

## Review Article

# The influence of dehydroepiandrosterone (DHEA) supplementation for in vitro fertilization in women with diminished ovarian reserve: a meta-analysis of randomized controlled trials

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Received June 16, 2017; Accepted November 17, 2017; Epub December 15, 2017; Published December 30, 2017

**Abstract:** Introduction: The efficacy of dehydroepiandrosterone (DHEA) for in vitro fertilization in women with diminished ovarian reserve remains controversial. We conduct a systematic review and meta-analysis to explore the influence of DHEA for in vitro fertilization. Methods: We search PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through November 2017 for randomized controlled trials (RCTs) assessing the effect of DHEA on in vitro fertilization. This meta-analysis is performed using the random-effect model. Results: Nine RCTs involving 884 patients are included in the meta-analysis. Overall, compared with control group in vitro fertilization in women with diminished ovarian reserve, DHEA supplement is associated with substantially increased clinical pregnancy (OR=1.47; 95% CI=1.08 to 2.01; P=0.02), and retrieved oocytes (Std. MD=0.37; 95% CI=0.11 to 0.63; P=0.005), but has no influence on oestradiol on hCG day (Std. MD=-0.14; 95% CI=-0.81 to 0.53; P=0.68), transferred embryos (Std. MD=0.43; 95% CI=-0.11 to 0.96; P=0.12), live birth rate (OR=1.41; 95% CI=0.38 to 5.22; P=0.60), miscarriage rate (OR=0.76; 95% CI=0.29 to 1.98; P=0.58). Conclusions: DHEA supplementation results in significantly improved clinical pregnancy and retrieved oocytes during in vitro fertilization in women with diminished ovarian reserve, but has no remarkable influence on oestradiol on hCG day, transferred embryos, live birth rate, and miscarriage rate.

**Keywords:** Dehydroepiandrosterone (DHEA), in vitro fertilization, diminished ovarian reserve, randomized controlled trials, meta-analysis

## Introduction

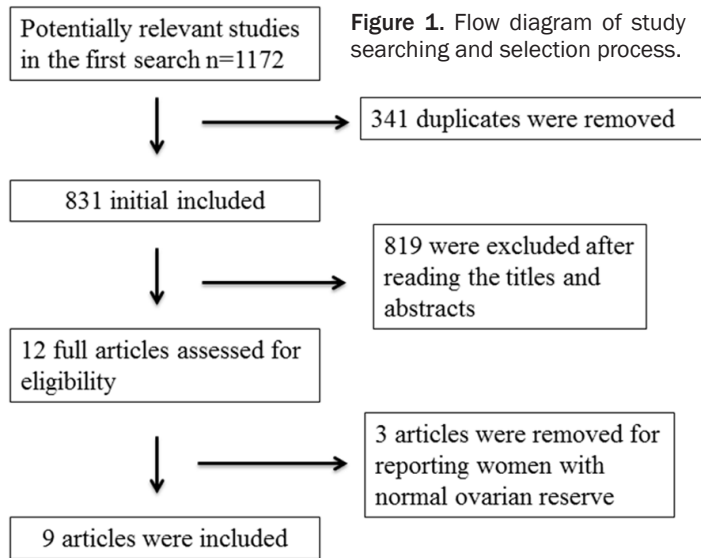
Subfertility is a worldwide problem because of the ovarian ageing because women prefer to pursue higher education and career advancement before making the decision to conceive [1-3]. Ovarian ageing results in the decline in quantity and quality of oocytes within the ovaries, the decline in fertility, and the increase in adverse pregnancy outcomes (e.g. miscarriage) [4-6]. Fast-tracked towards assisted reproductive technology may be an important choice for these women, but women with diminished ovarian reserve have poor response to ovarian stimulation [7, 8].

Ovarian ageing is determined by primordial follicle initiation, the rate of follicular growth and

follicle turnover [9, 10]. Many factors account for these processes, including intra-ovarian autocrine and paracrine growth regulators and gonadotrophic endocrinological control, and hormonal drugs such as dehydroepiandrosterone (DHEA) are theoretically available to regulate these processes [11]. DHEA is known as the most abundant steroid hormone and its levels have been found to decline gradually independently of menopausal status [12]. Previous studies have reported the beneficial effects of DHEA in terms of improving ovarian response and treatment outcome for in vitro fertilization in women with diminished ovarian reserve [13-15].

