REVIEW

Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis

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Abstract

Purpose We reviewed the influence of dehydroepiandrosterone (DHEA) supplementation in patients with poor ovarian response (POR) undergoing in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI).

Methods We searched Embase, MEDLINE, PubMed, and the Cochrane Library (1980–2015) for relevant papers and used the Newcastle–Ottawa Scale scoring system to evaluate study quality. Dichotomous data were expressed as pooled relative risk (RR) estimates with fixed or random effect models. Continuous variables were expressed as the weighted mean difference (WMD). All data were analyzed using Revman Software v. 5 and are shown with 95 % confidence intervals (CI).

Results Twenty-one studies met the inclusion criteria. DHEA pretreatment increased the clinical pregnancy rate (RR 1.53, 95 % CI 1.25–1.86), live birth rate (RR 1.87, 95 % CI 1.22–2.88), implantation rate (RR 1.56, 95 % CI 1.20–2.01), and antral follicle count (WMD 0.4, 95 % CI 0.14 to 0.66) while reducing miscarriages (RR 0.50, 95 % CI 0.27–0.90). After subgroup analysis, oocyte numbers and

anti-Müllerian hormone levels were also enhanced after DHEA treatment. However, the endometrial thickness and estradiol levels on the day of injecting hCG to induce ovulation were similar between the DHEA supplementation groups and controls.

Conclusions Based on the limited available evidence, DHEA supplementation seems to improve ovarian reserves and IVF/ICSI outcome in patients with POR. Further research is required to clarify the effect of DHEA exposure in assisted reproduction technology.

Keywords Dehydroepiandrosterone (DHEA) · Poor ovarian response · Fertilization in vitro · Intracytoplasmic sperm injection (ICSI) · Meta-analysis · Pre-treatment

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Introduction

Despite advancements in assisted reproductive technology (ART), poor ovarian response (POR) remains a major problem and presents a challenge in clinical practice [1]. The precise definition of POR has varied over time: advanced female age, poor ovarian response to gonadotropin stimulation, and abnormal markers of ovarian reserve have all been used to diagnose POR [2]. Recently, the Consensus Group for the European Society for Human Reproduction and Embryology (ESHRE) developed the Bologna criteria to help assign more uniform patient groups to clinical trials [3]. According to these criteria, poor responders are diagnosed with at least two of the three following criteria: (1) advanced maternal age (≥40 years) or other risk factors for POR, (2) a previous POR (≤3 oocytes with a conventional ovarian stimulation protocol), and (3) an abnormal ovarian reserve test (antral follicle count, AFC < 5). The reported diagnosis rates of POR ranged from 9 to 24 % among

patients undergoing in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) treatments [4]. A variety of methods has been applied to improve the ovarian response, including increased gonadotropin dosage, modulation with gonadotropin-releasing hormone (GnRH) flare-up regimes, adjunctive growth hormone treatment, minimal ovarian stimulation with clomiphene citrate, and unstimulated or "natural cycle" IVF. However, the outcomes of these treatments have been less than satisfactory [1, 5].

Dehydroepiandrosterone (DHEA) is an endogenous steroid produced in the zona reticularis of the adrenal cortex and by ovarian theca cells [6]. In the ovary, it promotes follicular development and granulosa cell proliferation by increasing intraovarian androgen concentrations [7]. DHEA can also enhance the level of follicular insulin-like growth factor-1 (IGF-1), which promotes folliculogenesis by enhancing the effect of gonadotropin and reducing follicular arrest [7–9]. Recently, treatment with DHEA has been shown to result in improved ovarian response in patients with POR [2, 6, 10–17]. An international survey showed that 26 % of IVF clinicians add DHEA as an adjuvant to IVF treatment protocols in such women [18]. However, conclusive clinical evidence of DHEA's influence is limited. Systematic reviews investigated the effect of DHEA in IVF outcomes but their sample size was small [19]. More information is also necessary to evaluate the role of DHEA as an adjuvant to controlled ovarian stimulation in poor-responders and in women with diminished ovarian reserve. During 2014 and 2015, there was an increased number of papers concerning DHEA treatment in patients with POR. Therefore, this review summarizes and discusses recent advances regarding DHEA treatment in such patients.

Methods

Literature search strategy

We performed an extensive literature search of Embase (1980 to July 2015), MEDLINE (1948 to July 2015), PubMed (1946 to July 2015), and the Cochrane Library for all relevant articles under the following Medical Subject Headings (MeSH) terms (https://www.nlm.nih.gov/mesh/MBrowser.html) to generate subsets of studies: (i) "DHEA" or "Dehydroepiandrosterone", (ii) "Poor ovarian response" or "POR" (because the definition of POR was developed in 2011) or "low response" or "diminished ovarian reserve," (iii) "IVF" or "ICSI." We combined these subsets together (subset i with ii and iii) using "AND" to determine citations that were relevant to the following statement: "DHEA treatment in poor ovarian response women undergoing IVF or ICSI". In addition, all primary papers'

bibliographies were explored to identify any cited publications that had not been identified by the database searches. Only articles written in English were included in the meta-analysis. Two reviewers conducted the searches independently (MZ and YW).

Inclusion/exclusion criteria

We searched specifically for papers that focused on women with POR and diminished ovarian reserve, who were undergoing ovarian stimulation and IVF/ICSI. In all cases, DHEA was given as a supplement before ovarian stimulation and any IVF/ICSI cycle. The main observed outcomes were clinical pregnancy rate, miscarriage rate, live birth rate, implantation rate, oocyte numbers, estradiol (E2) level on the day of administering human chorionic gonadotropin (hCG) for ovulation induction, endometrial thickness, and the ovarian reserve markers anti-Müllerian hormone (AMH) and antral follicle count (AFC). We excluded non-English language papers, overlapping studies, studies with unclear outcomes, and other articles lacking relevant observed factors.

Quality assessment

Two reviewers (MZ and YW) read the full text of the selected papers and included publications with predefined inclusion criteria independently. Two reviewers (MZ and YW) separately extracted data from each study, including the population, study design, inclusion and exclusion criteria, interventions, and controlled ovarian hyperstimulation (COH) protocols and outcomes. These data were subsequently arranged into a pre-determined form. A third reviewer (WN) arbitrated on article selection and any data extraction-related disagreements. The Newcastle–Ottawa Scale (NOS) scoring system was used to evaluate the quality and methodology of selected articles [20].

