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REVIEW - SYSTEMATIC

Safety and efficacy of compounded bioidentical hormone therapy (cBHT) in perimenopausal and postmenopausal women: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Importance: More information is needed about the efficacy and safety of compounded bioidentical hormone therapy (cBHT) in the published literature. A thorough synthesis of existing data is not currently available.

Objective: To provide a systematic review and meta-analysis of the existing evidence related to the safety and efficacy of commonly prescribed cBHT preparations in perimenopausal and postmenopausal women.

Evidence Review: PubMed, ClinicalTrials.gov, and The Cochrane Central Register of Controlled Trials were searched. Randomized controlled trials (RCTs) comparing cBHT with a placebo or FDA-approved products in perimenopausal or postmenopausal women were eligible. The risk of bias was assessed by the Cochrane risk of bias tool. The primary safety outcome was changes in lipid profile and glucose metabolism, and the primary efficacy outcome was the change of vaginal atrophy symptoms. The secondary outcomes included the change of endometrial thickness, risk of adverse events, vasomotor symptoms, change of serum hormone levels, and change of bone mineral density.

Findings: A total of 29 RCTs reported in 40 articles containing 1,808 perimenopausal and postmenopausal women were included. Two risk factors of cardiovascular disease, lipid profile, and glucose metabolism, were evaluated with cBHT. The results showed that compounded androgen was not associated with change of lipid profile or glucose metabolism. There was no change in endometrial thickness or serious adverse events. There were more androgenic side effects with compounded dehydroepiandrosterone compared with placebo as expected. Other safety measures including clinical cardiovascular events, endometrial biopsy, and risk of breast cancer were not studied. cBHT in the form of compounded vaginal androgen was found to significantly improve vaginal atrophy symptoms (SMD −0.66 [95% CI, −1.28 to −0.04]; $I^2 = 86.70\%$). This finding was supported by the association between compounded vaginal androgen and improved female sexual function scores. The changes of serum hormone levels were also evaluated. Despite the variations in absorption from different types of compounded hormones, routes, and strengths, the trends were consistent with published data from FDA-approved products.

Conclusions and Relevance: This review found that cBHT used in primarily short-term RCTs is not associated with adverse changes in lipid profile or glucose metabolism. cBHT in the form of vaginal androgens appears beneficial for vaginal atrophy symptoms. There are insufficient RCTs of cBHT to assess clinical risk of breast cancer, endometrial cancer, or cardiovascular disease. Long-term studies with clinical endpoints are needed.

Key Words: Compounded androgen – Compounded bioidentical hormone therapy – Compounded testosterone – Perimenopausal and postmenopausal women – Safety – Vaginal atrophy.

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In 2002, the Women's Health Initiative reported the health risks of oral conjugated equine estrogen with medroxyprogesterone acetate in postmenopausal women.[1] Since then, a substantial group of postmenopausal women using hormone therapy (HT) made the decision with their treating physicians to switch from synthetic hormones to bioidentical hormone therapy. Some physicians and patients determined that compounded bioidentical hormone therapy (cBHT) was appropriate. Several nationwide surveys showed a significant decline in prescriptions of FDA-approved hormone products over the past decade, in contrast with a continuous growth in cBHT. It was estimated that 1 to 2.5 million US women are cBHT users, and 26 to 33 million cBHT prescriptions were filled each year.[2-4] The new trend in HT raised concerns and discussions surrounding cBHT. The most prominent advantages of cBHT are its personalized approach and the flexibility in making customized strengths and dosage forms. Black box warnings are required on all FDA-approved estradiol and topical testosterone products, and Federal law exempts all compounded drugs from such labeling requirements. However, besides the absence of boxed warnings, other safety considerations regarding cBHT arose among physicians. These safety concerns included the increased risk of endometrial cancer, inconsistency of drug content, incomplete adverse events reporting, and unknown risk of cardiovascular disease, mostly from survey findings, case reports, nonrandomized studies, and expert opinions.[5,6] Because of concerns regarding cBHT, in 2018, the FDA requested the National Academies of Science, Engineering, and Medicine (NASEM) to evaluate the available evidence of cBHT regarding safety and effectiveness.[5] Thirteen clinical trials with relevance to the safety and effectiveness of cBHT were highlighted and discussed by the NASEM committee. A conclusion was reached that there was a lack of high-quality research to establish the safety and effectiveness of cBHT.[5] Furthermore, the highest level of evidence, a systematic review and meta-analysis had not been published.

We conducted a deep and thorough literature search and identified some studies that have not been cited by others in this field, including the NASEM committee. To obtain a comprehensive view of the safety and efficacy of commonly prescribed cBHT preparations, and to evaluate the robustness of evidence for using cBHT, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the safety and efficacy of cBHT in perimenopausal and postmenopausal women. In this review, the analyzed safety outcomes included two risk factors of cardiovascular disease, endometrial thickness, and adverse events. There were no available data on other measures of safety such as breast density on mammography, breast cancer, or clinical cardiovascular events. The primary efficacy outcome is vaginal atrophy symptoms. Change of serum hormone levels were also evaluated as a secondary outcome to provide information on absorption.

Key points

Question/Objective: What is the safety and efficacy profile of the common compounded bioidentical hormone therapy (cBHT) preparations in perimenopausal and postmenopausal women in the current literature?

Findings: Twenty-nine randomized controlled trials (RCTs) ($n = 1,808$) were included. The evaluated cBHT preparations were not associated with adverse changes in lipid profiles or glucose metabolism, endometrial thickness, or serious adverse events. Limited data were available to assess benefit with respect to vasomotor symptoms. No RCT was available to assess clinical events of breast or endometrial cancer or cardiovascular disease. cBHT in the form of vaginal androgen significantly improved vaginal atrophy symptoms.

Meaning: The meta-analysis found a benefit of cBHT in the form of vaginal androgens for vaginal atrophy symptoms. There are insufficient RCTs currently available to assess clinical risk of breast cancer, endometrial cancer, or cardiovascular disease. More studies are needed to evaluate the long-term clinical outcomes.

METHODS

Protocol and registration

This study was a protocol-based systematic review and meta-analysis registered at PROSPERO (ID: CRD42021209946. Available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=209946) and was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA) 27-item checklist.[7,8]

Search strategy

PubMed, ClinicalTrials.gov, and The Cochrane Central Register of Controlled Trials were searched for articles published from inception to December 2, 2020. There were no restrictions on the publication date, and the studies were limited to human clinical trials. The following keywords and MeSH terms were used in various combinations: hormone therapy, hormone replacement therapy, estrogen replacement therapy, estriol AND menopause, estradiol AND menopause, testosterone AND menopause, progesterone AND menopause, dehydroepiandrosterone (DHEA) AND menopause, compounded, compound, compounding, climacteric, menopause, postmenopausal, perimenopause. Detailed search strategy in each database was shown in Table S1, Supplemental Digital Content 1, http://links.lww.com/MENO/A895. The references of retrieved studies of interest were also screened for additional articles not identified by the original search.

Study eligibility and inclusion/exclusion criteria

RCTs with cBHT interventions were included for full review if they were conducted in perimenopausal or postmenopausal women (aged $\geq$ 18 y) who underwent natural menopause or surgical menopause. The control arm had to be based on a placebo or FDA-approved hormone products. In accordance with the NASEM report, cBHT preparations were defined as preparations compounded in a 503A compounding pharmacy, 503B outsourcing facilities, government healthcare facilities, for academic research, or for certain studies that were produced to assess off-label outcomes of FDA-approved products. Our review only focused on the nonsterile preparations, referring to the formulations prepared in a clean environment without requiring aseptic technique. Common dosage forms of nonsterile preparations include topical creams or gels, vaginal suppositories, oral tablets, or capsules, etc. There was no restriction on the route of administration or dosing strength during search. Sterile preparations, such as injections and implants, are compounded following different regulations, with different materials, and are less common than nonsterile products, thus were not included in the present study. Studies were excluded if (1) the evidence of using compounding preparations was not found; (2) cBHT was used for conditions not associated with menopause; (3) the compounds were not bioidentical hormones; (4) sterile compounding preparations were studied; or (5) no quantitative pretreatment and post-treatment outcomes of efficacy or safety were reported. Postmenopausal women on aromatase inhibitor therapy and given cBHT to relieve vaginal symptoms were not excluded because of the similar nature of estrogen deficiency as menopause.[9]

Data extraction and risk of bias assessment

Data were extracted into a preformulated data extraction spreadsheet by two independent reviewers (Y.L. and P.J.). Disagreements were resolved through consensus. Trial authors were contacted for any missing data or clarifications. All studies were assessed for risk of bias using the revised Cochrane risk-of-bias tool for randomized trials.[10] Briefly, six domains were examined for each study: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias assessment. Two reviewers independently assessed each included study. Three reviewers (Y.L., P.J., and D.J.N.) were involved. Discrepancies were resolved by the fourth reviewer (A.J.D.).

Outcomes

The primary outcomes include a safety outcome and an efficacy outcome. The safety outcome was the change of risk factors of cardiovascular disease. Because none of the included studies directly assessed cardiovascular events, the risk of cardiovascular disease was evaluated by surrogate markers of clotting factors, blood pressure (BP), lipid profiles, and glucose metabolism in this study. Because only two of the included studies assessed vasomotor symptoms, and the reported data were insufficient for meta-analysis, the primary efficacy outcome was the change of vaginal atrophy symptoms, which was measured by the severity score. Surrogate endpoints such as vaginal pH and female sexual function were also examined. To be included in the meta-analysis, continuous data needs to be reported as the mean difference $\pm$ standard deviation (SD) or mean $\pm$ SD with a P value for transforming into standardized mean difference (SMD). The pooled effects of cBHT on vaginal atrophy symptoms and female sexual function measured by various scales were synthesized following the method of Murad et al[11] and summarized as SMD corrected for scale directionality.

The secondary safety outcomes were the post-treatment endometrial thickness measured by transvaginal ultrasound (TVS) and the risk of adverse events. Other secondary outcomes were vasomotor symptoms, the change of serum hormone levels, and the change of bone mineral density (BMD).

Data synthesis

Meta-analyses of primary and secondary outcomes were performed using a random-effect model to account for heterogeneity between studies. For meta-analysis with only two or three trials, the random-effect model with Hartung-Knapp-Sidik-Jonkman method was conducted to address the influence of fewer studies in synthesis. The R software (version 4.0.1) package metafor (version 2.4) was used for statistical analysis. Trial-level and pooled estimates were reported as SMD/RR and 95% CIs; risk distribution was presented using forest plots with weighting according to a random-effect model. SDs were not directly reported in some studies. We derived them based on the reported data (eg, P values, t statistics, etc) using the published methods.[12-14]

In addition to the risk of bias assessment of individual clinical trials, publication bias was also assessed by evaluation of the asymmetry of the funnel plots. The proportion of heterogeneity between studies was assessed using the I^2 test statistic. An I^2 value less than 25% will be considered as low heterogeneity, 25% to 50% as moderate heterogeneity, and greater than 50% as high heterogeneity. Statistical significance was determined using a two-sided error threshold of 0.05. Certainty of evidence for each outcome was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.[7] Because of the lack of adjustment for multiple comparisons, the findings of the analyses should be interpreted as exploratory. All analyses and data cleaning were conducted using R 4.0.1.

