Efficacy of combined oral contraceptives for depressive symptoms and overall symptomatology in premenstrual syndrome: pairwise and network meta-analysis of randomized trials

Wit, A.E. de; Vries, Y.A. de; Boer, M.K. de; Scheper, C.; Fokkema, A.; Janssen, C.A.H.; ... ; Schoevers, R.A.

Efficacy of combined oral contraceptives for depressive symptoms and overall symptomatology in premenstrual syndrome: pairwise and network meta-analysis of randomized trials

Anouk E. de Wit, MD; Ymkje Anna de Vries, PhD; Marrit K. de Boer, MD, PhD; Celeste Scheper, BSc; Ante Fokkema, BSc; Catharina A. H. Janssen, MD, PhD; Erik J. Giltay, MD, PhD; Robert A. Schoevers, MD, PhD

OBJECTIVE: Combined oral contraceptives are often considered a treatment option for women with premenstrual syndrome or premenstrual dysphoric disorder also seeking contraception, but evidence for this treatment is scarce. We aimed to determine (1) the level of evidence for the efficacy of combined oral contraceptives in managing premenstrual depressive symptoms and overall premenstrual symptomatology and (2) the comparative efficacy of combined oral contraceptives (the International Prospective Register of Systematic Reviews registration number CRD42020205510).

DATA SOURCES: We searched Cochrane Central Register of Controlled Trials, PubMed, Web of Science, PsycINFO, EMCare, and Embase from inception to June 3, 2021.

STUDY ELIGIBILITY CRITERIA: All randomized clinical trials that evaluated the efficacy of combined oral contraceptives in women with premenstrual syndrome or premenstrual dysphoric disorder were considered eligible for inclusion in this meta-analysis.

STUDY APPRAISAL AND SYNTHESIS METHODS: A random effect Bayesian pairwise and network meta-analysis was conducted with change in premenstrual depressive symptoms and overall premenstrual symptomatology between baseline and 3 cycles as outcome. Certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

RESULTS: Of 3664 records, 9 eligible trials were included that studied 1205 women with premenstrual syndrome or premenstrual dysphoric disorder (mean age per study range, 24.6—36.5 years). The pairwise meta-analysis revealed that combined oral contraceptives were more efficacious than placebo in treating overall premenstrual symptomatology (standardized mean difference, 0.41; 95% credible interval, 0.17—0.67), but not premenstrual depressive symptoms specifically (standardized mean difference, 0.22; 95% credible interval, −0.06 to 0.47). However, none of the combined oral contraceptives were more effective than each other in reducing premenstrual depressive symptoms and overall premenstrual symptomatology.

CONCLUSION: Combined oral contraceptives may improve overall premenstrual symptomatology in women with premenstrual syndrome or premenstrual dysphoric disorder, but not premenstrual depressive symptoms. There is no evidence for one combined oral contraceptive being more efficacious than any other.

Key words: combined oral contraceptives, depressive symptoms, efficacy, network meta-analysis, overall symptomatology, premenstrual dysphoric syndrome, premenstrual syndrome, randomized clinical trials, systematic review

From the Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Drs de Wit and de Boer, Ms Scheper, Ms Fokkema, and Dr Schoevers); Department of Developmental Psychology, University of Groningen, Groningen, the Netherlands (Dr de Vries); Department of Gynecology, Groene Hart Ziekenhuis, Gouda, the Netherlands (Dr Janssen); and Department of Psychiatry, Leiden University Medical Center, Leiden University, Leiden, the Netherlands (Dr Giltay).

Received March 8, 2021; revised June 19, 2021; accepted June 27, 2021.

The authors report no conflict of interest.

No financial support was received for this study.

Data sharing: On publication of this article, the full data set and the script for analyzing the data will be freely available at https://osf.io/8zbu3/.

Corresponding author: Anouk E. de Wit, MD. a.e.de.wit@umcg.nl

• https://doi.org/10.1016/j.ajog.2021.06.090

Click Supplemental Materials under article title in Contents at ajog.org

AJOG at a Glance

Why was this study conducted?

This study aimed to estimate the efficacy of combined oral contraceptives for premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD).

Key findings

Aggregated evidence from randomized, placebo-controlled clinical trials in a pairwise meta-analysis suggested that combined oral contraceptives may improve overall premenstrual symptomatology in women with PMS or PMDD, but not premenstrual depressive symptoms. However, the network meta-analysis showed that there is no evidence for a particular combined oral contraceptive being more effective than others.

What does this add to what is known?

This study suggests that if combined oral contraceptives are preferred for treating PMS or PMDD, there is no evidence for a particular formulation being more effective than any other.

Introduction

Symptoms that occur in the luteal phase of the menstrual cycle and resolve after the onset of menstruation characterize the premenstrual syndrome (PMS) and its more severe variant premenstrual dysphoric disorder (PMDD).[1–4] A broad range of physical and affective symptoms may be present, but in women with PMDD, severe affective symptoms such as depression are the primary complaint.[1] Of menstruating women, up to 12.2% were affected by PMS and up to 5.3% by PMDD. In both disorders, cyclic changes in the production of progesterone are thought to trigger symptoms.[5–7] Because combined oral contraceptives contain a synthetic estradiol and progestin that together suppress the hypothalamic-pituitary-ovarian axis, treatment with these drugs is often considered for women with PMS or PMDD who also seek contraception. However, the evidence for their efficacy remains scarce.

Currently, ethinylestradiol drospirenone (20 μg, 3 mg) in a 24-day regimen is the only combined oral contraceptive that has been approved by the US Food and Drug Administration for the treatment of PMDD.[8] This approval was based on the results of 2 randomized clinical trials in women with PMDD reporting that the use of this formulation reduced overall premenstrual symptomatology compared with placebo.[9,10] However, other trials showed that the same ethinylestradiol drospirenone combination in a different treatment regimen in women with PMS[11] and the same combination but with a slightly higher ethinylestradiol dosage (30 μg) in women with PMDD were not effective.[12] Notably, 2 trials investigating the continuous use of ethinylestradiol levonorgestrel (20 μg, 90 μg) in women with PMDD did not show a consistent beneficial effect of on premenstrual depressive symptoms and overall premenstrual symptomatology.[13,14] Altogether, these inconsistent findings question the efficacy of combined oral contraceptives for treating premenstrual symptomatology in women with PMS and PMDD.