Statistical analysis

We calculated relative risk (RR) in fixed and random effect models [21, 22]. The results were combined to create forest plots with Revman Software (Version 5, The Cochrane Collaboration, Oxford, UK, 2003). Dichotomous data for each unit of analysis were calculated as an RR with a 95 % confidence interval (CI). Continuous variables are expressed here as the weighted mean difference (WMD) with 95 % CIs. Heterogeneity was evaluated with I^2-index values and reported for each outcome as a P value plus CI range and shown graphically using forest plots (Lewis and Clarke, 2001). For some continuous variables with high heterogeneity, we

applied subgroup analysis based on patient age or other influential factors.

Results

Systematic review

The search strategy yielded a total of 81 publications. Full texts were retrieved for all of these, and 21 fulfilled the inclusion criteria with no disagreement between the reviewers who were responsible for study selection (Fig. 1). Further details on these studies are listed in Table 1. All articles were intended to compare whether pre-treatment with DHEA could improve the IVF/ICSI outcomes of patients with POR. All trials were subjected to meta-analysis to compare IVF/ICSI outcomes, and eight trials were used to compare alternations in hormone levels before and after treatment. The quality control evaluations of all studies are listed in Table 2.

Primary outcomes

Clinical pregnancy rates

In all, 17 studies based on 1883 patients and 18 trials (one study included two separate trials) were used to calculate clinical pregnancy rates [2, 13–15, 17, 23–32]. Eight of these were randomized control trials (RCTs), 10 were cohort studies, and three were case–control studies. There was no indication of statistical heterogeneity in the case–control and RCT studies

Fig. 1 Flow diagram detailing selection of studies for inclusion

($I^2 = 37$ %). Our pooled analysis of these two types of studies showed statistically significant increases in the pregnancy rates of patients treated with DHEA compared with untreated control groups (12 trials RR 1.53, 95 % CI 1.25–1.86, $p < 0.0001$, Fig. 2a). Self-controlled trials are less informative for clinical pregnancy rate because patients only enter such studies if a first cycle of IVF/ICSF fails. Therefore, the pregnancy rate of the "control" group will always be 0 %, and DHEA treatment can only result in increased pregnancy rates. Thus, a high overall effect was observed in these types of studies (six trials, RR 14.98, 95 % CI 4.75–47.19, $p < 0.0001$, Fig. 2b).

Miscarriage rate

Seven trials including 204 patients were used to calculate miscarriage rates. These consisted of three RCTs, two cohort trials, and two case–control trials [2, 13–16, 30, 32]. There was no indication of statistical heterogeneity ($I^2 = 31$ %). Women undergoing DHEA treatment had lower miscarriage rates after treatment than the controls (seven trials, RR 0.50, 95 % CI 0.27–0.90, $p = 0.02$, Fig. 3).

Live birth rate

Six trials including 528 patients were used to calculate live birth rates: four were RCT trials and two were prospective cohort trials [2, 14, 15, 24, 30, 32]. There were significantly higher live birth rates in the DHEA treatment groups compared with controls (RR 1.87, 95 % CI 1.22–2.88, $p = 0.004$) with no indication of statistical heterogeneity ($I^2 = 26$ %, Fig. 4).

Secondary outcomes

Implantation rate

Three case–control trials, two RCTs, and a prospective cohort study covering 1398 patients were utilized to determine implantation rates [13, 15, 16, 24, 30]. The implantation rate in patients treated with DHEA was significantly increased compared with untreated control patients (five trials, RR 1.56, 95 % CI 1.20–2.01, $p = 0.0007$) with no indication of statistical heterogeneity ($I^2 = 0$ %, Fig. 5).

Oocyte numbers

Nine of the 18 trials that collected oocyte number data were self-control studies and were used for this analysis. Because ovarian reserves decrease sharply in women aged over 36 years [17] and will influence the retrieved oocyte number, we divided the studies into distinct categories based on patient age over or under 36 years old and analyzed them separately.
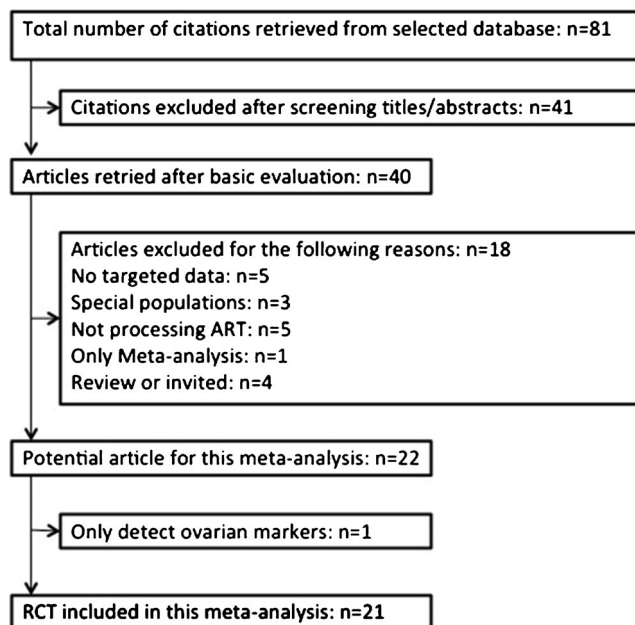
Table 1   Methodological characteristic of eligible articles

