Effect of Estetrol combined with drospirenone on female quality of life; A new trend in COCs: A systematic review and meta-analysis of published randomized controlled trials

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Abstract

Background: In our systematic review and meta-analysis we aim to summarize and evaluate user satisfaction, body weight control and general well-being of estetrol (E4) in combination with drospirenone (DRSP).

Methods: We followed the standard methods of Cochrane Handbook of Systematic Reviews for interventions and the PRISMA statement guidelines 2020 when conducting and reporting this study. A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials was conducted from inception until January 31, 2022. We selected randomized controlled trials (RCTs) assessing the efficacy of Estetrol (E4) when combined with drospirenone (DRSP) on women Safety and menopausal bleeding as well as general well-being, and all relevant outcomes were pooled in the meta-analysis using Review Manager Software

Results: We included ten RCTs in our study with only five RCTs included in the meta-analysis. In the fixed-model effect and the random-effect model there was significant difference with the use of E4 in combination with DRSP regarding all our outcomes as following: abdominal pain [2.2%, CI 95% (1.7,2.7), P< 0.001], acne [3.7%, CI 95% (3.1,4.3), P< 0.001], metrorrhagia [5%, CI 95% (4.2,5.7), P< 0.001], nausea [3.8%, CI 95% (2.9,4.7), P< 0.001], weight increase [2.4%, CI 95% (1.9,2.9), P< 0.001], treatment related adverse events [34.9%, CI 95% (27.2,42.6), P< 0.001], any adverse event lead to discontinuation [6.9%, CI 95% (2.6,11.2), P= 0.002], breast pain [3.6%, CI 95% (1.5,5.4), P< 0.001], dysmenorrhea [3.6%, CI 95% (1.9,5.3), P< 0.001], headache [6.8%, CI 95% (4.3,9.4), P< 0.001], and anxiety [2%, CI 95% (1.4,2.6), P< 0.001]. For absence of scheduled bleeding after second, third and sixth menopausal cycles there was no significant difference as following: [6.3%, CI 95% (-4.3,17), P= 0.243], [7.5%, CI 95% (-4.5%,17%), P=0.243], and [8.3%, CI 95% (-2.1,18.7), P=0.117]. While there was no significant difference in the percentage of occurrence of unscheduled bleeding after first: [1.3%, CI 95% (0,2.7), P=0.05], second [4.4%, CI 95% (1.7,7), P= 0.001], third [3.1%, CI 95% (0.8,5.3), P=0.007], sixth [2.6%, CI 95% (0.6,4.6), P=0.012], and twelfth [1.1%, CI 95% (0.7,1.5), P< 0.001].

Conclusion: In conclusion, our meta-analysis showed that use of E4 in combination with DRSP was associated with decrease abdominal pain, acne, metrorrhagia, nausea, and weight increase treatment related adverse events, any adverse event led to discontinuation, breast pain, dysmenorrhea, headache, and anxiety. On the other hand, it's not associated with decrease unscheduled bleeding after first, second, third, sixth, and twelfth month of menstrual cycle

Key words: estetrol, drospirenone, review, menstrual bleeding, bleeding, anxiety, headache.

Introduction:

When selecting a contraceptive method, it's of a great value to discuss many factors with the patient particularly health benefit, efficacy, tolerability of the patient and if the patient can use alternate method or not. The major fear is from venous thromboembolism which represent a ghost in our equation. Ethinyl-estradiol (EE) which is an estrogenic component is contained in the majority of combined oral contraceptive (COCs), which is safe if present in lower concentration and dose in (COCs). On the other hand, EE can lead to major multi-system adverse effects especially cardiovascular system (venous thromboembolism) particularly in susceptible patients with major risk factors. Additionally raise liver protein synthesis and some how affect metabolism of lipid and carbohydrate(1). So, it was a must to replace EE with E2 as it has less metabolic adverse effect, better safety profile(2, 3).

It was found that drospirenone (DRSP), which is a newer progestin, can bind more efficiently to progesterone receptor. By mean less glucocorticoid, estrogenic and androgenic adverse events and equivalent metabolic effect (4), on the other hand, maintain contraceptive property.

Estetrol (E4) is formed in fetal liver during pregnancy. It is a human-specific estrogen (5). Chemically synthesized E4 is similar to the natural hormone and has been studied in contraception, menopause, osteoporosis, and breast cancer(6-8). E4 when combined with DRSP prevents ovulation and is associated with a less vaginal bleeding, tolerability, and safety profile, and with higher satisfaction(6, 9). It also has limited effects on liver function and metabolic and endocrine parameters when used in doses up to 10 mg and for less than 3 months(10). The aim of our study is to assess the effect of E4 when combined with DRSP (E4/DRSP) on metabolic, endocrine parameters quality of life after 6 cycles of treatment.

Methods:

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria in conducting this meta-analysis.

Search strategy

We searched PubMed, Web of Science, The Cochrane Library, and Scopus for relevant material. The most recent search was conducted on January 31, 2022. "Estetrol" and "drospirenone" were used as combined search keywords with Medical Subject Headings (MeSH) phrases. Additionally, unpublished articles from the research period and references to included studies were combed.

Inclusion criteria

Articles that met the following criteria were included:

Participants: Adult females in good health.

They received estetrol and drospirenone in combination.

Safety and menopausal bleeding results are the outcomes of the study.

Study design: prospective as well as retrospective studies are both acceptable options.

Data extraction

We collected the following data from each study: (1) the name of the first author and the publishing year of the article, (2) study design, (3) inclusion criteria, (4) primary outcome (5) results for each study, (7) sample; (8) age at baseline (9)

Quality assessment

To assess the quality of RCTs, we used the Cochrane Handbook for Systematic Reviews of Interventions, Second Edition. Our technique review included a look at how selection and performance biases and detection and attrition biases affected the methodological quality. Studies with a quality score of "+" were found to be free from bias, while those with a quality score of "?" had one or more uncertain criteria, and those with a quality score of "-" were found to have several quality criteria but significant risk of bias.

