SCIREA Journal of Clinical Medicine

http://www.scirea.org/journal/CM

August 5, 2019

Volume 4, Issue 5, October 2019

Hormone Replacement Therapy – A Review

Asha K Rajan[1], Vedha pal Jeyamani.S[1*], Swarna Priya Basker[1], Kaviya.U[1], Merlin Joan Of Arc. M.C[1], Elizabeth Benita.S[1]

[1]Department of Pharmacy practice, Jaya College of paramedical sciences, Chennai, India

Corresponding Author:

S.Vedha pal Jeyamani

Professor,

Department of Pharmacy Practice,

Jaya college of Paramedical Sciences,

Thiruninrur, Chennai.

swetha21112000@gmail.com

ABSTRACT:

Sexual hormones are of essential importance for reproduction and later in life for metabolism, cardiovascular system and general well being of women. Menopause leads to a multiple loss of functions with decrease in estrogen, progesterone levels particularly in regions of brain, bone, skin, connective tissue, peripheral vessels and cardiovascular system. Alterations in this systems result in an increase in oxidation, weakened lipid metabolism, resulting in high cholesterol levels with increased risk of systemic disorders. Thus it becomes mandatory at times to consider a long term HRT with progestins and estrogens. Diabetic women's making use of HRT is more befitted on their blood glucose and cholesterol levels. Tibolone and Progestrone plus Estradiol therapy is

more befitted for therapy against breast cancer when compared to estrogen therapy alone. Thus the proper use of HRT in short duration would be befitted when compared to long term use leading to many complications of the same.

Keywords: Breast cancer, Hormone replacement therapy, Estrogen, Progestrone.

INTRODUCTION:

Since ancient times, many tried to present themselves young, youth, vigor. The easily obtainable hormones from hormone replacement therapy are estradiol, testosterone, DHEA, thyroid hormone, melatonin, growth hormone and progesterone. Menopause which is characterized by decreased hormone levels, by diminishing the progesterone and androgen levels, triggers a multiple loss of functions [1]. Thus these can eventually leads to alterations in cardiovascular system, bone system etc., can lead to increased risk of oxidation and weakened lipid metabolism, resulting in high cholesterol levels, which ultimately leads to Alzheimer's disease, myocardial infarction and apoplexy. The polymorphism include 2 major enzymes, 17-beta hydroxysteroid dehydrogenase type I which is a key enzyme in the production of estradiol, cytochrome P450, 19 GENE, CYP19, Aromatase which helps in the conversion rate from testosterone to estradiol, androstenedione to estrone, thus increasing tissue and plasma estrogen levels [2]. Diabetic women who undergo hormone replacement therapy can have their blood sugar under control, and lower cholesterol levels when compared to women who haven't undergone hormone replacement therapy. Breast cancer is due to gene polymorphism, hydroxylation and estrogen metabolism. Smoking and alcohol cessation are two main factors to be implemented in hormone replacement therapy [3].

Female sex hormone in postmenopausal women is expanding rapidly. Apart from the relief of menopausal symptoms, estrogen is effective in prevention of cardiovascular disease and osteoporotic fracture – the two leading cause of death in geriatrics. One of the greatest advantages of hormone replacement in elderly women is its ability to resists cardiovascular disease [4]. Estrogen therapy leads to most of the menopause-related psychological symptoms like depressed mood, anxiety, irritability and insomnia. Estrogen prevents collagen loss from the

dermis-menopause associate skin changes [5]. It is of interest in cosmetologists and dermatologists as a means of offering the older women a younger look. Estrogen supplement may arrest bone resorption and increase the bone mineral density. Estrogen improves urogenital symptoms like dysuria atrophic vaginitis or dyspareunia. Hormonal replacement therapy may protect against vascular disease [6].

Postmenopausal hormone replacement therapy:

Use of postmenopausal HRT has fluctuated over the past 50 years due to changes in risks and benefits. Use declined in 1970s after the publication of reports of an association between estrogen use and uterine carcinoma [7]. In 1980s, the combined drugs of estrogen progestin hormone were introduced. These drugs are currently among the most commonly prescribed medication in US and were taken by an estimated 2.9 million women in 1986 and increased to 6 million in 1992 [8]. Unopposed estrogen therapy appears to be associated with a reduced risk of both heart and osteopathic diseases, especially among current and long term users. However, it increases the risk of uterine and breast cancer. While the addition of progestin to HRT is not expected to change its association with osteoporosis, its effect of heart disease and breast cancer is less certain [9]. The mean reported age at menopause for 83% of women in National Health and Nutritional Examination survey sample who had experienced menopause was 45.9 years. 22% of the study experimented menopause as a result of bilateral oopholectomy, the age at menopause among this group was 40.1 years compared with 47.5 years among women who experienced natural menopause. Only 4% said they had used HRT during one intervirus but contraindicated this information in a subsequent interview [10].

