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The Impact of Hormone Therapy on Cardiovascular and Bone Health in Women with Premature or Early Menopause

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by

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Abstract

The Women's Health Initiative (WHI) studies were a catalyst for the dramatic decline in the number of postmenopausal women being prescribed hormone therapy (HT). The WHI published the largest randomized, double-blind, placebo-controlled trial regarding HT use in postmenopausal women. The WHI studies treated postmenopausal women with HT with a mean age of 63 years. Premature and early menopausal women have frequently not utilized HT based on the results of the WHI studies. The purpose of this literature review was to compare the WHI studies' results to studies that examined coronary heart disease (CHD) and bone health benefits and risks of HT use in premature or early menopause. Articles published in the last 22 years were initially incorporated to include the WHI studies. Articles were then further eliminated if they did not discuss CHD or osteoporosis in postmenopausal women less than 45 years of age. This systematic review recommends individualizing the use of HT in premature and early menopausal women by investigating their risk factors for breast cancer, deep vein thrombosis (DVTs), strokes, and CHD, along with performing a thorough review of their family history. If none of these risk factors exist, premature and early menopausal women should not be denied HT based on the WHI studies' results. Further random controlled trials (RCTs) and longitudinal studies need to be completed specifically on premature and early menopausal women to confidently substantiate the benefits of HT in the prevention of chronic diseases.

Keywords: Hormone replacement therapy, hormone therapy, menopause, osteoporosis, cardiovascular disease

Introduction

Hormones play a distinctive role in women's health. Natural menopause usually occurs around 51 years of age. Premature menopause occurs in women who enter menopause before 40 years of age. Premature menopause can happen naturally or after undergoing a hysterectomy with or without oophorectomy. Early menopause occurs before 45 years of age and can happen naturally or by undergoing a hysterectomy with or without an oophorectomy. Surgical menopause is characterized by women who have had a bilateral oophorectomy. Hormone therapy (HT) provides many protective benefits. Both premature and early menopausal women are at an elevated risk of unnecessary vasomotor symptoms, osteoporosis, and loss of cardiovascular protection without the utilization of HT. The nature of this literature review is to research both bone health and cardiac benefits versus risks of HT use in this patient population. The results will strengthen medical providers' confidence in providing safe, effective, and individualized care to premature and early menopausal women.

Statement of the Problem

The Women's Health Initiative (WHI) study was a driving force for the dramatic decline in HT's prescription practices and usage. Due to the harmful effects reported from the WHI study, including cardiovascular risks, many medical professionals wondered if risks outweighed the benefits of prescribing HT in women entering premature and early menopause. The outcome of this dilemma has left many of these women suffering from vasomotor effects, mood swings, sexual dysfunction, sleep disturbances, increased risk for coronary heart disease (CHD), and poor bone health. Medical professionals need to be aware of the misconceptions stemming from the published WHI studies about the risks of prescribing HT to their patients. Current medical research will guide medical professionals towards individualized care in prescribing HT to

women in premature/early menopause. Medical professionals that provide evidence-based care and complete a thorough medical and family history can safely and confidently prescribe HT.

Research Question

Due to the controversy of the WHI studies, providers need clear direction regarding the safety of HT. The importance of HT is especially evident in women entering menopause before 45 years of age. During this topic's research, many studies discussed the benefits versus risks of using HT. The research specifically led to two research questions. First, in contrast to the age included in the WHI trial (mean age of 63 years), does the use of HT versus no HT in women less than the age of 45 years provide more benefits than risks in preventing osteoporosis? Second, in contrast to the age included in the WHI trial (mean age of 63 years), does the use of HT versus no HT in women less than the age of 45 years provide more benefits than risks in preventing CHD?

Methods

A comprehensive literature review was performed using electronic search databases, including PubMed, CINHAL, AccessMedicine, and Clinical Key. Keywords included hormone replacement therapy, hormone therapy, menopause, osteoporosis, and cardiovascular disease (CVD). Articles were limited to the past 22 years to incorporate the WHI studies. The literature review yielded a total of around 5,057 articles. Exclusion criteria included periodicals, editorials, and articles published before 1998. Journal articles were further eliminated by limiting the age of study participants to less than 45 years, nonhuman trials, and journal articles without specific discussion of osteoporosis or cardiovascular benefits and risks. The types of studies included were randomized controlled trials (RCTs), prospective studies, peer-reviewed journal articles, longitudinal studies, and systematic reviews. After removing research articles

that met the exclusion criteria, 14 studies met all inclusion criteria. The 14 remaining studies focused on outcomes of osteoporosis and CHD benefits and risks of HT use in premature or early menopausal women.

Literature Review

A review of the data has shown that HT use in premature/early menopause is beneficial when used in the appropriate population. HT is proven to have protective benefits in CHD and the prevention of osteoporosis. HT also has improved the quality of life for women in both premature and early menopause by helping alleviate vasomotor symptoms, curb sleep disturbances, and improving sexual dysfunction and mood. As a clinician, it is essential to review the risks versus benefits of prescribing HT to patients by individualizing treatment and collaborating with them.

Pathophysiology of Premature/Early Menopause

Menopause is the cessation of menstruation that can occur either naturally or by having a hysterectomy with or without oophorectomy. Menopause that occurs naturally is called physiologic menopause. Menopause induced by having a hysterectomy with or without removing the ovaries is called artificial menopause (Decherney, Nathan, Laufer, & Roman, 2019). Perimenopause can occur from one to three years before menopause. During this period, menstrual flow gradually decreases and then ceases. As menopause approaches, menstrual cycles become more erratic with abnormal cycle length and increased menorrhagia (Papadakis & McPhee, 2020). Ovulation rarely occurs with menstrual cycles leading up to menopause. The reduction in secreted estrogen, especially estradiol, leads to minimal endometrial growth in between menstrual cycles. Closer to menopause, menstrual cycles become more prolonged, with missed periods or episodes of spotting only. Menopause is said to have occurred when there is a

cessation of bleeding for 1 year (Papadakis & McPhee, 2020).

Menopause occurs approximately around the age of 51 years (Papadakis & McPhee, 2020). Premature menopause is defined as menopause before the age of 40 years and may be linked to genetic or autoimmune causes. Premature menopause affects around 1% of women (Papadakis & McPhee, 2020). The definition of early menopause is menopause that occurs prior to the age of 45 years. Early menopause affects approximately 5% of women (Papadakis & McPhee, 2020). Both types of menopause can occur naturally in women who develop primary ovarian insufficiency (POI) or can be induced by surgical removal of the ovaries (Decherney et al., 2019). Women who undergo hysterectomies with oophorectomy are at an elevated risk of having severe vasomotor symptoms due to rapidly declining hormone levels. Other symptoms besides hot flashes include vaginal atrophy, sleep disturbances, fatigue, and mood changes. Early menopausal women are also at considerable risk of developing osteoporosis (Papadakis & McPhee, 2020).

WHI Clinical Trials

WHI is an organization that studies the most prevalent causes of morbidity and mortality in postmenopausal women. The main comorbidities studied include cancer, CVD, and osteoporotic fractures (Women's Health Initiative Study Group [WHISG], 1998). The WHI was formed in 1992, with a proposed end date of 2007. Postmenopausal women were enrolled in one of the 40 WHI nationwide clinics in either a clinical trial (CT) or observational study (OS). A total of approximately 64,500 women enrolled in the CT, and the OS included nearly 100,000 women. Women's ages ranged from 50-79 years, with a mean age of 63 years (WHISG, 1998).

The WHI trial was a randomized, double-blind, placebo-controlled trial with three different overlapping components. The first component, which did not meet the inclusion

criteria for this review, consisted of dietary modifications with a reduction in colorectal and breast cancer as the primary outcome and a secondary outcome of CVD reduction (WHISG, 1998). The WHISG (1998) had a separate HT component of the study that included another randomized, double-blind comparison among 27,500 women. The primary outcome looked at CHD; the secondary outcome was osteoporosis. The WHI trials used hazard ratios (HRs) and confidence intervals (CIs) to compare the results. The WHI hypothesized that breast cancer incidence would increase among the women in the studies' HT component (WHISG, 1998).