We used the Newcastle Ottawa scale (NOS) for observational studies. There were three major categories of eight items each, with a maximum of nine points. A NOS score of 5 to 7 indicates a moderate risk of bias; a NOS score of >7 signifies low risk. Studies with a NOS score of 5 are considered high risk. A third researcher was brought in to address any discrepancies.

Statistical analysis

We used Open meta-analyst software to conduct our meta-analysis. Data were represented as risk ratios (RR) and 95% confidence Intervals for all outcomes. With Cochrane's Q tests and I2 statistics, we determined the level of heterogeneity. P-value ≤ 0.05 or I2 $\geq$ 50% refereed to significant heterogeneity. In order to reduce the heterogeneity, we a random-effects model. When the p-value was greater than 0.1, it was deemed significant statistically.

Results:

Study selection process and characteristics of studies: Our search strategy found 213 articles in these databases. After reviewing their abstracts and titles, we ruled out 180 articles. Among the remaining 33 articles, 23 articles were excluded. Finally, ten studies were involved. (1–10) Of them, five studies were included in our analysis fig 1. The summary and baseline characteristics of RCTs are listed in Table 1 and Table 2.

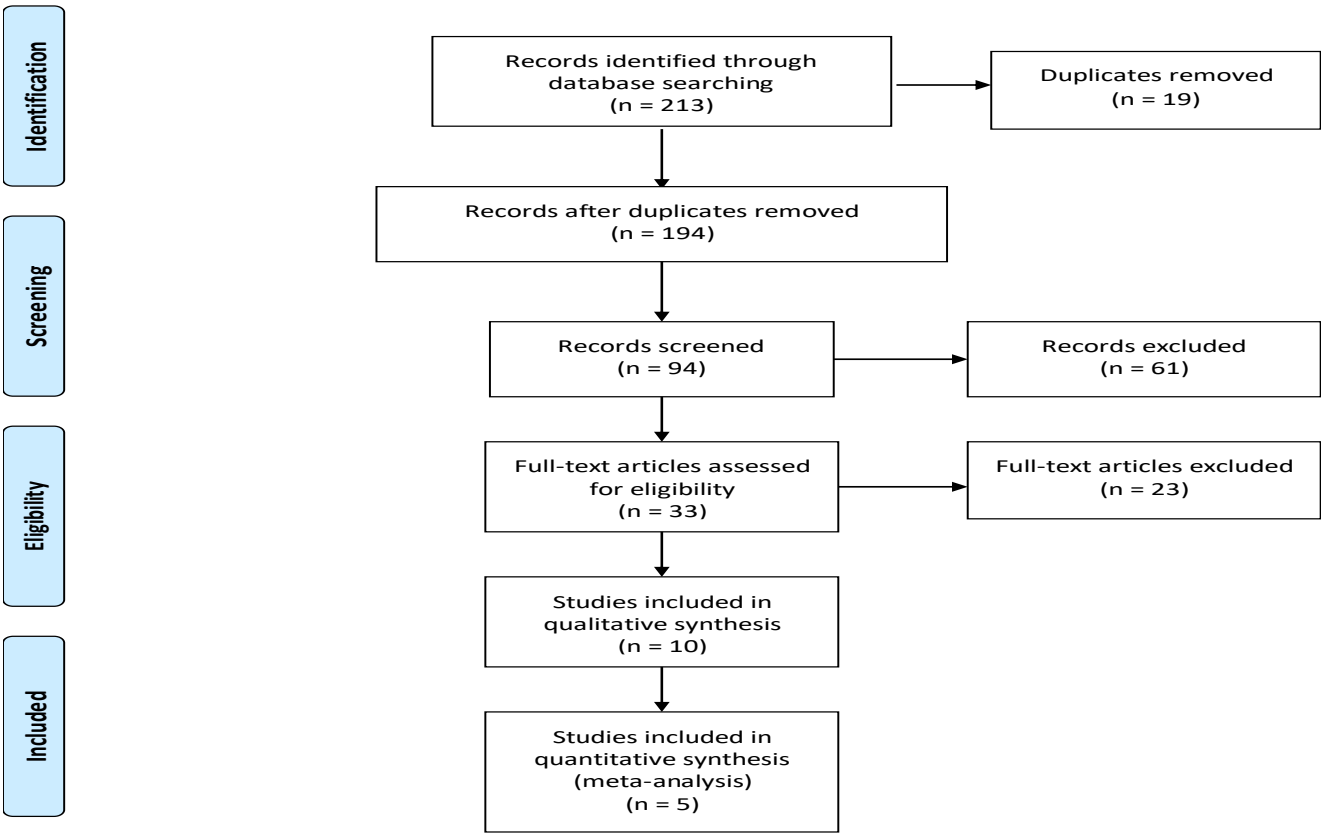


fig 1: Prisma flow diagram of selected studies

Safety Outcomes

Fixed-effect model outcomes

The incidence of abdominal pain, acne, metrorrhagia, nausea, and weight increase were as following: [2.2%, CI 95% (1.7,2.7), P< 0.001], [3.7%, CI 95% (3.1,4.3), P< 0.001], [5%, CI 95% (4.2,5.7), P< 0.001], [3.8%, CI 95% (2.9,4.7), P< 0.001], and [2.4%, CI 95% (1.9,2.9), P< 0.001]. The data for these outcomes were homogeneous as following:(P=0.183), (P=0.649), (P=0.255), (P=0.375), and (P=0.775) respectively. Fig.1-5