A total of 5,602 who faced their menopause by their last follow-up interview were included. An estimated of 45% women were between 25-74 years in age by 1970s. In between 1987 to 1992 as the younger members of the cohort attained menopause, the proportion of about 32% to 54% respectively [11]. This also had high probability of white women, who were educated and who live in the west. Use of menopausal hormone replacement therapy (HRT) has fluctuated over past 50 years with little changes in perception of risks and benefits [12]. The mean reported age for 83% of women undergoing menopause is 45.9 years. 22% of study cohort experienced menopause as a result of bilateral oophorectomy, the age of menopause among this group was 40.1 years compared with 47.5 among women who have menopause naturally [13].

The main application of hormone replacement therapy is to reduce or inhibit the symptoms of menopause, hot flushes and fractures. The patients to be exposed to Menopausal hormone therapy (MHT) should be checked for health issues and general health status [14]. Menopause is a normal physiological event taking place in women near the age of 40 to 50. Risk factors of MHT are obesity, smoking, immobility, etc [15]. Combined estrogen and progestin are meant to raise VTE twofold. But oral estrogen alone has reduced the borderline significance. An increased risk of MHT for stroke is amongst women over 60 years, but no risk for stroke in those who use 50mcg, or less than 50mcg [16]. The complications between MHT and cardio-vascular disease vary with age and time since the menopause. There seems to be an increased risk for breast cancer for both oral estrogen and combined therapy. Unopposed estrogen intake may cause endometrial cancer and hyperplasia. A meta-analysis has reported an increased risk of ovarian cancer. All women must be reviewed every 6 months for the continuation and cessation of MHT [17].

International menopause society (IMS) has provided recommendations in 2016 for women's midlife health and menopause hormone therapy (MHT). The term MHT includes estrogen, progesterone and combined regimens. MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy [18]. Other complaints such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction may improve during MHT. The overall strategy includes lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for peri and post menopausal women's. Women's experiencing a spontaneous menopause before and especially 40, develops higher risks of cardiovascular disease and osteoporosis and effective disorder such as dementia [19]. MHT should not be provided for physical effect of estrogen deficiency. Women undergoing MHT, should have a regular annual consultation. The dose must be titrated to lowest effective dose. There is an absolute weight gain at midlife which is not attributed to menopause [20].

Estrogen has been convincingly shown to be highly effective in preventing and reversing menopause related conditions such as urinogenital problem, hot flushes, postmenopausal bone loss. Observations proved that it causes hip fractures, myocardial infarction, and possibly colonic cancer. In case of estrogen replacement, it postponed the onset of Alzheimer's disease and extends life [21]. Fear of breast cancer and increased vaginal bleeding has lead to low-dose drugs. Intake of HRT is both short-term and long-term, but generally the continuation rates are poor. The predominant factors that influence HRT are fear of breast cancer, vaginal bleeding, weight

gain and other side effects. HRT is continued for about 2 years maximally [22]. Both effective and ineffective therapeutic outcome are reasons for discontinuation. Continuation of HRT is much higher in hyperectomized women. It should also be noted that HRT reduces mammographic screening [23].

The 2012 hormone replacement therapy position statement of the north American menopause society states that the current evidence support the use of HT for perimenopausal and postmenopausal when they balance the potential benefits and risks are favourable for individual women [24]. Certain data supports the initiation of HT around the time of menopause to treat menopause-related symptoms and prevent osteoporosis in women at high risk of fracture. NAMS acknowledges that no single or particular trail can extrapolate to all women, and thus different clinical trials must be done [25]. Benefits and risks of hormone replacement therapy includes, vasomotor symptoms, vaginal atrophy, interruption in sexual functions, overactive bladder, osteroporotic fracture including hip spine and all nonspine fractures. The symptoms in CVS includes coronary heart disease, carotid intima media thickness, venous thromboembolism, stroke, endometrial cancer, breast cancer, diabetes mellitus, thyroidism, lung cancer, cognitive aging and dementia, mood swings and depression [26]. Women who have intact uterus, prescribed with estrogen therapy should be additionally provided with progesterone. Duration of use and discontinuation of use are the two vital factors for the risk benefit ratio of the hormone replacement therapy. The therapy differs with estrogen therapy and estrogen progesterone therapy [27]. Formulation, route of administration, duration of therapy, produce varying effects. Safety profile of ET and EPT should be considered before the administration of the therapy.