Here, we sought to aggregate the results from clinical trials that randomized women with PMS or PMDD to combined oral contraceptives compared with any other hormonal or nonhormonal contraceptive treatment regimen or to placebo to examine the efficacy of combined oral contraceptives. We specifically aimed to determine (1) the efficacy of combined oral contraceptives for managing premenstrual depressive symptoms and overall premenstrual symptomatology in PMS and PMDD and (2) whether some combined oral contraceptives are more efficacious than others.

Methods

Per the recommended systematic review methodology, this review was developed and registered a priori with the International Prospective Register of Systematic Reviews (PROSPERO [registration number CRD42020205510]).[15] In the original PROSPERO protocol, the primary aim was to conduct a network meta-analysis, and only if this was not possible, to conduct a pairwise meta-analysis. Because all but 1 of the included randomized clinical trials had a placebo-controlled design, making it possible to conduct a (potentially better-powered) pairwise meta-analysis examining combined oral contraceptives as a group, the protocol was modified to include a pairwise meta-analysis as the primary analysis. We originally aimed to investigate whether studies with a greater proportion of women with PMDD reported larger effect sizes compared with placebo than those that included a smaller proportion of women with PMDD, using meta-regression analyses. However, because fewer than 10 studies could be included in this study, such analyses were not possible.

Eligibility criteria

The inclusion criteria for studies were as follows (within a Population, Intervention, Comparison, Outcomes, and Study framework):

1. Population: Premenopausal women diagnosed as having PMS or PMDD. The diagnosis of PMDD was preferably made according to the Diagnostic and Statistical Manual of Mental Disorders, IV or 5 criteria.[1,16] Other assessments of PMDD through the use of validated questionnaires were accepted if the criteria used required a rise of at least 1 emotional symptom (including but not limited to depressed mood, anxiety or tension, affective liability, and anger or irritability) plus 4 additional symptoms during the luteal or premenstrual phase that subsided within the first 3 days of the menses. For PMS, the same criteria were used except that no additional symptoms were required for the diagnosis.
2. Intervention: A specific combined oral contraceptive regimen

3. Comparison: Another combined oral contraceptive regimen or nonhormonal or hormonal contraceptives (eg, hormonal or copper intrauterine device) or placebo
4. Outcome: Depressive symptoms using a validated (self-report or observer-rated) scale
5. Study design: Randomized controlled trials

Information sources, search strategy, and study selection

We conducted a search for studies published in English in the Cochrane Central Register of Controlled Trials, PubMed, Web of Science, PsycINFO, EMCare, and Embase from their inception to June 3, 2021. Reference lists of included trials and of related reviews (searched for by a separate search) were checked to identify other potentially eligible trials or ancillary publications. Supplement 1 lists the full searches in PubMed.

Two reviewers (C.S. and A.F.) independently scanned all retrieved citations by title, abstract, and full text according to the prespecified inclusion criteria. Any discrepancies were resolved through discussion or recourse to a third reviewer (A.E.d.W.). Two reviewers (C.S. and A.F.) extracted data on summary estimates independently for each eligible trial using a standardized, pilot tested data extraction form.

Data extraction

The reviewers (C.S. and A.F.) independently collected information on methodology (level of blinding, crossover or parallel group design), interventions (formulation, dose, frequency, regimen and route of administration), participants (number of subjects per group, number of dropouts, mean age, and proportion of participants with PMDD, with comorbidity, or who reported being sexually active), and outcomes (ie, tools or scales, reported time points, phase of cycle reported). Reviewers resolved discrepancies by discussion and, when necessary, through adjudication by a third party (A.E.d.W.). We contacted study authors and drug manufacturers to supplement incomplete data regarding outcomes. The relative effect per comparison was summarized using the standardized mean difference (SMD) adjusted for small sample sizes (Hedges g correction), with a 95% credible interval (CrI).[17] A CrI is an interval within which an unobserved parameter value falls with a particular probability given the evidence provided by the observed data. Using an SMD as an outcome, intervals containing 0 suggest that the data are compatible with no effect or no difference among groups, as with the analogous 95% confidence intervals in frequentist statistics.

The primary outcome was a change in premenstrual depressive symptoms or new-onset depression between baseline and 3 cycles. The secondary outcome was the change in overall premenstrual symptomatology measured over the same period. For the primary outcome, preference was given to validated depressive symptom severity questionnaires. However, when such questionnaires were not used in a trial, data from negative affect or depressive symptom subscales from scales measuring related concepts were accepted. Similarly, overall premenstrual symptomatology measures were accepted when they had been assessed with validated symptom questionnaires for premenstrual complaints. This questionnaire had to assess both the affective and physical domain of PMS and provide a score that reflects the severity of premenstrual complaints. When symptoms of the primary or secondary outcome had been measured with more than one standardized rating scale, the scale with the best psychometric properties was chosen. If results were not separately reported for the premenstrual phase, effect sizes across phases were taken. Similarly, when 3-cycle data were not available, other data were used (eligible range, 1−48 cycles) that were as close to this point as possible. Intention-to-treat data were used, whenever possible.

Assessment of risk of bias

We assessed the studies' risk of bias using the modified Cochrane Risk of Bias tool 2.0.[18] In addition, we assessed the certainty of evidence contributing to network estimates of the primary outcome with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework using the Confidence in Network Meta-Analysis tool.[19−21] Judgments on the certainty of evidence were made for each of the following domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Supplement 2 lists the full details on the GRADE assessment.

Statistical approach

First, we performed a random-effects Bayesian pairwise meta-analysis with uninformative priors and Markov chain Monte Carlo sampling, to determine the efficacy of combined oral contraceptives (as a group) compared with placebo, in managing premenstrual depressive symptoms and overall premenstrual symptomatology. The "brms" package in R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) was used to build the model. Simulations were run for 4 chains with an adaptive phase of 10,000 iterations and a sampling phase of 500,000 iterations, thinned such that every tenth iteration was retained. Model convergence was assured by checking whether the density of the replications was similar to the ones in the observed data and checking the potential scale reduction factor.

