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Review

# Effect of chlormadinone acetate versus drospirenone-containing oral contraceptives on the endocrinal features of women with polycystic ovary syndrome: Systematic review and meta-analysis of randomized clinical trials

Amr Menshawy[a], Ammar Ismail[a], Mohamed Abdel-Maboud[a], Alaa Alaa El-din[a], Ahmed Elgebaly[a], Mohamed Gadelkarim[b], Eshak I Bahbah[c], Mohamed F. Abdelghany[d], Ahmed Samy[e], Ahmed M. Abbas[f,*]

[a] Faculty of Medicine, Al-Azhar University, Al-Azhar Medical Students' Association, Cairo, Egypt
[b] Faculty of Medicine, Alexandria University, Alexandria, Egypt
[c] Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[d] Department of Obstetrics and Gynaecology, Faculty of Medicine, South Valley University, Egypt
[e] Department of Obstetrics and Gynaecology, Faculty of Medicine, Cairo University, Egypt
[f] Department of Obstetrics and Gynaecology, Faculty of Medicine, Assiut University, Egypt

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ABSTRACT

*Background:* Polycystic ovary syndrome (PCOS) is a serious endocrinal disorder in women of reproductive age. Hormonal treatment with oral contraceptives, containing estrogen (ethinyl-estradiol, EE) with progestogen (drospirenone, DRSP) or (chlormadinone acetate, CMA), has improved symptoms and biomarkers of PCOS.
*Objective:* The aim of the present meta-analysis is to compare the effects of EE/DRSP versus EE/CMA on the endocrinal features of women with PCOS.
*Data sources:* Several electronic databases were searched for combinations of the following relevant MeSH terms were used: (ethinyl-estradiol OR EE) AND (drospirenone OR DRSP) AND (chlormadinone acetate OR CMA) AND (polycystic ovary syndrome).
*Methods:* Records were screened for eligible studies and data were extracted to an online data extraction form. Outcomes of Ferryman–Gallwey score (FGS), body mass index, dehydroepiandrosterone sulfate (DHEAS), free androgen index, sex hormone-binding globulin, delta-4-androstenedione (A) and total testosterone levels (T) were pooled as weighted mean difference (WMD) and 95% confidence interval (CI) in a fixed effect meta-analysis model.
*Results:* Three RCTs (EE/DRSP: n = 98 and EE/CMA: n = 87) were pooled in the analysis. The overall effect favoured EE/DRSP over EE/CMA in reducing (A) levels after three months (WMD -0.63; 95% CI [-0.94, -0.32], P < 0.001), FGS after six months (WMD -0.44; 95% CI [-0.99, -0.19], P = 0.0006), and total (T) after three months (WMD -0.12; 95% CI [-0.23, -0.01], P = 0.03).
*Conclusions:* EE/DRSP showed a more potent effect than EE/CMA in the reduction of FGS after six months, (A) levels and (T) levels after three months in patients with PCOS.


**Contents**



* Corresponding author at: Department of Obstetrics and Gynaecology Assiut University, Women Health Hospital Assiut, 71511, Egypt.
*E-mail address:* ahmedabbas@aun.edu.eg (A.M. Abbas).

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## Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease associated with metabolic dysfunction and cardiovascular risk [1], caused by dysfunctional reproductive endocrinology [2]. It affects 5–10% of women of reproductive age [3]. The diagnostic criteria of PCOS include clinical or laboratory hyperandrogenism, oligo/anovulation, and ultrasonographic picture of PCO [4]. Additionally, PCOS is commonly associated with obesity, and insulin resistance (IR) [4]. IR and its associated abnormalities are considered as the important pathogenic factors of type 2 diabetes mellitus [5], 30–40% of women with PCOS have impaired glucose tolerance, and 10% have type 2 diabetes [3]. Obesity is also a typical feature in women suffering from PCOS, whereby approximately 40–50% of women with PCOS are overweight or obese [5].