The WHISG's (1998) HT component of the WHI study was split into two different groups. The first group included women who had a hysterectomy and accounted for 45% of the participants' total population. These women would be treated with either conjugated equine estrogen (CEE) 0.625 mg/day or a placebo. The second group of participants in the HT component of the study included women with an intact uterus. These women were treated with the same CEE dose, plus continuous 2.5 mg/day of medroxyprogesterone acetate (MPA) or a placebo. The second group accounted for the remaining 55% of women enrolled in the study. The third component of the WHI trial randomized the use of calcium and vitamin D to prevent hip fractures as the primary outcome and looked at colorectal cancer as the secondary outcome (WHISG, 1998). The calcium and vitamin D component of this trial did not meet the inclusion criteria of this review.

The WHISG (1998) study participants were enlisted by population-based direct mailing campaigns to women in the age range of 50-79 years. There was also media promotion of the WHI studies. In addition to the age range, other inclusion criteria included the requirement that the women be postmenopausal, signed written consent, and have a high likelihood of being in the area for a minimum of three years. Women were excluded from the trial for safety reasons if

they had a previous history of breast cancer or other cancers, except for melanoma skin cancer, in the last 10 years, as well as low platelets and hematocrit levels. Other exclusion criteria excluded women with a life expectancy of fewer than three years. Lastly, women with compliance problems, such as alcoholism or dementia, were also eliminated from the WHI studies (WHISG, 1998).

In 1998, the WHISG wrote this article to explain the intricate design of the WHI trial. This journal article was the foundation for two separate journal articles published to report the second component of HT in postmenopausal women. The WHI studies split their studies into three studies to research women with an intact uterus and those with a hysterectomy with oophorectomy and their differing HT requirements. These two journal articles will be discussed in detail below. The results of the large WHI trial has changed the way providers practice today. Many postmenopausal women questioned whether they should start HT following the publication of the WHI trial. Many studies published after the WHI studies were modeled after the HT arms of the WHI trial. Countless systematic reviews have been published to further analyze the WHI trials (WHISG, 1998).

The Women's Health Initiative Investigators [WHII] (2002) was the first study published from the HT component of the WHI study focused on the risks and benefits of estrogen plus progestin in healthy postmenopausal women. Forty different clinics enrolled 16,608 postmenopausal women with an intact uterus in the United States into the study. The women in this study ranged from 50-79 years, with a mean age of 63.2 years. Because these women had an intact uterus, they were treated with CEE 0.625 mg/day, plus MPA 2.5 mg/day or a placebo. The total number of women given CEE plus MPA was 8,506, versus 8,102 women given the placebo. CHD was the primary outcome measured. Invasive breast cancer was an expected adverse

outcome of the study. Globally, the study also looked at the risks and benefits of stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death from other causes (WHII, 2002).

The WHII (2002) study randomly contacted women in the estrogen plus progestin study every 6 weeks by telephone to evaluate symptoms and bolster compliance with the regimen assigned to them. If any of the women had a clinical event, they had to follow-up every 6 months. Annual office visits were a requirement. A self-administered questionnaire had to be completed every 6 months, which addressed safety concerns and any adverse symptoms. Adherence to medication regimens was monitored by weighing the returned bottles. Yearly mammograms and clinical breast exams had to be completed. Baseline and follow-up electrocardiograms at 3 and 6 years were also mandatory (WHII, 2002).

The WHII (2002) study was planned for 8.5 years, but after a mean of 5.2 years, the data and safety monitoring board (DSMB) advised stopping the trial due to an increase in the number of invasive breast cancer cases. The estrogen plus progestin studies' participants had completed a minimum of 3.5 years and a maximum of 8.5 years of HT when the study was stopped. CHD's primary outcome revealed HR 1.29, nominal 95% CI [1.02, 1.63] with 286 cases. The total CVD (arterial and venous disease) showed a HR 1.22, CI [1.09, 1.36], respectively. Breast cancer findings included HR 1.26, CI [1.00, 1.59] with 290 cases. Hip fractures results yielded a HR 0.66, CI [0.45, 0.98]. Overall, the absolute excess risk per 10,000 person-years revealed that the estrogen plus progestin group had seven more CHD events, eight more strokes, eight additional PEs, and eight supplementary invasive breast cancers than the placebo group. In comparison, the absolute excess risk per 10,000 person-years revealed five fewer hip fractures and six fewer cases of colorectal cancer compared to placebo (WHII, 2002). WHII (2002) concluded that

estrogen plus progestin risks outweighed the benefits and that it should not be used for primary prevention of chronic diseases, specifically not for the study's primary outcome of CHD.

Even though the estrogen plus progestin study was discontinued early, the 2004 study by the Women's Health Initiative Steering Committee (WHISC) decided to continue the estrogen-only arm of the study of women who had a hysterectomy. This arm of the trial enrolled 10,739 postmenopausal women starting in 1993. In this trial, the women's age range was 50-79 years, with a mean age of 63.6 years. The WHI study's estrogen-alone arm ensured that different minorities were included in the trial and accounted for 23% of the total participants. The women were randomly allocated to receive either CEE at a dose of 0.625 mg/day or the placebo. This trial's primary outcome was CHD incidence, which included either nonfatal myocardial infarction (MI) or death from CHD. The primary safety outcome from the trial was invasive breast cancer. To summarize estrogen-alone therapy's risks and benefits globally, other primary endpoints included stroke, PE, colorectal cancer, hip fractures, and death from other causes (WHISC, 2004).

Baseline data for the participants revealed that the estrogen-alone trial women were mostly healthy (WHISC, 2004). The majority of women in the estrogen-alone trial had surgery for a hysterectomy between 40-49 years (43.2%). However, it is unknown whether these women used HT instantly after hysterectomy because the study participants did not include women between 40-49 years. The number of women that had a prior MI or coronary revascularization was 441 (4.1%). At the beginning of the trial, women had an average risk of CHD and breast cancer (WHISC, 2004).

The WHISC (2004) study used the same methodology instituted in the estrogen plus progestin trial. The only difference between them was the drug regimen (the elimination of

progestin). Participants with CHD outcomes, cancers, or fractures had equivalent definitions in both WHI studies' arms. Both of the WHI trials used the first incident to report the different findings in the trials. These outcomes included CHD, stroke, PE, breast cancer, colorectal cancer, hip fractures, and death (WHISC, 2004). The WHISC (2004) reported, "Calculations based on the observed sample size and age distribution gave power estimates of 72%, 55%, and 71% for CHD, hip fractures, and breast cancer, respectively" (p. 1703).

The WHISC (2004) estrogen-alone trial was able to continue until February 2, 2004. The National Institute of Health (NIH) decided to stop the estrogen-alone trial's intervention phase due to the study's inability to expose a CHD risk, the primary outcome of the study, CHD. There was an average of seven years of follow-up data completed when the estrogen-alone trial was discontinued. In addition, the estrogen-alone trial had results that revealed an increase in strokes similar to the estrogen plus progestin trial (WHISC, 2004).

The WHISC (2004) trial's intermediate CVD endpoints revealed positive results for cholesterol levels with estrogen-alone treatment similar to the estrogen plus progestin trial. In an 8.6% subsample of women, fasting blood lipid levels were done at baseline and again at 1 year. Low-density lipoprotein (LDL) levels were found to be lower in the CEE group than in the placebo group (-13.7% vs. -1.0%, $p < .001$). High-density lipoprotein (HDL) levels were higher in the CEE group than in the placebo group (15.1% vs. 1.1%, $p < .001$), respectively. Total cholesterol levels were similar between the CEE and placebo groups ($p = .41$). Triglyceride levels had a greater increase in the estrogen-alone trial compared to the placebo group (25.0% vs 3.0%, $p < .001$). Systolic blood pressure was elevated by a mean of 1.1 (0.4) mmHg in the estrogen-alone trial compared to the placebo ($p = .003$). Similar findings in the estrogen plus progestin trial were seen with lipoprotein levels (WHISC, 2004).

