

## Original Article

# Effectiveness of dehydroepiandrosterone in poor ovarian responders undergoing in vitro fertilization: a meta-analysis of randomized controlled trials

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**Abstract:** This meta-analysis aimed to evaluate whether DHEA could improve the probability of pregnancy in poor ovarian responders undergoing IVF/ICSI cycles. Electronic literature searches were carried out in MEDLINE, Scopus, EMBASE, Cochrane, CNKI, Wanfang, and VIP databases up to April 2016. All randomized controlled trials in which pretreatment with DHEA was compared with placebo or blank control were identified. Standard meta-analytic methodology was used for the combination of results and the exploration of bias. The primary outcome was clinical pregnancy rate, the secondary outcomes were the number of retrieved oocytes, cancellation rate, E<sub>2</sub> level on the day of hCG administration, miscarriage rate, and total dose of gonadotropin units. A total of nine studies (1072 cases) met the inclusion criteria. The clinical pregnancy rate (OR: 1.64, 95% CI: 1.20-2.24; P = 0.002), the number of retrieved oocytes (MD 1.27, 95% CI: 0.60-1.94; P = 0.0002) were significantly higher and the cancellation rate (OR 0.54, 95% CI: 0.33-0.87; P = 0.01) was significantly lower in the DHEA group. Miscarriage rate (OR: 0.54, 95% CI: 0.24-1.22; P = 0.14), E<sub>2</sub> level on the day of hCG administration (MD: -13.62, 95% CI: -300.33-273.10; P = 0.93), and total dose of gonadotropin (MD -257.40; 95% CI: -696.45-181.66; P = 0.25) did not significantly differ between two groups. Based on the present meta-analysis, pre-IVF DHEA treatment may improve the clinical pregnancy rate, increase the number of retrieved oocytes and lower the cancellation rate. The miscarriage rate, total dose of gonadotropin, and E<sub>2</sub> level on the day of hCG administration were not affected.

**Keywords:** DHEA, IVF, poor ovarian response, meta-analysis

## Introduction

In recent decades, an increasing number of women of reproductive age undergoing in vitro fertilization (IVF) suffer from poor ovarian response (POR). POR is described previously as the reduction in the quantity and quality of oocytes within the ovaries [1, 2] and has been reported to be responsible for the age-related decline in fertility [3-6], it increases incidence of adverse reproductive events, such as miscarriages [7, 8] and aneuploid pregnancies [9-11]. Recently ESHRE achieved a consensus regarding the definition of the poor response in IVF (Bologna Criteria). In this definition POR should at least meet the two of the following three conditions: (i) advanced maternal age or any other risk factor for POR; (ii) a previous

POR; and (iii) an abnormal ovarian reserve test (ORT) [12].

A previous study reported a relatively high percentage of poor ovarian responders in clinics ranging from 6 to 15% [13]. Various regimens with increased dose of gonadotropin, reduced dose of GnRH agonists or antagonists, addition of growth hormone, clomiphene stimulation, or natural cycle IVF have been adopted in the clinical setting; however, few of these regimens are efficient and are associated with poor results in IVF.

Dehydroepiandrosterone (DHEA) is a widely used androgen analogue to improve fertility in women. DHEA may enhance steroidogenesis, serve as a precursor for E<sub>2</sub> and testosterone,

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influence ovarian follicular growth by acting as a ligand for androgen receptors, and increase the IGF-1 level. It also induces polycystic ovary syndrome (PCOS)-like characteristics and increases the LH level, serves as a pre-hormone for follicular fluid testosterone, reduces age-related aneuploidy by affecting meiotic chromosome segregation, increases the number of small antral follicles (AFC) and the anti-Mullerian hormone (AMH) levels [14].

As an adjuvant, DHEA may increase the serum AMH level, the E<sub>2</sub> level on the day of hCG administration and decrease the FSH level on cycle Day 2 [15, 16]. So, DHEA pretreatment could result in a higher number of retrieved oocytes, fertilized oocytes, overall number of embryos, number of grade I embryos [17] and the ongoing pregnancy rate [16]. The miscarriage rate after DHEA administration was not only lower than in the average IVF patients but also comparable to that reported in normally fertile populations. Low miscarriage rate was statistically impossible to be achieved in DOR patients without the assumption of DHEA effect on embryo ploidy [18]. However, a recent study found that supplementation with DHEA had significant relationship with poor prognosis in women undergoing ovarian stimulation for IVF, no significant benefit could be found regarding the gonadotropin requirements, duration of stimulation oocyte, embryo yield and pregnancy rate [19]. Due to the controversial results and the lack of large-scale data analysis supporting its effectiveness and safety, the widespread use of DHEA cannot be currently recommended [20]. So we reviewed all randomized controlled trials (RCTs) and aimed to assess whether pre-DHEA treatment could improve the clinical results of IVF in poor ovarian responders.

## Materials and methods

### Search strategy

Databases of MEDLINE (1950 to April 2016), EMBASE (1974 to April 2016), Scopus (1823 to April 2016), China National Knowledge Infrastructure (CNKI, 1979 to April 2016), Wanfang (1990 to April 2016), VIP (1989 to April 2016), and Cochrane Library were searched for all relevant articles to identify RCTs that evaluated whether DHEA addition increased the probability of pregnancy in poor responders undergoing ovarian stimulation. The search terms were

(‘Dehydroepiandrosterone’ or ‘DHEA’) and ((‘Diminished ovarian reserve’ or ‘Poor ovarian response’ or ‘poor responder’ or ‘ovarian insufficiency’ or ‘premature ovarian aging’) and (‘in vitro fertilization’ or ‘IVF’ or ‘ICSI’)). Moreover, we screened the references included in the papers. If necessary, experts were contacted to obtain more information that we were unable to obtain using the above search strategy. The language was limited to English and Chinese.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study was a prospective randomized controlled trial to compare the effect of DHEA on ovarian stimulation parameters and the treatment outcomes in IVF; (2) study participants should be characterized as poor responders, and (3) the study reported clinical outcomes, such as pregnancy rate, number of oocytes retrieved, miscarriage and so on. The studies that clearly did not meet the inclusion criteria were excluded. Next, the remaining articles were read carefully to determine which articles would be included in our study.

All of the RCTs that compared the efficacy in patients with poor ovarian response in IVF treated with or without DHEA were included in this study, regardless of whether the trial was blinded. Only the studies published in Chinese or English were included.

The exclusion criteria used were as follows: (1) data description or sample information that was insufficiently clear; (2) inappropriate statistical methods; and (3) application of other drugs or therapies during the treatment.