Combined oral contraceptives (COCs) are common treatment modalities used for menstrual irregularities and hyperandrogenism in clinical practice [6]. They were first approved for contraceptive use in the United States in 1960, currently used by more than 100 million women worldwide and by almost 12 million women in the United States [7].

Chlormadinone acetate (CMA) is a steroidal progestin with additional anti-androgen and anti-gonadotropic properties [8]. Additionally, it is known as a 17-acetoxyprogesterone derivative molecule with a chlorine atom at C6 [9]. CMA has a strong affinity for the progesterone receptors, and they act mainly by blocking androgen receptors in target organs [8,9].

Drospirenone (DRSP) is derived from spirolactone. Therefore, the major effect of DRSP is antimineralocorticoid activity [10]. In addition, it has no androgenic effect, but does exhibit partial antiandrogenic activity; its antiandrogenic potency is about 30% of that of cyproterone acetate. DRSP has a long terminal half-life (about 32 h), and its bioavailability is about 76% [11].

Many randomized clinical trials (RCTs) were performed to compare the effects of two oral contraceptive pills containing either CMA or DRSP as the progestogen in women with PCOS [6,9,12]. We focused in this review on those types specifically as they are the most common formulations available in different countries with antiandrogenic properties, thus affect the endocrinal features of PCOS women.

Therefore, in this review, we aim to systematically evaluate the available evidence from randomized controlled trials which compare the effects of CMA versus DRSP containing oral contraceptives on the endocrinal features of PCOS women.

## Materials and methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [13], and we performed all steps in strict accordance to the Cochrane handbook of systematic reviews of intervention [14].

### *Search strategy*

We conducted a detailed search using several electronic databases included MEDLINE, SCOPUS, EMBASE, Dynamed Plus, ScienceDirect, TRIP database and the Cochrane Library. Combinations of the following relevant MeSH terms were used: (ethinylestradiol OR EE) AND (drospirenone OR DRSP) AND (chlormadinone acetate OR CMA) AND (polycystic ovary syndrome).

The title and abstract searches were also commenced. Research articles and conference abstracts were limited to the English Language. One investigator (AS) performed the searches. We retrieved all identified articles, and their reference lists were searched manually for additional relevant studies.

### *Eligibility criteria*

We considered all published studies satisfying the following criteria:

1) Population: female patients diagnosed with PCO, according to the Rotterdam 2003 criteria that include the presence of two out of three of the following features: clinical and/or biochemical hyperandrogenism, chronic anovulation and/or

oligoamenorrhea and ultrasonographic evidence of micro-polycystic ovaries [4].
2) Intervention: ethinyl-estradiol/Drospirenone (EE/DRSP)
3) Comparator: ethinyl-estradiol/Chlormadinone acetate (EE/CMA)
4) Outcomes: endocrinal parameters related to the treatment
5) Study design: randomized clinical trials (RCTs).

We excluded studies for the following reasons: (1) non-randomized trials, (2) in vitro and animal studies, and (3) studies whose data were unreliable for extraction and analysis. Duplicates were removed, and retrieved references were screened in two steps: the first step was to screen titles/abstracts for matching our inclusion criteria and the second step was to screen the full-text articles of eligible abstracts for eligibility to meta-analysis.

### *Study selection*

Title and abstract of all identified articles were screened independently by two reviewers (AM, AI) to assess relevance to this meta-analysis. In case of disagreement, the full text was retrieved and reviewed independently by a senior author (AMA) for a final decision.

All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two investigators scored the studies and collected the information independently. In case of discrepancies in scoring, a consensus was reached after discussion.

### *Data extraction and analysis*

This meta-analysis included studies comparing metabolic features wither clinically or laboratory in PCOS women using oral contraceptives containing (EE/CMA [Belara®, Gedeon Richter Ltd Pharmaceuticals, Hungary]) versus (EE/DRSP [Yasmin®, Bayer Pharmaceuticals, Germany]). Ferryman-Gallwey score of hirsutism, body mass index (BMI), serum Dehydroepiandrosterone sulphate (DHEAS), sex-hormone binding globulin (SHBG), total testosterone (T) after three and six months of treatment, delta-4-androstenedione (A) level and free androgen index (FAI) levels were extracted from the individual articles and entered into RevMan software (Review Manager, version 5.1, The Cochrane Collaboration, 2011; The Nordic Cochrane Centre, Copenhagen, Denmark) for meta-analysis. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated.

