Dehydroepiandrosterone for women in the peri- or postmenopausal phase (Review)

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[Intervention Review]

Dehydroepiandrosterone for women in the peri- or postmenopausal phase

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ABSTRACT

Background

During menopause a decreasing ovarian follicular response generally causes a fluctuation and eventual decrease in estrogen levels. This can lead to the development of various perimenopausal and postmenopausal symptoms (for example hot flushes, night sweats, vaginal dryness). Dehydroepiandrosterone (DHEA) is one of the main precursors of androgens, which in turn are converted to testosterone and estrogens. It is possible that the administration of DHEA may increase estrogen and testosterone levels in peri- and postmenopausal women to alleviate their symptoms and improve general wellbeing and sexual function (for example libido, dyspareunia, satisfaction). Treatment with DHEA is controversial as there is uncertainty about its effectiveness and safety. This review should clearly outline the evidence for DHEA in the treatment of menopausal symptoms and evaluate its effectiveness and safety by combining the results of randomised controlled trials.

Objectives

To assess the effectiveness and safety of administering DHEA to women with menopausal symptoms in the peri- or postmenopausal phase.

Search methods

The databases that we searched (3 June 2014) with no language restrictions applied were the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS. We also searched conference abstracts and citation lists in the ISI Web of Knowledge. Ongoing trials were searched in the trials registers. Reference lists of retrieved articles were checked.

Selection criteria

We included randomised controlled trials comparing any dose and form of DHEA by any route of administration versus any other active intervention, placebo or no treatment for a minimal treatment duration of seven days in peri- and postmenopausal women.

Data collection and analysis

Two authors independently extracted data after assessing eligibility for inclusion and quality of studies. Authors were contacted for additional information.

Main results

Twenty-eight trials with 1273 menopausal women were included in this review. Data could be extracted from 16 trials to conduct the meta-analysis. The overall quality of the studies was moderate to low with the majority of studies that were included in the meta-analysis having reasonable methodology. Compared to placebo, DHEA did not improve quality of life (standardised mean difference (SMD) 0.16, 95% confidence interval (CI) -0.03 to 0.34, P = 0.10, 8 studies, 287 women (132 from parallel and 155 from crossover trials), I^2 = 0%, moderate quality evidence; one trial of the nine that reported on this outcome was removed in a sensitivity analysis as it was judged to be at high risk of bias). DHEA was found to be associated with androgenic side effects (mainly acne) (odds ratio (OR) 3.77, 95% CI 1.36 to 10.4, P = 0.01, 5 studies, 376 women, I^2 = 10%, moderate quality evidence) when compared to placebo. No associations were found with other adverse effects. It was unclear whether DHEA affected menopausal symptoms as the results from the trials were inconsistent and could not easily be pooled to provide an overall effect due to different types of measurement (for example continuous, dichotomous, change and end scores). DHEA was found to improve sexual function (SMD 0.31, 95% CI 0.07 to 0.55, P = 0.01, 5 studies, 261 women (239 women from parallel trials and 22 women from crossover trials), I^2 = 0%; one trial judged to be at high risk of bias was removed during sensitivity analysis) compared to placebo.

There was no difference in the acne associated with DHEA when comparing studies that used oral DHEA (OR 2.16, 95% CI 0.47 to 9.96, P = 0.90, 3 studies, 136 women, I^2 = 5%, very low quality evidence) to one study that used skin application of DHEA (OR 2.74, 95% CI 0.10 to 74.87, P = 0.90, 1 study, 22 women, very low quality evidence). The effects did not differ for sexual function when studies using oral DHEA (SMD 0.11, 95% CI -0.13 to 0.35, P = 0.36, 5 studies, 340 women, I^2 = 0) were compared to a study using intravaginal DHEA (SMD 0.42, 95% CI 0.03 to 0.81, 1 study, 218 women). Test for subgroup differences: Chi^2 = 1.77, df = 1 (P = 0.18), I^2 = 43.4%. Insufficient data were available to assess quality of life and menopausal symptoms for this comparison.

There were insufficient data available to compare the effects of DHEA to hormone therapy (HT) for quality of life, menopausal symptoms, and adverse effects. No large differences in treatment effects were found for sexual function when comparing DHEA to HT (mean difference (MD) 1.26, 95% CI -0.21 to 2.73, P = 0.09, 2 studies, 41 women, I^2 = 0%).

Authors' conclusions

There is no evidence that DHEA improves quality of life but there is some evidence that it is associated with androgenic side effects. There is uncertainty whether DHEA decreases menopausal symptoms, but DHEA may slightly improve sexual function compared with placebo.

PLAIN LANGUAGE SUMMARY

Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Review question

Cochrane authors investigated whether DHEA (dehydroepiandrosterone) supplementation is safe and improves quality of life, menopausal symptoms, and sexual function for women in the peri- or postmenopausal phase.

Background

During menopause a fluctuation and eventually a decrease in estrogen levels occur. These hormonal changes can cause women to experience peri- or postmenopausal symptoms (for example flushes, night sweats, vaginal dryness). DHEA is a so-called precursor hormone which is converted by the body to estrogens and androgens. It is possible that supplementation with DHEA may increase estrogen and testosterone levels in peri- and postmenopausal women to decrease menopausal symptoms and improve general wellbeing and sexual function.

The aim of this review was to assess the effectiveness and safety of DHEA in menopausal women, comparing any dose and form of DHEA by any route of administration versus any other treatment, placebo, or no treatment for a minimum treatment duration of seven days.

Search date

The evidence was current to 3 June 2014.

Study characteristics

A total of 28 randomised controlled trials were included, with a total of 1273 menopausal women. Over 95% of the study populations were postmenopausal women. Women's ages ranged from 36 to 80 years. Treatment duration varied from one week to one year. In more than 80% of the trials DHEA was administered orally with the daily doses varying between 10 mg and 1600 mg.

Key results

We found no evidence that DHEA improves quality of life. There was some evidence that it was associated with androgenic side effects (for example acne, unwanted hair growth (hirsutism)). It was uncertain whether DHEA decreased menopausal symptoms, but DHEA may have slightly improved sexual function.

Quality of the evidence

The quality of the evidence was moderate for both quality of life and side effects. We downgraded the quality of evidence based on the lack of data on randomisation, allocation, or blinding; small study sizes overall; and limited data available.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

DHEA compared to control (placebo or no treatment)

Population: women in the peri- or postmenopausal phase
Settings:
Intervention: DHEA
Comparison: control (placebo or no treatment)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk control (placebo or no treatment)	Corresponding risk DHEA				
QoL, wellbeing (end scores) (sensitivity analysis) different scales for quality of life (QoL)	The mean QoL, wellbeing in the intervention groups was **0.16 standard mean differences higher** (-0.03 lower to 0.34 higher)			287 (132 from parallel and 155 from crossover) (8 studies)	⊕⊕⊕◯ **moderate**[1]	SMD 0.16 (-0.03 to 0.34)
Side effects (androgenic overall combined with acne) number of events	**25 per 1000**	**87 per 1000** (33 to 210)	**OR 3.77** (1.36 to 10.47)	250 (5 studies)	⊕⊕⊕◯ **moderate**[1]	
Side effects - androgenic side effects number of events	**44 per 1000**	**234 per 1000** (60 to 595)	**OR 6.57** (1.37 to 31.59)	92 (1 study)	⊕⊕◯◯ **low**[1,2]	Only 1 study for this outcome
Side effects - acne number of events	**13 per 1000**	**29 per 1000** (7 to 107)	**OR 2.26** (0.56 to 9.02)	158 (4 studies)	⊕⊕⊕◯ **moderate**[1]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded for imprecision due to wide confidence intervals
[2] Downgraded due to no other studies available for comparison of effects

BACKGROUND

Description of the condition

The menopause is said to have occurred once there is permanent cessation of menstruation. Prior to the final menstruation there is usually a gradual reduction in the frequency of menstrual periods, known as the perimenopause. Postmenopause is defined as the period of time following on from 12 months after a woman has experienced her last menstruation. During perimenopause there is a fluctuation in estrogen levels due to decreasing ovarian follicular response (Hoffman 2012; Rosen 2011; Speroff 2005). Most women become menopausal between 45 and 55 years of age, however there are also women who reach menopause at an earlier age for various reasons (for example premature ovarian insufficiency (sometimes due to chemotherapy) or bilateral oophorectomy). Menopausal women can develop a range of symptoms including vasomotor symptoms such as hot flushes and night sweats,and vaginal atrophy leading to vaginal dryness and dyspareunia, which can impact on sexual function (Genazzani 2002; Speroff 2005). Hormone therapy (HT) (estrogen alone or in combination with a progestin) is currently indicated for the treatment of menopausal symptoms. However, HT has been associated with a significant increase in the risk of various conditions including breast cancer, venous thromboembolism and stroke (Cameron 2005; Manson 2013; Marjoribanks 2012; Rossouw 2002; State-of-the-Science-Panel 2005; Taylor 2011).

Description of the intervention

Dehydroepiandrosterone (DHEA) is one of the main precursor sex steroids. DHEA is synthesized from cholesterol in the zone reticularis of the adrenal gland. It is converted to estrogens and testosterone by steroidogenic enzymes expressed in peripheral tissues such as the skeleton, breasts and ovary (Figure 1). DHEA peaks at the age of 25 years and then slowly declines to approximately 30% of the initial levels at postmenopause (Genazzani 2002; Rosen 2011; Speroff 2005). In the United States of America (USA) DHEA can be purchased without prescription but in most countries it is only available by prescription. DHEA may be administered orally, intravaginally or by alternative routes of administration (for example transdermal patches).

Figure 1. Biosynthesis of DHEA and estrogens.

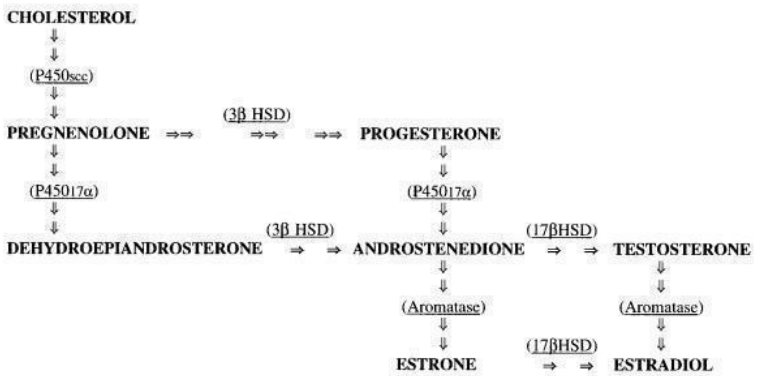


FIG. 1. Simplified diagram illustrating principle enzymes that catalyze the conversion of cholesterol to estradiol. Steroids are given in bold; enzymes are underlined and placed in parentheses (P450scc = cytochrome P450 side-chain cleavage; P45017α = cytochrome P450 17α-hydroxylase/C17-C20 lyase; HSD, hydroxysteroid dehydrogenase).

As DHEA and eventually estrogen can be synthesized from cholesterol, levels of circulating estrogen and DHEA may differ in overweight women (body mass index (BMI) > 25 kg/m^2) compared to women with a normal weight (BMI 18 to 25 kg/m^2) or underweight women (BMI < 18 kg/m^2) (Buster 2000; Miller 2002). Therefore, administered DHEA may have differing effects on women who are over- or underweight compared to those with a normal BMI.

Some inflammatory diseases (for example systemic lupus erythematosus, Sjögren syndrome) are associated with low circulating DHEA levels (Sawalha 2008). DHEA levels may correlate with disease activity, therefore DHEA supplementation may have a different effect in women with and without inflammatory disease.

How the intervention might work

Due to a fluctuation and eventual decrease in estrogen levels (estradiol in particular), women can develop various perimenopausal and postmenopausal symptoms. While the body is adjusting to these hormonal changes women may experience symptoms such as hot flushes and night sweats. Low estradiol levels can cause vaginal dryness, which may lead to diminished sexual function (Hoffman 2012; Speroff 2005). All of these symptoms may cause a decrease in the general wellbeing of peri- and postmenopausal women. It is suggested that testosterone increases sexual desire and sexual function (Davis 2008; Pluchino 2013). As DHEA is one of the main precursors of androgens, which in turn are converted to testosterone and estrogens (Figure 1) (Simpson 2003; Vanson 1996), it is possible that the administration of DHEA may increase estrogen and testosterone levels in peri- and postmenopausal women to alleviate their symptoms and improve general wellbeing (Buster 2000; Davis 2008; Mayo 2002; Pluchino 2013; Raven 2007).
The effects of DHEA on menopausal women may differ from HT because of the additional androgenic effect of DHEA (Dobs 2002; Labrie 2005). In postmenopausal women DHEA has been hypothesized to increase the incidence of breast cancer and caution is advised. However, there have been limited studies on this subject and the results of these studies are inconsistent (Morris 2001; Schwartz 2006; Shilkaitis 2005; Stoll 1999). No other serious adverse effects of DHEA have been described in the published literature. Doses of 50 mg and above have shown androgenic side effects (for example acne and increased hair growth) (Kroboth 1999; Panjari 2010).
Different effects of DHEA have been described using different routes of administration (Casson 1996). Intravaginal administration of DHEA has been reported to have a better effect on alleviating the symptom of vaginal atrophy and improving sexual function than oral administration of DHEA (Goel 2011).

Why it is important to do this review

Treatment with DHEA is controversial as there is uncertainty about its effectiveness and safety (Buster 2000; Panjari 2010; Raven 2007). Inconsistent findings have been published on the effects of DHEA in menopausal women and much of the data from clinical trials are limited by small sample sizes and short duration of treatment (Cameron 2005; Panjari 2010). This review should clearly outline the evidence for DHEA in the treatment of menopausal symptoms and evaluate its effectiveness and safety by combining the results of randomised controlled trials.

OBJECTIVES

To assess the effectiveness and safety of administering DHEA to women with menopausal symptoms in the peri- or postmenopausal phase.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (for example studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias.

Types of participants

Menopausal women: women who are going through the menopausal transition or women who are postmenopausal.
Perimenopause: the period of menopausal transition leading to a natural menopause, which ends 12 months after the final menstrual period. A specific staging can be found in the Stages of Reproductive Aging Workshop (STRAW) + 10 criteria (Harlow 2013).
Postmenopause: after one year with absence of menses and with follicle stimulating hormone (FSH) levels > 40 IU/L; also women following surgical menopause (removal of both ovaries) will be included.

Types of interventions

Trials comparing any dose and form of DHEA by any route of administration versus any other active intervention, placebo or no treatment were eligible for inclusion. Treatment duration was at least one week.

Types of outcome measures

Primary outcomes

Effectiveness

General wellbeing or quality of life (as defined by different scoring scales for example the Psychological General Well-Being Index (PGWB), the Medical Outcomes Study 36-item short form survey (SF-36), Life Satisfaction Index-Z (LSI-Z), Satisfaction with Life Scale (SWLS), Health Status Questionnaire (HSQ), Quality of Life scale (QoL), Beck Depression Inventory (BDI), Hamilton Depression Scale (HDRS)).

Any adverse effects

Adverse effects were described as they had been reported in the studies (for example events of breast cancer, cardiovascular events or androgenic side effects).

Secondary outcomes

Menopausal symptoms (for example vaginal dryness, hot flushes, night sweats) defined by different scoring scales including the Menopause Rating Scale (MRS) (Heinemann 2004), Kupperman Index (KI) and Greene Climacteric Scale (GCS).

Sexual function (for example libido, dyspareunia, satisfaction) defined by different scoring scales including the Female Sexual Function Index (FSFI), Brief Index of Sexual Functioning for Women (BISF-W), Changes in Sexual Functioning Questionnaire (CSFQ), Derogatis Interview for Sexual Functioning (DISF/DISF-SR), Golombok-Rust Inventory of Sexual Satisfaction (GRISS).

Search methods for identification of studies

We searched for all published and unpublished randomised controlled trials (RCTs) investigating the effects of DHEA in menopausal women, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator. We used EndNote for the bibliographic management of references found in the search output.

Electronic searches

(1) We searched the following electronic databases, trial registers and websites from inception to the present: Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials (Appendix 1), the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4), PsycINFO (Appendix 5) and CINAHL (Appendix 6). The MEDLINE search has been combined with the Cochrane highly sensitive search strategy for identifying RCTs which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0, chapter 6, 6.4.11). The EMBASE, PsycINFO and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

(2) Other electronic sources of trials were included (Appendix 7).

• Trial registers for ongoing and registered trials:

o www.clinicaltrials.gov (a service of the US National Institutes of Health),

o www.who.int/trialsearch/Default.aspx (World Health Organization International Clinical Trials Registry Platform search portal).

• DARE (Database of Abstracts of Reviews of Effects) in *The Cochrane Library* at http://onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html (for reference lists from relevant non-Cochrane reviews).

• Web of Knowledge at http://wokinfo.com/ (another source of trials and conference abstracts).

• OpenGrey at www.opengrey.eu/ for unpublished literature from Europe.

• LILACS database at http://regional.bvsalud.org/php/index.php?lang=en (for trials from the Portuguese and Spanish speaking world).

• PubMed and Google (for recent trials not yet indexed in MEDLINE).

Searching other resources

3. We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched relevant journals and conference abstracts that are not covered in the MDSG Specialised Register, in liaison with the Trials Search Co-ordinator.

Data collection and analysis

Selection of studies

Only RCTs studying the effectiveness and safety of DHEA administration to menopausal women were included. Data from crossover trials was included and analysed using the generic inverse variance method. The authors independently scanned the titles and abstracts of the articles retrieved by the search. Full texts of potentially eligible studies were retrieved and examined independently by the authors. The full text articles were selected according to the inclusion criteria. In the case of doubts or disagreement between the two authors, a third author was consulted to gain consensus on whether to include the trial or not. The selection process was documented with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Data extraction and management

The data obtained were extracted by two review authors. In the case of a disagreement between the two authors, a third author was consulted to achieve consensus. Data were extracted by using a data extraction form designed and pilot tested by the authors. If studies were reported in multiple publications, the data were extracted from the different publications and were combined into a single data extraction form so no data went missing. The following characteristics of included studies were included in the extraction form: methods, participants, interventions and outcomes.

Assessment of risk of bias in included studies

To assess the risk of bias in the included studies the Cochrane Collaboration's recommended tool is a domain based evaluation. We used this tool to assess the following domains and divide the assessments into high, unclear or low risk of bias.

- Selection bias (random sequence generation, allocation concealment).
- Performance bias (blinding of participants and personnel).
- Detection bias (blinding of outcome assessment).
- Attrition bias (incomplete outcome data).
- Reporting bias (selective reporting).
- Other bias (other sources of bias).

Disagreements were resolved by discussion or by a third review author. We described all judgements fully and presented the conclusions in the risk of bias table, which was incorporated into the interpretation of review findings by means of sensitivity analyses (see below). We took care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published study.

Measures of treatment effect

For dichotomous data we used the numbers of events in the control and intervention groups of each study to calculate the Mantel-Haenszel odds ratios (ORs). For continuous data, if all studies reported the same outcomes we calculated mean differences (MDs) between treatment groups. If similar outcomes were reported on different scales, we calculated the standardised mean difference (SMD). We treated ordinal data as continuous data. We calculated 95% confidence intervals (CIs) for all outcomes. Where data for the calculation of ORs or MDs were not available we used the most detailed numeric data available that facilitated similar analyses of included studies.

Unit of analysis issues

The primary analysis was done per woman randomised. Data that did not allow valid analysis were briefly summarized in an additional table and were not included in the meta-analysis. Statistical advice was sought regarding the analysis of crossover trials to facilitate the appropriate inclusion of crossover data in the meta-analysis.

Dealing with missing data

If relevant data were missing from an included study the original investigators of the trial were contacted to request the missing data from them. If the original investigator could not be contacted or did not reply, we determined whether to include or exclude the trial or only include the data that were fully available. If variance data for the primary outcome were missing (for example SD) then these were imputed from the range where possible.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Statistical heterogeneity was assessed by determining the I^2 statistic. We assumed that there was substantial heterogeneity when I^2 was calculated to be greater than 50% (Higgins 2003; Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. If there were 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies); this however was not performed.

Data synthesis

Where sufficient data were available, data were combined for the primary outcomes by using a fixed-effect model. The following comparisons were made:

1. DHEA versus control (placebo or no intervention);
2. Oral versus other routes of administration (e.g. intravaginal DHEA, transdermal patches);
3. DHEA versus HT (estrogen and progesterone in combination (ET + P) and separately (ET or P), androgen therapy or tibolone);
4. DHEA versus any other medical treatment (e.g. antidepressants or clonidine);
5. DHEA versus any other non-medical treatment (e.g. non-medical therapies such as acupuncture or complementary therapies).

Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, we conducted subgroup analyses for the primary outcomes to determine the separate evidence within the following subgroups:

1. BMI (< 18 kg/m^2, 18 to 25 kg/m^2, > 25 kg/m^2);
2. menopausal status (peri- or postmenopausal);
3. duration of the intervention ($\leq$ 6 weeks, > 6 to 26 weeks, > 26 weeks);
4. younger female (< 40 years, after bilateral oophorectomy or premature ovarian insufficiency);
5. hyposexual desire disorder or low libido;
6. inflammatory disease (e.g. systemic lupus erythematosus (SLE), Sjögren syndrome);
7. breast cancer.

In addition to the above we conducted a post hoc subgroup analysis by route of administration. Initially we had planned to look at studies comparing different routes but as there were no studies with this comparison we have opted to do a subgroup analysis to look at this evidence.

If we detected substantial heterogeneity we explored possible explanations in sensitivity analyses. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis of studies. These analyses were included and considered whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted;
3. alternative imputation strategies had been implemented;
4. the summary effect measure was relative risk (RR) rather than odds ratio (OR).

We also conducted a post hoc sensitivity analysis by removing a study at high risk of bias from the sexual function secondary outcome.

Overall quality of the body of evidence: summary of findings table

We prepared a summary of findings table using GRADEpro or Guideline Development Tool software. This table evaluated the overall quality of the body of evidence for the primary review outcomes (general wellbeing or quality of life and adverse effects) using the GRADE criteria (study limitations, consistency of effect, imprecision, indirectness and publication bias). Judgements about the quality of evidence (high, moderate or low) have been justified, documented and incorporated into the reporting of results for each outcome.

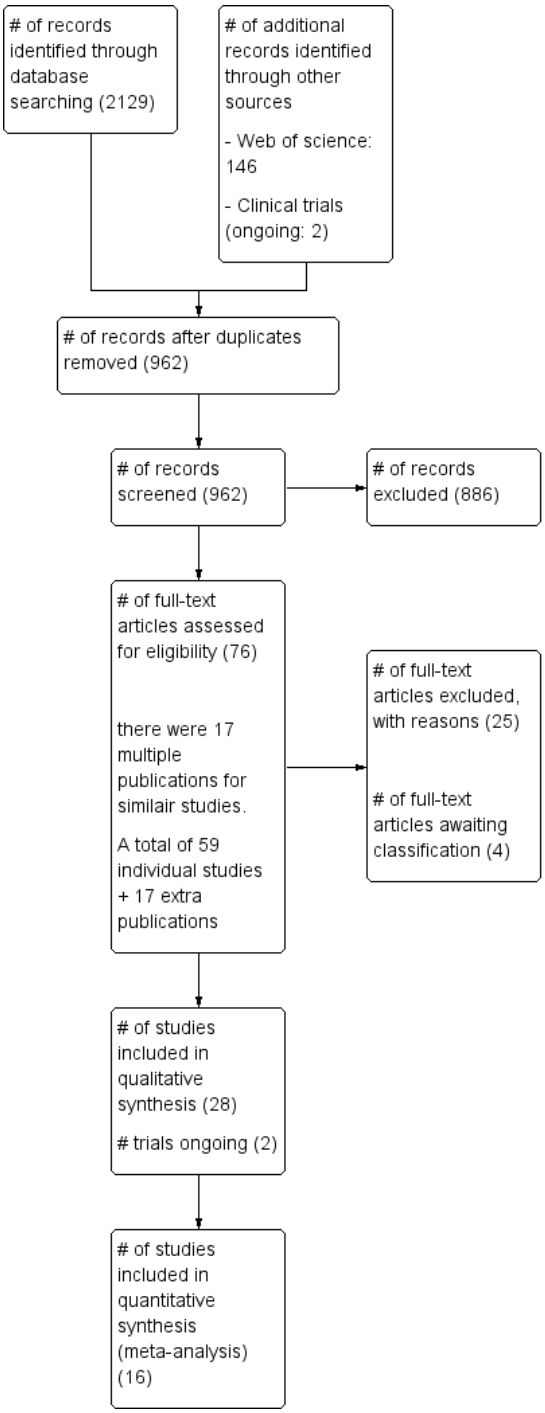
RESULTS

Description of studies

Results of the search

The search retrieved a total of 2277 titles with abstracts. These were screened to identify whether the intervention and study populations met the inclusion criteria. After this initial screening we retrieved the full text of 76 trials for assessment of eligibility and inclusion in the meta-analyses of this review. This process is reflected in the PRISMA flow chart (Figure 2). Of the 76 publications assessed, 17 were duplicate publications, resulting in a total of 59 individual trials. Of the 59 studies assessed, 28 were included, 25 excluded, 4 are awaiting classification and 2 trials were ongoing.

Figure 2. Study flow diagram.



Included studies

A total of 28 trials met the criteria for inclusion. Twelve studies were conducted in the USA (Amin 2005; Barnhart 1999; Casson 1998; Dayal 2005; Hirshman 2003; Hirshman 2004; Kratz 2000; Kritz-Silverstein 2008; Merritt 2012; Mortola 1990; Stanczyk 2009; Stangl 2010), five in Italy (Genazzani 2011; Lasco 2001; Pluchino 2008; Silvestri 2005; Stomati 1999), four in Canada (El-Alfy 2010; Labrie 1997; Labrie 2008; Labrie 2009a), one each in Australia (Panjari 2009), France (Nouveau 2008), India (Gupta 2013), Israel (Bloch 2013), Spain (Gomez-Santos 2011), Sweden (Forsblad-d'Elia 2009) and Switzerland (Finckh 2005). We were unable to retrieve the full text of one study (Amin 2005). Attempts were made to contact all authors of the included studies to obtain additional data and for clarification.

Participants

A total of 1273 women were randomised in the 28 included studies. The total study population was 1207 postmenopausal women and 66 perimenopausal women. All studies but one (Barnhart 1999) included postmenopausal women only. One study included 100 menopausal women after surgery only (Gupta 2013). Overall, the age ranged from 36 to 80 years. Women from different ethnicities were included, but not all studies reported on this. The most reported group was Caucasian women. A total of 33% of the studies included healthy menopausal women (for example without serious comorbidity, not using medication). Two studies only included women with specific comorbidities: Sjögren syndrome (Forsblad-d'Elia 2009) and fibromyalgia (Finckh 2005). Two studies included menopausal women with complaints of vaginal dryness, irritation or itching, or dyspareunia (Labrie 2008; Labrie 2009a). Two studies included women with hypoactive sexual desire disorder or low libido (Bloch 2013; Panjari 2009). One study included women with an increased cardiovascular risk (Silvestri 2005). The remaining studies did not report health status or comorbidities of the women who were included.

Study design

Nineteen parallel-designed RCTs and nine crossover-designed trials (Finckh 2005; Forsblad-d'Elia 2009; Hirshman 2003; Hirshman 2004; Labrie 1997; Merritt 2012; Mortola 1990; Silvestri 2005; Stangl 2010) were included in the review. Fifteen studies were included for (quantitative) meta-analysis.