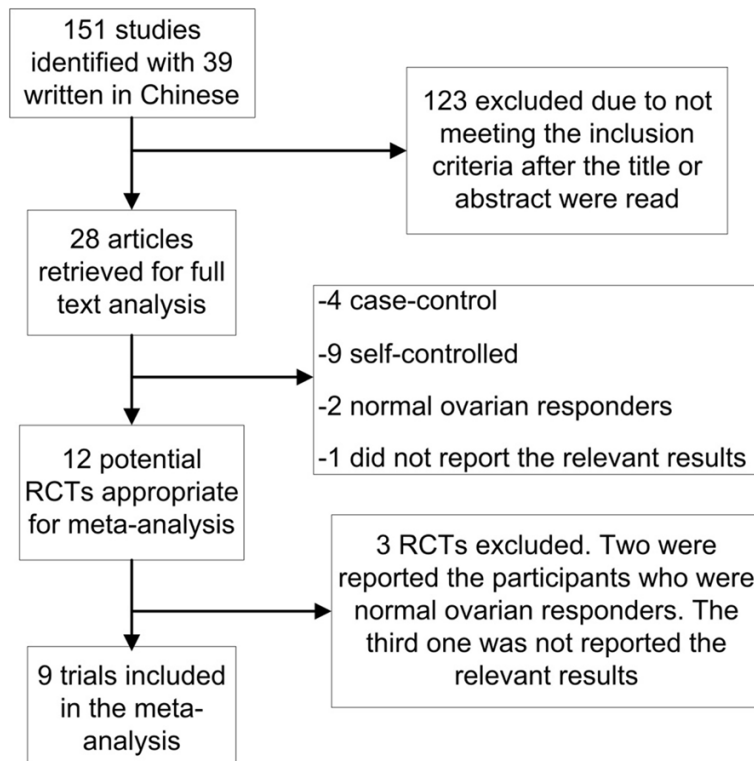
### Data extraction

Data extraction was performed by two authors independently. If disagreement happened, it was resolved by reaching consensus. Details about the demographic data (author, study period, location, number of patients included), method of randomization, and procedure (ovarian stimulation protocol, dose, and DHEA administration protocol) were extracted from each of the eligible studies.

### Risk of bias

In order to evaluate the validity, the quality of each study was assessed with risk of bias tool.

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**Figure 1.** Flow diagram of the article screening.

The modified JADAD scale, a 6-item scoring system [21, 22] has been used for its convenience, simplicity and quantifiability. But Cochrane risk assessment tool was more frequently recommended than JADAD measuring scale recently. Seven parameters were evaluated for each included study: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other risks. Items were judged as “low risk”, “unclear risk”, or “high risk”.

### Statistical analysis

The results were combined for meta-analysis through RevMan (Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Continuous variable was described as mean  $\pm$  standard deviation and in meta-analysis the difference between two groups is summarized as the mean differences (MD). Dichotomous data were described as proportions in each trial and in meta-analysis was expressed as an odds ratio (OR) to provide a pooled estimate. The consistency or heterogeneity between studies was statistically quantified with  $I^2$ .  $I^2$  took values between 0% and

100% with higher values denoting greater degree of heterogeneity ( $I^2 = 0\%$  to  $25\%$ : no heterogeneity;  $I^2 = 25\text{-}50\%$ : moderate heterogeneity;  $I^2 = 50\text{-}75\%$ : large heterogeneity;  $I^2 = 75\text{-}100\%$ : extreme heterogeneity) [23]. A fixed-effects model was used when no statistically significant heterogeneity was present, whereas a random-effects model was applied in the presence of statistically significant heterogeneity. Statistical significance was set at a P level of 0.05 [24]. Subgroup analysis was used to determine the cause of the heterogeneity or to answer specific questions about particular patient groups (such as different geographical locations), types of intervention or types of study.

A visual assessment of the funnel plots and quantitative assessments of Egger's test (STATA 11.0) were used to evaluate the potential presence of publication bias. P-values less than 0.05 based on Egger's test or asymmetric funnel plots indicated a potential publication bias [25]. Other reference factors were also considered, including whether the trial was conducted at multiple centers, whether the baseline was consistent between the two study groups, whether there were confounding factors or interactions, and whether the methods used for statistical analysis were correct.

## Results

### Screening results

Database searches yielded a total of 151 relevant studies, including 39 written in Chinese. After reviewed by the titles or abstracts, 123 were excluded for not meeting the inclusion criteria. The left 28 studies were then reviewed for the full text and 19 more studies were excluded, the possible reasons were shown in **Figure 1**. Thus totally 9 trials were included in this our analysis eventually (**Table 1**) [26-34].

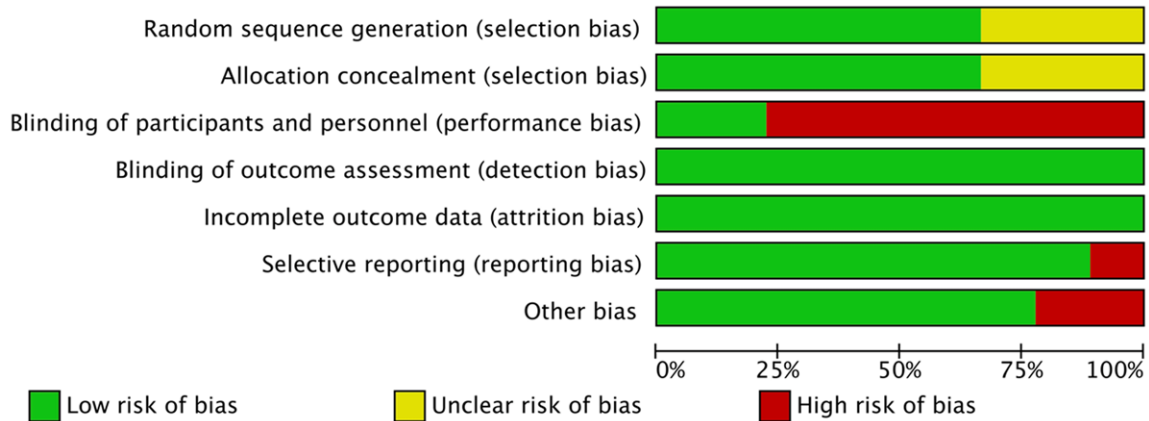
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**Table 1.** Characteristics of the included trials