Combined estrogen-progesterone menopausal therapy

The combined estrogen-progesterone therapy involves the co-administration of drugs containing, both estrogen progesterone for peri and post menopausal women. From the late 1990s there is a widespread use of hormonal replacement therapy [28]. Clinical trials were conducted to reduce the risk of breast cancer in subsequent different women with congenital effects. Post menopausal women who undergo estrogen only therapy develops higher risks of endometrial cancer. To counteract this, a combined therapy of estrogen and progesterone are provided. Studies were conducted in clinical trials with oral administration in mouse, monkey and rat. Pharmacokinetic investigations were performed in humans regarding absorption, distribution, metabolism and

excretion on hormone replacement therapy. This also includes chemical moiety of the hormone replacement therapy such as estrogen estrate, catechol estrogen etc are described. The symptoms for breast cancer include, breast tenderness, discomfort, pain or mastaglia, which are significantly increased in hormone replacement therapy. Urinary incontinence is one of the major adverse drug reaction reported in hormone replacement therapy. Other ADR include, headache, dizziness, gall bladder damage, dementia, cognitive function and diabetes. Also cervical cancer, ovarian cancer, colorectal cancer, lung cancer etc; are seen.

Tibolone: newer hormone-replacement therapy

The mean life expectancy of women at menopause is 32.7 years where one of every two have osteporotic fracture, one third have coronary heart disease, one fifth have stroke or other brain disease, and finally one eighth have breast cancer. In such cases, hormone replacement therapy could be implemented for postmenopausal health circumstances. This includes certain alternative therapies such as selective-estrogen-receptor modulators (SERMs) and selective tissue estrogenic activity regulators (STEARs) [29]. Tibolone, a synthetic STEAR with differential effects due to different tissue-specific metabolism, enzyme regulation, and receptor activation seems attractive. On metabolism, it gets converted to 2-alpha, beta-hydroxy metabolites which in turn produces estrogenic effect by activating estrogen receptors. In older womens, it causes apparent lack of pro-thrombotic effects. The long-term safety and efficacy of tibolone on major health outcomes in younger postmenopausal women are unknown. It mainly causes osteoporosis in older patients and increased advantage over breast and skeleton, deleterious effect on cardiovascular outcomes or thrombosis.

Hormone replacement therapy and the risk of breast cancer:

Breast cancer is a disease that cause anxiety and dread among women in western world. It is the most common cancer among women in US today. Breast cancer has received extensive attention through numerous epidemiologic studies over the past 40 years. Risk factors include demographic, familial, reproductive and menstrual, life style, environmental, and hormonal factors. Epidemiologic studies of HRT go back at least to 1974. Studies conducted in 1970s were almost universally negative, that is they show no association between HRT and breast cancer. Since 1985 several studies have appeared based on large populations of women. Recent studies support the association between duration of HRT use and breast cancer risk that was first noted in

the late 1970s [30]. It occurs at all groupings of women, naturally post menopausal surgically postmenopausal with or without ovaries and perhaps for premenopausal women, notably those with a late age menopause. Evidence exists that long term use of HRT may increase the risk of breast cancer. The increase is greater in reports from European countries than those from us. This is due to the use of different estrogenic compounds and to the progestin to HRT.

The incidence of breast cancer is increasing with age, 75% of women's are affected after 50 years of age. These women's can experience bothersome issues such as hot flushes, sleep disturbances, sexual dysfunction and memory impairment. Prescribing hormone replacement therapy would decrease the symptoms of menopause and decreases the risk of heart diseases. The *invitro* studies have proven that estrogen can act as cell-proliferating by acting on promotor sites of cellular regulatory genes [31]. Estrogen can stimulate the growth of breast cancer cells in tissue culture but can inhibit at high doses however direct carcinogenic effect has not been demonstrated. Endogenous secretion of hormone and development of breast cancer have been linked. Tamoxifen, a non-steroidal that has anti-estrogenic effects on the breast reduces the risk of contralateral breast cancers in women. Prophylactic oophorectomy has been shown to reduce the risk of breast cancer. The opinion of the current study is to refocus on the estrogen and its benefits and risks on breast cancer. The current benefit-risk ratio assessment of HRT use in risk with breast cancer must await for randomized clinical trials.