Interventions

The following comparisons were made in the included studies: DHEA versus placebo, head-to-head (DHEA versus other active treatment) comparisons, and DHEA versus no treatment. There were a total of:

- 23 included trials comparing DHEA versus placebo (Amin 2005; Barnhart 1999; Bloch 2013; Casson 1998; Dayal 2005; El-Alfy 2010; Finckh 2005; Forsblad-d'Elia 2009; Gomez-Santos 2011; Hirshman 2003; Hirshman 2004; Kratz 2000; Kritz-Silverstein 2008; Labrie 1997; Labrie 2008; Labrie 2009a; Lasco 2001; Merritt 2012; Mortola 1990; Nouveau 2008; Panjari 2009; Stanczyk 2009; Stangl 2010);
- six included trials comparing DHEA versus HT (Dayal 2005; Genazzani 2011; Gupta 2013; Pluchino 2008; Silvestri 2005; Stomati 1999). HT included estrogen therapy (ET); conjugated equine estrogen (Dayal 2005; Gupta 2013); transdermal estradiol alone (Stomati 1999); transdermal estradiol plus oral progesterone (ET + P) (Pluchino 2008) or oral estradiol plus dihydrogesterone (ET + P) (Genazzani 2011);
- three trials compared DHEA versus tibolone (a synthetic steroid hormone with estrogen and androgens as metabolites) (Genazzani 2011; Gupta 2013; Silvestri 2005);
- one trial compared DHEA versus no treatment (Gupta 2013).

Routes of administration

- A total of 24 trials used oral administration of DHEA (Amin 2005; Barnhart 1999; Bloch 2013; Casson 1998; Dayal 2005; Finckh 2005; Forsblad-d'Elia 2009; Genazzani 2011; Gomez-Santos 2011; Gupta 2013; Hirshman 2003; Hirshman 2004; Kratz 2000; Kritz-Silverstein 2008; Lasco 2001; Merritt 2012; Mortola 1990; Panjari 2009; Pluchino 2008; Silvestri 2005; Stanczyk 2009; Stangl 2010; Stomati 1999).

Daily doses for oral administration of DHEA varied between 10 mg and 1600 mg. One trial used a daily dose of 1600 mg; 2 trials 100 mg/day; 12 trials 50 mg/day; 1 trial 40 mg/day; 5 trials 25 mg/day; 2 trials 10 mg/day.

- A total of three trials used skin application for DHEA (creams) (El-Alfy 2010; Labrie 1997; Nouveau 2008).
- Two trials used intravaginal administration of DHEA (Labrie 2008; Labrie 2009a).

Outcomes

Primary outcome: effectiveness (quality of life, general wellbeing)

Fourteen studies reported quality of life or wellbeing. The results from 11 of these trials could be included in a meta-analysis (Barnhart 1999; Bloch 2013; Dayal 2005; Finckh 2005;

Hirshman 2003; Hirshman 2004; Kritz-Silverstein 2008; Labrie 1997; Labrie 2009a; Merritt 2012; Panjari 2009; Stangl 2010); nine trials reported end scores for quality of life scales after treatment (Bloch 2013; Dayal 2005; Finckh 2005; Hirshman 2003; Hirshman 2004; Kritz-Silverstein 2008; Merritt 2012; Panjari 2009; Stangl 2010) whereas two studies reported change scores (difference between baseline and end scores) (Barnhart 1999; Labrie 2009a). Three trials (Amin 2005; Kratz 2000; Labrie 1997) investigated quality of life or wellbeing but required additional data for inclusion in the meta-analysis.

Different questionnaires were used to assess quality of life including: Beck Depression Inventory (BDI) (Hirshman 2003; Hirshman 2004; Kritz-Silverstein 2008; Merritt 2012; Stangl 2010), Symptom Checklist-90 (SCL-90) (Merritt 2012; Stangl 2010), Women's Health Questionnaire (WHQ) (Dayal 2005), Psychological General Well-Being Index (PGWBI) (Finckh 2005; Labrie 2009a; Panjari 2009), Hamilton Depression Rating Score (HAM-D) (Barnhart 1999), SmithKline Beecham Quality of Life Self Report Questionnaire (SKQOL) (Barnhart 1999), Life Satisfaction Inventory-Z (LSI-Z) (Kritz-Silverstein 2008), Short Form Health Survey (SF-36) (Kritz-Silverstein 2008), Satisfaction With Life Scale (SWLS) (Kritz-Silverstein 2008), Mental Health Inventory (MHI) (Bloch 2013) and Menopause-specific Quality of Life Questionnaire (MENQOL) (Labrie 2009a; Panjari 2009). If studies used multiple questionnaires to assess quality of life we included scores from questionnaires that were validated and used in most publications (BDI, PGWBI and SCL-90). Where these questionnaires were not used, we included the scales we judged as most representative for quality of life.

Primary outcome: adverse effects

A total of 23 studies reported on side effects. Five trials could be included for meta-analysis; four trials that used oral administration (Bloch 2013; Finckh 2005; Lasco 2001; Panjari 2009) and one trial that used intravaginal administration (Nouveau 2008). Other studies could not be included for meta-analysis for the following reasons: 10 studies reported that there were no side effects (Casson 1998; Genazzani 2011; Gomez-Santos 2011; Hirshman 2003; Hirshman 2004; Pluchino 2008; Silvestri 2005; Stanczyk 2009; Stomati 1999); one study reported there were no significant side effects (Labrie 2008), and for one study the author confirmed that there were no significant side effects found (Labrie 2009a); two studies only reported adverse effects for women discontinuing the study (Barnhart 1999; El-Alfy 2010), it was unclear whether there were any (non-significant) side effects reported for these studies; one study, which had male and female participants, did not separate side effects by sex and could therefore not be included (Kritz-Silverstein 2008); only one trial reported adverse effects for DHEA versus HT and tibolone (Gupta 2013); results from most crossover trials (Forsblad-d'Elia 2009; Labrie 1997; Mortola 1990) could not be included due to lack of data (no combined statistical tests were done for adverse effects). Attempts were made to contact all authors to request additional data.

Adverse effects that were reported for DHEA treatment but could not be included for meta-analysis due to lack of information, as described above, were as follows:

acne (Labrie 1997), hirsutism (Forsblad-d'Elia 2009; Labrie 1997; Mortola 1990), contact dermatitis (El-Alfy 2010), parasthesia and numbness of upper extremity (Barnhart 1999), depressiveness (Forsblad-d'Elia 2009), calf cramps (Forsblad-d'Elia 2009), increase in nightly dreams (Forsblad-d'Elia 2009) and dizziness (Forsblad-d'Elia 2009).

Secondary outcome: menopausal symptoms

Five studies investigated the effect of the intervention on menopausal symptoms (Barnhart 1999; Dayal 2005; Genazzani 2011; Gupta 2013; Stomati 1999). Five studies reported continuous outcomes using scales to assess menopausal symptoms, three studies reported end scores after treatment and could be combined for meta-analysis. Scales used were: Green Climacteric Scale (Genazzani 2011), Kupperman Index (Stomati 1999) and an element of the Woman's Health Questionnaire (Dayal 2005). Two studies could not be included for meta-analysis because one study reported change scores (Barnhart 1999) and the other study reported dichotomous outcomes (Gupta 2013).

Secondary outcome: sexual function

A total of eight studies investigated sexual function as an outcome (Bloch 2013; Dayal 2005; Finckh 2005; Genazzani 2011; Kritz-Silverstein 2008; Labrie 2009a; Mortola 1990; Panjari 2009). Six studies reported end scores after treatment whereas one study reported change scores (Barnhart 1999) and could therefore not be included in this meta-analysis. Different parameters were used to assess sexual function including: the McCoy Female Sexuality Score (MFSQ), Female Sexual Function Index (FSFI), Derogatis Interview for Sexual Functioning (DISF), Sabbatsberg Sexual Self-rating Scoring (SSS) and Abbreviated Sexual Function Questionnaire (ASFQ). The most used questionnaires were the MFSQ and FSFI. One study stated that no changes in sexual drive had been reported but did not use a tool to quantify sexual drive (Mortola 1990). Most studies utilised questionnaires with a total score to represent sexual function as a whole as opposed to splitting up the various elements such as libido, dyspareunia etc. Where studies did provide scores for the separate elements of sexual function, libido was chosen as the function to represent sexual function. There were not enough data from the studies to undertake meaningful subanalyses of the various elements of sexual function.

Excluded studies

We excluded 25 studies: 8 studies were excluded because they were non-randomised controlled trials (Buster 2009; Chassany 2000;

Labrie 2013; Ott 2014; Rodrigo Pegado 2012; Stoll 1999; Yasui 2012; Zouboulis 2012); 1 study was quasi-randomised (Carranza-Lira 2002); 7 studies were excluded because the study population did not meet the criteria for inclusion in this review (women were premenopausal) (Barton 2006; Hartkamp 2004; Kamath 1998; Lovas 2003; Sanchez-Guerrero 2008; Stein 2011; Virkki 2010); 1 study because the treatment duration was less than a week (Hackbert 2002); 8 studies because of different study purposes, 7 of these studies were aimed at pharmacokinetics (Bates 1995; Buster 1992; Calvo 2008; Casson 1993; Casson 1995; Caufriez 2013; Pisarska 1998) and 1 was aimed at exercise tolerance (Burger 2003) and they were unlikely to have investigated our outcomes. We attempted contacting all authors to request additional data. Unfortunately no additional data became available.

Risk of bias in included studies

See Figure 3 for a summary of the risk of bias for each individual trial and Figure 4 for a summary of each risk of bias item across all included trials.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

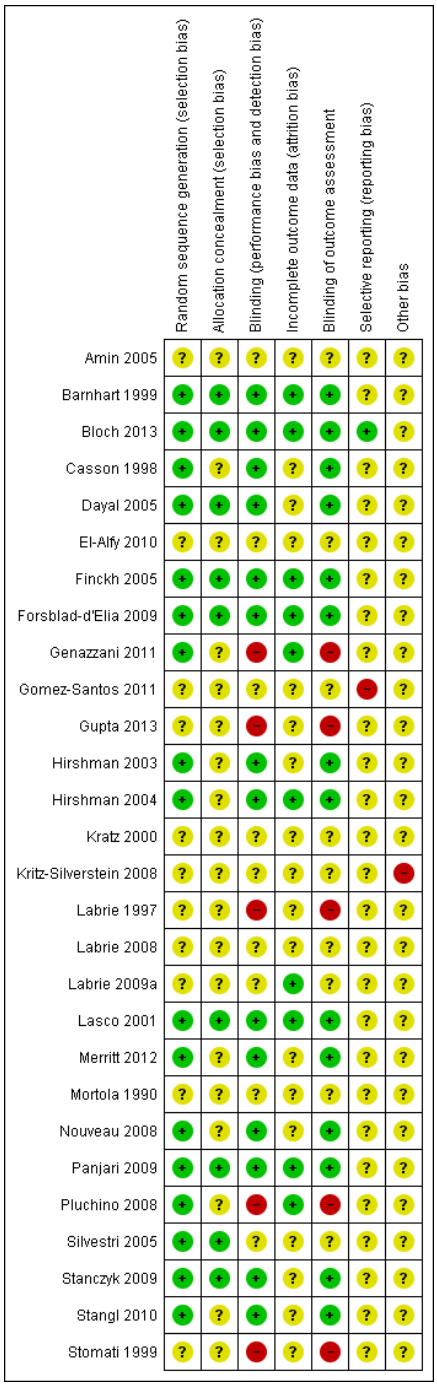
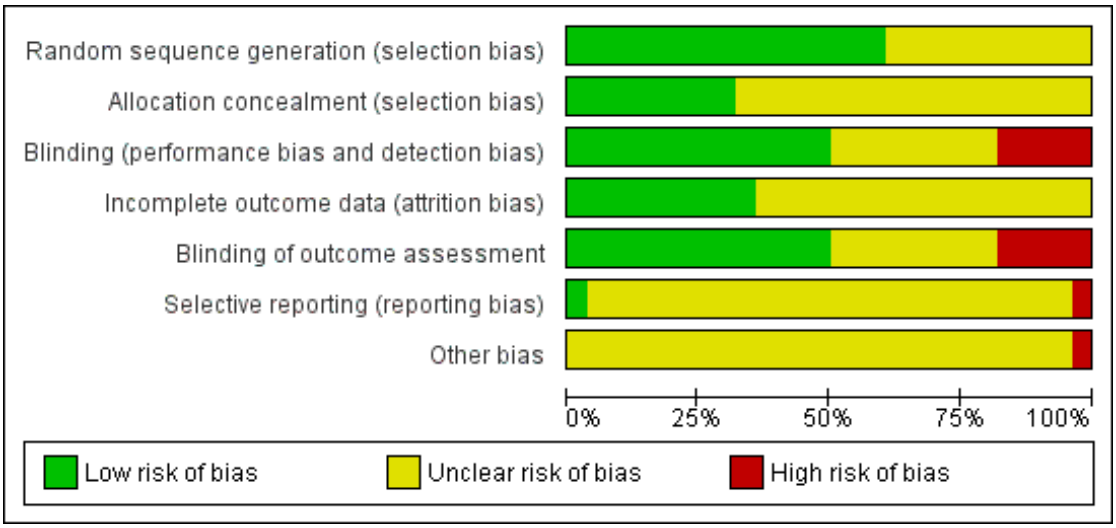


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

Of all 28 included trials, 19 were randomised with a parallel design and 9 were randomised with a crossover design. Seventeen trials described their methods of sequence generation, which were usually computer-generated, randomised block schemes or random number tables (Barnhart 1999; Bloch 2013; Casson 1998; Dayal 2005; Finckh 2005; Forsblad-d'Elia 2009; Genazzani 2011; Hirshman 2003; Hirshman 2004; Lasco 2001; Merritt 2012; Nouveau 2008; Panjari 2009; Pluchino 2008; Silvestri 2005; Stanczyk 2009; Stangl 2010). Eleven trials simply reported the trial as randomised without a description of the randomisation method (Amin 2005; El-Alfy 2010; Gomez-Santos 2011; Gupta 2013; Kratz 2000; Kritz-Silverstein 2008; Labrie 1997; Labrie 2008; Labrie 2009a; Mortola 1990; Stomati 1999).

Allocation concealment

Nine trials described their allocation concealment as a sequentially numbered list kept by the pharmacy, a non-investigator or using sealed envelopes (Barnhart 1999; Bloch 2013; Dayal 2005; Finckh 2005; Forsblad-d'Elia 2009; Lasco 2001; Panjari 2009; Silvestri 2005; Stanczyk 2009). Nineteen trials did not describe allocation concealment. Attempts were made to contact these authors to clarify allocation concealment techniques, unfortunately we were unable to retrieve the information needed.

Blinding

Blinding of participants and personnel

Fourteen studies (Barnhart 1999; Bloch 2013; Dayal 2005; Finckh 2005; Forsblad-d'Elia 2009; Genazzani 2011; Hirshman 2003; Hirshman 2004; Lasco 2001; Merritt 2012; Nouveau 2008; Panjari 2009; Stanczyk 2009; Stangl 2010) described blinding methods that we graded as low risk. Blinding in these trials was done by using treatments looking identical in appearance (for example identical looking DHEA and placebo capsules or creams). In some trials personnel were described as blinded as well, but the majority of the studies did not report on blinding personnel. Five studies (Genazzani 2011; Gupta 2013; Labrie 1997; Pluchino 2008; Stomati 1999) were graded as high risk for bias as they were not blinded. These trials compared different active treatments that were applied differently (for example transdermal patches versus oral capsules) or had different appearances. Nine studies (Amin 2005; El-Alfy 2010; Gomez-Santos 2011; Kratz

2000; Kritz-Silverstein 2008; Labrie 2008; Labrie 2009a; Mortola 1990; Silvestri 2005) did not describe their blinding process and were therefore graded as at unclear risk of bias.

Blinding of outcome assessments

If blinding was unlikely to have been broken for participants it was unlikely that the outcomes were influenced as the outcomes were generally done by self-assessment, for all outcomes. If a trial was not blinded it was likely that this may have influenced the outcomes. Therefore trials that did not use blinding were graded as high risk of bias for blinding. We judged the remaining trials as unclear as it was unclear whether blinding was done or was likely to have been broken.

Incomplete outcome data

Ten studies analysed all or most women who were randomised (> 95%) and we judged them to be at low risk of bias (Barnhart 1999; Bloch 2013; Finckh 2005; Forsblad-d'Elia 2009; Genazzani 2011; Hirshman 2004; Labrie 2009a; Lasco 2001; Panjari 2009; Pluchino 2008). Eighteen studies did not provide data on how many women completed the trial and were included for analysis and they were therefore graded as unclear.

Selective reporting

An official protocol was only available for one study, which reported all outcomes described as in the protocol (Bloch 2013). Two studies (Dayal 2005; Stangl 2010) did not report on one outcome each (daily symptom rates, SCL-90 scores) that were mentioned in their methods sections, but there was availability for other outcomes that were included and therefore overall bias was graded as unclear. For the remaining studies the official protocols were not found or retrieved but no missing data were found comparing outcomes measured in the methods sections and the results sections, we judged these studies as unclear. One study did not report the outcomes described in their study methods and had no other data available for meta-analysis and was therefore graded as high risk of bias (Gomez-Santos 2011).

Other potential sources of bias

In one study no descriptions of randomisation, allocation, blinding and attrition were reported and due to a difference in baseline scores the end scores were not reliable for both quality of life and sexual function. Due to this combination of factors the risk of bias was deemed high (Kritz-Silverstein 2008). We found no potential sources of within-study bias in the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** DHEA compared to control (placebo or no treatment) for women in the peri- or postmenopausal phase; **Summary of findings 2** Oral DHEA versus control subgrouped by differing routes of administration for women in the peri- or postmenopausal phase; **Summary of findings 3** DHEA versus HT for women in the peri- or postmenopausal phase

1. DHEA versus control

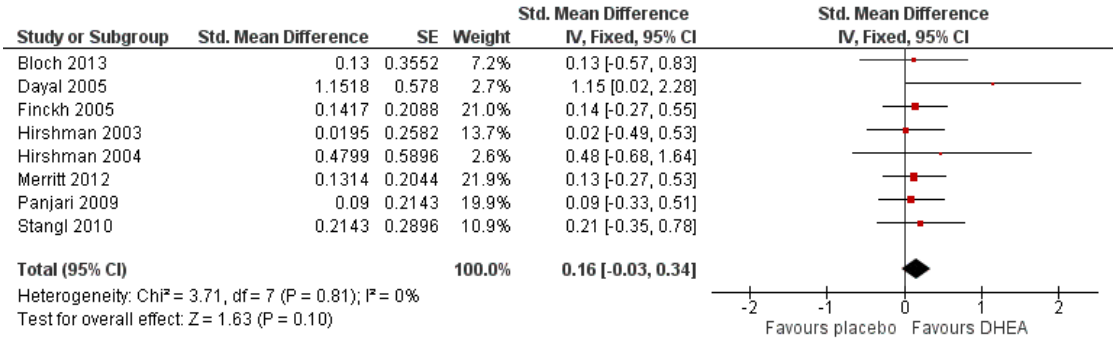
1.1 Quality of life (QoL): DHEA versus control (placebo or no treatment) (end scores)

DHEA did not significantly improve quality of life or wellbeing end scores compared to placebo (SMD -0.04, 95% CI -0.20 to 0.13, P = 0.67, 9 studies, 402 women (247 from parallel and 155 from crossover trials), I^2 = 67%) (Analysis 1.1). There were no studies that compared DHEA to no treatment for quality of life or wellbeing.

1.2 Quality of life (QoL): DHEA versus control (placebo or no treatment) (end scores) sensitivity analysis

As the I^2 value was greater than 50%, we repeated the analysis but this time we restricted eligibility to studies without a high risk of bias (SMD 0.16, 95% CI -0.03 to 0.34, P = 0.10, 8 studies, 287 women (132 from parallel and 155 from crossover trials), I^2 = 0%, moderate quality evidence) (Analysis 1.2; Figure 5). No large differences in treatment effect were found after conducting the sensitivity analysis. The heterogeneity observed in 1.1 was found to be caused by one study (Kritz-Silverstein 2008). This study showed imbalanced baseline scores and did not report information on the randomisation technique, allocation, blinding and attrition and was therefore graded as high risk of bias. We judged the end scores of this study to be unreliable as they did not represent the effect of the treatment due to the imbalanced baseline scores for quality of life. Therefore, we chose to present the result of the sensitivity analysis as the main result.

Figure 5. Forest plot of comparison: 1 DHEA versus control (placebo or no treatment), outcome: 1.2 Sensitivity analysis QoL and wellbeing (end scores).



The findings from two studies that could not be included for meta-analysis due to lack of data (no scores available) agreed with the results above (Kratz 2000; Labrie 1997). One other study that lacked data for inclusion and only had an abstract available (Amin 2005) reported a slight decrease of quality of life in the placebo group compared to DHEA treatment.

1.3 and 1.4 Quality of life (QoL): DHEA versus control - subgrouped based on low libido or hypoactive sexual desire disorder (HSDD) and treatment duration

See 'overall subgroups'.

1.5 Quality of life (QoL): DHEA versus control (placebo or no treatment) (change scores)

Two studies reported change scores (difference between baseline and end scores) (Barnhart 1999; Labrie 2009a). These could not be pooled due to a high level of heterogeneity (I^2 = 94%). Sensitivity analysis did not change this. Heterogeneity may be explained by route of administration. One study administered DHEA orally (Labrie 2009a) whereas the other study used intravaginal application (see Analysis 2.1).

1.6 Adverse effects: DHEA versus control (placebo or no treatment)

Nine studies reported there were no side effects found at all (Casson 1998; Genazzani 2011; Gomez-Santos 2011; Hirshman 2003; Hirshman 2004; Pluchino 2008; Silvestri 2005; Stanczyk 2009; Stomati 1999). For one study comparing DHEA with placebo (Labrie 2008) the author confirmed there were no significant side effects found, but it was unclear whether there were any minor adverse effects. There were no studies that compared DHEA to no treatment.

The results for androgenic side effects could only be pooled for acne and androgenic side effects (Bloch 2013; Finckh 2005; Lasco 2001; Nouveau 2008; Panjari 2009). The results showed evidence of an association with androgenic side effects (mainly acne) in 15% of the women on DHEA versus < 3% of women on placebo (OR 3.77, 95% CI 1.36 to 10.40, P = 0.01, 5 studies, 376 women, I^2 = 10%, moderate quality evidence). One study (Panjari 2009) reported on hirsutism as an androgenic side effect but was included for acne already. Therefore, this study could not be pooled for hirsutism as well due to risk of double counting participants.

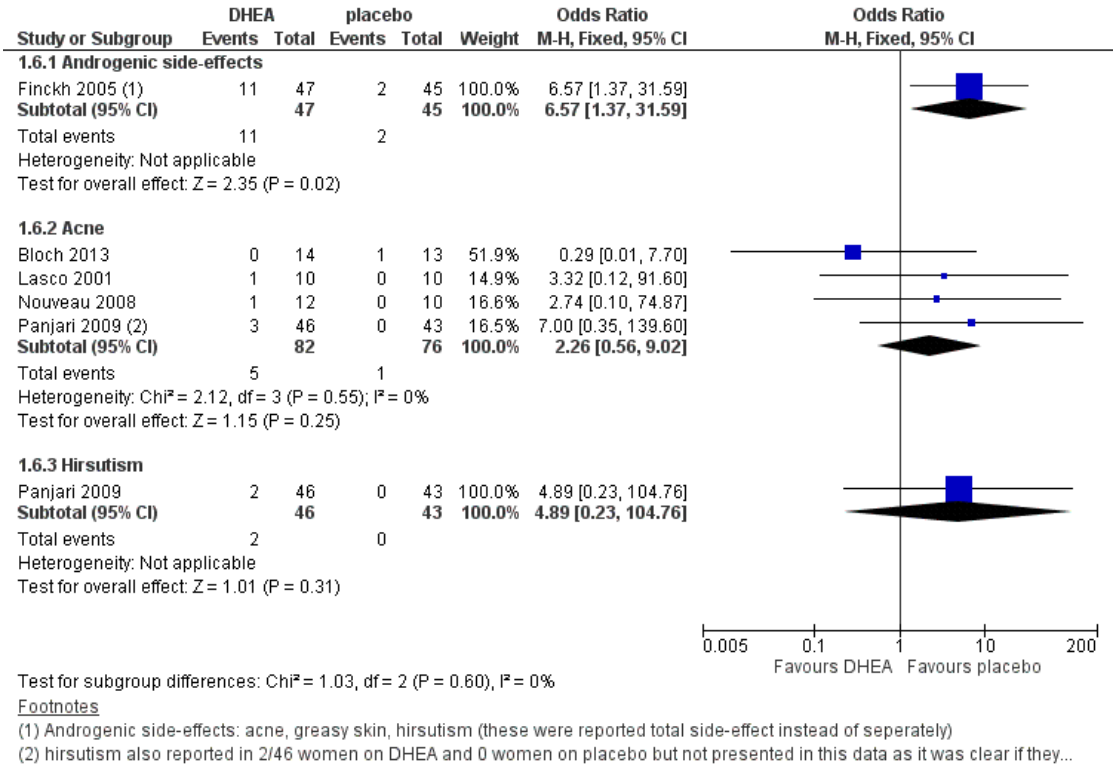
1.6.1. Androgenic side effects: DHEA versus control (placebo or no treatment)

Due to lack of data we could not combine hirsutism, acne and a greasy skin into overall 'androgenic side effects' for meta-analysis. Only one study (Finckh 2005) reported androgenic side effects as a total (including acne, greasy skin and hirsutism). Therefore a meta-analysis could not be conducted. This study showed an association between androgenic side effects and DHEA treatment.

1.6.2. Acne: DHEA versus control (placebo or no treatment)

There were no significant differences found in the frequency of acne between DHEA and placebo (OR 2.26, 95% CI 0.56 to 9.02, P = 0.25, 4 studies, 158 women, I^2 = 0%, moderate quality evidence) (Analysis 1.6; Figure 6). Two studies (Forsblad-d'Elia 2009; Labrie 1997) reported on acne as a side effect of DHEA treatment. For one study it was unclear whether this adverse effect was investigated for placebo as well (Labrie 1997) and the other study was a crossover trial which had no data available for paired tests on adverse effects (Forsblad-d'Elia 2009).

Figure 6. Forest plot of comparison: 1 DHEA versus control (placebo or no treatment), outcome: 1.6 Side effects.



1.6.3. Flushes: DHEA versus control (placebo or no treatment)

A meta-analysis could not be conducted as only one study reported sufficient data for flushes as a side effect (Bloch 2013). This study did not show an association between flushes and DHEA treatment. Data could not be pooled with other adverse effects due to the risk of double counting participants.

1.6.4. Hirsutism: DHEA versus control (placebo or no treatment)

A meta-analysis could not be conducted because only one study reported sufficient data for hirsutism as a side effect (Panjari 2009). This study did not show an association between hirsutism and DHEA treatment (OR 4.89, 95% CI 0.23 to 104.76). Data could not be pooled with other adverse effects due to the risk of double counting participants.

1.7 Adverse effects: DHEA versus control - acne subgrouped based on study duration

See 'subgroups overall'.

1.8 Menopausal symptoms: DHEA versus control (placebo or no treatment) (continuous)

Insufficient data were available to conduct a meta-analysis for DHEA versus placebo (Analysis 1.8). Two studies reported menopausal symptoms as a continuous outcome, one study (including 17 postmenopausal women) reported end scores (Dayal 2005) whereas the other study (including 66 perimenopausal women) reported change scores (Barnhart 1999). Both studies showed no decrease in menopausal symptoms for DHEA.

1.9 Menopausal symptoms: DHEA versus control (placebo or no treatment) (dichotomous)

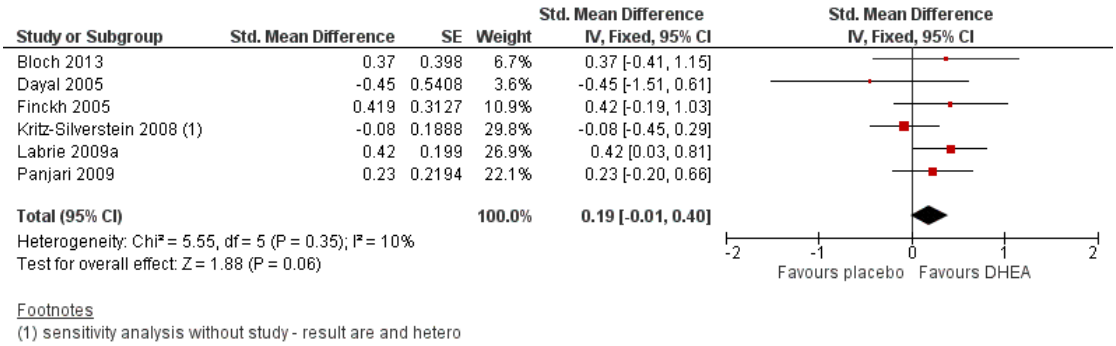
Only one study (Gupta 2013) compared DHEA versus no treatment in 50 menopausal women after surgery, therefore a meta-analysis could not be conducted. This trial showed a decrease in menopausal symptoms, for tiredness, night sweats and loss of libido. Other menopausal symptoms reported (hot flushes, insom-

nia, depression, vaginal dryness and pruritis vulvae) did not differ for the DHEA treatment and no treatment groups. This study was not blinded and this may have influenced the outcome.