Second, a random-effects Bayesian network meta-analysis with uninformative priors was used to determine the comparative efficacy of combined oral contraceptives in managing premenstrual depressive symptoms and overall premenstrual symptomatology. The "gemtc" package in R (version 4.0.3) was used to build the model with the same method of sampling and running simulations as for the pairwise meta-analysis. Using multivariate distributions, the model was accounted for correlations induced by multi-arm studies. Model convergence was checked using trace plots, density plots, and the Brooks-Gelman-Rubin diagnostic. Each specific combined oral contraceptive (including regimen and dose) was treated as a separate node. A network plot was drawn, with thickness of the lines between nodes based on the number of direct comparisons investigated.

Results

Study selection

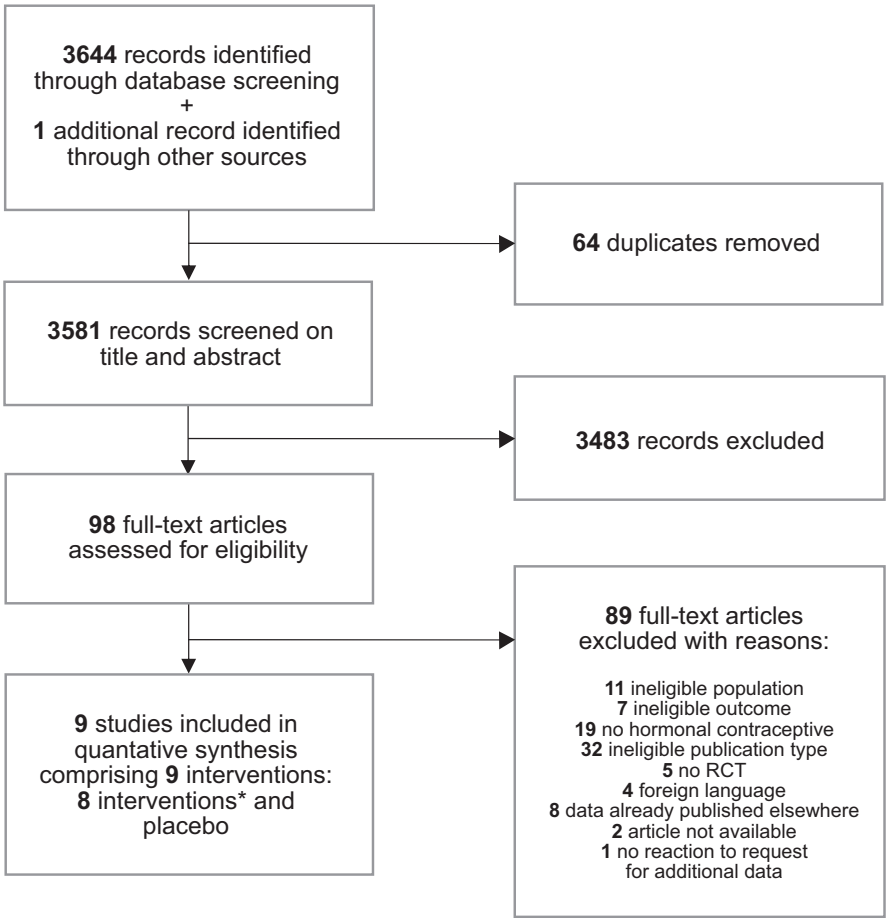
Our systematic search identified 3644 citations published between 1961 and June 3, 2021. One additional trial was identified through hand searching other reports. After removal of duplicates, 3581 articles were screened based on title and abstract, of which 98 were screened based on the full text. From these articles, 10 studies were considered eligible,[9−14,22−25] but 1 study was excluded owing to insufficient data and no author response to a request for additional data.[25] Moreover, 9 studies were included in the network meta-analysis (8 placebo-controlled[9−14,22,23] and 1 head-to-head[24]) (Figure 1), and 8 placebo-controlled studies were included in the pairwise meta-analysis.[9−14,22,23]

Study characteristics

The 9 included studies examined 9 different interventions (8 different combined oral contraceptives and 1 placebo) among 1205 women (weighted mean age, 32.3 years; range, 24.6−36.5). Across comparisons, the sample size per arm ranged from 16 to 231 participants (Table 1). All studies evaluated the effect of the premenstrual intervention (in the final week before the onset of menses) after 3 months of treatment. During this follow-up period, dropout was generally high with a weighted mean dropout rate of 26.3% (range, 0.0%−40.2%). Most studies included women with PMDD,[9−14] but 4 studies predominantly included women with PMS.[11,22−24]

Only 1 trial used a validated depression-specific questionnaire to measure premenstrual depressive symptoms (Beck Depression Inventory).[12] The other trials used the depressive symptom subscale of the Daily Record of Severity of Problems (DRSP)[9−11,13,14,22] or the negative affect subscale of the Daily Rating Form[23] or Women's Health Assessment Questionnaire (WHAQ).[24] Notably, 7 trials provided data on the efficacy of interventions on overall premenstrual symptomatology; 5 trials assessed overall premenstrual symptomatology with the DRSP total score.[9,10,13,14,22] The 2 other trials used the WHAQ[24] and the Calendar of Premenstrual Experiences,[12] respectively.

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram



The *asterisk* indicates ethinylestradiol drospirenone (20 μg, 3 mg; continuous), ethinylestradiol drospirenone (20 μg, 3 mg; 21/7), ethinylestradiol drospirenone (30 μg, 3 mg; 21/7), ethinylestradiol drospirenone (20 μg, 3 mg; 21/7), ethinylestradiol drospirenone (20 μg, 3 mg; 24/4), ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg; 21/7), estradiol nomegestrol (1.5 mg, 2.5 mg; 24/4), ethinylestradiol levonorgestrel (20 μg, 90 μg; continuous), ethinylestradiol desogestrel (20 μg, 150 μg; 24/4).