Study	Location	Design	Inclusion and exclusion criteria (definition of poor responder)	Number of participants	Intervention (DHEA doses and duration)	Stimulation protocol	Outcome reported
Wiser 2010	Israel	RCT	Inclusion: Age < 42, Gn dose ≥ 300 IU/day, retrieved oocytes < 5, poor-quality embryos, or cycle cancellation Exclusion: Patients over the age of 42, patients who received DHEA at any time before enrollment	DHEA: 17 Control: 16	Case: 25 mg tid po, > 6 weeks Control: Not stated	Standard long-protocol	①②③④
Moawad 2012	Egypt	RCT	Inclusion: Age < 40, retrieved oocytes < 5, or cycle cancellation whenever Gn dose ≥ 300 IU/day, or AMH < 1.7 µg/L Exclusion: Patients who received DHEA at any time before enrollment, AMH > 1.7 µg/L	DHEA: 58 Control: 47	Case: 25 mg tid po, > 12 weeks Control: None	Standard short-protocol	①②③⑤⑥⑦
Kara 2014	Turkey	RCT	Inclusion: AMH < 1 µg/L, or FSH > 15 IU/L, AFC < 4 Exclusion: No oocytes were retrieved, male factor, frozen-thawed embryo, fertilization didn't occur	DHEA: 104 Control: 104	Case: 25 mg tid po, > 12 weeks Control: None	Microdose flare protocol	①②③
Li 2014	China	RCT	Inclusion: Age ≥ 35, or retrieved oocytes < 5, or AFC < 5, or FSH > 10 IU/L Exclusion: Other endocrine disease, male factor, uterine malformation	DHEA: 43 Control: 38	Case: 25 mg tid po, 3 months Control: None	Antagonist protocol	①②③⑤⑥⑦
Tian 2014	China	RCT	Inclusion: FSH > 10 IU/L × 2 times Exclusion: Chemotherapy, radiotherapy autoimmune disease, received DHEA before, or conceived	DHEA: 79 Control: 73	Case: 25 mg tid po, > 1 month Control: Placebo	Not stated	①②⑤
An 2013	China	RCT	Inclusion: Age ≥ 40, bFSH > 9 IU/L, AFC < 5-7 Exclusion: Ems, PCOS, HPRL and other endocrine disease	DHEA: 81 Control: 92	Case: 25 mg tid po, 3 months Control: None	Standard long-protocol	①②③⑤⑥⑦
Yeung 2014	Hong Kong, China	RCT	Inclusion: Age < 40, subfertility > 1 year, AFC < 5 Exclusion: Ovarian cystectomy, oophorectomy, received cytotoxic, chemotherapy, received pelvic irradiation, history of testosterone or DHEA supplementation	DHEA: 16 Control: 16	Case: 25 mg tid po, 12 weeks Control: Placebo	Fixed antagonist protocol	①②③⑤⑦
Song 2015	China	RCT	Inclusion: Bologna criteria Exclusion: Not sated	DHEA: 56 Control: 56	Case: 25 mg tid po, 3 months Control: None	Standard short-protocol	①②③⑤⑥⑦
Kotb 2016	Egypt	RCT	Inclusion: Bologna criteria Age from 25 to 40 Exclusion: BMI > 35 kg/m <sup>2</sup> , single ovary, allergy to DHEA, diabetic women on insulin	DHEA: 70 Control: 70	Case: 25 mg tid po, 3 months Control: None	antagonist protocol	①②③⑤⑥

Outcomes: ① E2 level on the day of HCG administration; ② Number of oocytes retrieved; ③ Clinical pregnancy rate; ④ Live birth rate; ⑤ Total Gn units; ⑥ Cancellation rate; ⑦ Miscarriage rate. \*The rate is expressed as per cycle.

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**Figure 2.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
An 2014	?	?	-	+	+	+	+
Kara 2013	+	+	-	+	+	+	+
Kotb 2016	+	+	-	+	+	+	+
Li 2014	?	?	-	+	+	+	+
Moawad 2012	+	+	-	+	+	+	+
Song 2015	+	+	-	+	+	+	+
Tian 2014	?	?	+	+	+	-	+
Wiser 2010	+	+	-	+	+	+	-
Yeung 2014	+	+	+	+	+	+	-

**Figure 3.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Note: The items were judged as "low risk" "unclear risk" or "high risk", red means "high risk", green means "low risk" and yellow means "unclear risk".

### Risk of bias

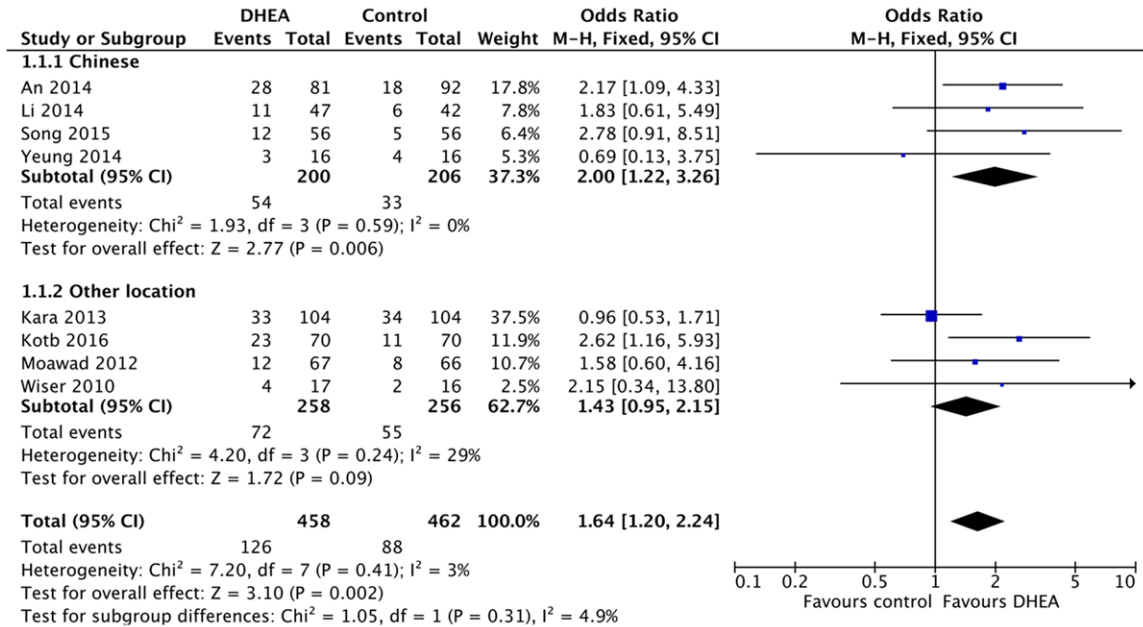
The methodological quality assessment of the 9 included studies is presented in **Figures 2, 3**. Of the 9 RCTs, most studies clearly adopted random sequence generation using random number tables. 2 studies [28, 31] were double blind, whereas the remaining 7 studies [26, 27, 29, 30, 32-34] were not blind. 6 studies [26-29, 33, 34] adopted adequate methods of allocation concealment, whereas the remaining 3 studies [30-32] did not describe concrete methods of concealment. 6 studies [26-29, 33, 34] adopted adequate methods of randomization (e.g., computer-generated randomization schemes). 3 studies [30-32] that did not mention enough information about their randomization methods were rated as unclear. In addition, 1 study [31] didn't report clinical pregnancy rate which was an important result, so it was rated as high risk of selective reporting. 2 studies [26, 28] reported too small sample size which gave rise to high risks of other bias. The quality of the tests conducted by such studies thus exhibited a moderate risk of selection bias and high risk of performance bias, reporting bias, other bias, which may affect the final results.

