Screening for ovarian cancer

Screening is the process of looking for the early stages of a disease while the disease is asymptomatic. There is no one good test. The key will be serial checks with a blood test.

In an attempt to establish the effect of early detection by screening for ovarian cancer mortality, Jacobs IJ et al.[18] randomised 202,638 postmenopausal women aged 50-74years to annual multi-modal screening (MMS) with serum CA-125 interpreted with the Risk of Ovarian Cancer Algorithm (ROMA), annual Trans-vaginal ultrasound screening (USS), or no screening in a 1:1:2. The primary outcome was death due to ovarian cancer by Dec 31, 2014, comparing MMS and USS separately with no screening. Results were available for >99.9 women in all three groups. At a median follow-up of 11·1 years, they diagnosed ovarian cancer in 1282 (0·6%) women: 338 (0·7%) in the MMS group, 314 (0·6%) in the USS group, and 630 (0·6%) in the 'no screening' group. Of these women, 148 (0·29%) women in the MMS group, 154 (0·30%) in the USS group, and 347 (0·34%) in the no screening group had died of ovarian cancer.

Although the mortality reduction was not significant in the primary analysis, they noted a significant mortality reduction with MMS when prevalent cases were excluded. They noted encouraging evidence of a mortality reduction in years 7-14.

In a subsequent median follow-up of 16•3 years, Menon (2021)[19] reported on 2055 women diagnosed with tubal or ovarian cancer: 522 cases (1•0%) of 50,625 in the MMS group, 517 cases (1•0%) of 50,623 in the USS group and 1016 cases (1•0%) of 101,314 in the 'no screening' group. Compared with no screening, there was a 47·2% (95% CI 19·7 to 81·1) increase in stage I and 24·5% (−41·8 to −2·0) decrease in stage IV disease incidence in the MMS group. Overall the incidence of stage I or II disease was 39·2% (95% CI 16·1 to 66·9) higher in the MMS group than in the no screening group, whereas the incidence of stage III or IV disease was 10·2% (−21·3 to 2·4) lower. 1206 women died of the disease: 296 (0·6%) of 50 625 in the MMS group, 291 (0·6%) of 50 623 in the USS group, and 619 (0·6%) of 101 314 in the no screening group. No significant reduction in ovarian and tubal cancer deaths was observed in the MMS (p=0·58) or USS (p=0·36) groups compared with the no screening group.

They concluded that the reduction in stage III or IV disease incidence in the MMS group was not sufficient to translate into lives saved, illustrating the importance of specifying cancer mortality as the primary outcome in screening trials. Given that screening did not significantly reduce ovarian and tubal cancer deaths, general population screening could not be recommended.

In 2011, the FDA approved HE4 biomarker test along with the CA-125 test, the most widely accepted biomarker for ovarian cancer for use in Risk of Ovarian Malignancy Algorithm (ROMA).[20] ROMA is a qualitative serum test that derives a numerical score from the results blood tests plus menopausal status, to identify patients presenting with an adnexal mass as being at high or low likelihood for having malignancy.

ROMA is indicated for women over 18years of age with an ovarian pelvic mass for which surgery is planned but who have not yet been referred to an oncologist. Results must be interpreted in conjunction with an independent clinical and radiological assessment.

In data from a 472-patient study presented at the annual meeting of the Society of Gynecologic Oncologists, Moore et al, (2011)[21] evaluated the utility of using an algorithm score of serum HE4 and CA-125 to determine the risk of ovarian malignancy in women with an adnexal mass and classified patients into high-risk and low-risk groups for having a malignancy. The sensitivity, specificity, negative predictive value, and positive predictive value of the ROMA test (Risk of Ovarian Malignancy Algorithm) were estimated. The results showed that ROMA used alone was highly accurate in assigning a combined pre- and postmenopausal patient population to ovarian cancer risk groups: 93.8% of Epithelial Ovarian Cancers were correctly classified as high likelihood. In postmenopausal women, the sensitivity of ROMA was 92.3%, its specificity was 76.0%, and its negative predictive value (NPV) was 97.4%. In premenopausal women, ROMA had a sensitivity of 100%, a specificity of 74.2%, and an NPV of 100%.