RCT, randomized clinical trial.

de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

Risk of bias of included studies

Notably, 4 of 9 trials (44.4%) examined were rated as high risk of bias,[11,12,22,23] and the other trials (53.6%) were rated as moderate (Supplement 2.1).[9,10,13,14,24] The certainty of evidence (GRADE) for all comparisons examined in the network meta-analysis was judged to be "very low" (Supplement 2 Table 1). Within-study bias (Supplement 2.1) and imprecision of the effect sizes (Supplement 2.4) caused most of these judgments. The judgments made for each of the domains are described in Supplement 2.

Premenstrual depressive symptoms

Based on the results of 8 placebo-controlled trials,[9−14,22−24] the pairwise meta-analysis revealed no evidence to prove that combined oral contraceptives were effective for premenstrual

TABLE 1
Characteristics of the included randomized clinical trials on the efficacy of combined oral contraceptives for women with PMS

	Age Mean (SD)	PMS/ PMDD	Intervention		Control		Dropouts %	RCT type	Analysis	Outcome scale	
			Formulation	n[a]	Formulation	n[a]				Depression severity	PMS severity
Eisenlohr-Moul et al,[11] 2017	32.7 (8.3)	64% PMS 36% PMDD	Ethinylestradiol drospirenone (20 μg, 3 mg, continuous) Ethinylestradiol drospirenone (20 μg, 3 mg, 21/7)	16 17	Placebo	22	24.0	Parallel, double blind	Complete cases	DRSP q1a,b,c	—
Freeman et al,[12] 2001	31.0 (5.6)	PMDD	Ethinylestradiol drospirenone (30 μg, 3 mg, 21/7)	21	Placebo	28	40.2	Parallel, double blind	Complete cases	BDI	COPE
Freeman et al, [13] 2012[b]	36.5 (7.8)	PMDD	Ethinylestradiol levonorgestrel (20 μg, 90 μg, continuous)	34	Placebo	46	20.0	Parallel, double blind	Complete cases	DRSP q1a,b, c+9+10	DRSP
Graham and Sherwin,[23] 1993	29.5 (5.0)	PMS	Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg; 21/7)	20	Placebo	25	28.0	Parallel, double blind	Complete cases	DRF	—
Halbreich et al,[14] 2012	36.1 (6.4)	PMDD	Ethinylestradiol levonorgestrel (20 μg, 90 μg, continuous)	133	Placebo	132	33.9	Parallel, double blind	Complete cases	DRSP q1a,b, c+9+10	DRSP
Lundin et al,[22] 2017	24.6 (4.1)	69% PMS 31% PMDD	Estradiol nomegestrol (1.5 mg, 2.5 mg, 24/4)	24	Placebo	20	10.2	Parallel, double blind	Complete cases	DRSP q1a,b,c	DRSP
Pearlstein et al,[10] 2005	31.5 (5.5)	PMDD	Ethinylestradiol drospirenone (20 μg, 3 mg, 24/4)	64	Placebo	64	60.9	Crossover, double blind	Intention-to-treat	DRSP q1a,b,c	DRSP
Wichianpitaya and Taneepanichskul,[24] 2013	27.3 (5.7)	PMS	Ethinylestradiol desogestrel (20 μg, 150 μg, 24/4)	45	Ethinylestradiol drospirenone (20 μg, 3 mg, 24/4)	45	0.0	Head-to-head, unblind	Intention-to-treat	WHAQ	WHAQ
Yonkers et al,[9] 2005	31.5 (5.7)	PMDD	Ethinylestradiol drospirenone (20 μg, 3 mg, 24/4)	231	Placebo	218	27.1	Parallel, double blind	Intention-to-treat	DRSP q1a,b,c	DRSP

Data are presented as median (SD), number, and percentage.

Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg) is a multiphasic combined oral contraceptive that has 4 different dosages of norethindrone throughout a 4-week cycle.

BDI, Beck Depression Inventory; *COPE*, Calendar of Premenstrual Experiences; *DRF*, daily Rating Form; *DRSP*, Daily Record of Severity of Problems; *PMDD*, premenstrual dysphoric disorder; *PMS*, premenstrual syndrome; *SD*, standard deviation; *WHAQ*, Women's Health Assessment Questionnaire.

[a] Number of women who were available for the analysis (so excluding the dropouts in case of complete cases analyses); [b] This reference describes 4 studies including 2 randomized clinical trials (the multinational and the North American trial). Because the North American trial is also described in another reference included in this meta-analysis,[14] we refer to the multinational trial when using this reference.[13]

de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

depressive symptoms compared with placebo (SMD, 0.22; 95% CrI, −0.06 to 0.47) (shown in the upper panel of Figure 2).