RESULTS

Search result and study characteristics

The flow diagram of the literature search and study selection is shown in Figure 1. Overall, 5,895 publications were initially identified, of which 2,884 were excluded by screening titles, abstracts, and availability of full-text, then 3,011 underwent full-text review. Further excluding following the

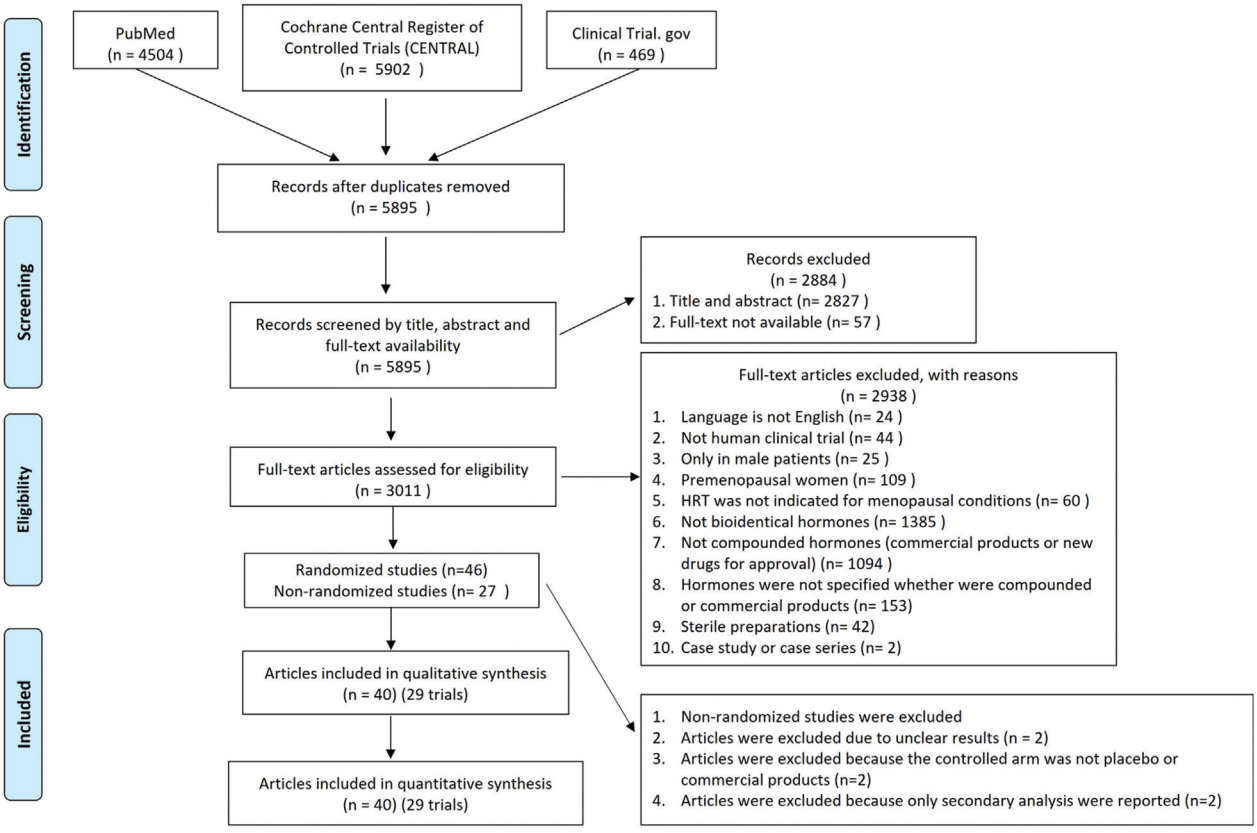

FIG. 1. Flow diagram of literature search to identify randomized controlled trials related to compounded bioidentical hormone therapy.

predefined exclusion criteria ruled out 2,938 articles. Non-randomized trials ($n = 27$) and randomized trials without suitable data for meta-analysis ($n = 6$) were also excluded. Detailed reasons of excluding were listed in Figure 1. A total of 29 RCTs reported in 40 articles containing 1,808 perimenopausal and postmenopausal women (aged 37-85 y) were included in the narrative review and the meta-analysis. Two trials ($n = 136$) were of patients studied for compounded estradiol and estriol,[15,16] 7 trials ($n = 281$) were for compounded progesterone,[17-25] 2 trials ($n = 53$) were for combination of compounded estrogens and progesterone,[26,27] 5 trials ($n = 285$) were for compounded testosterone,[28-34] and 13 trials ($n = 1,032$) were for compounded DHEA.[35-54] Compounded hormones were compared with placebos in 21 of these RCTs. Three RCTs compared between cBHT and FDA-approved products for the same therapeutic purpose despite different types of hormones. One RCT compared cBHT to both placebo and an FDA-approved product. Four RCTs studied the combination of cBHT and FDA-approved products to FDA-approved products alone. The basic characteristics of each trial are listed in Table 1.

Relevant RCTs included by NASEM were also indicated in Table 1. One of the NASEM reviewed RCTs was excluded from our study because in this DHEA study, some participants were on an unknown strength of concurrent estrogen replacement therapy while some were not.[55] The results for DHEA were unclear and may be misleading. Additional information regarding participants, preparation of compounded medications, and power analysis are summarized in Table S2, Supplemental Digital Content 1, http://links.lww.com/MENO/A895.

Risk of bias within studies and publication bias

All included trials were evaluated for their risks of bias. The overall risk of bias of each trial is shown in Table 1. Twenty-eight studies were rated overall with low to moderate risk of bias, among which three trials had potential risk of bias in one domain (See Figure S1, Supplemental Digital Content 1, http://links.lww.com/MENO/A895, which illustrated the risk of bias of each trial in each evaluated domain). One trial had imbalanced DHEA levels at the baseline. Statistical adjustment was utilized to reduce the imbalance before conducting the meta-analysis.[46,52,53] Two studies did not provide the number of patients that completed the trials; therefore, potential missing data existed.[20,23,51] Even though this is more of a reporting issue, to be conservative, we rated them at high risk of missing outcome data. The level of bias in these three studies was not likely to significantly impact conclusions; therefore, they were all rated with overall moderate risk. Only one study was considered high risk overall because only a small percentage of patients were available for vaginal cytology.[35] For outcomes irrelevant to vaginal cytology in the same trial, the risk of bias was low to moderate. No trials had the risk of selective reporting. Sensitivity analysis of excluding

TABLE 1. *Basic characteristics of the included studies.*

Study	Location	Design	Cases	Controls	Follow-up	Included outcomes[a]	Ethnicity	Overall risk of bias
Estrogen								
Vaginal (cBHT vs placebo)								
Tanmahasamut et al[15] 2020	Thailand	Double-blind, parallel	Compounded vaginal estradiol gel 25 μg/d × 2 wks, then twice per week ($n=40$)	Placebo ($n=40$)	1 mo 2 mo	Serum estradiol[b] Vaginal health Vaginal pH FSFI Endometrial thickness	Not reported[c]	Low
NCT00816556	US	Quadruple-blind, parallel	Compounded vaginal estriol cream 10 ug/d × 2 wks, then twice weekly ($n=18$) Compounded vaginal estradiol cream 10 ug ($n=19$)	Placebo ($n=19$)	3 mo	Change in serum estrone and estradiol[b] Vaginal atrophy score Adverse events		Low
Progesterone								
Vaginal (cBHT vs placebo/no treatment)								
Gerhard et al[20] 1998; Seely et al[23] 1999	US	Double-blind, crossover	Estraderm 0.2 mg + compounded vaginal progesterone 300 mg/d ($n=17$)	Estraderm 0.2 mg ($n=17$)	2 wks	Serum progesterone (immunoassay)	87% White	Overall moderate (potential high risk in one domain - missing outcome data)
Andreen et al[17] 2003; Andreen et al[18] 2005	Sweden	Double-blind, crossover	Estradiol 2 mg + compounded vaginal progesterone suppositories 400 mg/d × 14 d per cycle ($n=36$) Estradiol 2 mg + compounded vaginal progesterone suppositories 800 mg/d × 14 d per cycle ($n=36$)	Estradiol 2 mg + placebo suppositories ($n=36$)	3 mo	Serum progesterone (immunoassay)	Not reported	Moderate
Wihlback et al[25] 2005	Sweden	Double-blind, crossover	Progynon 2 mg + compounded vaginal progesterone suppository 800 mg/d × 14 d per cycle ($n=28$)	Progynon 2 mg + placebo suppositories ($n=28$)	2 mo	Serum progesterone (immunoassay)	Not reported	Moderate
Vaginal (cBHT vs FDA-approved hormone products)								
Antoniou et al[19] 1997	Greece	Open label, parallel	Estradiol 2 mg vaginal ring + compounded vaginal progesterone suppository 100 mg × 7 d per month ($n=28$)	Estradiol 50 ug transdermal patch + levonogestrel 52 mg IUD ($n=28$)	1 y	Endometrial thickness	Not reported	Low
Topical[d] (cBHT vs placebo)								
Leonetti et al[21] 1999[e]	US	Double-blind, parallel	Compounded topical progesterone cream 20 mg/d ($n=43$)	Placebo ($n=47$)	1 y	BMD Adverse effects	White	Moderate
Lewis et al[22] 2002[e]	New Zealand	Double-blind, parallel	Compounded topical progesterone cream 20 mg/d ($n=8$) Compounded topical progesterone cream 40 mg/d ($n=8$)	Placebo ($n=8$)	1 wk 3 wks	Plasma progesterone (immunoassay)	Not reported	Moderate
Stephenson et al[24] 2008	US	Double-blind, crossover	Compounded topical progesterone 20 mg/d ($n=30$)	Placebo ($n=30$)	1 mo	Adverse events	93.3% Caucasian; 3.3% Native American; 3.3% African American	Low

(Continued on next page)

TABLE 1 *(Continued)*

Study	Location	Design	Cases	Controls	Follow-up	Included outcomes[a]	Ethnicity	Overall risk of bias
Combination E+P								
Oral (cBHT vs. placebo)								
Thomas et al[27] 2014	France	Double-blind, crossover	Compounded estradiol 2 mg + compounded oral progesterone 100 mg/d from day 12 to day 21 per cycle ($n = 13$)	Placebo ($n = 13$)	2 mo	Serum estradiol (validated immunoassay)	Caucasian	Moderate
Topical[d] E + oral P (cBHT vs FDA-approved hormone products)								
Sood et al[26] 2013[e]	US	Double-blind, parallel	Compounded Bi-est 2 mg + compounded oral progesterone 100 mg ($n = 10$) Compounded Bi-est 2.5 mg + compounded progesterone 100 mg ($n = 10$) Compounded Bi-est 3 mg + compounded progesterone 100 mg ($n = 10$)	Vivelle-Dot 0.05 mg patch + Prometrium 100 mg ($n = 10$)	15 d	Serum progesterone (immunoassay)	Not reported	Moderate
Androgen								
Testosterone								
Vaginal (cBHT vs placebo/no treatment)								
Raghunandan et al[34] 2010	India	Non-blinded, parallel	Premarin 0.625 mg + compounded vaginal testosterone 10 mg twice weekly ($n = 25$)	Premarin 0.625 mg vaginal cream ($n = 25$)	3 mo	SPEQ sexual score Endometrial thickness Serum estradiol and testosterone[b]	Thai women	Moderate
Fernandes et al[31] 2014; Fernandes et al[30] 2016; Fernandes et al[32] 2018	Brazil	Non-blinded, parallel	Compounded vaginal testosterone cream 300 μg 3 ×/wk ($n = 20$)	Placebo ($n = 20$)	1.5 mo 3 mo	FSFI Serum estradiol, estrone, DHEA, DHEAS, free and total testosterone (immunoassay) Endometrial thickness Lipid profile Vaginal pH Vaginal health	80% White; 20% non-White	Moderate
Davis et al[61] 2018[e]	Australia	Double-blind, parallel	Compounded vaginal testosterone 300 μg/d × 2 wks, then 3 ×/wk ($n = 22$)	Placebo ($n = 22$)	6 mo	FSFI PFSF Serum total estradiol, testosterone, and estrone (LC-MS) Vaginal symptoms	Not reported	Moderate
Vaginal (cBHT vs FDA-approved hormone products)								
Fernandes et al[31] 2014; Fernandes et al[30] 2016; Fernandes et al[32] 2018	Brazil	Non-blinded, parallel	Compounded vaginal testosterone cream 300 μg 3 ×/wk ($n = 20$)	Premarin 0.625 mg vaginal cream ($n = 20$)	1.5 mo 3 mo	FSFI Serum estradiol, estrone, DHEA, DHEAS, free, and total testosterone (immunoassay) Endometrial thickness Lipid profile Vaginal pH Vaginal health	80% White; 20% nonwhite	Moderate
Melisko et al[33] 2017	US	Non-blinded, parallel	Compounded vaginal testosterone cream 5 mg/d × 2 wk, then 3×/wk (n = 36)	Estring 2 mg vaginal ring ($n = 40$)	3 months	Adverse effect	92% White; 1.3% Asian; 6.7% Hispanic	Low
Topical[d] (cBHT vs placebo)								
Barton et al[28] 2007	US	Double-blind, crossover	Compounded topical testosterone 10.4 mg/d ($n = 75$)	Placebo ($n = 75$)	1 mo	Serum estradiol, free, and total testosterone (validated immunoassay) CFSQ sexual function score	Not reported	Low
DHEA								
Oral (cBHT vs placebo)								
Mortola et al[47] 1990	US	Double-blind, crossover	Compounded oral DHEA 1,600 mg/d ($n = 6$)	Placebo ($n = 6$)	1 mo	Adverse events	Not reported	Moderate
Casson et al[38] 1993; Casson et al[39] 1995	US	Double-blind, crossover	Compounded oral DHEA 50 mg/d ($n = 11$)	Placebo ($n = 11$)	3 wks	Lipid profile Serum DHEA (immunoassay)	Not reported	Low