Author (Reference)	Number of subjects	Intervention	Study design	Dose of DHEA	Duration
Barad [13]	89 cases/101 controls (diminished ovarian reserve)	IVF	Case–control	75 mg/day	3.8 ± 0.3 months
Barad [12]	25 self-control (diminished ovarian reserve)	IVF	Prospective cohort study	75 mg/day	4.1 ± 0.5 months
Sonmezer [23]	19 self-control (POR)	IVF/ICSI	Prospective cohort study	75 mg/day	3-6 months
Gleicher [32]	22 cases/44 controls (diminished ovarian reserve)	None	Case–control	75 mg/day	2.4 ± 0.9 months
Wiser [14]	26 cases/25 controls (poor response)	IVF	RCT	75 mg/day	>2 months
Artini [33]	12 cases/12 controls (POR)	IVF/ICSI	RCT	75 mg/day	3 months
Moawad [24]	67 cases/66 controls (poor response)	IVF/ICSI	RCT	75 mg/day	>3 months
Fusi [25]	38 cases/24 controls and 39 self-controls (poor responses)	IVF	Prospective cohort study	75 mg/day	>3 months
Hyman [26]	32 self-control (poor responses)	IVF	Prospective cohort study	75 mg/day	>3 months
Singh [27]	30 self-control (poor responses)	IVF	Prospective cohort study	75 mg/day	4 months
Yeung [32]	10 cases/12 control (primary ovarian insufficiency)	IVF	RCT	75 mg/day	4 months
Yilmaz [36]	41 self-control (diminished ovarian reserve)	IVF/ICSI	Prospective cohort study	75 mg/day	>1.5 months
Jirge [15]	25 self-control (POR)	IVF	Prospective cohort study	75 mg/day	>2 months
Kara [28]	104 cases/104 controls (diminished ovarian reserve)	IVF/ICSI	RCT	75 mg/day	>3 months
Vlahos [2]	48 cases/113 controls (POR)	IVF	Prospective cohort study	75 mg/day	>3 months
Xu [16]	189 cases/197 controls (POR)	IVF/ICSI	Case–control	75 mg/day	3 months
Yeung [6]	16 cases/16 controls (poor response)	IVF/ICSI	RCT	75 mg/day	3 months
Zangmo [17]	50 self-control (poor responses)	IVF	Prospective cohort study	75 mg/day	4 months
Zhang [29]	42 cases/42 controls (diminished ovarian reserve)	IVF	RCT	75 mg/day	3 months
Tartagni [30]	53 cases/56 controls (poor responses)	IVF	RCT	75 mg/day	2 months
Tsui [31]	10 self-control (poor responses)	IVF	Prospective cohort study	90 mg/day	3 months

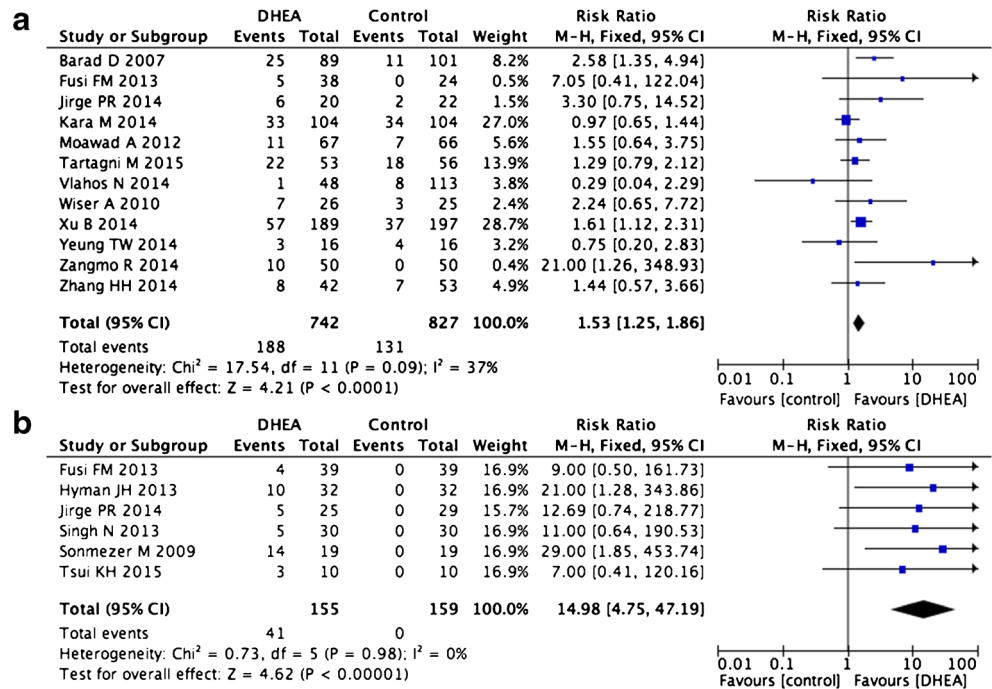*DHEA* dehydroepiandrosterone, *POR* poor ovarian response, *RCT* randomized control trials

Three trials including 69 patients that studied women younger than 36 years showed significant increases in oocyte number after DHEA treatment (WMD 2.38, 95 % CI 2.15–2.61, $p < 0.0001$, $I^2 = 1$ %, Fig. 6a) [15, 17, 23]. Six trials including 163 patients that studied women older than 36 also indicated increased oocyte numbers after DHEA treatment (WMD 1.31,

Table 2   Quality of controlled studies passing eligibility criteria presented by stratification of research methodology and Newcastle–Ottawa scale (for non-randomized observational studies)

Author (Year)	Study design	Randomisation	Blinding	Sample size estimation	Analysis	Newcastle-Ottawa scale		–
						Selection	Comparablility	Outcome
–	–	–	–	–	–			
Barad [13]	Case– control	None	None	N/A	Intention to treat analysis	***	*	**
Barad [12]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**
Sonmezer [23]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**
Gleicher [32]	Case–control	None	None	N/A	Intention to treat analysis	***	*	**
Wiser [14]	RCT							
Artini [33]	RCT							
Moawad [24]	RCT							
Fusi [25]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**
Hyman [26]	Prospective cohort study	None	None	N/A	Intention to treat analysis	**	*	**
Singh [27]	Prospective cohort study	None	None	N/A	Intention to treat analysis	**	*	**
Yeung [32]	RCT							
Yilmaz [36]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**
Jirge [15]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**
Kara [28]	RCT							
Vlahos [2]	Prospective cohort study	None	None	N/A	Intention to treat analysis	****	*	**
Xu [16]	Case–control	None	None	N/A	Intention to treat analysis	**	*	**
Yeung [6]	RCT							
Zangmo [17]	Prospective cohort study	None	None	N/A	Intention to treat analysis	**	*	**
Zhang [29]	RCT							
Tartagni [30]	RCT							
Tsui [31]	Prospective cohort study	None	None	N/A	Intention to treat analysis	***	*	**