### Primary outcome measure

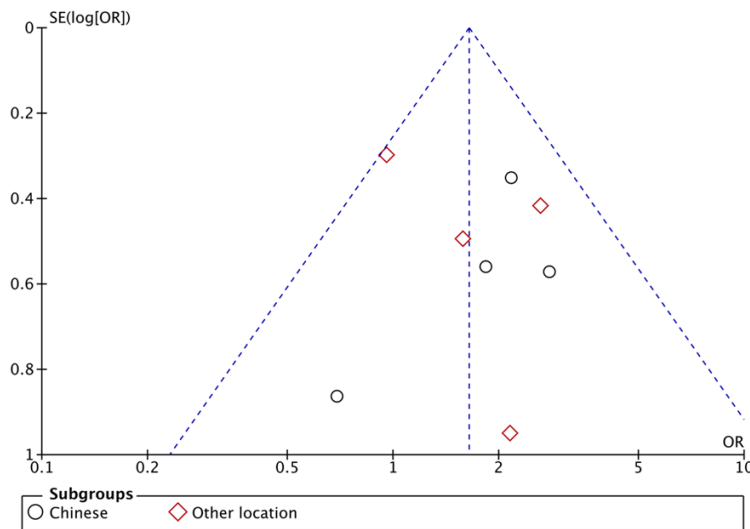
**Clinical pregnancy rate:** The clinical pregnancy rate (CPR) was reported in eight trials [26-30, 32-34]. Pooled data showed that there was a significant difference between the two groups (OR: 1.64, 95% CI: 1.20-2.24;  $P = 0.002$ ; **Figure 4**). The heterogeneity was non-significant ( $I^2 = 3\%$  and  $P = 0.41$ ), indicating that there was no



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**Figure 4.** Forest plot of the comparison of administration with DHEA versus no treatment control according to the clinical pregnancy rate.



**Figure 5.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the clinical pregnancy rate.

statistical inconsistency between the eight trials. The fixed-effects model was used, Funnel plot (Figure 5) and Egger's test revealed no publication bias (P = 0.593). The result of subgroup analysis stratified by location illustrated the effectiveness of DHEA in Chinese population (OR: 2.00, 95% CI: 1.22-3.26; P = 0.006; Figure 4). The heterogeneity was non-signifi-

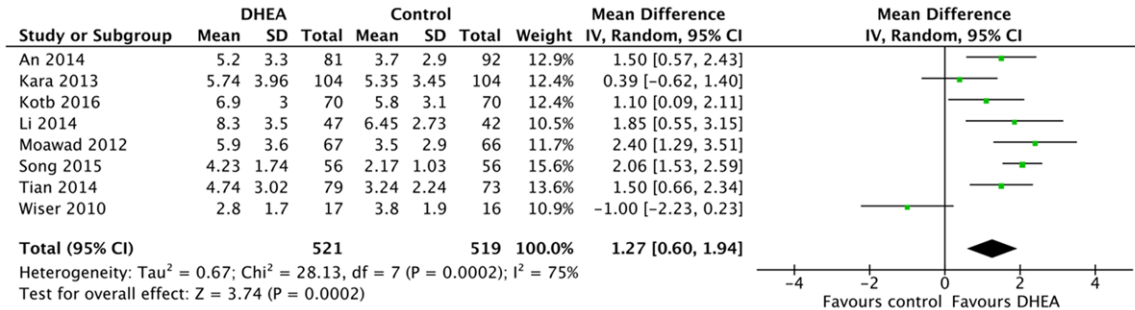
cant (I<sup>2</sup> = 0% and P = 0.59). Our meta-analysis result confirmed the previous report published by Narkwichean et al with less bias, as the inclusion criteria were stricter and only RCTs were included.

### Secondary outcomes measures

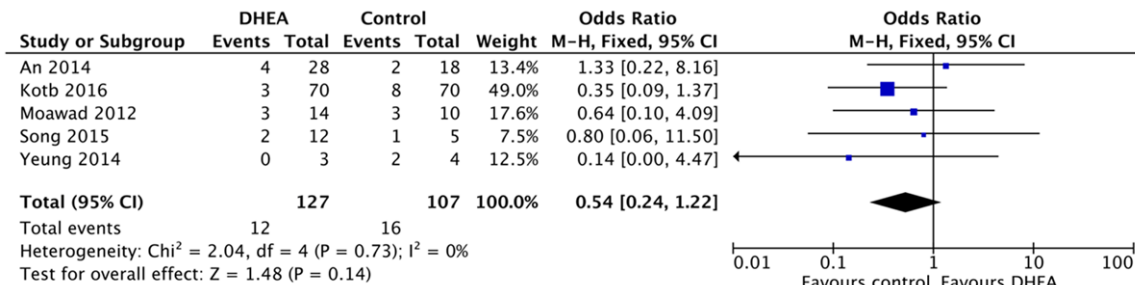
**Number of oocytes retrieved:** Some studies [26, 27, 29-34] reported the number of oocytes retrieved as an outcome. Meta-analysis of these studies for this outcome revealed a significant difference between DHEA pretreated and untreated groups (MD 1.27, 95% CI: 0.60-1.94;

P = 0.0002; Figure 6, Supplementary Figure 1). The heterogeneity was large in this comparison (I<sup>2</sup> = 75%, P = 0.0002). In addition, we conducted sensitivity analysis by excluding Wiser's study, whose limitations and weaknesses had been reported in a previous meta-analysis [35]. By excluding this study the consistency of the analysis was improved (I<sup>2</sup> = 48%, P = 0.07), and

