The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal Women: A Systematic Review and Meta-Analysis

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Importance: The incidence of dyslipidemia increases after menopause. Menopause hormone therapy (MHT) is recommended for menopause related disease. However, it benefits for lipid profiles is inconclusive.

Objective: To conduct a systematic review and meta-analysis of randomized controlled trials to evaluate the effects of MHT on lipid profile in postmenopausal women.

Evidence Review: Related articles were searched on PubMed/Medline, EMBASE, Web of Science, and Cochrane Library databases from inception to December 2020. Data extraction and quality evaluation were performed independently by two reviewers. The methodological quality was assessed using the “Cochrane Risk of Bias checklist".

Results: Seventy-three eligible studies were selected. The results showed that MHT significantly decreased the levels of TC (WMD: −0.43, 95% CI: −0.53 to −0.33), LDL-C (WMD: −0.47, 95% CI: −0.55 to −0.40) and LP (a) (WMD: −49.46, 95% CI: −64.27 to −34.64) compared with placebo or no treatment. Oral MHT led to a significantly higher TG compared with transdermal MHT (WMD: 0.12, 95% CI: 0.04–0.21). The benefits of low dose MHT on TG was also concluded when comparing with conventional-dose estrogen (WMD: −0.18, 95% CI: −0.32 to −0.03). The results also showed that conventional MHT significantly decreased LDL-C (WMD: −0.35, 95% CI: −0.50 to −0.19), but increase TG (WMD: 0.42, 95%CI: 0.18–0.65) compared with tibolone. When comparing with the different MHT regimens, estrogen (E) + progesterone (P) regimen significantly increased TC (WMD: 0.15, 95% CI: 0.09 to 0.20), LDL-C (WMD: 0.12, 95% CI: 0.07–0.17) and Lp(a) (WMD: 44.58, 95% CI:28.09–61.06) compared with estrogen alone.

Conclusion and Relevance: MHT plays a positive role in lipid profile in postmenopausal women, meanwhile for women with hypertriglyceridemia, low doses or transdermal MHT
INTRODUCTION

Several studies have shown that menopause transition is associated with an unfavorable effect on lipid profile, accompanying with an increase in the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and lipoprotein (a) [LP (a)], and sometimes with a decrease in the level of high-density lipoprotein cholesterol (HDL-C) (Anagnostis et al., 2015; Anagnostis et al., 2016). It is well-known that an unfavorable lipid profile plays a crucial role in the development and progression of cardiovascular disease (CVD) (McQueen et al., 2008; Lee et al., 2017), which is the leading cause of morbidity and mortality in postmenopausal women (Tandon et al., 2010).

Menopause signifies the permanent cessation of menstruation, resulting from loss of ovarian follicular activity and deficiency of estrogen. As postmenopausal women have significantly higher levels of LDL-C and TC than premenopausal women (Ambikairajah et al., 2019), estrogen has been found to play a protective role by regulating lipid metabolism. In this frame, estrogen-based menopause hormone therapy (MHT) could influence lipid profile in postmenopausal women. It has been reported that MHT is the most effective treatment for menopause-related symptoms caused by the loss of estrogen (Baber et al., 2016). Besides, MHT has been shown to have a favorable risk–benefit ratio for women without dyslipidemia who underwent treatment at the age under 60 years old or within 10 years after menopause onset (2019 Surveillance of Menopause, 2019). A meta-analysis conducted in 2001 concluded that MHT could decrease the levels of TC and LDL-C, and increase HDL-C level (Godsland, 2001). A review performed in 2017 showed that MHT significantly decreased LP (a) concentration (Anagnostis et al., 2016). Some studies have shown that MHT negatively influences TG level (Mercuro et al., 2003; Nii et al., 2016). However, a study conducted in 2016 indicated that TG level was lower in MHT group than that in non-MHT group (Ki et al., 2016). Pu et al. pointed out that hormone therapy with 17β-estradiol provided more benefits for decreasing TG level, while conjugated equine estrogen (CEE) showed a better effect on reducing the levels of both HDL-C and LDL-C (Pu et al., 2017). To date, long-term effects of MHT or different routes of administration of estrogen on the lipid profile were scarcely reported. In addition, it has been shown that both dosage and type of progestogen are of great importance for the lipoprotein fractions (Odmark et al., 2004). The Women’s Health Initiative (WHI) study demonstrated that CEEs with medroxyprogesterone acetate (MPA) had an increased risk of developing coronary heart disease (CHD) by 18%, while the CEE was not associated with an increased risk of CHD, raising a question concerning the safety of progestogen (Manson et al., 2013; Manson et al., 2017). But few meta-analyses have concentrated on the effects of progestogen on lipid profile. Given these limitations, an updated meta-analysis is precious to indicate the effects of MHT on the lipid profile. The present study aimed to systematically review and analyze data from randomized controlled trials (RCTs) to find out the effects of MHT concerning factors, including duration of therapy, route of administration, dosage, and types of regimens [estrogen-alone (E-alone) or estrogen plus progestogen (E + P)], on lipid profile in menopausal women.

METHODS

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement checklist (Moher et al., 2009), and that was registered on PROSPERO (Registration No. CRD42018092924).

Study Selection

PubMed/Medline, EMBASE, Web of Science, and Cochrane Library databases were comprehensively and systematically searched from inception to 31 December 2020, for studies published in English. The main search items were as follows: (“Menopause Hormone Therapy” OR “hormone therapy” OR “estrogen therapy” OR “estradiol therapy”) AND (“TC” OR “TG” OR “LDL” OR “HDL” OR “LP (a)” OR “lipid” AND (“postmenopausal women” OR “menopausal women” OR “menopause” OR “peri-menopausal women”). This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement checklist (Moher et al., 2009), and that was registered on PROSPERO (Registration No. CRD42018092924). Two authors screened and evaluated all the abstracts and potentially eligible articles, any discrepancies between reviewers in the study selection were resolved via consultation with a third reviewer.

Articles that meet the following requirements were included: 1) original RCTs that were published in English; 2) administration of MHT for postmenopausal concerning factors, such as duration of therapy, route of administration, dosage, and types of regimens (E-alone or estrogen E + P); 3) inclusion of placebo, no treatment or non-MHT as a control group. For different regimens, regarding the effects of different types of estrogen on lipid profile, the same type of estrogen was required in 2 groups; 4) reporting the levels of TC, TG, LDL, HDL or Lp (a) as the outcome measures for lipid profile, and data were

Clinical Trial Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018092924], identifier [No. CRD42018092924].

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available directly from articles or could be calculated by mathematical formulas. The unit of TC, TG, LDL, and HDL was uniformly converted to mmol/L, and the unit of Lp(a) was converted to mg/L. As tibolone can alleviate menopause symptoms, studies that compared the effects of tibolone with MHT on lipid profile were included, while studies that concentrated on only the effects of tibolone were excluded from this review.

**Data Extraction and Quality Assessment**

Data extraction of the studies included: 1) basic data of retrieved articles (title, the first author’s full name, year of publication, journal, etc.); 2) study design; 3) participants’ demographic characteristics (age, number of cases, etc.); 4) inclusion and exclusion criteria particularly for each article; 5) MHT-based data (name, dose, route of administration, the duration of treatment and type of regimen); 6) data related to control group (name, dose, route of administration, duration, type of regimen, etc.); 7) Serum lipid profiles. The data that provided baseline values and percentage changes after treatment only, which was unable to be converted into averages and standard deviations would be excluded. If raw data is needed, the corresponding author would be contacted to get more details. The Cochrane Risk of Bias check list (Higgins et al., 2011) was used to evaluate the risk of bias of randomized clinical trials. **Statistical Analysis**

Data analyzed was performed with the Cochrane Collaboration Review Manager (version 5.2) software, each outcome was expressed as mean ± standard deviation (SD). Heterogeneity among studies was estimated by $I^2$ statistic. If $I^2 \geq 50\%$, the random-effects model was used to perform the analysis; Otherwise, the fixed-effects model was utilized. We used the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Ver. 6.2) to resolve the post-treatment data in some trials (Higgins et al., 2021). Millimoles per liter (mmol/L) will be used to measure TC, TG, LDL, and HDL while milligrams per liter (mg/L) were used to measure Lp(a).