Hormone replacement therapy and stroke clinical trails

Bench research suggests that postmenopausal hormonal therapy is associated with beneficial effects on the brain and vascular system. Observed data suggest that postmenopausal hormone replacement therapy is associated with a 25%-50% lower rate of cardiovascular disease and other problems. To prove this, clinical trial is essential, so 3 major clinical trials that inform us about stroke and postmenopausal hormone replacement therapy. HERS, WEST, WHJ studies suggested that postmenopausal hormone therapy is not that effective for reducing the risk of stroke or death among women with vascular diseases [32]. The reported rates of stroke, myocardial infarction and vascular death allow for a more realistic assessment of the risk and benefits of hormone therapy among postmenopausal women.

Menopausal hormone therapy, age and chronic diseases

The release of the women's health initiative (WHI) study in 2002 was a shock to the medical community. Hormone therapy had generally considered to be highly beneficial for postmenopausal women and relieve from the symptoms [33]. It was through to protect women from osteoporosis, heart disease and cognitive decline and to improve quality of life. However WHI showed a statistically significant increase in number of disease state which includes breast cancer, cardiovascular disease and stroke. The data says that women at (50-60) may be protected from heart disease with only 2 slight increases in breast cancer. Vice versa in (>65) older women are more susceptible to breast cancer and heart disease and should avoid hormone therapy. Women and their health care providers should personalize clinical decisions with respect to risk and benefit of HT for chronic disease prevention, overall mortality and quality of life, especially since the world population of postmenopausal women is steadily increasing.

Hormone replacement therapy: cancer, controversies and women's health

Routine acceptance of use of hormone replacement therapy was shattered in 2002 when results of largest HRT randomized clinical trial, the women's health initiative, indicated that long term use of estrogen plus progestin, HRT not only was associated with increased risk of cancer but, contrary to expectations, did not decrease, and may have increased risk of cardiovascular disease. Understanding HRT use in 21st century and its influence requires engaging not only with the science of HRT but also the social, political and institutional context of this science [34]. Far from a simple tale of scientific progress, for four decades since the mid 1960s were millions of women prescribed powerful pharmacological agents already shown, three decades earlier to be carcinogenic. We must engage with core issues of accountability, complexity and fear of mortality and the conduct of socially responsible science. There are no short cuts.

Hormone replacement therapy and osteoporosis

Hormone replacement therapy is used to treat osteoporosis and fractures. Study selection includes, randomized and cohort studies. When compared with bone density outcomes, it was found that it consistently improve bone density with estrogen use [35]. The findings were very similar between oral and transdermal route, different drug regimens and types of progestins. The results support the increase of bone density with estrogen use and protecting against fractures. Raloxifene was found to be most common drug to increase bone density and protection against certain vertebral fractures. A large group of trails with tamoxifen indicated no statistical

significant use in fracture benefit, but it increases the bone density of lumbar spine, hip and wrist sites and was inconsistent between studies. In total of 6 cohort studies, 3-4 were reported to reduce the risk of hip fractures. In a recent meta-analysis of 22 trails of estrogen, 27% caused overall reduction of non-vertebral fractures, along with methodological limitations.

HRT and stroke:

Studies proved that postmenopausal hormonal therapy has a beneficial effect on brain and vascular system. The data suggest that, 25% to 50% hormonal replacement therapy decreases the risk of cardiovascular disease. Two trails focused on secondary prevention: Heart and estrogen replacement therapy (HERS), women's estrogen for stroke trail (WEST), women's health initiative (WHI). Stroke in women are major public health problem, and incidence is strongly age-dependent [36]. Hormone replacement therapy is not same as the oral contraceptives. Postmenopausal hormone replacement therapy is not effective against the risks of stroke in women's undergoing menopause. There might be an increased risk of fatal stroke in women's undergoing drug regimens of hormone replacement therapy. It is possible to block the adverse drug reactions (ADR) of hormone replacement therapy, and increase the beneficial effect in vascular diseases. There are many appropriate indications for the usage of hormone replacement therapies, but avoiding stroke isn't one of them. The reported rates of being affected with stroke, myocardial infarction, vascular death are more realistic assessment of the risks and benefits of hormone therapy among postmenopausal women.