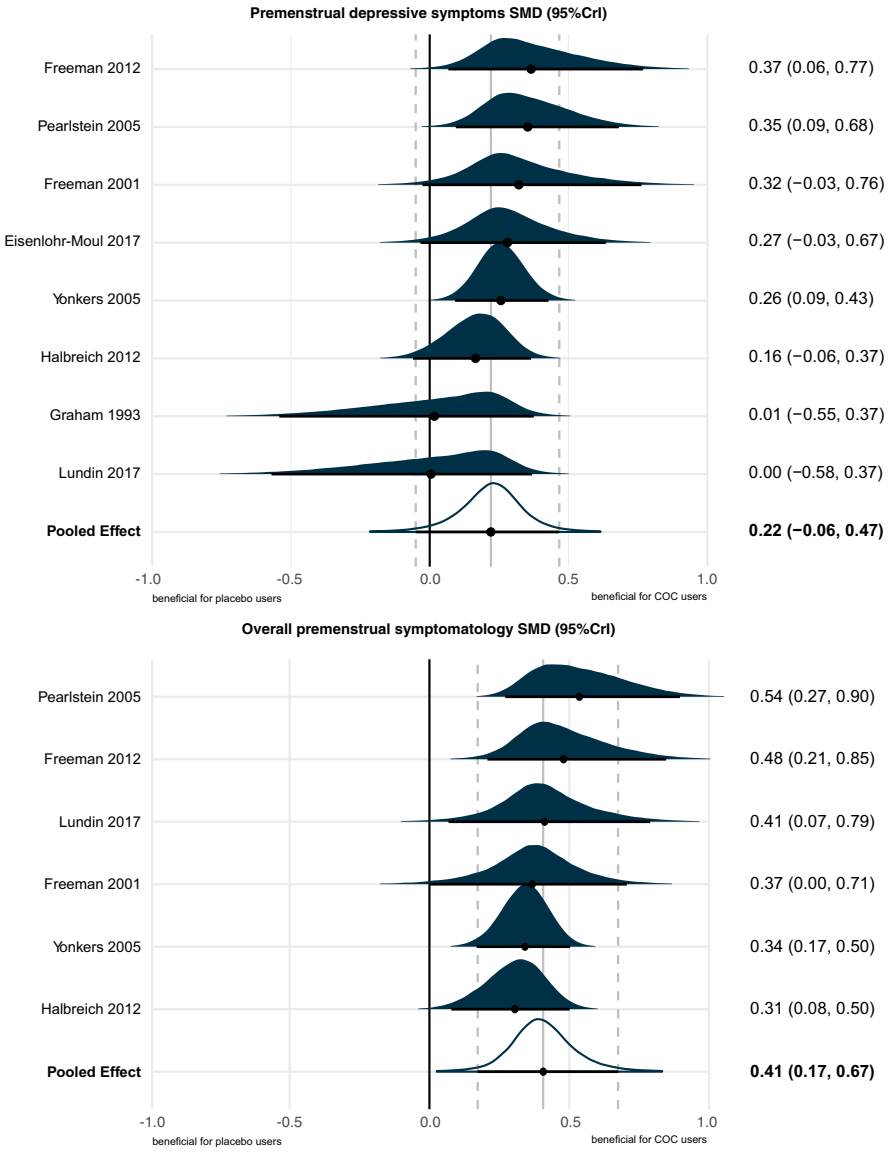
In the network meta-analysis, 1 additional head-to-head trial could be included.[24] This resulted in a network of 9 individual nodes where most interventions were linked only with placebo. Most comparisons were only studied once, but both ethinylestradiol levonorgestrel (20 μg, 90 μg) in a continuous regimen and ethinylestradiol drospirenone (20 μg, 3 mg) in a 24-day regimen were compared with placebo in 2 different studies (Figure 3). Therefore, comparisons between combined oral contraceptives and placebo were predominantly on the basis of direct evidence, whereas comparisons among combined oral contraceptives were predominantly based on indirect evidence. In line with the pairwise meta-analysis findings, the network meta-analysis showed that none of the combined oral contraceptives (including the specific regimens) were more effective than placebo or each other (comparative efficacy shown in lower panel of Table 2 and visualized in the upper panel of Figure 4).

Overall premenstrual symptomatology

A total of 6 placebo-controlled trials were included in the pairwise meta-analysis on the efficacy of combined oral contraceptives in reducing overall premenstrual symptomatology.[9−14,22,23] In contrast to the findings on premenstrual depressive symptoms, combined oral contraceptives were found to be moderately effective compared with placebo (SMD, 0.41; 95% CrI, 0.17−0.67) (shown in the lower panel of Figure 2).

However, when estimating the comparative efficacy of combined oral contraceptives in 7 trials with the network meta-analysis,[9,10,12−14,22,24] none of the combined oral contraceptives were more effective in improving overall premenstrual symptomatology compared with placebo or compared with each other (comparative efficacy shown in upper panel of Table 2 and visualized in the lower panel of Figure 4).

FIGURE 2
Forest plot of effects of combined oral contraceptives vs placebo



The effect sizes for each study are centered on the pooled effect size. Importantly, the effect sizes displayed are the estimates of the "true" effect size of study based on the Bayesian model (not the effect sizes reported in the original studies). The study by Freeman et al[13] describes 4 studies including 2 randomized clinical trials (the multinational and the North American trial). Because the North American trial is also described in the study by Halbreich et al,[14] we refer to the multinational trial when using the study by Freeman et al.[13]

COC, combined oral contraceptives; *CrI*, credible interval; *SMD*, standardized mean difference.

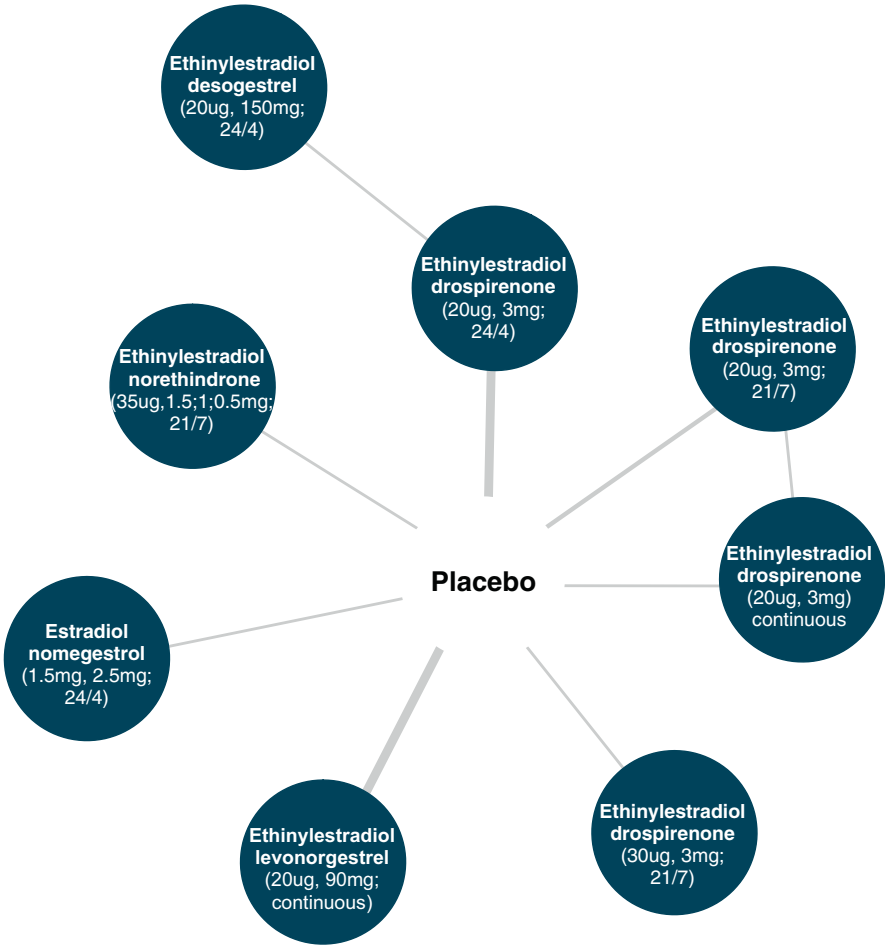
de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