**RESULTS**

A total of 9,497 records were searched through database, after removal of duplicates, 6,784 articles were screened full-text and...
## TABLE 1 | Baseline characteristics and clinical outcomes of menopausal women with menopause hormone therapy.

| ID | Author and Year | Control | Treatment | Duration of study (month) | Evaluated Outcomes |
|----|-----------------|---------|-----------|---------------------------|--------------------|
| 1  | Abbas et al. (2004) | Placebo | Placebo | 0.625 mg/day CEE (Oral) Estradiol 100 mcg/day (Transdermal) | 3 |
|    | Demirol et al. (2007) | Placebo | Placebo | 0.625 mg/d CET (Oral) 2.5 mg/d Tibolone (Oral) | 6 |
| 3  | Binder et al. (1996) | Placebo | Placebo | 0.625 mg/day CEE + 5 mg MPA (Oral) | 11 |
| 4  | Bukowska et al. (2005) | Placebo | Placebo | 17 beta-estradiol (Transdermal) at increasing-decreasing doses (25, 50, 75, and 50 ug/d) + oralprogestosterone 50 to 100 mg estradiol valerate 1mg + estriol 2 mg + levonorgestrel 0.25 mg | 3 |
| 5  | Bunyavejchevin and Limpaphayom. (2001) | Placebo | Placebo | 3 mg/day 17 beta-estradiol + 1 mg NETA (Oral) | 12 |
| 6  | Casanova et al. (2009) | Placebo | Placebo | 3 mg/day 17 beta-estradiol gel (percutaneous route or nasal route) +200 mg micronized progesterone (vaginal) | 12 |
| 7  | Casanova et al. (2015a, 2015b) | Placebo | Placebo | 3 mg/day 17 beta-estradiol gel (percutaneous route or nasal route) +200 mg micronized progesterone (vaginal) | 12 |
| 8  | Castelo-Branco (1999) | Placebo | Placebo | 35 mg/day 17 beta-estradiol +50 mg/day norethisterone (Intranasal sprays) | 24 |
| 9  | Castelo-Branco (2007) | Placebo | Placebo | 350 mg/day 17 beta-estradiol +50 mg/day norethisterone (Intranasal sprays) | 12 |
| 10 | Cayan et al. (2011) | Placebo | Placebo | 3 mg/day 17 beta-estradiol + 1 mg/day drospirenone (Oral) | 24 |
| 11 | Cheng et al. (1993) | Placebo | Placebo | 0.625 mg/day CEE + 2.5 mg/day medroxyprogesterone/day (Oral) | 12 |
| 12 | Christodoulakos et al. (2006) | Placebo | Placebo | 0.625 mg/day CEE + 5 mg/day MPA (Oral) | 6 |
| 13 | Haines et al. (1996) | Placebo | Placebo | 2 mg/d estradiol (Oral) | 6 |
| 14 | Conard et al. (1995) | Placebo | Placebo | 1 mg/day E2 + 2.5 mg nomegestrol acetate (Oral) | 3 |
| 15 | de Kraker et al. (2004) | Placebo | Placebo | 1 mg/day micronised 17 beta-estradiol +5 mg dydrogesterone (Oral) | 12 |

(Continued on following page)
### TABLE 1 | Baseline characteristics and clinical outcomes of menopausal women with menopause hormone therapy.

| ID  | Author and Year      | Control Intervention          | n  | Age (year, Mean ± SD) | Intervention n | Age (year, Mean ± SD) | Duration of study (month) | Evaluated Outcomes |
|-----|----------------------|--------------------------------|----|-----------------------|----------------|-----------------------|---------------------------|---------------------|
| 16  | Faguer de Moustier et al. (1989) | 1.5–3 mg/day of E2 (Percutaneous) | 16 | /                     | 2 mg/day micronized E2 (Oral) | 16 | /                     | 2                         | TC TG, HDL, LDL     |
| 17  | Draper et al. (1996) | Placebo | 64 | 53.6 ± 3.4            | 0.625 mg/day CEE (Oral) | 64 | 53.2 ± 3.3            | 2                         | TC LDL, HDL          |
| 18  | Duvernoy et al. (2002) | Placebo | 9  | 62 ± 11               | 10 µg/day ethinyl estradiol + 1 mg/day norethindrone acetate (Oral) | 9  | 62 ± 11               | 3                         | TC TG, HDL, LDL      |
| 19  | Espeland et al. (1998) | Placebo | 72 | 55.8 ± 4.2            | 0.625 mg/day CEE (Oral) | 74 | 55.8 ± 4.2            | 36                        | Lp(a)                |
| 20  | Farish et al. (1999) | 2.5 mg/day tibolone | 43 | 53 ± 7                | 0.625 mg/day CEE + 0.15 mg norgestrel (Oral) | 40 | 52 ± 8                | 18                        | TC TG, HDL, LDL, Lp(a) |
| 21  | Farish et al. (1996) | Oral oestradiol (2 mg/ day) | 36 | 46 ± 7                | oral oestradiol (2 mg/day) + norethisterone (1 mg/day) | 31 | 45 ± 6                | 12                        | TC TG, HDL, LDL, Lp(a) |
| 22  | Fernandes et al. (2008) | Placebo | 24 | 52.5 ± 4.8            | 2 mg/day micronized estradiol (Oral) | 25 | 51.6 ± 3.4            | 6                         | TC TG, HDL, LDL, Lp(a) |
| 23  | Perrone et al. (1999) | No treatment | 14 | 51.9 ± 4.3            | 0.625 mg/day CEE (Oral) + 10 mg MPA (days 1–12, Oral) | 14 | 51.0 ± 4.1            | 6                         | TC TG, HDL, LDL, Lp(a) |
| 24  | Graser et al. (2001) | Placebo | 40 | 55 ± 5                | 2 mg/day estradiol valerate + 3 mg/day dienogest (Oral) | 43 | 55 ± 6                | 6                         | TC TG, HDL, LDL, Lp(a) |
| 25  | Heikkinen et al. (1997) | Placebo | 95 | 52.5 ± 0.22           | 2 mg/day Estradiol valerate + 1 mg cyproterone acetate (Oral) | 65 | 52.9 ± 0.29           | 38                        | TC TG, HDL, LDL, Lp(a) |
| 26  | Teede et al. (2001) | Placebo | 30 | 60 ± 1                | 2 mg/day oestradiol anhydrous (oral) + 1 mg/day norethisterone acetate (oral) | 29 | 62 ± 2                | 24                        | TC TG, HDL, LDL, Lp(a) |
| 27  | Hemelaar et al. (2003) | Placebo | 49 | 55.0 ± 4.7            | 50 µg 17β-estradiol (transdermal) | 33 | 55.5 ± 4.8            | 17                        | TC TG, HDL, LDL, Lp(a) |
| 28  | Hemelaar et al. (2006) | Placebo | 116 | 56.8 ± 5.6           | 1 mg 17β-estradiol (oral) | 37 | 54.4 ± 4.3           | 17                        | TC TG, HDL, LDL, Lp(a) |
| 29  | Gregersen et al. (2019) | Placebo | 69 | 55.0 ± 4.7            | 1 mg 17β-estradiol (transdermal) | 33 | 55.5 ± 4.8            | 17                        | TC TG, HDL, LDL, Lp(a) |
| 30  | Conard et al. (1997) | Placebo | 16 | 54 ± 5                | 2 mg/day estradiol and 1 mg/day NET (Oral) | 71 | 55.5 ± 6.8            | 24                        | TC TG, HDL, LDL, Lp(a) |
| 31  | Jirapinyo et al. (2003) | Placebo | 60 | 54.6 ± 4.4            | 2 mg/day E2 + 1 mg/day NET (Oral) | 60 | 54.0 ± 4.3            | 12                        | TC TG, HDL, LDL, Lp(a) |
| 32  | Stevenson et al. (2004) | Placebo | 27 | 56.3 ± 1.2            | 0.05 mg/day estradiol (transdermal) + 0.125 mg/day norethisterone acetate patches | 28 | 59.8 ± 0.8            | 6                         | TC TG, HDL, LDL, Lp(a) |
| 33  | Koh et al. (2003) | Placebo | 26 | 60 ± 1                | 0.625 mg/day CEE + 100 mg/day MP | 53 | 59 ± 1                | 2                         | TC TG, HDL, LDL, Lp(a) |
| 34  | Koh et al. (2004) | Placebo | 26 | 60 ± 1                | 2.5 mg/day tibolone | 53 | 59 ± 1                | 2                         | TC TG, HDL, LDL, Lp(a) |
| 35  | Koh et al. (2005) | Placebo | 41 | 59.4 ± 1.0            | 100 mg MP/day + 0.3 mg/day CEE (Oral) | 41 | 59.4 ± 1.0            | 2                         | TC TG, HDL, LDL, Lp(a) |
## TABLE 1 | Baseline characteristics and clinical outcomes of menopausal women with menopause hormone therapy.