Phytoestrogens: therapeutic alternatives to traditional hormone replacement in postmenopausal women

The statistical data illustrate that diet containing phytoestrogens can decrease coronary heart disease (CHD) breast cancer and menopausal symptoms. These are the traditional way of hormone replacement therapy. These phytoestrogens are natural compounds that are structurally and functionally similar to 17beta estradiol and bind to estrodiol receptors [37]. It is thought to act as both agonist and antagonist. For example Tamoxifen are known to exhibit estrogenic activity in mice, agonist-antagonist in humans, and antiestrogenic in frogs in chicken. The estrogenic receptors are of two types: alpha and beta respectively. The major drawbacks include osteoporosis and cardiovascular effects. The clinical trials for cardiovascular effects were conducted minimally with specific enrolled patients. Several women followed "near vegetarian

diet". The hypothesis of hormone replacement therapy include, the individual reaction to HRT is caused by the genetic conditions, long term HRT is correlated with higher risk of breast cancer and CV. Breakdown mechanism and productive mechanism of steroid genesis are correlated with higher tissue levels of estrogens. Alternative therapies and prevention of high estradiol levels and breast cancer includes; progesterone (sulphate inhibitor), because estradiol is sulphated in breast cancer and livial (tibolone) a synthetic steroid.

Risk of breast cancer with HRT:

Recently two major epidemiological studies have proven that hormone replacement therapy in postmenopausal women increases the risk ratio of breast cancer. One of the studies is found to produce CVS disorders and thrombosis. Other studies suggest that, the time of initiation of HRT is critical for achieving beneficial outcome [38]. The study includes the clinical trial of hormone replacement therapy of 5 years implemented in women which was estrogen based and gave better therapeutic outcomes. It improved well being, quality of life, vaginal epithelium, sexual enjoyment, bladder capacity and increased longevity. ADR includes thromboembolism and pre-existing breast cancer, etc. From 1996 to 2001 increased number of women was supposed to mammogram, with increased breast cancer. There is a hyperplasia of breast, due to which malignancy develops. A 22 year study on a women undergoing hormone replacement therapy showed better benefits with less number of ADR than the women who doesn't undergo hormone replacement therapy. The international menopause society introduced two new recommendation such as women's midlife health and menopause hormone therapy, which helps in the management of women in menopause transition. The therapies include, estrogen, progesterone and combined regimens. More than that information has been gained from international consensus statement published by bodies such as IMS, the European menopause and andropause society. Weight management and prevention of weight gain are essential components in the care of postmenopausal women. Contrary to widespread belief, menopausal hormone therapy is not associated with weight gain and may ameliorate perimenopausal accumulation of abdominal fat.

At least 30 epidemiological studies have been designed to identify an association between hormone replacement therapy and breast cancer risk. In general, the design, quality and analytical studies have improved over the years with an increase in the number of studies too. The results reveal that there is a small increase in risk of breast cancer with many years of estrogen use [39].

This review indicates, analysis of ever versus never use of estrogen-replacement therapy associated with breast cancer risk, duration of estrogen-replacement therapy affects risk and increase in risk after long-term for women with either natural or surgical menopause. Conflict also occurs due to the drug regimen prescribed for HRT. The conclusions reveal that, there doesn't appear to be an increased risk for breast cancer for even ever versus never use of HRT. Recent studies support the effect of over use of HRT associated with increased risk of breast cancer repeatedly. Recent studies provide hints about the different effects of different estrogen administrations. The magnitude of increase is greater in reports of European countries than in US. This variation can be due to different estrogen compounds in addition to progestin's to hormone replacement therapy.

The International Menopause Society have implemented these 2016 recommendations for the better maintenance and management of the women's going through menopause and midlife health issues. The 2016 recommendations includes levels of evidence and good practice points in addition to section specific references [40]. Information has also been drawn from International consensus statement published in the bodies of IMS, the Europeon Menopause and Andropause society. The governing principle of MHT include, MHT remains effective therapy for urogenital atrophy and vasomotor symptoms. Other menopause related complaints such as muscle pain, joint pain, mood swings, sleep disturbances, sexual dysfunction, and quality of life are improved. It should also be provided associated with diet, exercise, smoking cessation safe levels of alcohol consumption and maintaining peri and postmenopausal health. As MHT includes a wide range of hormonal products, safe levels of usage along with risk and benefits should be provided by counseling. Women's experiencing iatrogenic menopause, that is before 40 to 45 years, have greater risks for cardio-vascular disease, osteoporosis and dementia. Premature ovarian insufficiency or premature menopause is defined as primary hypogonadism in normal karyotype with normal menstrual cycles. It is characterized by symptoms and signs such as, oligomenorrhea and amenorrhea [41]. Etiological factors include both primary and secondary, such as chromosomal rechanges, gene variations and polymorphism. For management history of ultrasound scanning, thyroid, adrenal antibody assay karyotyping vaginal examination and hormone analysis are necessary.