Fig. 2 Risk difference for clinical pregnancy rate in patients treated with DHEA or not

a

Study or Subgroup	DHEA Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barad D 2007	25	89	11	101	8.2%	2.58 [1.35, 4.94]
Fusi FM 2013	5	38	0	24	0.5%	7.05 [0.41, 122.04]
Jirge PR 2014	6	20	2	22	1.5%	3.30 [0.75, 14.52]
Kara M 2014	33	104	34	104	27.0%	0.97 [0.65, 1.44]
Moawad A 2012	11	67	7	66	5.6%	1.55 [0.64, 3.75]
Tartagni M 2015	22	53	18	56	13.9%	1.29 [0.79, 2.12]
Vlahos N 2014	1	48	8	113	3.8%	0.29 [0.04, 2.29]
Wiser A 2010	7	26	3	25	2.4%	2.24 [0.65, 7.72]
Xu B 2014	57	189	37	197	28.7%	1.61 [1.12, 2.31]
Yeung TW 2014	3	16	4	16	3.2%	0.75 [0.20, 2.83]
Zangmo R 2014	10	50	0	50	0.4%	21.00 [1.26, 348.93]
Zhang HH 2014	8	42	7	53	4.9%	1.44 [0.57, 3.66]
Total (95% CI)		**742**		**827**	**100.0%**	**1.53 [1.25, 1.86]**
Total events	188		131			

Heterogeneity: Chi^2 = 17.54, df = 11 (P = 0.09); I^2 = 37%
Test for overall effect: Z = 4.21 (P < 0.0001)

b

Study or Subgroup	DHEA Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fusi FM 2013	4	39	0	39	16.9%	9.00 [0.50, 161.73]
Hyman JH 2013	10	32	0	32	16.9%	21.00 [1.28, 343.86]
Jirge PR 2014	5	25	0	29	15.7%	12.69 [0.74, 218.77]
Singh N 2013	5	30	0	30	16.9%	11.00 [0.64, 190.53]
Sonmezer M 2009	14	19	0	19	16.9%	29.00 [1.85, 453.74]
Tsui KH 2015	3	10	0	10	16.9%	7.00 [0.41, 120.16]
Total (95% CI)		**155**		**159**	**100.0%**	**14.98 [4.75, 47.19]**
Total events	41		0			

Heterogeneity: Chi^2 = 0.73, df = 5 (P = 0.98); I^2 = 0%
Test for overall effect: Z = 4.62 (P < 0.00001)

95 % CI 0.73–1.90, $p < 0.0001$, I^2 = 72 %, Fig. 6b) [12, 14, 17, 25, 26, 31]. We also compared the results from case–control trials. Of nine such trials, we selected five (total 280 patients) and discarded four when controlling for age, DHEA treatment time, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) doses for COH [2, 14, 16, 33, 34]. This analysis also indicated a larger retrieved oocyte number after DHEA treatment (WMD 0.27, 95 % CI 0.12–0.42, $p = 0.0004$, I^2 = 49 %, Fig. 6c).
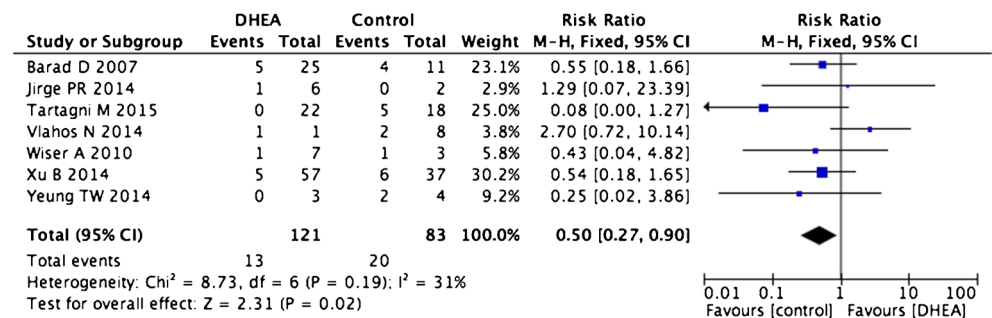
E2 level on the day of hCG administration

Eleven trials included information about the E2 level on the day of hCG administration. Six of these were self-control comparisons [12, 14, 15, 23, 25, 27]. We excluded one because the study population of Singh et al. [27] was divided according to age, but also had positive results for DHEA treatment. These studies indicated that DHEA increased peak E2 levels on the day of hCG administration (five trials, WMD 240.64, 95 % CI 23.7–457.58, $p = 0.03$; Fig. 7a) [12, 14, 15,

23, 25]. A random effect was used instead of a fixed effect because of the higher heterogeneity between trials (I^2 = 77 %). For case–control studies, after normalizing for age, DHEA treatment time, FSH, and LH dose for COH, we selected four out of five trials, but the result did not display significant differences between two groups (WMD −81.44, 95 % CI −195.94 to +33.46, $p = 0.16$, I^2 = 51 %), and the controls were even higher (Fig. 7b) [14, 16, 28, 34].
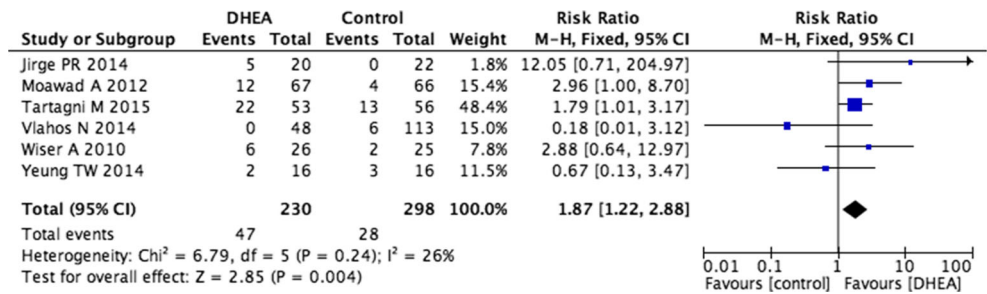
Endometrial thickness

Seven studies including eight trials compared endometrial thickness on the day of administering hCG. Four self-control studies showed no difference before and after DHEA supplementation (WMD 0.29, 95 % CI −0.16 to +1.03, $p = 0.45$, I^2 = 0 %) [14, 23, 25, 26]. Four articles that compared DHEA pre-treatment groups with control groups also showed no differences in this factor, although they did display high levels of heterogeneity (WMD 0.73, 95 % CI −0.64 to +2.10, $p = 0.30$, I^2 = 95 %, Fig. 8) [14, 16, 24, 30].