The WHISC (2004) found no significant difference in CHD rates between the estrogen-only and the placebo groups (49 vs. 54 per 10,000 person-years). The results were equivalent to a 9% reduction in CHD events in the estrogen-only group compared to the placebo group. The estrogen-alone trial's primary outcome had a goal for CEE to reduce CHD by 25% to be deemed significant. Strokes among the women increased by 39% in the estrogen-alone trial ($p = .007$), respectively. A 33% increase in deep vein thrombosis (DVT) reached statistical significance ($p = .03$). Total cardiovascular events were 12% higher in the estrogen-alone group compared to the placebo group ($p = .02$), respectively. The primary safety outcome, invasive breast cancer, was lower in the estrogen-alone group by 23% ($p = .06$), just shy of meeting statistical significance (WHISC, 2004).

The WHISC (2004) reported the most significant percentage of decline among the groups treated with CEE was in fractures. There was a 30-39% reduction in fractures in the estrogen-alone group of the trial. The CEE group reported 11 hip fractures compared to the placebo group, which reported 17 hip fractures ($p =.01$). A total of 139 fractures were caused by osteoporosis in the group that received estrogen-only therapy compared to 195 total fractures in the placebo group ($p < .001$). The global index of health benefits versus risks was by and large neutral (HR 1.01, 95% CI [0.91, 1.12]). The WHI authors reported estrogen-alone use does not affect mortality rates or all cause-specific mortality (WHISC, 2004).

The WHISC (2004) study concluded that hip fractures' risk was reduced among postmenopausal women who received estrogen-only, although, with an increased risk of strokes. The WHISC (2004) reported no significant relationship between estrogen-only therapy and a reduction of CHD risk in postmenopausal with a hysterectomy. Because of their findings, the WHISC (2004) does not recommend prescribing estrogen-alone for the primary purpose of

preventing chronic diseases in women.

Even though the WHI study is the largest randomized, double-blind, placebo-controlled trial ever done, some limitations challenge the trials' strength. The first limitation of this study was that the authors only used one dose and administration route of estrogen and progestin in the trials. Using one dose and route of administration assumes that one treatment and administration route fits all. Secondly, the women's average age in the WHI trials was over the age of 63 years, which is over 12 years past the mean age of menopause. Because the women's average age was 63 years, many women in the study were likely to be asymptomatic before HT's initiation. For example, 43.2% of women in the estrogen-alone trial had undergone a hysterectomy between 40-49 years. They were not treated with HT until they were between the ages of 50-79. This limitation adds strength to the hypothesis that HT is more beneficial when women start HT at the onset of menopause versus many years later. Thirdly, due to the average age being 63 years, some of these women could have had plaque buildup in their arteries or veins prior to the beginning of the trial. HT does not remove plaque buildup that already exists in blood vessels in women. Therefore, the increased risks for stroke and DVTs could have existed before the initiation of HT. These limitations can create the question of whether the results from the WHI trials should be applied to women of all ages (specifically premature/early menopausal women), whether asymptomatic women should be started on HT, and if women 12 years past menopause would experience any benefits from HT use.

A fourth limitation in both the estrogen plus progestin and estrogen-only trial is that they were both discontinued early, limiting the accuracy of formulating long-term effects of the use of HT. Lastly, the estrogen-only trial experienced a high rate of women who stopped taking the study medications, along with a higher than expected crossover rate from the placebo group to

the CEE group, due to the early discontinuation of the estrogen plus progestin arm of the WHI study in 2002. These findings could lead to false-positive results in the CEE group as far as HT benefits and risks. These limitations provide evidence that more RCTs are needed to evaluate the risks and benefits of not only the different forms of HT available but specifically in the premature/early postmenopausal women population.

Comparison Studies to WHI Clinical Trials

After the WHI results were released, Crawford et al. (2019) conducted a longitudinal prospective cohort study that analyzed the WHI trials' implications on HT utilization. The Study of Women's Health Across the Nation (SWAN) is a group that conducts longitudinal studies on menopause. The SWAN study is a longitudinal seven site, community-based study. The SWAN study included non-Hispanic Caucasian women and one other racial/ethnic background, such as Chinese, African Americans, Japanese, and Hispanic. The SWAN study's enrollment criteria included women between the ages of 42-52 with an intact uterus and one or both ovaries, no use of reproductive hormones in the last 3 months, and who were not pregnant or lactating. The authors surveyed data from a baseline visit and 13 additional visits between the years of 1996-2013. The data included surveys on lifestyle behaviors, menopausal symptoms, and healthcare utilization. The SWAN study collected data on a total of 3,018 participants. The SWAN study used logistic regression to compare pre-versus-post WHI associations to predict HT initiation and continuation in postmenopausal women (Crawford et al., 2019). Crawford et al. (2019) also did a comparison study of the reasons for pre-versus-post WHI initiation and continuation. To accomplish this task, participants had to respond to a questionnaire about their reasons for starting and for discontinuing HT. The participants' results were categorized and tabulated according to the questionnaires' answers (Crawford et al., 2019).

Crawford et al. (2019) found that the initiation of HT in menopausal women dropped from 8.6% pre-WHI to 2.8% post-WHI ($p < .001$). There was a decrease in the continuation of HT in menopausal women from 84% to 62% ($p < .001$). Crawford et al. (2019) showed that post-WHI group use of non-systemic estrogen therapy (ET) increased from 13.3% to 65.3%. HT use decreased in many subgroups, which was consistent with a wide distribution of post-WHI recommendations. One adverse finding of the study by Crawford et al. (2019) is that HT decreased in populations deemed to have the most significant benefit from HT. These populations included younger menopausal women and women suffering from vasomotor symptoms. Furthermore, the results by Crawford et al. (2019) revealed that concerns spotlighted in the WHI studies were a critical factor in the decline of both initiation and continuation of HT.

Crawford et al. (2019) found that the most common reason participants initiated HT was to prevent CVD and osteoporosis (29.2 -40.9% pre-WHI). Even still, HT initiation declined considerably post-WHI to prevent the same conditions (2-10.5%). Media reports and provider advice were the most commonly reported reasons leading to HT's discontinuation, which both had a $p < .001$ for pre-WHI versus post-WHI difference. Crawford et al. (2019) claimed that the WHI study results led to younger, more symptomatic women being denied the recommended HT among this age group. Crawford et al. (2019) disagreed with the outcome of the WHI studies being used to determine treatment for these younger, more symptomatic women due to postmenopausal women in the WHI studies having an average age of 63 years. Post-WHI recommendations against HT's use were widely accepted throughout the United States regardless of age, race/ethnicity, natural menopause, menopause due to hysterectomy, geographic area, education level, or provider type (Crawford et al., 2019). These results indicate a need for increased education and the importance of weighing risks versus benefits of HT to provide

menopausal women evidence-based care (Crawford et al., 2019).

The SWAN study participants were monitored annually, which is a limitation due to the inability to know the specific dates of initiation and discontinuation of HT among the participants. Therefore, the duration of therapy was not easily accessible. Instead, the study focused on visit-to-visit continuation. The sample size of the study was also a limitation (N = 3,019). Larger participant sample sizes would be more beneficial in providing more robust evidence to validate the real implications of the WHI study and the use of HT. In addition, Crawford et al. (2019) acknowledged that a more extensive study would better support their results because the HT components of the WHI trials included a much larger number of women (N = 27,500).