Data from a study of 462 patients reviewed by the FDA and published in the instructions for use of ROMA[22] showed that when combined with standard methods used by physicians to assess likelihood of ovarian cancer in a combined population of pre-menopausal and post-menopausal women, ROMA had a sensitivity of 88.4%, a specificity of 67.2%, and a NPV of 96.2%.

Use of the ROMA is anticipated to facilitate primary care physician identification of patients with a high likelihood of malignancy that should be referred to, and surgically managed by, a gynecologic oncologist. There are studies of ovarian cancer screening with ROMA. As the specificity is less than 80% while the sensitivity and Negative Predictive Values are both greater than 80%, serial ROMA tests might be the route to use this test for screening.

In summary, there is a basis for serial ovarian screening with ROMA test as opposed to CA-125 or transvaginal ultrasound in the peri-menopause, perhaps every 2-3years until there are large population based prospective studies with ROMA.

Prevention of alzheimer's dementia in the critical peri-menopausal period

Onwude (2021)[4] states that Dementia is now the biggest killer of women in the UK, surpassing heart disease, which remains the leading cause of death for men. This progressively worsening global pandemic is currently estimated to affect 50 million people worldwide, with projections of increasing to 132 million by 2050.The majority of sufferers live in low- and middle-income countries. The massive global costs of caring for dementia sufferers are projected to rise to US$2 trillion by 2030. That aside, the human costs include profound disability and dependence for the afflicted, and risk of developing depression and anxiety disorders for the carers.[4]

Alzheimer's dementia (AD) accounts for 70% of the four common types of dementia, and it is the variety associated with the fluctuating levels of Estrogen at the peri- menopause.

Based on the knowledge that Alzheimer's dementia is homed in the hippocampus, and that this organ is suffused with Estrogen receptors,[23] a potential link was postulated between Estrogen and Alzheimer's dementia. Indeed the hypothalamus, as the primary area of the brain that is used for declarative memory becomes deplete of Estrogen receptors during the menopause. There is evidence that hippocampal pathology is central and that the hippocampal shape and volume can predict the onset of AD to the development of AD.[24,25]

The definitive cause of AD is the deposition and accumulation of abnormal protein fragments called Tau proteins and β-amyloid proteins, colloquially referred to as 'plaques and tangles' in the brain, which kill brain cells - a process that is known to start in the hippocampus. These abnormal proteins are pathognomonic of AD.[26]

There are various levels of evidence which provide support for the role of Estrogen, including in-vitro studies,[27] animal experimentation[28] and a growing body of human clinical research of how Estrogen, a cheap, simple and safe hormone, when administered in the peri-menopausal transition, could prevent up to 35% cases of AD.[29–41]

Estrogen-only and prevention of alzheimer's dementia at the peri-menopause

The Critical Peri-menopausal Window Theory has been recognised for some time. With regards to AD, the evidence shows that if ERT is administered in the peri-menopausal period, there is a potential to prevent Alzheimer's Dementia. This is consistent with the accepted wisdom that although the symptoms of AD generally occur in later life, the disorder begins in midlife, around the ages 40-65years[42] Some studies have explored the critical window theory for the potential benefits of supplying ERT before the menopause. In a longitudinal cohort study, Shao et al.,[29] showed that peri-menopausal ERT within 5years of the menopause, plus use for 10 or more years was significantly associated with a 35% reduced risk of AD [95% CI 0.43-0.98]. This finding is supported by other prospective cohort studies.[30,31] ERT started after 5 or more years after the menopause was still associated with a 14% reduced but not significant risk of Alzheimer's Dementia [95% CI 0.49-1.51].[29]

Estrogen combined with progestogen and prevention of alzheimer's dementia at the peri-menopause