Fig. 3 Risk difference for miscarriage rate in patients treated with DHEA or not

Study or Subgroup	DHEA Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barad D 2007	5	25	4	11	23.1%	0.55 [0.18, 1.66]
Jirge PR 2014	1	6	0	2	2.9%	1.29 [0.07, 23.39]
Tartagni M 2015	0	22	5	18	25.0%	0.08 [0.00, 1.27]
Vlahos N 2014	1	1	2	8	3.8%	2.70 [0.72, 10.14]
Wiser A 2010	1	7	1	3	5.8%	0.43 [0.04, 4.82]
Xu B 2014	5	57	6	37	30.2%	0.54 [0.18, 1.65]
Yeung TW 2014	0	3	2	4	9.2%	0.25 [0.02, 3.86]
Total (95% CI)		**121**		**83**	**100.0%**	**0.50 [0.27, 0.90]**
Total events	13		20			

Heterogeneity: Chi^2 = 8.73, df = 6 (P = 0.19); I^2 = 31%
Test for overall effect: Z = 2.31 (P = 0.02)

Fig. 4 Risk difference for live birth rate in patients treated with DHEA or not

Study or Subgroup	DHEA Events	DHEA Total	Control Events	Control Total	Weight	Risk Ratio M–H, Fixed, 95% CI
Jirge PR 2014	5	20	0	22	1.8%	12.05 [0.71, 204.97]
Moawad A 2012	12	67	4	66	15.4%	2.96 [1.00, 8.70]
Tartagni M 2015	22	53	13	56	48.4%	1.79 [1.01, 3.17]
Vlahos N 2014	0	48	6	113	15.0%	0.18 [0.01, 3.12]
Wiser A 2010	6	26	2	25	7.8%	2.88 [0.64, 12.97]
Yeung TW 2014	2	16	3	16	11.5%	0.67 [0.13, 3.47]
Total (95% CI)		**230**		**298**	**100.0%**	**1.87 [1.22, 2.88]**
Total events	47		28			

Heterogeneity: Chi^2 = 6.79, df = 5 (P = 0.24); I^2 = 26%
Test for overall effect: Z = 2.85 (P = 0.004)

Ovarian reserve markers

We also investigated the AMH levels and AFC in the same patients before and after DHEA supplementation. Because decreases in ovarian reserve markers are correlated with increased age [35], some articles divided women into groups according to age. Therefore, our meta-analysis divided these studies into subgroups to reduce heterogeneity. Two articles with different population groups showed a significant increase in AMH level for all age groups after DHEA treatment (WMD 1.44, 95 % CI 1.27–1.6, $p < 0.0001$, I^2 = 0 %, Fig. 9a) [17, 27]. The other five articles [2, 15, 29, 31, 36] also showed similar results (WMD 0.38, 95 % CI 0.26–0.5, P < 0.0001, I^2 = 0 %; Fig. 9b). Six self-control studies also indicated that DHEA treatment increased the AFC, with no significant heterogeneity observed (WMD 0.4, 95 % CI 0.14–0.66, $p = 0.002$, I^2 = 24 %, Fig. 10) [15, 26, 27, 29, 31, 36].
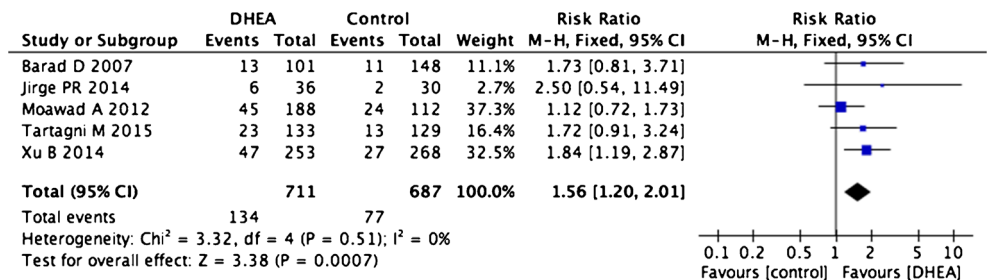
Discussion

The purpose of this meta-analysis was to evaluate whether DHEA supplementation would increase ovarian response as well as IVF/ICSI outcome. Our results suggested that it improves both outcomes. In total, 21 publications were analyzed, which included eight RCTs, 10 cohort studies, and three case–control studies. All included observational studies were either RCT or fulfilled the NOS scoring system. Unlike previous meta-analyses, we accepted self-controlled studies. These types of trials accounted for a large proportion of the total studies performed, especially for comparisons of AMH levels and AFC. Self-controlled studies are typically thought to have

a bias towards more ideal outcomes because of how they are performed; thus, we analyzed these groups separately from two-group studies [19]. When facing high heterogeneity, we used subgroup analysis wherever possible to avoid comparing different populations with potentially different responses to DHEA treatment or gonadotropin doses [17, 27]. A paucity of high-quality studies remains the main limitation to establish the effectiveness of DHEA treatment in ovarian response and IVF/ICSI outcomes in clinical settings.

Another challenge was to evaluate the various criteria that different studies used to assess POR. Many papers were published before the ESHRE consensus and included incomplete POR definitions. However, we chose to include their contributions to the analysis of DHEA treatment in patients with POR. In addition, trials focusing on patients with low functional ovarian (age-specific) reserve were included in this analysis. Because our aim was to study the influence of DHEA on ovarian response, the inclusion of these studies was relevant. When faced with limited information on how POR was defined, all authors discussed each case individually to form a consensus about whether to include individual studies for this meta-analysis.