1.10 Sexual function: DHEA versus control (placebo or no treatment)

DHEA may have improved sexual function (SMD 0.19, 95% CI -0.01 to 0.40, P = 0.06, 6 studies, 376 women (354 women from parallel trials and 22 women from crossover trials), I^2 = 10%) (Figure 7). However, one trial including 115 postmenopausal women (Kritz-Silverstein 2008) showed imbalanced baseline scores and did not report information on the randomisation technique, allocation, blinding and attrition and was therefore graded as at high risk of bias. Therefore, we chose to conduct a sensitivity analysis.

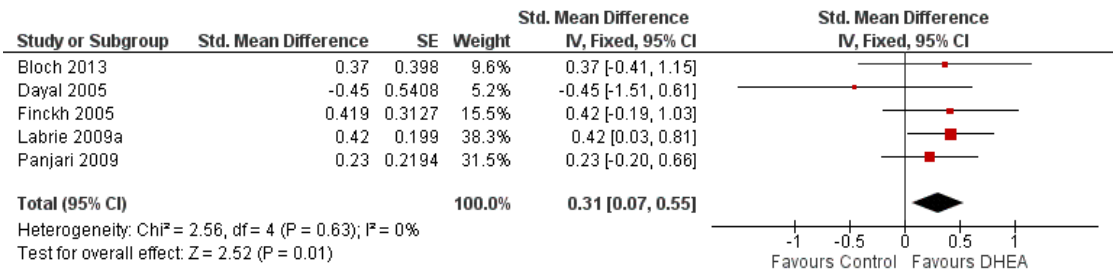
Figure 7. Forest plot of comparison: 1 DHEA versus control (placebo or no treatment), outcome: 1.11 Sexual function (end scores).



1.11 Sexual function: DHEA versus control (placebo or no treatment) sensitivity analysis

After conducting a post hoc sensitivity analysis excluding one study with a high risk of bias, DHEA was shown to be significantly more effective on sexual function compared to placebo (SMD 0.31, 95% CI 0.07 to 0.55, P = 0.01, 5 studies, 261 women (239 women from parallel trials and 22 women from crossover trials), I^2 = 0%, moderate quality of evidence) (Figure 8). We judged the end scores of the excluded study to be unreliable as it did not represent the effect of the treatment found in this study due to imbalanced baseline scores for sexual function. Therefore, we choose to present the results of the sensitivity analysis as the main results. The reported improvement in sexual function was minimal although significant and may not be clinically significant as, for example, an SMD of 0.31 would translate to a change of only 2.3 points on the Sabbatsberg-Sexual Self rating (SSS) scale, which ranges from 0 to 84. No studies investigated DHEA versus no treatment.

Figure 8. Forest plot of comparison: 1 DHEA versus control (placebo or no treatment), outcome: 1.11 Sexual function (end scores) (sensitivity analysis).



2. Oral versus other routes of administration (e.g. intravaginal, transdermal patches)

No studies directly compared oral DHEA versus other routes of administration. Therefore, we chose to compare studies using oral DHEA versus studies that used different routes of administration of DHEA.

2.1 Quality of life (QoL): oral DHEA versus control subgrouped by route of administration (e.g. intravaginal, transdermal patches)

There were insufficient data available to conduct a meta-analysis for effectiveness based on route of administration (Analysis 2.1). Only one trial (including 107 postmenopausal women) that investigated a different route of administration than oral administration (intravaginal application) reported QoL change scores (Labrie 2009a); and only one trial studied oral DHEA and reported change scores for QoL (Barnhart 1999). The I^2 value was greater than 50% (94%) therefore these studies could not be pooled for meta-analysis. Intravaginal administration showed a beneficial effect for DHEA on QoL, whereas the other study did not show any differences in treatment effect.

2.2 Adverse effects: oral DHEA versus control subgrouped by route of administration (e.g. intravaginal DHEA, transdermal patches)

No evidence was found that acne was associated more with oral application of DHEA (OR 2.16, 95% CI 0.47 to 9.96, P = 0,90, 3 studies, 136 women, I^2 = 5%, very low quality of evidence) than with skin application of DHEA (OR 2.74, 95% CI 0.10 to 74.87, P = 0,90, 1 study, 22 women, very low quality evidence), with the test for subgroup differences showing Chi^2 = 0.02 (df = 1, P = 0.90, I^2 = 0%) (Analysis 2.2). The studies that investigated intravaginal administration did not report on acne whereas acne (or other skin effects) was reported in all trials investigating skin application (El-Alfy 2010; Labrie 1997; Nouveau 2008) and acne was reported in five more trials investigating oral administration (Bloch 2013; Finckh 2005; Forsblad-d'Elia 2009; Lasco 2001; Panjari 2009). Data for different side effects could not be matched for an overall analysis because it was unclear if these side effects were reported in the same or different participants. This information was needed to create a proper analysis.

2.3 Menopausal symptoms: oral DHEA versus control subgrouped by route of administration (e.g. intravaginal DHEA, transdermal patches)

There were no trials using other routes of administration that investigated menopausal symptoms as an outcome.

2.4 Sexual function: oral DHEA versus control subgrouped by route of administration (e.g. intravaginal DHEA, transdermal patches)

No significant differences were found between studies looking at oral administration (SMD 0.11, 95% CI -0.13 to 0.35, P = 0.36, 5 studies, 340 women, I^2 = 0) and a study using intravaginal DHEA (SMD 0.42, 95% CI 0.03 to 0.81, 1 study, 218 women) with the test for subgroup differences showing Chi^2 = 1.77 (df = 1, P = 0.18, I^2 = 43.4%) (Analysis 2.4). One trial including 115 postmenopausal women (Kritz-Silverstein 2008) reported imbalanced baseline scores and was therefore graded as high risk of bias. Therefore, we repeated the analysis but this time without studies with a high risk of bias. The results from the sensitivity analysis also revealed no evidence for differences between oral administration and intravaginal application of DHEA on sexual function (SMD 0.31, 95% CI 0.07 to 0.55, P = 0.88, 5 studies, 261 women (of which 107 received intravaginal DHEA or placebo capsules, 239 women were from parallel trials and 22 women from crossover trials), I^2 = 0%).

3. DHEA versus hormone therapy (HT) (estrogen and progesterone in combination and separately, androgen therapy or tibolone)

3.1 Quality of life (QoL): DHEA versus hormone therapy (HT) (estrogen and progesterone in combination and separately, androgen therapy or tibolone)

Only one study reported results of DHEA versus estrogen (Dayal 2005). Therefore a meta-analysis could not be conducted. This study found no significant difference between treatment effects of DHEA compared to HT on QoL.

There were no trials that compared DHEA to a different form of HT for QoL or wellbeing.

3.2 Adverse effects: DHEA versus hormone therapy (HT) (dichotomous)

See 3.4.

3.3 Menopausal symptoms: DHEA versus hormone therapy (HT)

It was unclear whether DHEA differed from HT in effects on menopausal symptoms. Two studies were included for the meta-analysis of estrogen therapy (ET) (Genazzani 2011; Stomati 1999). The I^2 value was greater than 50% (74%) therefore these studies could not be pooled for meta-analysis (Analysis 3.3). One study showed a small beneficial effect on menopausal symptoms for HT (Stomati 1999) whereas the other showed a more beneficial effect for DHEA (Genazzani 2011).

One study that investigated dichotomous outcomes (type and frequency of menopausal symptoms) and could therefore not be included in the meta-analysis showed no significant differences in frequency of various menopausal symptoms between treatments (Gupta 2013). One trial showed no difference in frequency of menopausal symptoms between treatments (Gupta 2013). One study (Genazzani 2011) including 24 postmenopausal women investigated continuous outcomes and showed a slightly beneficial effect for DHEA.

3.4 Sexual function: DHEA versus HT

DHEA did not significantly improve sexual function compared to HT. Two trials (Dayal 2005; Genazzani 2011) compared the effects of DHEA and HT on sexual function. There was no significant difference found between these treatments in these two trials (MD 1.26, 95% CI -0.21 to 2.73, P = 0.09, 2 studies, 41 women, I^2 = 0%) (Analysis 3.4).

Only one trial investigated DHEA versus tibolone (Genazzani 2011). This trial included 24 postmenopausal women and reported a beneficial effect for DHEA compared to tibolone for improvement of sexual function.

4. Adverse effects: DHEA versus HT (dichotomous)

Only one study (Gupta 2013) that included menopausal women after surgery (n = 25 received DHEA, n = 25 received conjugated equine estrogen (CEE) as ET, n = 25 received tibolone) investigated this outcome and therefore a meta-analysis could not be conducted. This study showed an increase in reported acne and hair loss with DHEA compared to ET.

The same study (Gupta 2013) investigated DHEA versus tibolone, but other studies had investigated this comparison for adverse effects only and a meta-analysis could not be conducted. This study showed little evidence on adverse effects associated with any of the treatments. The study reported more acne and hair loss with DHEA compared to tibolone treatment.

5. DHEA versus any other medical treatment (e.g. antidepressants or clonidine)

No trials were found for this comparison on any of following outcomes: QoL or wellbeing, adverse effects, menopausal symptoms or sexual function.

6. DHEA versus any other non-medical treatment (e.g. non-medical therapies such as acupuncture or complementary therapies)

No trials were found for this comparison on any of following outcomes: QoL or wellbeing, adverse effects, menopausal symptoms or sexual function.

Overall subgroups

There were no or insufficient data available to create subgroups for BMI, menopausal status, younger females, inflammatory disease and breast cancer patients. Trials that were conducted measuring low libido or HSDD could not be pooled due to high heterogeneity (I^2 = 67%). The heterogeneity was caused by one study with imbalanced baseline scores and a high risk of bias overall (Kritz-Silverstein 2008). Therefore, we repeated the analysis but this time without such studies with high risk of bias. This analysis showed no differences in outcomes for any comparison. Subgroup analyses that were conducted for treatment duration did not show any differences in the outcomes for any comparison.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Oral DHEA versus control subgrouped by routes of administration for women in the peri- or postmenopausal phase***

Population: Women in the peri- or postmenopausal phase
Settings:
Intervention: DHEA versus placebo (via different routes of administration)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	DHEA				
QoL, wellbeing (change scores) - oral administration	The mean QoL, wellbeing in the intervention groups was **0.05 standard deviations lower** (0.53 lower to 0.43 higher)			66 (1 study)	⊕◯◯◯ **very low**[1]	SMD -0.05 (-0.53 to 0.43)
QoL, wellbeing (change scores) - intravaginal application	The mean QoL/wellbeing in the intervention groups was **1.23 standard deviations higher** (0.82 to 1.65 higher)			107 (1 study)	⊕◯◯◯ **very low**[1,2,3]	SMD 1.23 (0.82 to 1.65)
Side effects: acne - skin application	**0 per 1000**	**126per 1000**** (52 to 798)	**OR 2.74** (0.1 to 74.87)	22 (1 study)	⊕◯◯◯ **very low**[1,2]	
Side effects: acne - oral administration	**15 per 1000**	**32 per 1000** (7 to 133)	**OR 2.16** (0.47 to 9.96)	136 (3 studies)	⊕◯◯◯ **very low**[4,5]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio
**As the assumed risk in the control group for acne is 0 it is impossible to calculate the comparative risks so we have assumed a risk of 0.05 in the placebo group.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

*** *There were no studies that compared different routes of treatment within the study. We have separated studies based on their route of administration and compared the results from these studies with each other.*

[1] Downgraded due to no other studies available for comparison of effects
[2] Downgraded due to limited information on randomisation, allocation and blinding
[3] Included subjects with complaints of vaginal dryness, itching, dyspareunia
[4] Results are controversial (2/3 studies favour placebo, whereas 1 favours DHEA)
[5] Downgraded due to large CIs

DHEA versus HT for women in the peri- or postmenopausal phase

Population: Women in the peri- or postmenopausal phase
Settings:
Intervention: DHEA versus HT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HT	DHEA				
QoL, general wellbeing DHEA versus ET	The mean QoL in the intervention groups was **1.63 higher** (2.25 lower to 5.52 higher)			17 (1 study)	⊕○○○ **very low**[1]	
QoL, general wellbeing DHEA versus ET + P	No studies available					
QoL, general wellbeing DHEA versus tibolone	No studies available					
Acne DHEA versus ET	**0 per 1000**	**472 per 1000** (45 to 943)	**OR 17** (0.9 to 320.37)	50 (1 study)	⊕○○○ **very low**[1]	
Acne DHEA versus tibolone	**0 per 1000**	**472 per 1000**** (45 to 944)	**OR 17** (0.9 to 320.37)	50 (1 study)	⊕○○○ **very low**[1,2]	
Acne DHEA versus ET + P	No studies available					

*The basis for the **assumed risk is** the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**As the assumed risk in the control group for acne is 0 it is impossible to calculate the comparative risks so we have assumed a risk of 0.05 in the placebo group.

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded due to no other studies available for comparison of effects
[2] Study was not blinded - may have influenced the outcomes

DISCUSSION

Summary of main results

In this review there is no evidence from the pooled sensitivity analysis of eight studies that DHEA is associated with an improvement in quality of life or wellbeing compared to placebo, hormone therapy (HT) or no treatment. The quality of the studies in this analysis that reported quality of life was considered to be moderate (see summary of findings for the main comparison). DHEA treatment was associated with more androgenic side effects, in 15% of women (predominantly acne) compared to less than 3% in the control group. The quality of this evidence was deemed to be moderate. Nine studies reported that no side effects were found.

Limited data were available on the use of DHEA for menopausal symptoms. The results of studies that reported on menopausal symptoms were difficult to pool as their outcomes were inconsistently reported (for example as dichotomous or continuous outcomes, change and end scores) and this may explain the inconsistent results. Two studies reported beneficial effects on menopausal symptoms for DHEA (versus no treatment and HT), however one study was unblinded and may therefore have been biased. More research is needed to see whether DHEA effectively decreases menopausal symptoms.

The pooled studies reported that sexual function was potentially improved with DHEA compared to placebo. After conducting a sensitivity analysis, excluding one trial with a high risk of bias, this result changed to evidence of slightly improved sexual function with DHEA compared to placebo. However, treatment to obtain this slight improvement would not be clinically justified in light of the possible side effects with this treatment. Even though DHEA might slightly improve sexual function compared to placebo there was no evidence that DHEA improved sexual function more than HT. However, the results for DHEA versus HT were based on just two trials with small sample sizes and large confidence intervals and therefore the quality of the evidence was low.

Overall completeness and applicability of evidence

Of the 28 trials included in this review, 24 trials investigated DHEA versus control (placebo or no treatment) and 14 provided data on quality of life or wellbeing. All trials included postmenopausal women except for one trial that included perimenopausal women. The majority found evidence that DHEA does not improve quality of life. This level of evidence was judged to be moderate. No clear associations were found for any side effects, however the data for side effects were limited. In order to investigate the effects of DHEA and the risk of developing breast cancer, follow-up should be for at least five years after the time of daily intake of DHEA.

The evidence from this review showed that DHEA did improve sexual function. However the trials were small or moderate in size and therefore more research is needed to investigate this outcome as the evidence might change. Different questionnaires were used to assess quality of life, menopausal symptoms and sexual function; in some cases these were assessed as part of a wider evaluation. Where studies did provide scores for the separate elements of sexual function, libido was chosen as the function to represent this outcome.

Three different routes of administration were reported, oral administration, intravaginal and skin application. The majority of the trials used oral administration of DHEA. There were not enough data available to investigate any differences in treatment effects for quality of life and menopausal symptoms. There were no studies that directly compared the different routes of administration of DHEA. Therefore we have separated the studies based on the route of administration and pooled these results to see if there were any differences between the different routes. No differences were found between oral administration and intravaginal application for sexual function. However only one study reported this outcome using intravaginal application, therefore the quality of the evidence is low. No differences were found for acne as an adverse effect. Again, the data were limited and the evidence is graded low.

Five out of 28 trials investigated DHEA versus HT. Not enough data were available to assess the comparative effect on quality of life. No evidence was found that DHEA improves sexual function compared to HT. Only two small trials were included and the quality of the evidence was low. Further research is needed to investigate this outcome. For menopausal symptoms, we could not pool any data and further research is needed. There were no studies for inclusion that compared DHEA to any other medical treatments or non-medical treatments.

Quality of the evidence

The overall quality of the evidence for most outcomes was moderate or low. We downgraded the quality of the evidence to moderate for the main outcomes, mainly due to risk of bias and imprecision (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). Not all trials described their randomisation technique or methods used to conceal allocation. Overall, study sizes were small and confidence intervals varied from medium to wide. We were unable to quantify the effect of publication bias due to the small numbers of studies for any one outcome. It is possible that studies investigated our outcomes but found no treatment effect and therefore did not publish their findings.

Potential biases in the review process

If studies had a pharmacological intervention and did not report our outcomes we attempted to contact the authors for additional information. In cases where these attempts were unsuccessful, we judged these studies as either likely or unlikely to have investigated our outcomes and excluded them if they were judged to be unlikely to have investigated the outcomes. This might have introduced a slight bias in the study selection. Changes to the protocol have been made (please see Differences between protocol and review). None of the changes were made as a result of the findings of the included studies but were made to improve the structure of the review.

Agreements and disagreements with other studies or reviews

No evidence was found for improvement of quality of life in menopausal women. These findings are in agreement with findings from one other systematic review (Grimley Evans 2006) and one literature review (Panjari 2010). We found that androgenic side effects (mainly acne) were associated with DHEA. DHEA was reported to be associated with androgenic side effects in other descriptive reviews as well (Cameron 2005; Kroboth 1999; Panjari 2010). The effects of DHEA on menopausal symptoms were conflicting, and little literature is available on DHEA treatment for menopausal symptoms. One literature review stated that DHEA did not affect perimenopausal symptoms (Cameron 2005). Thus far it is still unclear whether DHEA may have a beneficial effect on menopausal symptoms. Evidence for a slight beneficial effect of DHEA on sexual function was found in menopausal women, whereas other descriptive reviews reported little or no evidence of this (Buvat 2003; Cameron 2005; Panjari 2010; Sparke 2002). The studies included in our review were consistent overall in their findings, however the studies were small and more research is needed to investigate whether DHEA does truly improve sexual function. Publication bias may have played a part in causing these results as there may be studies that did not find an improvement in sexual function and have not published their findings.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review are mainly based on the effects of DHEA in postmenopausal women. DHEA was associated with a beneficial effect on sexual function compared with placebo, however this was based on a sensitivity analysis after one study with a high risk of bias was excluded and the quality of evidence is moderate. Effects of DHEA on peri- and postmenopausal symptoms are unclear as the reported results were inconsistent. No evidence was found for improvement of quality of life using DHEA. No serious side effects have been reported thus far with daily use of DHEA dosages up to 1600 mg/day (90% of the studies administered a daily dose of $\leq$ 50mg/day) with a maximum treatment duration of one year. However, DHEA was found to be associated with androgenic side effects, compared to placebo and HT, of which acne was the most commonly reported.

Implications for research

DHEA treatment does not have a beneficial effect on quality of life. Even though the data have been limited by small studies, the results for quality of life have been consistent overall. Further research into the effects of DHEA on menopausal symptoms is desirable as there were limited data available to evaluate whether DHEA treatment could decrease menopausal symptoms. To evaluate the effects of DHEA on sexual function in menopausal women further research is desirable as the results of this review have shown that there is evidence for beneficial effects in sexual function for women using DHEA treatment but the results are limited by small sample sizes and few studies. New trials should use adequate randomisation and allocation techniques and should be blinded (double-blinding preferred).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amin 2005

Methods	Design: Randomised, controlled, parallel trial Country: USA
Participants	Study population: N = 22 postmenopausal women with low endogenous DHEA-S levels (DHEA N = 11, control N = 11) Exclusion: smokers and use of HRT
Interventions	1. Oral micronized DHEA 40 mg 2. Placebo Treatment duration: daily for 1 year
Outcomes	Cognitive or psychological function (using LSI-A, among other assessments)
Notes	HRT = hormone replacement therapy LSI-A = Life Satisfaction Index-A Only abstract available. No full report found or available. Tried contacting the authors, unsuccessfully The abstract states the following: "in the LSI-A, the placebo group showed a slight decrease in scores over time when compared to the treatment group (P = 0.04)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be 'double-blind'. However also states "the treatment group was given a 40 mg daily dose of oral micronized DHEA for one year, with monthly dose titration by an unblinded investigator to maintain levels of DHEA-S between 300 and 450 microgram/dL."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	Outcomes may have been influenced if blinding was broken

Amin 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No full text nor official protocol available
Other bias	Unclear risk	Unclear

Barnhart 1999

Methods	Design: single centre, randomised, controlled, parallel trial Country: USA
Participants	Study population: N = 66 perimenopausal women (DHEA N = 33, control N = 33) Age: 48.8 ± 2 (DHEA) and 48.3 ± 3 (control) (overall age ranged between 45 and 55 years) Race: 82% Caucasian, 15% African American, and 2% Asian Inclusion: perimenopausal women with symptoms of fatigue, lack of energy, anxiety, tension, irritability, depression, insomnia, forgetfulness, concentration difficulties, decreased libido, or global reports of a decreased sense of wellbeing Exclusion: contra-indication to hormonal replacement therapy; exposure to an injectable or implantable sex steroid within 6 months (including estrogen replacement or DHEA supplementation) or a systemic steroid within 90 days of treatment; used antidepressants or antianxiolytics, or both; current diagnosis of major psychiatric disorder, diabetes mellitus, hypercholesterolemia or cardiovascular disease; abnormal renal or liver function
Interventions	1. Oral DHEA 50 mg 2. Identical placebo Treatment duration: daily for 3 months
Outcomes	Serum endocrine profiles, lipid parameters, Quality of Life (e.g. Ham-D and SKQOL), perimenopausal symptoms, adverse effects
Notes	Age is expressed as mean ± SD Ham-D = Hamilton Depression Rating Scale SKQOL = SmithKline Beecham Quality of Life Self Report Questionnaire Three women discontinued the study because of adverse events: one developed a rash, one complained of abdominal pain and fatigue (both randomised to placebo) and one reported paresthesia and numbness of an upper extremity (randomized to DHEA). Three additional women withdrew consent during the study period Intention-to-treat analysis of all 66 women was conducted using the last available data carried to the end of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Retrieved after contacting authors: "random number generation conducted by investigational pharmacy"

Barnhart 1999 (*Continued*)

Allocation concealment (selection bias)	Low risk	Retrieved after contacting authors: "block randomization conducted by investigational pharmacy."
Blinding (performance bias and detection bias) All outcomes	Low risk	"To receive a daily capsule of 50 mg DHEA, or identical placebo capsule for 3 months"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Because dropout was small (9%) and balanced, the primary analysis was conducted for those who completed the trial"
Blinding of outcome assessment	Low risk	**"**perimenopausal symptoms were evaluated by both validated subject and clinician-administered assessments"
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found
Other bias	Unclear risk	Funding by Bristol Myer Squibb Clinical Research Award and a grant from the University of Pennsylvania Research Foundaton, Delaware affiliate of the American Heart Association

Bloch 2013

Methods	Design: single centre, randomised, controlled, parallel study Country: Israel
Participants	Study population: N = 48, postmenopausal women (n = 27 of which DHEA (n = 14) and control (n = 13)) and men (n = 21) Stratification was done for postmenopausal women. The following information was based on postmenopausal women Age: 52.2 ± 6.3 (control) and 55.8 ± 3.7 years (DHEA) Inclusion: age between 45 and 65 years. All women were postmenopausal (at least one year of amenorrhoea); meet DSM-IV HSDD (hypo-active sexual desire disorder) criteria by the Structured Clinical Interview for DSM-IV Axis I Disorders Exclusion: any psychiatric diagnoses of psychosis, current major depression or dysthymia; drug or alcohol abuse; major systemic illness or hypogonadism; antidepressant, hormone replacement therapy or androgen treatment; breast, ovary or uterine cancer and first degree breast cancer in women; no failed trial with DHEA
Interventions	1. Oral DHEA 100 mg (50 mg twice a day) 2. Placebo - dummy pills, identical in appearance to the active pills Treatment duration: daily for 6 weeks
Outcomes	Sexual function (using DISF, FSFI), wellbeing (MHI), side effects and hormone serum levels

Bloch 2013 (*Continued*)

Notes	Age and BMI are expressed as mean ± SD DISF = Derogatis interview for Sexual Functioning FSFI = Female Sexual Function Index MHI = Mental Health Inventory 16 women were included in intention-to-treat analysis (13 in each arm), 1 was excluded because of non-compliancy (1 woman did not complete the full trial, due to lack of motivation) Side effects reported at week 6 were: hot flushes (3 women, 2 on DHEA and 1 on placebo), and acne (1 woman on placebo)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random patient serial numbers with active vs placebo ratio of 1:1 were generated and randomly assigned to eligible patients"
Allocation concealment (selection bias)	Low risk	Information retrieved after contacting the author: "All packaging of medication and randomization was done at the hospital's pharmacy and allocation was done by myself and a research assistant who then gave the medication to the treating physician who was blinded to the treatment condition."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both physicians and research assistants were blinded to the treatment condition" "The placebo group received dummy pills daily, identical in appearance to the active pills, according to the same protocol as the active group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were addressed
Blinding of outcome assessment	Low risk	"The interviewer and manager of the patients (LA) is a certified senior gynecologist and sexual therapist who discussed the diagnosis for each case with the psychiatrist (MB). Both physicians and research assistants were blinded to the treatment condition."
Selective reporting (reporting bias)	Low risk	Study is registered at clinicaltrials.gov (http://clinicaltrials.gov/show/NCT00916396). All outcomes have been reported

Bloch 2013 (*Continued*)

Other bias	Unclear risk	Unclear

Casson 1998

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: USA
Participants	Study population: n = 13 postmenopausal women Inclusion: healthy postmenopausal non-smokers with serum DHEAS levels of < 125 μg/dL Exclusion: the subjects were screened for thyroid or liver disease
Interventions	1. Oral micronized DHEA tablet of 25 mg 2. Identical wax vehicle excipient placebo tablet Treatment duration: once daily for 6 months
Outcomes	Serum steroid levels; growth hormone levels; serum lipoproteins; metabolic, immune and morphometric indices and safety profile
Notes	No detectable side effects were seen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by a nurse from a computer-generated random number table."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	It states it is 'double blinded', placebo and DHEA tablets were identical, however no further description of blinding personnel, likely to be blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Low risk	Blinding unlikely to have been influenced
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Dayal 2005

Methods	Design: single centre, randomised, 4-armed parallel trial (included both a head-to-head and placebo-controlled comparison) Country: USA Setting: Univerisity of Pennsylvania Medical Center (UPMC) Study period: February 1999 through February 2001
Participants	Study population: N = 50 (32 randomised) (n = 12 (DHEA), n = 5 (ET), n = 9 (DHEA + ET), n = 6 (placebo) Age: between 44 and 70 years (mean 56.6) Race: 78% white Inclusion: study participants were menopausal women, with a history of no menstrual cycle for at least one year or at least six months of amenorrhea with a documented follicle-stimulating hormone (FSH) level > 40 mIU/ml. These subjects had no exposure to hormone therapy (specifically estrogen therapy (ET) or DHEA supplementation) for at least 60 days prior to enrollment, had a normal Pap smear and mammogram within the last year, and had normal liver transaminase levels, renal function, total cholesterol, and triglyceride (TG) levels Exclusion: women were excluded if they had any contraindication to ET (known or suspected cancer of the breast, endometrial hyperplasia/carcinoma, undiagnosed vaginal bleeding, active thromboembolic disorders, or history of cerebrovascular disease, coronary artery disease (CAD), or myocardial infarction (MI)), a current diagnosis of diabetes mellitus, uncontrolled hypertension, abnormal liver or renal function, major psychiatric disorder (major depression, bipolar disorder, psychotic disorder, drug addiction), or any contraindication to the use of MRI (pacemaker, magnetic aneurysm clip, severe claustrophobia)
Interventions	1. Oral DHEA 50 mg 2. Conjugated quine estrogen (CEE) 0.625 mg 3. Oral DHEA 50 mg + CEE 0.625 mg 4. Placebo treatment duration: daily for 12 weeks
Outcomes	Muscle size, strength, quality of life and vasomotor symptoms (using the the Women's Health Questionnaire) and lipids
Notes	To be able to include the results for quality of life in our meta-analysis, end scores were calculated based on the percentage change scores that were reported at the end of the trial, the standard deviation of the baseline measurements was then used for these calculated end scores as well Only the DHEA, CEE and placebo group in our meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"subjects were randomized, into four treatment groups using a computerized program generating random numbers"