| ID   | Author and Year | Control | Intervention | n   | Age (year, Mean ± SD) | Treatment | n   | Age (year, Mean ± SD) | Duration of study (month) | Evaluated Outcomes |
|------|----------------|---------|--------------|-----|-----------------------|-----------|-----|-----------------------|--------------------------|----------------------|
| 36   | Labos et al. (2013) | No treatment | 1 mg/day 17β-estradiol + 0.5 mg/day norethisterone acetate(Oral) | 36 50.56 ± 5.798 | 12 | TC TG HDL LDL |
| 37   | Lahdenperä et al. (1996) | 0.05 mg/day 17-beta-estradiol (Transdermal) + 10 mg medroxyprogesterone acetate(Oral) | 2 mg/day 17-beta-estradiol and 1 mg/day norethisterone acetate (Oral) | 36 52.6 ± 2.0 | 12 | TC TG HDL LDL |
| 38   | Lewis-Barned et al. (1999) | Placebo | 2 mg/day 17β-estradiol + 0.5 mg/day norethisterone acetate(Oral) | 16 65.3 ± 8.0 | 12 | TC TG HDL LDL |
| 39   | Luyer et al. (2001) | Placebo | 2 mg/day 17β-estradiol and 1 mg/day norethisterone acetate (Oral) | 16 52 ± 3 | 12 | TC TG HDL LDL |
| 40   | Davidson et al. (2000) | Placebo | 0.625 mg /day CEE(Oral) | 16 52 ± 3 | 12 | TC TG HDL LDL |
| 41   | Terauchi et al. (2012) | Placebo | 0.625 mg /day CEE(Oral) | 16 52 ± 3 | 12 | TC TG HDL LDL |
| 42   | Mendoza et al. (2002) | 2.5 mg/day tibolone | 50 µg/day 17β-estradiol (transdermal) + 1 mg/day norethisterone acetate | 55 50.7 ± 4.2 | 12 | TC TG HDL LDL |
| 43   | Meschia et al. (1998) | Placebo | 50 µg 17β-estradiol (transdermal) + 10 mg MPA (days 1–12) | 41 53 ± 4.2 | 12 | TC TG HDL LDL |
| 44   | Seed et al. (2000) | Placebo | 1 mg/day 17β-estradiol | 66 57.1 ± 6.8 | 12 | TC TG HDL LDL |
| 45   | Mijatovic et al. (1999) | Placebo | 1 mg/day 17β-estradiol + 0.25 mg NETA(Transdermal) | 66 57.1 ± 6.8 | 12 | TC TG HDL LDL |
| 46   | Milner et al. (1996) | Placebo | 1 mg/day 17β-estradiol | 66 57.1 ± 6.8 | 12 | TC TG HDL LDL |
| 47   | Monk-Jensen et al. (1994) | Placebo | 1 mg/day 17β-estradiol | 41 53 ± 4.2 | 12 | TC TG HDL LDL |
| 48   | Oral and Ozbaışar (2003) | Placebo | 1 mg/day 17β-estradiol | 66 57.1 ± 6.8 | 12 | TC TG HDL LDL |
| 49   | Pan et al. (2002) | Placebo | 2 mg/day 17β-estradiol + 1 mg/day norethisterone acetate (Oral) | 34 60.5 ± 2.5 | 24 | TC TG HDL LDL |
| 50   | Kotecha et al. (2020) | Placebo | 2.5 mg tibolone | 34 60.5 ± 2.5 | 24 | TC TG HDL LDL |
| 51   | Villa et al. (2011) | Placebo | 1 mg/day 17β-estradiol | 20 51.9 ± 2.4 | 24 | TC TG HDL LDL |

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| ID   | Author and Year            | Control Intervention | n | Age (year, Mean ± SD) | Treatment Intervention | n | Age (year, Mean ± SD) | Duration of study (month) | Evaluated Outcomes |
|------|---------------------------|----------------------|---|-----------------------|------------------------|---|-----------------------|--------------------------|---------------------|
| 52   | Samantray KV et al. (1994)| placebo              | 15| 48.4 ± 2.6            | 0.625 mg/day CEE (Oral)| 15| 47.7 ± 3.1            | 3                        | TC TG HDL LDL          |
|      |                           | placebo              | 15| 48.4 ± 2.6            | 0.625 mg/day CEE + 2.5 mg/day MPA (Oral) | 15| 49.3 ± 2.8            |                          |                     |
| 53   | Samsoe et al. (2002)      | placebo              | 40| 56.2 ± 4.6            | 1 mg/day E2 + 0.25 mg/day NETA (Oral) | 40| 55.6 ± 4.3            | 12                       | TC TG HDL LDL Lp(a)    |
|      |                           | placebo              | 40| 56.2 ± 4.6            | 1 mg/day E2 + 0.5 mg/day NETA (Oral) | 40| 56.7 ± 5.1            |                          |                     |
| 54   | Sanada et al. (2003)      | No treatment         | 15| 54.8 ± 4.8            | 0.625 mg/day CEE + 2.5 mg MPA (Oral) | 18| 55.1 ± 5.2            | 3                        | TC TG HDL LDL          |
|      |                           | No treatment         | 15| 54.8 ± 4.8            | 0.3 mg/day CEE + 2.5 mg MPA (Oral) | 18| 55.3 ± 5.3            |                          |                     |
| 55   | Sendag et al. (2002)      | 0.05 mg/day 17β estradiol+0.25 mg norethindrone acetate (Transdermal) | 42| 47.36 ± 3.8          | 0.625 CCG mg/day + 10 MPA mg (Oral) | 42| 47.57 ± 3.9            | 6                        | TC TG HDL LDL          |
| 56   | Siseles et al. (1995)     | 2.5 mg/day tibione  | 13| /                     | 5 mg MPA + 0.625 mg/day CEE (Oral) | 11| /                     | 6                        | TC TG HDL LDL          |
| 57   | Stadberg et al. (1996)    | 1 mg E2/day + 0.25 mg/day NETA(Oral) | 19| 58.5 ± 4.8            | 2 mg E2/day + 1 mg/day NETA(Oral) | 21| 58.5 ± 5.8            | 12                       | TC TG HDL LDL Lp(a)    |
|      |                           | 1 mg E2/day + 0.5 mg/day NETA(Oral) | 20| 58.5 ± 4.8            | 2 mg E2/day + 1 mg/day NETA(Oral) | 21| 58.5 ± 5.8            |                          |                     |
| 58   | Taechakraichana et al. (2000)| 30 mg/day ethinyl E2 + 150 mg desogestrel(Oral) | 40| 51.0 ± 0.6            | 0.625 mg/day CEE + 5 mg medrogestone(Oral) | 40| 52.3 ± 0.6            | 12                       | TC TG HDL LDL          |
| 59   | Taskinen et al. (1996)    | 50 mg/day 17β-estradiol(Transdermal) +10 mg MPA | 57| 52.3 ± 2.3     | 2 mg/day 17β-estradiol + 1 mg NETA(Oral) | 55| 52.5 ± 2.5            | 12                       | TC TG HDL LDL          |
| 60   | Tilly-Kiesi et al. (1996) | 50 μg/day 17β-estradiol(Transdermal) +10 mg MPA | 38| 52.6 ± 2.0     | 2 mg/day 17β-estradiol and 1 mg/ day norethisterone acetate(Oral) | 37| 52.3 ± 2.1            | 12                       | TC TG HDL LDL          |
| 61   | Vaisar et al. (2021)      | Placebo              | 56| 50.7 ± 4.8 (48,55)   | 100 ug/day estradiol (Transdermal) | 45| 51.1 ± 4.8            | 6                        | TC TG HDL LDL          |
| 62   | Tuck et al. (1997)        | Placebo              | 15| 54.5 ± 6.1           | 0.625 mg/day CEE(Oral) | 15| 54.5 ± 6.1            | 6                        | TC TG HDL LDL          |
| 63   | Ulloa et al. (2002)       | Placebo              | 11| 55.1 ± 1.2           | 0.625 mg/day CEE + 5 mg MPA(Oral) | 17| 53.8 ± 1.0            | 2                        | TC TG HDL LDL          |
| 64   | Villa et al. (2008)       | Placebo              | 16| 53.54 ± 3.7          | 1 mg/day E2 + 10 mg MPA(Oral) | 16| 52.44 ± 3.2           | 3                        | TC TG HDL LDL          |
|      |                           | Placebo              | 16| 53.54 ± 3.7          | 2 mg/day E2 + 10 mg MPA(Oral) | 16| 54.5 ± 4.1            |                          |                     |
| 65   | Wakatsuki and Sagara (1998)| 0.625 mg/day CEE(Oral) | 28| /                    | 0.625 mg/day CEE(Oral) + 5 mg MPA(Oral) | 21| /                    | 3                        | TC TG HDL LDL          |
|      |                           | 0.625 mg/day CEE(Oral) | 28| /                    | 0.625 mg/day CEE(Oral) + 2.5 mg MPA(Oral) | 21| /                    |                          |                     |
| 66   | Wakatsuki et al. (2002)   | No treatment         | 12| 53.4 ± 7.3           | 0.625 mg/day CEE(Oral) | 16| 52.4 ± 3.3            | 3                        | TC TG HDL LDL          |
|      |                           | No treatment         | 12| 53.4 ± 7.3           | 50 μg/day 17β-estradiol(Transdermal) | 16| 54.7 ± 5.9            |                          |                     |
| 67   | Wakatsuki et al. (2003)   | No treatment         | 14| 53.4 ± 7.3           | 0.3125 mg/day CEE(Oral) | 17| 54.8 ± 6.8            | 3                        | TC TG HDL LDL          |
|      |                           | No treatment         | 14| 53.4 ± 7.3           | 0.625 mg/day CEE(Oral) | 15| 54.8 ± 7.3            |                          |                     |
| 68   | Miller et al., 1995       | placebo              | 174| /                    | 0.625 mg/day CEE(Oral) | 175| /                    | 36                       | TC TG HDL LDL          |
|      |                           | placebo              | 174| /                    | 0.625 mg/day CEE(Oral) + cyclic 10 mg/day MPA (12 d/month) | 174| /                    |                          |                     |
|      |                           | placebo              | 174| /                    | 0.625 mg/day CEE(Oral) + 2.5 mg/day MPA | 174| /                    |                          |                     |
|      |                           | placebo              | 174| /                    | 0.625 mg/day CEE(Oral) + cyclic 200 mg/day micronized progesterone (12d/month) | 178| /                    |                          |                     |

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finally 73 articles were included in this meta-analysis (Figure 1). Clinical characteristics of included articles were described in Table 1. The details for risk of bias are available in Figure 2 and Figure 3.

Comparing the Effects of MHT on Lipid Profile With Placebo or no Treatment

Forty-seven studies (Cheng et al., 1993; Munk-Jensen et al., 1994; Samantray KV et al., 1994; Conard et al., 1995; Miller et al., 1995; Binder et al., 1996; Draper et al., 1996; Haines et al., 1996; Milner et al., 1996; Perrone et al., 1996; Conard et al., 1997; Heikkinen et al., 1997; Tuck et al., 1997; Espeland et al., 1998; Meschia et al., 1998; Lewis-Barned et al., 1999; Mijatovic et al., 1999; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) compared the effects of MHT therapy and placebo on blood lipids. The duration of MHT was classified into the following periods: < 3 months, 3–5 months, 6–12 months, 13–24 months, and >24 months. For articles that evaluated the effects of MHT on lipid profile at multiple time points, the result in each time point was included as separate data.