In contrast, being a study over 17 years that included at least one other racial/ethnic backgrounds strengthens the SWAN study. The WHII (2002) and WHISC (2004) studies' participants were mostly Caucasian women (estrogen plus progestin 83.9% and estrogen-only 75.5%). Measurement of the data before and after the WHI release helps confirm the WHI studies' effect on postmenopausal women's HT use. Crawford et al. (2019) state a lack of studies that differentiate initiation from the continuation of HT. Incidentally, more longitudinal studies are needed to evaluate the implications of the WHI studies further.

HT Use for Prevention of Osteoporosis in Premature/Early Menopause

While completing this literature review, many studies have concluded that HT is beneficial in preventing osteoporosis. A review of the evidence by the United States Preventative Services Task Force (USPSTF, 2017) updated recommendations from 2012 regarding HT for the primary prevention of chronic conditions and published an update in the *Journal of the American Medical Association (JAMA)*. USPSTF specifically looked at evidence

of the benefits and risks of oral and transdermal HT for the prevention of chronic conditions. Additionally, the USPSTF (2017) reviewed data to assess if HT use among different subgroups (such as age) or the time of intervention after menopause would have mixed conclusions. To execute the objective of the update from the USPSTF (2017), the authors evaluated 18 fair to good-quality trials. They reviewed trials that compared the use of estrogen plus progestin versus placebo and trials that compared estrogen-only versus placebo (USPSTF, 2017).

The USPSTF (2017) reviewed five trials (N = 20,499) that specifically looked at estrogen plus progestin's benefits on bone health. The USPSTF (2017) found a significant reduction in fractures among randomized women (RR 0.80, 95% CI [0.68, 0.94]), respectively. The USPSTF (2017) also reviewed the WHI trial, which significantly reduced fractures caused by osteoporosis using estrogen-only therapy. However, in the WHI post-intervention trial, hip fractures reduction was not statistically significant after an average of 10.7 years. Another study reviewed by the USPSTF (2017) called The Estrogen Replacement and Atherosclerosis (ERA) study discovered fewer fractures of any type occurring in women who were prescribed estrogen-only versus placebo (RR 0.42 95% CI [0.17, 1.04]).

The USPSTF (2017) acknowledged that evidence lacks other subgroups such as age, race/ethnicity, and intervention timing. Yet, the USPSTF (2017) recommended with moderate certainty against the use of HT in asymptomatic postmenopausal women for the primary prevention of chronic conditions. The authors assigned a Grade D recommendation for the use of HT for the prevention of chronic diseases. The USPSTF (2017) states unequivocally in their review that their recommendations against the use of HT should not be followed when treating women who undergo hysterectomy or have premature menopause.

Furthermore, the authors recommend the need for more studies to expand the available

evidence among the subgroups and further evaluate the benefits and harms of HT use. They recommended a meta-analysis of individual patient data as a type of study that could help weigh the benefits and risks of HT use amongst these understudied groups. Current research has demonstrated that more clinical trials comparing various types, routes of administration, and dosages of HT are needed to evaluate the safest form of HT to prescribe to postmenopausal women. There is a need for more studies investigating the benefits and risks of HT use in premature and early menopause.

Even though the USPSTF published a Grade D recommendation about HT's use in postmenopausal women, Faubion, Kuhle, Shuster, and Rocca (2015) found that evidence within their narrative review points to adverse long-term health effects in women who experience premature/early menopause. An increase in overall mortality, CHD, and osteoporosis are significant implications of undergoing premature/early menopause. The authors did not use a systematic approach to reviewing articles. Instead, they discussed papers by judgment or by using their personal experiences and completed their interpretation of the findings, which was a limitation to this study (Faubion et al., 2015).

During the systematic review of the evidence, Faubion et al. (2015) found studies that reported that bone loss among premenopausal women with BSO was two-fold higher than in women with natural menopause. Early BSO in women proved that after 12 months, there was a substantial increase in urinary N-terminal telopeptide (NTx) and decreased bone mineral density (BMD) compared to women of similar age with functioning ovaries. Faubion et al. (2015) found further evidence that women who entered menopause between the ages of 40-44 years have a more considerable drop in vertebral BMD than women who experience menopause naturally around the age of 51 years. BMD did decrease over time between the ages of 40-44 years in

contrast to women with natural menopause. However, after 55 years, there was no disparity between vertebral BMD loss between natural or premature/early menopause (Faubion et al., 2015).

Studies on the risk of fractures in postmenopausal populations have resulted in similar findings, with bone loss risk diminishing with estrogen therapy. Confusingly, fracture risk after 70 years has been inconsistent with studies showing an increase in fractures before the age of 70 years and after the age of 70. Faubion et al. (2015) reported no increased risk of non-vertebral fractures in early menopausal BSO women, whether they were treated with estrogen therapy or not, after two decades of follow-up care. They further reported definite benefits of HT use in early menopausal women, even though some evidence is conflicting. Faubion et al. (2015) concluded at the end of their review that, "Women who undergo premature or early menopause should receive individualized HT and counseling" (p. 483). Women without clear-cut contraindications to HT should consider HT's continued use until the natural age of menopause, around 51 years (Faubion et al., 2015).

Similarly, an observational cross-sectional design study performed by Hadjidakis, Kokkinakis, Sfakianakis, and Raptis (2003) evaluated the effects of time and type of menopause on BMD at various ages, specifically in 5-year segments ranging from 45-70 years. The study included a total of 514 women: 177 with normal menopause (NMP), 210 women with surgical menopause (SUMP), and 127 with premature natural menopause (EMP). The average age of each group reported was NMP 49.1 ± 3.9; SUMP 38.3 ± 4.7; and EMP 38.1 ± 4.2 years, respectively. Hadjidakis et al. (2003) used Dual Energy X-ray Absorptiometry (DEXA), specifically L2-L4 vertebrae and proximal femur, to assess the BMD of each group of women. All three groups of women had similar BMI values. The SUMP group of women had a

hysterectomy with bilateral oophorectomy due to uterine myomas. The EMP group of women did not have any endocrine problems predisposing them to early menopause. Also, all women had similar risk factors for osteoporosis. Hadjidakis et al. (2003) excluded women with renal, hepatic, or neoplastic diseases from their study. A consistent process to determine the women were in menopause was used (Hadjidakis et al., 2003).

The 2003 trial published by Hadjidakis et al. revealed that the women in the EMP group had significantly more vertebral bone loss than the NMP group of women at both the age ranges of 45-50 and 50-55 years ($p < .001$). There was also more vertebral BMD loss in the SUMP than the women's NMP groups, which showed statistical significance ($p < .001$) in the 45-50 age segment. The proximal femur DEXA results discovered that for the age range of 45-50 years, the SUMP group had a larger BMD than the EMP group ($p < .001$), respectively. Femoral neck BMD loss was higher among the SUMP group of women compared to the NMP group of women after the age of 55 years. There was no significant difference in any 5-year age ranges between the SUMP and EMP groups in BMD loss. The SUMP women had the fewest women with osteoporosis compared to the EMP and NMP women in almost all of the different age segments. Reduced risk of osteoporosis among SUMP women could result from mixed cortical-trabecular bone resisting the effects of having a surgical hysterectomy with oophorectomy (Hadjidakis et al., 2003).

Hadjidakis et al. (2003) concluded that in both EMP and SUMP in the age group of 45-55, women have a considerably lower BMD than women who naturally go through menopause. Femoral neck BMD in EMP women is smaller in the SUMP women at age 45-65. The SUMP women demonstrated a significant increase in femoral neck BMD loss after the age of 55 years compared to NMP women. Bone metabolism in premature menopausal women may

differentiate between EMP and SUMP women due to the EMP women's results having increased osteoporosis. The results of this study advocated for women who undergo bilateral oophorectomy with a hysterectomy or suffer from premature/early menopause be treated with HT until closer to their natural age of menopause (around the age of 51 years) to help prevent rapid bone loss (Hadjidakis et al., 2003).