Dayal 2005 (*Continued*)

Allocation concealment (selection bias)	Low risk	Random number generation conducted by investigational pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	After contacting author: "Capsules were constructed by investigational pharmacy and were identical for active and placebo."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts. Author could not provide additional data
Blinding of outcome assessment	Low risk	Self-assessment, blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	For the duration of the study, patients were instructed to rate symptoms on the daily symptom rating (DSR) calendar at home. The results were not reported. Official protocol not found or available. Author could not provide additional data
Other bias	Unclear risk	Unclear

El-Alfy 2010

Methods	Design: randomised, placebo-controlled, parallel trial Country: Canada
Participants	Study population: N = 75 (placebo (n = 15), 0.1% DHEA (n = 15), 0.3% DHEA (n = 15), 1% DHEA (n = 15), 2% (n = 15) Age: 60 to 65 years Race or ethnicity: white women BMI: the body mass index of all women ranged between 18.5 and 29.0 kg/m² Inclusion: healthy postmenopausal white women. All subjects had a medical history, complete physical examination, serum biochemistry as well as full blood analysis Exclusion: none of the women had received any hormone replacement therapy for at least the last 6 months before the beginning of the study. No subject was under treatment with lipid or glucose lowering agents. There was no active or history of thromboembolic disease, significant metabolic or endocrine disease and no clinically significant gastrointestinal, liver or gallbladder disease. None of the women suffered from migraine or diabetes mellitus not controlled by conventional therapy. None had received corticosteroid treatment within the last 6 weeks before the beginning of the study or treatment with b-carotenoid, retinoic acid, hydroquinone or a-hydroxyacid (including inhaled, topical or oral). None of the women suffered hypertension ≥160 95 mmHg or not controlled by standard therapy, confirmed clinically significant depression or confirmed severe psychiatric disturbance. None of the women had received any experimental drug within the 30 days before the screening visit or any previous treatment with androgens or anabolic steroids within the 6 months before the screening visit. None had received

	any antidepressant, antipsychotic or analgesic within 30 days before the beginning of the study. Smoking any number of cigarettes was an exclusion criterion. There was no former or present narcotic addiction or alcoholism. There was no hepatic or renal impairment or condition known to affect drug or steroid metabolism
Interventions	1. 0.1% DHEA cream 2. 0.3% DHEA cream 3. 1% DHEA cream 4. 2% DHEA cream 5. 0% DHEA cream (placebo) Treatment duration: 3.0 mL applied on the face, arms, back of hands, upper chest and right thigh twice daily for 13 weeks
Outcomes	Skin responses, side effects
Notes	Reasons for withdrawals reported as: 0.1% DHEA:1 at week 4 (skin problems), 1 week 8 (keratosis) 0.3% DHEA - none 1% DHEA - 5 at week 7 (serum levels DHEA above 11 ng/mL-1) 2% DHEA - 1 at day 6 (contact dermatitis), 1 at week 4 (contact dermatitis), 10 at week 7 (serum levels DHEA above 11 ng/mL-1) *For meta-analysis we will only use the 2% results of the 2% DHEA group*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Each subject was randomly assigned to one of the following five groups: 0% DHEA (placebo), 01% DHEA, 03% DHEA, 1% DHEA and 2% DHEA." Randomisation technique not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Likely that the creams were identical in appearance, however not described. Does not state 'blinded' in report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for withdrawals are stated
Blinding of outcome assessment	Unclear risk	If not blinded or blinding was broken it may have influenced the outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found

Other bias	Unclear risk	Funding was provided by Endorecherche Inc

Finckh 2005

Methods	Design: single centre, randomised, placebo-controlled, crossover trial Country: Switzerland Recruitment: patients were recruited through the Swiss Association of Fibromyalgic Patients and the Rheumatology Clinic of University Hospital of Vaud (CHUV)
Participants	Study population: N = 52 postmenopausal women Age: 59.2 ± 8.8 (DHEA), 58.7 ± 9.7 (placebo), range 36 to 83 years Race: all caucasian Inclusion: confirmed fibromyalgia by 1990 American College of Rheumatology classification criteria 21; female gender; postmenopausal status (or bilateral oophorectomy); and ability to complete questionnaires Exclusion: current treatment with narcoleptics or steroids; history of sex hormone-responsive cancer (breast, ovarian, or endometrial cancer); advanced liver, kidney, or heart disease; history of chronic inflammatory disease (i.e. rheumatoid arthritis, SLE)
Interventions	1. Oral DHEA capsule 50 mg 2. Identical placebo containing mannitol Treatment duration: daily for 3 months. Washout period for 1 month
Outcomes	Quality of life (by using PGWBI), regional pain, sexual function (by using McCoy FSQ), cognitive function, side effects
Notes	Age expressed as mean ± SD PGWBI = Psychological General Well Being Index McCoy FSQ = McCoy Female Sexuality Questionnaire For meta-analysis the scores have been used as they have been analysed in the paper (for analysis of QoL 47 women were included for DHEA and 45 for placebo and for sexual function 20 women were included for DHEA and 22 for placebo) Androgenic side effects were more common with DHEA: 11 patients (25%) complained of greasy skin, acne, or increased growth of body hair, compared to 2 patients (4%) with placebo (P = 0.023, McNemar)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were randomized to either DHEA or placebo in balanced blocks of 6 by means of a random number generator"
Allocation concealment (selection bias)	Low risk	"The medication codes were kept in sealed envelopes until the end of the study." *Author confirmed these envelopes were opaque*

Blinding (performance bias and detection bias) All outcomes	Low risk	"Both patients and investigators were blinded to the treatment group assignment" "Study capsules of DHEA 50 mg and identical opaque placebo capsules containing mannitol were produced and packet by the hospital's pharmacy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data addressed
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken - self-assessed outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Forsblad-d'Elia 2009

Methods	Design: randomised, placebo-controlled, crossover trial Country: Sweden Setting: patients were identified from registers in two rheumatology clinics in Western Sweden
Participants	Study population: N = 23 postmenopausal women (initial DHEA (n = 13), initial placebo (n = 10) Age: 60.7 ± 8.6 years Inclusion: postmenopausal women with primary Sjogren's syndrome and subnormal levels of DHEA-S Exclusion: patients with a history of breast cancer or uterine cancer, previous stroke or known diathesis for thrombosis, difficult acne, or a significant liver disease and patients with changes in treatment with disease-modifying antirheumatic drugs (DMARD) or changes in low dose glucocorticosteroids taken for Sjogren's during the previous 3 months were excluded from the trial, as were patients taking more than 10 mg prednisolone per day
Interventions	1. Oral DHEA 50 mg 2. Placebo Treatment duration: daily for 4 months, washout period 1 month, crossover
Outcomes	Serum levels of DHEA and 12 of its metabolites, sex steroids and disease related variables, side effects
Notes	Author was contacted to retrieve more information on side effects. Two patients experienced adverse events resulting in discontinuation of the study drug: one woman due to increase in nightly calf cramps during DHEA, and the other to a suspected transitory is-

	chemic attack during placebo. Other reported adverse events during DHEA period were acne and increase in perspiration, increase in nightly dreams, depressiveness, dizziness and hirsutism. During placebo period gastric pain and headache Age is expressed as mean ± SD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were randomized to either DHEA or placebo in balanced blocks of 6 by means of a random number generator"
Allocation concealment (selection bias)	Low risk	"The medication codes were kept in sealed envelopes until the end of the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both patients and investigators were blinded to the treatment group assignment" "Study capsules of DHEA 50 mg and identical opaque placebo capsules containing mannitol were produced and packet by the hospital's pharmacy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data have been addressed
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken and self-administered questionnaires
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Study population had subnormal DHEA levels

Genazzani 2011

Methods	Design: multicentre, randomised controlled (head-to-head), parallel trial Country: Italy Recruitment: patients referred from the Department of Obstetrics and Gynecology, University of Pisa and from the Francavilla Fontana Hospital 'D. Camberlingo'
Participants	Study population: N = 48 (DHEA (n = 12), estradiol + dihydrogesterone (n = 12), tibolone (n = 12) and oral vitamin D (n = 12) Age: between 50 and 60 years (mean age 54.5 ± 3.3 years). Placebo 55.2 ± 2.9, DHEA 53.5 ± 3.8, HRT 54.5 ± 2.9, tibolone 53.8 ± 3.1 Inclusion: healthy postmenopausal women who reported climacteric symptoms. All subjects had natural menopause and were healthy. Natural menopause was defined retro-

	spectively after 12 consecutive months without natural menstrual periods, and age at menopause was the age at last menstruation. Exclusion: previous or current endocrine disorders, such as thyroid or adrenal dysfunction or altered prolactin circulating levels; treatment of cardiovascular diseases, hypertension or psychiatric disorders; previous or current hormone treatments known to influence endocrine function; smoking; presence of any kind of pelvic and breast disease
Interventions	1. Oral DHEA 10 mg daily 2. Oral estradiol (1 mg) plus dihydrogesterone (5 mg) (HRT) (Femoston Conti®, Solvay Pharma SpA) 3. Oral tibolone tablet (2.5 mg) (Livial®, Schering-Plough SpA) 4. Oral vitamin D (400 IU) plus calcium carbonate (1250 mg) (women refused HRT) *- this group was not randomised and thus not included in our meta-analysis*
Outcomes	Climacteric symptoms (by using the Green scale) and female sexuality (by using the MFSQ)
Notes	Age expressed as means ± SD MFSQ = McCoy Female Sexuality Questionnaire All those patients who enrolled in the study completed the follow up without any adverse effects The scores ± SD for climacteric symptoms were estimated from reported figures. For tibolone the scores were estimated for sexual function from reported figures as well. Unfortunately we were unable to retrieve the exact scores ± SD from the authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization, in three hormone-treated groups, was made using a computer-generated block, random-permutation procedure."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All those patients who enrolled in the study completed the follow-up, without any adverse events."
Blinding of outcome assessment	High risk	"self-administered questionnaires" but not blinded
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available

Other bias	Unclear risk	Received funding from 'Nil'. No conflicts of interest were declared

Gomez-Santos 2011

Methods	Design: randomised, placebo-controlled, parallel trial Country: Spain Recruitment: subjects were recruited from the "Health Centre of Espinardo"
Participants	Study population: n = 61 postmenopausal women (DHEA (n = 41), control (n = 20)) Age: 52 ± 1 (DHEA) and 51 ± 2 (control) BMI: 33.08 ± 0.62 (DHEA) and 34.45 ± 1.19 (control) Inclusion criteria were as follows: overweight women, obesity type I or II and without changes in their normal diet during treatment. Menopause was defined as the date of the last menses followed by 12 months of no menses and a follicle-stimulating hormone level higher than 30 mIU/mL Exclusion criteria were as follows: women following any special diet, steroid or thyroid medication, or diagnosed with diabetes mellitus, chronic renal failure, hepatic disease or cancer
Interventions	1. Oral DHEA-S 100 mg 2. Placebo Treatment duration: once daily for 3 months
Outcomes	Human plasma fatty acid profile in plasma, side effects
Notes	"Potential adverse effects were monitored by means of interviews, physical examinations and standard laboratory tests". Side effects not reported in results section

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly divided into two groups: 'placebo' receiving a placebo and 'treated' (n = 41, 52 ± 1 y)"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be "Double-blind", but no description of how blinding done was obtained
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	Unclear if blinding could have been broken it may have influenced the outcomes

Gomez-Santos 2011 (*Continued*)

Selective reporting (reporting bias)	High risk	"Potential adverse effects were monitored by means of interviews, physical examinations and standard laboratory tests". Unfortunately the results of this monitoring have not been reported and we were unsuccessful in contacting the authors
Other bias	Unclear risk	Unclear

Gupta 2013

Methods	Design: single centre, randomised, controlled comparative trial Country: India Setting: Department of Obstetrics and Gynaecology of SMS Medical College Jaipur
Participants	Study population: N = 100 surgically menopausal women (premarin (CEE (n = 25), DHEA (n = 25), tIbolone (n = 25), no treatment (n = 25) Inclusion: asymptomatic patients as regards to menopausal symptoms who had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy 3 days earlier Exclusion: patients with carcinoma endometrium, liver, breast or ovary, endocrine diseases (diabetes, thyroid), cardiovascular, cerebrovascular and peripheral vascular disease, hypertension, severe renal disease or liver disease, bone metabolic diseases, obesity (BMI (30), smokers and alcoholics, and with history of thrombophlebitis or immunosuppressive drugs were excluded from the study
Interventions	1. Oral Premarin (CEE 0.625 mg) 2. Tibofem (2.5 mg) 3. Evandra (DHEA 25 mg) All daily 4. No treatment Treatment duration: 12 months
Outcomes	Menopausal symptoms, lipid variables, bone densitometry, side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation technique unclear. "The control and cases were allotted to their respective groups randomly"
Allocation concealment (selection bias)	Unclear risk	Not described

Gupta 2013 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Stopping rate for HRT was 2 % at 1 month and another 2 % at 6 months" - unclear if these subjects were included or excluded in analysis
Blinding of outcome assessment	High risk	Self-assessment, but not blinded, likely to influence the outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Hirshman 2003

Methods	Design: single centre, randomised, placebo-controlled, crossover trial Country: USA Recruitment: all participants were volunteers recruited by newspaper advertisement, and they were paid USD 100 for their participation
Participants	Study population: N = 30 postmenopausal women Age: 54.3 ± 7.07 (range 39 to 70) years Race: Caucasian (n = 27), African-American (n = 3) Inclusion: the participants met the World Health Organization's criteria for postmenopausal status of 1 year's absence of menses or bilateral oophorectomy that preceded the study by one year Exclusion: potential participants were excluded from the study if they reported a serious mental illness (e.g., schizophrenia, depression), a serious physical illness within the last year (e.g. cardiac arrest), a history of drug or alcohol abuse, or current use of benzodiazepines, narcotics, or amphetamines
Interventions	1. Oral DHEA pills of 50 mg (2 pills of 25 mg) 2. Lactose tablets (placebo) Treatment duration: daily for 4 weeks directly followed by crossover (no washout period)
Outcomes	Recognition memory decision process, effect on depression (by measuring BDI), adverse effects
Notes	Age expressed as mean ± SD BDI = Beck depression inventory. No adverse events were reported Additional data were requested, unfortunately not obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hirshman 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Information retrieved after contacting author: "our within participant designs uses a crossover design; our between participant designs uses a simple block randomization"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"Daily doses of DHEA and placebo consisted of two white pills." Information retrieved after contacting author: "placebo and drug identical in both studies"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	After contacting author "no attrition due to side effects in either study". Unclear if there were any other withdrawals
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	"All participants were volunteers recruited by newspaper advertisement, and they were paid $100 for their participation" No washout period

Hirshman 2004

Methods	Design: single centre, randomised, placebo-controlled crossover trial Country: USA Recruitment: all subjects were volunteers recruited by newspaper advertisement and were paid USD 300.00 for their participation
Participants	Study population: n = 6 postmenopausal women Age: 58.5 ± 2.16 (range 53 to 68) years BMI: 30.2 ± 1.47 (range 26.7 to 33.7) Inclusion: Participants met the World Health Organization's criteria for postmenopausal status of 1 year's absence of menses (four participants) or bilateral oophorectomy that preceded the study by at least 1 year (two participants). None of the participants were using hormone replacement therapy. All women enrolled had a normal mammogram within the prior year and a normal Pap smear within the prior 3 years Exclusion: Potential participants were excluded from the study if a preenrollment medical evaluation revealed contraindications to DHEA treatment (i.e. personal history of, or active, breast cancer or other estrogen- dependent neoplasms, acute liver disease, undiagnosed vaginal bleeding, uncontrolled hypertension, history of clotting disorders, and history of psychiatric or cognitive disorders). Women whose preenrollment assays of DHEAS, estradiol, or testosterone were above the normal postmenopausal women's range were excluded. Similarly, subjects whose body mass index (BMI) exceeded 35

	were excluded. Current use of a range of substances that influence cognition (e.g. amphetamines, benzodiazepines, narcotics, and nicotine) was also grounds for exclusion
Interventions	1. Oral DHEA capsule 50 mg 2. Placebo (consisted of lactose) identical to DHEA capsule Treatment duration: daily for 4 weeks, 1 week washout, followed by crossover treatment
Outcomes	Androgen blood levels, effects on cognition (performance on recognition memory, perceptual identification, digit span memory, visual attentional vigilance)
Notes	Age and BMI expressed as mean ± SEM

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects who met the eligibility requirements were randomly assigned (in a block-randomization scheme) to receive DHEA (placebo) in the first 4-week period and placebo (DHEA) in the second 4-week period"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"DHEA was compounded by Belmar Pharmaceutical (Lakewood, CO). Oral placebos consisted of lactose and were presented in capsules identical to those containing hormones." "All investigators and participants were blind to treatment status."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were addressed. "Four women, who underwent screening, were not allowed to participate in the study. The reasons for exclusion of these women were (1) detection of a pituitary tumor based on preenrollment blood work; (2) detection of psychiatric illness based on preenrollment psychiatric testing; (3) BMI and hormonal values that exceeded the selection criteria; and (4) failure to have a Pap smear in the preceding 3 years."
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	Protocol not found or available

Hirshman 2004 (*Continued*)

Other bias	Unclear risk	Unclear

Kratz 2000

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: USA Enrolment: subjects were recruited through the Los Angeles County Women's Hospital and through the USC Alzheimer's Disease Research Center. Nineteen subjects were recruited through advertisement and word of mouth from the Los Angeles County Women's Hospital. One subject was recruited after mailing a letter which described the study to potential subjects identified from the USC Alzheimer's Disease Research Center (ADRC)
Participants	Study population: N = 20 postmenopausal women (n = 11 (DHEA), n = 9 (placebo) Age: 52.1 ± 4.3 (DHEA), 52.3 ± 5.9 (placebo) Race: 70% was hispanic (n = 14), 30% caucasian (n = 6) Inclusion: aged between 46 and 66 years. All subjects received a general physical examination and a pelvic examination to ensure that they were postmenopausal and in good health Exclusion: hormone therapy or suffering from any severe psychopathology
Interventions	1. Oral DHEA 25 mg 2. Placebo Treatment duration: daily for 6 months
Outcomes	Neuropsychological tests (including BDI, SCL-90), hormone assays
Notes	Age is expressed as mean ± SD Lack of data to include in meta-analysis SCL-90 = Symptom Check List-90 BDI = Beck Depression Index

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "randomized". Randomisation technique is not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States "double-blind", blinding is not further described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts

Kratz 2000 (*Continued*)

Blinding of outcome assessment	Unclear risk	If blinding was broken it may have influenced the outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Kritz-Silverstein 2008

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: USA Enrolment: between june 2001 and May 2001
Participants	Study population: N = 225 (men n = 110, women n = 115 of which n = 57 (DHEA), n = 58 (placebo) Study stratified for women. Only information and the results of these women will be used in our review Age: 68.9 ± 8.1 (DHEA) and 68.5 ± 6.7 (placebo), range 55 to 85 years Inclusion: participants were healthy, community dwelling individuals, not selected on the basis of DHEA level at entry. Non-smokers and not currently using HRT
Interventions	1. Oral DHEA 50 mg 2. Placebo Treatment duration: daily for 12 months
Outcomes	Cognitive function (including Beck Depression Inventory, Life Satisfaction index-Z, Satisfaction With Life Scale, SF-36 and Female Sexual Function Index), serum hormone levels
Notes	Age is expressed as mean ± SD BDI = Beck Depression Inventory LSI-Z = Life Satisfaction Index-Z SWLS = Satisfaction With Life Scale SF- 36 = Medical Outcomes Study 36-item Short Form Survey FSFI = Female Sexual Function Index Scores of FSFI and BDI have been used in meta-analysis. Baseline scores for BDI 5.3 ± 0.6 (DHEA) versus 4.3 ± 0.6 (placebo) and FSFI 13.3 ± 1.6 (DHEA) versus 16.4 ± 1.6 (placebo) were unbalanced, whereas end scores were improved more in the DHEA group (4.0 ± 0.6) versus placebo (3.5 ± 0.6) for both outcomes. Unfortunately we do not have a standard deviation for the 'change scores' from baseline to end scores, and end scores alone not representative for this study. Therefore this study has been excluded for sensitivity analysis Study reports adverse effects, but unfortunately it does not report adverse effects for men and women separately therefore we were unable to include these adverse effects in our review

Risk of bias

Kritz-Silverstein 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation technique unknown. Baseline measurements are unbalanced between both treatment groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States double-blind, however blinding is not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	If blinding was broken it may have influenced the outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	High risk	Baseline measurements are unbalanced between both treatment groups for both quality of life and sexual function outcomes which caused the end scores not to be representative "The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this manuscript. Funding was received from National Institutes of Aging Grant AG018339 and National Center for Research Resources Grant M01RR 00827"

Labrie 1997

Methods	Design: randomised, placebo-controlled, crossover trial Country: Canada
Participants	Study population: n = 14 healthy postmenopausal women Age: 60 to 70 years (mean 63.7 ± 0.76) Inclusion: non-smokers. All women had a medical history, complete physical examination, and serum biochemistry profile including lipids, complete blood count, urinalysis, and detailed serum hormone determinations during the screening phase of the protocol Exclusion: HRT or medication known to act on bone metabolism during the previous 5 years. Suffering from an endocrine disorder. Taking lipid- or glucose-lowering agents

Labrie 1997 (*Continued*)

Interventions	1. DHEA 10% cream 2. Placebo Treatment duration: placebo treatment for 6 months preceding or following 12 months DHEA therapy
Outcomes	Secondary effects (adverse effects, wellbeing), bone density, vaginal cytology, endometrial histology, sebum secretion, serum hormone-binding globulin (HBG)
Notes	Paper states there were two women with an increase in facial hair growth on the upper lip, and two other women developed slight acne during treatment. Wellbeing and increase in energy were reported in 80% of women. Unclear if this was measured in all women or only in the active treatment group. Not enough data to include in quantative meta-analysis. Author was contacted, unfortunately we were unable to retrieve additional data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Author of study assumes it was "properly randomized", however randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded, treatment durations of placebo and DHEA are not equal
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	High risk	Not blinded, outcomes may have been influenced
Selective reporting (reporting bias)	Unclear risk	Offical protocol not available or found
Other bias	Unclear risk	Unclear

Labrie 2008

Methods	Design: single centre, randomised, placebo-controlled trial Country: Canada
Participants	Study population: n = 40 postmenopausal women (n = 10 (DHEA 1.8%), n = 10 (DHEA 1.0%), n = 10 (DHEA 0.5%), n = 10 (DHEA 0.0%) Age: between 40 and 75 years BMI: between 18.5 and 29.9 kg/m^2 Inclusion: no menses for $\geq$ 1 year or; FSH levels $\geq$ 40 IU/L (within 60 days prior to day

Labrie 2008 (*Continued*)

	1) in women with no menses ≥ 6 but < 12 months or hysterectomized women who were premenopausal at the time of hysterectomy, with unknown ovarian status or six weeks or more following bilateral oophorectomy with or without hysterectomy. Women who have self-identified at least one moderate to severe of the following symptoms: vaginal dryness, vaginal and/or vulvar irritation or itching, dysuria; vaginal pain associated with sexual activity; vaginal bleeding associated with sexual activity. Women between 40 and 75 years of age. Women having a low maturation index (no greater part of guidance than 5% of superficial cells on vaginal smear). Women having a vaginal pH above 5. Normal mammography within 24 months of enrolment. Normal breast examination. No former or present narcotic addiction or alcoholism. Bodyweight within 18.5 and 29. 9 of ideal bodyweight according to body mass index (BMI) (WHO). No hepatic or renal impairment or condition known to affect drug or steroid metabolism. Normal baseline hematology, clinical chemistry, and urinalysis. Endometrial thickness of 4mmor less at transvaginal ultrasonography Exclusion: undiagnosed abnormal genital bleeding, previous diagnosis of cancer, except skin cancer (non-melanoma), history of hormone-dependant cancer (uterus, breast), active or history of thromboembolic disease, significant metabolic or endocrine disease, clinically significant gastrointestinal, liver or gallbladder disease, migraine headache, diabetes mellitus not controlled by conventional therapy, eczema, cutaneous allergies. significant complication on previous hormonal therapy., use of hormonal implants < 6 months prior to study entry. Any oral estrogen, progestin or DHEA exposure (HRT and vaginal creams) or use of natural estrogens (phytoestrogens) or herbal products to treat postmenopausal symptoms in the 8 weeks prior to baseline assessments
Interventions	1. Intravaginal ovule of 1.8% (23.4 mg) DHEA 2. Intravaginal ovule of 1.0% (13 mg) DHEA 3. Intravaginal ovule of 1.8% (6.5 mg) DHEA 4. Intravaginal ovule of 0% (0 mg) DHEA (placebo) Treatment duration: daily for 1 week
Outcomes	Serum DHEA and its metabolites, safety profile
Notes	"This was a 7-day study only aimed at pharmacokinetics. Safety is always studied but no significant side effect has been observed"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "randomized", randomisation technique not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States "double-blinded", unclear how blinding was done

Labrie 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	Unclear as blinding is not clear and the outcomes may have been influenced if the study was not blinded
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found
Other bias	Unclear risk	Unclear

Labrie 2009a

Methods	Design: multicentre, randomised, placebo-controlled, parallel trial Country: Canada
Participants	Study population: n = 218 postmenopausal women (216 were included for ITT analysis) (n = 53 (0.0% DHEA), n = 53 (0.25% DHEA), n = 56 (0.5% DHEA) and n = 54 (1. 0% DHEA) The following information will only include the 0.0% (placebo) and 1.0% DHEA groups Age: median 58, range 49 to 70 years (placebo) and median 59, range 46 to 69 years(1. 0% DHEA) BMI: between 18.5 and 35 kg/m² Inclusion: no menses for at least 1 year; or FSH levels of 40 mIU/mL or more (within 60 d before day 1) in women with no menses for 6 months or more but less than 12 months, or hysterectomized women who were premenopausal at the time of hysterectomy; or 6 weeks or more (of screening visit) after bilateral oophorectomy. Women having self-identified at least one moderate to severe of the following symptoms: vaginal dryness (none, mild, moderate, or severe); vaginal, vulvar irritation or itching (none, mild, moderate, or severe) ; vaginal pain associated with sexual activity (none, mild, moderate, or severe) Exclusion: undiagnosed abnormal genital bleeding. Previous diagnosis of cancer, except skin cancer (nonmelanoma). Endometrial hyperplasia at biopsy performed at screening or endometrial cancer. Active or history of thromboembolic disease. Significant metabolic or endocrine disease. Clinically significant gastrointestinal, liver, or gallbladder disease. Recurrent migraine headache not controlled by conventional therapy. Diabetes mellitus not controlled by conventional therapy. Significant complication on previous hormone therapy. Use of estrogen-alone injectable drug therapy or progestin implant within 3 months before study entry (screening visit)
Interventions	1. intravaginal ovule containing 0,25% DHEA = 3.25 mg DHEA 2. intravaginal ovule containing 0,5% DHEA = 6.5 mg DHEA 3. intravaginal ovule containing 1.0% DHEA = 13 mg DHEA 4. intravaginal ovule containing 0,0% DHEA = 0 mg DHEA Treatment duration: all daily for 12 weeks The DHEA ovules or suppositories (Vaginorm) containing Prasterone in a lipophilic base were manufactured by Recipharm (Karlskoga, Sweden)
Outcomes	Signs and symptoms of vaginal atrophy (e.g. quality of life, libido, sexual dysfunction)