The most direct criteria used to assess the influence of DHEA pre-treatment were clinical pregnancy, miscarriage, and live birth rates. Our data showed a consistent effect of DHEA in increasing clinical pregnancy and live birth rates, while decreasing the miscarriage rate. These results emphasize the positive influence of DHEA for patients with POR. DHEA treatment has also been shown to improve outcomes in women who do not display POR but still pursued IVF/ICSI treatments. Like Tartagni et al. reported that DHEA supplementation in infertile women who underwent IVF treatment led to a

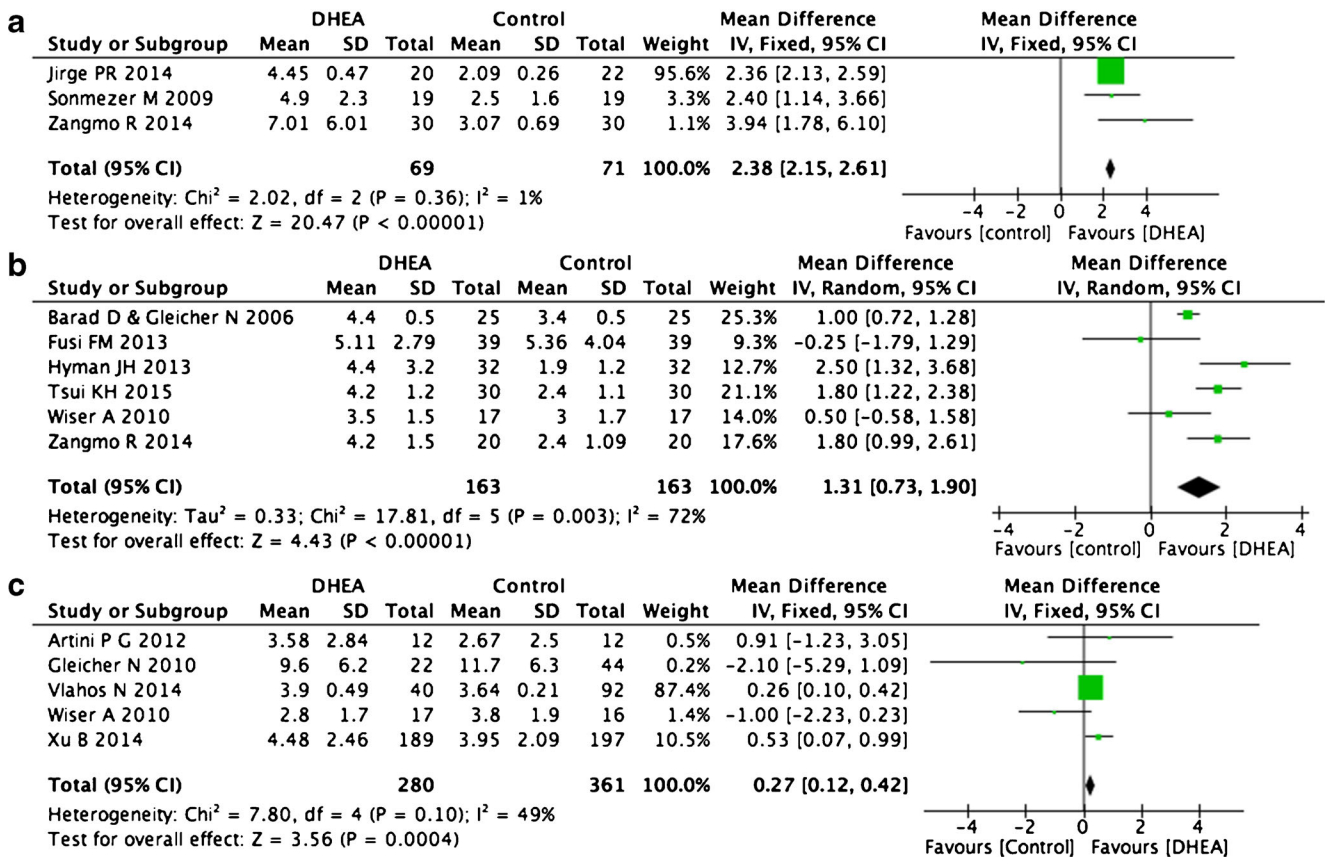**Fig. 5** Risk difference for implantation rate in patients treated with DHEA or not

Study or Subgroup	DHEA Events	DHEA Total	Control Events	Control Total	Weight	Risk Ratio M–H, Fixed, 95% CI
Barad D 2007	13	101	11	148	11.1%	1.73 [0.81, 3.71]
Jirge PR 2014	6	36	2	30	2.7%	2.50 [0.54, 11.49]
Moawad A 2012	45	188	24	112	37.3%	1.12 [0.72, 1.73]
Tartagni M 2015	23	133	13	129	16.4%	1.72 [0.91, 3.24]
Xu B 2014	47	253	27	268	32.5%	1.84 [1.19, 2.87]
Total (95% CI)		**711**		**687**	**100.0%**	**1.56 [1.20, 2.01]**
Total events	134		77			

Heterogeneity: Chi^2 = 3.32, df = 4 (P = 0.51); I^2 = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)

Fig. 6 Weighted mean difference for oocyte numbers in patients treated with DHEA or not

significantly higher live birth rate and lower miscarriage rate [37]. Artini et al. suggested that DHEA might decrease the level of hypoxic inducible factor1, and there were significantly more mature oocytes retrieved from selected follicles in the DHEA treatment group compared with controls (0.50 ± 0.52 vs. 0.08 ± 0.29, $p = 0.018$) [34]. Combined with our data, these studies illustrate the positive influence of DHEA as an adjuvant in women undergoing IVF/ICSI cycles.

The secondary criteria we applied included oocyte numbers, endometrial thickness, implantation rate, and E2 level on the