Comment

Main findings

The results of this pairwise and network meta-analysis suggest that combined oral contraceptives, compared with placebo, may improve overall premenstrual symptomatology in both women with PMS and PMDD. However, we found no support for their efficacy in treating premenstrual depressive symptoms, and none of the combined oral contraceptives were more efficacious than any other.

FIGURE 3
Network of treatment comparisons for premenstrual depressive symptoms



Each node represents a different combined oral contraceptive or placebo. The thickness of lines between the nodes is proportional to the number of randomly assigned patients contributing to direct comparisons. Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg) is a multiphasic combined oral contraceptive that has 4 different dosages of norethindrone throughout a 4-week cycle. The dosages before the "slash" refer to the different dosages of the synthetic estrogen, and the ones after the "slash" to those of the synthetic progestin.

de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

Strengths and limitations

The main strength of this study is the use of a comprehensive literature search which enabled us to include 7 randomized clinical trials that were not examined in the previous meta-analysis.[11–14,22–24] In addition, the network meta-analysis enabled us to estimate the comparative efficacy of combined oral contraceptives using both direct and indirect evidence.[26] However, only 1 or 2 trials were available for each comparison and many trials had a relatively small sample size. The combination of these 2 factors limits the certainty of evidence for each comparison as was reflected by the GRADE assessment, which resulted in a "very low" certainty rating of the summary of evidence owing to relatively large imprecision of the estimates from each study. Moreover, there were only 2 trials that used combined oral contraceptives as a comparison group. Therefore, the estimates of efficacy of one combined oral contraceptive vs another are primarily based on indirect evidence (mainly through placebo). In addition, the limitations of individually included trials inevitably limited the quality of our analysis. Only 3 of the 9 trials included in the network meta-analysis, examined all participants randomized into a trial irrespective of what happened subsequently (also known as intention-to-treat analysis).[10,24,27] This may have increased the risk of overestimation of the efficacy of combined oral contraceptives, because the use of per-protocol or observed cases analysis violates the principles of randomization. Loss to follow-up was substantial in almost all trials, which further question the prognostic balance afforded by randomization. Finally, unregistered trials that were not published (as a full journal article) were not included in the search. In case of publication bias against null findings, this may have resulted in an overestimation of effects. However, because we mainly report null findings (except for the effect of oral contraceptives compared with placebo for overall premenstrual symptomatology), we do not expect this to have a large effect on our results.

Comparison with existing literature

We are aware of only one previous meta-analysis that attempted to estimate the efficacy of combined oral contraceptives in treating PMDD. This meta-analysis did not include measures on premenstrual depressive symptoms, but did report that, compared with placebo, ethinylestradiol drospirenone (20 μg, 3 mg) use in a 24-day regimen was effective in reducing overall premenstrual symptomatology in women with PMDD.[28] Therefore, this finding stands in direct opposition to the results reported here, showing that the same formulation was not superior to other types of combined oral contraceptives or placebo in treating PMS and PMDD. However, there are important differences in the way the data were evaluated that could explain the difference in findings. First, the previous meta-analysis used a fixed-effect rather than a random-effects model for

TABLE 2
Comparisons for efficacy of combined oral contraceptives on premenstrual depressive symptoms (lower triangle) and overall premenstrual symptomatology (upper triangle)

Combined oral contraceptive		Placebo		Premenstrual depressive symptoms		Overall premenstrual symptomatology		
Ethinylestradiol drospirenone (20 μg, 3 mg; 24/4)	−0.04[a] (−1.20 to 1.08)	—	—	−0.68[a] (−1.57 to 0.21)	−0.09[a] (−0.95 to 0.76)	−0.19[a] (−1.35 to 0.91)	—	−0.47[a] (−1.11 to 0.09)
0.67[a] (−0.63 to 1.96)	Estradiol nomegestrol (1.5 mg, 2.5 mg; 24/4)	—	—	−0.64[a] (−2.05 to 0.84)	−0.05[a] (−1.17 to 1.12)	−0.15[a] (−1.52 to 1.21)	—	−0.44[a] (−1.41 to 0.53)
0.08[a] (−0.97 to 1.17)	−0.75[a] (−1.82 to 0.28)	Ethinylestradiol drospirenone (20 μg, 3 mg; 21/7)	—	—	—	—	—	—
−0.09[a] (−1.14 to 1.01)	−0.84[a] (−2.13 to 0.46)	−0.17[a] (−1.13 to 0.79)	Ethinylestradiol drospirenone (20 μg, 3 mg; continuous)	—	—	—	—	—
0.74[a] (−0.08 to 1.56)	−0.01[a] (−1.36 to 1.29)	0.66[a] (−0.71 to 1.98)	0.83[a] (−0.55 to 2.16)	Ethinylestradiol desogestrel (20 μg, 150 μg; 24/4)	0.59[a] (−0.66 to 1.81)	0.48[a] (−0.98 to 1.89)	—	0.20[a] (−0.91 to 1.24)
0.07[a] (−0.74 to 0.82)	−0.68[a] (−1.78 to 0.33)	−0.01[a] (−1.12 to 1.03)	0.15[a] (−0.96 to 1.20)	−0.67[a] (−1.83 to 0.43)	Ethinylestradiol levonorgestrel (20 μg, 90 μg; continuous)	−0.10[a] (−1.26 to 1.00)	—	−0.38[a] (−1.02 to 0.20)
−0.15[a] (−1.16 to 0.91)	−0.89[a] (−2.16 to 0.38)	−0.22[a] (−1.51 to 1.06)	−0.05[a] (−1.35 to 1.23)	−0.88 (−2.19 to 0.45)	−0.21[a] (−1.22 to 0.87)	Ethinylestradiol drospirenone (30 μg, 3 mg; 21/7)	—	−0.28[a] (−1.24 to 0.67)
0.71[a] (−0.32 to 1.77)	−0.04[a] (−1.32 to 1.23)	0.63[a] (−0.66 to 1.92)	0.80[a] (−0.50 to 2.09)	−0.03[a] (−1.34 to 1.31)	0.64[a] (−0.38 to 1.73)	0.85[a] (−0.41 to 2.12)	Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg; 21/7)	—
0.34[a] (−0.18 to 0.91)	−0.41[a] (−1.32 to 0.49)	0.26[a] (−0.67 to 1.19)	0.43[a] (−0.50 to 1.36)	−0.40[a] (−1.36 to 0.60)	0.27[a] (−0.24 to 0.87)	0.49[a] (−0.40 to 1.37)	−0.37[a] (−1.26 to 0.53)	Placebo