The meta-analysis of data demonstrated that intake MHT could significantly reduce the serum TC (Miller et al., 1995; Binder et al., 1996; Bunyavejchevin and Limphaphayom, 2001; Cayan et al., 2011; Cheng et al., 1993; Conard et al., 1995; Conard et al., 1997; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) (WMD: −0.43, 95% CI: −0.53 to −0.33, I² = 93%) (Figure 4A) and LDL (Miller et al., 1995; Binder et al., 1996; Bunyavejchevin and Limphaphayom, 2001; Cayan et al., 2011; Cheng et al., 1993; Conard et al., 1995; Conard et al., 1997; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) (WMD: −0.47, 95% CI: −0.55 to −0.40, I² = 87%) throughout almost all treatment duration (Figure 4B). Except the duration between half year to 1 year (WMD: −0.08, 95% CI: −0.13 to −0.03), there was no significant difference in reducing TG (Cheng et al., 1993; Conard et al., 1995; Miller et al., 1995; Binder et al., 1996; Conard et al., 1997; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) (WMD: −0.47, 95% CI: −0.55 to −0.40, I² = 87%) throughout almost all treatment duration (Figure 4B). Except the duration between half year to 1 year (WMD: −0.08, 95% CI: −0.13 to −0.03), there was no significant difference in reducing TG (Cheng et al., 1993; Conard et al., 1995; Miller et al., 1995; Binder et al., 1996; Conard et al., 1997; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) (WMD: −0.47, 95% CI: −0.55 to −0.40, I² = 87%) throughout almost all treatment duration (Figure 4B). Except the duration between half year to 1 year (WMD: −0.08, 95% CI: −0.13 to −0.03), there was no significant difference in reducing TG (Cheng et al., 1993; Conard et al., 1995; Miller et al., 1995; Binder et al., 1996; Conard et al., 1997; Davidson et al., 2000; Draper et al., 1996; Duvernoy et al., 2002; Fernandez et al., 2008; Graser et al., 2001; Gregersen et al., 2019; Haines et al., 1996) (WMD: −0.47, 95% CI: −0.55 to −0.40, I² = 87%) throughout almost all treatment duration (Figure 4B).

Table 1 | Baseline characteristics and clinical outcomes of menopausal women with menopause hormone therapy.

| ID | Author and Year       | Control Intervention | n  | Age (year, Mean ± SD) | Treatment Intervention | n  | Age (year, Mean ± SD) | Duration of study (month) | Evaluated Outcomes |
|----|-----------------------|----------------------|----|-----------------------|------------------------|----|-----------------------|--------------------------|----------------------|
| 69 | Xu et al. (2016)       | 0.3 mg/day CEE + 100 mg MP(Oral) | 35 | 53.7 ± 4.2           | 0.625 mg/day CEE + 100 mg MP(Oral) | 37 | 53.1 ± 3.1           | 12                        | TC TG, HDL, LDL       |
|    |                       | 0.3 mg/day CEE + 100 mg MP(Oral) | 35 | 53.7 ± 4.2           | 0.625 mg/day CEE + 100 mg MP(Oral) | 35 | 53.1 ± 3.1           | 6                        | TC TG, HDL, LDL       |
| 70 | Yang et al. (1999)    | 2.5 mg/day tibolone   | 20 | 50.5 ± 3.42          | 2 mg/day 17β-estradiol + 1 mg/day norethisterone acetate(Oral) | 20 | 51.5 ± 3.09          | 6                        | TC TG, HDL, LDL       |
| 71 | Yang et al. (2002)    | placebo               | 18 | 50.5 ± 2.79          | 2 mg/day E2(Oral)       | 22 | 51.5 ± 3.70          | 4                        | TC TG, HDL, LDL       |
| 72 | Zegura et al. (2008)  | Placebo               | 30 | 55.4 ± 4.6           | 50 μg/day E2(Transdermal) | 21 | 49.2 ± 4.0           | 6                        | TC TG, HDL, LDL       |
|    |                       | Placebo               | 30 | 55.4 ± 4.6           | 2 mg/day E2 + 1 mg/day NETA(Oral) | 31 | 55.1 ± 4.1           | 6                        | TC TG, HDL, LDL       |
| 73 | Ziaei et al. (2010)   | Placebo               | 50 | 52.5 ± 4.06          | 0.625 mg/day CEE + 2.5 mg MPA(Oral) | 50 | 51.5 ± 2.82          | 6                        | TC TG, HDL, LDL       |

Table 1 | Continued: Baseline characteristics and clinical outcomes of menopausal women with menopause hormone therapy.

Abbreviation: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; E2, Estradiol; SD, Standard Deviation

*Corresponding author*
Comparing the Effects of Oral MHT With Transdermal MHT

A total of 16 studies (Hemelaar et al., 2003; Bukowska et al., 2005; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Zegura et al., 2006; Casanova et al., 2015; Casanova et al., 2009; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996; Abbas et al., 2004) that enrolled 670 participants in oral MHT group and 676 in transdermal MHT group were analyzed. When comparing the effects between 2 groups, the result indicated that oral MHT could significantly decreased LDL-C (Hemelaar et al., 2003; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: 0.23, 95% CI: −0.31 to −0.14, I² = 28%) (Figure 5B) while there was no significant difference in TC (Hemelaar et al., 2003; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: −0.13, 95% CI: −0.30 to 0.04, I² = 69%) (Figure 5A).

However, the result revealed that oral MHT may significantly increase TG (Bukowska et al., 2005; Hemelaar et al., 2003; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: 0.12, 95% CI: 0.04 to 0.21, I² = 50%) (Figure 5C), while both HDL (Bukowska et al., 2005; Hemelaar et al., 2003; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Abbas et al., 2004) (WMD: −0.02, 95% CI: −0.10 to 0.06, I² = 84%) (Figure 5D) and Lp(a) (Meschia et al., 1998; Seed et al., 2000; Hemelaar et al., 2003; Bukowska et al., 2005; Hemelaar et al., 2006; Zegura et al., 2006) (WMD: 5.04, 95% CI: −20.32 to 30.41, I² = 0%) had no significance (Figure 5E).

Comparing the Effects of a Low-Dose Estrogen With a Conventional-Dose of Estrogen

The studies were classified according to the dosage of estrogen. A total of 10 studies (Cheng et al., 1993; Stadberg et al., 1996; Taechakraichana et al., 2000; Sanada et al., 2003; Wakatsuki et al., 2003; de Kraker et al., 2004; Koh et al., 2004; Christodoulakos et al., 2006; Villa et al., 2008; Xue et al., 2016) that enrolled 584 participants in low-dose estrogen group and 594 in conventional dose estrogen group were analyzed. 1mg/day or less of Estradiol valerate or 17 β-

Comparing the Effects of Oral MHT With Transdermal MHT

A total of 16 studies (Hemelaar et al., 2003; Bukowska et al., 2005; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Zegura et al., 2006; Casanova et al., 2015; Casanova et al., 2009; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996; Abbas et al., 2004) that enrolled 670 participants in oral MHT group and 676 in transdermal MHT group were analyzed. When comparing the effects between 2 groups, the result indicated that oral MHT could significantly decreased LDL-C (Hemelaar et al., 2003; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: 0.23, 95% CI: −0.31 to −0.14, I² = 28%) (Figure 5B) while there was no significant difference in TC (Hemelaar et al., 2003; Meschia et al., 1998; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: −0.13, 95% CI: −0.30 to 0.04, I² = 69%) (Figure 5A).

However, the result revealed that oral MHT may significantly increase TG (Bukowska et al., 2005; Hemelaar et al., 2003; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Tilly-Kiesi et al., 1996) (WMD: 0.12, 95% CI: 0.04 to 0.21, I² = 50%) (Figure 5C), while both HDL (Bukowska et al., 2005; Hemelaar et al., 2003; Perrone et al., 1996; Seed et al., 2000; Casanova et al., 2015; Casanova et al., 2009; Zegura et al., 2006; Castelo-Branco et al., 2007; Faguer de Moustier et al., 1989; Hemelaar et al., 2006; Lahdenperä et al., 1996; Sendag et al., 2002; Taskinen et al., 1996; Abbas et al., 2004) (WMD: −0.02, 95% CI: −0.10 to 0.06, I² = 84%) (Figure 5D) and Lp(a) (Meschia et al., 1998; Seed et al., 2000; Hemelaar et al., 2003; Bukowska et al., 2005; Hemelaar et al., 2006; Zegura et al., 2006) (WMD: 5.04, 95% CI: −20.32 to 30.41, I² = 0%) had no significance (Figure 5E).
estradiol, 0.3 mg/day or less of conjugated estrogens were defined as low dose estrogen.