However, some clinical studies find that DHEA supplement shows no benefits to clinical preg-

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nancy, retrieved oocytes and oestradiol on hCG day for in vitro fertilization [16-19]. Considering these conflicting results, we therefore perform a systematic review and meta-analysis of RCTs to investigate the efficacy of DHEA supplement on in vitro fertilization.

## Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20].

### Search strategy and study selection

Two investigators have independently searched the following databases (inception to November 2017): PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: dehydroepiandrosterone, and in vitro fertilization. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: women with diminished ovarian reserve undergoing in vitro fertilization; (ii) intervention: DHEA supplement; (iii) comparison: placebo; (iv) study design: RCT. Patients are excluded if they receive DHEA at any time

before enrollment, or fail a previous in vitro fertilization cycle.

### Data extraction and outcome measures

We have extracted the following information: author, number, age, body mass index (BMI), duration of infertility, and follicle-stimulating hormone (FSH) etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary. No simplifications and assumptions are made. The primary outcome is clinical pregnancy. Secondary outcomes include the retrieved oocytes, oestradiol on hCG day, transferred embryos, live birth rate, and miscarriage rate.

### Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [21]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score  $\leq 2$  is considered to be of low quality. If the Jadad score  $\geq 3$ , the study is thought to be of high quality [22].

### Statistical analysis

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (retrieved oocytes, oestradiol on hCG day, and transferred embryos) and odds ratios (ORs) with 95% CIs for dichotomous outcomes (clinical pregnancy, live birth rate, and miscarriage rate). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the  $I^2$  statistic, and  $I^2 > 50\%$  indicate significant heterogeneity [23]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is assessed by Begg's test and Egger's regression test. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

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**Table 1.** Characteristics of included studies

NO.	Author	DHEA group						Placebo group						Jada score
		Number	Age	BMI (kg/m <sup>2</sup> )	Duration of infertility (years)	FSH (IU/l)	Methods	Number	Age	BMI (kg/m <sup>2</sup> )	Duration of infertility (years)	FSH (IU/l)	Methods	
1	Narkwichean 2017	27	36.8±3.9	24.5±4.7	2.95±1.26	-	75 mg/day or placebo for at-least 12 weeks	25	35.2±5.3	23.7±3.3	3.07±1.52	-	Matched placebo	
2	Kotb 2016	70	40.05±3.1	25.6±3.4	7.9±2.5	12.1±0.9	25 mg three times daily for 12 weeks	70	39.7±0.5	25.1±3.4	7.2±2.6	11.9±0.8	Matched placebo	
3	Li 2014	42	37.8±4.6	-	7.18±3.0	10.35±3.27	75 mg daily orally for 3 months	47	36.9±4.7	-	6.88±2.49	9.93±3.51	Matched placebo	3
4	Kara 2014	104	30.97±5.76	-	5.31±1.23	16.31±0.91	75 mg daily for 12 weeks	104	31.15±5.58	-	6.09±1.02	17.13±0.98	Matched placebo	2
5	Yeung 2014	16	36 (35-38)	21.4 (20.4-23.8)	4 (1.5-14.0)	11.0 (8.0-14.2)	25 mg three times a day	16	37 (35-38)	21.5 (18.7-22.7)	8 (1.0-13.5)	13.6 (11.2-16.7)	Matched placebo	5
6	An 2013	81	35.8±4.1	-	5.6±5.4	9.3±2.6	75 mg daily for 3 months	92	35.9±2.9	-	6.7±4.9	10.0±2.0	Matched placebo	5
7	Moawad 2012	67	37.4±6.4	29.1±3.8	6.58±2.17	-	75 mg daily for 12 weeks	66	37.1±7.2	28.7±4.1	7.12±3.25	-	Matched placebo	3
8	Artini 2012	12	36.58±3.32	21.7±3.1	4.6±3.5	5.78±1.45	25 mg three times a day	12	37.00±4.61	21.6±3.1	5.0±4.2	6.68±1.79	Matched placebo	4
9	Wiser 2010	17	36.9±4.7	26.1±5.5	-	9.4 (4.3-15.9)	75 mg daily for 6 weeks	16	37.8±4.6	25.7±4.6	-	9.6 (5.0-15.5)	Matched placebo	3

Data are expressed as mean ± standard deviation or median (25th to 75th centile). BMI: body mass index; FSH: follicle-stimulating hormone.