Statistical heterogeneity between studies was assessed by I-squared ($I^2$) statistics and values of $\geq$50% were indicative of high heterogeneity. When heterogeneity was significant, a random-effect model was used for meta-analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity. Pooled analyses of data from all studies were performed for outcomes.

### *Risk of bias assessment*

The risk of bias was assessed according to the Cochrane risk of bias tool, which described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [14]. Assessment included the following domains: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment is categorized as low, unclear or high risk of bias.

### *Publication bias*

The number of included studies in the analysis was less than ten studies, so we cannot assess the publication bias using Egger test [15].

## Results

### *Search results characteristics of included studies*

Our search retrieved one hundred thirty-seven unique citations from searching electronic databases. Following title and abstract screening, nine full-text articles were retrieved and screened for eligibility. Of them, six articles were excluded, and three RCTs [6,12,16] (EE/DRSP: n = 98 and EE/CMA: n = 87) were reviewed in detail and included in this meta-analysis (PRISMA flow diagram; Fig. 1). The references of the included RCTs were manually searched, but no further reports were added.

For the included studies, a summary of their design and baseline characteristics of enrolled participants is shown in Table 1.

### *Potential source of bias*

The quality of the included studies was from moderate to high, according to the Cochrane risk of bias assessment tool. A summary of quality assessment domains is shown in Fig. 2, while authors' judgments with justifications are shown in Supplementary File No 1.

