Does Dehydroepiandrosterone supplementation improve reproductive outcomes in patients with normal ovarian reserve undergoing in vitro fertilization? A systematic review and meta-analysis

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Structured abstract

Objective

The aim of this systematic review and meta-analysis is to study the efficacy of Dehydroepiandrosterone in infertile patients with normal ovarian reserve.

Design

Systematic review and meta-analysis.

Setting

Centers for reproductive care.

Patients

Infertility patients with normal ovarian reserve.

Intervention

A comprehensive electronic literature search was conducted in Pubmed, the Cochrane Library and Web of Science up to March 2021. Randomized controlled trials studying the effect of DHEA supplementation on reproductive outcomes in patients with normal ovarian reserve were included.

Main Outcome Measures

The outcomes of interest were clinical pregnancy rate, live birth rate and miscarriage rate.

Results

DHEA supplementation, compared with placebo or no treatment, was associated with a significant increase in the number of oocytes retrieved (MD = 0.85, 95% CI: 0.23-1.48; p = 0.007). Moreover, we found a significant decrease in miscarriage rate (OR = 0.31, 95% CI: 0.11-0.86; p = 0.02) in DHEA group. In contrast, there were no statistically significant differences in live birth rate (OR = 1.79, 95% CI: 1.01-3.18; p = 0.05), clinical pregnancy rate (OR = 1.37, 95% CI: 0.87-2.15; p = 0.18) or in the number of metaphase II oocytes retrieved (MD = 0.4 CI 95%: - 0.01-0.80; p = 0.05) between the two groups.

Conclusions

Our study suggested that DHEA supplementation could improve the number of oocytes retrieved and the miscarriage rate but could not demonstrate an increase in the clinical pregnancy rate, live birth rate or the number of metaphase II oocytes retrieved.

Key Words

Dehydroepiandrosterone supplementation

Pregnancy outcome

Normal ovarian reserve

Introduction

Infertility is a common condition with important psychological, economic, demographic and medical implications. The demand for assisted reproductive techniques has increased in recent years, one of the main causes has been delayed childbearing. The growing role of women in the labor market, a greater access to university and post-university studies and also to reliable contraceptive methods have contributed to this (1). Its management is often a challenge, especially in those patients in whom a low number of oocytes is obtained after adequate ovarian stimulation.

Recently, the possible effect of dehydroepiandrosterone (DHEA) in infertility patients and especially in those with poor ovarian reserve[1] (POR) has been studied for its potential effect on oocyte quantity and quality, but its effectiveness and mechanism of action are not yet known exactly.

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAs) are precursors for intracellular production of estrogens and androgens; they are synthesized mainly in the reticular zone of the cortex of the adrenal glands but also in the ovarian theca cells.

It has been postulated that DHEA is able to modify early follicular maturation by regulating androgen receptor transcription, increasing FSH receptor expression and modulating FSH activity in granulosa cells. In this way, it is able to increase the number of growing preantral follicles and small antral follicles (2). In addition, it has been proposed that DHEA and DHEAs may increase oocyte quality due to the increase in IGF-1 as it has important actions on the proliferation and differentiation of granulosa cells (3,4) and also because of the ability of DHEA to increase the number of cohesins with consequent decrease in oocyte aneuploidy (5,6).

There have been several systematic reviews and meta-analyses in which an increase in clinical pregnancy and live birth rate has been reported in patients with POR who received DHEA supplementation prior to IVF/ICSI (7,8,9,10,11,12). However, we have not found any systematic review evaluating the effect of DHEA in infertile patients with normal ovarian reserve (NOR) undergoing assisted reproductive treatment. The aim of this systematic review and meta-analysis was to examine the literature and extract the results of randomized controlled trials (RCTs) that investigated the efficacy of DHEA supplementation in infertile women with normal ovarian reserve undergoing IVF/ICSI compared to a control group.

[1]In 2011 the European Society of Human Reproduction and Embryology published the Bologna criteria in order to obtain a standardized definition of POR: presence of at least two of the following characteristics (i) patients aged ≥40 years or other risk factor for POR; (II) a previous low response; (III) altered ovarian reserve.(13)

Material and methods

Study design and registry

This is a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating reproductive outcomes after DHEA treatment in patients with NOR undergoing IVF/ICSI. The review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). The study protocol was registered in PROSPERO prior to the systematic literature search.