Combined Estrogen plus Progestogen therapy (HRT) may increase the risk of AD. The position of Estrogen as the effective prevention is shown by the result that peri-menopausal combined HRT (Estrogen and Medroxyprogesterone acetate) within 5years of the menopause and use for 10 or more years was associated with a non- significant 35% reduced risk of Alzheimer's dementia [95% CI 0.36-1.18] while peri-menopausal ERT within 5years of the menopause and use for 10 or more years was associated with a statistically significant 35% reduced risk of Alzheimer's Dementia.[29]

Shao et al.[29] also showed in their longitudinal cohort study of oral combined Estrogen + progestogens, that menopausal HRT therapy 5 or more years after the onset of the menopause was associated with a 32% increased but not significant risk of Alzheimer's dementia [95% CI 0.78-2.24]. This was confirmed by the Women's Health Initiative Memory Study,[32] a randomized placebo controlled study of oral combined Estrogen and progestogens where menopausal HRT four or more years after the menopause was associated with a significantly (doubled) increased risk of AD [Hazards Ratio 2.02, 95% CI 1.21-3.48].

It is now generally accepted that ERT does not reverse established AD.[33–35] Once a woman has developed AD, hormone replacement treatment, particularly combined Estrogen + progestogen (HRT) does not help but might even worsen the condition.

Estrogen prevents AD – a summary of the science

Firstly, the scientific basis for the development of AD, which includes the influences of Tau proteins and β-amyloid proteins on brain cells and cell death and the knowledge that Estrogens inhibit both Tau hyperphosphorylation and β-amyloid protein accumulation, as well as providing protection against β-amyloid protein neuro-toxicity is supported by in vivo experiments in rats.[26]

Secondly, the evidence from MRI shape analysis shows significant regional sparing of the medial aspect of the right hippocampal head and lateral aspect of the body extending to the tail, in the area corresponding to the Cornu Ammonis, including part of the subiculum, in hormone therapy users compared to non-users.[28]

Thirdly the results of the longitudinal prospective cohort studies are consistent.[29–31] This evidence from observational studies go some way to satisfy the most important conditions where an observational study can support a cause and effect relationship.[29] Fourthly, the experimental MRI studies of hippocampal volumes with or without Estrogen are also supportive.[24,25] Finally, there is abundant biologic plausibility. It is well established that Alzheimer's Disease starts in the hippocampus, the area for learning and memory and that the hippocampus is lush in Estrogen receptors and suffers decreased in volume and size in the menopause, and that peri-menopausal Estrogens maintain the lushness of the hippocampi.

Depression in the peri-menopausal critical window

Some of the symptoms seen on screening questionnaires for Depression (PHQ-9) overlap with symptoms on the Menopause-specific Quality of Life Questionnaire.[43] Many studies have recognized the association between depression in middle-aged women and the peri-menopause and menopause.[44] Most of these have explored the options of combination treatments for the menopause with standard anti-depressant treatments.

It will not be surprising then to find that the peak age of depression in women is between 40-59years in the UK and USA[45] which is the age range for the peri-menopausal woman. It is generally accepted that the peri-menopause is a window of vulnerability for the development of both depressive symptoms and a diagnosis of major depressive disorder. The risk for depressive symptoms is elevated during peri-menopause even in women with no prior history of depression.

Many women experience a new onset of depressive symptoms at the menopausal transition or peri-menopause. If there is underlying low-level depression to begin with, peri-menopause can increase the intensity of depressive symptoms. Some of these women are already treated with a combination of menopausal hormones and antidepressants.

Association between depression and the peri-menopause

Graziottin and Serafini (2009)[46] reviewed the interaction between changes in menopausal hormone levels, mood disorders, associated neuropsychological co-morbidities and ageing, and evaluated the currently available therapeutic options for peri-menopausal mood disorders. They evaluated treatment of light to moderate mood disorders with hormonal therapy (HRT), treatment of major depression with antidepressants and lastly the synergistic effect between HRT and antidepressants in treating menopausal depression.