(Continued on next page)

TABLE 1 *(Continued)*

Study	Location	Design	Cases	Controls	Follow-up	Included outcomes[a]	Ethnicity	Overall risk of bias
Casson et al[40] 1998	US	Double-blind, parallel	Compounded oral DHEA 25 mg/d ($n=7$)	Placebo ($n=6$)	1 mo 3 mo 6 mo	Serum DHEAS, DHEA, total testosterone (immunoassay) Adverse events	Not reported	Moderate
Finckh et al[41] 2005	US	Double-blind, crossover	Compounded oral DHEA 50 mg/d ($n=52$)	Placebo ($n=52$)	3 mo	McCoy FSQ sexual score	Caucasian	Low
Jankowski et al[44] 2006[e]	US	Double-blind, parallel	Compounded oral DHEA 50 mg/d ($n=34$)	Placebo ($n=36$)	1 y for BMD. 2 wks, 3 mo, 6 mo, and 1 y for serum DHEAS	BMD Serum DHEAS (immunoassay) Severe adverse effects	Predominantly caucasian	Low
Von Muhlen et al[52] 2007; Von Muhlen et al[53] 2008; Kritz-Silverstein et al[46] 2008	US	Double-blind, parallel	Compounded oral DHEA 50 mg/d ($n=58$)	Placebo ($n=57$)	3 mo 6 mo 1 y	BMD Bone markers Serum DHEA, DHEAS, total testosterone, and estradiol (validated immunoassay) Adverse effects FSFI total	Not reported	Overall moderate (Potential high risk in one domain - the randomization process)
Panjari et al[48] 2009 a; Panjari et al[49] 2009 b[e]	Australia	Double-blind, parallel	Compounded oral DHEA 50 mg/d ($n=47$)	Placebo ($n=46$)	6 mo 1 y	SSRS (26 wks) Serum total testosterone, DHEA, estrone, estradiol, DHEAS (LC-MS-MS and GC-MS) Lipid profile Endometrial thickness Adverse events Glucose metabolism	Not reported	Low
Stanczyk et al[50] 2009	US	Double-blind, parallel	Compounded oral DHEA 25 mg/d ($n=10$)	Placebo ($n=10$)	3 mo 6 mo	Serum DHEA, DHEAS, testosterone, estrone, estradiol, and free testosterone (immunoassay)	Not reported	Moderate
Kenny et al[45] 2010[e]	US	Double-blind, parallel	Compounded oral DHEA 50 mg/d ($n=49$)	Placebo ($n=50$)	6 mo	BMD Bone markers Serum DHEAS, estradiol, estrone, testosterone, SHBP (validated immunoassay)	91% White; 1% Hispanic; 6% Black; 2% Other	Low
Stangl et al[51] 2011	US	Double-blind, crossover	Compounded oral DHEA 50 mg/d ($n=24$)	Placebo ($n=24$)	1 mo	Serum DHEA, DHEAS, estrone, testosterone (LC-MS-MS)	Not reported	Overall moderate (potential high risk in one domain—missing outcome data)
Gomez-Santos et al[42] 2011 a; Gomez-Santos et al[43] 2011 b	Spain	Double-blind, parallel	Compounded oral DHEA 100 mg/d ($n=41$)	Placebo ($n=20$)	3 mo	Serum DHEAS (immunoassay) Lipid profile Glucose metabolism	Not reported	Moderate
Bloch et al[37] 2013	Israel	Double-blind, parallel	Compounded oral DHEA 100 mg/d ($n=13$)	Placebo ($n=13$)	3 wks 6 wks	Serum DHEAS, total testosterone and estradiol (GC-MS)	Not reported	Low
Vaginal (cBHT vs placebo)								
Barton et al[35] 2018 a; Barton et al[36] 2018 b; NCT01376349	US	Double-blind, parallel	Compounded vaginal DHEA gel 3.25 mg ($n=147$). Compounded vaginal DHEA gel 6.5 mg ($n=149$)	Placebo ($n=147$)	3 mo	FSFI serum DHEAS, estradiol, estrone, total, and free testosterone[b] Vaginal atrophy score Bone markers Adverse events Vaginal pH	95% White; 3.4% Black; 0.2% Asian; 1.4% Missing	High risk for VMV results due to missing outcome data. Moderate risk for the other results.

BMD, bone mineral density; CFSQ, the Changes in Sexual Functioning Questionnaire; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; E, estrogen; FSFI, female sexual function index; GC-MS, gas chromatography mass spectrometry; LC-MS-MS, liquid chromatography with tandem mass spectrometry; McCoy FSQ, the McCoy Female Sexuality Questionnaire; NASEM, the National Academies of Sciences, Engineering, and Medicine; P, progesterone; PFSF, the Profile of Female Sexual Function; SHBP, sex hormone-binding protein; SPEQ, the Short Personal Experience Questionnaire; SSRS, Sabbatsberg Sexual Self-Rating Scale; VMV, vaginal maturation value.

[a]All reported outcomes were screened but only the outcome data that can be transformed into meta-analysis was included.

[b]The method used to measure serum hormone levels was not reported in the published article.

[c]Not reported—information was not reported in the study.

[d]Or ''transdermal,'' as was used in NASEM report.

[e]Studies that were included in the NASEM report.

the four trials yielded results (not shown) similar to these including the four trials as reported below. In addition, the funnel plot suggests that there is no evidence of publication bias in this review (Figure S2, Supplemental Digital Content 1, http://links.lww.com/MENO/A895).

Primary safety outcome analysis—the risk factors of cardiovascular disease

Four surrogate biomarkers were prespecified in the protocol to assess the risk of cardiovascular disease associated with cBHT: clotting factors, BP, serum lipid profile, and glucose metabolism. Meta-analyses were only performed for lipid profile and glucose metabolism due to an inadequate number of studies in clotting factors and BP.

The change in lipid profile was assessed in seven RCTs ($n = 237$ patients).[32,34,39,40,43,47,48] The duration of therapy varied from 1 month to 1 year. Compounded vaginal testosterone and oral DHEA were evaluated. In the synthesized data, compounded androgen therapy was not associated with changes of total cholesterol (SMD −0.53 [95% CI, −1.26 to 0.21]; $I^2 = 80.9\%$), triglycerides (SMD −0.59 [95% CI, −1.35 to 0.18]; $I^2 = 82.4\%$), LDL (SMD −0.12 [95% CI, −0.46 to 0.22]; $I^2 = 19.3\%$) or HDL (SMD 1.07 [95% CI, 2.39 to −0.26]; $I^2 = 94.2\%$) compared with placebo. In the subgroup analysis, neither vaginal testosterone nor oral DHEA showed significant changes in lipids as is shown in Figure 2A to D. For the effect of cBHT on glucose metabolism, 2 RCTs using compounded DHEA 50 mg daily in 121 postmenopausal women for 3 months to 1 year were pooled.[43,48] No significant changes were observed in fasting glucose (SMD −0.32 [95% CI, −4.52 to 3.88]; $I^2 = 66.9\%$), fasting insulin (SMD −0.03 [95% CI, −0.44 to 0.38]; $I^2 = 0.0\%$) or the Homeostatic Model Assessment for Insulin Resistance (SMD 0.23 [95% CI, −0.19 to 0.66]; $I^2 = 0.0\%$) (Fig. 2E).

Thrombotic and anticoagulant factors were evaluated in only one eligible RCT.[24] In this short-term crossover study, 30 healthy postmenopausal women were enrolled to receive either 20 mg/d of a compounded progesterone cream or a placebo for 1 month. No significant differences were observed in the individual or group averages of coagulation factors V and VII, fibrinogen, antithrombin III, and plasminogen activator inhibitor 1 . BP was measured in 2 of the included RCTs involving 78 patients with high risk of hypertension. However, the reported data was not sufficient to be transformed to SMD

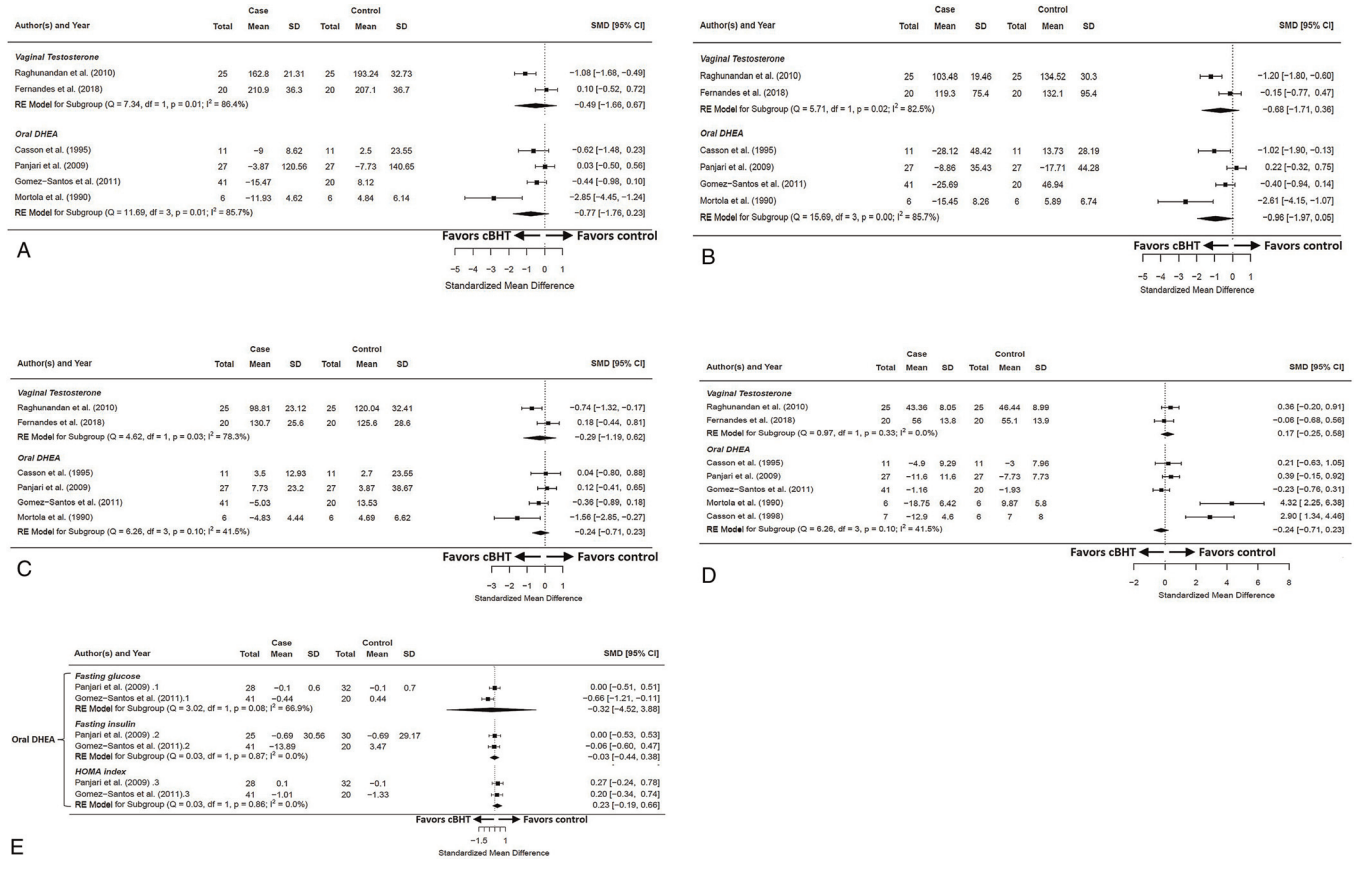

FIG. 2. Random-effects meta-analysis of the association between cBHT and the risk factors of cardiovascular disease: (**A**) the change of total cholesterol; (**B**) the change of triglycerides; (**C**) the change of LDL; (**D**) the change of HDL; (**E**) the change of glucose metabolism. Some SDs were not provided in the original studies, and thus were derived for meta-analysis using methods provided by Shi et al and Weir et al.[11,12] The same method was applied to all the other analysis in this study. To ensure all ''favor cBHT'' is on the left and all ''favor control'' is on the right, the SMD of HDL was calculated by ''control minus case,'' while the others were calculated by usual method of ''case minus control.'' cBHT; compounded bioidentical hormone therapy; DHEA, dehydroepiandrosterone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMD, standardized mean difference.