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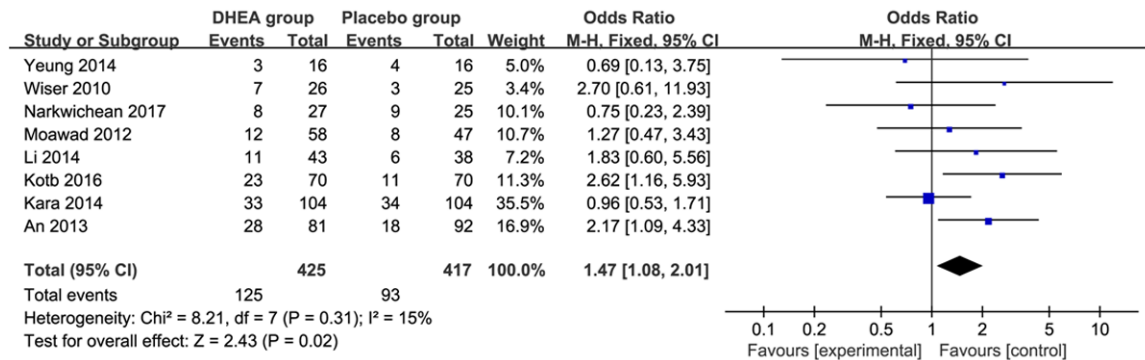


Figure 2. Forest plot for the meta-analysis of clinical pregnancy.

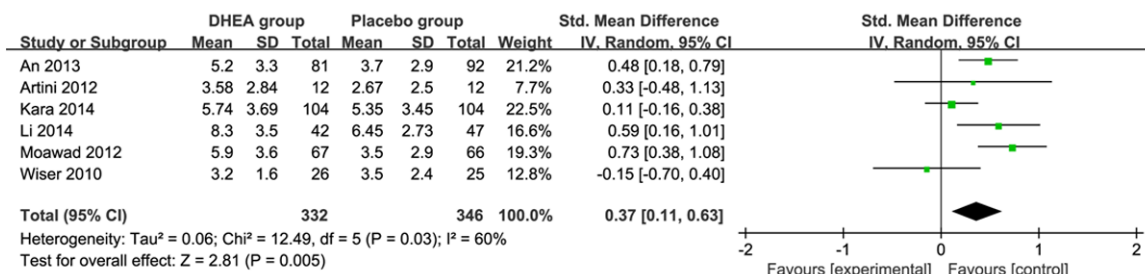


Figure 3. Forest plot for the meta-analysis of retrieved oocytes.

### Results

#### Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. 1172 potentially relevant articles are identified initially. Finally, nine RCTs that meet our inclusion criteria are included in the meta-analysis [16-19, 24-28].

The baseline characteristics of the nine eligible RCTs in the meta-analysis are summarized in **Table 1**. The nine studies are published between 2010 and 2017, and sample sizes range from 24 to 208 with a total of 884. All included patients are diagnosed with diminished ovarian reserve. The treatment intervention is 75 mg daily DHEA versus placebo. The duration of DHEA supplement range from 6 weeks to 12 weeks.

Among the nine studies included here, eight studies reported the clinical pregnancy [16, 17, 19, 24-28], six studies reported the retrieved oocytes [17, 18, 25-28], four studies reported the oestradiol on hCG day [17-19, 28], four

studies reported the transferred embryos [17, 18, 27, 28], three studies reported the live birth rate [16, 17, 19], and three studies reported the miscarriage rate [16, 19, 27]. Jadad scores of the nine included studies vary from 3 to 5, and all nine studies are considered to be high-quality ones according to quality assessment.