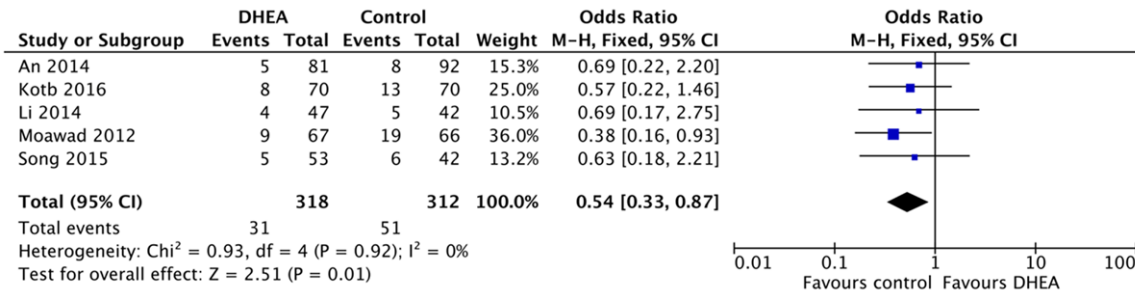
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**Figure 6.** Forest plot of the comparison of administration with DHEA versus no treatment control with regards to the number of oocytes retrieved.



**Figure 7.** Forest plot of the comparison of administration with DHEA versus no treatment control with regards to the miscarriage rate.



**Figure 8.** Forest plot of the comparison of administration with DHEA versus no treatment control according to the cancellation rate.

there was still a significant difference between the two groups (MD 1.57, 95% CI: 1.09-2.05, P < 0.00001).

### Miscarriage rate

Five trials [27, 28, 32-34] reported the miscarriage rate. Meta-analysis of these studies for the outcome of miscarriage rate showed no significant difference between the two groups (OR: 0.54, 95% CI: 0.24-1.22; P = 0.14; **Figure 7**, **Supplementary Figure 2**), and no heterogeneity was found (I<sup>2</sup> = 0%, P = 0.73).

### Cancellation rate

Some studies [27, 30, 32-34] reported the cancellation rate as an outcome. Meta-analysis of these five studies for the outcome of cancellation rate showed a significant difference between the DHEA and untreated groups (OR 0.54, 95% CI: 0.33-0.87; P = 0.01; **Figure 8**, **Supplementary Figure 3**). There was no heterogeneity in this comparison (I<sup>2</sup> = 0%, P = 0.92) and the fixed-effects model was used. It appears that DHEA may increase the success

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rate. The Egger's test revealed no publication bias ( $P = 0.082$ ).

### *E<sub>2</sub> level on the day of hCG administration*

Five trials [26, 27, 29, 31, 34] reported the E<sub>2</sub> level on the day of hCG administration. Pooled data suggested no significant difference in the E<sub>2</sub> level on the day of hCG administration between the two groups (MD: -13.62, 95% CI: -300.33-273.10;  $P = 0.93$ ; [Supplementary Figures 4, 5](#)). The heterogeneity was extremely large ( $I^2 = 86\%$ ,  $P < 0.00001$ ).

### *Total Gn units*

Meta-analysis of six [27, 30-34] studies that reported the outcome of the total Gn dose used in stimulation showed no significant difference between the group treated with DHEA -and with no treatment (MD -257.40; 95% CI: -696.45-181.66;  $P = 0.25$ ; [Supplementary Figures 6, 7](#)). There was extremely large heterogeneity in this comparison ( $I^2 = 98\%$ ,  $P < 0.00001$ ).

## Discussion

With the wide usage in poor ovarian response IVF patients, DHEA became a fashionable supplement nowadays. The present meta-analysis pooled nine RCTs. Compared with previous published meta-analyses, our meta-analysis included more recent RCTs with considerably larger sample sizes on the effect of DHEA supplementation in POR undergoing IVF/ICSI. We drew more reliable conclusions [35-37].

The results showed a statistical difference in the CPR per cycle when pre-DHEA treatment was used. But as some studies didn't report the CPR per transfer, it still needs more data to draw a solid conclusion which may reflect a more precise result and will be more meaningful for clinicians as well.

It was noted that the cancellation rate significantly decreased in the study group, so the improved efficiency of IVF could be concluded. And also there was a significant difference in the number of retrieved oocytes between the two groups. Although there was large heterogeneity in drawing this conclusion, this may be good news for the final clinical outcome. The total Gn dose used didn't significantly differ between the two groups, but the decreased

tendency showed in the DHEA pre-treatment group might get a better cost-effectiveness. Although E<sub>2</sub> on the day of hCG administration did not significantly differ between the two groups, the E<sub>2</sub> level tended to increase following DHEA treatment, which indicated a good endocrine environment for the embryos to implant. Although some evidences supported the above observed benefits for adding DHEA as an adjunction, they were still not strong enough. Therefore, more RCTs with larger sample sizes are needed in the future.

Heterogeneity was observed among the eligible studies, considerable clinical variability was present regarding: 1) although there was Bologna Criteria for poor ovarian response, the situations in 9 randomized controlled trials were not completely consistent, 2) the protocols for pituitary down regulation, ovarian stimulation and luteal support were different, 3) the protocols of DHEA administration were not the same completely. As the eligible RCTs were characterized by methodological issues that deserve commenting and should be addressed, further trials should uniform the inclusion criteria of POR and the protocol in COS, optimise the dose and the duration of DHEA administration. Furthermore, true methods of randomization of patients to each treatment regimen along with allocation concealment should be implemented to improve the methodological integrity of the meta-analysis and assure the validity of the results. Last but not least, none of the included studies performed sample size calculation, and no study was double blind.

It was 15 years ago when Casson et al. first reported the benefits of DHEA supplementation in women with diminished ovarian reserve. The authors speculated DHEA might have a role in increasing the serum concentrations of IGF-1, which in turn might improve the response to gonadotropins [38]. In the following years many experts argued this miracle adjunction until the first RCT published by Wiser et al. in 2010. Although there were still some shortcomings, such as a small number of patients and the short duration of DHEA use, an important finding in the study was the fact that POR patients with a previous pregnancy had a better prognosis than those with primary infertility [39]. So it was recommended that in the future stratification could be introduced in a trial, not



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only the times of undergoing IVF/ICSI, but also the age, doses and the duration of DHEA administration should be considered. Although many articles were published from 2012-2016, they still had defects more or less. One of the latest cohort trial reported that there was no benefit observed in pre-DHEA administration group [19], but the sample size in two arms was not balanced.