for a meta-analysis.[20,23,42,43] In these two studies, a combination of compounded vaginal progesterone and Estraderm, or compounded oral DHEA alone, both showed significant reduction of systolic BP and diastolic BP in these patients compared with placebo, although the difference between Estraderm alone and Estraderm + compounded progesterone combination was not significant.[20,23]

Overall, in the meta-analysis including short-term studies, there were no significant adverse findings of cBHT on lipid profile or glucose metabolism.

Secondary safety outcomes analysis—endometrial thickness and adverse events

Endometrial thickness was measured in five trials ($n = 273$ patients), with four studies comparing with placebo,[15,34,48,49] and two studies comparing with therapies using FDA-approved products.[19,32] The duration of therapy varied from 2 months to 1 year. Four cBHT regimens, which utilized testosterone, estradiol, or progesterone, were delivered by the vaginal route. DHEA was given by oral route. None of the individual studies showed a significant difference in the endometrial thickness

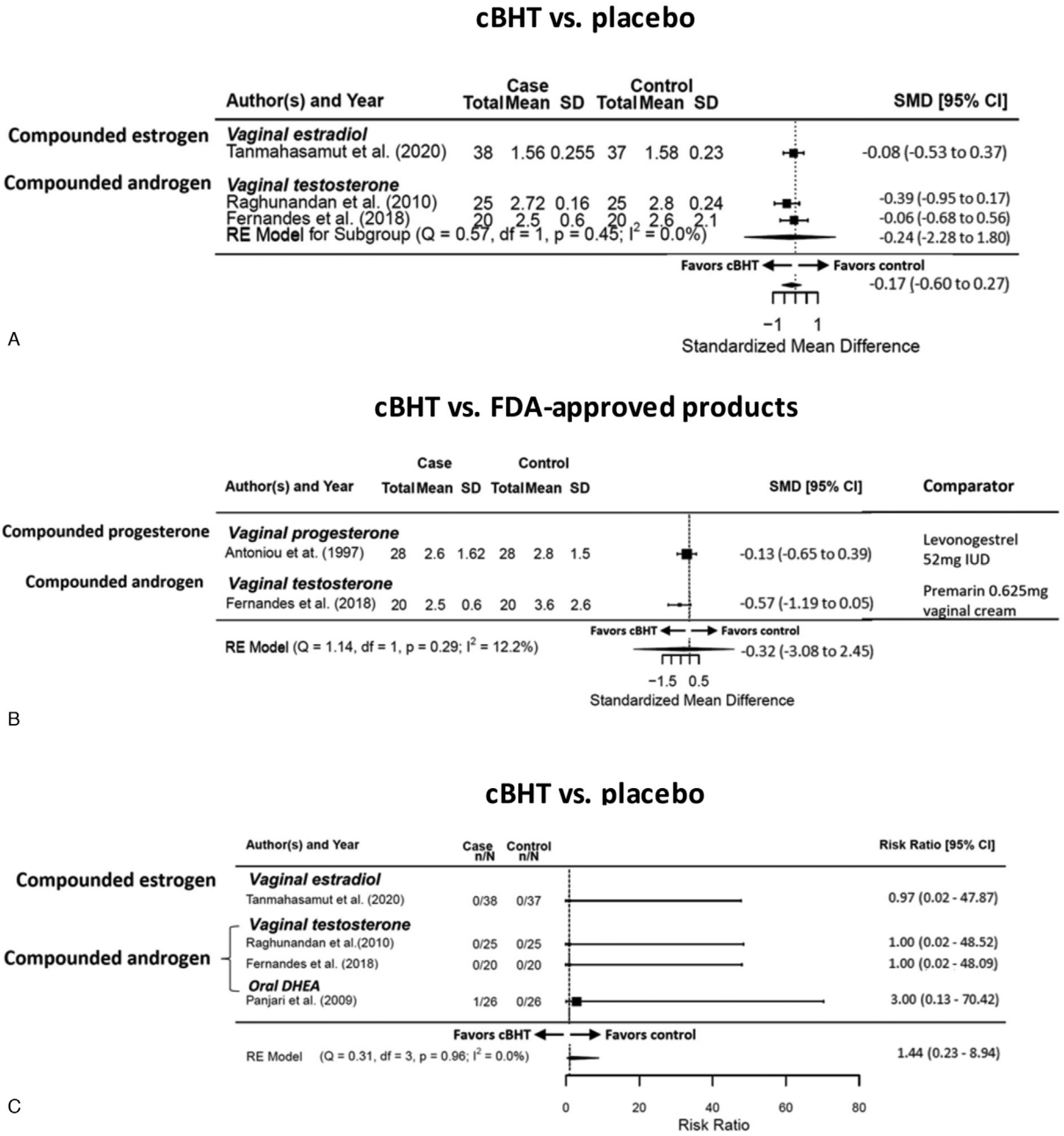

FIG. 3. Random-effects meta-analysis of the association between cBHT and the posttreatment endometrial thickness when compared with (**A**) placebo; or (**B**) therapies with FDA-approved products. (**C**) The association between cBHT and the risk of endometrial thickness exceeding 5 mm.

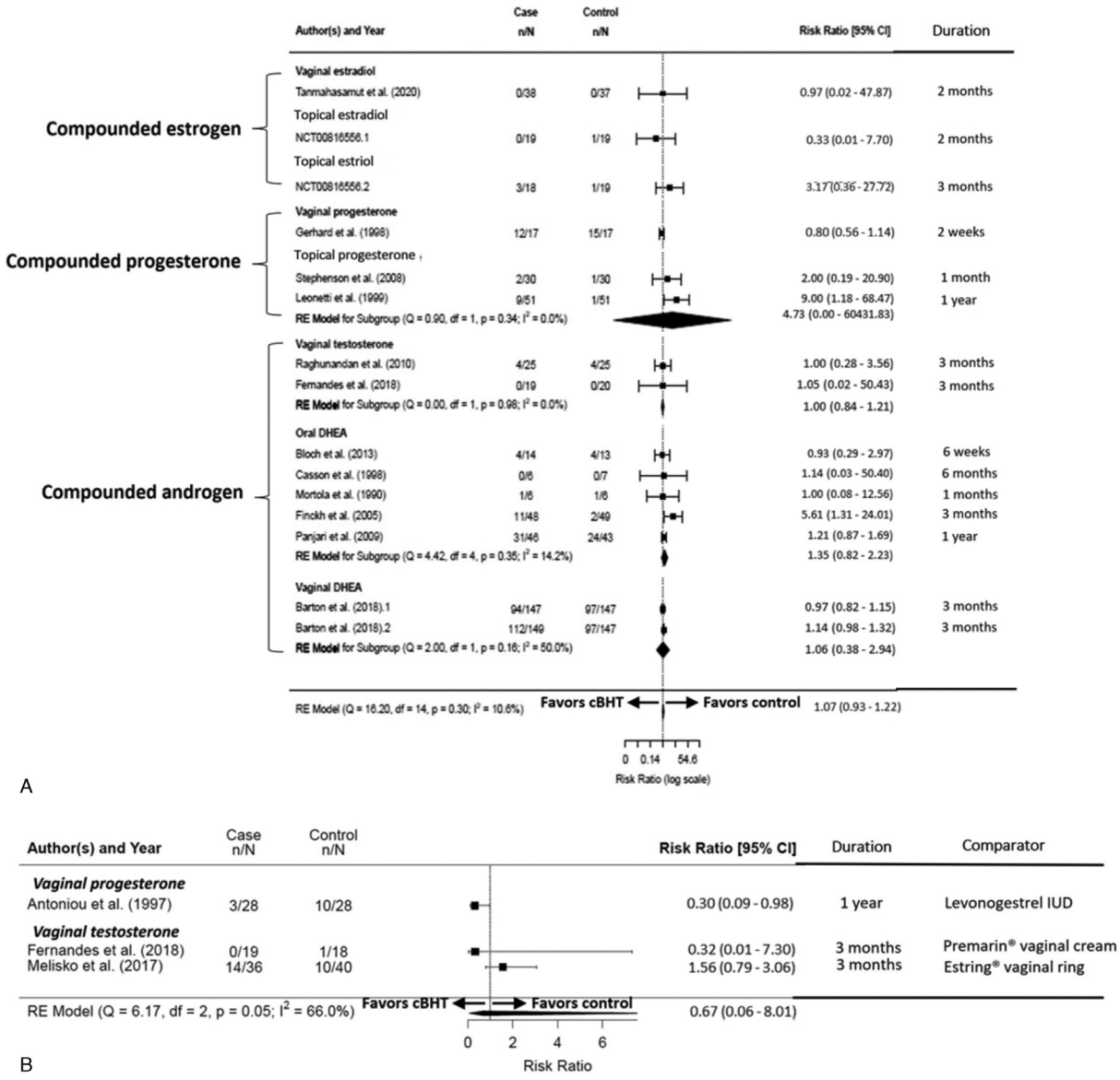

FIG. 4. Random-effects meta-analysis of the association between cBHT and the risk of total adverse events compared with (**A**) placebo; or (**B**) therapies using FDA-approved products.

between cBHT and controls, same as in the meta-analysis (cBHT vs placebo: SMD −0.17 [95% CI, −0.61 to 0.27]; $I^2 = 0.0\%$, Figure 3A. Vaginal testosterone versus placebo: SMD −0.24 [95% CI, −2.28 to 1.80]; $I^2 = 0.0\%$, Figure 3A. cBHT versus FDA-approved products: SMD −0.32 [95% CI, −3.08 to 2.45]; $I^2 = 12.2\%$, Fig. 3B). When examining the incidence of an endometrial thickness exceeding 5 mm, which is highly associated with the risk of endometrial cancer,[53] cBHT containing compounded estradiol or androgen was not associated with a higher incidence (cBHT vs placebo: RR 1.44 [95% CI, 0.23-8.94]; $I^2 = 0.0\%$. Compounded androgen versus placebo: RR 1.60 [95% CI, 0.20-12.71]; $I^2 = 0.00\%$) (Fig. 3C). Only endometrial thickness measured by TVS was used as a safety feature in these studies, not endometrial biopsies which is the gold standard to exclude endometrial hyperplasia or carcinoma.