Search strategy

The search for clinical trials was performed through different online databases (Web of Science, the Cochrane Library, Pubmed) to identify studies that evaluated the effect of dehydroepiandrosterone on reproductive outcomes in patients with NOR, published in the last 10 years (March 27, 2011 through March 27, 2021). For this purpose, the search strategy included the combination of the following Medical Subject Heading (MeSH) terms: "Dehydroepiandrosterone" or "DHEA"; and "fertilization in vitro" or "reproductive techniques" or "ovulation induction" or "intracytoplasmic sperm injections". No language restrictions were established. The details of the search strategy are specified in the supplemental data section (Supplemental data).

Eligibility criteria

Selection criteria were established prior to the literature search. Studies were selected according to the following criteria: (1) controlled, randomized, parallel studies; (2) studies in which DHEA supplementation was used in monotherapy as experimental medication, regardless of dose and duration of treatment; (3) studies in which the control group received placebo or no medication; (4) studies in which patients met at least one criterion of normal ovarian reserve: FSH <10 IU/l, Anti-Müllerian Hormone 2-6.8 ng/ml, inhibin B >45 pg/ml or antral follicle count (AFC) of 5-15. Trials that included patients of any age or ethnicity were eligible. Studies published only as abstracts in journals were not considered, as their design and quality could not be adequately assessed. Animal studies, studies that were not completed and studies that did not allow data extraction, as well as reviews, comments or letters were also excluded.

Selection of studies and data extraction

According to the selection criteria mentioned above, two reviewers (MC and MP) selected the studies independently; first through the titles and abstracts and then by checking that they met the inclusion criteria with the full-text review. Subsequently, each reviewer extracted the data of interest from each study. Any disagreements were resolved by discussion among the reviewers. The following data were extracted from the manuscripts: authorship, year of publication, demographics (type of study, number of patients included and definition of normal ovarian reserve), methodological (method of randomization, allocation concealment), procedural (dose and duration of DHEA, type and protocol of

ovarian stimulation, number of embryos transferred) and main outcome data (live birth rate, clinical pregnancy rate and miscarriage rate) and secondary outcome data (mean and standard deviation of oocytes and metaphase II (MII) oocytes retrieved).

Quality assessment

Two reviewers (MP and MC) independently used the Risk of Bias (RoB) tool developed by Cochrane. Risk of bias was assessed using the following parameters: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) masking of outcome assessment; 5) incomplete outcome data; 6) selective reporting. The risks of bias graphs were constructed with Review Manager 5.4 software (Cochrane Collaboration, Oxford, UK).

Statistical analysis

Meta-analysis was performed using RevMan 5.4 software (Cochrane Collaboration, Oxford, UK). Heterogeneity was measured with Higgins I^2.(15) A value of I^2 greater than 50% was considered to indicate significant heterogeneity, in which case a random effects model was applied; otherwise, we applied a fixed effects model. Dichotomous outcomes (clinical pregnancy rate, live birth rate and miscarriage rate) were analyzed by calculating the odds ratio (OR) with 95% confidence intervals (CI) while continuous outcomes (oocytes and MII oocytes retrieved) were analyzed by calculating standard mean differences (MD) with 95% CI. For the analysis of continuous variables, only the results expressed as mean and standard deviation were included. Statistical significance was established at a p value <0.05. The risk of bias between studies was not measured due to the low number of included studies, in accordance with the Cochrane Handbook recommendation (16).