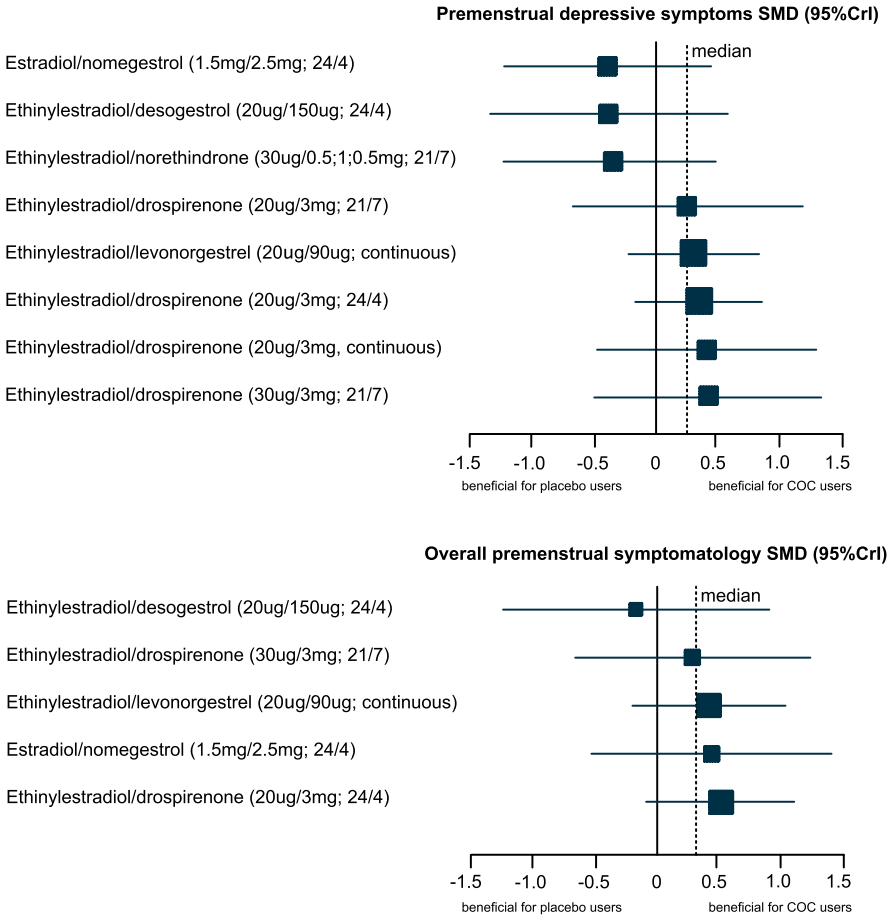
Data are expressed as SMD with 95% credible intervals in the column-defining intervention compared with the row-defining intervention. Higher SMD values correspond with fewer symptoms in the column-defining hormonal contraceptive. Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg) is a multiphasic combined oral contraceptive that has 4 different dosages of norethindrone throughout a 4-week cycle. The dosages before the "comma" refer to the different dosages of the synthetic estrogen, and the ones after the "comma" to those of the synthetic progestin.

SMD, standardized mean difference.

[a] None of the results were significant and all evidence was of low certainty.

de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

FIGURE 4
Forest plot of treatment efficacy of combined oral contraceptives compared with placebo



The size of the SMD dots are proportional to the precision of the estimate (1/standard error). Ethinylestradiol norethindrone (35 μg, 0.5; 1; 0.5; 0 mg) is a multiphasic combined oral contraceptive that has 4 different dosages of norethindrone throughout a 4-week cycle. The dosages before the "comma" refer to the different dosages of the synthetic estrogen, and the ones after the "comma" to those of the synthetic progestin.

COC, combined oral contraceptive; *CrI*, credible interval; *SMD*, standardized mean difference.

de Wit. Efficacy of combined oral contraceptives in premenstrual syndrome. Am J Obstet Gynecol 2021.

analyzing the data. Fixed-effects models assume that there is a single underlying "true" effect size, which requires that all factors that could influence the effect size are the same in all trials. Because this assumption is rarely met, we argue that a random-effects model is more suitable. Second, the previous meta-analysis used frequentist inference testing rather than Bayesian inference testing. Although both approaches are reasonable, the contradictory results suggest that the efficacy of ethinylestradiol drospirenone (20 μg, 3 mg) in a 24-day regimen is not very robust to differences in analytical strategy.

Implications for current clinical practice and future research

This meta-analysis shows that combined oral contraceptives represent a reasonable therapeutic option to treat overall premenstrual symptomatology in women with PMS or PMDD also seeking contraception. However, combined oral contraceptives were not effective in treating premenstrual depressive symptoms. Physicians should take this into account when prescribing combined oral contraceptives, because depressive symptoms are often the main symptoms in women with PMDD. In women who predominantly complain about depressive symptoms, other commonly used treatment options for women with PMDD, such as selective serotonin reuptake inhibitors and cognitive-behavioral therapy, might be a more effective approach.[29,30] However, certainty of evidence for all available treatments is very low to moderate at best, which highlights that optimal treatment strategies are not yet well established.