Adverse events were assessed in 19 RCTs (n = 1,373 patients) by the reported adverse events and withdrawals due to adverse effects.[15,16,19-21,24,32-37,40,41,47,48,54] The duration of cBHT use ranged from 2 weeks to 1 year. In the subgroup meta-analysis of each type of hormone, compared with placebo, compounded estrogen (RR 1.41 [95% CI, 0.07-27.25]; $I^2 = 0.00\%$), compounded progesterone (RR 1.87 [95% CI, 0.01-449.55]; $I^2 = 63.55$), and compounded androgen (RR 1.09 [95% CI, 0.89-1.33]; $I^2 = 0.00\%$) were not associated with increased risk of total adverse events. Consistent result was found in the synthesized analysis combining all types of hormones when compared with either placebo (RR 1.07 [95% CI, 0.93-1.22]; $I^2 = 10.6\%$) (Fig. 4A), or therapies using FDA-approved hormone products (RR 0.67 [95% CI, 0.06-8.01]; $I^2 = 66.0\%$) (Fig. 4B). Secondary analysis was performed for each type of

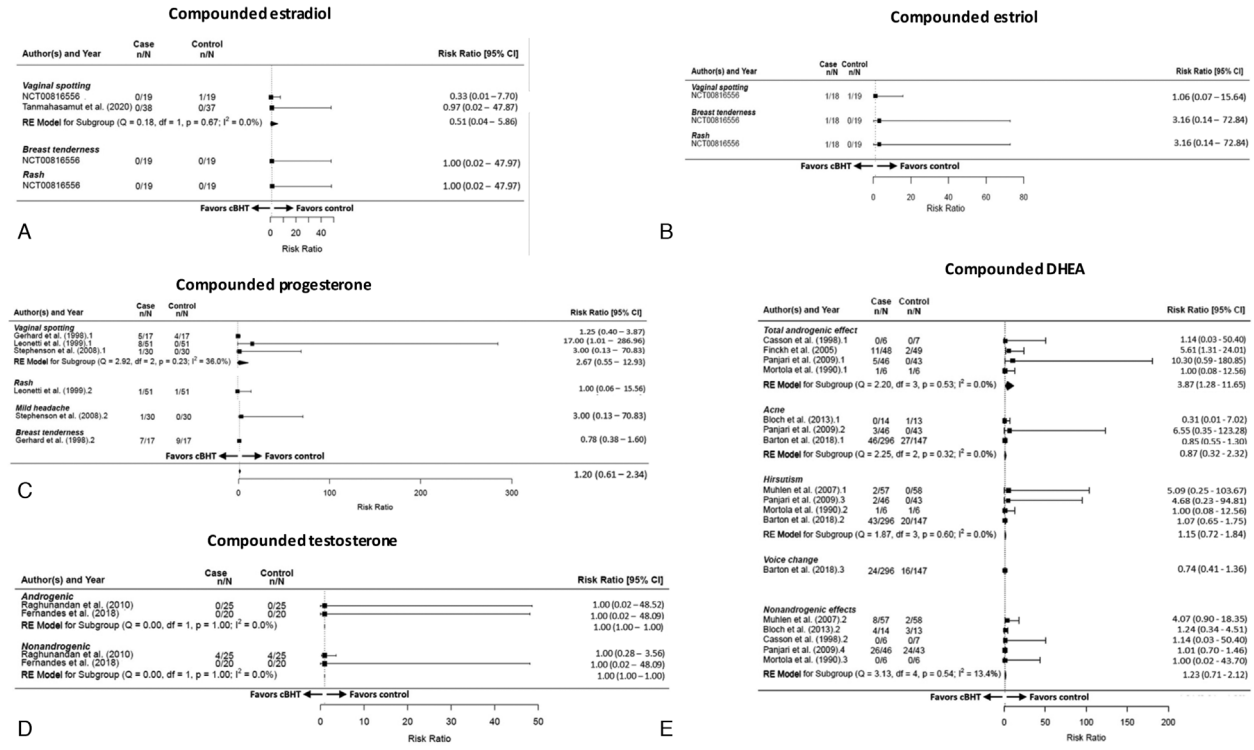

FIG. 5. Random-effects meta-analysis of the risk of adverse event with (**A**) compounded estradiol; (**B**) compounded estriol; (**C**) compounded progesterone; (**D**) compounded testosterone; and (**E**) compounded DHEA. DHEA; dehydroepiandrosterone.

hormone to investigate the incidence of some common adverse effects compared with placebo. The common adverse effects reported were vaginal spotting, breast tenderness, rash, and androgenic effects such as acne, hirsutism and voice change. Compounded estradiol, estriol, progesterone, testosterone, and DHEA were not associated with increased risk of adverse effects (Fig. 5), with one exception — a higher risk of total androgenic effect was found with compounded DHEA compared with placebo (RR 3.87 [95% CI, 1.28-11.65]; $I^2 = 0.0\%$), although no significantly increased risk of acne, hirsutism, or nonandrogenic effects was observed in the subgroup analysis (Fig. 5E). In addition, cBHT was not associated with more patient withdrawals caused by adverse effects compared with either placebo or therapies using FDA-approved hormone products (See Figure S3. Supplemental Digital Content 1, http://links.lww.com/MENO/A895).

Primary efficacy outcome analysis—change of vaginal atrophy symptoms

Vaginal atrophy is one of the most bothersome symptoms in menopausal women. It was evaluated by the vaginal symptom scores in 5 RCTs ($n = 298$ patients).[15,16,29,30,35,36] The treatment durations ranged from 1 to 6 months. Vaginally delivered cBHT was used in all included studies. No significant changes were found for vaginal estrogen or vaginal testosterone in the subgroup analysis, probably because of a small number of studies for each type of hormone (Fig. 6A). However, when the data of vaginal testosterone and vaginal DHEA were combined, there was a significant association between vaginally applied androgen and improved symptoms (SMD −0.66 [95% CI, −1.28 to −0.04]; $I^2 = 86.70\%$).

Vaginal atrophy, specifically vaginal dryness and dyspareunia, is a major contributor to female sexual dysfunction and is closely related to all domains of the Female Sexual Function Index (FSFI).[56] The change of FSFI and other female sexual function scores can be surrogate measures for the change of vaginal atrophy. FSFI was assessed in a total of five RCTs using vaginal estradiol, vaginal testosterone, vaginal DHEA, or oral DHEA ($n = 598$ patients).[15,29,31,35,36,46] Treatment durations were from one and a half months to 1 year. Because of the different absorption profile between vaginal and oral dosage forms, meta-analysis was performed separately for the vaginal hormones and oral DHEA. In the synthesized data of all vaginal hormone combined, vaginal cBHT was associated with improvements in arousal, lubrication, satisfaction, pain, and the overall score (Fig. 6B). When combining testosterone and DHEA to examine the efficacy of compounded vaginal androgen ($n = 527$ patients), significant associations were found in the improvements of arousal (SMD −0.31 [95% CI, −0.48 to −0.14]; $I^2 = 0.0\%$), lubrication (SMD −0.30 [95% CI, −0.53 to −0.08]; $I^2 = 32.4\%$), satisfaction (SMD −0.38 [95% CI, −0.55 to −0.21]; $I^2 = 0.0\%$), and pain (SMD −0.44 [95% CI, −0.70 to −0.18]; $I^2 = 44.2\%$). The subgroup analysis restricted to compounded vaginal testosterone ($n = 102$ patients) consistently revealed significantly improved function in lubrication (SMD −0.69 [95% CI, −0.86 to −0.51]; $I^2 = 0.0\%$) and satisfaction (SMD −0.71 [95% CI, −1.21 to −0.21]; $I^2 = 0.0\%$) (Fig. 6B). To further validate the results obtained

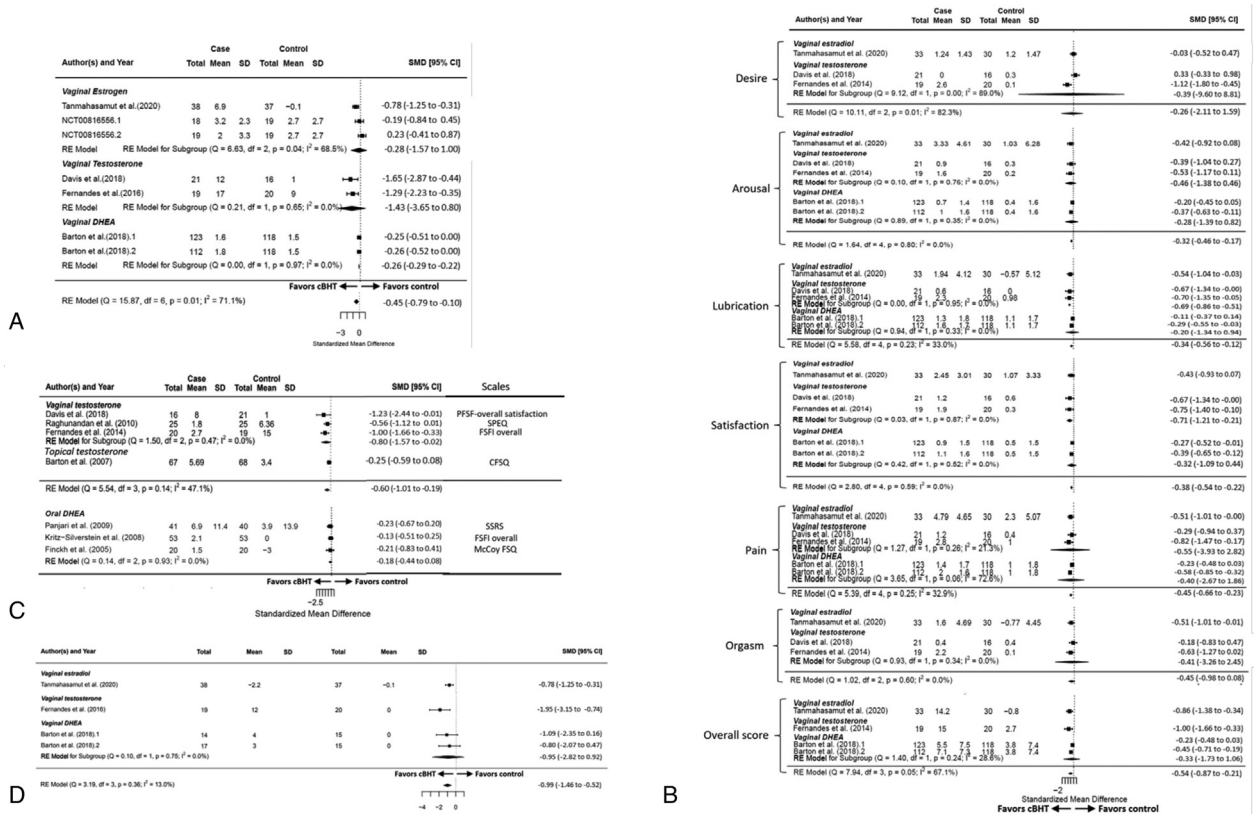

FIG. 6. Random-effects meta-analysis of the association between cBHT and (**A**) the change of vaginal atrophy symptom scores; (**B**) the change of FSFI domains and the overall score; (**C**) the change of female sexual function total scores evaluated by different scales; (**D**) the change of vaginal pH. To ensure all ''favor cBHT'' is on the left and all ''favor control'' is on the right, the SMD of vaginal atrophy symptom scores, FSFI, and other female sexual function total scores were calculated by ''control minus case.'' cBHT, compounded bioidentical hormone therapy; CFSQ, the Changes in Sexual Functioning Questionnaire; FSFI, female sexual function index; McCoy FSQ, the McCoy Female Sexuality Questionnaire; PFSF, the Profile of Female Sexual Function; SMD; standard mean difference; SPEQ, the Short Personal Experience Questionnaire; SSRS, Sabbatsberg Sexual Self-Rating Scale.

from FSFI, the changes of total female sexual function scores of different scales were analyzed. Similarly, significant associations were detected for compounded testosterone (SMD −0.60 [95% CI, −1.01 to −0.19]; $I^2 = 47.1\%$) (Fig. 6C). However, there was no association between oral DHEA and improved total sexual function scores (Fig. 6C).