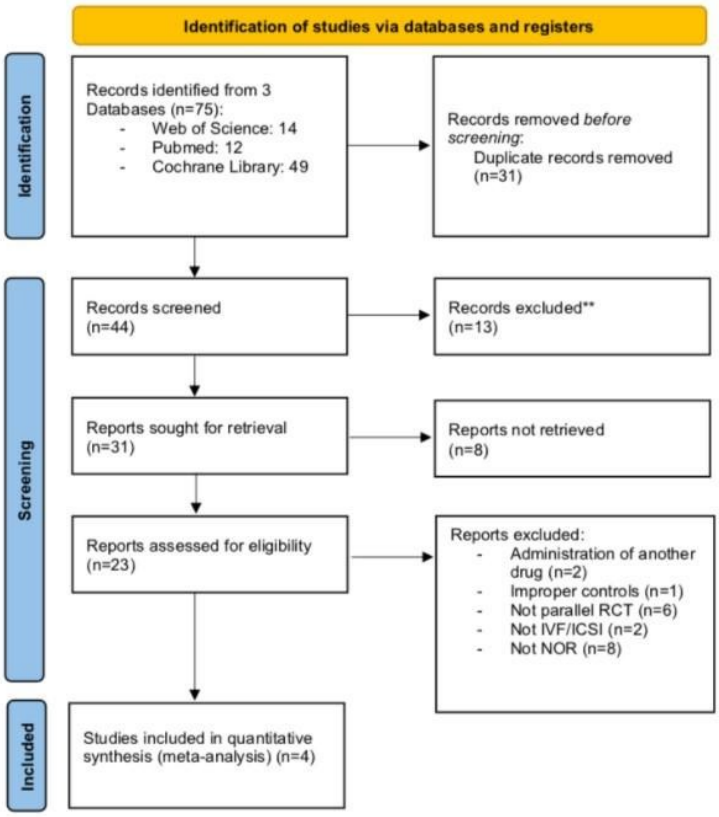
Results

Description of included studies

We identified 75 studies from the 3 databases. After removing 31 duplicate studies and then examining titles and abstracts of the rest, 31 studies remained. After reviewing the full texts of these 31 studies, 4 RCTs were finally included. Figure 1 shows the detailed data retrieval process by which these 4 RCTs (17,18,19,20) were eligible for systematic review and meta-analysis.

Of the total of 327 patients included in this systematic review, 160 patients were in the DHEA group and 167 patients were in the control (placebo) group. All included trials targeted patients with normal ovarian reserve whose definition was based primarily on antral follicle count or laboratory parameters. Most of the patients included in the review were between 35 and 40 years old. In all studies, two embryos or more were transferred if possible. However, the stimulation protocol and the administration and duration of DHEA pretreatment were different for each study. The basic characteristics of the included studies are shown in Table 1.

Figure 1.



RCT = randomized controlled study. IVF: in vitro fertilization. ICSI= Intracytoplasmic sperm injection. NOR: Normal ovarian reserve.

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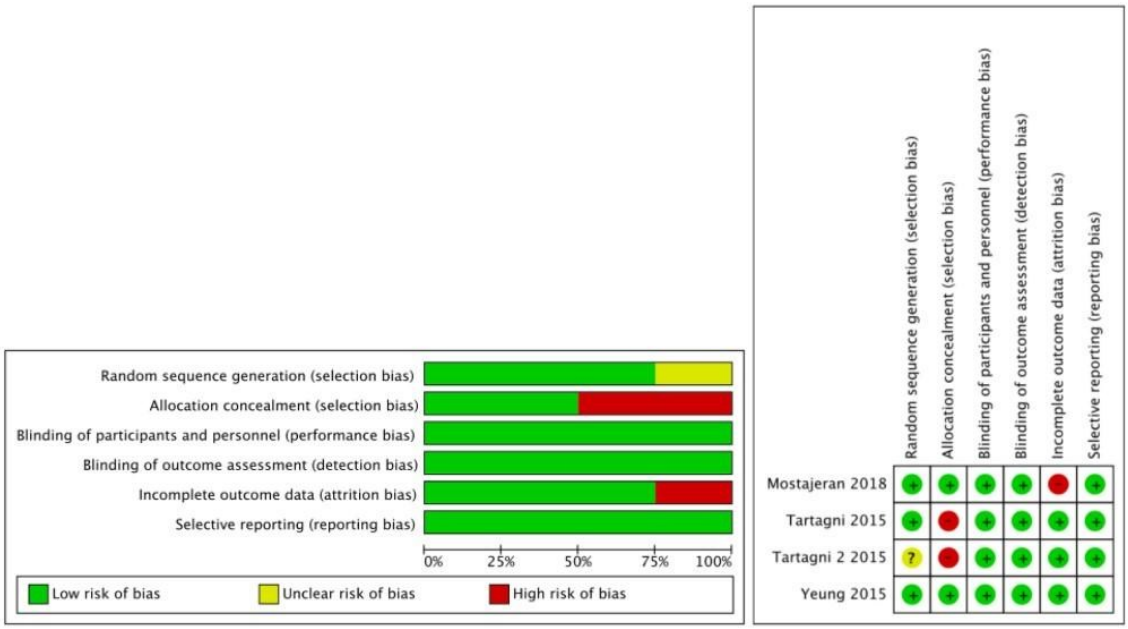
Risk of bias of the included studies