Labrie 2009a (*Continued*)

Notes	We have only included the results of 0.0% (placebo) and 1.0% (highest DHEA dose) treatment for meta-analysis Study reported a significant decrease in severity scores of vaginal dryness and pain at sexual activity. For pain at sexual activity there was a decrease of 58% for the 1.0% DHEA cream, with P < 0.0001 versus placebo. And for vaginal dryness there was a decrease of 68% for the 1.0% DHEA cream, with P = 0.014 versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" but unclear which randomisation technique has been used
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States double blind, but blinding process is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	**"**The percentage of participants who had questionnaire data through the final visit at week 12 was greater than 90% in each treatment group for each questionnaire; therefore, it was not considered necessary to conduct a completers or evaluable population analysis in addition to the ITT analysis." "Missing values for any endpoint for a participant were replaced using a last value"
Blinding of outcome assessment	Unclear risk	Unclear as blinding is not clear and the outcomes may have been influenced if the study was not blinded
Selective reporting (reporting bias)	Unclear risk	Original protocol not found or available
Other bias	Unclear risk	Unclear

Lasco 2001

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: Italy
Participants	Study population: n = 20 postmenopausal women (n = 10 (DHEA) and n = 10 (placebo) Age: 57.6 ± 4.5 (DHEA) and 55.1 ± 3.8 (placebo) years BMI: 23.7 ± 3.2 (DHEA) and 23.9 ± 3.1 (placebo) kg/m² Inclusion: 20 healthy adrenal-androgen deficient postmenopausal women (serum DHEA-S concentrations < 2.5 μmol/L), who had never been treated

Lasco 2001 (*Continued*)

	with hormonal replacement therapy Exclusion: acute or chronic illnesses were excluded by means of clinical examination and routine laboratory investigation. Exclusion criteria also included history of diabetes mellitus and other metabolic or endocrine disorders
Interventions	1. Oral micronized DHEA 25 mg 2. Identical placebo tablet Treatment duration: once daily for 12 months
Outcomes	Metabolic effects, adverse effects
Notes	Age and BMI are expressed as mean ± SD "No relevant side effects were recorded during the study period; only one patient developed slight acne at the beginning of treatment and it disappeared spontaneously later."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Information retrieved after contacting the author. "We assigned subjects to treatment by using a computerized randomization/ enrollment system which assigned unique randomization numbers."
Allocation concealment (selection bias)	Low risk	After contacting author. "Treatment assignment was revealed at the end of the study and the list was kept by Professor Cucinotta D. Treatment assignment was revealed at the end of the study or following the onset of an adverse event (only one case)."
Blinding (performance bias and detection bias) All outcomes	Low risk	"DHEA was provided as tablets of a micronized galenic compound, prepared by a local chemist's shop. In group 2 patients received an identical placebo tablet."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were addressed
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Merritt 2012

Methods	Design: single centre, randomised, placebo-controlled, crossover trial Country: USA Recruitment: recruited by newspaper advertisement who were paid USD 300.00 for their participation
Participants	Study population: N = 48 postmenopausal women Age: 63.5 ± 6.85 years BMI: 27.46 ± 4.36, range 19-35 kg/m² Inclusion: participants met the World Health Organization's criteria for postmenopausal status of one year's absence of menses or bilateral ovariectomy that preceded the study by at least one year. No participant was using any form of hormone replacement therapy. All women enrolled had a normal mammogram within the prior year and a normal Pap smear within the prior three years Exclusion: participants were excluded if a pre-enrolment medical evaluation revealed contraindications to DHEA, estrogen or androgen treatment (i.e. personal history ofor active breast cancer or other estrogen-dependent neoplasms, acute liver disease, undiagnosed vaginal bleeding, uncontrolled hyper- tension, deep venous thrombosis, pulmonary embolus, history of clotting disorders, history of psychiatric or cognitive disorders). Women whose pre-enrolment assays of DHEAS, estradiol or testosterone were above the normal post- menopausal women's range or whose body mass index (BMI) exceeded 35 were excluded. Our finals ample included women with BMIs from Use of substances that influence cognition(e.g. amphetamines, benzodiazepines, narcotics, nicotine, steroid hormones, and steroid receptor antagonists) was also grounds for exclusion, as was a serious physical illness within the last year
Interventions	1. Oral DHEA capsules 50 mg 2. Placebo identical to DHEA capsule, containing lactose Treatment duration: daily for 4 weeks
Outcomes	Sex steroid serum levels, affective measures (using Beck Depression Inventory and Symptoms Checklist-90) and cognitive measures
Notes	Age and BMI are expressed as mean ± SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were assigned to receive DHEA or placebo in a block-randomization scheme"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo (identical in appearance to DHEA capsules). "All investigators and participants were blind to treatment status"

Merritt 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any withdrawals
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken and self-administered questionnaires
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Mortola 1990

Methods	Design: single centre, randomised, placebo-controlled, crossover trial Country: USA
Participants	Study population: n = 6 postmenopausal women (one woman had undergone bilateral oophorectomy and the remainder had spontaneous menopause of more than 1 year duration) Age: 46 to 61 years Inclusion: menopause was confirmed by elevated FSH and LH levels. No subject had taken hormone replacement therapy or other prescribed medication for the previous year Exclusion: medical illness was excluded by history, physical examination, serum chemistry profile, including renal liver and thyroid panels, urinalysis, and complete blood count
Interventions	1. Oral DHEA 1600 mg (4 x 400 mg) 2. Placebo Both were packaged in gelatin capsules Treatment duration: daily for 28 days, followed by washout period of two weeks and then followed by a 28 days crossover treatment
Outcomes	Endocrine-metabolic parameters, adverse effects
Notes	Unable to contact the authors One subject reported increased facial hair during DHEA treatment, and one did so during placebo administration. No changes in sexual drive or appetite were reported. No other adverse consequences were noted. Unclear how many women were randomised to each treatment group. Therefore not possible to include in meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", randomisation technique was not described
Allocation concealment (selection bias)	Unclear risk	Not stated

Mortola 1990 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	May have influenced the outcomes if not blinded
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Nouveau 2008

Methods	Design: single centre, randomised, controlled, parallel trial Country: France
Participants	Study population: n = 40 postmenopausal women (n = 20 (DHEA), n = 20 (placebo)) Age: 55 to 70 years (mean 60 ± 4)
Interventions	1. DHEA cream (containing 1% DHEA) 2. Placebo, identical in appearance to active treatment Treatment duration: twice daily applied to the face and the back of one hand for 4 months
Outcomes	Skin changes, adverse effects
Notes	Each volunteer was left free to apply the preferred amount of cream according to their usual habits "Any sign of androgen excess such as body hair growth or greasy skin was not spontaneously reported. Ten weeks after the beginning of the treatment, one woman of the DHEA group presented some lesions of acne which resolved without any complementary treatment, just by reducing the frequency of cream application during the following 2 weeks. The code was not broken for this volunteer."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The volunteers had been allocated using a randomization procedure for both the treatment group and the application side. The randomization list was balanced by a group of 10 using the procedure Proc Plan from the SAS statistical software release 8. 1."

Nouveau 2008 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	States to be double blinded" "The volunteers were divided into two groups; one received a cream preparation containing 1% DHEA and the other received the vehicle only, i.e. exactly the same formulation without the active ingredient (DHEA)." "one woman of the DHEA group presented some lesions of acne which resolved without any complementary treatment, just by reducing the frequency of cream application during the following 2 weeks. The code was not broken for this volunteer". Very likely to have been double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Low risk	Self-assessment, blinding unlike to have been broken
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found
Other bias	Unclear risk	"A little more than half of the subjects were under hormone replacement therapy, i.e. estrogen-progestin treatment (10 in the vehicle group, 12 in the DHEA treated group, the mean number of years on therapy was 5±4 years)."

Panjari 2009

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: Australia Enrolment: women from metropolitan Melbourne, Australia participated between February 2006 and April 2008
Participants	Study population: n = 93 postmenopausal women (n = 47 (DHEA) and n = 46 (placebo) Age: 55.1 ± 4,5 (DHEA), 53.9 ± 4.7 (placebo), total range between 40 and 65 years BMI: 24.5 ± 3.5 (DHEA) and 26.8 ± 3.4 (placebo) Comorbidity: hypoactive sexual desire disorder, low libido Inclusion: all participants were 12 months postmenopause and were required to have a normal mammogram and Pap smear and endometrial double thickness 4 mm and no other abnormal findings on transvaginal ultrasound. Women were required to be sexually active, defined as being involved in any form of sexual activity at least once a month. All participants demonstrated evidence of hypoactive sexual desire disorder (HSDD) by answering affirmatively five questions about changes in their sex life following menopause,

	including a meaningful decrease in level of desire and sexual activity that was concerning to them consistent with the DSM IV definition Exclusion: a body mass index (BMI) < 18 kg/m^2 or > 34 kg/m^2, dyspareunia, undiagnosed genital bleeding, severe depression, or had pharmacological treatment for depression within 2 months of the screening visit or a history of severe psychiatric illness. Women with more than three satisfactory sexual events per week were excluded. Use of androgen therapy (testosterone implant within the last 28 weeks, transdermal testosterone cream within the last 8 weeks, tibolone within the last 12 weeks, oral testosterone within the last 4 weeks, and injected testosterone within the last 6 weeks) or estrogen, including vaginal conjugated equine estrogen, vaginal estrogen ring, or estrogen-progestin combinations in the last 2 months were excluded (use of vaginal estriol or low dose estradiol pessaries or cream was allowed). Use of phytoestrogens within 1 week prior to screening and therapies known to induce liver enzyme metabolism or alter the metabolism of DHEA resulted in exclusion.Women were also excluded if they had any serious medical conditions, history of breast or gynecological cancer, abnormal TSH level or abnormal liver function, moderate to severe acne, hirsutism, androgenic alopecia, or use of antiandrogen therapy for acne or hirsutism in the preceding 5 years, reported alcohol consumption more than three standard drinks per day, or had, in the opinion of the investigators, any clinically significant pretreatment illness, which would impact on the health and well-being of the woman or her ability to participate in the study
Interventions	1. Oral DHEA capsule 50 mg 2. Identical placebo Treatment duration: once daily for 1 year
Outcomes	Efficacy measurements (sexual function, quality of life), safety assessments (adverse effects), hormone measurements (serum levels of e.g. DHEA)
Notes	Age and BMI are expressed as mean ± SD Androgenic adverse events occurred exclusively in the DHEA group with three reported instances of acne and two of increased facial hair. One participant had both acne and increased facial hair and she withdrew from the study after 26 weeks. The other participant with facial hair also withdrew after 26 weeks. The three cases of acne were all classified as mild. There were no reported instances of voice deepening, alopecia, or clitoromegaly There were a total of 55 adverse effects reported of which 24 adverse events reported in the placebo group and 31 in the DHEA group. Only androgenic adverse events were specified (5/55) Quality of life was measured by PGWB score (psychological general wellbeing) (range 0 to 110)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was computer generated by Endorecherche, Canada with stratification for hysterectomy status."

Panjari 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Allocation concealment was maintained as treatment codes were controlled by the Alfred Hospital Pharmacy Melbourne, which dispensed the coded medication directly to participants in 3-month batches."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The investigators, study center personnel, and participants remained blinded throughout the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Seventy-nine of the 89 women (89%) completed the 26-week treatment period. Eighty-five women were included in the 26-week efficacy analysis and 63 women who completed 52 weeks were included in the safety analyses" All outcomes have been addressed and reasons for withdrawal have been stated
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found
Other bias	Unclear risk	Unclear

Pluchino 2008

Methods	Design: single, randomised, controlled (head-to-head), parallel trial Country: Italy Enrolment: patients were divided in two groups according only to their DHEA and DHEAS plasma levels, i.e. higher than or lower than 2.40 ng/mL for DHEA and 0.55 g/mL for DHEAS
Participants	Study population: n = 32 postmenopausal women (n = 10 (DHEA), n = 10 (HRT) and n = 12 (HRT + DHEA) The HRT + DHEA group was not randomised, therefore we will not include this group in our further analyses Age: between 50 and 58 years BMI: 27.65 ± 1.84 (DHEA), 28.65 ± 2.04 (HRT) Inclusion: all subjects had natural menopause and were healthy Exclusion: previous or current endocrine disorders, such as thyroid or adrenal dysfunction and altered prolactin circulating levels; treatments for cardiovascular diseases, hypertension or psychiatric disorders; previous or current hormonal treatments known to influence endocrine function (including HRT); smoking; presence of any kind of pelvic and breast disease. Natural menopause was defined retrospectively after 12 consecutive months without natural menstrual periods and age at menopause was the age at last menstruation

Pluchino 2008 (*Continued*)

Interventions	1. Oral 10 mg DHEA supplementation daily 2. HRT consisting out of a twice weekly transdermal 50 μg estradiol (TE) patch (Dermestril 50, Rottapharm) + oral micronized progesterone (mP) 100 mg/day (prometrium 100, Rottapharm) 3. Both 1 and 2. (this group was not randomised and therefore not included) Treatment duration: 12 months
Outcomes	Hormonal milieu and adverse effects
Notes	Reported that there were no adverse effects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was made using a computer-generated block random-permutation procedure."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All the patients enrolled in the study completed the follow-up, without any adverse events."
Blinding of outcome assessment	High risk	Outcomes may have been influences (not blinded)
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Silvestri 2005

Methods	Design: randomised, double-blind, controlled (head-to-head), double crossover trial Country: Italy
Participants	Study population: n = 30 postmenopausal women were recruited, 16 were randomised after screening Age: 45 to 70 years Inclusion: menopausal status was assessed by the absence of menses of at least 6 months and by plasma levels of estradiol 17 < 25 ng/ml, coupled with baseline FSH > 40 mIU/mL. Age between 45 and 70 years, presence of more than two risk factors for coronary artery disease causing a 10 year cardiovascular risk of 40% (Table 1), intact uterus.

	No subject had taken any cholesterol-lowering agent, estrogen therapy, or antioxidant vitamin supplements during the previous 2 months. Aspirin and non-steroidal anti-inflammatory agents were stopped 10 days prior to the study Exclusion: patients with clinically significant findings on physical exam or presence of known clinically significant diseases interfering with study evaluation, those currently using medications (or products) that interfere with forearm blood flow were excluded from the study
Interventions	1. Oral DHEA-s 50 mg 2. Oral conjugated equine estrogen (CEE) 0.625 mg 3. Oral tibolone 2.5 mg Treatment duration: 4 weeks, washout of 1 week, followed by crossover treatment
Outcomes	Endothelial function
Notes	Information retrieved after contacting author. "No adverse events in any of the treatment phases" - "we did not measure patients related outcomes"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	After contacting author: "Randomisation was obtained through a computer-generated random list"
Allocation concealment (selection bias)	Low risk	After contacting author: "Drugs were administered by investigators unaware of the clinical data and not involved in the study assessments. All patients were naive on the treatments."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States to be "double-blinded", however it is a head-to-head trial, everyone received an active treatment. Unlikely that all active tablets had identical appearances unless they have used multiple placebo tablets. However this is unknown
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Unclear risk	If blinding was broken it may have influenced the outcomes
Selective reporting (reporting bias)	Unclear risk	Official protocol not found or available
Other bias	Unclear risk	Unclear

Stanczyk 2009

Methods	Design: single centre, randomised, placebo-controlled, parallel trial Country: USA
Participants	Study population: n = 20 postmenopausal women (after recruiting and screening of 58 women) (n = 10 (DHEA) and n = 10 (placebo)) Age: 55 to 65 years BMI: ranged from 28 to 33 kg/m² Inclusion: healthy postmenopausal women, not taking hormone therapy for at least 3 months or ingesting prescription or non-prescription herbal medications. Postmenopausal status was determined by menstrual cycle history, as well as follicle-stimulating hormone (> 25 mIU/mL) and E2 (G25 pg/mL) levels at time of entry into the study Exclusion: hormone use or serious medical conditions requiring prescription medications or non-compliance with the number of study-related visits
Interventions	1. Oral tablet containing 25 mg of DHEA 2. Placebo tablet (identical) Treatment duration: daily for 6 months
Outcomes	Pharmokinetics and metabolites, adverse effects
Notes	Reported that "there were no adverse effects reported by any of the women"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization schedule was generated using the Statistical Analysis Systems software."
Allocation concealment (selection bias)	Low risk	"Identical-looking bottles were serially numbered from 1 to 20. They were filled with drug or placebo according to the randomization schedule by the study pharmacy that kept the randomization schedule in a locked, secure cabinet. The women were assigned sequentially from 1 to 20." "The study drug allocation was unblinded only upon completion of the entire study"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The individuals examining and questioning the women did not know the therapy to which the woman was assigned, as the drug and placebo tablets looked identical, including the bottles containing the tablets, which were identified only with the study number."

Stanczyk 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for withdrawal have been stated and only data from women who finished the trial have been used for meta-analysis
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken
Selective reporting (reporting bias)	Unclear risk	Official protocol not available or found
Other bias	Unclear risk	"This work was supported in part by grant M01 RR-43 from the General Clinical Research Center branch of the National Center for Research Resources, National Institutes of Health"

Stangl 2010

Methods	Design: single centre, randomised, placebo-controlled, crossover trial Country: USA Recruitment: all participants were volunteers recruited by newspaper advertisement and were paid USD 300.00 for their participation
Participants	Study population: n = 24 postmenopausal women Age: 65.25 ± 7.89, range 55 to 80 years BMI: 27.70 ± 3.85 kg/m² Inclusion: participants met the World Health Organization's criteria for post-menopausal status of one year's absence of menses or bilateral ovariectomy that preceded the study by at least one year Exclusion: participants were excluded if a pre-enrolment medical evaluation revealed contraindications to DHEA, estrogen or androgen treatment (e.g. personal history of, or active, breast cancer or other estrogen-dependent neoplasms,history of clotting disorders,). Women whose pre-enrolment assays of DHEAS, estradiol or testosterone were above the normal postmenopausal women's range or BMI > 35 were excluded. Use of substances that influence cognition (e.g. amphetamines, benzodiazepines, nicotine) was also grounds for exclusion, as was a serious physical illness within the last year. All women enrolled had a normal mammogram within the prior year and a normal Pap smear within the prior three years
Interventions	1. 50 mg of oral DHEA 2. Identical placebo (consisted of lactose) Treatment duration: 4 weeks, 1 week washout, followed by 4 weeks crossover treatment
Outcomes	Cognitive and affective measures (including BDI and SCL 90-R)
Notes	Age and BMI are expressed as mean ± SD BDI = Beck Depression Inventory SCL 90-R = Symptom Checklist 90-R

Stangl 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were assigned to receive DHEA or placebo in a block-randomization scheme."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"All investigators and participants were blind to treatment status."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any dropouts
Blinding of outcome assessment	Low risk	Blinding unlikely to have been broken and self-assessment outcomes
Selective reporting (reporting bias)	Unclear risk	Protocol not found or available. Adverse effects were investigated, but not reported
Other bias	Unclear risk	Unclear

Stomati 1999

Methods	Design: single centre, randomised, controlled (head-to-head), parallel study Country: Italy
Participants	Study population: n = 22 postmenopausal women (n = 8 (DHEAS), n = 8 (estradiol), n = 6 (DHEAS + estradiol) Age: range 50 to 55 years BMI: normal body mass index - not specified Exclusion: previous or current estrogen-dependent neoplasia, thromboembolic disease, liver, pancreatic or renal disease and diabetes mellitus
Interventions	1. 50 mg of oral DHEAS daily 2. 50 mg of oral DHEAS daily + 50 μg estradiol patch 3. 50 μg estradiol patch continuously Treatment duration: three months
Outcomes	Neuroendocrine tests, subjective symptoms (e.g. by using Kupperman questionaire), hormonal assays
Notes	"No side effects requiring interruption of treatment were reported in any group during the three months of therapy."

Stomati 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly divided in three groups, according to the type of treatment" - randomisation technique unknown
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts due to side effects, unclear if there were any other withdrawals
Blinding of outcome assessment	High risk	Not blinded, outcomes may have been affected as everyone received an active treatment
Selective reporting (reporting bias)	Unclear risk	Protocol not found or available
Other bias	Unclear risk	Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barton 2006	Not all menopausal women
Bates 1995	Study was aimed at pharmacokinetics. No other data available (unsuccessful in contacting authors for additional data)
Burger 2003	No full text available. No additional data available (authors were contacted)
Buster 1992	No full text available. Study was aimed at pharmacokinetics. Unsuccessful in contacting authors for additional data
Buster 2009	Non-RCT
Calvo 2008	Study was aimed at pharmacokinetics. No other data available
Carranza-Lira 2002	Quasi-randomised (alternate allocation)

(*Continued*)

Casson 1993	Study was aimed at pharmacokinetics. No other data available (unsuccessful in contacting authors for additional data)
Casson 1995	Study was aimed at pharmacokinetics. No other data available (unsuccessful in contacting authors for additional data)
Caufriez 2013	Study was aimed at pharmacokinetics and sleep. Unsuccessful in contacting authors for additional data
Chassany 2000	Non-RCT
Hackbert 2002	Treatment duration < 1 week
Hartkamp 2004	Not all menopausal women
Kamath 1998	Premenopausal women
Labrie 2013	Non-RCT
Lovas 2003	Not all menopausal women
Ott 2014	Non-RCT
Pisarska 1998	No full text available. Study was aimed at pharmacokinetics. Unsuccessful in contacting authors for additional data
Rodrigo Pegado 2012	Non-RCT
Sanchez-Guerrero 2008	Not all menopausal women
Stein 2011	Premenopausal women
Stoll 1999	Non-RCT
Virkki 2010	Not all menopausal women
Yasui 2012	Non-RCT
Zouboulis 2012	Non-RCT

Characteristics of studies awaiting assessment *[ordered by study ID]*

Igwebuike 2008

Methods	Design: single centre, randomised, placebo-controlled trial
Participants	Study population: n = 31 postmenopausal women (n = 17 (DHEA), n = 14 (placebo)) Age: 64.6 ± 1.0 years Race: Caucasian Inclusion: postmenopausal women Exclusion: participants with a plasma concentration of DHEA-S greater than 110 g/mL or with evidence of diseases such as diabetes, cardiovascular disease, or thyroid dysfunction were excluded due to the potential effects these diseases may have on the outcome measures. Participants using psychotropic drugs, progesterone, testosterone, corticosteroids, or DHEA within the preceding 6 months were excluded
Interventions	1. Oral DHEA 50 mg plus exercise training 2. Placebo plus exercise training Treatment duration: daily for 12 weeks
Outcomes	The effects of combined endurance and resistance training on improvements in body composition, physical performance, and cardiometabolic risk
Notes	Age is expressed as mean ± SD. Did not report any of the outcomes we are investigating

Labrie 2007

Methods	Design: randomised, placebo-controlled, parallel trial
Participants	Study population: n = 75 postmenopausal women Age: 60 to 65 years Race: Caucasian BMI: 18.5 to 29.9 kg/m² Inclusion: healthy postmenopausal Caucasian women aged 60 to 65 years Exclusion: no subject had taken hormone replacement therapy during the previous 6 months. No endocrine disorder, and none was under treatment with lipid- or glucose-lowering agents. No active or history of thromboembolic disease, significant metabolic or endocrine disease and no clinically significant gastrointestinal, liver or gallbladder disease. No migraine and no diabetes mellitus not controlled by conventional therapy. No corticosteroid treatment < 6 weeks of study entry as well as treatment with -carotenoid, retinoic acid, hydroquinone, -hydroxyacid (including inhaled, topical or oral). No hypertension equal to or above 160/95 mmHg or not controlled by standard therapy as well as no confirmed clinically significant depression or confirmed severe psychiatric disturbance. No administration of any investigational drug < 30 days of screening visit or previous treatment with androgens or anabolic steroids within 6 months prior to the screening visit. There was no exposure to or use of antidepressants, antipsychotics, or analgesics, < 30 days prior to enrollment. Smoking any number of cigarettes. No former or present narcotic addiction or alcoholism. BMI between 18.5 and 29.9 kg/m². There was no hepatic or renal impairment or condition known to affect drug or steroid metabolism
Interventions	1. 2.0% DHEA cream (emulsion) 2. 1.0% DHEA cream (emulsion) 3. 0,3% DHEA cream (emulsion) 4. 0,1% DHEA cream (emulsion)

Labrie 2007 (*Continued*)

	5. Placebo (emulsion) Treatment duration: applied twice daily on the face, upper chest, arms and legs for 7 days
Outcomes	Metabolism of DHEA and related steroid
Notes	Study is aimed at pharmakinetics. Did not report any of our outcomes. Author was contacted, waiting for response

Labrie 2007a

Methods	Design: randomised controlled parallel trial Country: Canada
Participants	Study population: 36 healthy postmenopausal women (n = 12 DHEA cream, n = 12 DHEA gel, n = 12 oral DHEA) Age: between 60 and 70 years Exclusion: metabolic or endocrine disorder, coronarian disease or hypertension. No treatment with androgens or anabolic steroids
Interventions	1. 100 mg oral DHEA (two capsules of 50 mg) 2. 4 g of 10% DHEA gel applied on a total 30 cm × 30 cm area of the thighs 3. 4 g of 10% DHEA cream applied on a total 30 cm × 30 cm area of the thighs Treatment duration: daily for 14 days
Outcomes	Bioavailability and metabolism of DHEA
Notes	No outcomes for inclusion in our review reported, author was contacted to request additional data, awaiting

Labrie 2008a

Methods	Design: randomised, controlled, parallel trial Country: Canada
Participants	Study population: 150 healthy postmenopausal women Age: between 60 and 65 years Race: Caucasian Exclusion: hormone replacement therapy during the previous 6 months. Endorcrine disorder, treatment with lipid or glucose-lowering agents, thromboembolic disease, metabolic or endocrine disease, gastrointestinal, liver or gallbladder disease. Migraine or diabetis mellitus controlled by conventional therapy. corticosteroid treatment <6 weeks of study entry or treatment with -carotenoid, retinoic acid, hydroquinone, -hydroxyacid (including inhaled, topical or oral) . administration of any investigational drug within 30 days of screening visit or previous treatment with androgens or anabolic steroids < 6 months prior to the screening visit. There was no exposure to or use of antidepressants, antipsychotics, or analgesics, < 30 days prior to enrolment. Smoking
Interventions	1. 3 g 0.3% DHEA emulsion 2. Placebo emulsion Treatment duration: twice daily for 12 months
Outcomes	Serum DHEA and its metabolites

Labrie 2008a (*Continued*)

Notes	No outcomes for inclusion in our review reported, author was contacted to request additional data, awaiting response

Characteristics of ongoing studies *[ordered by study ID]*

Labrie 2005

Trial name or title	Phase II-III Placebo-Controlled, Study to Evaluate the Effects of DHEA on Vasomotor Symptoms (Hot Flashes) in Postmenopausal Women
Methods	Randomised, parallel trial
Participants	Inclusion: healthy postmenopausal women with 50 or more moderate to severe hot flushes, between 40 to 70 years of age Exclusion: • Body mass index (BMI) of 35 kg/m^2 or more • Significant metabolic and endocrine diseases • Diagnosis of cancer • Use of steroids or drugs that interfere with the metabolism of estrogen • Use of any systemic estrogen, progestin, or DHEA in the eight weeks prior to randomisation • Use of alternative therapies or natural products to treat postmenopausal symptoms in the four weeks prior to randomisation • Palpable fibroids or uterine prolapse: Grade 2 or 3 • Cigarette smoking
Interventions	1. DHEA (prasterone) 2. Placebo Treatment duration: 16 weeks
Outcomes	The number and intensity of hot flashes and evaluation of safety, quality of life, psychological general wellbeing and sexual life by questionnaires
Starting date	August 2005
Contact information	Clinique des Traitements Hormonaux Sainte-Foy, Quebec, Canada, G1V 4G2
Notes	ClinicalTrials.gov identifier: NCT00317148

Labrie 2014

Trial name or title	Intravaginal Prasterone (DHEA) Against Vulvovaginal Atrophy Associated With Menopause
Methods	Randomised, parallel trial
Participants	Inclusion: • Postmenopausal women (hysterectomized or not) • Women between 40 and 80 years of age