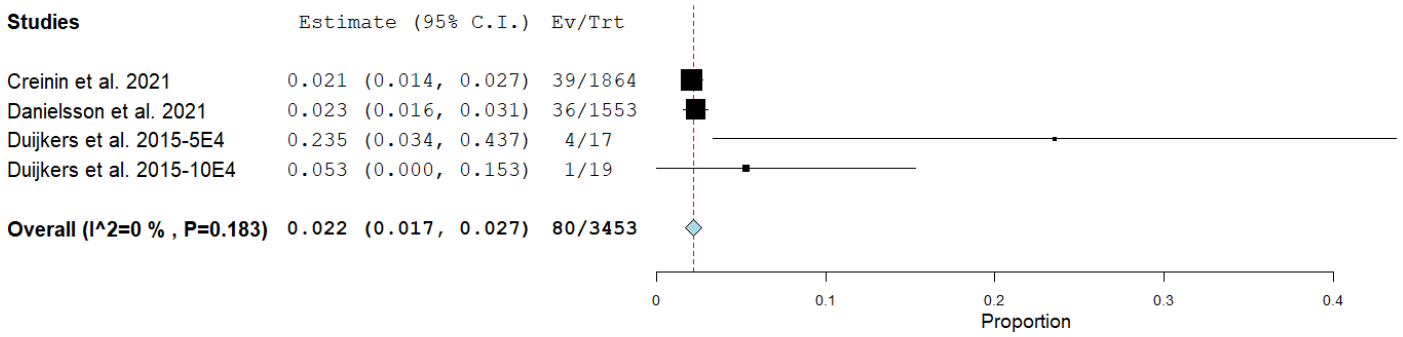


Figure 1: A forest plot of abdominal pain as an outcome for E4/DRSP use

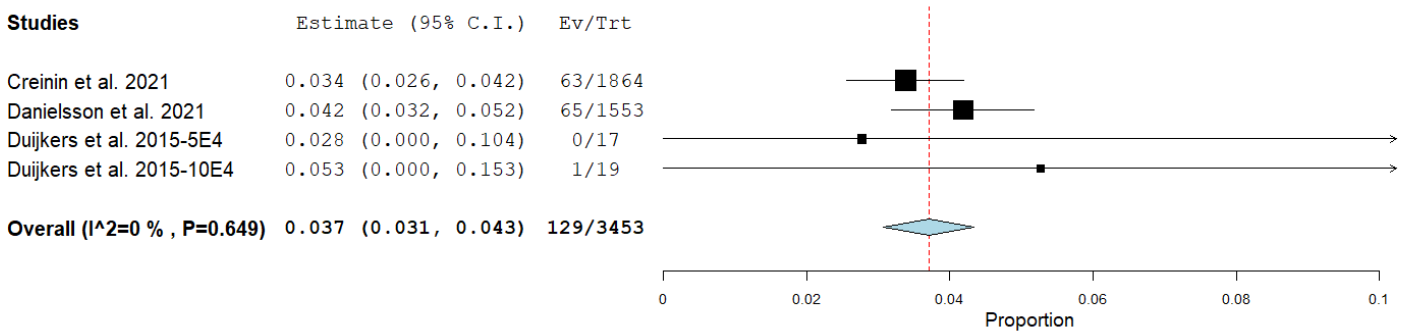


Figure2: A forest plot of acne as an outcome for E4/DRSP use

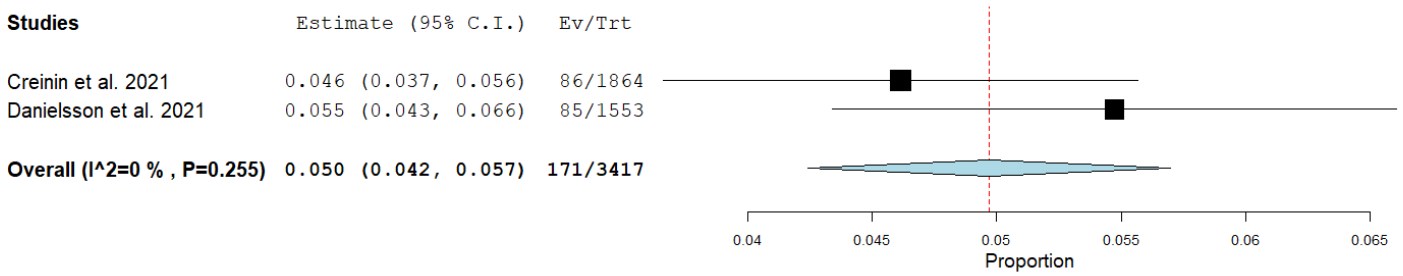


Figure3: A forest plot of metrorrhagia as an outcome for E4/DRSP use

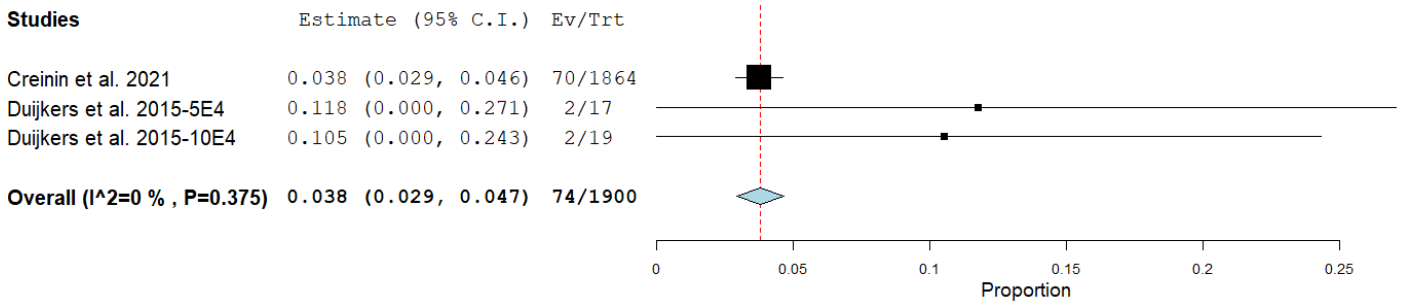


Figure4: A forest plot of nausea as an outcome for E4/DRSP use

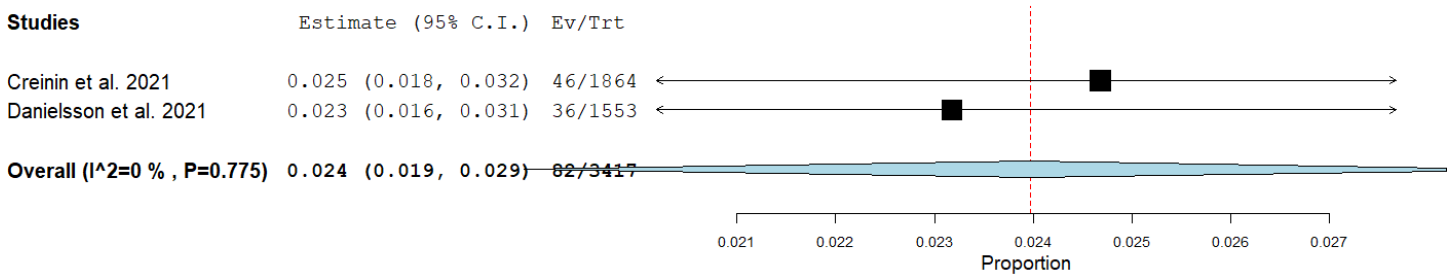


Figure5: A forest plot of weight increased as an outcome for E4/DRSP use

Random-effect model outcomes

We used random effect model to reduce heterogeneity between studies. The incidence of treatment related adverse events, any adverse