day of hCG administration, as well as other ovarian reserve markers. The number of retrieved oocytes was calculated in part to evaluate any direct effect of DHEA on follicle generation. After matching treatment duration, age, and gonadotropin dose, we separated the retrieved oocyte numbers into three subgroups. As expected, both self-controlled and case–control (including RCT) subgroups showed increased numbers of retrieved oocytes after DHEA treatment. However, our meta-analysis showed that DHEA supplementation promoted the implantation rate but did not improve endometrial thickness.
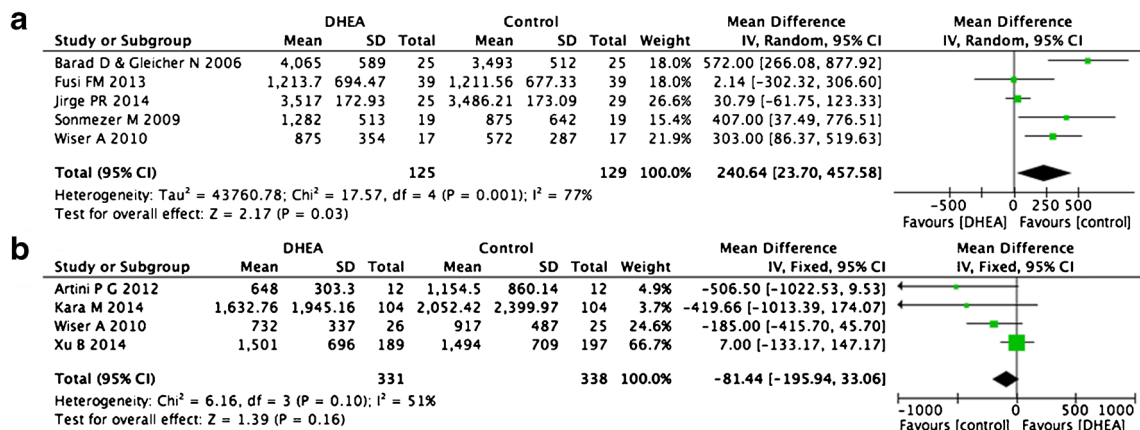
Fig. 7 Weighted mean difference for E2 on hCG day in patients treated with DHEA or not
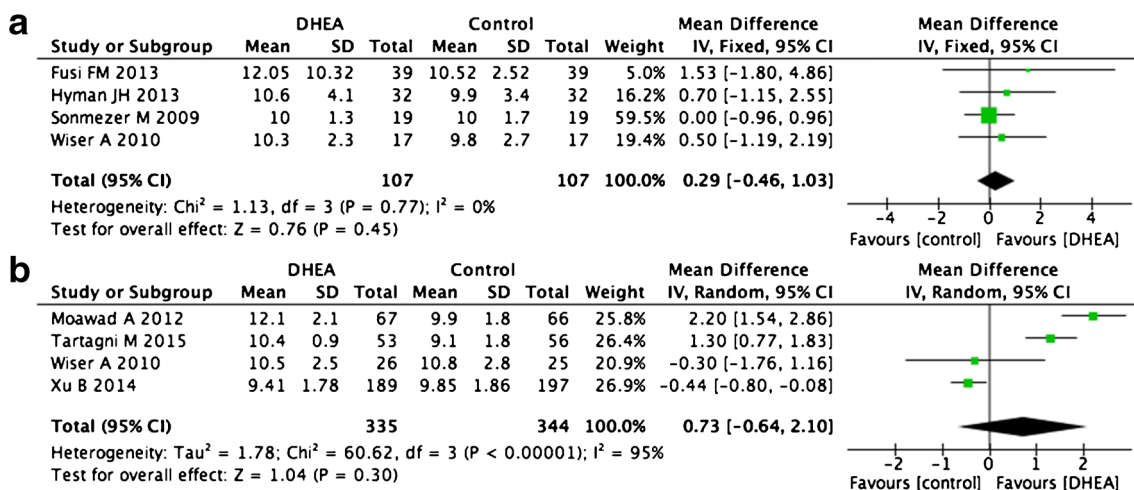
Fig. 8 Weighted mean difference for endometrial thickness in patients treated with DHEA or not

This outcome might have reflected better embryo quality [17]. However, this factor was difficult to assess because it is a subjective indicator with differing criteria and scoring systems. In addition, few publications provided data on embryo quality, which made it difficult to perform any meta-analysis. In addition, as a number of studies that tracked this indicator displayed highly heterogeneous results, so were excluded from our meta-analysis [13, 24, 28, 30]. Intriguingly, Barad et al. [11, 13] found that DHEA treatment resulted in fewer oocytes, fewer normal, and transferred embryos, but higher clinical pregnancy rates. The results presented here partly agree with those findings concerning DHEA's positive effects on clinical pregnancy rates. However, our analysis indicates that DHEA treatment leads to increased oocyte numbers. Based on these apparently conflicting results, further study on the relationship between DHEA treatment and oocyte numbers is necessary.

Clinicians have usually performed self-controlled studies for AMH levels and AFC before and after DHEA treatment.

Usually, both of these parameters have been shown to decrease with aging [35]. But we confirmed significant improvements in these parameters after DHEA supplementation. A previous study on follicular developmental indicated that DHEA exposure stimulated the initiation of growth in primordial follicles, improves gonadotrophin-response, promotes granulosa cell proliferation, enhances AMH expression, and delays the effect of ovary aging [38]. The same group also observed increased primordial follicle initiation and prenatal follicle development in both cortical grafts and the remaining ovarian tissue, which supports our analysis that indicates higher AMH and AFC levels after DHEA treatment. Tsui et al. used genetic methods to explain the function of DHEA. A significant difference in the expression of genes in women with POR before and after DHEA supplementation (all $p < 0.05$) was observed [31]. Gene ontology (GO) analysis showed that genes related to extracellular matrix formation were upregulated, including HAS2, VCAN, and THBS1. By contrast, genes related to cell development,
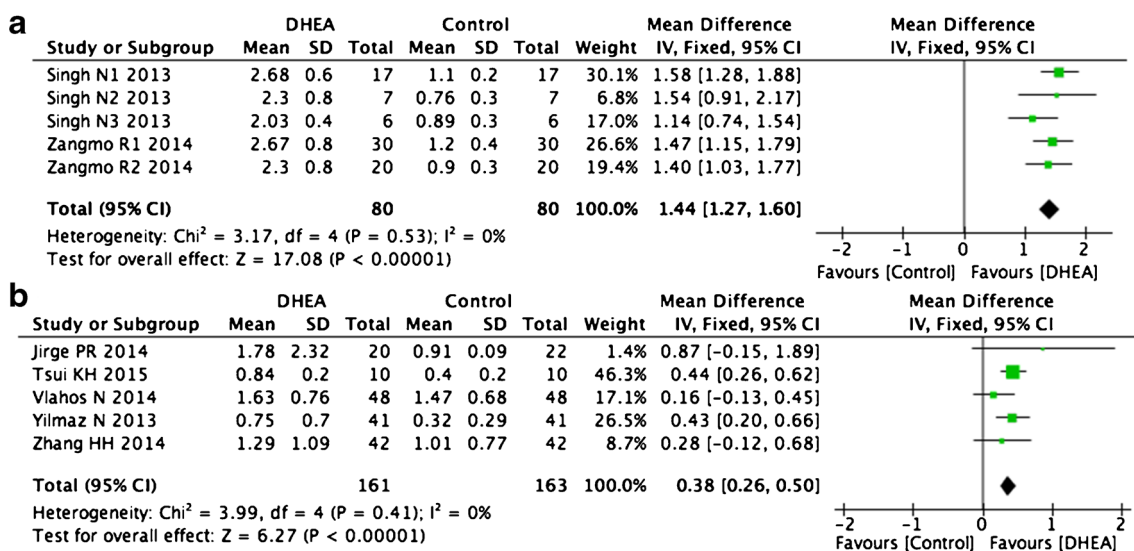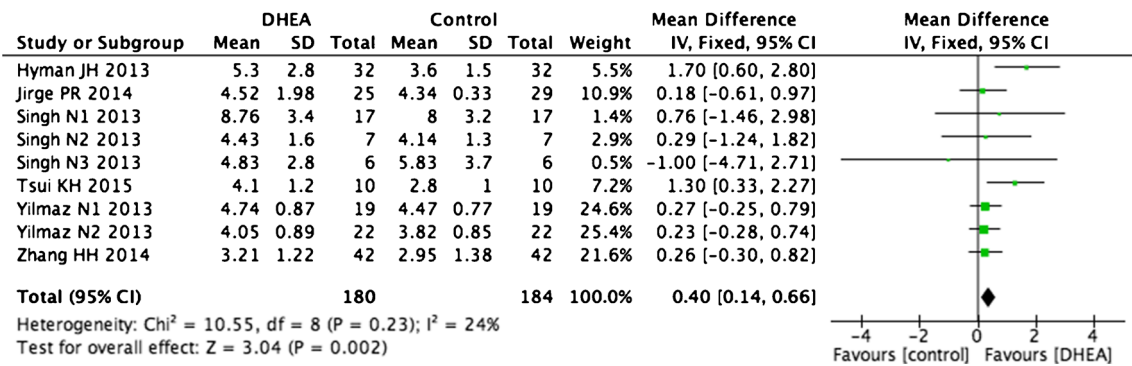