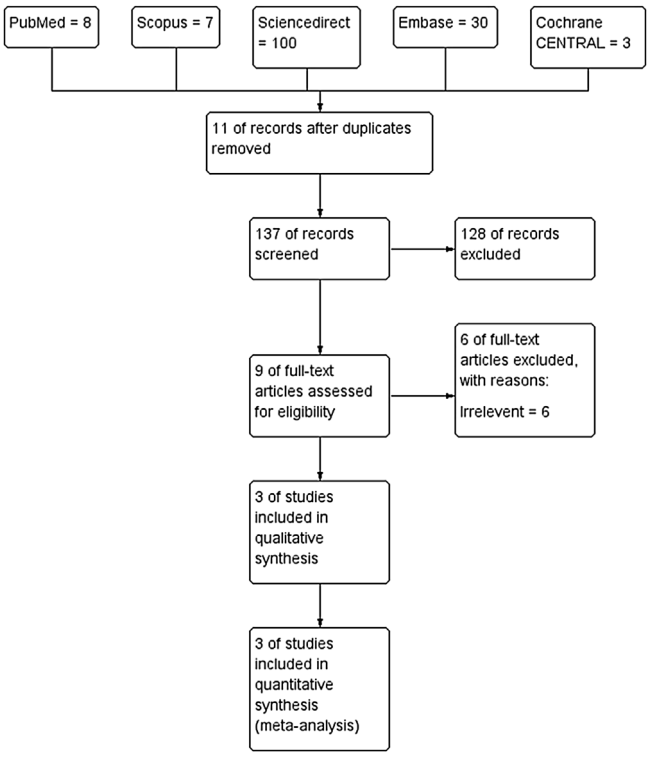


**Fig. 1.** PRISMA Flow Chart of the study selection process.

**Table 1**
Design and baseline characteristics of the included studies.

| Author | Study design | diagnosis of PCOS | Groups | Sample Size | Age Mean ± SD (years) | BMIMean ± SD, (kg/m2) | DHEAS Mean ± SD, (mg/dl) | SHBG Mean ± SD, (nmol/L) | Total T Mean ± SD, (nmol/L) | FAI Mean ± SD, (Tx100/ SHBG) | A Mean ± SD, (pg/mL) | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yildizhan et al., 2015 | randomized, prospective, open-label study | The diagnosis of PCOS was made according to the 2003 Rotterdam criteria when two of the following three features were present: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries on ultrasound examination. | EE/ DRSP | 56 | 25.36 ± 2.91 | 24.82 ± 3.32 | 186.25 ± 82.51 | 25.73 ± 10.70 | 2.07 ± 1.10 | 9.39 ± 6.63 | NA | EE/DRSP is found to have more favorable effects on lipid profiles, hsCRP levels, insulin resistance and hyperandrogenism when compared with the EE/CMA and appears to be more beneficial for the long term cardiovascular and metabolic aspects of PCOS |
| | | | EE/ CMA | 50 | 24.82 ± 3.20 | 23.56 ± 3.32 | 154.60 ± 66.82 | 24.84 ± 8.35 | 1.81 ± 0.76 | 7.97 ± 4.32 | NA | |
| Colonna et al., 2012 | randomized study | Female patients, seen in outpatient settings, affected by mild to severe acne and plasma hormonal hyperandrogenic features were enrolled in the study. | EE/ DRSP | 32 | 25.6 ± 4.4 | 23.35 ± 3.60 | 3.414 ± 1.05 | 39.80 ± 11.08 | 2.08 ± 0.31 | 6.29 ± 1.52 | 4.42 ± 0.72 | EE/DRSP represents an effective and safe treatment in women with acne and polycystic ovary syndrome (PCOS) and appears to be a more potent therapeutic option. |
| | | | EE/ CMA | 27 | 25.4 ± 3.4 | 23.27 ± 3.63 | 3.473 ± 1.03 | 40.25 ± 11.41 | 2.13 ± 0.32 | 6.41 ± 1.65 | 4.35 ± 0.57 | |
| Leo et al., 2010 | randomized study | The diagnosis of PCOS was based on the Rotterdam 2003 criteria that include the presence of two out of three of the following features: clinical and/or biochemical hyperandrogenism, chronic anovulation and/or oligomenorrhea and ultrasonographic evidence of micropolycystic ovaries | EE/ DRSP | 10 | (16–35)* | NA | 1.69 ± 0.8 | 25 ± 12 | 840 ± 105 | NA | 1780 ± 440 | Both DRSP and CMA caused a great reduction of androgens and a progressive increase in serum concentrations of SHBG. They appear to be more beneficial for the long term treatment of PCOS |
| | | | EE/ CMA | 10 | | NA | 1.65 ± 0.7 | 27 ± 10 | 780 ± 120 | NA | 1795 ± 410 | |

*(range), BMI; body mass index, DHEAS; dehydroepiandrosterone sulphate, SHBG; sex hormone binding globulin, T; testosterone, FAI; free androgen index, A; delta-4-androstenedione, SD; standard deviation.

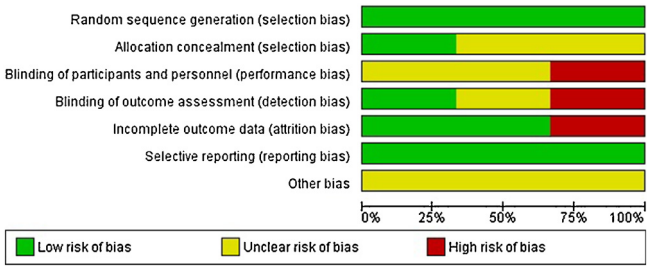


**Fig. 2.** Diagram of quality of included studies.

## Outcomes

*Ferryman–Gallwey score (FGS) after six months*

The overall effect favored EE/DRSP over EE/CMA in reducing FGS after six months (WMD -0.44; 95% CI [-0.99, -0.19], P = 0.0006, Fig. 3). Pooled studies were heterogeneous (P = 0.09; $I^2$ = 65%).

*Body mass index (BMI) after six months*

The overall effect show no significant difference between the two groups in BMI after six months (WMD -0.18; 95% CI [-0.39, 0.03], P = 0.10, Fig. 4). Pooled studies were homogenous (P = 0.72; $I^2$ = 0%).