Labrie 2014 (*Continued*)

	• Women having ≤ 5% of superficial cells on vaginal smear at baseline • Women having a vaginal pH above 5 at baseline • Women who have self-identified moderate or severe symptom(s) of vaginal atrophy • Willing to participate in the study and sign an informed consent Exclusion: • Previous enrolment in EndoCeutics studies performed with intravaginal DHEA • Previous diagnosis of cancer, except skin cancer (non melanoma) • Clinically significant metabolic or endocrine disease (including diabetes mellitus) not controlled by medication • The administration of any investigational drug within 30 days of screening visit • Clinically significant abnormal serum biochemistry, urinalysis or haematology
Interventions	1. Intravaginal DHEA 2. Placebo Treatment duration: 12 weeks
Outcomes	Vaginal maturation index, vaginal pH, vulvovaginal atrophy symptom, tolerance to intravaginal prasterone (by evaluation of vaginal mucosa)
Starting date	February 2014
Contact information	Contact: Isabelle Côté, B. Sc. CCRP. 1-855-653-0033 ext 204. isabelle.cote@endoceutics.com
Notes	ClinicalTrials.gov identifier: NCT02013544

DATA AND ANALYSES

Comparison 1. DHEA versus control (placebo or no treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 QoL/wellbeing (end scores)	9		Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.20, 0.13]
2 Sensitivity analysis QoL/wellbeing (end scores)	8		Std. Mean Difference (Fixed, 95% CI)	0.16 [-0.03, 0.34]
3 QoL (subgrouped on Low Libido/HSDD)	9		Std. Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 Low Libido/HSDD	2		Std. Mean Difference (Fixed, 95% CI)	0.10 [-0.26, 0.46]
3.2 Libido normal/unknown	7		Std. Mean Difference (Fixed, 95% CI)	-0.08 [-0.27, 0.11]
4 QoL (subgrouped on treatment duration)	9		Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.20, 0.13]
4.1 <6 weeks	3		Std. Mean Difference (Fixed, 95% CI)	0.23 [-0.11, 0.57]
4.2 6 to 26 weeks	3		Std. Mean Difference (Fixed, 95% CI)	0.13 [-0.13, 0.39]
4.3 >26 weeks	3		Std. Mean Difference (Fixed, 95% CI)	-0.46 [-0.75, -0.16]
5 QoL/General Wellbeing (change scores)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Side-effects	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Androgenic side-effects	1	92	Odds Ratio (M-H, Fixed, 95% CI)	6.57 [1.37, 31.59]
6.2 Acne	4	158	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.56, 9.02]
6.3 Hirsutism	1	89	Odds Ratio (M-H, Fixed, 95% CI)	4.89 [0.23, 104.76]
7 Acne subgrouped on study duration	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 < 6 weeks	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.70]
7.2 >6 weeks to 26 weeks	1	22	Odds Ratio (M-H, Fixed, 95% CI)	2.74 [0.10, 74.87]
7.3 >26 weeks	2	109	Odds Ratio (M-H, Fixed, 95% CI)	5.25 [0.58, 47.36]
8 Menopausal symptoms (continuous)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Endscores	1	17	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.70, 1.40]
8.2 Change scores	1	66	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.42, 0.55]
9 Menopausal symptoms (dichotomous)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Flushes	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Hot flushes and palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Insomnia	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Night sweats	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.5 Depression	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.6 Loss of libido	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.7 Vaginal dryness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.8 Pruritis vulvae	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.9 Urethral syndrome	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.10 Tiredness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Sexual Function (end scores)	6		Std. Mean Difference (Fixed, 95% CI)	0.19 [-0.01, 0.40]
11 Sexual function (end scores) (sensitivity analysis)	5		Std. Mean Difference (Fixed, 95% CI)	0.31 [0.07, 0.55]

Comparison 2. Oral DHEA versus control subgrouped by route of administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 QoL/wellbeing (change scores)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Oral administration	1	66	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.53, 0.43]
1.2 Intravaginal application	1	107	Std. Mean Difference (IV, Fixed, 95% CI)	1.23 [0.82, 1.65]
2 Side-effects: acne	4	158	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.56, 9.02]
2.1 Skin application	1	22	Odds Ratio (M-H, Fixed, 95% CI)	2.74 [0.10, 74.87]
2.2 Oral administration	3	136	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.47, 9.96]
4 Sexual Function (end scores)	6		Std. Mean Difference (Fixed, 95% CI)	0.19 [-0.01, 0.40]
4.1 Oral administration	5		Std. Mean Difference (Fixed, 95% CI)	0.11 [-0.13, 0.35]
4.2 Intravaginal application	1		Std. Mean Difference (Fixed, 95% CI)	0.42 [0.03, 0.81]

Comparison 3. DHEA versus HT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 QoL/General Wellbeing	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 ET	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Combined	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Tibolone	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Menopausal symptoms (continuous)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 ET	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Combined	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Tibolone	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sexual Function	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 ET/ET+P	2	41	Mean Difference (IV, Fixed, 95% CI)	1.26 [-0.21, 2.73]
4.2 Tibolone	1	24	Mean Difference (IV, Fixed, 95% CI)	4.60 [0.92, 8.28]

Comparison 4. DHEA versus HT (side effects) (dichotomous)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acne	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	17.0 [0.90, 320.37]
1.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	17.0 [0.90, 320.37]
2 Hair loss	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	10.67 [0.54, 209.64]
2.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	10.67 [0.54, 209.64]
3 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.53]

3.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.04]
4 Nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.21]
4.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.72]
5 Leg cramps	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Breast Tenderness	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.40]
6.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.25]
7 Bloating	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.84]
7.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.04]
8 Weight gain	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.84]
8.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.04]

Comparison 5. DHEA versus HT (menopausal symptoms) (dichotomous)

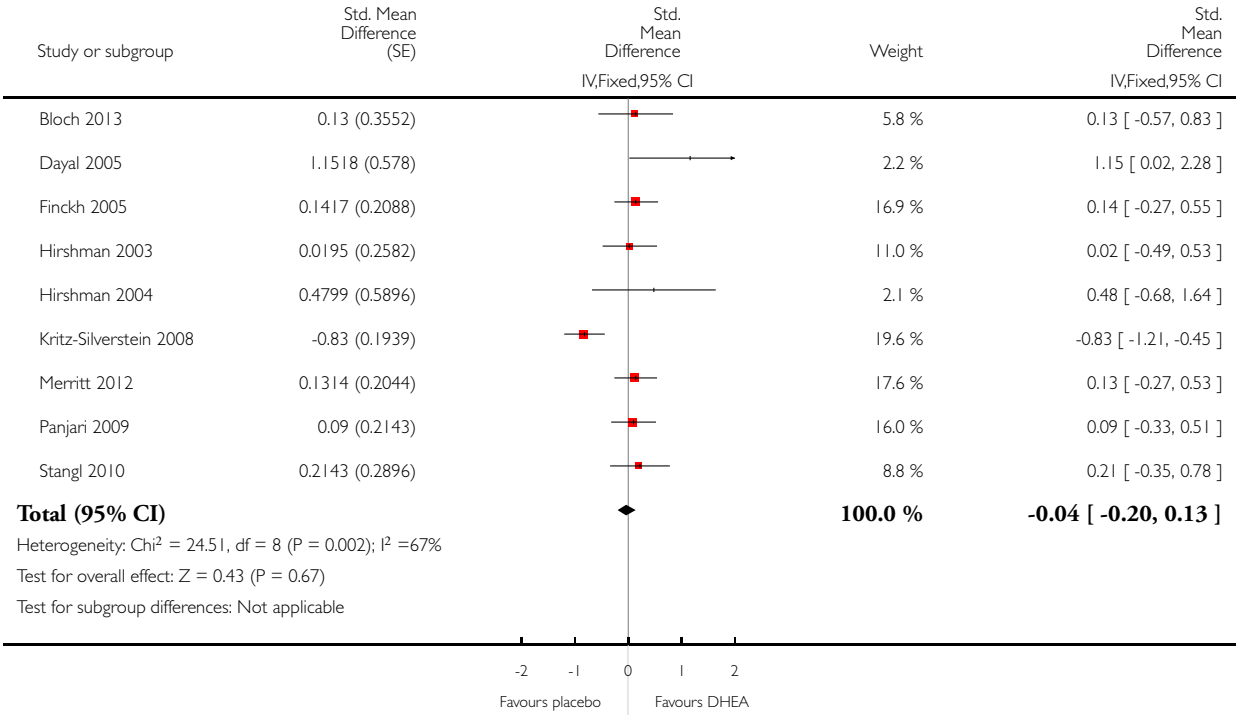
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tiredness	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.26]
1.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.84]
1.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.84]
2 Hot flushes and palpitations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.28, 7.00]
2.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.28, 7.00]
3 Night sweats	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.18, 5.51]
3.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.14, 3.59]
4 Vaginal Dryness	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.93]
4.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [0.12, 80.39]
5 Pruritis Vulvae	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.93]
5.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [0.12, 80.39]
6 Urethral Syndrome	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.65]
6.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.93]
7 Depression	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.25]
7.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Loss of libido	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 ET	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.25]
8.2 Tibolone	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 1 QoL/wellbeing (end scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 1 QoL/wellbeing (end scores)

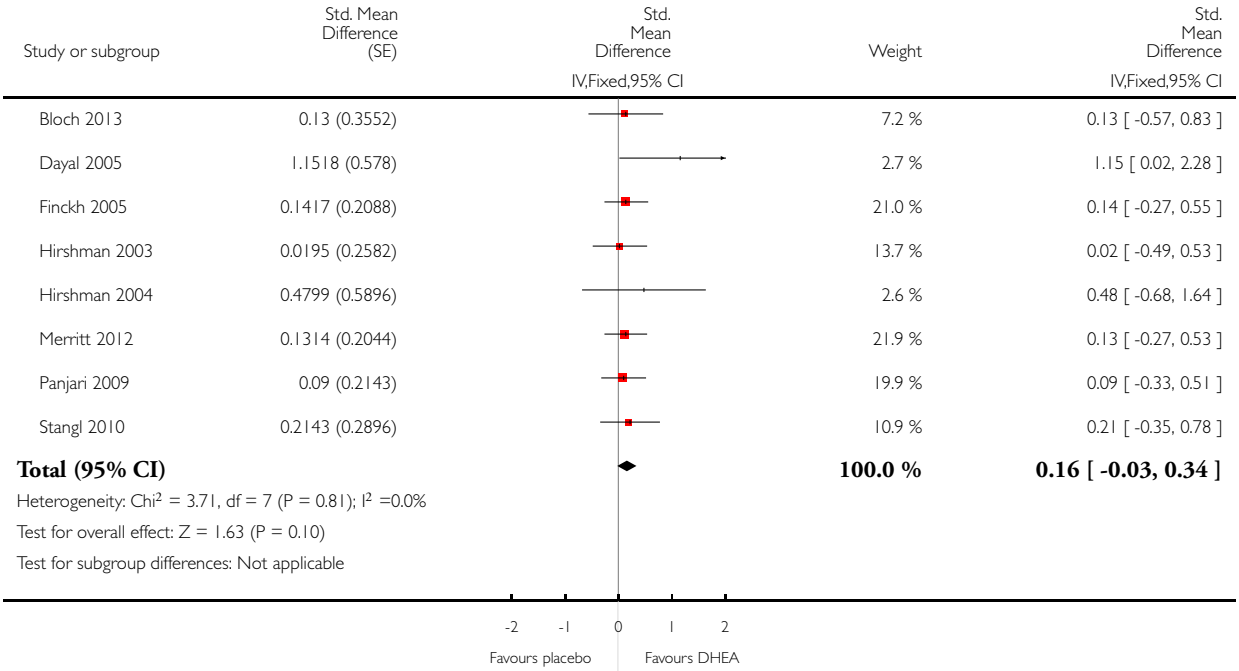


Analysis 1.2. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 2 Sensitivity analysis QoL/wellbeing (end scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 2 Sensitivity analysis QoL/wellbeing (end scores)

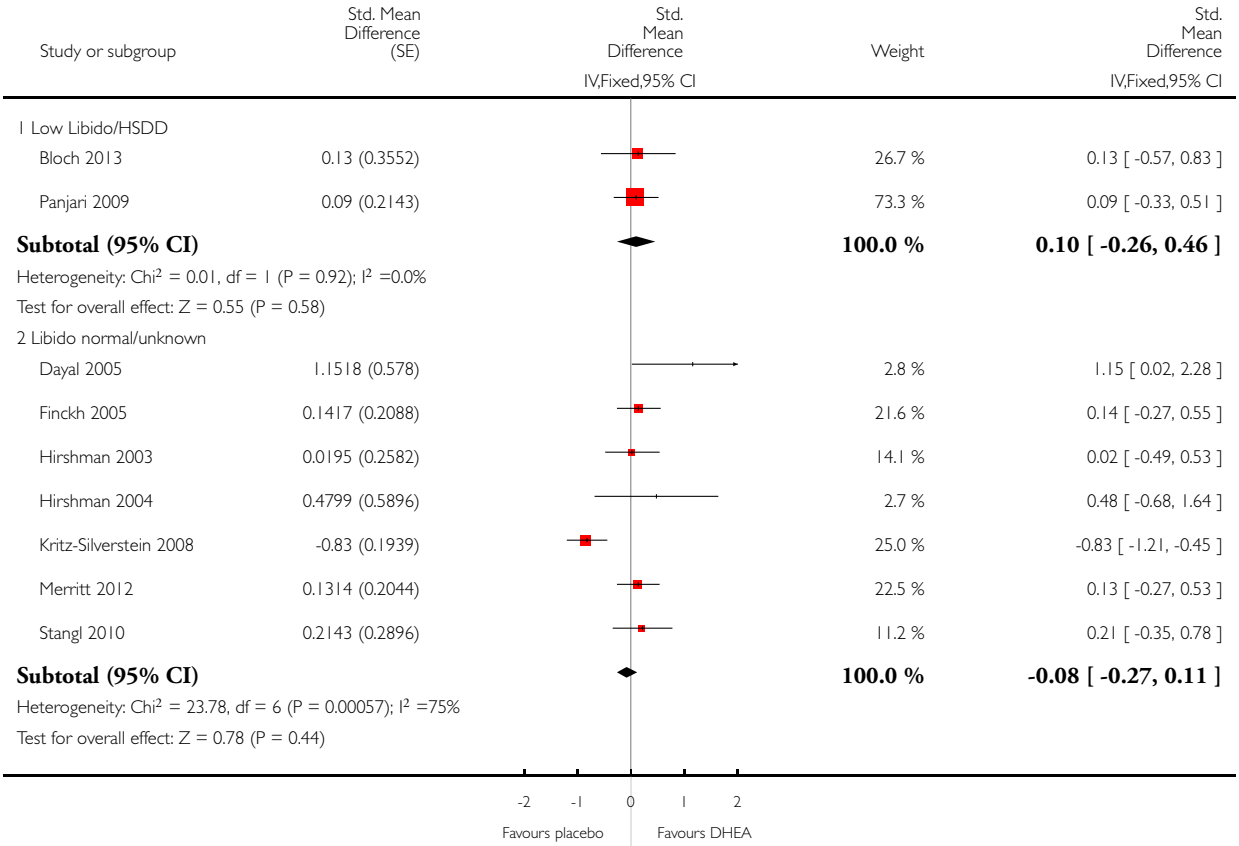


Analysis 1.3. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 3 QoL (subgrouped on Low Libido/HSDD).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 3 QoL (subgrouped on Low Libido/HSDD)



Analysis 1.4. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 4 QoL (subgrouped on treatment duration).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 4 QoL (subgrouped on treatment duration)

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 <6 weeks				
Bloch 2013	0.13 (0.3552)		5.8 %	0.13 [-0.57, 0.83]
Dayal 2005	1.1518 (0.578)		2.2 %	1.15 [0.02, 2.28]
Finckh 2005	0.1417 (0.2088)		16.9 %	0.14 [-0.27, 0.55]
Subtotal (95% CI)			**24.9 %**	**0.23 [-0.11, 0.57]**
Heterogeneity: Chi^2 = 2.80, df = 2 (P = 0.25); I^2 =29%				
Test for overall effect: Z = 1.33 (P = 0.18)				
2 6 to 26 weeks				
Merritt 2012	0.1314 (0.2044)		17.6 %	0.13 [-0.27, 0.53]
Panjari 2009	0.09 (0.2143)		16.0 %	0.09 [-0.33, 0.51]
Stangl 2010	0.2143 (0.2896)		8.8 %	0.21 [-0.35, 0.78]
Subtotal (95% CI)			**42.4 %**	**0.13 [-0.13, 0.39]**
Heterogeneity: Chi^2 = 0.12, df = 2 (P = 0.94); I^2 =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
3 >26 weeks				
Hirshman 2003	0.0195 (0.2582)		11.0 %	0.02 [-0.49, 0.53]
Hirshman 2004	0.4799 (0.5896)		2.1 %	0.48 [-0.68, 1.64]
Kritz-Silverstein 2008	-0.83 (0.1939)		19.6 %	-0.83 [-1.21, -0.45]
Subtotal (95% CI)			**32.7 %**	**-0.46 [-0.75, -0.16]**
Heterogeneity: Chi^2 = 9.63, df = 2 (P = 0.01); I^2 =79%				
Test for overall effect: Z = 3.06 (P = 0.0022)				
Total (95% CI)			**100.0 %**	**-0.04 [-0.20, 0.13]**
Heterogeneity: Chi^2 = 24.51, df = 8 (P = 0.002); I^2 =67%				
Test for overall effect: Z = 0.43 (P = 0.67)				
Test for subgroup differences: Chi^2 = 11.96, df = 2 (P = 0.00), I^2 =83%				

Analysis 1.5. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 5 QoL/General Wellbeing (change scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 5 QoL/General Wellbeing (change scores)

Study or subgroup	DHEA N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Barnhart 1999	33	27.8 (33)	33	31 (82)		-0.05 [-0.53, 0.43]
Labrie 2009a	54	3.06 (1.909)	53	0.67 (1.936)		1.23 [0.82, 1.65]

Analysis 1.6. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 6 Side-effects.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 6 Side-effects

Study or subgroup	DHEA n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Androgenic side-effects					
Finckh 2005 (1)	11/47	2/45		100.0 %	6.57 [1.37, 31.59]
Subtotal (95% CI)	**47**	**45**		**100.0 %**	**6.57 [1.37, 31.59]**
Total events: 11 (DHEA), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 Acne					
Bloch 2013	0/14	1/13		51.9 %	0.29 [0.01, 7.70]
Lasco 2001	1/10	0/10		14.9 %	3.32 [0.12, 91.60]
Nouveau 2008	1/12	0/10		16.6 %	2.74 [0.10, 74.87]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	DHEA n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Panjari 2009 (2)	3/46	0/43		16.5 %	7.00 [0.35, 139.60]
Subtotal (95% CI)	**82**	**76**		**100.0 %**	**2.26 [0.56, 9.02]**
Total events: 5 (DHEA), 1 (placebo)					
Heterogeneity: Chi^2 = 2.12, df = 3 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 Hirsutism					
Panjari 2009	2/46	0/43		100.0 %	4.89 [0.23, 104.76]
Subtotal (95% CI)	**46**	**43**		**100.0 %**	**4.89 [0.23, 104.76]**
Total events: 2 (DHEA), 0 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Test for subgroup differences: Chi^2 = 1.03, df = 2 (P = 0.60), I^2 =0.0%					

(1) Androgenic side-effects: acne, greasy skin, hirsutism (these were reported total side-effect instead of seperately)

(2) hirsutism also reported in 2/46 women on DHEA and 0 women on placebo but not presented in this data as it was clear if they same women also had acne

Analysis 1.7. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 7 Acne subgrouped on study duration.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 7 Acne subgrouped on study duration

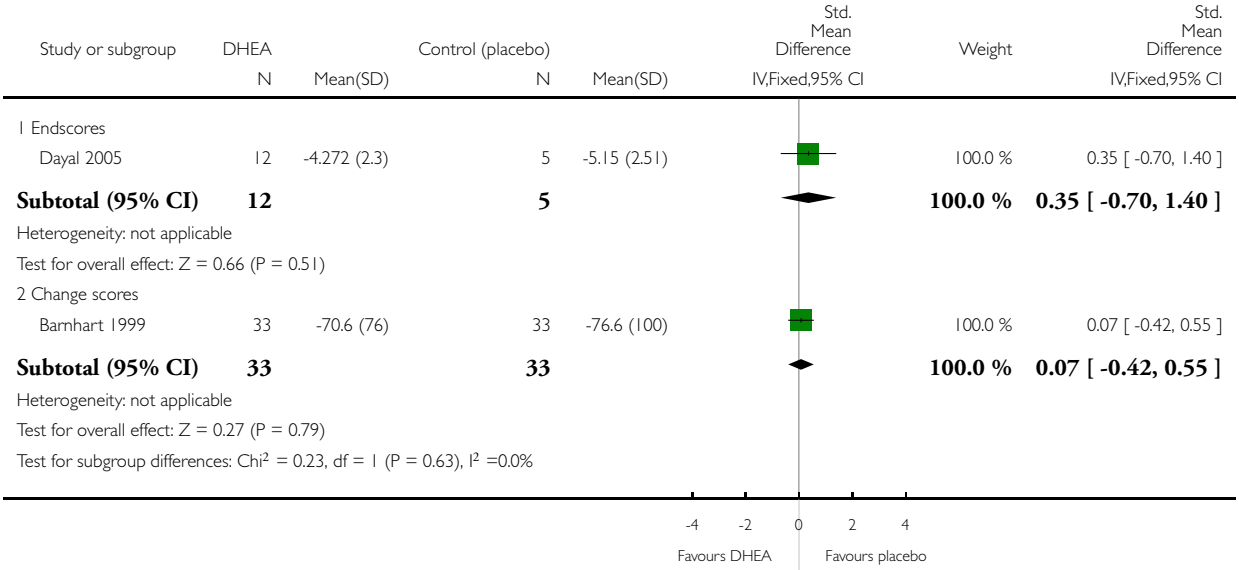
Study or subgroup	DHEA n/N	Placebo/no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 < 6 weeks					
Bloch 2013	0/14	1/13		100.0 %	0.29 [0.01, 7.70]
Subtotal (95% CI)	**14**	**13**		**100.0 %**	**0.29 [0.01, 7.70]**
Total events: 0 (DHEA), 1 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 >6 weeks to 26 weeks					
Nouveau 2008	1/12	0/10		100.0 %	2.74 [0.10, 74.87]
Subtotal (95% CI)	**12**	**10**		**100.0 %**	**2.74 [0.10, 74.87]**
Total events: 1 (DHEA), 0 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
3 >26 weeks					
Lasco 2001	1/10	0/10		47.5 %	3.32 [0.12, 91.60]
Panjari 2009	3/46	0/43		52.5 %	7.00 [0.35, 139.60]
Subtotal (95% CI)	**56**	**53**		**100.0 %**	**5.25 [0.58, 47.36]**
Total events: 4 (DHEA), 0 (Placebo/no treatment)					
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Chi^2 = 2.09, df = 2 (P = 0.35), I^2 =4%					

Analysis 1.8. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 8 Menopausal symptoms (continuous).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 8 Menopausal symptoms (continuous)



Analysis 1.9. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 9 Menopausal symptoms (dichotomous).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 9 Menopausal symptoms (dichotomous)

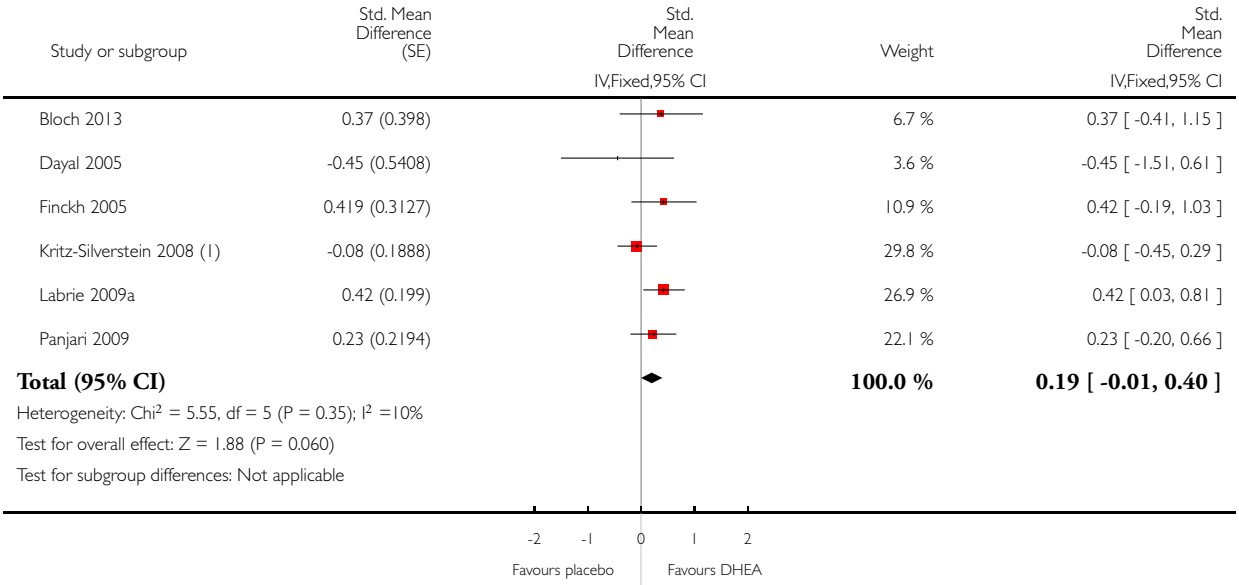
Study or subgroup	DHEA n/N	No treatment n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Flushes				
Bloch 2013	2/14	1/13		2.00 [0.16, 25.11]
2 Hot flushes and palpitations				
Gupta 2013	4/25	9/25		0.34 [0.09, 1.30]
3 Insomnia				
Gupta 2013	0/25	5/25		0.07 [0.00, 1.40]
4 Night sweats				
Gupta 2013	3/25	10/25		0.20 [0.05, 0.87]
5 Depression				
Gupta 2013	0/25	4/25		0.09 [0.00, 1.84]
6 Loss of libido				
Gupta 2013	0/25	9/25		0.03 [0.00, 0.63]
7 Vaginal dryness				
Gupta 2013	1/25	4/25		0.22 [0.02, 2.11]
8 Pruritis vulvae				
Gupta 2013	1/25	4/25		0.22 [0.02, 2.11]
9 Urethral syndrome				
Gupta 2013	1/25	5/25		0.17 [0.02, 1.55]
10 Tiredness				
Gupta 2013	6/25	15/25		0.21 [0.06, 0.71]

Analysis 1.10. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 10 Sexual Function (end scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 10 Sexual Function (end scores)



(1) sensitivity analysis without study - result are and hetero

Analysis 1.11. Comparison 1 DHEA versus control (placebo or no treatment), Outcome 11 Sexual function (end scores) (sensitivity analysis).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 1 DHEA versus control (placebo or no treatment)

Outcome: 11 Sexual function (end scores) (sensitivity analysis)

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Bloch 2013	0.37 (0.398)		9.6 %	0.37 [-0.41, 1.15]
Dayal 2005	-0.45 (0.5408)		5.2 %	-0.45 [-1.51, 0.61]
Finckh 2005	0.419 (0.3127)		15.5 %	0.42 [-0.19, 1.03]
Labrie 2009a	0.42 (0.199)		38.3 %	0.42 [0.03, 0.81]
Panjari 2009	0.23 (0.2194)		31.5 %	0.23 [-0.20, 0.66]
Total (95% CI)			**100.0 %**	**0.31 [0.07, 0.55]**

Heterogeneity: Chi^2 = 2.56, df = 4 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 2.52 (P = 0.012)