Fig. 9 Weighted mean difference for AMH in patients treated with DHEA or not

Study or Subgroup	DHEA			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Hyman JH 2013	5.3	2.8	32	3.6	1.5	32	5.5%	1.70 [0.60, 2.80]
Jirge PR 2014	4.52	1.98	25	4.34	0.33	29	10.9%	0.18 [-0.61, 0.97]
Singh N1 2013	8.76	3.4	17	8	3.2	17	1.4%	0.76 [-1.46, 2.98]
Singh N2 2013	4.43	1.6	7	4.14	1.3	7	2.9%	0.29 [-1.24, 1.82]
Singh N3 2013	4.83	2.8	6	5.83	3.7	6	0.5%	-1.00 [-4.71, 2.71]
Tsui KH 2015	4.1	1.2	10	2.8	1	10	7.2%	1.30 [0.33, 2.27]
Yilmaz N1 2013	4.74	0.87	19	4.47	0.77	19	24.6%	0.27 [-0.25, 0.79]
Yilmaz N2 2013	4.05	0.89	22	3.82	0.85	22	25.4%	0.23 [-0.28, 0.74]
Zhang HH 2014	3.21	1.22	42	2.95	1.38	42	21.6%	0.26 [-0.30, 0.82]
Total (95% CI)			**180**			**184**	**100.0%**	**0.40 [0.14, 0.66]**

Heterogeneity: Chi² = 10.55, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 3.04 (P = 0.002)

Fig. 10 Weighted mean difference for AFC in patients treated with DHEA or not

differentiation, and apoptosis regulation were downregulated. This evidence highlights the function of DHEA at the transcriptional level. However, evidence opposing the view of DHEA as a beneficial adjuvant to increase AMH/AFC levels in IVF/ICSI has been presented. For example, Hyman et al. recruited 32 women into a self-controlled trail and found that DHEA did not influence the recruitment of preantral or tiny antral follicles (there were no differences in AMH or inhibin B levels). However, DHEA treatment did rescue small antral follicles from atresia (increased AFC) [26]. Again, more studies are needed to address the mechanism of DHEA in IVF/ICSI cycles. Besides, genetic factors might be reasons behind the varying effects of DHEA in different individuals. For example, Weghofer et al. found that free testosterone significantly affected clinical pregnancy potential ($\beta = 1.101 \pm 0.508$, $p = 0.03$) unless women possessed abnormal FMR1 genotypes [39].

Traditionally, based on the effect DHEA has on the reproductive system, it has been used as an androgen replacement for a number of years [40–43]. In IVF/ICSI cycles, the use of DHEA supplementation was initially based on the clinical experience that increased intraovarian androgen levels would increase retrieved oocyte numbers and reduce the required gonadotropins dose [44]. This clinical concept has been supported through a number of studies, which have begun to uncover the molecular mechanism behind DHEA treatment. Similar to ovarian follicles, DHEA levels decrease with age [45]. Because DHEA is a precursor of estradiol and testosterone, it can affect ovarian follicle generation through the activation of relative receptors and via steroid production [45]. IGF-1 is also suspected to be one of the molecular pathways enhanced by DHEA treatment [12]. Shoae-Hassani et al. suggested that DHEA might provide a suitable microenvironment for endometrial innervation [46]. It not only enhanced the survival rates of dissociated neurons in culture but also could activate the AKT protein kinase pathway as well as nerve growth factor, which enhanced neuronal activity. DHEA might indirectly increase survival rate of neural cells by stimulating the production of brain-derived neurotropic factor, which is known to promote the differentiation and survival of neurons.

Conclusions

We included data from more than 1000 patients in this meta-analysis. DHEA supplementation appears to have improved IVF/ICSI outcomes and ovarian response in patients with POR. However, because very few RCT trials analyzing DHEA adjuvant therapy in IVF/ICSI cycles have been performed for women with POT, some questions remain about whether this treatment improves outcomes. Thus, until additional high-quality clinical trials (particularly RCTs) can confirm or reject this hypothesis, the beneficial role of DHEA cannot be conclusively proven in patients with POR.

Authors' roles

YS was responsible for designing and coordinating the study. All authors were responsible for data collection, data analysis, and data interpretation. MZ and JX were responsible for the statistical analysis and for writing the manuscript and contributed equally to this study. WN was responsible for reviewing the manuscript. All authors read and approved the final manuscript.

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