## Dehydroepiandrosterone sulfate (DHEAS)

I *DHEAS after three months:*

Pooled analysis shows no significant difference between the two groups in DHEAS after three months (WMD -0.10; 95% CI [-0.68, 0.47], P = 0.72, Fig. 5). Pooled studies were homogenous (P = 0.70; $I^2$ = 0%).

- *DHEAS after six months:*

Pooled analysis show no significant difference between the two groups in DHEAS after six months (WMD -0.10; 95% CI [-0.88, 0.68], P = 0.80, Fig. 6). Pooled studies were homogenous (P = 0.32; $I^2$ = 36%).

## Free androgen index (FAI) after six months

The overall effect show no significant difference between the two groups in FAI after six months (WMD -0.53; 95% CI [-1.10, 0.03], P = 0.06, Fig. 7). Pooled studies were homogenous (P = 0.12; $I^2$ = 58%).

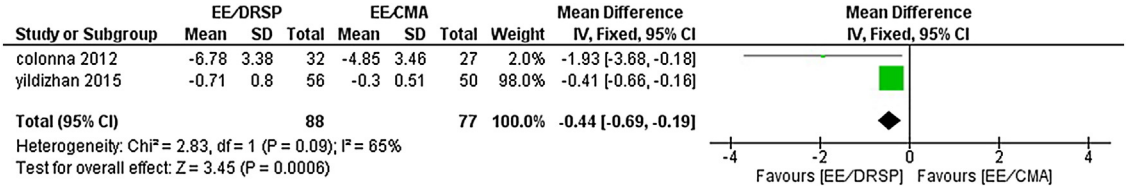


**Fig. 3.** Forest plot for Ferryman–Gallwey score (FGS) after six months.

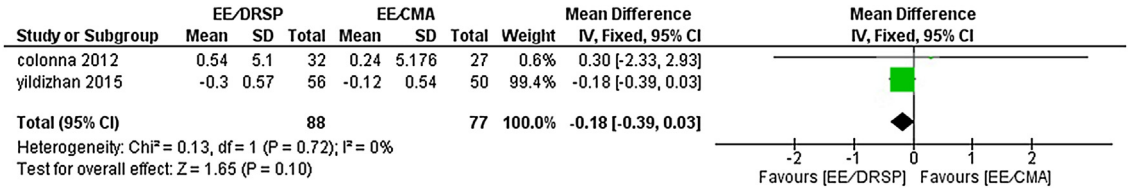


**Fig. 4.** Forest plot for body mass index (BMI) after six months.

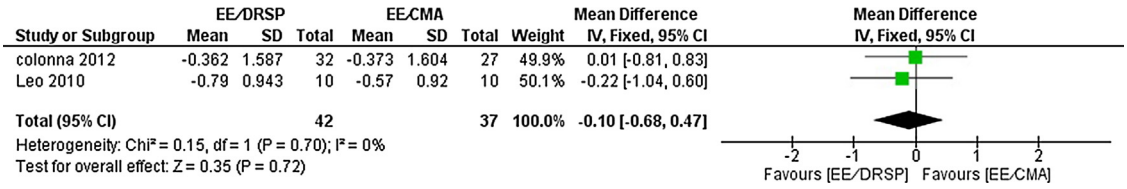


**Fig. 5.** Forest plot for Dehydroepiandrosterone sulphate (DHEAS) after three months.

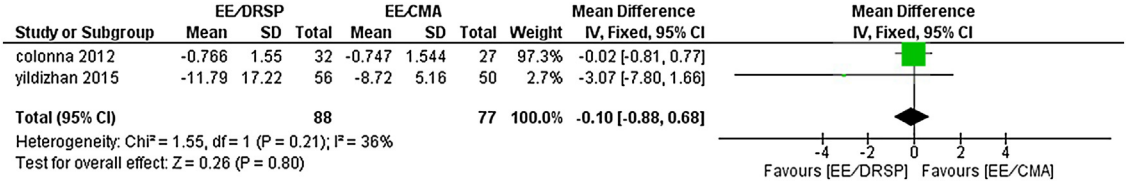


**Fig. 6.** Forest plot for Dehydroepiandrosterone sulphate (DHEAS) after three months.

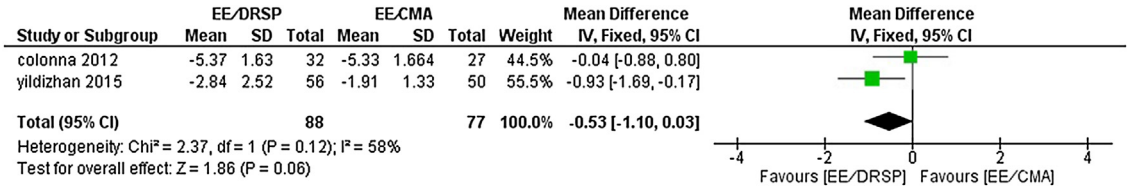