Another RCT reviewed that DHEA supplementation may significantly improve IVF outcomes in infertile women in advanced reproductive age and with normal ovarian reserve [40]. A trial reported by Tracy et al. should be noted for it was the first RCT that assessed the comprehensive serum, follicular fluid hormone profiles and changes of ovarian response markers in poor responders throughout DHEA pre-treatment, they believed that higher follicular DHEA-S levels indicated top-quality embryos due to reduced aneuploidy [28], yet the samples were still small, further large-size trials are needed to confirm the results, the molecular and nutritional fingerprint analyses in batches after the clinical phase of the study would also be considered.

DHEA supplementation might have positive effect on gene expression of CCs, including promotion of ECM formation and inhibition of apoptosis. It could modulate ovarian immunity through its conversion to other downstream steroids, by balancing the Th1/Th2 immune response, or by modulating the types and behavior of T lymphocytes. It also improved ovarian function in women with poor ovarian response by activating anti-apoptotic processes in cumulus cells. But the mechanism is not clearly known [41, 42].

The side effects associated with the recommended dose of DHEA were rare. The published studies did not report any significant adverse or androgenic side effects [26, 38, 43, 44]. However, the potential side effects were androgenic, like acne, facial hair growth and rarely deepening of the voice [45], but convinced evidences need further large RCTs.

Poor ovarian response remains a confused problem in IVF today. It makes hundreds of couples give up treatment or seek oocyte donation. Currently, no single pharmacological intervention is available to reliably increase the probability of pregnancy in poor responders. Th-

erefore, the fact that adding DHEA as an adjunct during ovarian stimulation increases the probability of pregnancy needs to be well evaluated in further adequately-powered trials especially in live birth rate.

In conclusion, the present meta-analysis provides evidence that DHEA addition increases the clinical pregnancy rate and the oocytes retrieved, decreases the cancellation rates in IVF POR patients. So it seems like a better option to implement DHEA pre-treatment in these patients. But rigorous, multicenter, randomized controlled trials with large sample sizes are still needed to verify and update this information for the use in clinical practice.

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### Disclosure of conflict of interest

None.

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### References

- [1] Broekmans FJ, Kwee J, Hendriks DJ, Mol BW and Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006; 12: 685-718.
- [2] Broekmans FJ, Faddy MJ, Scheffer G and Velde ER. Antral follicle counts are related to age at natural fertility loss and age at menopause. *Menopause* 2004; 11: 607-614.
- [3] Santoro N, Isaac B, Neal-Perry G, Adel T, Weingart L, Nussbaum A, Thakur S, Jinnai H, Khosla N and Barad D. Impaired folliculogenesis and ovulation in older reproductive aged women. *J Clin Endocrinol Metab* 2003; 88: 5502-5509.
- [4] Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W and Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril* 2001; 76: 874-878.
- [5] Templeton A, Morris JK and Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996; 348: 1402-1406.

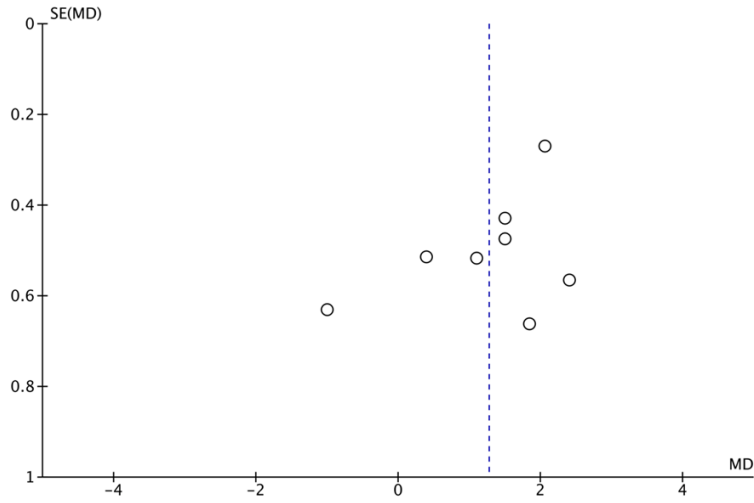
## The effectiveness of DHEA in poor ovarian responders undergoing IVF