Routine acceptance of the hormone replacement therapy was shattered in 2002, when clinical trials resulted that, the increased proportions of estrogen and progestin can result in increased risk

for cancer, but in contrary, it also increases the risk of cardiovascular disease. In June 2004, a group of historians, biologists, clinicians, and women health advocates met to discuss about the social extent of hormone replacement therapy [42]. We have to consider the social extent of the pharmaceutical industry, the biomedical emphasis on individual risks, and hormones. The chronology of hormone replacement therapy started from 1930s till 2000s. The women health care advocates, in turn highlightened the role of advocacy in uncovering hidden risks of pharmaceuticals. Recognizing the importance of epidemiological evidence to arguments in favor and against HRT, the epidemiologists focused on debates over the changes in data links between cancer, cardiovascular disease and hormones. Central biologists focus on endocrine systems. Thus understanding the use in 20th century and influencing in 21st century requires engaging not only with science, but also social, political and institutional content.

Hormonal therapy was considered as highly beneficial for postmenopausal women and regarded as gold standard for relief of hormonal symptoms and was an effect against osteoporosis, heart disease, cognitive decline and in general improves quality of life. But however it significantly increases disease states, breast cancer, cardiovascular disease and stroke. Common age for menopausal was considered as 63 which was older age, in response to rationalize risks of various diseases. The data suggest that, heart disease can compensate breast cancer and decreases the risk of incidence [43]. Problems regarding ADR would produce colorectal cancer, endometrial cancer, lung cancer, ovarian cancer, stroke and diabetes mellitus. The worldwide use of hormone therapy was been increased dramatically from 1980 to 2002.

Recent trends in HRT:

We are constantly changing the use of menopausal hormone replacement therapy and its doses due to the increasing rates of mammography and breast cancer, specifically in Martin County, California, where there has been increased incidence of breast cancer [27]. The methods used in this article of research includes a cohort study launched in 2006 and monitor the changes in breast density, breast tenderness, personal and biological risks among women's routine screening mammography between 2006 to 2007. Breast cancer incidents rates were assessed with tumor histology and estrogen receptor status from 1990-2007 using epidemiological data from northern California. Prevalence among the women has declined shortly from 21.2% in 1998 to 6.7% by 2006-07. Estrogen only use have declined from 26.9 in 1998 to 22.4 by 2007. Invasive breast

cancer rates have also been declined shortly through the 2001 to 2004. Self-reported screening mamographic rates haven't been declined through the years. Use of alternative or complementary agents did not differ significantly between numerous hormone users. Thus it is concluded that there is a dramatic reduction in EPHT.

A randomized controlled clinical trial has been conducted for the health risks associated with their long term use of hormone replacement therapy. The impact of HRT in short term and long term use in aged women's was reported. The results indicate the substantial use of HRT for short term use for middle aged women. Menopause is clearly defined as an event starting after 12 months of the woman's last period, and the median age of the menopause is 51 [35]. Some experience menopause from 40 to until 55. During this menopause transition, ovaries shrink and the hormones secreted by them fluctuate in different patterns. This type of dramatical variability can result in symptomatology during their postmenopausal periods, and these complications usually include, vasomotor changes and urogenital atrophy. The urogenital tract is also sensitive to the decline of estrogen, which include vaginal dryness and vaginal atrophy. HRT includes the intake of small amount of hormones that the natural aging process takes away. Once the treatment is started, it takes about 2 weeks to reduce the negative symptoms of menopause transition.