One limitation of a cross-sectional study is that there is no validated way to evaluate behaviors over time. Specifically, there was no way to track what the women did between the 5-year segments that could have improved or accelerated BMD loss. A second limitation is that cross-sectional studies cannot measure new cases' incidences due to the limitation of not following the women more often in-between periods. A third limitation is the size of the study ($N = 514$). More participants in the study would strengthen the results of HT being beneficial in preventing BMD loss in women with EMP and SUMP. Consequently, in order to further validate the results from Hadjidakis et al. (2003), more studies need to be done to substantiate their results and reinforce the recommendation in favor of using HT.

Ran, Yu, Chen, and Lin (2017) performed another study that reviewed the effects of using HT to prevent bone loss in postmenopausal women. This study was a prospective, double-blind, randomized, parallel, placebo-controlled study. The authors researched HT's effectiveness and safety in preventing bone loss in Chinese women during the menopausal shift and development of early menopause. In addition, Ran et al. (2017) had a goal to add Level I evidence by examining the effects of 5-year HT on overall health for osteoporosis prevention. Chinese women were first separated by their state of menopause (transitional or early) and were randomly assigned to either the HT or placebo group. The primary outcome of the study was the effectiveness of HT in BMD and bone metabolism. Secondary outcomes were the safety of HT

on lipoprotein levels, breast cancer, and CVD (Ran et al., 2017).

Each group had specific inclusion criteria. Ran et al. (2017) included a total of 220 women initially enrolled in the trial. The final number of women left in the trial after losing some participants over the 5 years was 86 women in the menopause transition group (HT $n = 43$, placebo $n = 43$) and 67 participants in the early menopause group (HT $n = 35$, placebo $n = 32$). The women were randomly assigned to receive either estradiol valerate plus MPA or placebo, which was similar in appearance to the HT drug. Women also received calcium and vitamin D supplements of 500 mg and 200 IU/day two times per day and had a standard exercise program to follow daily. Women that were transitioning to menopause ranged from 40-55 years of age. In comparison, women in the early menopausal group ranged from age 45 to 60 years. All women were in good health both mentally and physically. The trial consisted of a 5-year intervention period (Ran et al., 2017).

Ran et al. (2017) had concrete outcome measures such as using DEXA, alkaline phosphatase (ALP), Ca/Cr, N-telopeptides/creatinine (NTX/Cr), and thoracic and lumbar x-rays at specific intervals to look at the effectiveness of HT amongst the groups. In order to assess HT's safety, women in this study had to have routine lab analysis of their blood, urine, hepatic and renal function, blood glucose, and lipid panels at different time intervals. Uterine complications within the groups of women were evaluated by having pelvic exams, Papanicolaou smear, transvaginal uterine ultrasonography, breast exams, and endometrial biopsies completed yearly (Ran et al., 2017).

The study by Ran et al. (2017) revealed results that demonstrated that early menopausal women treated with HT had an improvement in L2-L4 BMD that met statistical significance ($p <$ .01 vs. baseline). There was improvement throughout the entire 5 years in this group. In

contrast, the early menopausal group received a placebo had a significant decline in L2-L4 BMD ($p < .05$ vs. baseline) throughout the 5-year trial. The transitioning menopausal group that received HT also had substantial improvement in L2-L4 BMD in the first year of therapy. After the second year, there was a mild reduction of values at the femoral neck for the transitioning menopausal women. Even though the benefits continued to decline slowly in the transitioning menopausal women that received HT over 5 years, BMD loss was still less than the starting BMD in transitioning menopausal women who did not receive HT. The placebo group in the transitioning menopausal group had a small 0.8% increase in the first year. There was a significant drop in BMD after the first year ($p < .05$ vs. baseline). There was a statistically significant difference ($p = .0072$) between the transitioning menopausal women and early menopausal women. In conclusion, both Chinese women transitioning into menopause and who enter early menopause will benefit from the maintenance of current BMD or an increase in BMD with the initiation of HT (Ran et al., 2017).

The main limitation of this study is that the study only includes Chinese women. Therefore, you cannot confidently say that the increase in BMD is valid for all racial/ethnic groups. Besides adding other racial/ethnic populations, a more extensive sample-size study would also add validity to the findings. Ran et al. (2017) only used one administration route and the same estrogen and progestin dose in their study. Thus, one cannot generalize the results to all administration routes and dosages of HT.

While HT is known to increase BMD and prevent fractures in postmenopausal women, Castelo-Branco et al. (2014) researched the long-term effects of HT use 20 years after treatment. Castelo-Branco et al. (2014) published a prospective study that evaluated the incidence of vertebral fractures in early postmenopausal women after 20 years of follow-up. The study's goal

was to compare a group of women who received HT to a group of women who did not receive HT and evaluate the incidence of fractures 20 years later. The initial trial started in 1990 and began with 177 women aged 43-57 years old (mean age of 49.1 ±3.9 years). At the end of the trial (20-21 years later), 128 women were unavailable for follow-up, leaving only 49 women left to evaluate the amount of bone loss and vertebral fractures among the two groups of women. The 49 women were split into two groups, one group that received HT for an average of 5.5 years and the control group that did not receive HT. Different clinical and demographic information was assessed, and the use of the Genant semiquantitative scale was used by radiology to diagnose osteoporotic fractures (Castelo-Branco et al., 2014).

Of the 49 patients enlisted in the Castel-Branco et al. (2014) study, 32 (65.3%) were given HT, and 17 (34.7%) did not receive HT. The results were somewhat unexpected; Castelo-Branco et al. (2014) revealed that a more significant number of the patients that received HT for a mean of 5.5 years had more vertebral fractures after 20-21 years than the group of early postmenopausal women that did not receive HT ($p < .05$). The multivariate analysis took a look at the clinical and demographic data of the two groups of women (current age, age at menopause, body mass index [BMI], type of menopause, and medications for osteoporosis) and finalized the results as accurate. Even though the sample size of the study published by Castelo-Branco et al. (2014) was small, the authors still concluded that HT use in early postmenopausal women does not provide long-term prevention of fractures once HT was stopped.

One limitation of this study is that there was no way to view the women's baseline x-ray images at the beginning of the trial. The lack of x-ray images before the start of the trial questions the trial's legitimacy because it is unknown whether the women had fractures or early signs of osteoporosis before receiving HT. Another weakness of this trial is that the women self-

reported their health problems, physical activities, diet, medical history, tobacco, and alcohol use. Additionally, the study's small sample size ($N = 49$) further limits the value of the results. Because of these weaknesses, Castelo-Branco et al. (2014) reported that their findings should be used cautiously. The authors of this trial acknowledged these limitations and agree that there are needs for broader prospective, longitudinal, and interventional studies. Future studies need to look at HT's effects after menopause to analyze the benefits and risks and the long-term impacts once women stop using HT (Castelo-Branco et al., 2014).

Cardioprotective Benefits of HT in Premature/Early Menopause

Many studies have investigated the cardiovascular benefits of treating premature/early menopausal women with HT. A systematic review by Faubion et al. (2015) uncovered a link between CVD and death in postmenopausal women less than 45 years of age. Faubion et al. (2015) further reported the results of studies that indicated there was a two time increased risk of angina. There was also an increase in angina severity 1 year after having a MI in menopausal women less than 40 years of age compared to women who undergo menopause naturally at age 50 years or older. According to one of the studies evaluated by Faubion et al. (2015), heart failure risk was increased by 66% in postmenopausal women less than the age of 45 years, with the risk decreasing by 4% for each year closer to natural menopause. The increased risk of CVD in early/premature menopause has evidence to support this finding, linking estrogen deficiency as the cause lacks supporting evidence. Faubion et al. (2015) also stated that their review's results discovered that women with bilateral salpingo-oophorectomy (BSO) before the age of 45 years raised the risk of mortality due to increased CVD risks among these women. HT may lessen the mortality risk among early menopausal BSO women. Faubion et al. (2015) reviewed observational studies the indicated that premature/early menopausal women were at an elevated

risk of stroke, specifically ischemic stroke. Faubion et al. (2015) reviewed a study called the Multi-Ethnic Study of Atherosclerosis, which found a relationship between increased risks of CHD and stroke in early surgical and naturally menopausal women. These findings suggest that estrogen therapy was beneficial among early menopausal women, specifically women, less than 50. This study's conclusion stated that early menopause was linked to an elevated CVD and mortality risk among early menopausal women, with a more significant elevation in risk in the early BSO women than early naturally menopausal women. The authors recommended HT use to decrease CVD risk in early natural and surgical menopause (Faubion et al., 2015).