The quality of the included studies was assessed using the RoB tool by evaluating 6 parameters. All included studies were of double-blind, placebo-controlled design with the randomization procedure performed by computer. However, two studies (17,18) did not specify how allocation was concealed and were therefore considered to be at high risk of selection bias. In addition, one study (20) was considered to be at high risk of attrition bias due to the fact that 5 patients assigned to the DHEA group had a spontaneous pregnancy before IVF treatment and were excluded from the study. The details of the RoB are presented in Figure 2.

Figure 2.



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Outcomes

Primary outcomes

Clinical pregnancy rate

The clinical pregnancy rate of the intervention group was higher than that of the control group in all but one trial (19). Of the total of 160 participants in the intervention group, 63 (39.4%) achieved a clinical pregnancy. In contrast, 54 (32.3%) of 167 women achieved a clinical pregnancy in the control group. The 4 RCTs (17,18,19,20) were selected for meta-analysis of clinical pregnancy rate. There were no statistically significant differences between patients who received DHEA supplementation and those who did not in the clinical pregnancy rate [OR=1.37, 95%CI: 0.87-2.15; p=0.18], there was no significant heterogeneity between studies according to the fixed effects model [I^2=34%]. Figure 3 a.

Live birth rate

The live birth rate was evaluated in 3 RCTs(17,18,19); out of 115 patients who received DHEA supplementation, 40 obtained a live newborn (34.8%); while in the control group, 27 out of 118 patients achieved a live newborn (22.9%). In the meta-analysis performed, the live birth rate wasn't statistically significant higher in the DHEA supplemented group than in the control group [OR=1.79, 95%CI:1.01-3.18; p=0.05]; moderate but acceptable heterogeneity was found with the fixed effects model [I^2=49%]. Figure 3 b.

Miscarriage rate

Miscarriage rates were published in all included studies and was 2.5% (4/160) in the intervention group and 9% (15/167) in the control group. All 4 RCTs(17,18,19,20) were included in the meta-

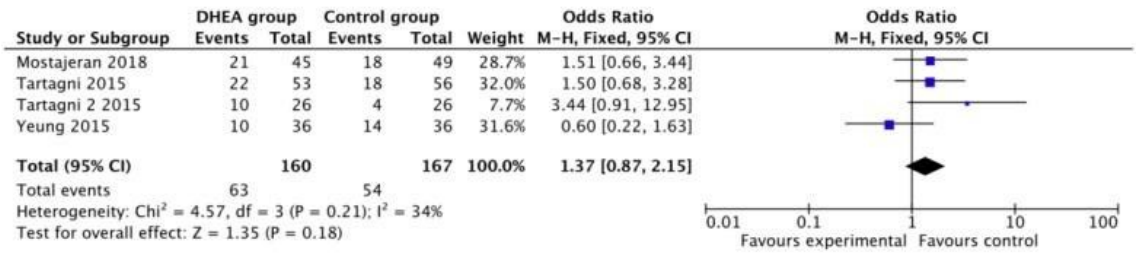
analysis. There was a lower rate of miscarriage in DHEA supplemented patients compared to patients in the control group [OR=0.31, 95%CI:0.11-0.86; p=0.02] and no heterogeneity was observed with the fixed effects model [I^2 = 0%]. Figure 3 c.