The meta-analysis result showed that the low-dose estrogen led to a significant reduction in TG (Cheng et al., 1993; Sanada et al., 2003; Villa et al., 2008; Wakatsuki et al., 2003; Christodoulakos et al., 2006; Stadberg et al., 1996; Koh et al., 2004; Taechakraichana et al., 2000; Xue et al., 2016) (WMD: −0.18, 95% CI: −0.32 to −0.03, I² = 93%) (Figure 6C) and HDL-C (Cheng et al., 1993; Sanada et al., 2003; Villa et al., 2008; Wakatsuki et al., 2003; Christodoulakos et al., 2006; de Kraker et al., 2004; Stadberg et al., 1996; Koh et al., 2004; Taechakraichana et al., 2000; Xue et al., 2016) (WMD: −0.05, 95% CI: −0.07 to −0.04, I² = 36%) (Figure 6D) comparing with the conventional-dose estrogen. There was no significant on TC (Cheng et al., 1993; Sanada et al., 2003; Villa et al., 2008; Wakatsuki et al., 2003; Abbas et al., 2004; Christodoulakos et al., 2006; de Kraker et al., 2004; Stadberg et al., 1996; Koh et al., 2004; Taechakraichana et al., 2000) (WMD: −0.11, 95% CI: −0.26 to 0.04, I² = 86%) (Figure 6A) and LDL-C (Cheng et al., 1993; Stadberg et al., 1996; Taechakraichana et al., 2000; Sanada et al., 2003; Wakatsuki et al., 2003; de Kraker et al., 2004; Koh et al., 2004; Christodoulakos et al., 2006; Villa et al., 2008; Xue et al., 2016) (WMD: 0.06, 95% CI: −0.17 to 0.29, I² = 96%) (Figure 6B). Because of only one study evaluated the effects of different doses on Lp(a), meta-analysis was not carried out.

### Comparing the Effects of Conventional MHT With Tibolone

As tibolone is widely used in mitigating the menopause symptoms, it is necessary to compare the effects of conventional MHT therapy with tibolone on lipids profile. A total of 13 studies (Cayan et al., 2011; Kotecha et al., 2020; Milner et al., 1996; Ziaei et al., 2010; Christodoulakos et al., 2006; Castelo-Branco et al., 1999; Farish et al., 1999; Koh et al., 2003; Koh et al., 2005; Mendoza et al., 2002; Pan et al., 2002; Siseles et al., 1995; Yang et al., 1999) that enrolled 646 participants in conventional MHT group and 828 in tibolone group were analyzed. The outcomes of meta-analysis presented the significantly increasing TG (Cayan et al., 2011; Kotecha et al., 2020; Milner et al., 1996; Ziaei et al., 2010; Christodoulakos et al., 2006; Castelo-Branco et al., 1999; Farish et al., 1999; Koh et al., 2003; Koh et al., 2005; Mendoza et al., 2002; Pan et al., 2002; Siseles et al., 1995; Yang et al., 1999) (WMD: 0.42, 95% CI: 0.18 to 0.65, I² = 98%) (Figure 7C) and HDL-C (Cayan et al., 2011; Kotecha et al., 2020; Milner et al., 1996; Ziaei et al., 2010; Christodoulakos et al., 2006; Castelo-Branco et al., 1999; Farish et al., 1999; Koh et al., 2003; Koh et al., 2005; Mendoza et al., 2002; Pan et al., 2002; Siseles et al., 1995; Yang et al., 1999) (WMD: 0.36, 95% CI: 0.27 to 0.45, I² = 95%) (Figure 7D) concentration while significantly decreasing LDL-C (Cayan et al., 2011; Kotecha et al., 2020; Milner et al., 1996; Ziaei et al., 2010; Christodoulakos et al., 2006; Castelo-Branco et al., 1999; Farish et al., 1999; Koh et al., 2003; Koh et al., 2005; Mendoza et al., 2002; Pan et al., 2002; Siseles et al., 1995; Yang et al., 1999) (WMD: −0.35, 95% CI: −0.50 to −0.19, I² = 87%) (Figure 7B) concentration in conventional MHT group. No significant difference was identified in TC (Cayan et al., 2011; Kotecha et al., 2020; Milner et al., 1996; Christodoulakos et al., 2006; Castelo-Branco et al., 1999; Farish et al., 1999; Koh et al., 2003; Koh et al., 2005; Mendoza et al., 2002; Pan et al., 2002; Siseles et al., 1995; Yang et al., 1999) (WMD: 0.15, 95% CI: −0.15 to 0.44, I² = 96%) (Figure 7A) and Lp(a) (Milner et al., 1996; Farish et al., 1999; Demir et al., 2007; Kotecha et al., 2020) (WMD: −18.31, 95% CI: −51.84 to 15.22, I² = 56%) (Figure 7E) concentration between two groups.

### Comparing the Effects of Estrogen alone (E-Alone) With Estrogen–Progestogen (E + P) Regimen

In total, 8 studies (Samantray KV et al., 1994; Miller et al., 1995; Farish et al., 1996; Wakatsuki and Sagara, 1996; Davidson et al., 2000; Hemelaar et al., 2003; Zegura et al., 2006; Fernandes et al., 2008) that enrolled 836 participants in E-alone group and 818 in E + P group met the criteria of eligibility. The micronized progestogen was utilized in all these 8 studies.

The results revealed that E + P regimen significantly increased the concentration of TC (Miller et al., 1995; Davidson et al., 2000; Fernandes et al., 2008; Hemelaar et al., 2003; Samantray KV et al., 1994; Zegura et al., 2006; Farish et al., 1996; Wakatsuki and Sagara, 1996) (WMD: 0.15, 95% CI: 0.09 to 0.20, I² = 18%) (Figure 8A), LDL-C (Miller et al., 1995; Fernandes et al., 2008; Hemelaar et al., 2003).
FIGURE 4 | Comparing MHT with placebo or no treatment. The treatment duration was classified into the following periods in each lipid index: <3 months, 3–6 months, 6–12 months, 13–24 months, and >24 months. MHT led to a significant reduction in TC concentration, LDL-C concentration and Lp(a) concentration compared with placebo or no treatment. (A) TC concentration; (B) LDL-C concentration; (C) TG concentration; (D) HDL-C concentration; (E) Lp(a) concentration.
| Study          | Total          | Mean     | SD     | Placebo/No treatment | Mean     | SD     | Mean Difference | MD     | 95% CI       | Weight |
|---------------|---------------|----------|--------|----------------------|----------|--------|----------------|--------|-------------|--------|
| Cagan 2011    | 20            | 2.75     | 0.60   | 27.34                | 1.03     | -1.08  | [1.15, -0.80]  | 1.25%  |             |        |
| Conard 1990   | 18            | 3.75     | 0.44   | 15.32                | 0.78     | -0.07  | [1.52, 0.39]   |        |             |        |
| Cooper 1990   | 18            | 3.78     | 0.98   | 15.38                | 1.46     | -0.02  | [0.81, -0.46]  | 2.51%  |             |        |
| Duvigneaud 2005 | 16           | 3.28     | 0.93   | 15.62                | 0.78     | -0.34  | [0.95, -0.27]  | 0.91%  |             |        |
| Giuseppe 1995a | 10           | 4.52     | 0.75   | 14.42                | 0.49     | -0.10  | [0.63, 0.41]   | 1.07%  |             |        |
| Giuseppe 1995b | 13           | 4.20     | 0.67   | 14.42                | 0.49     | -0.42  | [0.87, 0.02]   | 1.27%  |             |        |
| Girard 2003    | 10            | 5.10     | 0.10   | 30.31                | 0.20     | -0.56  | [0.66, -0.45]  | 2.51%  |             |        |
| Ida 2019      | 30            | 3.02     | 0.45   | 30.35                | 0.23     | -0.57  | [0.76, -0.38]  | 2.00%  |             |        |
| Jacobi 1997a  | 17            | 3.43     | 0.60   | 15.41                | 1.02     | -1.18  | [1.82, -0.54]  | 0.86%  |             |        |
| John 2004a    | 28            | 4.06     | 0.15   | 27.41                | 1.17     | -0.98  | [1.36, -0.60]  | 2.19%  |             |        |
| Laye 2001     | 13            | 2.07     | 0.54   | 12.28                | 0.47     | -0.75  | [1.15, -0.35]  | 1.40%  |             |        |
| Mary 2005b    | 33            | 3.80     | 1.10   | 83.30                | 1.00     | -0.10  | [0.53, 0.33]   | 1.30%  |             |        |
| Mary 2005c    | 34            | 4.02     | 0.90   | 83.30                | 1.00     | -0.12  | [0.25, 0.00]   | 0.85%  |             |        |
| Masakura 2012a | 72            | 3.39     | 0.76   | 67.32                | 0.65     | -0.13  | [0.36, 0.19]   | 1.86%  |             |        |
| Masakura 2012b | 73            | 3.18     | 0.81   | 67.32                | 0.65     | -0.34  | [0.45, -0.22]  | 1.46%  |             |        |
| Michael 2003a | 64            | 3.47     | 0.88   | 90.40                | 1.04     | -0.37  | [0.91, -0.23]  | 1.55%  |             |        |
| Sammarrella 1994a | 15        | 4.38     | 1.00   | 15.40                | 0.87     | -0.32  | [0.35, 0.09]   | 0.81%  |             |        |
| Sammarrella 1994b | 15      | 3.81     | 0.69   | 15.40                | 0.87     | -0.23  | [0.79, 0.33]   | 1.00%  |             |        |
| Sanada 2003a  | 18            | 3.43     | 0.99   | 15.38                | 0.87     | -0.38  | [1.13, 0.05]   | 0.95%  |             |        |
| Tuck 1997     | 15            | 3.44     | 0.43   | 15.39                | 0.98     | -0.38  | [1.27, 0.81]   | 1.94%  |             |        |
| Utsumi 2002   | 17            | 3.03     | 0.84   | 11.39                | 0.73     | -0.23  | [1.50, -0.30]  | 0.94%  |             |        |
| Vilk 1998a    | 19            | 3.36     | 1.04   | 14.31                | 0.83     | -0.31  | [1.11, 0.41]   | 0.88%  |             |        |
| Vilk 2008b    | 14            | 3.86     | 0.87   | 14.34                | 0.83     | -0.21  | [1.59, 0.56]   | 0.88%  |             |        |
| Villariero 2002a | 16        | 3.43     | 0.73   | 12.38                | 1.09     | -0.36  | [1.26, 0.50]   | 0.84%  |             |        |
| Villariero 2002b | 16       | 3.62     | 0.62   | 12.38                | 1.09     | -0.20  | [1.19, 0.79]   | 0.47%  |             |        |
| Villariero 2002c | 17        | 3.38     | 0.69   | 14.32                | 1.30     | -0.56  | [1.36, 0.24]   | 0.64%  |             |        |
| Villariero 2003a | 15        | 3.35     | 0.70   | 14.32                | 1.30     | -0.57  | [1.34, 0.23]   | 0.68%  |             |        |
| Random effects model | 709 |             |        |                     | 0.81 | [0.32, 0.33] | 36.85% |