event lead to discontinuation, breast pain, dysmenorrhea, headache, and anxiety were as following: [34.9%, CI 95% (27.2,42.6), P< 0.001], [6.9%, CI 95% (2.6,11.2), P= 0.002], [3.6%, CI 95% (1.5,5.4), P< 0.001], [3.6%, CI 95% (1.9,5.3), P< 0.001], [6.8%, CI 95% (4.3,9.4), P< 0.001], and [2%, CI 95% (1.4,2.6), P< 0.001]. The data for these outcomes were heterogeneous as following:(P< 0.001, I2=93%), (P< 0.001, I2=94%), (P=0.002, I2=76.6%), (P=0.014, I2=71.6%), (P< 0.001, I2=76%), and (P=0.55, I2=65.5%). Fig.6-11

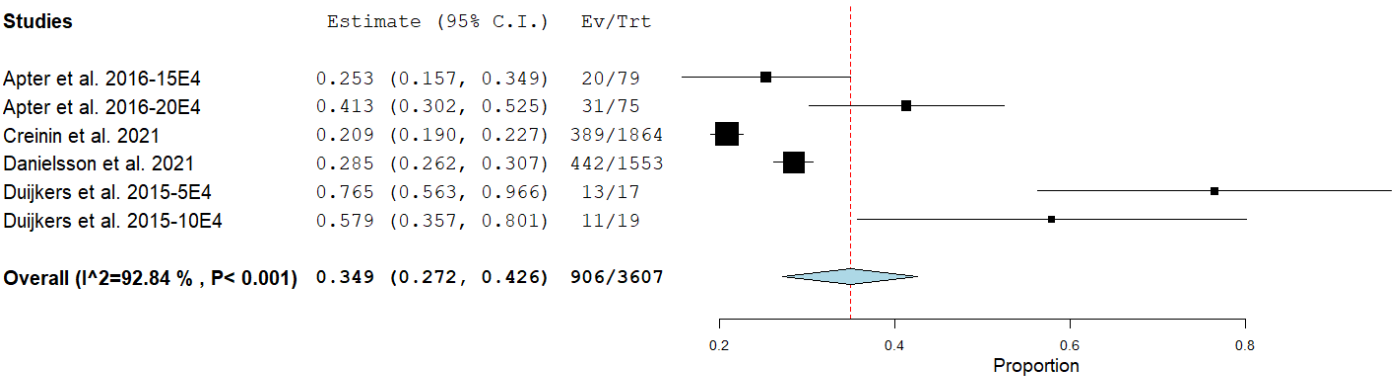


Figure6: A forest plot of Drug-related TE-AEs as an outcome for E4/DRSP use

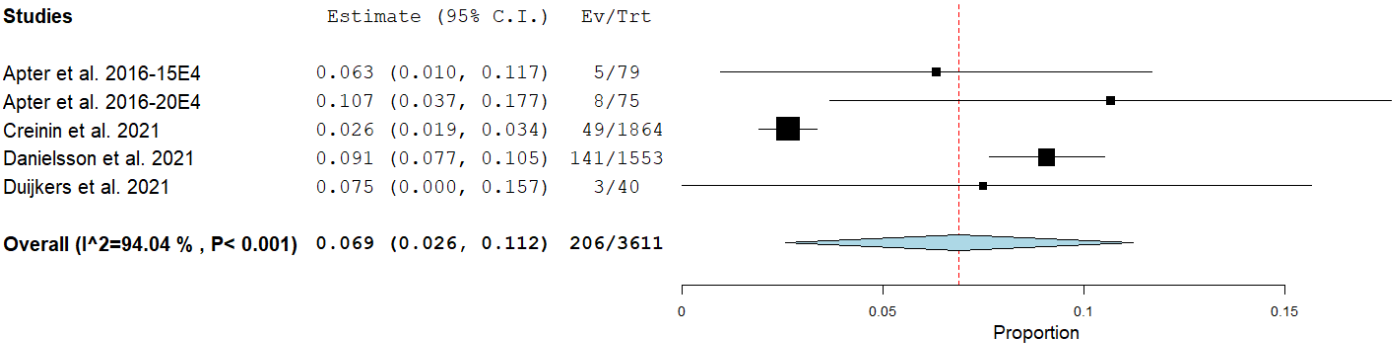
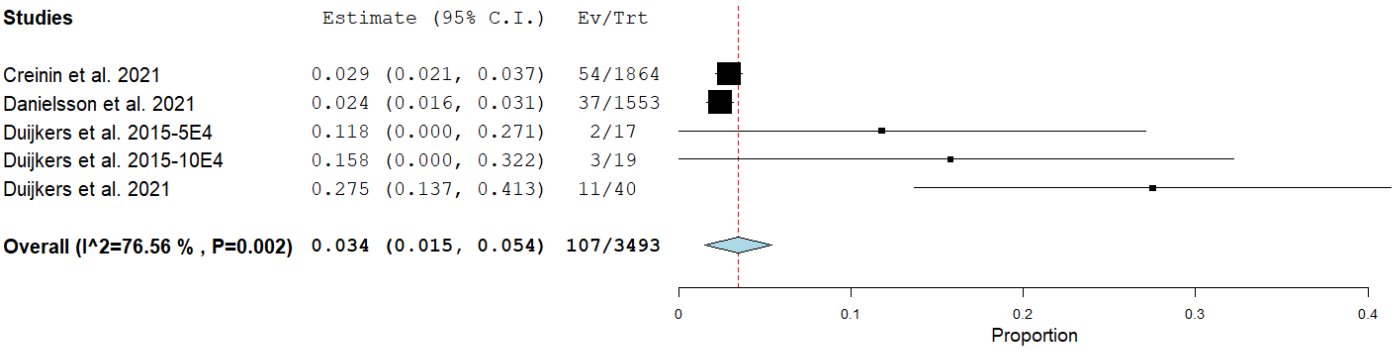