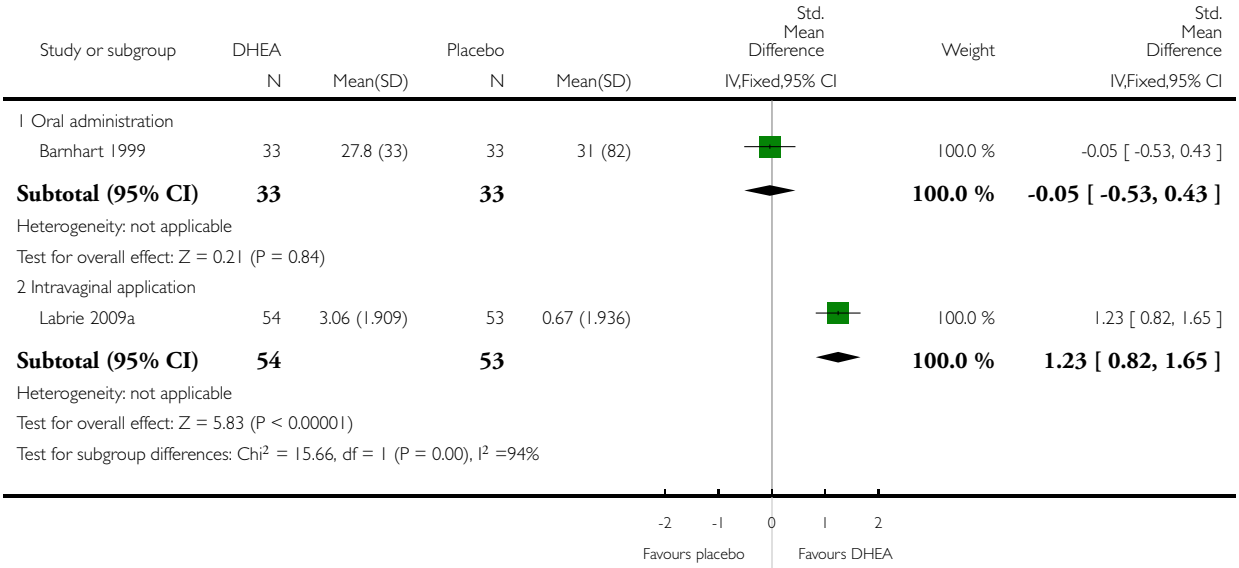
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Oral DHEA versus control subgrouped by route of administration, Outcome 1 QoL/wellbeing (change scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 2 Oral DHEA versus control subgrouped by route of administration

Outcome: 1 QoL/wellbeing (change scores)

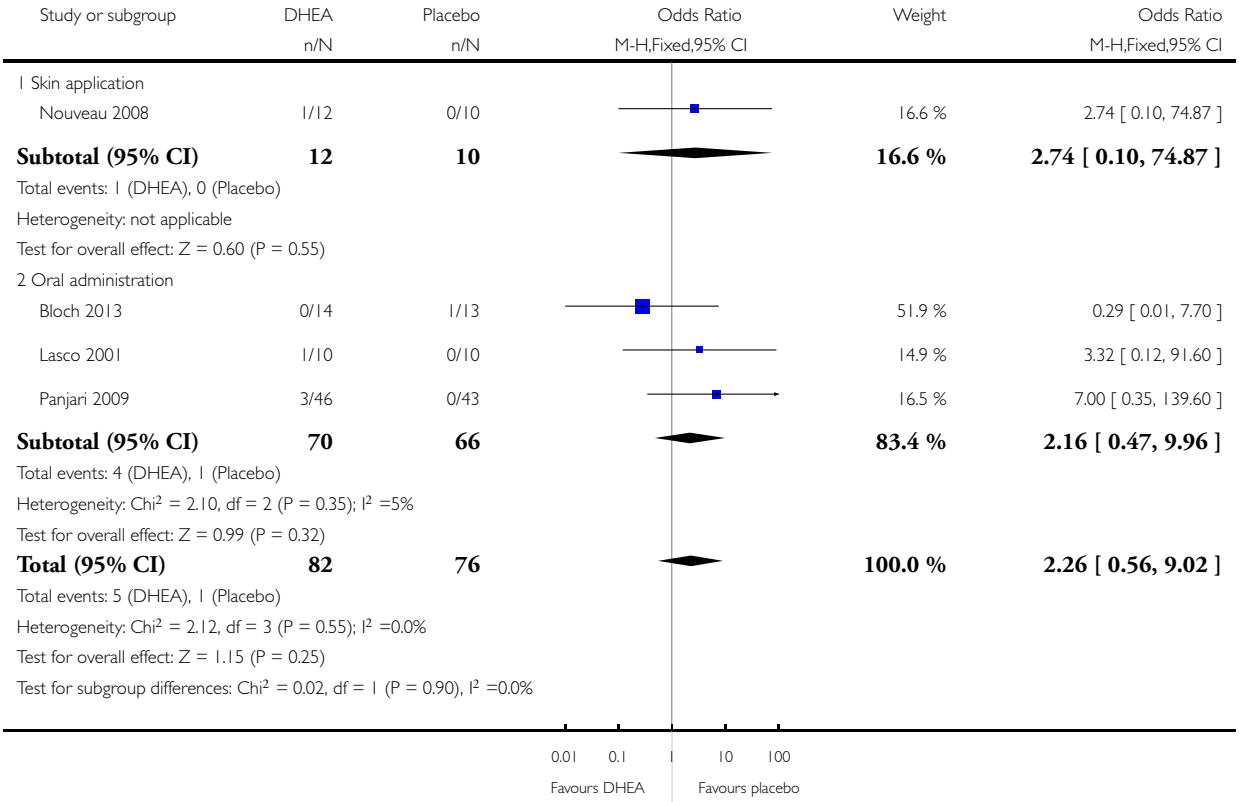


Analysis 2.2. Comparison 2 Oral DHEA versus control subgrouped by route of administration, Outcome 2 Side-effects: acne.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 2 Oral DHEA versus control subgrouped by route of administration

Outcome: 2 Side-effects: acne

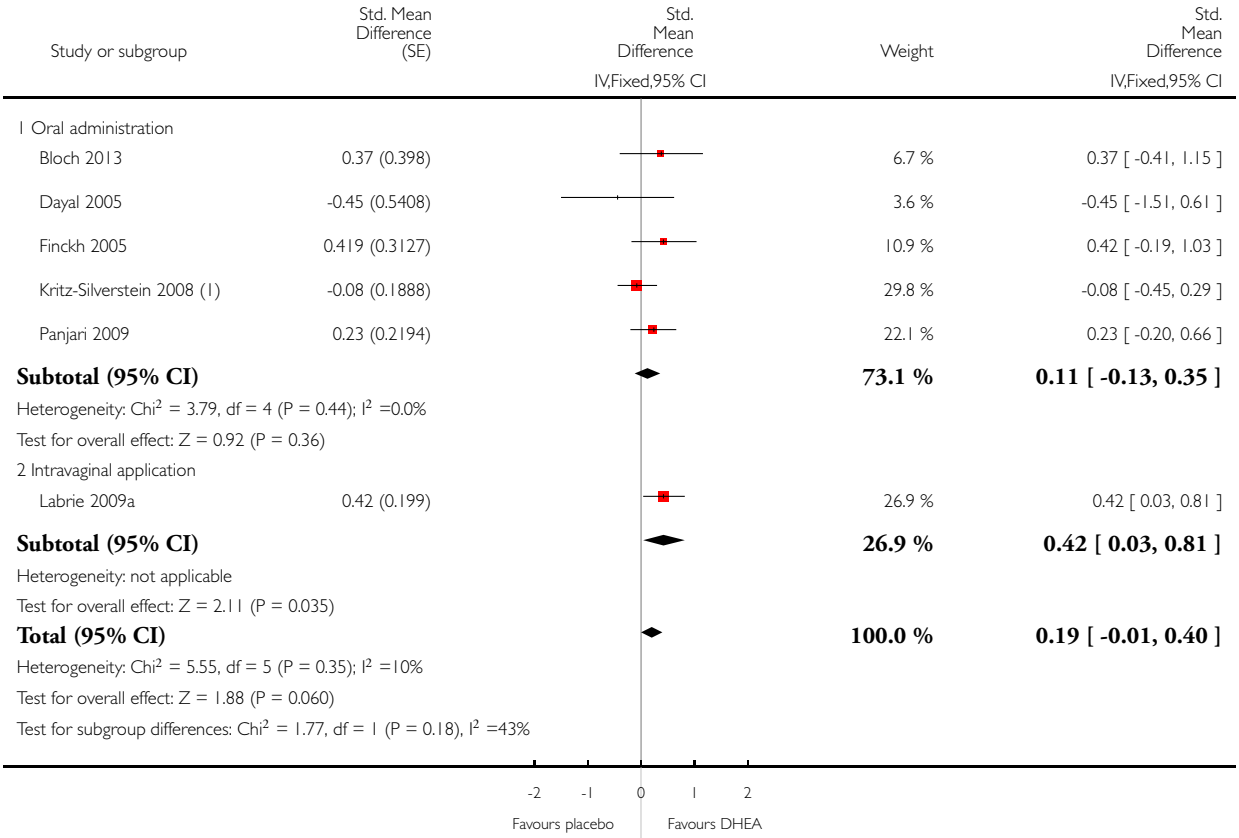


Analysis 2.4. Comparison 2 Oral DHEA versus control subgrouped by route of administration, Outcome 4 Sexual Function (end scores).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 2 Oral DHEA versus control subgrouped by route of administration

Outcome: 4 Sexual Function (end scores)



(1) sensitivity analysis without study - result are and hetero

Analysis 3.1. Comparison 3 DHEA versus HT, Outcome 1 QoL/General Wellbeing.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 3 DHEA versus HT

Outcome: 1 QoL/General Wellbeing

Study or subgroup	DHEA N	Mean(SD)	HT N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 ET						
Dayal 2005	12	16.731 (3.18)	5	15.1 (3.93)		1.63 [-2.25, 5.52]
2 Combined						
3 Tibolone						

Analysis 3.3. Comparison 3 DHEA versus HT, Outcome 3 Menopausal symptoms (continuous).

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 3 DHEA versus HT

Outcome: 3 Menopausal symptoms (continuous)

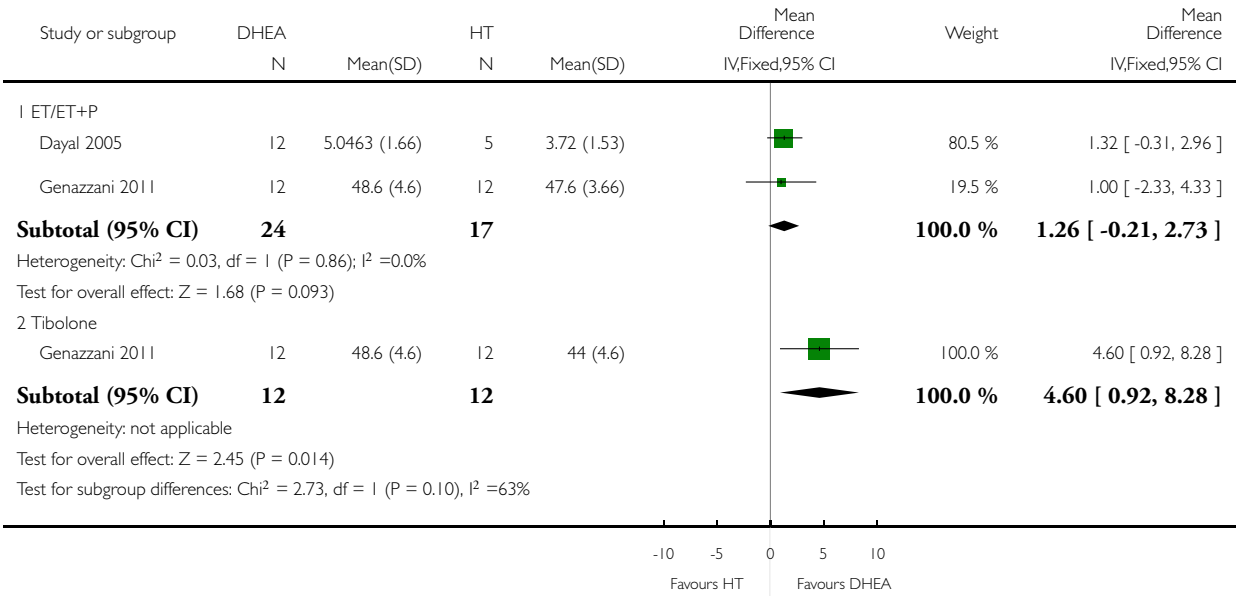
Study or subgroup	DHEA N	Mean(SD)	HRT N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 ET						
Stomati 1999	8	-4.75 (4.2426)	6	-3 (4.654)		-0.37 [-1.44, 0.70]
2 Combined						
Genazzani 2011	12	-8 (1)	12	-9 (0.9)		1.01 [0.16, 1.87]
3 Tibolone						
Genazzani 2011	12	-8 (1)	12	-9 (0.8)		1.07 [0.20, 1.93]

Analysis 3.4. Comparison 3 DHEA versus HT, Outcome 4 Sexual Function.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 3 DHEA versus HT

Outcome: 4 Sexual Function



Analysis 4.1. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 1 Acne.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 1 Acne

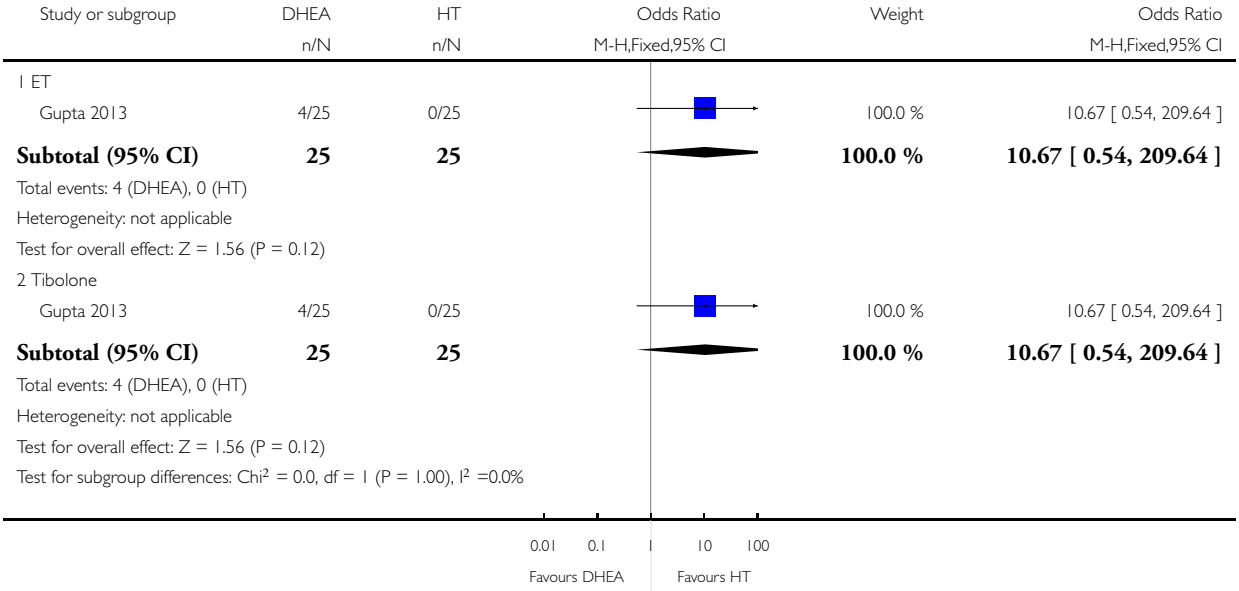
Study or subgroup	DHEA n/N	HT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 ET					
Gupta 2013	6/25	0/25		100.0 %	17.00 [0.90, 320.37]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**17.00 [0.90, 320.37]**
Total events: 6 (DHEA), 0 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.89 (P = 0.059)					
2 Tibolone					
Gupta 2013	6/25	0/25		100.0 %	17.00 [0.90, 320.37]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**17.00 [0.90, 320.37]**
Total events: 6 (DHEA), 0 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.89 (P = 0.059)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%					

Analysis 4.2. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 2 Hair loss.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 2 Hair loss

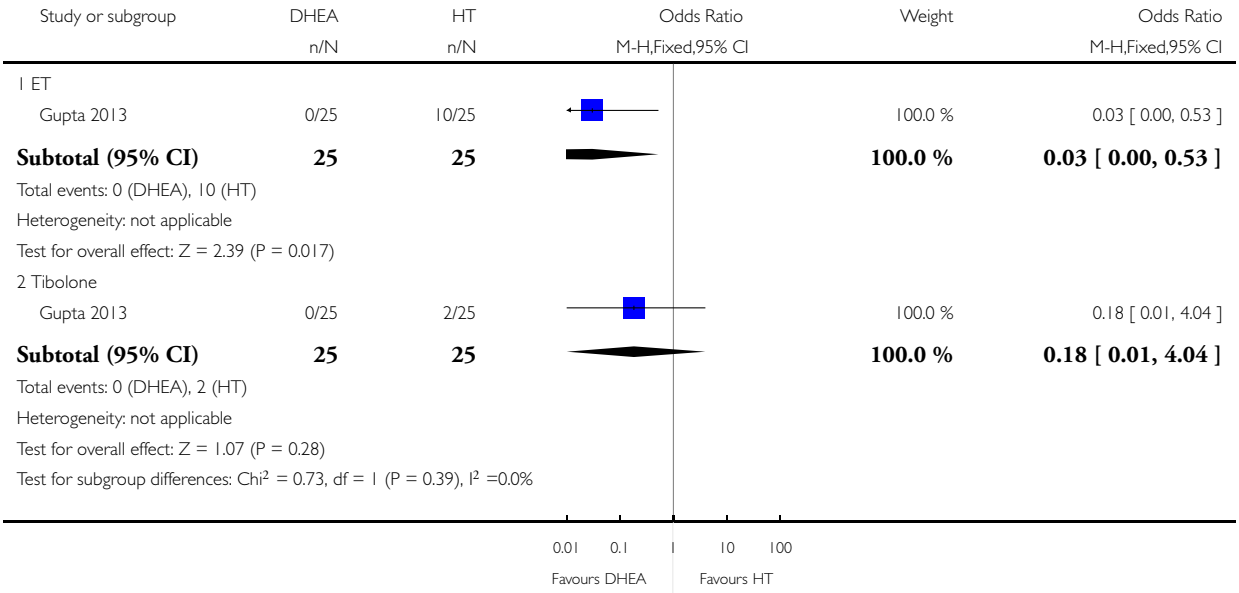


Analysis 4.3. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 3 Headache.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 3 Headache

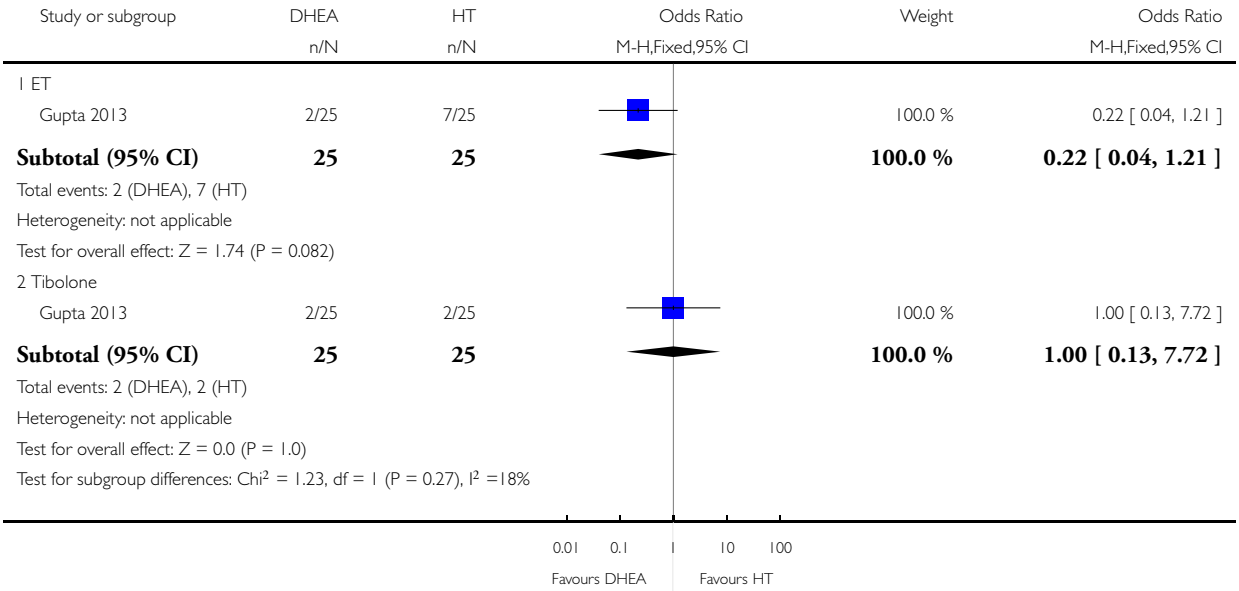


Analysis 4.4. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 4 Nausea.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 4 Nausea



Analysis 4.5. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 5 Leg cramps.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 5 Leg cramps

Study or subgroup	DHEA n/N	HT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 ET					
Gupta 2013	0/25	0/25			Not estimable
Subtotal (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (DHEA), 0 (HT)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Tibolone					
Gupta 2013	0/25	0/25			Not estimable
Subtotal (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (DHEA), 0 (HT)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

Analysis 4.6. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 6 Breast Tenderness.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 6 Breast Tenderness

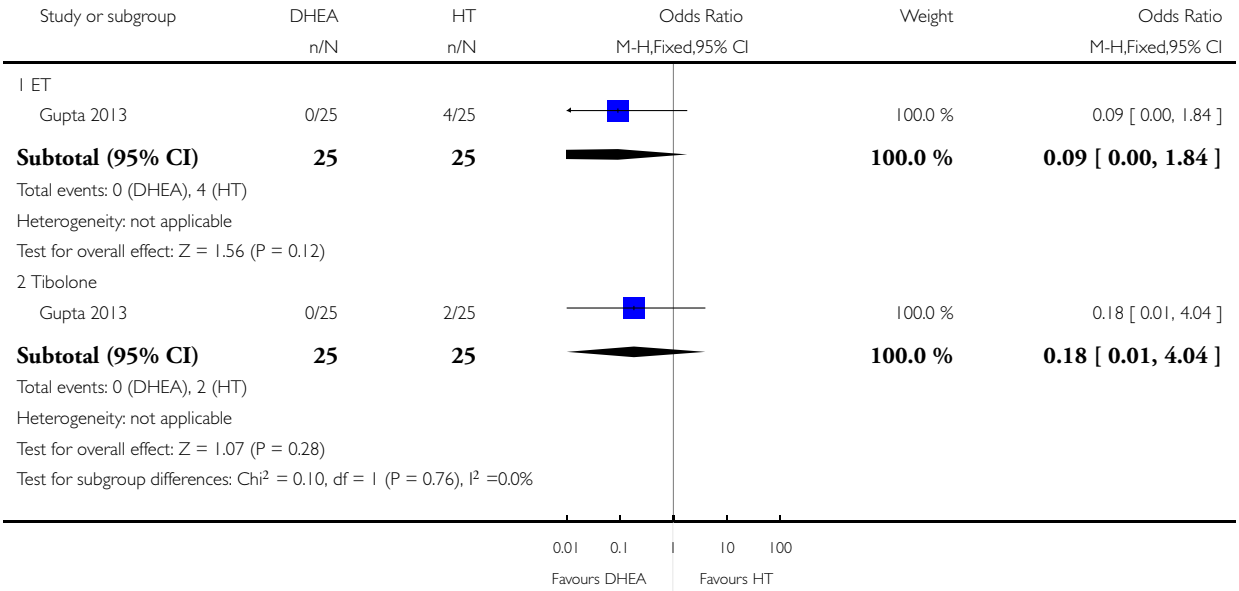
Study or subgroup	DHEA n/N	HT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 ET					
Gupta 2013	0/25	5/25		100.0 %	0.07 [0.00, 1.40]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**0.07 [0.00, 1.40]**
Total events: 0 (DHEA), 5 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.74 (P = 0.082)					
2 Tibolone					
Gupta 2013	0/25	1/25		100.0 %	0.32 [0.01, 8.25]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**0.32 [0.01, 8.25]**
Total events: 0 (DHEA), 1 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi^2 = 0.44, df = 1 (P = 0.51), I^2 =0.0%					

Analysis 4.7. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 7 Bloating.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 7 Bloating

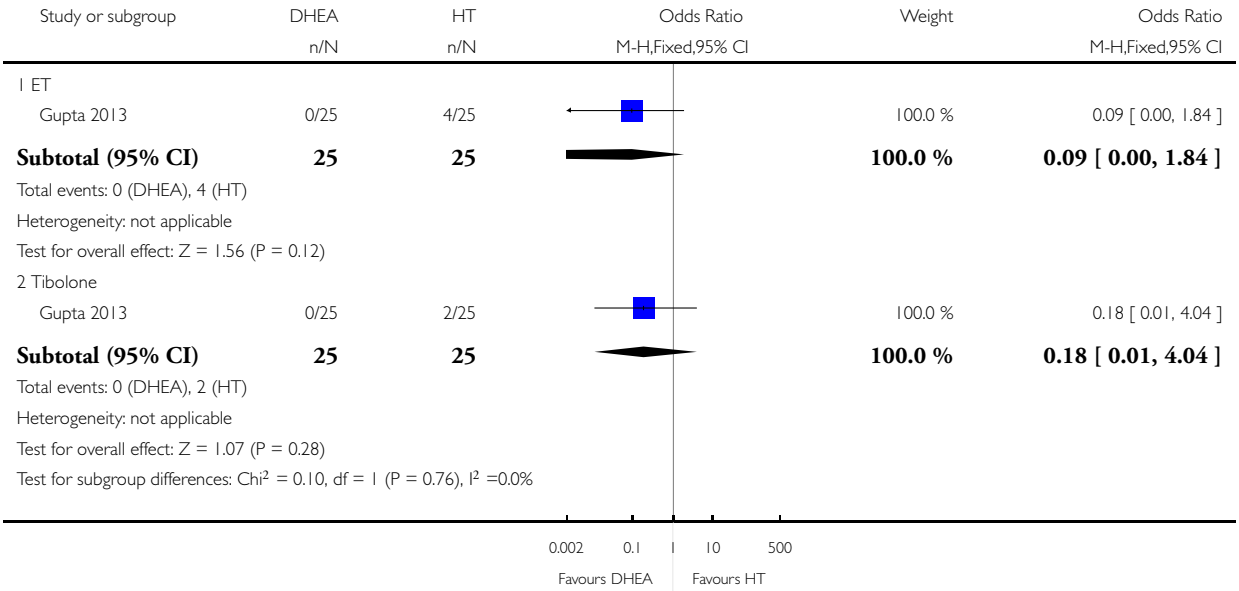


Analysis 4.8. Comparison 4 DHEA versus HT (side effects) (dichotomous), Outcome 8 Weight gain.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 4 DHEA versus HT (side effects) (dichotomous)

Outcome: 8 Weight gain



Analysis 5.1. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 1 Tiredness.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 1 Tiredness