Rivera et al. (2009) performed a cohort long-term follow-up study investigating whether mortality was connected to CVD in women who undergo unilateral or bilateral oophorectomy prior to menopause. The authors also looked into whether estrogen had any benefit in reducing the mortality rate linked to CVD in these women. The women were observed from 1950 to 1987. The study was set up as a comparison trial where women with oophorectomy were compared to women who had not had their ovaries removed. There were a total of 1,274 women in the unilateral oophorectomy trial, 1,091 women in the bilateral oophorectomy trial, and 2,383 referent women in the study (Rivera et al., 2009).

Rivera et al. (2009) study results provided further evidence that there was a significant increase in mortality related explicitly to CVD in women who undergo bilateral oophorectomy before the age of 45 years than in referent women (HR 1.67, 95% CI [1.16, 2.40], $p = .006$). In contrast, women in the unilateral oophorectomy group exhibited a decreased mortality risk in correlation to CVD compared to the referent group (HR 0.82, CI [0.67, 0.99], $p = .04$), respectively. Additionally, women treated with estrogen up to the age of 45 years or longer had an elevated HR for mortality (HR 1.84, CI [1.27, 2.68], $p < .001$), respectively. For the group of

women who received estrogen therapy, Rivera et al. (2009) found that the risk of mortality from CVD was reduced (HR 0.65, CI [0.30, 1.41], $p = .28$). Rivera et al. (2009) concluded a heightened risk for CVD mortality in women with bilateral oophorectomy before the age of 45. Furthermore, the authors agreed that estrogen therapy might help reduce the risk of death linked to CVD in women who have had bilateral oophorectomy completed before the age of 45 years (Rivera et al., 2009).

Rivera et al. (2009) used electronic medical records to observe some findings, such as the history of oophorectomy and estrogen use, rather than receiving this type of information directly from the women in their study. Verbal recall from women would strengthen the evidence. Many medications listed in charts are not always reliable due to medication lists and other chart sections not being regularly updated. Overall, the study population included a high percentage of Caucasian and European women, which is not an accurate depiction of all racial/ethnic backgrounds. The authors did not look at socioeconomic factors, which also could have affected the results. Additionally, 98% of the women in the bilateral oophorectomy trial had a hysterectomy. All these factors weaken the evidence and provide evidence that other factors caused increased CVD and increased mortality among the participants,

An additional systematic review by Sullivan, Sarrel, and Nelson (2016) investigated the evidence of HT use in young women with POI and early menopause. The authors reviewed 116 journal articles in their research. The types of articles in their review included long-term and short-term RCTs and meta-analysis studies. Sullivan et al. (2016) examined the benefits and risks of HT use related to CVD, among many other conditions. They examined 11 articles exclusively pertaining to CVD risks and benefits of HT. One of the main challenges in POI is an estrogen deficiency. Because of the lack of estrogen, women who suffer from POI have an

increased risk of CVD and ischemic stroke (Sullivan et al., 2016).

One meta-analysis reviewed by Sullivan et al. (2016) provided evidence that menopause before the age of 45 years has an elevated risk of CHD, cardiovascular mortality, and overall mortality compared to women who encountered menopause after the age of 50 years. Women with POI have decreased vascular endothelial function. Decreased vascular endothelial function can lead to atherosclerosis (Sullivan et al. (2016). The use of HT for 6 months significantly impacted vascular endothelial function, decreasing atherosclerosis among women. This review concluded that women should be counseled on the importance of lifestyle modifications, lipid level management, HTN, and the value of HT's early initiation. There are numerous studies, including long-term studies, on CVD benefits with the use of HT in women who enter menopause naturally (Sullivan et al., 2016).

Unfortunately, studies related to CVD benefits using HT in women with POI and early menopause are lacking. Therefore, the lack of other studies limits the strength of evidence for the support of HT and the benefits of preventing CVD in women with POI and early menopause. Even with this limitation, Sullivan et al. (2016) recommended HT use for women suffering from POI and early menopause. HT should be individualized and initiated in a dose that matches normal ovarian hormone production. Furthermore, HT should be continued in this population up until the natural age of menopause, approximately the age of 51 years (Sullivan et al., 2016).

A large study, the Kronos Early Estrogen Prevention Study (KEEPS), was conducted to investigate the benefits and risks of HT use in postmenopausal women. The KEEPS was a multi-center, 4-year follow-up study performed after the early dissolution of the WHI study. The goal of KEEPS was to examine the CVD benefits of timely HT use in postmenopausal women. KEEPS was a randomized, double-blind, placebo-controlled study to explore if introducing HT

early in healthy postmenopausal women ($N = 720$) with oral conjugated equine estrogen (o-CEE) or transdermal 17ß-estradiol (t-E_2) would lower the rate of the development of atherosclerosis. KEEPS was the first randomized, placebo-controlled study to use two different formulations of HT. Carotid artery intima-media thickness (CIMT) changes were used to measure the amount of atherosclerosis in each group of women and were the primary outcome of KEEPS. The secondary outcome measured was the coronary artery calcium (CAC) in each woman to determine if any women had an increased risk for CVD. Participants in the KEEPS were between the ages of 42-58 and within six months to three years of natural menopause (Miller et al., 2019).

Miller et al. (2019) had well-planned inclusion and exclusion criteria to ensure that they were enrolling healthy women. Women with a CAC of greater than 50 Agaston Units (AU) at the time of screening were excluded from the trial. KEEPS also differentiated their trial from the WHI and other studies by eliminating women with a BMI over 35 kg/m^2, diabetes, HTN, dyslipidemia (including the use of statins), previous history of CVD, tobacco use of more than 10 cigarettes per day, history of cancer, or other chronic medical conditions. KEEPS also used a lower dose of oral estrogen (0.45 mg/d) in comparison to the WHI study (0.625 mg/d). The women who received either oral estrogen or transdermal estrogen also received micronized progesterone at a 200 mg/d for the first 12 days of each month. The KEEPS utilized micronized progesterone instead of MPA due to the WHI study's findings that progesterone increased breast cancer risk. The placebo group participants received all three versions of a placebo pill, patch, and 12 days of a placebo capsule (Miller et al., 2019).

The results of the KEEPS trial revealed no significant statistical difference in the rate of increase in the primary outcome of CIMT with the use of HT. CIMT results with the use of o-

CEE (*n* = 230) showed a baseline, M = 0.7268 mm, 95% CI [0.7152, 0.7384]; after 4 years (*n* = 185), M = 0.7591 mm, [0.7465, 0.7717]; estimated change in CIMT, M = 0.008 mm, [0.0065, 0.0095]. CIMT results with the use of t-E_2 (*n* = 222) revealed a baseline, M = 0.7176 mm, CI [0.7058, 0.7294]; after 4 years (*n* = 176), M = 0.7488 mm, [0.7359, 0.7616]; estimated change in CIMT, M = 0.0077 mm, [0.0061, 0.0092], respectively (Miller et al., 2019). In comparison, placebo (*n* = 275) CIMT results at baseline were, M = 0.7213 mm, CI [0.7106, 0.7319]; after 4 years (*n* = 217), M = 0.7502 mm, [0.7388, 0.7619]; estimated change in CIMT, M = 0.0072, [0.0058, 0.0086], respectively. Among the three groups the average annual increase in CIMT was 0.007 mm/y (Miller et al., 2019).