Heterogeneity: $I^2 = 79\%$, $Q = 0.054$, $df = 1233.7$ ($p < 0.001$)

Test for effect in subgroup: $z = 6.11$ ($p < 0.01$)

**FIGURE 4** (Continued)
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FIGURE 4 | (Continued).
2003; Samantray KV et al., 1994; Zegura et al., 2006; Farish et al., 1996; Wakatsuki and Sagara, 1996) (WMD: 0.12, 95% CI: 0.07 to 0.17, $I^2 = 29\%$) (Figure 8B), HDL-C (Miller et al., 1995; Fernandes et al., 2008; Hemelaar et al., 2003; Samantray KV et al., 1994; Zegura et al., 2006; Farish et al., 1996; Wakatsuki and Sagara, 1996) (WMD: 0.10, 95% CI: 0.03 to 0.18, $I^2 = 87\%$) (Figure 8D), and Lp(a) (Farish et al., 1996; Espeland et al., 1998; Davidson et al., 2000; Hemelaar et al., 2003; Zegura et al., 2006) (WMD: 44.58, 95% CI: 28.09 to 61.06, $I^2 = 90\%$) (Figure 8E) concentration compared with E-alone. No significant difference was found in TG (Miller et al., 1995; Fernandes et al., 2008; Hemelaar et al., 2003; Samantray KV et al., 1994; Zegura et al., 2006; Farish et al., 1996; Wakatsuki and Sagara, 1996) concentration between these two groups (WMD: 0.05, 95% CI: $-0.04$ to $0.13$, $I^2 = 64\%$) (Figure 8C).

### Sensitivity Analysis and Publication Bias Assessment

Considering that most of the pooled outcomes had an $I^2$ greater than 50%, one-by-one exclusion was performed as a sensitivity analysis to confirm the robustness of the outcomes. While omitting the study de Kraker 2004 (de Kraker et al., 2004), low-dose estrogen seems to decrease TC significantly (MD: $-0.17$, 95% CI: $-0.31$ to $-0.02$) (Figure 9). The cause of unstable results may be attributed to the difference type of estrogen used in this study. Also, an unstable result was found in TG of comparing E-alone and E + P regimen. When study of writing group 1995 (Miller et al., 1995) was excluded, E + P group could significantly higher TG (MD: $0.08$, 95% CI: $0.01$ – $0.15$) (Figure 10) than Estrogen alone. The longer period of using MPA may be a source of instability. Egger test and funnel plots suggested that there was little indication of publication bias in studies with more than 10 trials (Figure 11).

### DISCUSSION

#### Endogenous Sex Hormones and CVD Risk for Women

Endogenous sex hormones are involved in the pathogenesis of cardiovascular disease (CVD) in women. Studies have shown that estradiol (E2), the major form of ovarian estrogen before

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**FIGURE 4** (Continued).
FIGURE 5 | Comparing oral estrogen with transdermal estrogen. Oral MHT significantly decreased LDL-C concentration and increased TG concentration compared with that in transdermal MHT group. (A) TC concentration; (B) LDL-C concentration; (C) TG concentration; (D) HDL-C concentration; (E) Lp(a) concentration.
menopause, plays an active role in metabolic actions (Franck et al., 2013). Higher estrone levels were related to a higher brachial flow-mediated dilation (ie, better endothelial function) (Thurston et al., 2018). After menopause there is a drastic change in the endogenous hormonal milieu, with a decrease in estradiol. And the circulating estrone (E1) levels are relatively higher than

![FIGURE 6 | Studies comparing low-dose estrogen with conventional-dose estrogen. A low-dose estrogen led to a significant reduction in TG concentration compared with a conventional-dose estrogen. (A) TC concentration; (B) LDL-C concentration; (C) TG concentration; (D) HDL-C concentration; (E) Lp(a) concentration.](image-url)
FIGURE 7 | Studies comparing conventional MHT with Tibolone. The conventional MHT could decrease LDL-C concentration, increase TG concentration and HDL-C concentration compared with Tibolone. (A) TC concentration; (B) LDL-C concentration; (C) TG concentration; (D) HDL-C concentration; (E) Lp(a) concentration.
Studies comparing estrogen alone with estrogen plus progestogen regimen. The estrogen plus progestogen regimen could significantly increase TC, LDL-C, HDL-C, and Lp(a) concentration compared with estrogen alone. 

(A) TC concentration; (B) LDL-C concentration; (C) TG concentration; (D) HDL-C concentration; (E) Lp(a) concentration.

**FIGURE 8**
E2. E1 is produced mostly by the conversion of androgens in peripheral tissues, and could be also converted from E2 by 17β-Hydroxysteroid dehydrogenase, E1 secretion also decreased after menopause and was equivalent to nearly 1/3 before menopause (Qureshi et al., 2020). Studies showed that higher E1 is associated with more stable plaque (Cortés Yamnia et al., 2020) and better endothelial function (Thurston et al., 2018), lower levels of E1 have been associated with increased all-cause mortality among postmenopausal women (de Padua Mansur et al., 2012), which proved the importance of estrogen on CVD. In addition to E1 and E2, sex hormone binding globulin (SHBG) and testosterone (T) may be associated with future risk of CVD also. One study showed that a more androgenic hormone profile (i.e., higher levels of free T and lower levels of SHBG) was associated with greater Coronary Artery Calcium (CAC) progression up to 10 years in postmenopausal women (de Padua Mansur et al., 2012), which proved the importance of estrogen on CVD. In addition to E1 and E2, sex hormone binding globulin (SHBG) and testosterone (T) may be associated with future risk of CVD also. One study showed that a more androgenic hormone profile (i.e., higher levels of free T and lower levels of SHBG) was associated with greater Coronary Artery Calcium (CAC) progression up to 10 years in postmenopausal women (Subramanya et al., 2019), which proved the importance of estrogen on CVD. In addition to E1 and E2, sex hormone binding globulin (SHBG) and testosterone (T) may be associated with future risk of CVD also. One study showed that a more androgenic hormone profile (i.e., higher levels of free T and lower levels of SHBG) was associated with greater Coronary Artery Calcium (CAC) progression up to 10 years in postmenopausal women (Subramanya et al., 2019), which proved the importance of estrogen on CVD. In addition to E1 and E2, sex hormone binding globulin (SHBG) and testosterone (T) may be associated with future risk of CVD also.

The Effects of MHT on Lipid Profile in Postmenopausal Women

Our systematic review indicated that compared with placebo or no treatment, MHT could significantly decrease the concentrations of TC, LDL-C, and Lp(a). Lp(a) is an independent risk factor for CVD and recurrent ischemic stroke (Nordestgaard et al., 2010), the previous study showed the similar result of MHT on Lp(a) with us (van Dam-Nolen et al., 2021). As for the TG concentration, previous study had showed that MHT could significantly increase it (Stevenson et al., 2015). However, no significant difference in TG between two groups was found in our study. Hence, generally speaking, MHT was associated with favorable changes in lipid parameters whether short-term or long-term using in postmenopausal women.

The bioavailability of oral estrogen is mainly low due to first-pass metabolism, which may result in adverse reactions that influence the risk of CVD. Transdermal MHT is more appropriate for cases with a high-risk of CVD or dyslipidemia than oral agents. The results of our study showed that oral MHT significantly increased TG concentration compared with transdermal MHT. In addition, a meta-analysis conducted in 2006 revealed that oral MHT adversely affected C-reactive protein (CRP) level (Ambikairajah et al., 2019). Therefore, for women with hypertriglyceridemia or other high-risk factors of CVD, transdermal route is recommended. However, oral MHT is associated with positive effects in LDL-C concentration in our study. As we know, the LDL-C concentration is the main risk factor for the occurrence and development of atherosclerosis, and was regarded as an important index to assess the risk of

![Sensitivity analysis for TC in the subgroup of low-dose estrogen.](https://example.com)
atherosclerotic CVD (ASCVD) (Stone et al., 2013; Jacobson et al., 2015). Hence, for women without any risk of CVD or hypertriglyceridemia, oral MHT could possibly provide greater benefits.