They found that depression across the menopause has a multifactorial aetiology. Predictive factors included previous depressive episodes such as premenstrual syndrome and/or postpartum depression; co-morbidity with major menopausal symptoms especially hot flashes, nocturnal sweating, insomnia, menopause not treated with HRT; major existential stress; elevated body mass index; low socioeconomic level and ethnicity. Postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with premenopausal women and has better outcomes when antidepressants are combined with HT. They concluded that current evidence suggested that a combination of the antidepressant with HRT seems to offer the best therapeutic potential in terms of efficacy, rapidity of improvement and consistency of remission in the follow-up.

In their cross-sectional study in Taiwan, Lin HL et al.[44] examined the relationships between depressive symptoms, menopausal status and menopausal symptoms in middle-aged women. The menopausal status was categorized into pre-menopause, peri-menopause, post-menopause, and surgical menopause. Using a Taiwanese Depression Questionnaire with a cut-off point, a total of 3359 women aged 40-55 years were selected. Among these women, 145 women (4.7%) experienced higher levels of concurrent depressive symptoms. The increase in depressive symptoms was significantly associated with menopausal status and most of the menopausal symptoms. After controlling for age, marital status, education, income, smoking, hormone therapy, and menopause symptoms, the peri-menopause was still significantly associated with depression in midlife women (odds ratio 1.97; 95% confidence interval 1.24-3.14).

They concluded that independent of menopausal symptoms, peri-menopausal status increases the risk of depression.

Maki PM et al.[47] led a multi-institutional panel of clinicians and scientists to look at the peri-menopause, defined as the menopause transition stages as a window of vulnerability for the development of both depressive symptoms and major depressive episodes. Maki et al assert that the guidelines were needed because depression during the peri-menopausal phase can occur along with menopausal symptoms, and these two sets of symptoms are hard to tease apart, which makes it difficult for clinicians to appropriately treat these women. Many women experience a new onset of depressive symptoms. If there is underlying low-level depression to begin with, peri-menopause can increase the intensity of depressive symptoms. There had been a need for expert consensus as well as clear clinical guidance regarding how to evaluate and treat depression in women during the peri-menopause.

During peri-menopause, women often juggle multiple responsibilities and face multiple stressors. They care for their own children, experience children leaving the home, help aging parents, retain primary responsibility for the home, and face increasing job demands at a time when they may be approaching the peak of their career. All of this can be extremely stressful, Maki explained.

Some of the findings of the panel include that: The peri-menopause is a window of vulnerability for the development of both depressive symptoms and a diagnosis of major depressive disorder;

a. The risk for depressive symptoms is elevated during peri-menopause even in women with no prior history of depression;

b. Several common symptoms of peri-menopause (hot flashes, night sweats, sleep and sexual disturbances, weight/energy changes, cognitive changes) complicate, co-occur and overlap with the presentation of depression during this stage;

c. Life stressors including caring for children and parents, career and relationship shifts, aging and body changes and family illness can adversely affect mood;

d. Proven therapeutic options for depression (antidepressants, cognitive behavioral therapy and other psychotherapies) should remain as front-line anti-depressive treatments for major depressive episodes during peri-menopause;

e. Clinicians should consider treating co-occurring sleep disturbance and night sweats as part of treatment for menopause-related depression;

f. Estrogen therapy alone is ineffective as a treatment for depressive disorders in postmenopausal women;

g. Hormonal contraceptives may improve depressive symptoms in women approaching menopause;

h. The evidence is insufficient for the recommendation of botanical or alternative approaches for treating depression related to peri-menopause.

There is insufficient evidence to recommend botanical or alternative approaches for treating depression related to peri-menopause.

Summary

The Peri-menopausal Critical Period is an ideal time to start serial screening in middle-aged women for breast cancer by mammography, ovarian cancer by the Risk of Ovarian Malignancy Algorithm (ROMA) which combines the results of HE4, CA125, and menopausal status into a numerical score and Depression by validated questionnaires like the PHQ-9. It is also an ideal time to start Estrogen only HRT to prevent Alzheimer's Dementia in women who have had a hysterectomy. In similar women who still have their uterus, Estrogen of HRT can be opposed with an Intrauterine device loaded with a Progestogens.[48]

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Conflicts of interest

None of the authors has reported any conflicts of interest.

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