Secondary outcomes

Oocytes and MII oocytes retrieved

The analysis results of two RCTs (17,18) showed that the number of retrieved oocytes was higher in the DHEA group than in the control group [0.85, 95% CI: 0.23-1.48; p = 0.007]. However, no statistically significant differences were found in the number of metaphase II oocytes retrieved [MD = 0.40 CI 95%: - 0.01-0.80; p = 0.05] . No significant heterogeneity was found between studies according to the fixed effects model [I^2 = 0%] for either outcome. Figure 3 d-e.

a.



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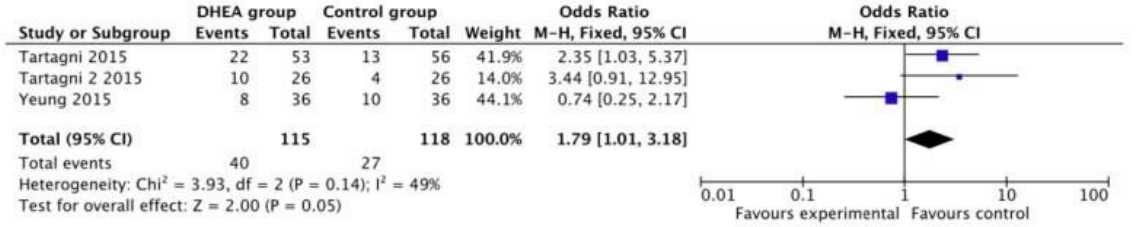

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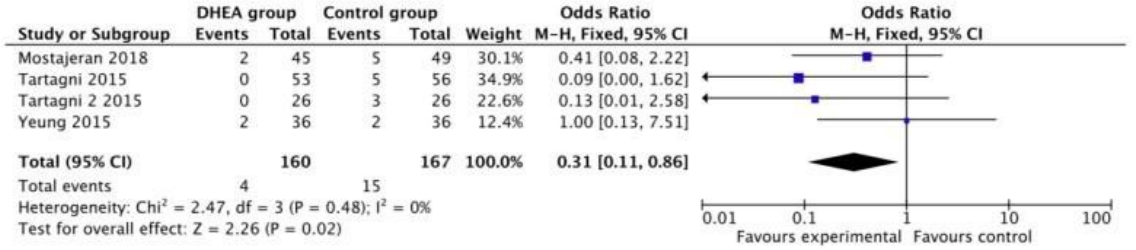

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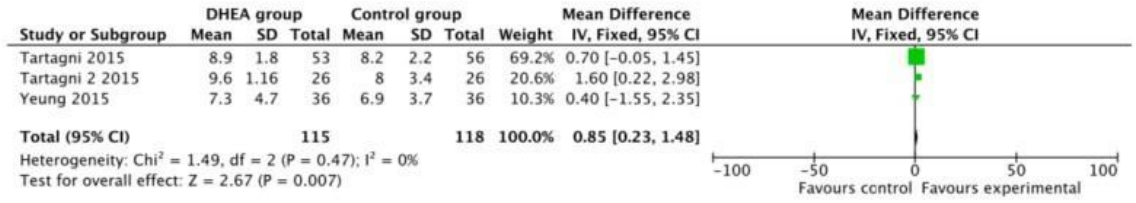

e.

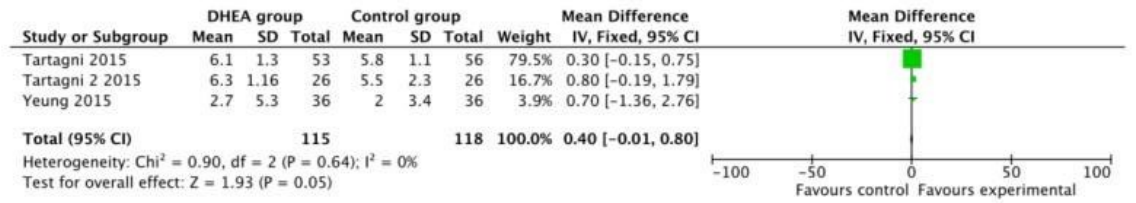

Figure 3.