Vaginal pH is another measurement highly correlated with vaginal atrophy symptoms in postmenopausal women.[57] Three trials utilized vaginal pH to evaluate the efficacy of vaginal estrogen or androgen in 175 women.[15,30,35,36] Treatment duration ranged from 2 to 3 months. Association between reduction of vaginal pH and vaginal estradiol or vaginal testosterone was shown in independent trial (Fig. 6D). Compounded vaginal androgen, analyzed by combining a study with vaginal testosterone and a study with vaginal DHEA, did not reveal significant association (SMD −1.30 [95% CI, −2.80 to 0.19]; $I^2 = 0.0\%$). However, the meta-analysis of all types of vaginal hormones found the association between reduced vaginal pH and vaginal cBHT compared with placebo treatment (SMD −0.99 [95% CI, −1.46 to −0.52]; $I^2 = 13.0\%$) (Fig. 6D).

Overall, vaginal dosage forms of cBHT were associated with improved vaginal atrophy symptoms in available placebo controlled RCTs. Vaginal androgen, especially vaginal testosterone, was also associated with improved female sexual function, but oral DHEA was not.

Other secondary outcomes analysis—vasomotor symptoms, change of serum hormone levels and BMD

Vasomotor symptoms, even though they are common in postmenopausal women, were not thoroughly studied in the included RCTs. There were only two trials investigating the improvement of vasomotor symptoms following cBHT. Leonetti et al[21] showed the symptoms were significantly relieved in most patients after 1 year of therapy of topical progesterone ($n = 47$ patients). In the other study, oral combined estrogen plus progesterone failed to show significant symptom relief after 2 months ($n = 13$ patients).[27] Data were inadequate to perform meta-analysis.

In the 29 RCTs, 2 studies tested hormone levels in saliva,[17,19] in contrast with 23 trials that measured serum hormones. Therefore, the meta-analysis focused on serum hormone levels. In all included trials, serum samples were taken in the morning right before the next dose and at least 1 month after initiation, when steady state was achieved. For studies with multiple time points, the last steady-state timepoint was used in the meta-analysis (Fig. 7). The changes of the steady-state hormone levels after corresponding cBHT

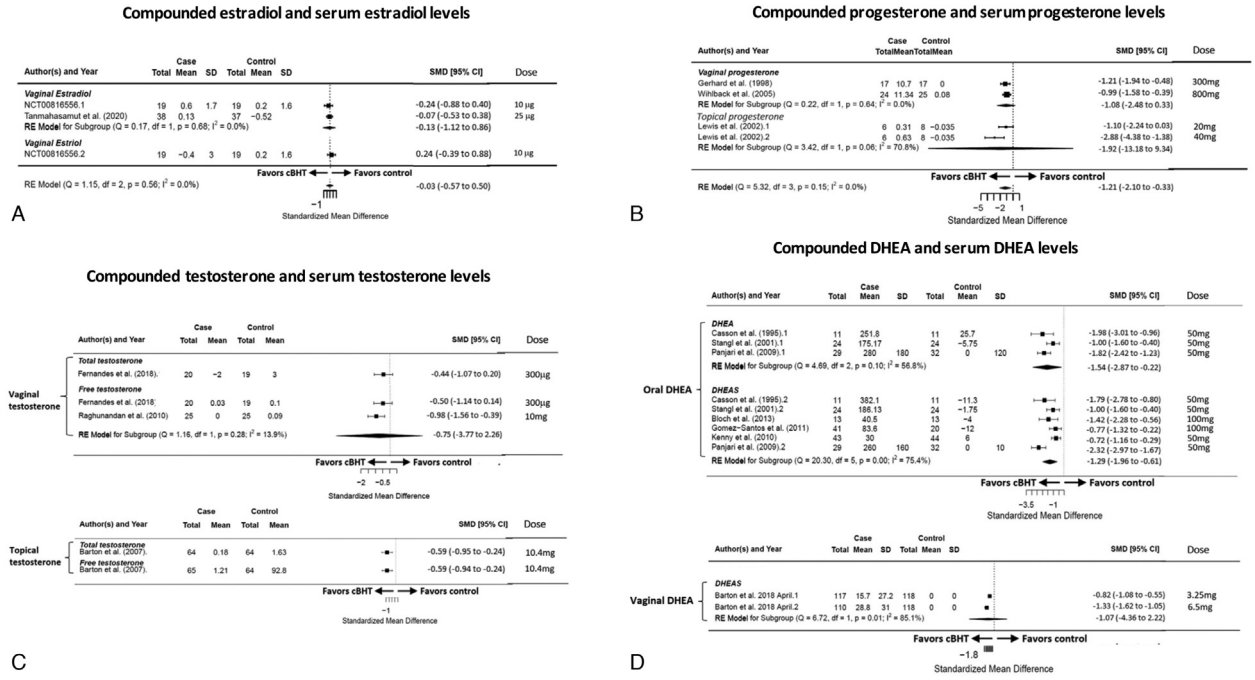

FIG. 7. Random-effects meta-analysis of the association between cBHT and the changes of its corresponding serum hormone levels. (**A**) Compounded estrogen and the change of serum estradiol levels; (**B**) compounded progesterone and the change of serum progesterone level; (**C**) compounded testosterone and the change of serum free and total testosterone levels; (**D**) compounded DHEA and the change of serum DHEA or DHEAS levels. To ensure all ''favor cBHT'' is on the left and all ''favor control'' is on the right, the SMD of serum hormone levels were calculated by ''control minus case.'' cBHT, compounded bioidentical hormone therapy; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; SMD, standard mean difference.

were assessed in 2 RCTs for compounded estradiol ($n = 51$ patients),[15,16] 1 for compounded estriol ($n = 37$ patients),[16] 3 for compounded progesterone ($n = 80$ patients),[20,22,25] 3 for compounded testosterone ($n = 217$ patients),[28,32,34] and 7 for compounded DHEA ($n = 615$ patients).[35-37,39,43,45,48,51] Treatment duration varied from 2 weeks to 1 year.

For compounded estrogen, no significant change of serum estradiol was detected with vaginal estradiol in two RCTs (Fig. 7A). Compounded vaginal estriol was studied in only one trial. Serum estriol level was not reported. No change was detected in the serum estradiol as expected because estriol does not convert to estradiol (Fig. 7A). Compounded vaginal or topical (or ''transdermal,'' as was referred to in the NASEM report) progesterone significantly increased serum progesterone levels in all three independent studies; however, the association was not significant in the meta-analysis ($n = 56$ patients) (Fig. 7B). Serum estradiol levels were not affected in the two trials using compounded vaginal progesterone. Two studies using 300 μg of compounded vaginal testosterone consistently showed no change of serum testosterone levels compared with placebo.[29,32] With 5 mg of compounded vaginal testosterone in a trial comparing with an FDA-approved vaginal estrogen, significant elevation of serum total testosterone was found in the testosterone group.[33] When 10 mg of compounded testosterone was delivered through vaginal or topical route in two trials, significantly increased testosterone levels were also detected in serum.[28,34] Absorption of compounded testosterone may be dose dependent. No significant association was seen in the meta-analysis (Fig. 7C). Compounded oral DHEA was significantly associated with elevated serum levels of DHEA (SMD −1.54 [95% CI, −2.87 to −0.22]; $I^2 = 56.8\%$), and its sulfate—DHEAS (SMD −1.29 [95% CI, −1.96 to −0.61]; $I^2 = 75.4\%$) (Fig. 7D). Significantly increased estrone, free testosterone, and total testosterone were also observed following use of compounded DHEA (See Figure S4, Supplemental Digital Content 1, http://links.lww.com/MENO/A895). Only one trial studied vaginal DHEA, and significant increase of serum DHEAS was shown at two different doses of DHEA.[35,36] In addition, two RCTs studied combination estrogen plus progesterone, one used oral route and the other used topical Bi-est plus oral progesterone.[26,27] Oral estradiol 2 mg in combination with oral progesterone 100 mg significantly increased serum estradiol level. The other trial compared between three doses of a compounded Bi-est (estriol: estradiol 80:20) cream plus compounded oral progesterone, and an FDA-approved estradiol patch plus an FDA-approved progesterone product.[26] This trial showed comparable serum progesterone levels in all groups. This is the only comparison in all available RCTs that compared between cBHT and an FDA-approved product of the same dosage form and strength. The 100 mg compounded oral progesterone resulted in similar change of serum progesterone as Prometrium. But lower serum estradiol levels were observed in patients using compounded Bi-est cream.

BMD was assessed in 4 RCTs ($n = 347$ patients) with durations from 6 months to 1 year, among which 3 studies used compounded oral DHEA,[44,45,53] and 1 study utilized

compounded progesterone cream.[21] No significant association was found between cBHT and changes of BMD (See Figure S5A, Supplemental Digital Content 1, http://links.lww.com/MENO/A895). Two of the included RCTs studied the 1-year effect of compounded oral DHEA 50 mg, with each study showing a significant increase in lumbar BMD independently. When the two studies were pooled in secondary analysis, the improvement was not significant, likely due to the small number of studies (See Figure S5B, Supplemental Digital Content 1, http://links.lww.com/MENO/A895). No significant change in bone markers was observed following cBHT (See Figure S6, Supplemental Digital Content 1, http://links.lww.com/MENO/A895).

DISCUSSION

Summary of main findings

In this systematic review and meta-analysis of 29 RCTs involving 1,808 perimenopausal and postmenopausal women, cBHT was not significantly associated with altered lipid profile and glucose metabolism, which are risk factors for cardiovascular disease. There were insufficient data on BP and clotting factor for a meta-analysis. No significant change of endometrial thickness measured by TVS was observed with cBHT in studies lasting 2 months to 1 year. Endometrial sampling that might identify endometrial proliferation, hyperplasia, or cancer was not performed as a safety measure. The risk of adverse events resulting from cBHT was comparable to placebo, except for a higher risk of androgenic side effects observed with compounded DHEA therapy. In the efficacy analysis, vaginal forms of androgen were associated with improved vaginal atrophy symptoms. This finding was also supported by the results of improved female sexual function and reduced vaginal pH following vaginally delivered androgen. Vaginal estrogen was not associated with significantly improved vaginal atrophy symptom scores but was shown to reduce vaginal pH and improve FSFI lubrication, orgasm, and total scores. Oral DHEA, however, was not effective in improving total sexual function scores in included trials. There were inadequate data to assess vasomotor symptoms in the meta-analysis.

Serum hormone levels do not necessarily predict efficacy or safety; however, The North American Menopause Society (NAMS) and NASEM often express the need for more information to show cBHT is being absorbed. FDA also recommends human pharmacokinetics study to be performed when comparing different designs of hormone products during clinical evaluation. While these organizations might not recommend monitoring levels for treating symptoms, a survey recently presented at NAMS 2021 Annual Meeting involving more than 400 US cBHT practitioners showed almost all physicians evaluated hormone levels on a regular basis in their practice.[58] Therefore, examining the absorption of cBHT is necessary. Pharmacokinetic studies suggested that although the absorption was influenced by the types of hormones, routes, and strengths, consistent trends were shown across studies. Compounded combination of oral estradiol 2 mg with progesterone 100 mg significantly increased serum estradiol level, and the level remained in the physiologic range for reproductive-aged women. Compounded vaginal estrogen at 10 μg or 25 μg is unlikely to increase serum estradiol, while vaginal progesterone at 300 mg or topical progesterone at 40 mg may have significant systemic absorption. Topical testosterone at 10 mg significantly increased both total and free testosterone levels. Vaginal androgen may also increase corresponding serum androgen levels when doses reach several milligrams. Oral DHEA at 50 to 100 mg led to consistent elevation of serum DHEA and DHEAS.

The findings were generated from RCTs, and there was a consistent trend across studies despite heterogeneity likely due to various cBHT regimens. Therefore, the certainty of evidence is considered moderate to high. The collective findings from this meta-analysis will help to expand our current knowledge of cBHT, to suggest the need of re-evaluating the safety and efficacy of the commonly prescribed cBHT preparations, and to provide guidance on future clinical trials of cBHT.