A systemic review summarized by the results of 24 placebo-controlled randomized trials, showed a clear beneficial effects of hormone replacement therapy. The short term use of hormone replacement therapy may improve mood and depressive symptoms which are usually negative symptoms during menopause. Women who are depressive and cannot be cured with hormone replacement therapy should be treated by psychiatric counseling [40]. Estrogen when administered systemically or topically may improve sexual functions in women. Estrogen therapy is protective against the connective tissue loss and possibly reverses the process of HRT in women. Women undergoing HRT for long term use such as for 1 year may include bleeding HRT. To avoid such issues estrogens are combined with progesterone which can promote bleed-free HRT and minimize the risk of endometrial hyperplasia. The dose can be halved with intervals so as to reduce the side effects of hormone replacement therapy. Hormone replacement therapy replaces the ovarian hormones in premature ovarian insufficiency. The vaginal route administration of progesterone and estrogen produces fewer side effects than compared to systemic route. 12 to 14 days of administration of progesterone can fight against endometrial

hyperplasia and endometrial cancer. Now a day, conjugated estrogens are used to avoid the need of progesterone and are beneficial for women with progesterone intolerance.

Certain key studies have viewed the current risks in HRT, menopause depends upon age, physical activity and hormonal imbalance through which the results can be adjusted for. Due to the lack of quality control, the International Menopause Society has instructed their members not to prepare handmade troches, creams and pessaries [12]. The use of hormone replacement therapy, vaginal estrogens and non-hormonal therapies are shrinking low, and menopause remains in untreated condition. Natural body identical sex hormones are typically derived from plant sources such as soya or wild yam and these are called as “bio-identical HRT”. Estradiol hormones were originally discovered in 1935 and currently available as tablets, patches, gel and pessaries. For women under 60 years of age, E2 tablets are effective. Thrombosis risk increases steadily with age and all the oral HRTs are associated with increased risk of thrombosis in older women.

CONCLUSION:

Hormone replacement therapy could be a boon or a bane according to the way and duration it is made us of. The risk for breast cancer and cardiovascular complications in it may be due to the various estrogenic compounds and progestin compounds present in it. Thus it is highly recommended to understand the complications and appropriate usage of HRT and make its ideal use wisely.

REFERENCE:

[1] Salpeter S.R, Walsh J.M, Greyber E, Ormiston T.M, Salpeter E.E. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med*. 2004,19:791-804.

[2] Hammar M, Christau S, Nathorst-Boos J, Rud T, Garre K. A double-blind, randomized trial comprising the effects of tibolone and continuous combined hormone replacement therapy in post menopausal women with menopausal symptoms. *Br J Obster Gynecol*. 1998, 105:904-911.

[3] Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B *et al*. Randomised trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (HERS) research group. *JAMA.* 1998, 280:605-613.

[4] Kloosterboer HJ. Tibolone: a steroid with a tissue specific mode of action. *J Steroid Biochem Mol Biol*. 2001, 76:231-238.

[5] Grodstein F, Stampfer MJ, Colditz GA, Willet WC, Mnason JE, Joffe M et al. Postmenopausal hormone therapy and mortality. *N Engl J Med*. 1997, 336:1769-1775.

[6] Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA. Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. *Osteoporosis Int.* 2008, 19:1153-1160.

[7] Nelson HD, Fu R, Griffin JC, Nygren P, Smith ME, Humphrey L. systematic review: comparative effectiveness of medictions to reduce risk of breast cancer. *Ann Intern Med.* 2009, 151:703-715, W-226-235.

[8] Archer DF, Hendrix S, Gallagher JC, Rymer J, Skouby S, Ferenczy A et al. endometrial effects of tibolone. *J Clin Endocrinol Metab*. 2007, 92:911-918.

[9] Swanson SG, Drosman S, Helmond FA, Stathopoulus VM. Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multi-centre, randomized, double-blind, placebo-controlled study. *Menopause.* 2006, 13:917-925.

[10] Speroff L. The million women study and breast cancer. *Maturitas.* 2003, 46:1-6.

[11] Shapiro S. The million women study: potential biases do not allow uncritical acceptance of the data [editorial]. *Climacteric.* 2004, 7:3-7.

[12] Glass AG, Lacey JV, Carreon D, Hoover RN. Breast cancer incidence: combined roles of menopausal hormone therapy, screening mammography and estrogen status. J *Natl Cancer Inst.* 2007, 99:1152-1161.

[13] Ravdin PM, Cronin KA, Howlader N et al. The decrease in breast cancer incidence in 2003 in the United States. *N Engl J Med.* 2007, 356:1670-1674.

[14] Wren BG. The origin of breast cancer. *Menopause.* 2007, 14:1060-1068.

[15] Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med*. 1985, 312:146-151.