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Adverse events

In three (17,18,19) of the included RCTs it was specified that the included patients did not experience adverse effects, but in Mostajeran et al study it was not specified (20).

Discussion

This systematic review and meta-analysis summarizes the current scientific evidence on the efficacy of DHEA supplementation before or during controlled ovarian stimulation in infertile patients with normal ovarian reserve undergoing IVF. Four randomized controlled trials were included.

Pretreatment with DHEA to improve fertility has been a topic under constant review in recent years. Most of the studies have focused on the use of DHEA to improve ovarian response and reproductive outcomes in patients with poor ovarian reserve. In 2013, Narkwichean et al published a systematic review and meta-analysis in which no statistically significant difference was found in clinical pregnancy rate or miscarriage rate in patients with POR supplemented with DHEA(21). Subsequently, numerous systematic reviews and meta-analyses were published in which an improvement in the clinical pregnancy rate and live birth rate and a decrease in the miscarriage rate were observed in patients with POR treated with DHEA (7,8,9,10,11,12). However, no differences in the number of oocytes retrieved could be demonstrated in these studies; even in the study of Xu et al. a lower number of oocytes retrieved was observed in DHEA-supplemented patients (12). Due to the promising effects on reproductive outcomes of DHEA in patients with POR and the lack of evidence on its effect in infertile patients with normal ovarian reserve, we decided to perform this systematic review and meta-analysis. This meta-analysis included 4 RCT with 327 patients with normal ovarian reserve who underwent IVF. We analyzed the effect of DHEA supplementation on clinical pregnancy rate, live birth rate, miscarriage rate, and number of oocytes and MII oocytes retrieved. We found that patients who received DHEA supplementation as an intervention had a significantly higher number of oocytes retrieved and a significantly lower miscarriage rate. On the other hand, we did not find statistically significant differences in the live birth rate or the clinical pregnancy rate. We also found no differences in the number of metaphase II oocytes retrieved. In the included studies, no adverse effects were reported with DHEA treatment.

Because of the delay in childbearing and the oxidative stress to which oocytes are subjected by current lifestyles and exposure to toxins (22), the number of infertile couples demanding assisted reproduction treatments has been increasing. Multiple strategies have been studied to increase the quantity and quality of oocytes in infertile patients with the aim of improving reproductive outcomes. Dehydroepiandrosterone supplementation is one of these strategies, although its exact mechanism of action is still unknown. The study by Tsui et al. showed that DHEA supplementation positively affected cumulus cell gene expression, promoted extracellular matrix formation and inhibited apoptosis with a consequent increase in antral follicles (23). On the other hand, Chu et al. found that DHEA was able to delay the physiological loss of cohesins in oocytes that has been related to the occurrence of oocyte aneuploidy(6); furthermore, Gleicher et al. suggested that DHEA supplementation was able to

increase the percentage of euploid embryos obtained in patients with low ovarian reserve with a consequent decrease in the rate of miscarriages (5, 24).

This meta-analysis is the first to our knowledge so far to evaluate the effect of DHEA in infertile patients with normal ovarian reserve. We included only randomized controlled studies in order to minimize biases related to other types of studies. Strict selection criteria and rigorous methodology are the strengths of this study. Nevertheless, our meta-analysis has several limitations. First, there was a study in which the definition of NOR was based on antral follicle count (19), unlike the other studies in which the definition was based on analytical criteria; the definition of normal ovarian reserve should be standardized in order to conduct RCTs with a more homogeneous population. Secondly, the dosage and duration of DHEA treatment was different in each study, as was the ovarian stimulation protocol. Thirdly, the meta-analysis of some results was performed with a low number of patients because we were unable to obtain sufficient data from the original study.

Although no statistically significant differences were observed in the clinical pregnancy rate or the live birth rate, there was a trend towards improvement in both rates with DHEA supplementation; also, as we have commented previously; 5 patients supplemented with DHEA who became pregnant spontaneously were not taken into account for the meta-analysis; these patients could have benefited from DHEA supplementation.