Agreements and disagreements with other reviews

This study was conducted in the wake of the recent NASEM report that evaluated the safety, effectiveness, and utilization of cBHT. A similar objective and search strategy as the NASEM report was applied to this study. In addition to including articles containing the key terms of cBHT in the title, keywords, or abstract as NASEM did, we expanded the full-text review to any article that did not specifically state using commercial products. We thus uncovered additional studies not reviewed by NASEM. To overcome the methodological limitations and insufficient power in individual studies, we extracted and pooled data that used the same methodology and measures into a meta-analysis. We evaluated risk factors for cardiovascular disease and identified limited information in RCTs, with data available only on lipid profile and glucose metabolism for meta-analysis. These risk factors were not adequately discussed in the NASEM report. In this review, no significant adverse changes of lipid profile or glucose metabolism were found with the use of compounded androgen. A systematic review and meta-analysis of DHEA therapy in postmenopausal women with normal adrenal function also showed similar results in lipids and glucose.[59] Consistent evidence was discussed in the 2005 NAMS position statement and in the recent 2019 international global statement regarding testosterone therapy.[60,61] It must be noted that clinical cardiovascular events have not been studied with cBHT. FDA approved oral conjugated equine estrogen, although exhibited favorable lipid profile, was found to associate with increased CVD events.[62,63] While we do not have specific evidence of this risk for cBHT, we cannot rule it out as a possibility, so caution must be exercised. The meta-analysis, including various formulations of compounded estradiol, progesterone, testosterone, and DHEA, showed no change in endometrial thickness. Although

endometrial thickening is correlated with a higher risk of endometrial cancer, short-term studies of endometrial thickness are inadequate to assess the risk of endometrial cancer. The change of endometrial thickness was not assessed in the NASEM report. In 2019, four major professional societies had reached a consensus on the clinical need for testosterone therapy for female sexual dysfunction in a Global Consensus Position Statement, which seven other professional organizations endorsed.[61] Only topical testosterone products that are FDA-approved for use in males were recommended in the consensus to be given off-label for women.[61] In the current review, two high-quality RCTs using 300 μg/mL compounded vaginal testosterone cream showed improved sexual function scores individually and in the meta-analysis, consistent with NASEM's findings from other randomized trials.[29,31] However, the androgenic side effects which concerned NASEM were not seen in the meta-analysis. These data suggest a reconsideration by professional societies of the benefits and risks of compounded testosterone for female patients.

Even though compounded estriol and estradiol have the least available studies so far, consistent data have been seen with approved bioidentical hormone products. Low-dose vaginal estradiol was recommended by the 2020 NAMS position statement for vaginal atrophy because of the low systemic absorption, favorable safety profile, and satisfactory efficacy profile.[64] No significant change of serum estradiol was identified in women using vaginal estradiol in previous systemic reviews.[65,66] Our review identified similar findings from two RCTs involving compounded low-dose vaginal estriol or estradiol cream/gel. Furthermore, a well-powered RCT with low risk-of-bias also demonstrated the benefits of a compounded vaginal estradiol preparation for vaginal atrophy.[15] In contrast, compounded oral estradiol increased serum estradiol levels to a comparable level as FDA-approved oral estradiol.[27,67] The pharmacokinetic study of compounded Bi-est creams conducted by Sood et al has attracted much attention. Notably, this study has several major limitations. The estradiol and estriol were compounded in Vanicream, which was not designed as a drug delivery system for hormones in compounded medications. Instead, it is more commonly utilized for topical applications and skincare. Moreover, an *in vitro* study has shown higher percutaneous absorption of progesterone in VersaBase cream—a widely used vehicle for cBHT, than in Vanicream.[68] Therefore, the lower hormone delivery by Vanicream found in this study may not be extrapolated to other compounded formulations using different vehicles. Not only does the delivery vehicle affect the bioavailability of hormones, but different dosage forms also can result in different drug release and absorption profiles. This variability in bioavailability, drug release, and absorption profiles is a principal concern for the use of cBHT. Without proving the bioequivalence, the transdermal patch used in this study is not suitable to be compared side by side with a compounded cream. These limitations prevent the generalization of the findings to other cBHT preparations, and they were also acknowledged in the NASEM report.

There is no FDA-approved oral DHEA product available to validate our findings of the compounded oral DHEA; however, consistent impact on serum hormone levels has been observed across the studies and the meta-analysis. Importantly, elevated serum hormone levels were still in the postmenopausal range or at the lower end of premenopausal levels. In this review, a well-designed RCT showed the positive effects of a compounded vaginal DHEA gel in serum hormone levels, dyspareunia, and female sexual dysfunction.[35,36] Similar benefits were also published with Intrarosa, the vaginal insert, and only FDA-approved DHEA product.[69]

We did not find a significant association between cBHT and increased BMD during 6 months or 1-year of therapy.

More RCTs will be needed to inform conclusions regarding other outcomes such as blood pressure and clotting factors. Questions remain about the risk of breast cancer, cognitive function, and mental health. High-quality RCTs are lacking in these important areas as of today.

Strengths and limitations

To our knowledge, this is the first comprehensive review of the safety and efficacy of cBHT in perimenopausal and postmenopausal women using meta-analysis. Other strengths of this review include a thorough literature search reviewing more than 3,000 full-text articles to identify cBHT-related studies and uncover data that has not been evaluated before. Only RCTs were analyzed in this review, indicating the high quality and reliability of the evidence. Among these RCTs, 25 out of 29 studies had a low to moderate risk of bias, and the impact from the four studies with a high risk of potential bias has been tested and shown not to affect the overall trend of the results. All data were transformed to SMD in the meta-analysis, enabling the synthesis of the same outcome data measured in various ways. Additionally, all included compounded testosterone trials were well powered with low to moderate risk of bias and similar characteristics of participants, suggesting they are high-quality evidence. For those trials that were underpowered, or power analysis was not reported, this limitation can be minimized using the meta-analysis to reach higher power. A conservative statistical model was employed to the meta-analysis containing a small number of trials, and multiple analytical methods were used to validate the results, which ensured the reliability and confidence of the findings.

The review has several limitations. First, not all studies provided suitable data for meta-analysis, and not all HT-related outcomes were measured in these studies. Surrogate endpoints were used for some outcomes. There are small numbers of subjects with short durations in many trials. For example, endometrial biopsy after 1 year of therapy is more clinically meaningful than endometrial thickness measured at less than 1 year of therapy when assessing the risk of endometrial cancer. Clinical endpoints such as clinical cardiovascular events and endometrial biopsies may be priorities for future trials to examine. Second, none of the enrolled participants were followed up beyond 1 year. Long-term

follow-up will be necessary for future studies. Third, only one clinical trial was identified which directly compared a cBHT formulation to an FDA-approved formulation. The results of that trial showed the two formulations yield similar outcomes, and we would like to see more data with other formulations. We hope the current study will urge researchers to include such comparisons in future trials. The current regulatory environment limits the claims compounders may make comparing their formulations to FDA-approved formulations. Therefore, perhaps this leads to reduced incentives to conduct this type of study. Fourth, fewer RCTs of compounded estradiol and estriol are available compared with other hormone regimens. A further review of compounded estradiol and estriol, including high-quality nonrandomized trials, may be valuable. Fifth, there may be missing studies from the 153 articles that did not specify if the hormones were compounded or commercial products. Sixth, the patient-specific dosing regimens were not fully reflected in these studies, possibly due to the complexity of the process in a controlled clinical trial. Incorporating personalized dosing is likely to improve patient outcomes, so the efficacy results reported in this study were more conservative without dosing adjustment. Future trials may consider involving interventions that allow certain adjustments. Seventh, some outcomes were evaluated by small studies and not all details of all dosage forms and routes of administration were consistent in these RCTs. Eighth, a majority of the studies measuring serum hormone levels adopted validated immunoassays. For more accurate and reliable measurements, future clinical trials should consider using liquid chromatography/tandem mass spectrometry. Lastly, other utilizations of cBHT, such as *in vitro* fertilization, primary ovarian insufficiency, or for male patients, were not evaluated because the population was outside the scope of this review.

Applicability

Patients are better informed about medical options than ever before. As clinicians and regulators seek to better understand the benefits and risks of various therapies, it is important that the totality of available information be considered through an unbiased lens. This study is one step toward assessing the clinical literature for cBHT in perimenopausal and postmenopausal women. Additional data are available from various sources that did not meet the criteria for inclusion in the current study. Compounded androgen, with a relatively larger number of studies, was found associated with potential benefits in improving vaginal atrophy symptoms and female sexual dysfunction. More studies are desired for compounded estrogen and progesterone to consolidate the findings in the present study. The need for personalized medicine are growing. The current evidence from placebo-controlled trials does not identify specific safety concerns; however, current evidence is based on short-term studies with limited endpoint measures. Results from meta-analysis suggest that some patients may experience some benefits from vaginal androgen therapy. It is noteworthy that potential benefit of vaginal estradiol in female sexual dysfunction was also suggested in a good-quality RCT. Although meta-analysis cannot be performed with the single study of vaginal estradiol, the data should not be ignored. More studies are needed to further investigate this formulation. Current data are insufficient to assess hot flashes and BMD. Bioavailability and pharmacokinetics of cBHT is difficult to evaluate due to diversity of preparations; however, consistent trends were observed across included RCTs using serum samples. Systemic absorption was found with compounded oral estradiol plus progesterone, compounded topical testosterone, higher dose of compounded vaginal androgens (ie, 10 mg of vaginal testosterone, or 3.25 mg of vaginal DHEA), and compounded oral DHEA, but absorption was not detected with low doses of compounded vaginal estrogens (ie, 25 μg) or vaginal testosterone (ie, 300 μg). Compounded oral progesterone resulted in comparable change of serum progesterone as an FDA-approved product in a RCT. These pharmacokinetic measurements were limited by using immunoassay instead of the gold standard LC-MS/MS. Well-designed long-term studies to better assess risk and benefit are needed. More studies are also needed to perform meta-analysis on bioavailability and pharmacokinetic measurements, especially for topical estrogens.

CONCLUSIONS

In this systematic review and meta-analysis of primarily short-term RCTs in perimenopausal and postmenopausal women, and recognizing the limits of the available evidence, cBHT was found beneficial with respect to vaginal androgens without showing major safety concerns for lipid profile, glucose metabolism, endometrial thickness, or severe adverse events. Consistent trends in changes of serum hormone levels were observed across included studies. There are not enough published clinical trials to assess the effects of cBHT on hot flashes and no benefits were found on BMD in current short-term studies. More long-term studies are needed to draw conclusions on the clinical cardiovascular events, the risk of breast cancer, endometrial cancer, and the prevention of bone loss.