Figure7: A forest plot of ad lead to discontinuation as an outcome for E4/DRSP use



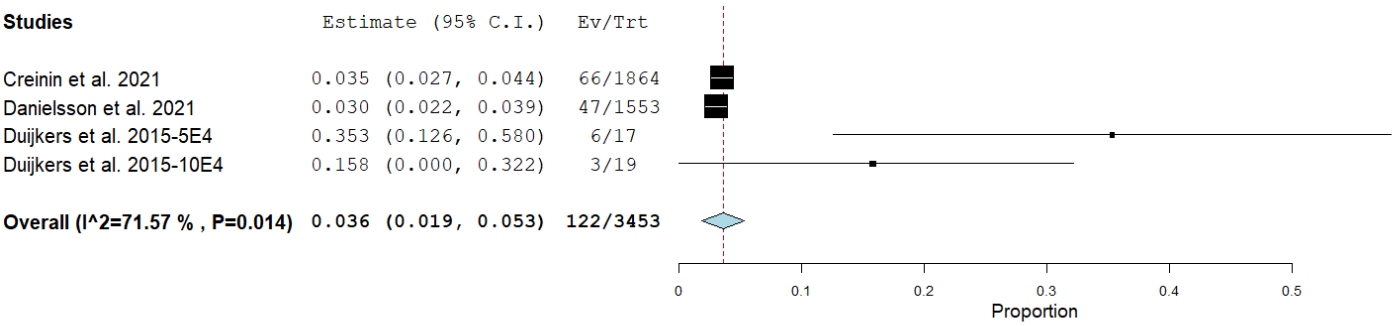


Figure9: A forest plot of dysmenorrhea as an outcome for E4/DRSP use

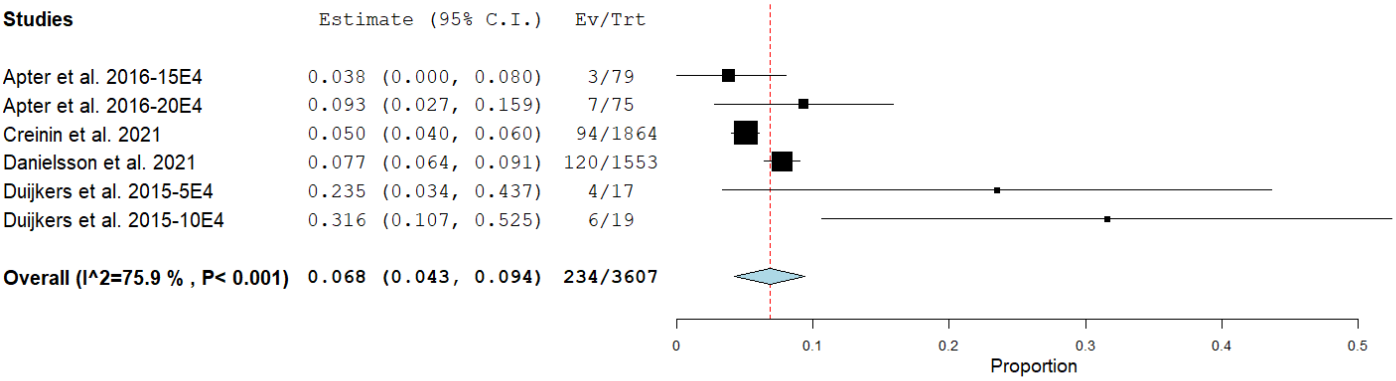


Figure10: A forest plot of headache as an outcome for E4/DRSP use

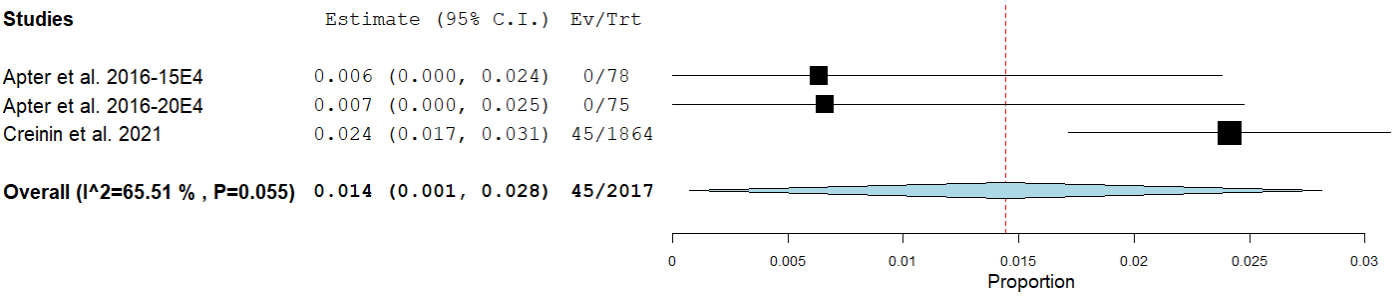


Figure11: A forest plot of Anxiety depression as an outcome for E4/DRSP use

Absence of scheduled bleeding

We used a random-effect model to reduce heterogeneity between studies.