The importance of this study lies in the fact that DHEA seems to be capable of reducing the abortion rate in patients with normal ovarian reserve, probably due to the improvement in the quality of the oocytes.

Conclusions

The findings of this meta-analysis are similar to those of other meta-analyses that studied the effect of DHEA in patients with poor ovarian reserve. We found that the use of DHEA before ovarian stimulation in women with NOR was associated with a decrease in the miscarriage rate and an increase in the number of oocytes retrieved. In addition, no adverse effects were identified with DHEA supplementation. Nevertheless, more well-designed randomized controlled trials are needed to recommend the use of DHEA in infertile patients with normal ovarian reserve and to study which subpopulations might benefit most from DHEA supplementation.

Conflicts of interest

None of the authors have any conflicts of interest or financial ties to disclose. No funding source had involvement in the publication of this manuscript. This research has not received specific aid from public sector agencies, the commercial sector or non-profit entities.

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Figure captions

Figure 1. Preferred Outcome Items for Systematic Reviews and Meta-analysis flow diagram detailing selection of studies for inclusion. RCT = randomized controlled study. IVF: in vitro fertilization. ICSI= Intracytoplasmic sperm injection. NOR: Normal ovarian reserve.
Figure 2. Methodological quality graph. Risk of bias graph and Risk of bias summary.
Figure 3. (a-e): Meta-analysis results. Meta-analysis of studies of DHEA supplementation versus controls for outcome of clinical pregnancy rate (a), live birth rate (b), miscarriage rate (c), oocytes retrieved (d), MII oocytes retrieved.

Tables

Table 1. Methodological characteristics of eligible articles.

Authors and year	Inclusion criteria	Patients (n)		COS protocol	DHEA supplementation	Embryo transfer	Reproductive outcomes	Adverse events
		DHEA group	Control group					
Mostajeran et al. (2018)	Age >35; BMI 18-25; NOR (defined as FSH < 10 IU/L; AMH 2.0- 6.80 ng/ml; inhibin B > 45 pg/m)	45	49	Long stimulation protocol	25 mg three times daily 8 weeks before stimulation	Fresh embryo transfer, day 3 embryos (2 embryos per transfer)	1) Clinical pregnancy rate 2) Miscarriage rate	Not specified
Yeung et al. (2016)	Age <40; subfertility >1 year; NOR (defined as AFC 5-15)	36	36	Fixed antagonist protocol	25 mg three times daily 12 weeks before stimulation	Fresh embryo transfer, day 2/5 embryos (2 embryos per transfer)	1) Oocytes retrieved 2) High quality embryos 3) Clinical pregnancy rate 4) Live birth rate 5)Miscarriage rate	No adverse events
Tartagni et al. (2015)	Age 36-40; normal BMI; menstrual cycle length 24-34 days; NOR (defined as FSH < 10 IU/L; AMH 2.0- 6.80 ng/ml; inhibin B > 45 pg/ml)	53	56	Long stimulation protocol	75 mg/24 h 8 weeks before and during stimulation	Fresh embryo transfer, day 3 embryos (up to 3 embryos per transfer)	1) Oocytes retrieved 2) Mature oocytes retrieved 3) High quality embryos 4) Clinical pregnancy rate 5) Live birth rate 6) Miscarriage rate	No adverse events
Tartagni et al. (2015)	Age 36-40; normal BMI; menstrual cycle length 24-34 days; NOR (defined as FSH < 10 IU/L; AMH 2.0- 6.80 ng/ml; inhibin B > 45 pg/ml)	26	26	Long stimulation protocol	75 mg/24 h 8 weeks before stimulation	Fresh embryo transfer, day 2-3 embryos (up to 3 embryos per transfer)	1) Oocytes retrieved 2) Mature oocytes retrieved 3) High quality embryos 4) Clinical pregnancy rate 5) Live birth rate 6) Miscarriage rate	No adverse events

COS: Controlled ovarian stimulation , BMI:Body mass index, NOR:Normal ovarian reserve, FSH: Follicle stimulating hormone, AMH: Anti-Müllerian Hormone, AFC: Antral follicle count.

*Intended for in black-and-white reproduction on the Web and in print.