**Fig. 7.** Forest plot for free androgen index (FAI) after six months.

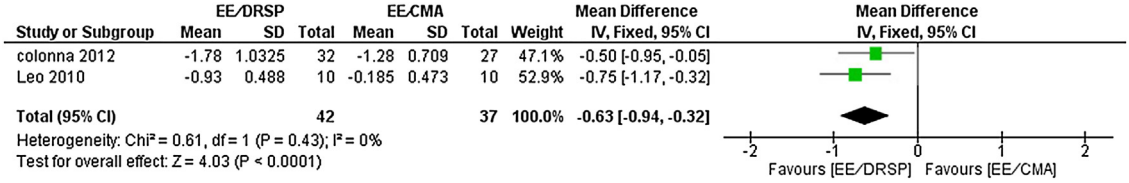


**Fig. 8.** Forest plot for delta-4-androstenedione (A) levels (ng/mL) after three months.

### Delta-4-androstenedione (A) levels (ng/mL) after three months

The overall effect favored EE/DRSP over EE/CMA in reducing (A) levels after three months (WMD -0.63; 95% CI [-0.94, -0.32], P < 0.001, Fig. 8). Pooled studies were homogenous (P = 0.43; $I^2$ = 0%).

*Sex hormone-binding globulin (SHBG)*

I *SHBG after three months:*

The pooled analysis favored EE/CMA over EE/DRSP in reducing SHBG after three months (WMD 24.34; 95% CI [15.23, 33.44], P < 0.001, Fig. 9). Pooled studies were heterogeneous (P = 0.001; $I^2$ = 90%).

- *SHBG after six months:*

The overall effect favoured EE/CMA over EE/DRSP in reducing SHBG after six months (WMD 1.89; 95% CI [1.09, 2.69], P < 0.001, Fig. 9). Pooled studies were homogenous (P = 0.65; $I^2$ = 0%).

### Total testosterone (T) levels

I *Total T levels after three months:*

The pooled analysis favoured EE/DRSP over EE/CMA in reducing total T after three months (WMD -0.12; 95% CI [-0.23, -0.01], P = 0.03, Fig. 10). Pooled studies were homogenous (P = 0.49; $I^2$ = 0%).