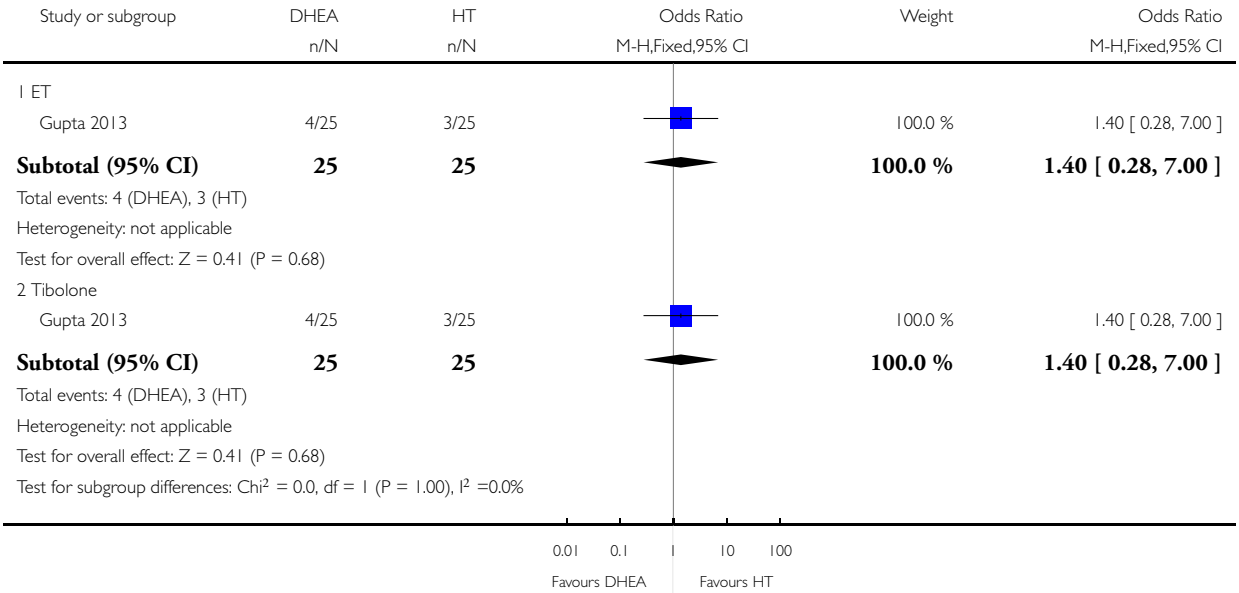
Study or subgroup	DHEA n/N	HT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 ET					
Gupta 2013	6/25	5/25		50.0 %	1.26 [0.33, 4.84]
Subtotal (95% CI)	**25**	**25**		**50.0 %**	**1.26 [0.33, 4.84]**
Total events: 6 (DHEA), 5 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
2 Tibolone					
Gupta 2013	6/25	5/25		50.0 %	1.26 [0.33, 4.84]
Subtotal (95% CI)	**25**	**25**		**50.0 %**	**1.26 [0.33, 4.84]**
Total events: 6 (DHEA), 5 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
Total (95% CI)	**50**	**50**		**100.0 %**	**1.26 [0.49, 3.26]**
Total events: 12 (DHEA), 10 (HT)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%					

Analysis 5.2. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 2 Hot flushes and palpitations.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 2 Hot flushes and palpitations

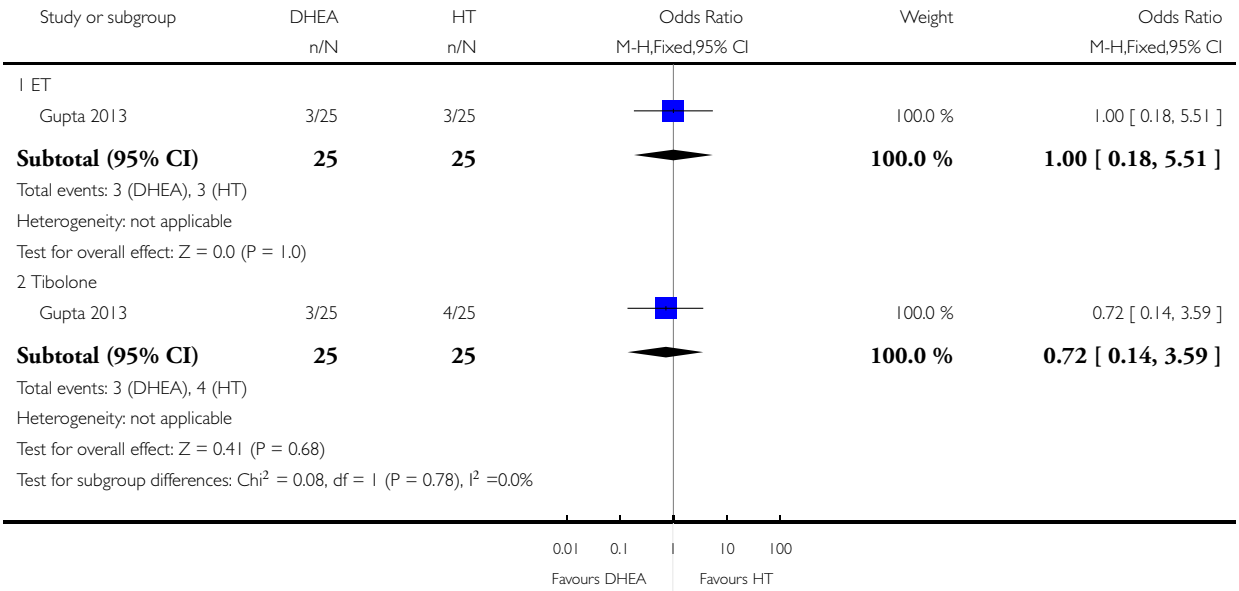


Analysis 5.3. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 3 Night sweats.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 3 Night sweats

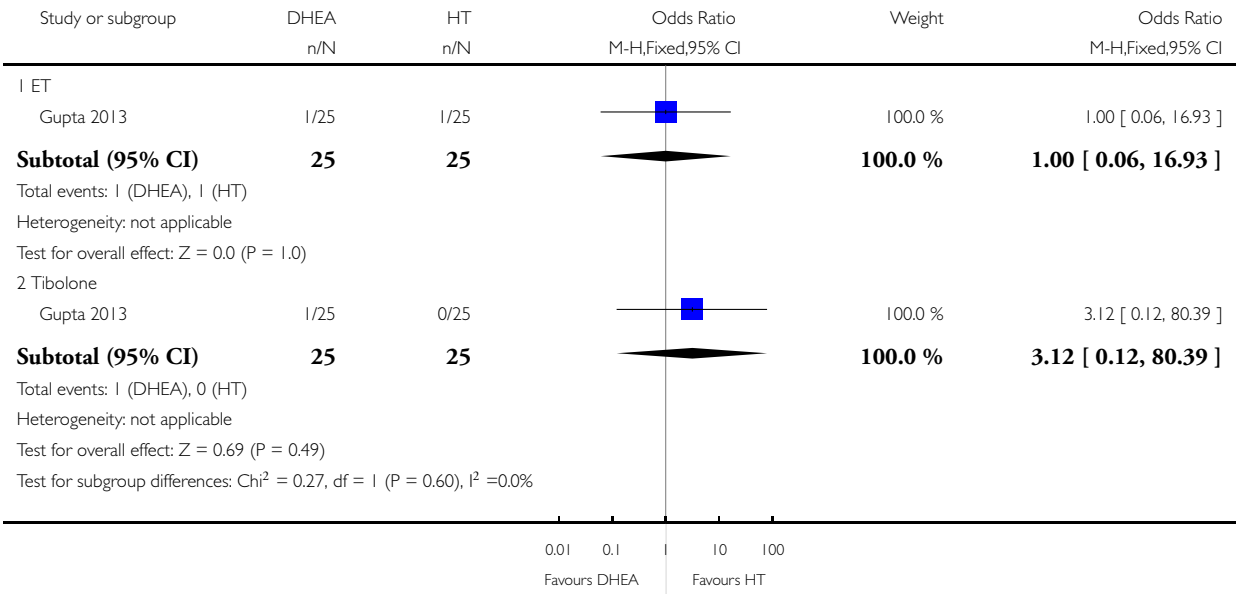


Analysis 5.4. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 4 Vaginal Dryness.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 4 Vaginal Dryness

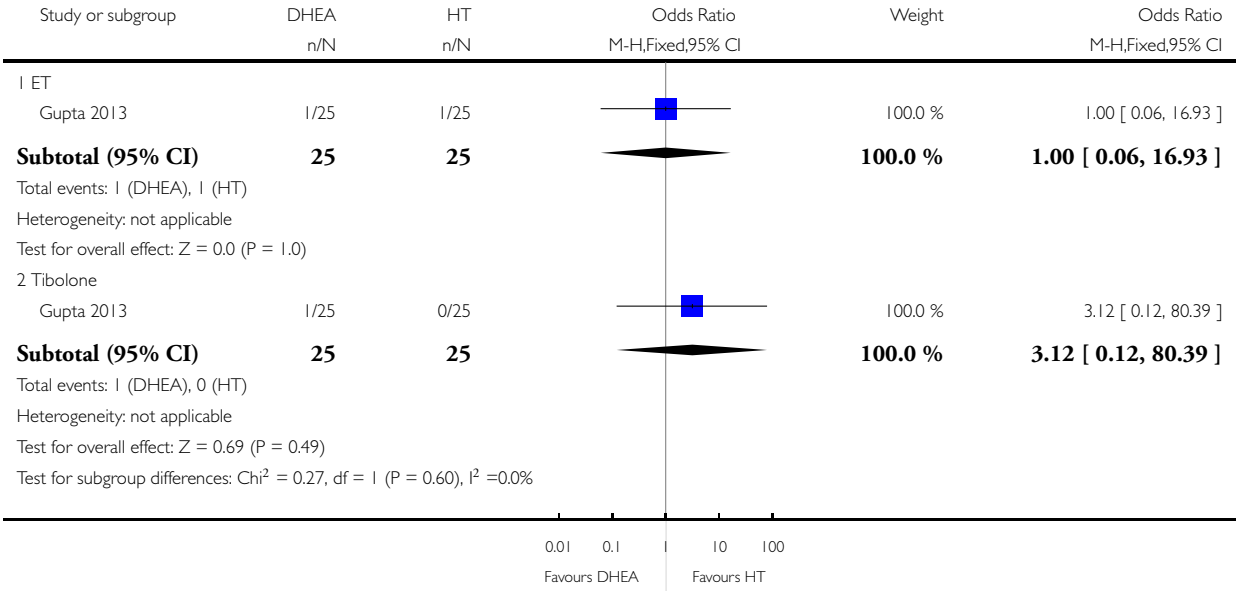


Analysis 5.5. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 5 Pruritis Vulvae.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 5 Pruritis Vulvae

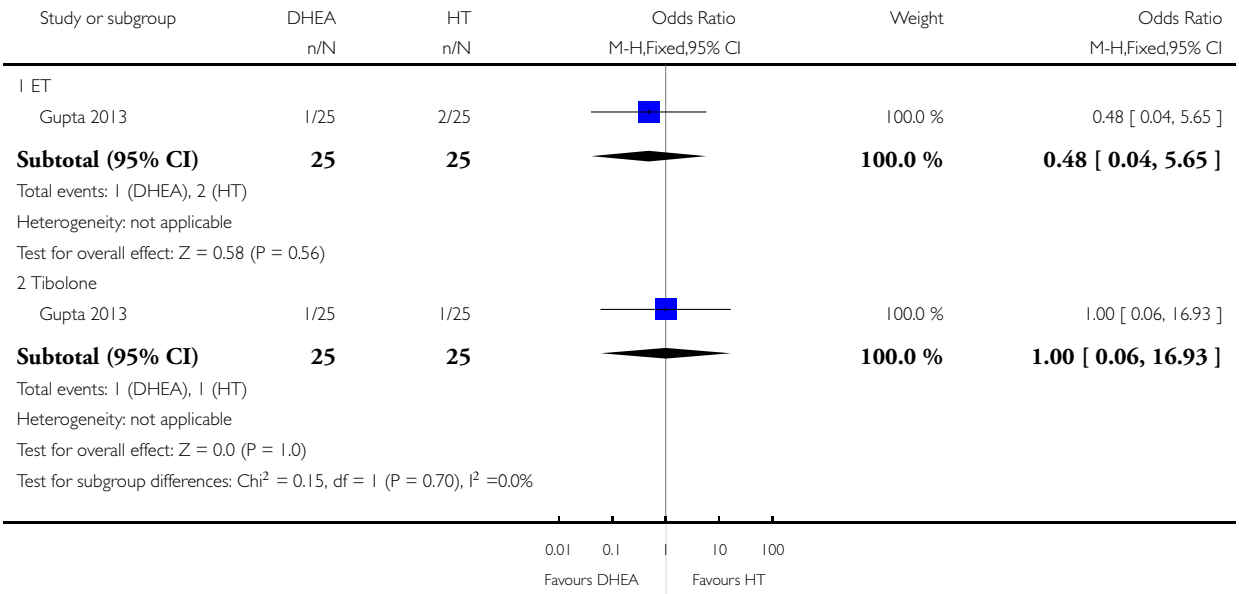


Analysis 5.6. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 6 Urethral Syndrome.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 6 Urethral Syndrome



Analysis 5.7. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 7 Depression.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 7 Depression

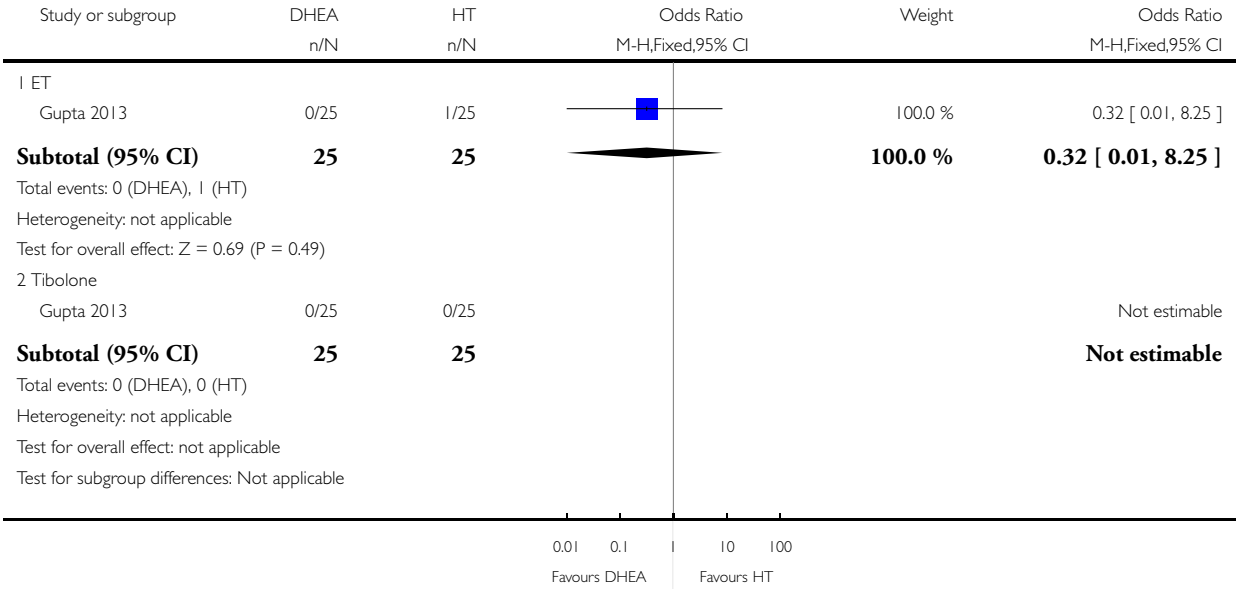
Study or subgroup	DHEA n/N	HT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 ET					
Gupta 2013	0/25	1/25		100.0 %	0.32 [0.01, 8.25]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**0.32 [0.01, 8.25]**
Total events: 0 (DHEA), 1 (HT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 Tibolone					
Gupta 2013	0/25	0/25			Not estimable
Subtotal (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (DHEA), 0 (HT)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 5.8. Comparison 5 DHEA versus HT (menopausal symptoms) (dichotomous), Outcome 8 Loss of libido.

Review: Dehydroepiandrosterone for women in the peri- or postmenopausal phase

Comparison: 5 DHEA versus HT (menopausal symptoms) (dichotomous)

Outcome: 8 Loss of libido



APPENDICES

Appendix 1. Menstrual Disorders and Subfertility Group search strategy (PROCITE platform)

Menstrual Disorders and Subfertility (MDSG) database search.
Keywords CONTAINS "menopausal"or"*Menopause"or"perimenopause"or"perimenopausal"or "Postmenopausal"or "postmenopause"or"climacteric "or "vasomotor"or"hot flashes"or "hot flushes"or"vaginal atrophy"or "vaginal dryness" or "night sweats"or "night sweats-outcome"or"night time awakenings"or "nocturnal diaphoresis"or"sexual function"or"sexual fuctioning"or "Sexual functioning"or "sexual satisfaction" or Title CONTAINS "menopausal"or"*Menopause"or"perimenopause"or"perimenopausal"or "Postmenopausal"or "postmenopause"or"climacteric "or "vasomotor"or"hot flashes"or "hot flushes"or"vaginal atrophy"or "vaginal dryness" or "night sweats"or "night sweats-outcome"or"night time awakenings"or "nocturnal diaphoresis"or"sexual function"or"sexual fuctioning"or "Sexual functioning"or "sexual satisfaction"
AND
Keywords CONTAINS "DHEA"or "DHEAS" or"dehydroepiandrosterone"or "androstenedione" or "Prasterone" or Title CONTAINS "DHEA"or "DHEAS" or"dehydroepiandrosterone"or "androstenedione" or "Prasterone"

Appendix 2. CENTRAL search strategy (Ovid platform)

From inception to 10 February 2014; search updated on 3 June 2014
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 (climacteric or menopaus$).tw. (4318)
2 (postmenopaus$ or perimenopaus$).tw. (8532)
3 vasomotor.tw. (899)
4 exp Menopause, Premature/ or exp Menopause/ (5295)
5 exp Climacteric/ (5514)
6 exp Perimenopause/ (62)
7 exp Postmenopause/ (3510)
8 exp Hot Flashes/ (457)
9 (hot flash$ or hot flush$).tw. (1014)
10 night sweat$.tw. (107)
11 Nocturnal diaphoresis.tw. (2)
12 vagina$ dry$.tw. (119)
13 sexual function$.tw. (931)
14 sexual satisfaction.tw. (149)
15 vagina$ atrophy.tw. (80)
16 or/1-15 (13614)
17 exp Dehydroepiandrosterone Sulfate/ or exp Dehydroepiandrosterone/ (490)
18 Dehydroepiandrosterone.tw. (629)
19 DHEA$.tw. (557)
20 androstenedione.tw. (396)
21 Prasterone.tw. (14)
22 dehydroisoandrosterone.tw. (0)
23 dha sulfate.tw. (1)
24 androstenolone.tw. (3)
25 or/17-24 (1028)
26 16 and 25 (213)

Appendix 3. MEDLINE search strategy (Ovid platform)

From inception to 10 February 2014; search updated on 3 June 2014
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 (climacteric or menopaus$).tw. (37286)
2 (postmenopaus$ or perimenopaus$).tw. (42140)
3 vasomotor.tw. (10342)
4 exp Menopause, Premature/ or exp Menopause/ (44481)
5 exp Climacteric/ (47888)
6 exp Perimenopause/ (748)
7 exp Postmenopause/ (18274)
8 exp Hot Flashes/ (2212)
9 (hot flash$ or hot flush$).tw. (3446)
10 night sweat$.tw. (1409)
11 Nocturnal diaphoresis.tw. (7)
12 vagina$ dry$.tw. (617)
13 sexual function$.tw. (8686)
14 sexual satisfaction.tw. (1342)
15 vagina$ atrophy.tw. (309)
16 or/1-15 (101033)

17 exp Dehydroepiandrosterone Sulfate/ or exp Dehydroepiandrosterone/ (10083)
18 Dehydroepiandrosterone.tw. (9609)
19 DHEA$.tw. (6434)
20 androstenedione.tw. (8040)
21 Prasterone.tw. (82)
22 dehydroisoandrosterone.tw. (220)
23 dha sulfate.tw. (54)
24 androstenolone.tw. (59)
25 or/17-24 (19764)
26 16 and 25 (1887)
27 randomized controlled trial.pt. (360999)
28 controlled clinical trial.pt. (87042)
29 randomized.ab. (281866)
30 randomised.ab. (55469)
31 placebo.tw. (153268)
32 clinical trials as topic.sh. (166848)
33 randomly.ab. (205060)
34 trial.ti. (120220)
35 (crossover or cross-over or cross over).tw. (58959)
36 or/27-35 (912453)
37 exp animals/ not humans.sh. (3871615)
38 36 not 37 (841156)
39 26 and 38 (281)

Appendix 4. EMBASE search strategy (Ovid platform)

From inception to 10 February 2014; search updated on 3 June 2014
Database: Embase

1 exp menopause/ or exp early menopause/ or exp menopause related disorder/ or exp "menopause and climacterium"/ (98833)
2 exp climacterium/ (7155)
3 exp postmenopause bleeding/ or exp postmenopause/ or exp postmenopause osteoporosis/ (54600)
4 exp hot flush/ (11311)
5 (climacteric or menopaus$).tw. (51753)
6 (postmenopaus$ or perimenopaus$).tw. (56450)
7 vasomotor.tw. (12370)
8 (hot flash$ or hot flush$).tw. (4839)
9 night sweat$.tw. (2592)
10 Nocturnal diaphoresis.tw. (11)
11 vagina$ dry$.tw. (993)
12 sexual function$.tw. (12965)
13 sexual satisfaction.tw. (2075)
14 or/1-13 (153865)
15 exp prasterone/ (12291)
16 Dehydroepiandrosterone.tw. (10653)
17 DHEA$.tw. (8281)
18 androstenedione.tw. (8525)
19 Prasterone.tw. (110)
20 dehydroisoandrosterone.tw. (193)
21 dha sulfate.tw. (49)
22 androstenolone.tw. (48)
23 or/15-22 (23993)

24 14 and 23 (2738)
25 Clinical Trial/ (893176)
26 Randomized Controlled Trial/ (367106)
27 exp randomization/ (64837)
28 Single Blind Procedure/ (18996)
29 Double Blind Procedure/ (120415)
30 Crossover Procedure/ (39883)
31 Placebo/ (235150)
32 Randomi?ed controlled trial$.tw. (100442)
33 Rct.tw. (13654)
34 random allocation.tw. (1338)
35 randomly allocated.tw. (20433)
36 allocated randomly.tw. (1956)
37 (allocated adj2 random).tw. (745)
38 Single blind$.tw. (14429)
39 Double blind$.tw. (144232)
40 ((treble or triple) adj blind$).tw. (359)
41 placebo$.tw. (201652)
42 prospective study/ (263739)
43 or/25-42 (1415726)
44 case study/ (24045)
45 case report.tw. (261912)
46 abstract report/ or letter/ (904483)
47 or/44-46 (1184797)
48 43 not 47 (1377829)
49 24 and 48 (672)

Appendix 5. PsycINFO search strategy (Ovid platform)

From inception to 10 February 2014; search updated on 3 June 2014
Database: PsycINFO

1 exp Menopause/ (2848)
2 (climacteric or menopaus$).tw. (3823)
3 (postmenopaus$ or perimenopaus$).tw. (2229)
4 vasomotor.tw. (1149)
5 (hot flash$ or hot flush$).tw. (436)
6 night sweat$.tw. (110)
7 Nocturnal diaphoresis.tw. (1)
8 vagina$ dry$.tw. (107)
9 sexual function$.tw. (3897)
10 sexual satisfaction.tw. (1500)
11 vagina$ atroph$.tw. (32)
12 or/1-11 (10927)
13 Dehydroepiandrosterone.tw. (759)
14 DHEA$.tw. (690)
15 androstenedione.tw. (212)
16 Prasterone.tw. (2)
17 dehydroisoandrosterone.tw. (5)
18 dha sulfate.tw. (1)
19 androstenolone.tw. (1)
20 or/13-19 (1022)

21 12 and 20 (103)
22 random.tw. (39521)
23 control.tw. (307334)
24 double-blind.tw. (17545)
25 clinical trials/ (7255)
26 placebo/ (3679)
27 exp Treatment/ (566963)
28 or/22-27 (865080)
29 21 and 28 (53)

Appendix 6. CINAHL search strategy (EBSCO platform)

From inception to 10 February 2014; search updated on 3 June 2014

#	Query	Results
S22	S15 AND S21	230
S21	S16 OR S17 OR S18 OR S19 OR S20	1,246
S20	TX androstenedione	262
S19	TX Prasterone	18
S18	TX DHEA	366
S17	TX Dehydroepiandrosterone	1,064
S16	(MM "Dehydroepiandrosterone")	390
S15	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	25,518
S14	TX Nocturnal diaphoresis	1
S13	TX sexual satisfaction	1,056
S12	TX sexual function*	2,371
S11	TX vagina* atrophy	128
S10	TX vagina* dry*	230
S9	TX night sweat*	345
S8	TX hot flush*	466
S7	TX hot flash*	2,018
S6	TX Climacteri*	1,659

(*Continued*)

S5	(MH "Climacteric+") OR (MH "Hot Flashes")	15,561
S4	TX perimenopaus*	3,096
S3	TX postmenopaus*	11,557
S2	TX Menopaus*	11,502
S1	(MH "Menopause+") OR (MM "Menopause, Premature") OR (MM "Perimenopause") OR (MM "Postmenopause")	13,395

Appendix 7. Search strategies for other databases

The search strategy for trials registers

ClinicalTrials.gov; http://www.clinicaltrials.gov and ICTRP (The World Health Organization International Trials Registry Platform search portal) http://www.who.int/trialsearch/Default.aspx
'DHEA' AND 'Menopause'
'DHEA' AND 'postmenopause'
'Dehydroepiandrosterone' AND 'Menopause'
'Dehydroepiandrosterone' AND 'Postmenopause'

The search strategy for DARE (Database of Abstracts of Reviews of Effects)

The Cochrane Library at http://onlinelibrary.wiley.com/o/cochrane/cochrane˙cldare˙articles˙fs.html (for reference lists from relevant non-Cochrane reviews)
'DHEA' AND 'Menopause'
DHEA' AND 'postmenopause'
'Dehydroepiandrosterone' AND 'Menopause'
'Dehydroepiandrosterone' AND 'Postmenopause'

The search strategy for the Web of Knowledge

http://wokinfo.com/
'DHEA' AND 'Menopaus*'
'DHEA' AND 'postmenopaus*'
'Dehydroepiandrosterone' AND 'Menopaus*'
'Dehydroepiandrosterone' AND 'Postmenopaus*'

The search strategy for the OpenGrey

http://www.opengrey.eu/
'DHEA' AND 'Menopause'
DHEA' AND 'postmenopause'
'Dehydroepiandrosterone' AND 'Menopause'
'Dehydroepiandrosterone' AND 'Postmenopause'

The search strategy for LILACS

http://regional.bvsalud.org/php/index.php?lang=en
'DHEA' AND 'Menopaus*'
'DHEA' AND 'postmenopaus*'
'Dehydroepiandrosterone' AND 'Menopaus*'
'Dehydroepiandrosterone' AND 'Postmenopaus*'
(limit to LILACS)

The search strategy for PubMed and Google (for recent trials not yet indexed in MEDLINE)

PubMed; http://www.ncbi.nlm.nih.gov/pubmed
'DHEA' AND 'Menopause'
DHEA' AND 'postmenopause'
'Dehydroepiandrosterone' AND 'Menopause'
'Dehydroepiandrosterone' AND 'Postmenopause'
Google Scholar; http://scholar.google.co.nz/
'DHEA' AND 'Menopause'
DHEA' AND 'postmenopause'
'Dehydroepiandrosterone' AND 'Menopause'
'Dehydroepiandrosterone' AND 'Postmenopause'

CONTRIBUTIONS OF AUTHORS

CS - drafted protocol and full review text, abstract and full text screening and data extraction

SA - read, adjusted and approved draft, main part of abstracts and full text screening and data extraction

AC - read, adjusted and approved draft, abstracts and full text screening

CF - provided expert advice on background, read and adjusted draft

VJ - provided methodological advice as well having read, adjusted and approved draft

DECLARATIONS OF INTEREST

None

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Internal sources

- None, Other.

External sources

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Internship Funding

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has been changed from: "Dehydroepiandrosterone for menopausal women" to "Dehydroepiandrosterone for women in the peri- and postmenopausal phase" as these terms were more woman-centred. Objectives were changed from "women with menopausal symptoms" into "women in the peri- or postmenopausal phase". We found "women in the peri- and postmenopausal phase" described our study population better, as menopausal symptoms were not our main outcome.

For assessment of adverse effects we assessed cardiovascular risk and breast cancer risk by measuring the frequency of cardiovascular events and breast cancer events in trials. This was not specified in the protocol. We did not assess other cardiovascular risk parameters or breast cancer parameters.

We replaced 'hormone replacement therapy' with 'hormone therapy'. Tibolone (a synthesized hormone) has been added to hormone therapy but has been separated from estrogen (with or without progestin) therapies.

We chose to include an additional subgroup analysis looking at route of administration as we were unable to conduct a direct comparison of different application route as planned. We chose to do a sensitivity analysis for our secondary outcome sexual function as well (excluding studies with a high risk of bias) as we judged the remaining results to be more accurate and more reliable.

None of these changes were made as a result of the findings of included studies, but to improve the structure of the review.