Regarding the percentage of absence of scheduled bleeding after second, third and sixth menopausal cycles were as following: [6.3%, CI 95% (-4.3,17), P= 0.243], [7.5%, CI 95% (-4.5%,17%), P=0.243], and [8.3%, CI 95% (-2.1,18.7), P=0.117]. The results were insignificant and the data for these outcomes were heterogeneous as following:(P< 0.001, I2=98%), (P< 0.001, I2=98%), and (P=0.55, I2=95.3%). Fig.12

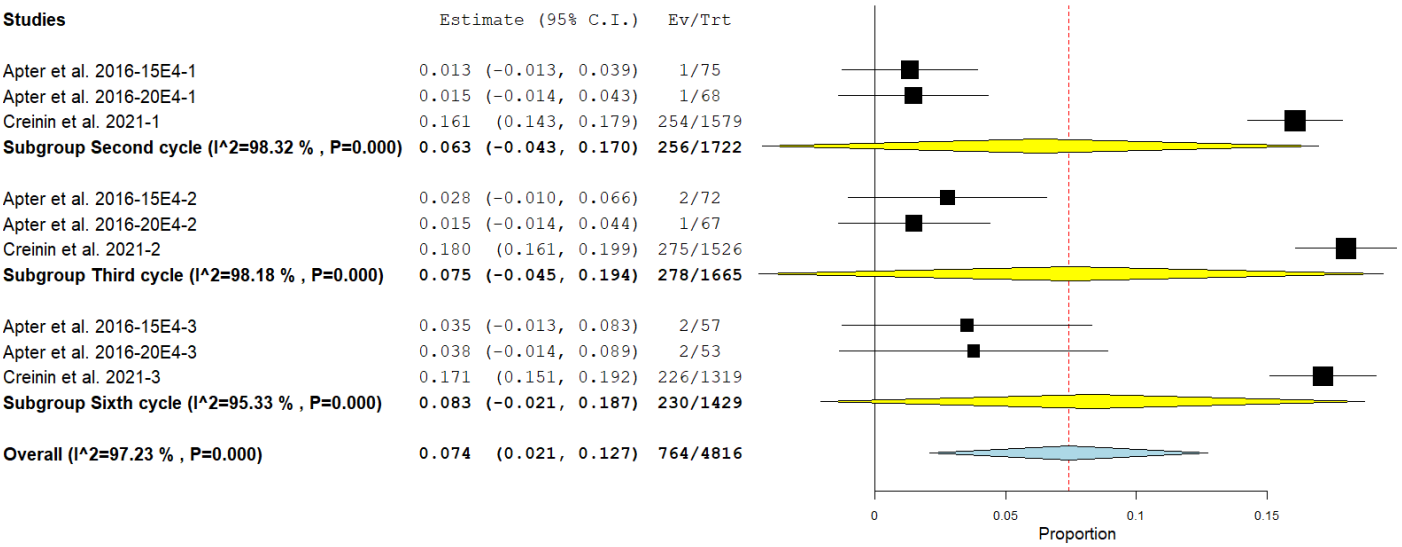


Figure12: A forest plot of absence of scheduled bleeding as an outcome for E4/DRSP use

Occurrence of unscheduled bleeding

We used random effect model to reduce heterogeneity between studies. Regarding the percentage of occurrence of unscheduled bleeding after first, second, third, sixth and twelfth menopausal cycles were as following: [1.3%, CI 95% (0,2.7), P=0.05], [4.4%, CI 95% (1.7,7), P= 0.001], [3.1%, CI 95% (0.8,5.3), P=0.007], [2.6%, CI 95% (0.6,4.6), P=0.012], and [1.1%, CI 95% (0.7,1.5), P< 0.001]. The data for these outcomes were heterogeneous except after twelfth cycle as following:(P< 0.001, I2=92%), (P< 0.001, I2=93%), (P=0.002, I2=94%), (P=0.014, I2=89%), and (P=0.636, I2=0%). Fig.13