In contrast to what is often thought, there was no evidence for a difference in efficacy among formulations containing drospirenone and other formulations or a 24-day regimen vs other regimens. This suggests that other arguments could justify the decision to choose 1 contraceptive over another in women with PMS or PMDD seeking treatment with a combined oral contraceptive. Because drospirenone is associated with an increased risk of blood clots compared with other hormonal contraceptives,[31] this may argue against preferentially prescribing a drospirenone-containing contraceptive. However, the insufficient evidence in favor of a specific combined oral contraceptive over another in treating PMS or PMDD may be caused by a lack of statistical power. This clearly highlights the need for additional large randomized clinical trials to answer the question of which treatment options are most effective in women with PMS and PMDD. Preferably, these trials should include both women with PMS and women with PMDD, to ensure that findings are generalizable to the full range of severity of premenstrual complaints which in addition would allow to examine whether combined oral contraceptives are equally effective in women with PMDD vs PMS.

Conclusions

The results of this pairwise and network meta-analysis show that combined oral contraceptives may improve overall premenstrual symptomatology in

women with PMS or PMDD, but there is currently no evidence to favor a specific combined oral contraceptive over another. Moreover, there was no evidence to suggest that combined oral contraceptives are effective in treating premenstrual depressive symptoms, which are often the primary complaints of women with PMDD. Few trials were available for each formulation of combined oral contraceptives, and certainty of evidence for each comparison was rated as very low. Therefore, more randomized clinical trials with head-to-head comparisons of combined oral contraceptives are needed to determine which formulation is most effective for premenstrual complaints in women with PMS and PMDD. ■

ACKNOWLEDGMENTS

We thank Jan W. Schoones, MA, information specialist from Leiden University Medical Center, for assistance in developing the search strategy. We are grateful for additional data that were provided to us by Cynthia A. Graham, professor at the University of Southampton; Cecilia Lundin, PhD student at Uppsala University; and Lynne Smith of Pfizer.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Available at: https://www.psychiatry.org/psychiatrists/practice/dsm. Accessed May 1, 2021.

2. Yonkers KA, O'Brien PS, Eriksson E. Premenstrual syndrome. Lancet 2008;371:1200–10.

3. Wittchen H-U, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. Psychol Med 2002;32:119–32.

4. Potter J, Bouyer J, Trussell J, Moreau C. Premenstrual syndrome prevalence and fluctuation over time: results from a French population-based survey. J Womens Health (Larchmt) 2009;18:31–9.

5. Rapkin AJ, Korotkaya Y, Taylor KC. Contraception counseling for women with premenstrual dysphoric disorder (PMDD): current perspectives. Open Access J Contracept 2019;10:27–39.

6. Management of premenstrual syndrome: Green-top Guideline No. 48. BJOG 2017;124:e73–105.

7. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. Am Fam Physician 2016;94:236–40.

8. United States Food & Drug Administration. Yaz (drospirenone/ethinyl estradiol) for Oral Contraception and Premenstrual Dysphoric Disorder. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021873_yaz_toc.cfm. Accessed January 7, 2021.

9. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol 2005;106:492–501.

10. Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception 2005;72:414–21.

11. Eisenlohr-Moul TA, Girdler SS, Johnson JL, Schmidt PJ, Rubinow DR. Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives: results of a three-arm randomized controlled trial. Depress Anxiety 2017;34:908–17.

12. Freeman EW, Kroll R, Rapkin A, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. J Womens Health Gend Based Med 2001;10:561–9.

13. Freeman EW, Halbreich U, Grubb GS, et al. An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome. Contraception 2012;85:437–45.

14. Halbreich U, Freeman EW, Rapkin AJ, et al. Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. Contraception 2012;85:19–27.

15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane. 2021. Available from www.training.cochrane.org/handbook. Accessed May 1, 2021.

16. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV). 2006 Available at: https://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.152.8.1228. Accessed May 1, 2021.

17. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods 2002;7:105–25.

18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

19. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36–44.

20. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS Med 2020;17:e1003082.

21. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Syst Rev 2020;16:e1080.

22. Lundin C, Danielsson KG, Bixo M, et al. Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle—a double-blind, placebo-controlled randomized trial. Psychoneuroendocrinology 2017;76:135–43.

23. Graham CA, Sherwin BB. The relationship between mood and sexuality in women using an oral contraceptive as a treatment for premenstrual symptoms. Psychoneuroendocrinology 1993;18:273–81.

24. Wichianpitaya J, Taneepanichskul S. A comparative efficacy of low-dose combined oral contraceptives containing desogestrel and drospirenone in premenstrual symptoms. Obstet Gynecol Int 2013;2013:487143.

25. Shehata NAA, Moety GAFA, El Wahed HAA, Fahim AS, Katta MA, Hussein GK. Does adding fluoxetine to combined oral contraceptives containing drospirenone improve the management of severe premenstrual syndrome? A 6-month randomized double-blind placebo-controlled three-arm trial. Reprod Sci 2020;27:743–50.

26. Higgins JP, Welton NJ. Network meta-analysis: a norm for comparative effectiveness? Lancet 2015;386:628–30.

27. Yonkers KA, Simoni MK. Premenstrual disorders. Am J Obstet Gynecol 2018;218:68–74.

28. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database of Syst Rev 2012:CD006586.

29. Marjoribanks J, Brown J, O'Brien PM, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev 2013:CD001396.

30. Busse JW, Montori VM, Krasnik C, Patelis-Siotis I, Guyatt GH. Psychological intervention for premenstrual syndrome: a meta-analysis of randomized controlled trials. Psychother Psychosom 2009;78:6–15.

31. United States Food & Drug Administration. FDA Drug Safety Communication: safety review update on the possible increased risk of blood clots with birth control pills containing drospirenone. 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-safety-review-update-possible-increased-risk-blood-clots-birth-control. Accessed January 5, 2021.