#### Primary outcome: clinical pregnancy

This outcome data is analyzed with the random-effects model, and the pooled estimate of the eight included RCTs suggested that compared to control group for in vitro fertilization, DHEA supplement is associated with significantly increased clinical pregnancy (OR=1.47; 95% CI=1.08 to 2.01; P=0.02), with low heterogeneity among the studies (I<sup>2</sup>=15%, heterogeneity P=0.31) (**Figure 2**).

#### Sensitivity analysis

Low heterogeneity is observed among the included studies for the clinical pregnancy. Thus, we do not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

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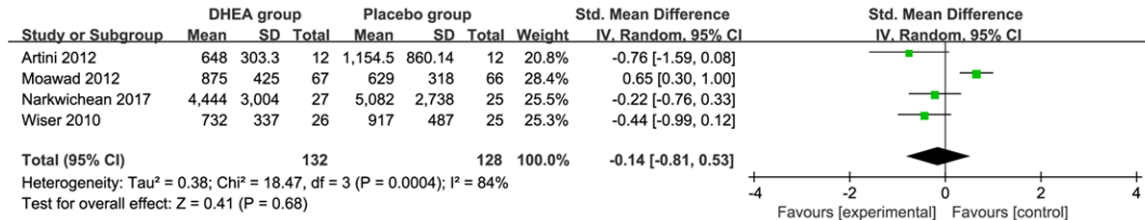


Figure 4. Forest plot for the meta-analysis of oestradiol on hCG day (pmol/L).

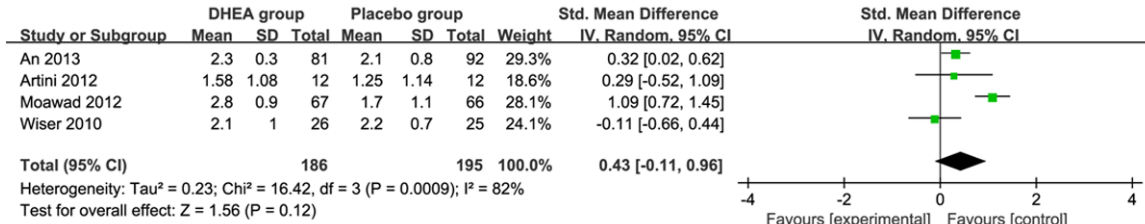


Figure 5. Forest plot for the meta-analysis of transferred embryos.

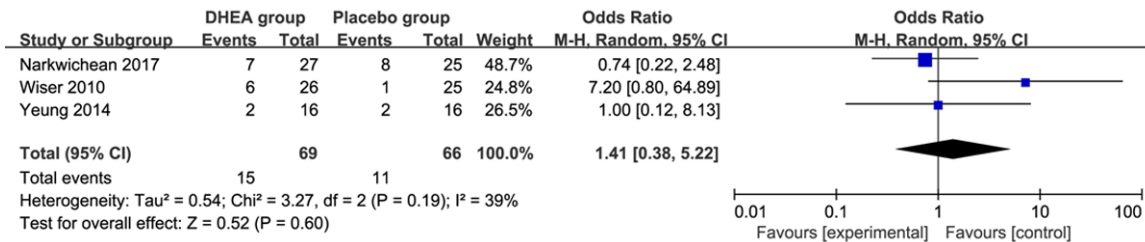


Figure 6. Forest plot for the meta-analysis of live birth rate.

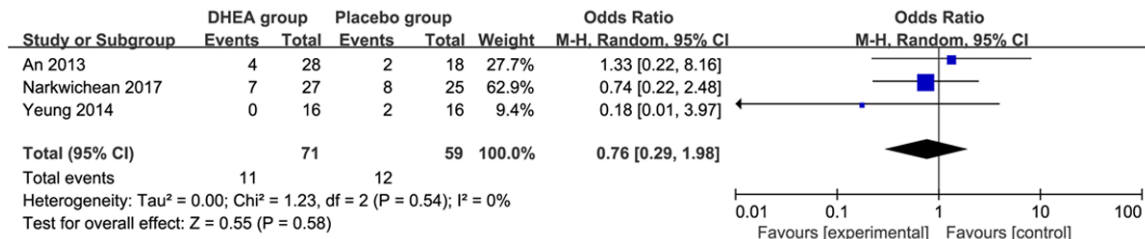


Figure 7. Forest plot for the meta-analysis of miscarriage rate.