Miller et al. (2019) also reported their secondary outcome did not have a statistical difference between the rate of change of CAC amongst the three groups after 4 years of follow-up. Postmenopausal women treated with o-CEE had CAC scores that increased from the baseline median score of 12.72 AU (*n* = 230) to a median CAC score of 20.66 AU after 4 years (*n* = 188). Postmenopausal women treated with t-E_2 had CAC scores that increased from the baseline median score of 13.68 AU (*n* = 222) to a median CAC score of 21.65 AU after 4 years (*n* = 180), respectively (Miller et al., 2019). Compared to the placebo group at baseline (*n* = 275), CAC median score was 15.97 AU and increased after 4 years to a median CAC score of 22.69 AU (*n* = 221). CAC scores increased by an average of 19% over the 4 year KEEPS trial (Miller et al., 2019).

Nevertheless, Miller et al. (2019) reported that postmenopausal women treated with o-CEE who had CAC > 5 at 48 months was lower than postmenopausal women treated with the placebo (7.4% vs. 14.5%). These findings were consistent with the WHI trial outcome, except that the WHI studies used a higher oral estrogen dose. The KEEPS trial concluded that

postmenopausal women who undergo treatment with HT with either low dose oral or transdermal estrogen plus 12 days per month of progesterone did not significantly improve or worsen atherosclerosis development (Miller et al., 2019).

A limitation of the KEEPS is its duration and size. A trial with a more extended follow-up period with more participants would allow for further examination of the long-term effects of the use of HT and the truth about the improvement in CVD risks. Additionally, KEEPS trial participants were mainly non-Hispanic white women (80%), and 74% of women in the study earned a minimum of a bachelor's degree. This population of participants does not give an accurate representation of all postmenopausal women in the United States. Lastly, KEEPS studied mostly healthy postmenopausal women with a limited risk of CVD. Therefore, the KEEPS trial may not be an accurate representation of postmenopausal women with increased CVD risks. The KEEPS trial received funding from pharmaceutical companies such as Pfizer, AstraZeneca, Merck, and others, leading one to question bias in the trial (Miller et al., 2019).

Along with reviewing the evidence and providing a recommendation on bone health, the USPSTF (2017) reviewed articles and provided evidence for their recommendations for the use of HT by examining the benefits versus risks for developing CHD. The USPSTF (2017) pooled the outcomes of three studies describing the risk of CHD in women that were randomized to receive either estrogen plus progestin or placebo (N = 18, 081): The results found a greater probability of CHD among the women that received HT (RR 1.23, 95% CI [1.01, 1.52]), which did not meet statistical significance. The trials had a mean follow-up of 5 years. The WHI trial had a post-intervention follow-up study comparing the group of women who received HT with estrogen plus progestin to the participants that took the placebo. This study occurred 2.4 years after the women in the WHI trial had stopped taking estrogen plus progestin. The results found

no significant difference in the risk of CHD in the two groups of women (HR, 1.04, CI [0.89, 1.21]), respectively (USPSTF, 2017).

The USPSTF (2017) systematically reviewed three studies (N = 11,310) with the use of estrogen-only versus placebo, and the results were similar to the estrogen plus progestin findings; no statistical significance was found between the HT group and placebo group in the evaluation of CHD (RR 0.95, 95% CI [0.79, 1.14]). A postintervention trial of women in the WHI trial occurred 3.9 years after discontinuation of the estrogen-only study. Once again, a comparison between the women who received estrogen therapy versus placebo had no significant difference in the risk of CHD (HR, 0.97, CI [0.75, 1.25]), respectively (USPSTF, 2017). Due to their findings of no statistically significant outcomes in their review, the USPSTF (2017) concluded with moderate certainty that estrogen plus progestin and estrogen-only HT should not be used for the primary prevention of chronic conditions in asymptomatic postmenopausal women. The USPSTF (2017) assigned a Grade D recommendation to HT therapy to prevent chronic diseases.

Discussion

The estrogen plus progestin and estrogen-only arms of the WHI trials were discontinued early due to adverse findings and an inability to prove the primary outcome of CHD (nonfatal MI and CHD death) prevention among women aged 50-79 years. The estrogen plus progestin study was stopped after 5.2 years due to increased invasive breast cancer among women (WHII, 2002). Similarly, the NIH's estrogen-only study was stopped after approximately seven years of follow-up due to an increased risk of strokes. However, CHD events decreased among the participants, with a 9% reduction in CHD events when the study was halted (WHISC, 2004). An increased risk of stroke was discovered in both arms of the WHI trials. The WHI trials also reported an upsurge in the number of women with DVTs.

One of the surprising findings in the WHI trial was that invasive breast cancer decreased among the women in the estrogen-only arm of the WHI studies. Invasive breast cancer was 23% lower in the estrogen-only group than the estrogen plus progestin group, which had 166 invasive breast cancers diagnosed in the women. The increase in invasive breast cancers was equal to a 2% increase from the trial's start (WHISC, 2004).

Both arms of the WHI studies demonstrated osteoporosis prevention benefits. Women in the estrogen plus progestin arm of the trial had a 24% decrease in total fractures. The estrogen-only arm also had a reduction between 30% to 39% in fractures among the participants. Total osteoporotic reduction in fractures met statistical significance for both the estrogen plus progestin and estrogen-only groups. Unfortunately, the WHII (2002) and WHISC (2004) studies concluded that HT should not be used to prevent chronic diseases, including CVD and osteoporosis. Both studies agreed that the risks outweighed the health benefits of HT use among postmenopausal women between the ages of 50-79 years (WHII, 2002; WHISC, 2004).

The WHI results vastly altered medical providers' confidence in prescribing HT to postmenopausal women suffering from vasomotor symptoms. Crawford et al. (2019) provided evidence of the WHI studies' implications on HT's utilization among postmenopausal women. The SWAN study provided statistically significant data ($p < .001$) indicating a drastic decline in both initiation and continuation of HT use in postmenopausal women after the publication of the WHI trials. The WHI results were extensively advertised to the public, which led to many symptomatic women, including women who underwent menopause prematurely or early, to be left untreated with HT even though the published risks were not studied among this population of women. Crawford et al. (2019) urged both women and providers to educate themselves on the benefits and risks of HT and then individually analyze those results to provide evidence-based

care to menopausal symptomatic women.

Benefits of HT Use in the Prevention of Osteoporosis

The utilization of HT in women who experience menopause either prematurely or early, and those who enter menopause naturally have been proven to have a decreased risk of osteoporosis. The estrogen plus progestin and estrogen-only arms of the WHI clinical trials discovered that HT is beneficial, but at the expense of other risk factors. As stated many times throughout this literature review, one main limitation to the WHI clinical trials was that they did not evaluate women less than the age of 50 years.

Faubion et al. (2015) and Hadjidakis et al. (2003) published studies that revealed evidence of the risk of the increased amount of bone loss that occurs in premature and early menopause compared to women that undergo natural menopause around the average age of 51 years. Faubion et al. (2015) reported that bone loss is twice as high in women with BSO than women who experience natural menopause. Furthermore, Hadjidakis et al. (2003) provided additional evidence of the detrimental effects on BMD in women that experience premature or early surgical or natural menopause in the many different age ranges studied. Faubion et al. (2015) and Hadjidakis et al. (2003) concluded that HT use could prevent osteoporosis in premature and early postmenopausal women without contraindications to its use. Premature and early postmenopausal women should receive individualized HT. Ran et al. (2017) provided further statistically significant evidence of both early menopause and transitioning menopausal women benefiting from the utilization of HT.

Even though the USPSTF (2017) attached a Grade D recommendation to the addition of HT for osteoporosis treatment, they acknowledged that their recommendation should not include premature/early postmenopausal women due to the lack of research among this population.