[16] Carter CL, Corle DK, Micozzi MS et al. A prospective study of the development of breast cancer in 16, 692 women with benign breast disease. *Am J Epidemiol*. 1988, 128:467-477.

[17] Tavassoli FA, Norris HJ. A comparison of the results of long term fellow up for atypical intraduct hyperplasia and intraduct hyperplasia of the breast. Cancer. 1990, 65:518-529.

[18] Hartman LC, sellers TA, Frost MH et al. Benign breast disease and the risk of breast cancer. *N Engl J Med.* 2005, 353:229-237.

[19] Hanahan D, Weinberg R. The hallmarks of cancer. *Cell*. 2000, 100:57-70.

[20] Welch HG, Black WC. Using autopsy series to estimate the disease reservoir for ductal carcinoma in situ of the breast. *Ann Intern Med*. 1997, 127:1023-1028.

[21] Bartow SA, Pathak DR, Black WC et al. prevalence of benign, atypical and malignant breast lesions in populations at different risk for breast cancer. *Cancer.* 1987, 60:2751-2760.

[22] Jemal A, Ward E Thun M. Recent trends in breast cancer incidence rates by age and tumor characteristics among US women. *Breast Cancer Res*. 2007, 9:108.

[23] Canfell K, Banks E, Mao AM, Beral IV. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust*. 2008, 188:641-644.

[24] Colditz GA. Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. *Breast Cancer Res.* 2007, 9:108-112.

[25] Chen WY, Colditz GA, Rosner B et al. Unopposed estrogen therapy and the risk of breast cancer. *Arch Intern Med*. 2006, 166:1027-1032.

[26] Clarke CA, Glasser SL, Uratsu CS et al. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population based evidence. *J Clin Oncol*, 2006, 24: 49-50.

[27] Kennedy DL, Baum C, Forbes MB. Noncontraceptive estrogens and progestin: use patterns over time. *Obstet Gynecol*. 1985,65:441-6.

[28] Ernster VL, Bush TL, Huggins GR et al. Benefits and risks of menopausal estrogen and/or progestin hormone use. *Prev Med*. 1988,17:201-23.

[29] Hunt K, Vessey M, McPherson K. Mortality in a cohort of long term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol*. 1990, 97:1080-6.

[30] Lindsay R, Cosman F Nieves J. Estrogen: effects and actions in osteoporosis. *Osteoporosis Int*. 1993, 3:150-2.

[31] Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking and cardiovascular morbidity in women over 50: the Framingham study. *N Engl J Med*. 1985 313:1038-43.

[32] Bush TL, Barrett-Connor E, Cowan LD et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the lipid research clinics program follow-up study. *Circulation*. 1987, 75:1102-9.

[33] Egeland GM, Matthews KA, Kuller LH et al. Characteristics of noncontraceptive hormone users. *Prev Med*. 1988, 17:403-11.

[34] Harris RB, Laws AA, Reddy VM et al. Are women using postmenopausal estrogen? A community survey. *Am J Public Health*. 1990,80:1266-8.

[35] Derby CA, Hume AL, Barbour MM et al. Correlates of postmenopausal estrogen use and trends through the 1980s in two southeastern new England communities. *Am J Epidemiol*. 1993,137:1125-35.

[36] Johannes CB, Crawford SL, Posner JG et al. Longitudinal patterns and correlates of hormone replacement therapy use in middle aged women. *Am J Epidemiol*. 1994, 140:439-52.

[37] Grabrick DM, Hartmann LC, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *J Am Med Assoc*. 2000, 284:1791-8.

[38] Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. *N Eng J Med*. 1994, 33:5-9.

[39] Guinea VF, Oisson H, Moller T, Hess KR, Taylor SH, Fahey T et al. Effect of pregnancy on prognosis for young women with breast cancer. *Lancet*. 1994, 3443:1587-9.

[40] Marsden J, Sacks NM. Hormone replacement therapy and breast cancer. *Endocr Relat Cancer*. 1996, 3:81-97.

[41] Helewa M, Levesque P, Provencher D. Breast cancer, pregnancy and breastfeeding. *J Obstet Gynaecol Can*. 2002, 24:164-71.

[42] Li Ci, Malone KE, Porter PL, Weiss NS, Tang MTC, Cushing Haugen KL et al. Relationship between long duration and different regimens of hormone therapy and risk of breast cancer. *J Am Med Assoc.* 2003, 289:3254-63.

[43] Ross RK, Paganini Hill, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst.* 2000, 4:328-32.