- [6] Menken J, Trussell J and Larsen U. Age and infertility. *Science* 1986; 233: 1389-1394.
- [7] Gleicher N, Weghofer A and Barad DH. Defining ovarian reserve to better understand ovarian aging. *Reprod Biol Endocrinol* 2011; 9: 23.
- [8] Trout SW and Seifer DB. Do women with unexplained recurrent pregnancy loss have higher day 3 serum FSH and estradiol values? *Fertil Steril* 2000; 74: 335-337.
- [9] Freeman SB, Yang Q, Allran K, Taft LF and Sherman SL. Women with a reduced ovarian complement may have an increased risk for a child with Down syndrome. *Am J Hum Genet* 2000; 66: 1680-1683.
- [10] Warburton D. Biological aging and the etiology of aneuploidy. *Cytogenet Genome Res* 2005; 111: 266-272.
- [11] Hodges CA, Ilagan A, Jennings D, Keri R, Nilson J and Hunt PA. Experimental evidence that changes in oocyte growth influence meiotic chromosome segregation. *Hum Reprod* 2002; 17: 1171-1180.
- [12] Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 2011; 26: 1616-1624.
- [13] Milton Leong, Pasquale Patrizio. Poor responders: How to define, diagnose and treat? Available at: <http://www.ivf-worldwide.com/survey/poor-responders/results-poor-responders.html>. Accessed January 2, 2016.
- [14] Fouany MR and Sharara FI. Is there a role for DHEA supplementation in women with diminished ovarian reserve? *J Assist Reprod Genet* 2013; 30: 1239-1244.
- [15] Xu B, Li Z, Yue J, Jin L, Li Y, Ai J, Zhang H and Zhu G. Effect of dehydroepiandrosterone administration in patients with poor ovarian response according to the Bologna criteria. *PLoS One* 2014; 9: e99858.
- [16] Singh N, Zangmo R, Kumar S, Roy KK, Sharma JB, Malhotra N and Vanamail P. A prospective study on role of dehydroepiandrosterone (DHEA) on improving the ovarian reserve markers in infertile patients with poor ovarian reserve. *Gynecol Endocrinol* 2013; 29: 989-992.
- [17] Zangmo R, Singh N, Kumar S, Vanamail P and Tiwari A. Role of dehydroepiandrosterone in improving oocyte and embryo quality in IVF cycles. *Reprod Biomed Online* 2014; 28: 743-747.
- [18] Gleicher N, Ryan E, Weghofer A, Blanco-Mejia S and Barad DH. Miscarriage rates after dehydroepiandrosterone (DHEA) supplementation in women with diminished ovarian reserve: a case control study. *Reprod Biol Endocrinol* 2009; 7: 108.
- [19] Vlahos N, Papalouka M, Triantafyllidou O, Vlachos A, Vakas P, Grimbizis G, Creatsas G and Zikopoulos K. Dehydroepiandrosterone administration before IVF in poor responders: a prospective cohort study. *Reprod Biomed Online* 2015; 30: 191-196.
- [20] Urman B and Yakin K. DHEA for poor responders: can treatment be justified in the absence of evidence? *Reprod Biomed Online* 2012; 25: 103-107.
- [21] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12.
- [22] Oremus M, Wolfson C, Perrault A, Demers L, Momoli F and Moride Y. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. *Dement Geriatr Cogn Disord* 2001; 12: 232-236.
- [23] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560.
- [24] Lau J, Ioannidis JP and Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; 127: 820-826.
- [25] Harbord RM, Egger M and Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006; 25: 3443-3457.
- [26] Wisner A, Gonen O, Ghetler Y, Shaviv T, Berkovitz A and Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod* 2010; 25: 2496-2500.
- [27] Moawad A and Shaer M. Long-term androgen priming by use of dehydroepiandrosterone (DHEA) improves IVF outcome in poor-responder patients. *Middle East Fertil Soc J* 2012; 17: 7.
- [28] Yeung TW, Chai J, Li RH, Lee VC, Ho PC and Ng EH. A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and in vitro fertilization outcomes in poor responders. *Fertil Steril* 2014; 102: 108-115, e101.
- [29] Kara M, Aydin T, Aran T, Turktekin N and Ozdemir B. Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve? *Eur J Obstet Gynecol Reprod Biol* 2014; 173: 63-65.
- [30] Li J, Ren C, Zhang A, Du T and Liu H. Effect of Dehydroepiandrosterone (DHEA) Supplementation on IV-FET of Patients with Diminished Ovarian reserve (DOR). *J Liaoning Med Uni* 2014; 35: 3.
- [31] Tian H, Wang Q, Gong X and La X. Randomized controlled trail on the number of retrieved oocytes from women with diminished ovarian re-

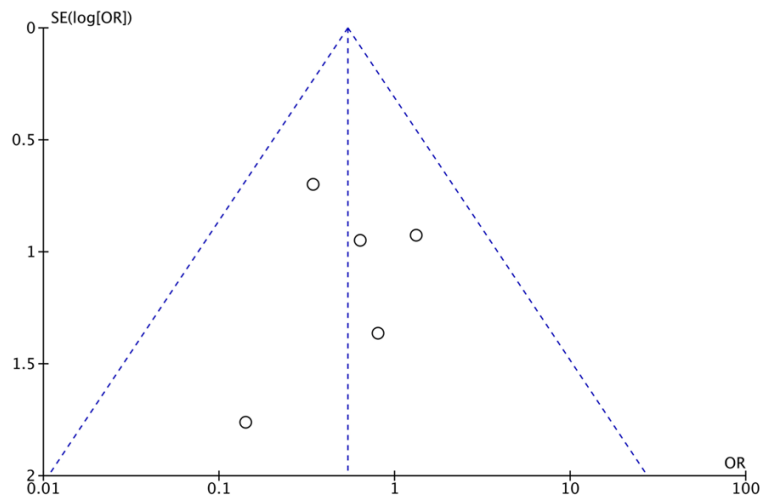
## The effectiveness of DHEA in poor ovarian responders undergoing IVF

- serve treated with DHEA supplementation. *J Xinjiang Med Uni* 2014; 37: 3.
- [32] An J, Wang Y, Ni Y and Chai S. Application of Dehydroepiandrosterone (DHEA) Supplementation in In Vitro Fertilization and Embryo Transfer Cycles. *Reprod Contracep* 2013; 33: 4.
- [33] Song H, Wu Y, Tian G, Li Y, Hua W and Huang Y. Influence of pretreatment with dehydroepiandrosterone in patients with poor ovarian response. *J Reprod Med* 2015; 24: 4.
- [34] Kotb MM, Hassan AM and AwadAllah AM. Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* 2016; 200: 11-15.
- [35] Narkwichean A, Maalouf W, Campbell BK and Jayaprakasan K. Efficacy of dehydroepiandrosterone to improve ovarian response in women with diminished ovarian reserve: a meta-analysis. *Reprod Biol Endocrinol* 2013; 11: 44.
- [36] Li J, Yuan H, Chen Y, Wu H, Wu H and Li L. A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection. *Int J Gynaecol Obstet* 2015; 131: 240-245.
- [37] Zhang M, Niu W, Wang Y, Xu J, Bao X, Wang L, Du L and Sun Y. Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis. *J Assist Reprod Genet* 2016; 33: 981-91.
- [38] Casson PR, Lindsay MS, Pisarska MD, Carson SA and Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Hum Reprod* 2000; 15: 2129-2132.
- [39] Gleicher N, Weghofer A and Barad DH. Dehydroepiandrosterone (DHEA) reduces embryo aneuploidy: direct evidence from preimplantation genetic screening (PGS). *Reprod Biol Endocrinol* 2010; 8: 140.
- [40] Tartagni M, Cicinelli MV, Baldini D, Tartagni MV, Alrasheed H, DeSalvia MA, Loverro G and Montagnani M. Dehydroepiandrosterone decreases the age-related decline of the in vitro fertilization outcome in women younger than 40 years old. *Reprod Biol Endocrinol* 2015; 13: 18.
- [41] Tsui KH, Lin LT, Horng HC, Chang R, Huang BS, Cheng JT and Wang PH. Gene expression of cumulus cells in women with poor ovarian response after dehydroepiandrosterone supplementation. *Taiwan J Obstet Gynecol* 2014; 53: 559-565.
- [42] Zhang J, Qiu X, Gui Y, Xu Y, Li D and Wang L. Dehydroepiandrosterone improves the ovarian reserve of women with diminished ovarian reserve and is a potential regulator of the immune response in the ovaries. *Biosci Trends* 2015; 9: 350-359.
- [43] Gleicher N, Weghofer A and Barad DH. Improvement in diminished ovarian reserve after dehydroepiandrosterone supplementation. *Reprod Biomed Online* 2010; 21: 360-365.
- [44] Barad D, Brill H and Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. *J Assist Reprod Genet* 2007; 24: 629-634.
- [45] Panjari M and Davis SR. DHEA therapy for women: effect on sexual function and wellbeing. *Hum Reprod Update* 2007; 13: 239-248.