- *Total T levels after six months:*

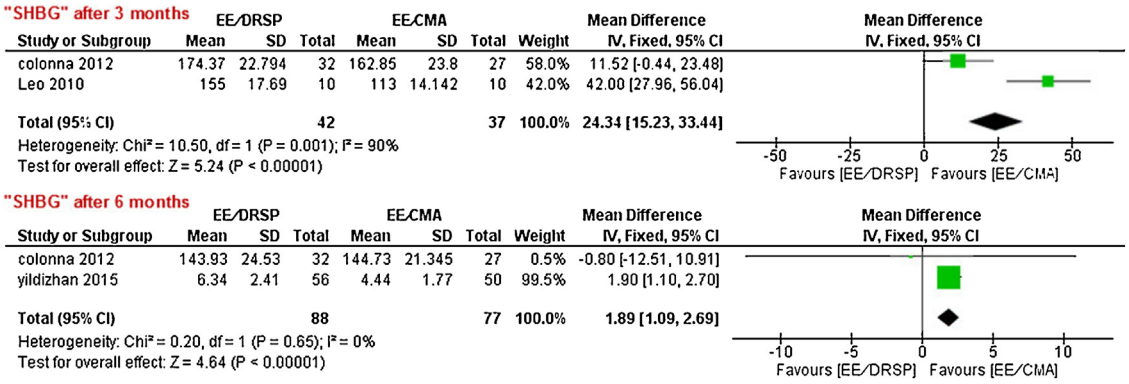


**Fig. 9.** Forest plot for Sex hormone-binding globulin (SHBG) after three and six months.

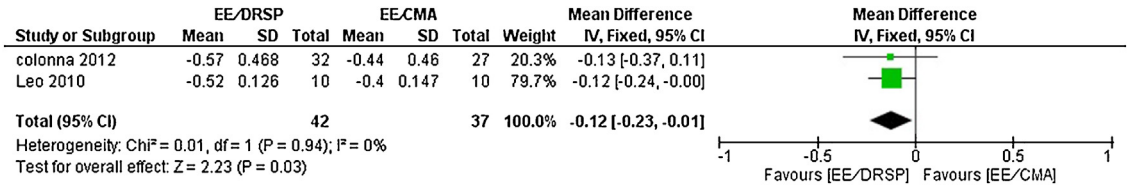


**Fig. 10.** Forest plot for Total testosterone (T) levels after three months.

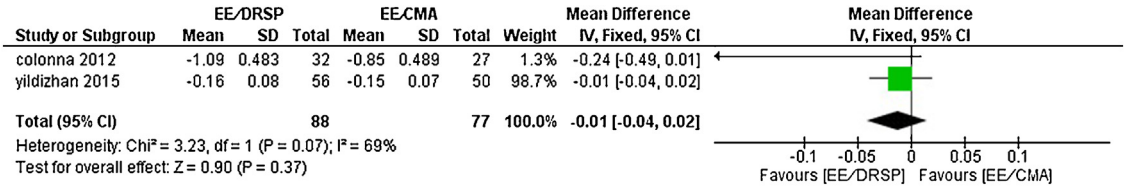


**Fig. 11.** Forest plot for Total testosterone (T) levels after 6 months.

The overall effect show no significant difference between the two groups in total T after six months (WMD -0.01; 95% CI [-0.04, 0.02], P = 0.37, Fig. 11). Pooled studies were heterogeneous (P = 0.07; $I^2$ = 69%).

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the effects of CMA versus DRSP containing oral contraceptives on the endocrinal features of PCOS women.

Hormonal treatment with oral estroprogestins (EPs) can reduce plasma level of free (biologically active) testosterone, together by decreasing its production at the ovarian level and by elevating the production of SHBG in the liver, a protein that binds testosterone, decreasing its biological activity also at skin level [17]. Certain EPs containing, besides estrogen (EE) component, a progestin that posses antiandrogenic properties, are more effective in hyperandrogenic states.

Oral EP comprising EE 30 mg plus DRSP 3 mg has exhibited chief antiandrogenic action [18,19], comparable to EP comprising EE 35 mg plus cyproterone acetate (CPA) two mg [20]. Moreover, EP comprising EE 30 mg plus CMA 2 mg presented antiandrogenic effects [8,21]. The present meta-analysis provides highest-level evidence comparing the effects of EE/DRSP and EE/CMA on hyperandrogenic women with polycystic ovary syndrome.

### *Efficacy of EE-DRSP versus EE-CMA*

The overall effect favored EE-DRSP over EE-CMA in reducing FGS after six months at the included studies [6,16] and the present meta-analysis, pooling of studies were heterogeneous. Likewise, reducing delta-4-androstenedione levels favored EE/DRSP over EE/CMA after three months among the included studies [12,16] and the present meta-analysis, pooled studies were homogenous.