### Secondary outcomes

Compared to control group for in vitro fertilization, DHEA supplement results in substantially improved retrieved oocytes (Std. MD=0.37; 95% CI=0.11 to 0.63; P=0.005; **Figure 3**), but has no remarkable impact on oestradiol on hCG day (Std. MD=-0.14; 95% CI=-0.81 to 0.53; P=0.68; **Figure 4**), transferred embryos (Std. MD=0.43; 95% CI=-0.11 to 0.96; P=0.12; **Figure 5**), live birth rate (OR=1.41; 95% CI=0.38 to 5.22; P=0.60; **Figure 6**), miscarriage rate

(OR=0.76; 95% CI=0.29 to 1.98; P=0.58; **Figure 7**).

### Serious adverse events

All included studies report no serious adverse events related to DHEA treatment.

### Publication bias

Potential publication bias is observed based on Begg's test (P=0.386) and Egger's regression test (0.251).



## Discussion

Several studies have demonstrated a beneficial effect of DHEA on the pregnancy rate and retrieved oocytes in infertile women [16, 29]. DHEA is reported to enhance ovarian response and pregnancy rates in women with diminished ovarian reserve [30]. Several theories may explain how DHEA improves ovarian response: (1) DHEA can result in the direct increase in primordial follicles, preantral follicles and antral follicles pool, antimullerian hormone (AMH) levels that stimulate early follicular development [31, 32]. (2) DHEA is able to increase granulosa cells FSH receptors and follicular sensitivity to FSH and improve steroidogenesis [33]. (3) DHEA can promote follicular growth and improve oocyte quality via improving insulin growth factor 1 levels [34].

One previous meta-analysis is reported by Narkwichean et al. and only three clinical studies are included in the meta-analysis. The results indicate that DHEA supplementation can not significantly increase clinical pregnancy rate and reduce miscarriage rates in women with diminished ovarian reserve [35]. Eight clinical studies regarding the effect of DHEA on diminished ovarian reserve are included in another meta-analysis that is published in 2015, but only one of them is RCT. That meta-analysis shows that DHEA can significantly increase the clinical pregnancy rate, but has no influence on oocyte retrieval, implantation, and abortion [36].

Our meta-analysis include nine RCTs involving 884 women with diminished ovarian reserve. The results suggest that DHEA supplementation can significantly increase clinical pregnancy and retrieved oocytes for in vitro fertilization in women with diminished ovarian reserve, but shows no influence on oestradiol on hCG day, transferred embryos, live birth rate, and miscarriage rate. Although there is no significant heterogeneity for the primary outcome, some of the included RCTs have some bias. For example, one RCT published by Wiser et al. is limited by the insufficient sample size and inappropriate statistical methods (Fisher's Exact test) [17], and their data can not support the conclusion that administration of DHEA increases the probability of live birth [37].

In addition, patients in DHEA group obtain conventional dose, 75 mg daily in all the included

RCTs. Previous study reports that patients with adrenal insufficiency (lacking DHEA) receiving 50 mg DHEA have significant improvement of the well-being, and a lower dose of DHEA (25 to 30 mg daily) may be more suitable for long-term treatment of some women because of androgenic side effects [38]. More studies should investigate the optimal dose of DHEA for long-term treatment in women with diminished ovarian reserve.

This meta-analysis has several potential limitations that should be taken into account. Firstly, our analysis is based on nine RCTs, but five of them have a relatively small sample size ( $n < 100$ ). More RCTs with larger sample size should be conducted to confirm this issue. Next, the DHEA duration for in vitro fertilization ranges from 6 weeks to 12 weeks, which may have some impact on the pooling results. Finally, the optimal dose and duration of DHEA supplement for women with diminished ovarian reserve remains elusive.

## Conclusions

DHEA supplement has some benefits to women with diminished ovarian reserve and should be recommended to be administrated in clinical work with caution.

## Disclosure of conflict of interest

None.

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