Considering the safety factor, the minimum effective dose of estrogen was recommended (Menopause Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association, 2018). However, whether the low-dose MHT could achieve the same effects on lipid profile as conventional-dose MHT is still confused. One study indicated that low-dose MHT was associated with higher levels of TC and LDL-C, lower TG level (Casanova et al., 2015). Our study showed the similar benefit on TG in low-dose MHT group, but no significant difference in TC and LDL-C levels between two groups. Furthermore, low-dose MHT was found could decrease HDL-C level. Epidemiologically, a low plasma level of HDL-C was associated with an increased risk of ischemic CVD (Haase et al., 2012). Taken together, the advantage of low-dose MHT on lipid profile was possibly only confined to the TG level.

Tibolone is a synthetic hormone with estrogenic, progestogenic, and androgenic properties, and was widely used for alleviating menopausal symptoms in postmenopausal women. Tibolone has shown promising effects on improving depression and libido, and does not increase breast density (Cummings et al., 2008). As for its effects on lipid profile, a meta-analysis performed in 2017 indicated that there was no significant difference in the reduction of Lp(a) concentration by E-alone compared with E + P (Anagnostis et al., 2017). The results in our study showed that E + P regimen weakened the benefits of estrogen mono-therapy. However, it should be noted that the progestogens included in our analysis were mainly composed of synthetic progestogen, and further research is required to explore whether natural progesterone could positively influence lipid profile.

Progestogens are indicated as a part of systemic hormone therapy in women with an intact uterus, preventing estrogen-induced endometrial hyperplasia and cancer during estrogen exposure. However, an increased risk of CHD in women receiving estrogen plus progestogen therapy rather than in those receiving CEE alone was reported (Falkeborn et al., 1992). Thus, it should be indicated whether progestogen contributes to adverse outcomes of CVD. However, no largescale RCT has evaluated the lipid profile according to the type of progestogen used. A previous observational study revealed that the addition of progestogens blunts the lipid-related effects (Shufelt and Manson, 2021), and a meta-analysis performed in 2017 indicated that there was no significant difference in the reduction of Lp(a) concentration by E-alone compared with E + P (Anagnostis et al., 2017). The results in our study showed that E + P regimen weakened the benefits of estrogen mono-therapy. However, it should be noted that the progestogens included in our analysis were mainly composed of synthetic progestogen, and further research is required to explore whether natural progesterone could positively influence lipid profile.
worthy of attention. The meta-analysis had showed that tamoxifen can alter the lipid profile in females, particularly by decreasing TC, LDL-C and HDL-C (Alomar et al., 2022). Rraloxifene can increase HDL-C and lower LDL-C and TC (Yang et al., 2021). Thus, SERMs is beneficial to blood lipids in general.

In addition, although the result showed the positive effects of MHT on lipid profile, it needs to be emphasized that MHT is not recommended as first-line therapy for dyslipidemia or for reducing the risk of cardiovascular disease (Panagiotis et al., 2020). For postmenopausal women with carotid atherosclerosis, the prospective study had showed that total estradiol was associated with presence of vulnerable carotid plaque as well as increased risk of stroke (Glisic et al., 2018). Therefore, it is recommended to start MHT in women <60 years of age or <10 years since menopause for the beneficial effects on CVD outcomes (2019 Surveillance of Menopause, 2019; El Khoudary et al., 2020).

![Funnel plots examining publication bias. The Egger test suggested that there was no evidence of publication bias in studies with more than 10 articles. (A) MHT vs. Placebo or no treatment; (B) oral MHT vs. transdermal MHT; (C) Conventional MHT vs. Tibolone; (D) Estrogen vs. Estrogen-Progestogen; (E) Low-dose MHT vs. Conventional MHT.](image)
For dyslipidemia, the most commonly used medication is HMG-CoA reductase inhibitors (ie, statins). Statin therapy can also have effects on gonada steroidogenesis, since this process requires cholesterol as a biochemical substrate. LDL-C has been shown to be a preferential precursor for the production of ovarian steroid hormones (Grummer and Carroll, 1988). However, no reduction in E2 or E1 in postmenopausal women taking statins, despite a significant decrease in their LDL-C levels (Bairey Merz et al., 2002). But there are many studies showing an association between statin treatment and a reduction in testosterone levels (Stamerra et al., 2021). For polycystic ovary syndrome (PCOS) women, statins could decrease testosterone and Luteinizing hormone (LH)/Follicle stimulating hormone (FSH) ratio (Seyam et al., 2017), which is beneficial in treatment of PCOS. However, the role of statins for primary prevention in postmenopausal women is debated (Cangemi et al., 2017). Evidence-based data of statins for the reduction of CVD events and all-cause mortality in primary prevention in postmenopausal women is needed (El Khoudary et al., 2020).

Limitations
The limitations of the present study should be pointed out. Firstly, among the eligible studies, few studies were specifically designed to evaluate the effects of MHT on lipid profile as the primary outcome, restricting the generalization of our findings. Secondly, the lipid profile at baseline in the majority of the included studies was almost normal, while it remained elusive whether MHT would have the similar effects on lipid profile in women with dyslipidemia. Thirdly, owing to the small sample size, the comparison between the effects of different types of progestogen on lipid profile was not comprehensively performed. Therefore, further research needs to be conducted to eliminate the above-mentioned limitations and to confirm our findings.

REFERENCES

Abbas, A., Fadel, P. J., Wang, Z., Arbique, D., Jalal, I., and Vongpatanasin, W. (2004). Contrasting Effects of Oral versus Transdermal Estrogen on Serum Amyloid A (SAA) and High-Density Lipoprotein-SAA in Postmenopausal Women. Arterioscler Thromb. Vasc. Biol. 24 (10), e164–7. doi:10.1161/01.ATV.0000140198.16664.8e

Alomar, S. A., Prabahar, M. A. K., Arafah, O. A., Almarshood, F., Baradwan, S., Aboudi, S. A. S., et al. (2022). The Effect of Tamoxifen on the Lipid Profile in Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Exp. Gerontol. 139, 111680. doi:10.1016/j.exger.2021.111680

Amirkarajeh, A., Walsh, E., and Cherbutin, N. (2019). Lipid Profile Differences during Menopause: a Review with Meta-Analysis. Menopause 26 (12), 1327–1333. doi:10.1097/GME.0000000000001403

Anagnostis, P., Galanis, P., Chatzigorgogiou, V., Stevenson, J. C., Godslans, I. F., Lambrinoudaki, I., et al. (2017). The Effect of Hormone Replacement Therapy and Tibolone on Lipoprotein (A) Concentrations in Postmenopausal Women: A Systematic Review and Meta-Analysis. Maturitas 99, 27–36. doi:10.1016/j.maturitas.2017.02.009

Anagnostis, P., Stevenson, J. C., Crook, D., Johnston, D. G., and Godslans, I. F. (2016). Effects of Gender, Age and Menopausal Status on Serum Apolipoprotein Concentrations. Clin. Endocrinol. (Oxf) 85 (5), 733–740. doi:10.1111/cen.13085

Anagnostis, P., Stevenson, J. C., Crook, D., Johnston, D. G., and Godslans, I. F. (2015). Effects of Menopause, Gender and Age on Lipids and High-Density Lipoprotein Cholesterol Subfractions. Maturitas 81 (1), 62–68. doi:10.1016/j.maturitas.2015.02.262

Baber, R. J., Panay, N., and Fenton, A. (2016). 2016 IMS Recommendations on Women’s Midlife Health and Menopause Hormone Therapy. Climacteric 19 (2), 109–150. doi:10.3109/13697137.2015.1129166

Bairey Merz, C. N., Olson, M. B., Johnson, B. D., Bittner, V., Hodgson, T. K., Berga, S. L., et al. (2002). Cholesterol-lowering Medication, Cholesterol Level, and Reproductive Hormones in Women: the Women’s Ischemia Syndrome Evaluation (WISE). Am. J. Med. 113, 723–727. doi:10.1016/s0002-9343(02)01366-9

Binder, E. F., Birge, S. J., and Kohrt, W. M. (1996). Effects of Endurance Exercise and Hormone Replacement Therapy on Serum Lipids in Older Women. J. Am. Geriatr. Soc. 44 (3), 231–236. doi:10.1111/j.1532-5415.1996.tb00907.x

Bukowska, H., Stanosz, S., Zochowska, E., Millo, B., Sieja, K., Chelstowski, K., et al. (2005). Does the Type of Hormone Replacement Therapy Affect Lipoprotein (A), Homocysteine, and C-Reactive Protein Levels in Postmenopausal Women? Metabolism 54 (1), 72–78. doi:10.1016/j.metabol.2004.07.015

Bunyavejchewin, S., and Limpaphayom, K. K. (2001). The Metabolic and Bone Density Effects of Continuous Combined 17-beta Estradiol and Noresthisterone Acetate Treatments in Thai Postmenopausal Women: a Double-Blind Placebo-Controlled Trial. J. Med. Assoc. Thai 84 (1), 45–53.
Cangemi, R., Romiti, G. F., Campolongo, G., Rucio, S., Sciamer, S., Gianfriili, D., et al. (2017). Gender Related Differences in Treatment and Response to Statins in Primary and Secondary Cardiovascular Prevention: The Never-Ending Debate. Pharmacol. Res. 117, 148–155. doi:10.1016/j.phrs.2016.12.027

Casanova, C., Radavelli, S., Lhullier, F., and Spritzer, P. M. (2009). Effects of Oral or Nonoral Estradiol-Micronized Progesterone or Low-Dose Oral Estradiol-Drospirenone Therapy on Metabolic Variables and Markers of Endothelial Function in Early Postmenopause. Fertil. Steril. 92 (2), 605–612. doi:10.1016/j.fertnstert.2008.06.049

Castelo-Branco, C., Casals, E., Figuera, F., Sanjuan, A., Vicente, J. I., Balasar, J., et al. (1999). Two-year Prospective and Comparative Study on the Effects of Tibolone on Lipid Pattern, Behavior of Apolipoproteins and Bone Metabolism. A. B. Menopaus. 6 (2), 92–97. doi:10.1007/s10422-199900620-00004

Christodoulakos, G. E., Lambrinoudaki, I. V., Economou, E. V., Papadias, C., Cayan, F., Gen, R., Akbay, E., Dilek, U., and Dilek, S. (2011). The Effect of Tibolone on Glucose and Lipid Metabolism in Healthy Postmenopausal Women. J. Clin. Endocrinol. Metab. 100 (3), 1028–1037. doi:10.1210/jc.2014-3301

Cayan, F., Gen, R., Akbay, E., Dilek, U., and Dilek, S. (2011). The Effect of Hormone Therapy and Tibolone on Glucose and Lipid Metabolism in Healthy Postmenopausal Women. Turk Geriatri Dergis 14, 19–25.