Another small longitudinal study published by Castelo-Branco et al. (2014) looked at the long-term effects on bone loss with HT use 20 years after treatment. Castelo-Branco concluded in their study that even though there are short-term benefits seen with the use of HT in early postmenopausal women, their study provided evidence against long-term benefits of prevention of fractures once HT was stopped. Despite the evidence displayed by the authors that support the use of HT in premature/early postmenopausal women, these studies are weakened by their small sample sizes.

Consequently, there is an increased need for larger randomized, placebo-controlled studies and longitudinal studies within this population to strengthen the evidence with the utilization of HT in the prevention of osteoporosis. More studies will reduce the number of premature/early postmenopausal women who suffer from unnecessary bone loss.

Benefits of HT in Prevention of CHD

The WHI trials concluded that postmenopausal women aged 50 to 79 years treated with HT did not establish a clear benefit over risk to recommend HT for the prevention of CHD. However, over two-thirds of the participants were over the age of 60, almost 10 years past the age that HT is typically started (WHISG, 1998). The large percentage of women being over age 60 leads to the question of wondering if the timing of HT initiation would influence the benefits of HT in the prevention of CHD, specifically if initiated in premature/early menopausal women. The hypothesis that timing matters is supported when the data was split into the age groups of 50-59, 60-69, and 70-79. For the group of women who were prescribed estrogen-only, there was a 14% increase in CHD events than the placebo group, which had an increase of 24% in annual events among women aged 50-59 years. Comparingly, women who received estrogen-only therapy between the ages of 70-79 had an increase of 88% compared to the 84% increase in

CHD's annual cases. The annual rates of strokes, DVTs, invasive breast cancers, and mortality all increased with age (WHISC, 2004). This data further supports the benefits of HT use in premature and early menopause, with the benefits diminishing greatly around the age of 60.

Faubion et al. (2015) provided evidence to support the theory of timing being an essential factor in CHD prevention among younger postmenopausal women. Faubion et al. (2015) reviewed a meta-analysis which uncovered a link between CVD and death in women who suffer from premature/early menopause compared to women with menopause at the age of 50 years or older. Rivera et al. (2009) further strengthened the hypothesis that premature/early postmenopausal women will have increased cardiovascular benefits with HT. Women who underwent bilateral oophorectomy before the age of 45 years had an increased rate of mortality associated with CVD compared to women in the referent group. On the flip side, women treated with estrogen therapy benefited from a decrease in both CHD and mortality.

Sullivan et al. (2016) also provided evidence to support CVD's elevated risk and ischemic stroke in their study, looking at the POI. Women who suffer from POI are at an increased risk of atherosclerosis due to decreased vascular endothelial function. Lack of estrogen is the leading cause of POI. Women that suffer from POI, and hence early menopause, are suffering from an estrogen deficiency. Without estrogen replacement, these women are at an elevated risk of developing atherosclerosis and suffer from the many conditions linked to atherosclerosis, including CHD. The women in the WHI studies were between the ages of 50 and 79, yet women who suffer from early menopause are treated using the WHI as guidelines. Even with the WHI results, Sullivan et al. (2016) recommend that women who suffer from early menopause receive individualized treatment with HT until the natural age of menopause.

The WHI studies are used by many providers to guide care for postmenopausal women.

Because of the WHI's adverse side effects, many women have decided not to use HT. Notably, women who suffer from premature/early menopause are not being treated. When taking a closer look at the WHI trials' evidence, some of the data reported is somewhat misleading. For example, in the estrogen plus progestin clinical trial, there was a reported increase in CHD events equal to a RR of 29% compared to placebo. Along with that finding, the WHI also reported a RR of 41% increase of stroke among the women that received estrogen plus progestin. Conversely, the actual number of incidences of these results was only seven more CHD events and eight more strokes per 10,000 person-years in the group of women that received estrogen plus progestin (WHII, 2002).

Even though the relative risk was increased in the WHI studies for stroke and CHD when you compare them to absolute risks, the evidence is less convincing. The calculated absolute risk for total CVD events in the women treated with estrogen plus progestin, which includes both CHD and strokes, is equal to approximately 8% risk. The estrogen plus progestin group's absolute risk was only 2% higher than the placebo group, having a 6% increased absolute risk of total CVD events (WHII, 2002). Similarly, in the WHI estrogen-only arm, the absolute risk of total CVD events increased by 15% versus the placebo group, which had a 14% absolute risk (WHISC, 2004).

After examining the data in the WHI trial and then reviewing the KEEPS trial results, the evidence seems to point to the age and baseline medical history characteristics to be a factor in the WHI's negative results. The KEEPS trial's inclusion criteria eliminated women with diabetes, HTN, dyslipidemia (including use of statins), previous history of CVD, tobacco use, and history of cancer (Miller et al., (2019). When examining the WHI studies' baseline characteristics, both the estrogen plus progestin and estrogen-only arms included the groups of

women the KEEPS trial eliminated (WHISG, 1998). For example, 48% of the participants in the WHI's estrogen-only study had been on treatment for hypertension. Almost half (48%) of the women in the WHI's estrogen-only study were current smokers or had a previous smoking history. In addition, women in both the estrogen plus progestin and estrogen-only WHI studies had an average BMI of 28.5% and 30.1%, which means that many women in these two studies were considered overweight and obese (WHII, 2002; WHISC, 2004). The increase in CVD events among the WHI studies could be more related to the participants' increased age and the fact that the participants had baseline characteristics that would increase their risks of CHD, strokes, and breast cancer. Even though the KEEPS trial results did not result in statistically significant data, the results did not reveal increased CVD events compared to the WHI studies.

Conclusion

This literature review indicates that the initiation of HT in women with premature/early menopause will reduce vasomotor symptoms and potentially decrease their risk of osteoporosis and CVD. These findings of this literature review support the individualization of HT in premature/early menopausal women by looking at their risk factors for breast cancer, DVTs, strokes, and CVD, along with performing a thorough review of their family history. If none of these risk factors exist, premature/early menopausal women should not be denied HT based on the results of the WHI studies. The WHI trials did not enroll women who suffered from premature/early menopause; therefore, the results should only be utilized by the population included in their studies. If providers perform a careful evaluation of a women's medical history, in addition to looking for contraindications, they will find that HT is safe and efficacious for premature/early menopausal patients. Women will receive greater benefits than harm by being prescribed HT early and continuing use up to their natural age of menopause (around 51 years).

Additionally, HT treatment should start at the lowest effective dose and be increased as needed to improve vasomotor symptoms.

Further large random controlled clinical trials and longitudinal studies need to be completed on the specific population of women who are postmenopausal before the age of 45 to substantiate the benefits of HT use in this population. More studies are needed to compare the various forms of HT in postmenopausal women before the age of 45 years to evaluate if there is one form that is the safest. The additional studies will help clear up confusion about the safety of HT use and help providers gain more confidence in their choice to prescribe HT to premature/early postmenopausal women. In the meantime, further education is needed for current practicing providers about the increased benefits, specifically in bone health and cardioprotective benefits, as well as the impact of decreased overall mortality in women less than the age of 45 years when prescribed HT.

Applicability to Clinical Practice

The information collected and presented in this literature review will help medical professionals make an evidence-based decision regarding the safety and advantageous use of HT in premature/early menopausal women. One of this literature review's primary purposes is to provide further evidence and eliminate some misconceptions triggered by the WHI studies about HT use safety in postmenopausal women. The evidence provided will allow medical professionals to be confident in their decision to prescribe HT to women less than the age of 45 years old. HT is beneficial in improving vasomotor symptoms of menopause and can also be cardioprotective, prevent early osteoporosis, and decrease mortality in this population. By individualizing the treatment for premature and early postmenopausal women, medical professionals can provide evidence-based care that will improve these women's quality of life,

along with preventing bone loss and CHD.

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