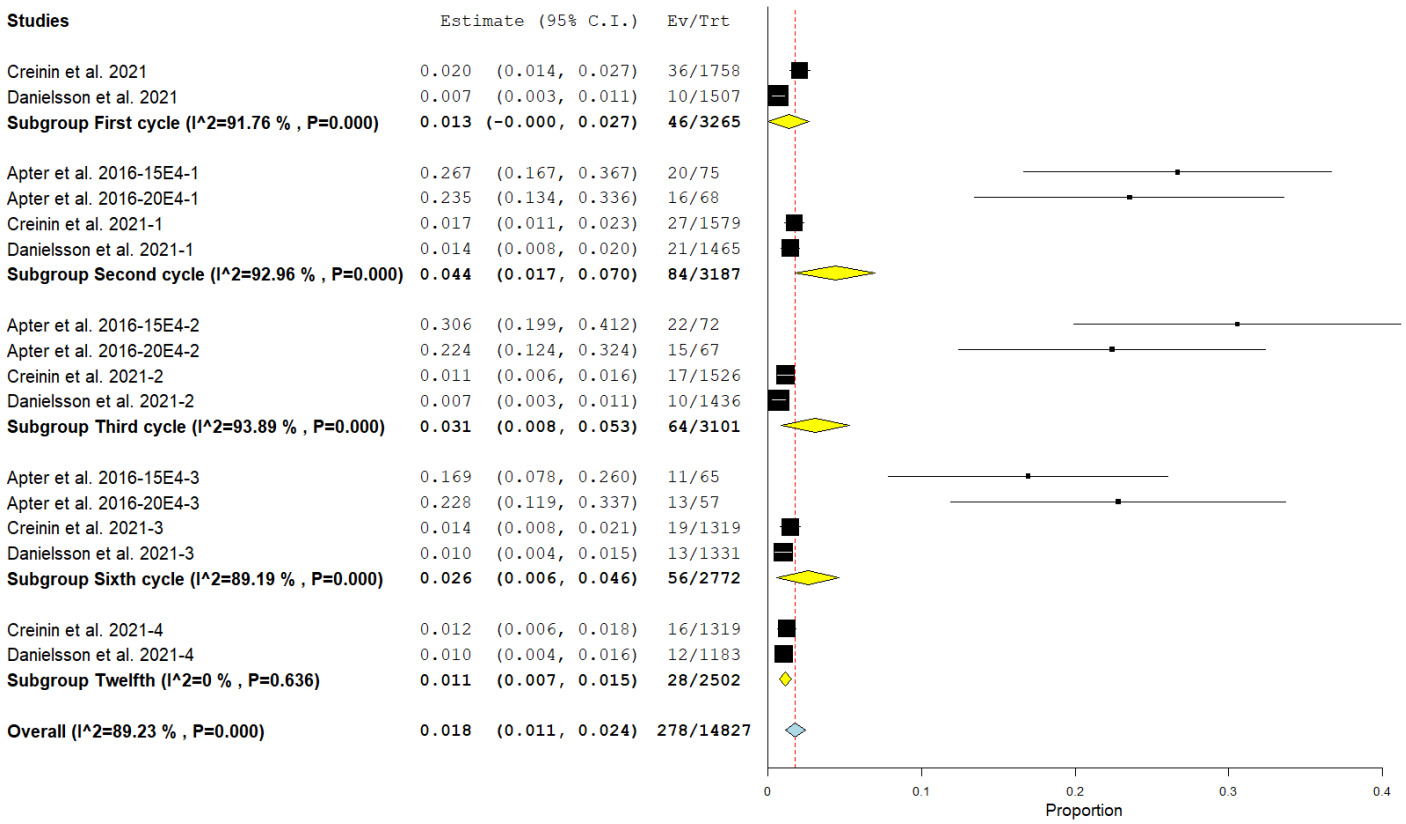


Figure13: A forest plot of occurrence of scheduled bleeding as an outcome for E4/DRSP use

Systematic review

Regarding Apter et al. 2017(8), they found that the combination of 15 mg estetrol and 3 mg DRSP resulted in a high level of user acceptance and satisfaction, as well as good body-weight management.

Regarding Douxfils et al. 2020(5), Following six cycles of E4 DRSP therapy, hemostasis parameters changed less or were comparable to those seen after EE/LNG treatment in this research. Compared to EE/DRSP, combined oral contraceptive pills (COCs) influence on hemostasis parameters was more apparent, supporting the idea that the estrogenic component of combined oral contraceptive pills is the most crucial factor.

Regarding klipping et al. 2021(8), Combining 15 mg of E4 with 3 mg of DRSP produced a distinct metabolic profile that may be more beneficial.

In kluft et al. 2016(9), Women who use E4-containing COCs may have a decreased risk of Venous Thromboembolism compared to women who take EE-containing COCs due to their lower hepatic and vascular estrogenicity. According to their data, at least for intermediate outcomes, this hypothesis holds true.

Finally, regarding Mawet et al. 2015(10), There was less impact on liver, lipid, bone, and growth endocrine markers with E4/DRSP and E4/LNG than with the EE/DRSP combination in this research.

Discussion:

Summary of the findings

Our systematic review includes ten RCTs. Of them, five RCTs were included in our meta-analysis. The results of our meta showed that there is significant difference in the use of E4/DRSP in terms of abdominal pain, acne, metrorrhagia, nausea, weight gain, incidence of treatment related adverse events, any adverse event led to discontinuation, breast pain, dysmenorrhea, headache, anxiety, and percentage of occurrence of unscheduled bleeding after second, third, sixth and twelfth menopausal cycles. While the results were insignificant in terms of percentage of absence of scheduled bleeding after first menopausal cycle.

Agreements and disagreements with previous studies

Recently, the influence of E4/DRSP supplementation to control peri-menopausal symptoms has been widely debated. The results of our meta-analysis are in the same direction as Apter et al.2017 (11) in terms of high-user acceptability and satisfaction, and with a favorable body weight control. They showed a significant reduction in abdominal pain, acne, metrorrhagia, nausea, and scheduled bleeding after second, third and sixth menopausal cycles. Also, our study showed no significant difference with the use of E4/DRSP in breast pain, dysmenorrhea, headache, and anxiety which is coherent with the results reported by Douxfils et al 2020 (12) and Kelly et al.(13). Also, our results showed that E4/DRSP combination has some ability to reduce abdominal pain, acne, metrorrhagia, nausea, weight increase and incidence of treatment related adverse events, which is consistent with Guang-Sheng et al.(14).

Strength points and limitations

Our study has several strength points (1) we conducted all steps in strict accordance with the Cochrane Handbook of Systematic Reviews for interventions, (2) we followed the standard reporting guidelines of PRISMA statement to report this work, (3) we ran a comprehensive search of multiple electronic databases to identify all relevant studies. Nonetheless, our study has a few limitations. There are very limited RCTs with controversial conclusions examining the impact of E4/DRSP on different maternal and neonatal outcomes. We

recommend future well-designs RCTs to investigate this impact, address an unmet clinical need, and fill this evidence gap in the literature.

Conclusion

In conclusion, our meta-analysis showed that the use of E4/DRSP in combination was significant in all measured outcomes except for percentage of absence of scheduled bleeding after first menopausal cycle.

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Study ID	Study design	Combination details	Inclusion criteria	Primary outcomes	Results
Apter et al. 2016	Open-label, multicenter, randomized, trial	(1) 15 mg E4 plus 3 mg DRSP (15E4/DRSP), n=79 (2) 20 mg E4 plus 3 mg DRSP (20E4/DRSP), n=75	Healthy women aged 18–35 years with a body mass index between 18 and 30 kg/m2 and a regular menstrual cycle (24–35 days) were eligible for inclusion.	Vaginal bleeding patterns and cycle control.	This study showed that modalities investigated, combination has the mo pattern and cycle contro
Apter et al. 2017	Open-label, multicenter, randomized, trial	(1) 15 mg E4 plus 3 mg DRSP (15E4/DRSP), n=79 (2) 20 mg E4 plus 3 mg DRSP (20E4/DRSP), n=75	Healthy women aged 18–35 years with a body mass index between 18 and 30 kg/m2 and a regular menstrual cycle (24–35 days) were eligible for inclusion.	Satisfaction rate	This study showed tha combined with 3 m associated with high-us satisfaction and reaso control.
Creinin et al. 2021	Open-label, multicenter, trial	Each containing 24 E4 15 mg/DRSP 3 mg tablets and 4 placebo tablets, n=1864	Investigators enrolled heterosexually active women, aged 16 to 50 years inclusive with a body mass index (BMI) ≤35.0 kg/m2, a history of regular menstrual cycles (21–35 days) when not using hormonal contraception, and no use of medications or supplements that increase liver metabolism.	Vaginal bleeding patterns and cycle control.	E4/DRSP was an effecti with a predictable bleed adverse events rates for