Furthermore, reducing total Testosterone levels favored EE/DRSP over EE/CMA after three months according to De Leo et al. [12], however, it did not favor any of the two groups according to Colonna et al. [16]. Pooled studies were homogenous. However, after six months the overall effect showed no significant difference between the two groups and the pooled studies were heterogeneous [6,16].

Increasing SHBG favored EE/DRSP over EE/CMA after three months and six months according to the present meta-analysis and De Leo et al. [12], pooled data was homogenous. However, it did not favor any of the two groups at three months or 6 months according to Colonna et al. [16]. Of note, it appears to be essential to recall those clinical manifestations of hyperandrogenism, similarly to be an indicator of hormonal imbalance, are the source of a main psychological discomfort for the affected patients [17,22]. Therefore, recovering the hormonal balance would alleviate psychological discomfort.

The overall effect shows no significant difference between the two groups in BMI after six months in the present meta-analysis and the included studies [6,16], pooling of data was homogenous. Similarly, the DHEAS level did not change between the two groups among the included studies and the present meta-analysis after three months [12,16] or six months [6,16], pooled studies were homogenous.

Analogously, the overall effects showed no significant difference between the two groups at the level FAI after six months at the present meta-analysis and the clinical trial of Colonna et al. [16]. However, there was a significant difference in favor of EE/DRSP over EE/CMA according to Yildizhan et al. [6], the pooled studies were homogenous.

The superiority of EE/DRSP effect on the previously described endocrinal parameters can be explained by the major antiandrogenic properties of DRSP. DRSP's antiandrogenic effect is greater than that of CMA and spironolactone [23]. On the other hand, previous studies reported that the use of EE/DRSP combined oral contraceptives was associated with a significantly increased risk of deep vein thrombosis and pulmonary embolism [24]. The exact mechanism by which DRSP might increase the risk of venous thrombotic events is unknown. Therefore, the results of this meta-analysis should be interpreted cautiously and the assessment of the risk benefit ratio should be balanced before prescription of any of the two drugs.

### *Strengths and limitations of the study*

The strengths of the current meta-analysis comprise a comprehensive search of published and unpublished clinical trials studies from multiple electronic databases. Nevertheless, we could not include any unpublished study. Funnel plots presented asymmetrical distribution of the effect size; this could not be established statistically by Egger's test, as the number of eligible studies is < 10 studies as stated by Egger et al. [15]. Additionally, there was a transparent assessment of the quality of evidence.

The main limitation of this meta-analysis is the small number of included studies. There were one included open-labeled clinical trial [6], and the rest of the included studies included insufficient data to judge the blinding of participants and personnel which increase the risk of performance bias. Moreover, the discrepancy of subgroup and the lack of stratification by severity strata at randomization among the included studies hinder the accuracy of results of the efficacy of both regimens.

### *Overall completeness of evidence*

Of the 199 patients, there were 14 patients (7.04%) lost from the 3 RCTs. However, the reasons for all losses were specified. Also, an intention to treat analysis was conducted in all trials; they analyzed all patients allocated to treatment groups including withdrawals after randomization.

### *Implications for future research*

Owing to the relatively small sample size, the conclusions require additional certification and justification. Therefore, we encourage the application of EE/DRSP regimen versus EE/CMA

regimen on long scale clinical trials to identify the long-term efficacy and safety. Further clinical trials studies are required to study the convenience of EE/DRSP and EE/CMA in comparison with other agents especially with EE/CPA among different level of severity of the disease.

## Conclusion

EE/DRSP regimen is as effective as EE/CMA regimen in the treatment of PCOS patients in terms of; reducing BMI after six months, DHEAS level after three or six months, FAI level after six months, and total Testosterone levels after six months. With significantly favorable impact to EE-DRSP regimen among reducing FGS after six months, delta-4-androstenedione levels after three months, and total Testosterone levels after three months. Of note, EE/DRSP showed a higher significant impact among in increasing SHBG after three months and six months over EE/CMA. Further large-scale and long-term studies are needed to elucidate the long-term efficacy and safety.

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The authors received no funding from an external source.

## Declaration of interest

The authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jogoh.2019.03.025.

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