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REFERENCES

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333. doi: 10.1001/jama.288.3.321.
2. Pinkerton JV, Santoro N. Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. *Menopause* 2015;22:926-936. doi: 10.1097/GME.0000000000000420.
3. Pinkerton JV, Constantine GD. Compounded non-FDA-approved menopausal hormone therapy prescriptions have increased: results of a pharmacy survey. *Menopause* 2016;23:359-367. doi: 10.1097/GME.0000000000000567.
4. Crawford SL, Crandall CJ, Derby CA, et al. Menopausal hormone therapy trends before versus after 2002: impact of the Women's Health Initiative Study Results. *Menopause* 2018;26:588-597. doi: 10.1097/GME.0000000000001282.
5. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy; Jackson LM, Parker RM, Mattison DR, editors. The Clinical Utility of Compounded Bioidentical Hormone

Therapy: A Review of Safety, Effectiveness, and Use. Washington (DC)2020. doi: 10.17226/25791.
6. Stuenkel CA. Compounded bioidentical menopausal hormone therapy – a physician perspective. *Climacteric* 2021;24:11-18. doi: 10.1080/13697137. 2020.1825668.
7. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;10:ED000142. doi: 10.1002/14651858.ED000142.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-269, W64. doi: 10.7326/0003-4819-151-4-200908180-00135.
9. Kallak TK, Baumgart J, Goransson E, Nilsson K, Poromaa IS, Stavreus-Evers A. Aromatase inhibitors affect vaginal proliferation and steroid hormone receptors. *Menopause* 2014;21:383-390. doi: 10.1097/GME.0b013e31829e41df.
10. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898.
11. Murad MH, Wang Z, Chu H, Lin L. When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. *BMJ* 2019;364:k4817. doi: 10.1136/bmj.k4817.
12. Shi J, Luo D, Weng H, et al. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods* 2020;11:641-654. doi: 10.1002/jrsm.1429.
13. Weir CJ, Butcher I, Assi V, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. *BMC Med Res Methodol* 2018;18:25. doi: 10.1186/s12874-018-0483-0.
14. Lakens D, Hilgard J, Staaks J. On the reproducibility of meta-analyses: six practical recommendations. *BMC Psychol* 2016;4:24. doi: 10.1186/s40359-016-0126-3.
15. Tanmahasamut P, Jirasawas T, Laiwejpithaya S, Areeswate C, Dangrat C, Silprasit K. Effect of estradiol vaginal gel on vaginal atrophy in postmenopausal women: a randomized double-blind controlled trial. *J Obstet Gynaecol Res* 2020;46:1425-1435. doi: 10.1111/jog.14336.
16. A trial to evaluate the efficacy of low dose vaginal estrogens in the treatment of atrophic vaginitis. Available at: https://clinicaltrials.gov/ct2/show/NCT00816556. Accessed January 10, 2021.
17. Andreen L, Bixo M, Nyberg S, Sundstrom-Poromaa I, Backstrom T. Progesterone effects during sequential hormone replacement therapy. *Eur J Endocrinol* 2003;148:571-577. doi: 10.1530/eje.0.1480571.
18. Andreen L, Sundstrom-Poromaa I, Bixo M, Andersson A, Nyberg S, Backstrom T. Relationship between allopregnanolone and negative mood in postmenopausal women taking sequential hormone replacement therapy with vaginal progesterone. *Psychoneuroendocrinology* 2005;30:212-224. doi: 10.1016/j.psyneuen.2004.07.003.
19. Antoniou G, Kalogirou D, Karakitsos P, Antoniou D, Kalogirou O, Giannikos L. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints versus estradiol-releasing vaginal ring with a vaginal progesterone suppository: clinical and endometrial responses. *Maturitas* 1997;26:103-111. doi: 10.1016/s0378-5122(96)01087-0.
20. Gerhard M, Walsh BW, Tawakol A, et al. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. *Circulation* 1998;98:1158-1163. doi: 10.1161/01.cir.98.12.1158.
21. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999;94:225-228. doi: 10.1016/s0029-7844(99)00266-5.
22. Lewis JG, McGill H, Patton VM, Elder PA. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. *Maturitas* 2002;41:1-6. doi: 10.1016/s0378-5122(01)00250-x.
23. Seely EW, Walsh BW, Gerhard MD, Williams GH. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. *Hypertension* 1999;33:1190-1194. doi: 10.1161/01.hyp.33.5.1190.
24. Stephenson K, Neuenschwander PF, Kurdowska AK, Pinson B, Price C. Transdermal progesterone: effects on menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women. *Int J Pharm Compd* 2008;12:295-304.
25. Wihlback AC, Nyberg S, Backstrom T, Bixo M, Sundstrom-Poromaa I. Estradiol and the addition of progesterone increase the sensitivity to a neurosteroid in postmenopausal women. *Psychoneuroendocrinology* 2005;30:38-50. doi: 10.1016/j.psyneuen.2004.05.005.
26. Sood R, Warndahl RA, Schroeder DR, et al. Bioidentical compounded hormones: a pharmacokinetic evaluation in a randomized clinical trial. *Maturitas* 2013;74:375-382. doi: 10.1016/j.maturitas.2013.01.010.
27. Thomas J, Metereau E, Dechaud H, Pugeat M, Dreher JC. Hormonal treatment increases the response of the reward system at the menopause transition: a counterbalanced randomized placebo-controlled fMRI study. *Psychoneuroendocrinology* 2014;50:167-180. doi: 10.1016/j.psyneuen.2014.08.012.
28. Barton DL, Wender DB, Sloan JA, et al. Randomized controlled trial to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment Group protocol N02C3. *J Natl Cancer Inst* 2007;99:672-679. doi: 10.1093/jnci/djk149.
29. Davis SR, Robinson PJ, Jane F, White S, White M, Bell RJ. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *J Clin Endocrinol Metab* 2018;103:4146-4154. doi: 10.1210/jc.2018-01345.
30. Fernandes T, Costa-Paiva LH, Pedro AO, Baccaro LF, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. *Menopause* 2016;23:792-798. doi: 10.1097/GME.0000000000000613.
31. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. *J Sex Med* 2014;11:1262-1270. doi: 10.1111/jsm.12473.
32. Fernandes T, Pedro AO, Baccaro LF, Costa-Paiva LH. Hormonal, metabolic, and endometrial safety of testosterone vaginal cream versus estrogens for the treatment of vulvovaginal atrophy in postmenopausal women: a randomized, placebo-controlled study. *Menopause* 2018;25:641-647. doi: 10.1097/GME.0000000000001059.
33. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol* 2017;3:313-319. doi: 10.1001/jamaoncol.2016.3904.
34. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *J Sex Med* 2010;7:1284-1290. doi: 10.1111/j.1743-6109.2009.01667.x.
35. Barton DL, Shuster LT, Dockter T, et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer* 2018;26:1335-1343. doi: 10.1007/s00520-017-3878-2.
36. Barton DL, Sloan JA, Shuster LT, et al. Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). *Support Care Cancer* 2018;26:643-650. doi: 10.1007/s00520-017-3960-9.
37. Bloch M, Meiboom H, Zaig I, Schreiber S, Abramov L. The use of dehydroepiandrosterone in the treatment of hypoactive sexual desire disorder: a report of gender differences. *Eur Neuropsychopharmacol* 2013;23:910-918. doi: 10.1016/j.euroneuro.2012.09.004.
38. Casson PR, Andersen RN, Herrod HG, et al. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993;169:1536-1539. doi: 10.1016/0002-9378(93)90431-h.
39. Casson PR, Faquin LC, Stentz FB, et al. Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women. *Fertil Steril* 1995;63:1027-1031. doi: 10.1016/s0015-0282(16)57542-6.
40. Casson PR, Santoro N, Elkind-Hirsch K, et al. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril* 1998;70:107-110. doi: 10.1016/s0015-0282(98)00121-6.
41. Finckh A, Berner IC, Aubry-Rozier B, So AK. A randomized controlled trial of dehydroepiandrosterone in postmenopausal women with fibromyalgia. *J Rheumatol* 2005;32:1336-1340. doi: null. 2005-07-01.
42. Gomez-Santos C, Hernandez-Morante JJ, Tebar FJ, Granero E, Garaulet M. Differential effect of oral dehydroepiandrosterone-sulphate on metabolic syndrome features in pre- and postmenopausal obese women. *Clin Endocrinol (Oxf)* 2012;77:548-554. doi: 10.1111/j.1365-2265.2011.04306.x.
43. Gomez-Santos C, Larque E, Granero E, Hernandez-Morante JJ, Garaulet M. Dehydroepiandrosterone-sulphate replacement improves the human plasma fatty acid profile in plasma of obese women. *Steroids* 2011;76:1425-1432. doi: 10.1016/j.steroids.2011.07.011.
44. Jankowski CM, Gozansky WS, Schwartz RS, et al. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. *J Clin Endocrinol Metab* 2006;91:2986-2993. doi: 10.1210/jc.2005-2484.

45. Kenny AM, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc* 2010;58:1707-1714. doi: 10.1111/j.1532-5415.2010.03019.x.
46. Kritz-Silverstein D, von Muhlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc* 2008;56:1292-1298. doi: 10.1111/j.1532-5415.2008.01768.x.
47. Mortola JF, Yen SS. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab* 1990;71:696-704. doi: 10.1210/jcem-71-3-696.
48. Panjari M, Bell RJ, Jane F, Adams J, Morrow C, Davis SR. The safety of 52 weeks of oral DHEA therapy for postmenopausal women. *Maturitas* 2009;63:240-245. doi: 10.1016/j.maturitas.2009.03.020.
49. Panjari M, Bell RJ, Jane F, et al. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med* 2009;6:2579-2590. doi: 10.1111/j.1743-6109.2009.01381.x.
50. Stanczyk FZ, Slater CC, Ramos DE, et al. Pharmacokinetics of dehydroepiandrosterone and its metabolites after long-term oral dehydroepiandrosterone treatment in postmenopausal women. *Menopause* 2009;16:272-278. doi: 10.1097/gme.0b013e31818adb3f.
51. Stangl B, Hirshman E, Verbalis J. Administration of dehydroepiandrosterone (DHEA) enhances visual-spatial performance in postmenopausal women. *Behav Neurosci* 2011;125:742-752. doi: 10.1037/a0025151.
52. von Muhlen D, Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. The Dehydroepiandrosterone And WellNess (DAWN) study: research design and methods. *Contemp Clin Trials* 2007;28:153-168. doi: 10.1016/j.cct.2006.04.009.
53. von Muhlen D, Laughlin GA, Kritz-Silverstein D, Bergstrom J, Bettencourt R. Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial. *Osteoporos Int* 2008;19:699-707. doi: 10.1007/s00198-007-0520-z.
54. Prasterone (dehydroepiandrosterone) in treating postmenopausal cancer survivors with vaginal symptoms. Available at: https://clinicaltrials.gov/ct2/show/NCT01376349. Accessed March 1, 2021.
55. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)* 1998;49:421-432. doi: 10.1046/j.1365-2265.1998.00507.x.
56. Cagnacci A, Venier M, Xholli A, Paglietti C, Caruso S; Study A. Female sexuality and vaginal health across the menopausal age. *Menopause* 2020;27:14-19. doi: 10.1097/GME.0000000000001427.
57. Tucker KM, Godha K, Mirkin S, Archer DF. Vaginal pH: a simple assessment highly correlated with vaginal morphology and symptoms in postmenopausal women. *Menopause* 2018;25:762-766. doi: 10.1097/GME.0000000000001081.
58. Biundo B, Carvalho M, Banov D, Day AJ. Compounded hormones for female patients: a survey assessment of clinical practices in the US. NAMS 2021 Annual Meeting Poster presentation. P-6. Available at: https://www.menopause.org/docs/default-source/agm/nams-2021-oral-and-poster-presentation-abstracts.pdf.
59. Elraiyah T, Sonbol MB, Wang Z, et al. Clinical review: The benefits and harms of systemic testosterone therapy in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2014;99:3543-3550. doi: 10.1210/jc.2014-2262.
60. North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2005;12:496-511quiz 649. doi: 10.1097/01.gme.0000177709.65944.b0.
61. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab* 2019;104:4660-4666. doi: 10.1210/jc.2019-01603.
62. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;273:199-208. doi: 10.1001/jama.1995.03520270033028.
63. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534. doi: 10.1056/NEJMoa030808.
64. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause* 2020;27:976-992. doi: 10.1097/GME.0000000000001609.
65. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol* 2014;124:1147-1156. doi: 10.1097/AOG.0000000000000526.
66. Rueda C, Osorio AM, Avellaneda AC, Pinzon CE, Restrepo OI. The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review. *Climacteric* 2017;20:321-330. doi: 10.1080/13697137.2017.1329291.
67. Kim SM, Kim SE, Lee DY, Choi D. Serum estradiol level according to dose and formulation of oral estrogens in postmenopausal women. *Sci Rep* 2021;11:3585. doi: 10.1038/s41598-021-81201-y.
68. Allen LV. Progesterone 50 mg/g in VersaBase Cream. *US Pharm* 2017;42:47-48.
69. Labrie F, Archer D, Bouchard C, et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. *Menopause* 2009;16:897-906. doi: 10.1097/gme.0b013e31819e8930.