Danielsson et al. 2021	Open-label, multicentre, trial	Each containing 24 E4 15 mg/DRSP 3 mg tablets and 4 placebo tablets, n=1553	Study sites enrolled healthy heterosexually active, premenopausal women (18–50 years) with a body mass index (BMI) ≤35.0 kg/m2, a history of regular menstrual cycles when not on hormonal treatment (21–35 days), and a negative serum pregnancy test before starting study treatment.	Vaginal bleeding patterns and cycle control.	E4/DRSP provided effe predictable bleeding pat safety profile.
Douxfils et al. 2020	Single-center, randomized, open-label, controlled, three-arm, parallel study	Each containing 24 E4 15 mg/DRSP 3 mg tablets and 4 placebo tablets, n=39	Healthy females aged 18–50 years with a body mass index between 18 and 30 kg/m2 and a natural menstrual cycle of a maximum of 35 days were eligible for inclusion.	Procoagulant factors	In this study, chan parameters after treatme were more minor o observed for EE/LNG pronounced changes v versus EE/DRSP, w hypothesis that the es mainly mediates the hemostasis parameters.
Duijkers et al. 2015	Single-center, open, parallel, phase II, dose-finding pilot study	(1) 5 mg E4 plus 3 mg DRSP (15E4/DRSP), n=17 (2) 10 mg E4 plus 3 mg DRSP (20E4/DRSP), n=19	The main inclusion criteria were as follows: age 18 to 35 years; ovulation in the pretreatment cycle between cycle day 9 (±1) and day 24 (±1), with a subsequent	Ovulation inhibition according to the Hoogland score	Combined with a prog suppressed ovarian a when given at a dosage

			progesterone concentration≥16 nmol/l and a Luteal phase duration of at least 6 (±1) days; body mass index (BMI) of 18 to 30 kg/m2.		
Duijkers et al. 2021	Single-center, randomized, open-label, parallel, phase 2 study	15 mg E4 plus 3 mg DRSP (15E4/DRSP), n=41	Healthy women aged 18 to 35 years with a body mass index (BMI) between 18.0 and 35.0 kg/m2 with menstrual cycles occurring every 21 to 35 days.	Ovarian function	E4 15 mg/DRSP 3 mg ovulation inhibition an suppression, comparab combined oral contra EE/DRSP.
klipping et al. 2021	Single-center, randomized, open-label, controlled, 3-arm, parallel, exploratory study	15 mg E4 plus 3 mg DRSP (15E4/DRSP), n=38	Participants included were healthy females aged 18 to 50 years with a body mass index between 18.0 and 30.0 kg/m2 and a natural menstrual cycle of a maximum of 35 days.	Endocrine parameters	E4/DRSP treatment ha endocrine and metabo effects on gonadotrop angiotensinogen, SHBG were less pronounced products.
kluft et al. 2016	Open-label, parallel, dose-finding, single-center	(1) 5 mg E4 plus 3 mg DRSP (15E4/DRSP), n=15 (2) 10 mg E4 plus 3 mg DRSP (20E4/DRSP), n=15	Healthy women 18-35 years of age with a body mass index (BMI) of 18-30 kg/m2 were eligible For inclusion. Subjects who were using a hormonal contraceptive at the time of	Coagulation markers	The reduction in c suggested an anticoa DRSP.

			screening had at least one washout cycle prior to the start of the study.		
Mawet et al. 2015	Open-label, dose-finding phase II study conducted at a single center	(1) 5 mg E4 plus 3 mg DRSP (15E4/DRSP), n=17 (2) 10 mg E4 plus 3 mg DRSP (20E4/DRSP), n=19	Healthy women aged 18 to 35 years with a BMI between 18 and 30 kg/m2 were eligible for inclusion in the study.	Liver function, lipid metabolism, and bone and growth endocrine parameters	E 4-containing combin function, lipid metabol growth endocrine param

Table1: Summary of included studies. Abbreviations: DRSP; drospirenone, LNG; levonorgestrel, E4; Estetrol, EE; ethinylestradiol, COCs; combined contraceptive pills, BMI; body mass index.

Study ID	Study arms	Sample	Age, M±SD	BMI, M±SD
Apter et al. 2016	15E4/DRSP	79	24.3±4.6	22.9±3
	20E4/DRSP	75	24±4.5	23.1±2.8
Apter et al. 2017	15E4/DRSP	79	24.3±4.6	22.9±3
	20E4/DRSP	75	24±4.5	23.1±2.8
Creinin et al. 2021	15E4/DRSP	1864	27.3±6.5	25.9±4.7
Danielsson et al. 2021	15E4/DRSP	1553	27.1±6.9	23±3.5
Douxfils et al. 2020		38	26.7±7	23.33±2.7
Duijkers et al. 2015	5E4/DRSP	19	24.3±3.11	22.54±2.33
	10E4/DRSP	19	23.7±3.67	23.2±3.21
Duijkers et al. 2021	15E4/DRSP	41	25.5±4.52	22.66±2.47
klipping et al. 2021	15E4/DRSP	38	26.7±7	23.33±2.7
kluft et al. 2016	5E4/DRSP	NR	NR	NR
	10E4/DRSP	NR	NR	NR
Mawet et al. 2015	5E4/DRSP	17	24.5±3.2	22.7±2.4
	10E4/DRSP	19	23.7±3.7	23.2±3.2

Table: Baseline of included studies. Abbreviations: DRSP; drospirenone, E4; Estetrol, BMI; body mass index, NR; not reported.