Conard, J., Gompel, A., Pelissier, C., Mirabel, C., and Basdevant, A. (1997). Comparison of the Effects of Tibolone and Estrogen Therapy on Carotid Plaque Composition and Risk of Stroke in Subjects with Carotid Atherosclerosis. Circ. Res. 87 (4), 842–850. doi:10.1161/01.res.87.4.842

Falkeborn, M., Persson, I., Adami, H. O., Bergström, R., Eaker, E., Lihell, H., et al. (1992). The Risk of Acute Myocardial Infarction after Oestrogen and Oestrogen-Progestogen Replacement. Br. J. Obstet. Gynaecol. 99 (10), 821–826. doi:10.1111/j.1471-0528.1992.tb1414.x

Farish, E., Barnes, J. F., Fletcher, C. D., Ekeval, K., Calder, A., and Hart, D. M. (1999). Effects of Tibolone on Serum Lipoprotein and Apolipoprotein Levels Compared with a Cyclical Estradiol/progestogen Regimen. Menopause 6 (2), 98–104. doi:10.1097/00042192-19990620-00005

Franks, M. J., Clegg, D. J., and Hevener, A. L. (2013). The Role of Estrogens in Control of Energy Balance and Glucose homeostasis.[J]. Endocr. Rev. (3), 309–338.

Gris, M., Mujad, B., Rueda-Ochoa, O. L., Aslanaz, E., Laven, J. S. E., Kavoussi, M., et al. (2018). Associations of Endogenous Estradiol and Testosterone Levels with Plaque Composition and Risk of Stroke in Subjects with Carotid Atherosclerosis. Circ. Res. 122, 97–105. doi:10.1161/CIRCRESAHA.117.316681

Gregersen, I., Hastrup, J., Holven, K. B., Løvdahl, L., Ueland, T., Mowinckel, M. C., et al. (2019). Effect of Hormone Replacement Therapy on Lipid, Lipoprotein, and Apolipoprotein (A) Concentrations: Analysis of Studies Published from 1974-2000. Fertil. Steril. 75 (5), 898–915. doi:10.1016/j.fertnstert.2004.05.006

Gräser, T., Müller, A., Druckman, R., and Oettel, M. (2001). Effects of a Combination of 2 MG Estradiol Valerate and 3 MG Dinogest on Coagulation, Lipid Profile, and Glucose Metabolism in Postmenopausal Women. Drugs of Today 37, 87–99.

Haase, C. L., Tybjærg-Hansen, A., Qayyum, A. A., Schou, J., Nordestgaard, B. G., and Frikke-Schmidt, R. (2012). LCAT, HDL Cholesterol and Ischemic
of Small Dense-Low Density Lipoprotein and Free Radical Production in Postmenopausal Women. J. Atheroscler. Thromb. 23 (7), 810–818. doi:10.5551/jat.33175
Nordengard, B. G., Chapman, M. J., Ray, K., Bören, J., Andreotti, F., Watts, G. F., et al. (2010). Lipoprotein(a) in a Cardiovascular Risk Factor: Current Status. Eur. Heart J. 31, 2844–2853. doi:10.1093/eurheartj/ehq386
Odmark, I. S., Bäckström, T., Haeger, M., Jonsson, B., and Bixo, M. (2004). Effects of Continuous Combined Estrogen/medroxyprogesterone Acetate and 17beta-Estradiol/norethisterone Acetate on Lipids and Lipoproteins. Maturitas 48 (2), 137–146. doi:10.1016/j.maturitas.2003.08.004
Oral, B., and Ozbasar, D. (2003). The Effect of Sodium Monolaurate Phosphate Therapy on Lipid and Lipoprotein Metabolism in Postmenopausal Women. Eur. J. Obstet. Gynecol. Reprod. Biol. 107 (2), 180–184. doi:10.1016/s0301-2152(02)00404-9
Pan, H. A., Wang, S. T., Chen, C. H., Pai, M. C., Wu, M. H., and Huang, K. E. (2002). Flow Resistance in Carotid and Middle Cerebral Arteries in Postmenopausal Women: a Comparative Study of Tibolone and Continuous Combined Hormone Replacement Therapy. Climacteric 5 (3), 259–265. doi:10.1080/136937102.0250017
Panagiotis, P., Johannes, B., Cano, A., Ceausu, L., Chedraui, P., Durmusoglu, F., et al. (2020). Association of Endogenous Sex Hormone Levels with Coronary Artery Calcium Progression Among post-menopausal Women in the Multi-Ethnic Study of Atherosclerosis (MESA). J. Cardiovasc. Comput. Tomogr. 13, 41–47. doi:10.1016/j.jcct.2018.09.010
Taechrakichanana, N., Limpaphayom, K., Ninlagnar, T., Panyakamlakerd, M., Chaitkittisilp, S., and Dusitun, N. (2000). A Randomized Trial of Oral Contraceptive and Hormone Replacement Therapy on Bone mineral Density and Coronary Heart Disease Risk Factors in Postmenopausal Women. Obstet. Gynecol. 95 (1), 87–94. doi:10.1016/S0029-7844(00)00493-7
Tandon, V. R., Mahajan, A., Sharma, S., and Sharma, A. (2010). Prevalence of Cardiovascular Risk Factors in Postmenopausal Women: A Rural Study. J. Midlife Health 1 (1), 26–29. doi:10.14013/jmhc.2010.09.002
Taskinen, M. R., Puolakka, J., Pyörälä, T., Luotola, H., Björn, M., Kääriäinen, J., et al. (1996). Hormone Replacement Therapy Lowers Plasma Lp(a) Concentrations. Comparison of Cyclic Transdermal and Continuous Estrogen-Progestin Regimens. Arterioscler. Thromb. Vasc. Biol. 16 (10), 1215–1221. doi:10.1161/01.ATV.16.10.1215
Teede, H. J., Liang, Y. L., Kotsopoulos, D., Zougas, S., Craven, R., and McGraith, B. P. (2001). A Placebo-Controlled Trial of Long-Term Oral Combined Continuous Hormone Replacement Therapy in Postmenopausal Women: Effects on Arterial Compliance and Endothelial Function. Clin. Endocrinol. (Oxf) 55 (5), 673–682. doi:10.1111/j.1365-2265.2001.03182.x
Terauchi, M., Honjo, H., Mizumuna, H., and Aso, T. (2012). Effects of Oral Estradiol and Levonorgestrel on Cardiovascular Risk Markers in Postmenopausal Women. Arch. Gynecol. Obstet. 285 (6), 1647–1656. doi:10.1007/s00404-012-2222-9
Thurston, R. C., Bhasin, S., Chang, Y., Barinas-Mitchell, E., Matthews, K. A., Jasuja, R., et al. (2018). Reproductive Hormones and Subclinical Cardiovascular Disease in Midlife Women. J. Clin. Endocrinol. Metab. 103, 3070–3077. doi:10.1210/jc.2018-00579
Tilly-Kiesi, M., Lappi, M., Puolakka, J., Luotola, H., Pyörälä, T., and Taskinen, M. R. (1996). Different Effects of Continuous Oestrogen-Progestin and Transdermal Oestroprogestin with Cyclic Progestin Regimens on Low-Density Lipoprotein Subclasses. Eur. J. Clin. Invest. 26 (12), 1125–1133. doi:10.1046/j.1365-2362.1996.04594.x
Tuck, C. H., Holleran, S. and Berglund, L. (1997). Hormonal Regulation of Lipoprotein(a) Levels: Effects of Estrogen Replacement Therapy on Lipoprotein(a) and Acute Phase Reactants in Postmenopausal Women. Arterioscler. Thromb. Vasc. Biol. 17 (9), 1822–1829. doi:10.1161/01.ATV.17.9.1822
Ulloa, N., Arteaga, E., Bustos, P., Durán-Sandoval, D., Schulze, K., Castro, G., et al. (2002). Sequential Estrogen-Progestin Replacement Therapy in Healthy Postmenopausal Women: Effects on Cholesterol Efflux Capacity and Key Proteins Regulating High-Density Lipoprotein Levels. Metabolism 51 (11), 1410–1417. doi:10.1016/s0026-0495(02)35580