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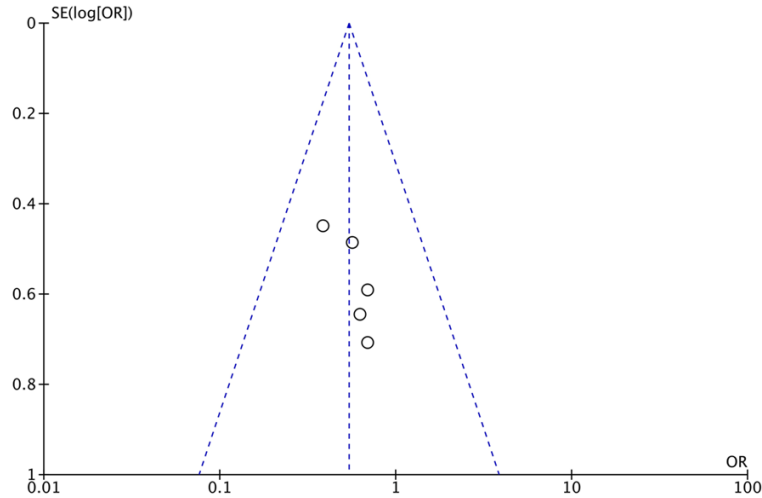


**Supplementary Figure 1.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the oocytes retrieved.

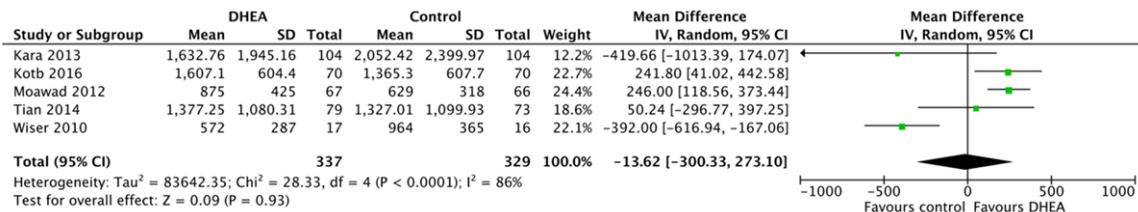


**Supplementary Figure 2.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the miscarriage rate.

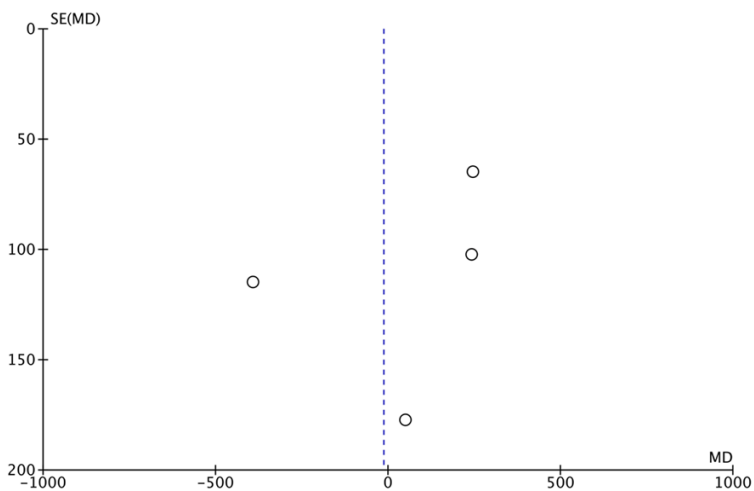
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**Supplementary Figure 3.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the cancellation rate.



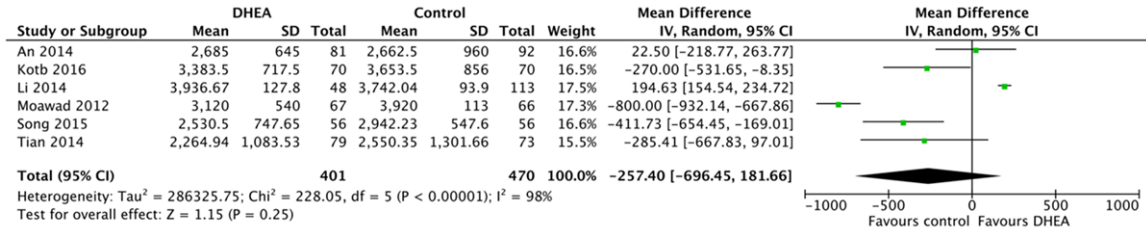
**Supplementary Figure 4.** Forest plot of the comparison of administration with DHEA versus no treatment control for the estradiol on the day of hCG administration.



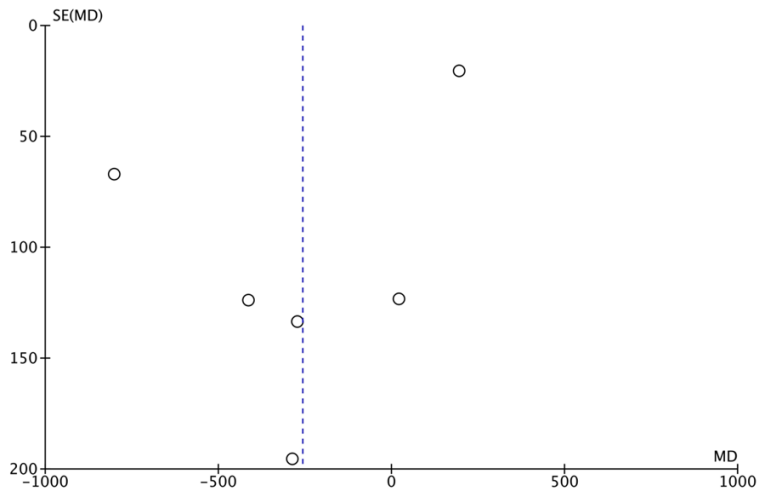
**Supplementary Figure 5.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the estradiol on the day of hCG administration.



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**Supplementary Figure 6.** Forest plot of the comparison of administration with DHEA versus no treatment control for the total dose of Gn units.



**Supplementary Figure 7.** Funnel plot of the comparison of administration with DHEA versus no treatment control according to the total dose of Gn units.