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Estetrol/Drospirenone safety in a population with cardiovascular risk factors★,☆,☆☆

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ABSTRACT

Objectives: To evaluate cardiovascular safety outcomes in estetrol 15 mg/drospirenone 3 mg users with cardiovascular risk factors.

Study design: We performed a secondary analysis of two open-label contraceptive phase-3 trials that enrolled participants 16 to 50 years to use estetrol/drospirenone for up to 13 cycles. Study exclusion criteria included > 35 years and smoking, body mass index > 35 kg/m^2, and baseline blood pressure (BP) > 140/90 mmHg. We compared adverse event rates in participants with and without cardiovascular risk factors and assessed discontinuation rates for cardiovascular adverse events.

Results: Of 3417 participants, 1410 (41.3%) had one or more, and 309 (9.0%) had two or more cardiovascular risk factors. We found no difference in discontinuation for any adverse events in participants with and without cardiovascular risk factors. Six (0.18%) participants discontinued for a cardiovascular complaint including four with risk factors: three (0.09%) due to hypertension (all had baseline BP ≥130/85 mmHg and one or more additional risk factors) and one due to venous thrombosis (BP ≥130/85 mmHg). Of 375 participants with baseline BP ≥130/85 mmHg, 0.8% (95% CI 0%–1.7%) discontinued for hypertension while among the 192 participants with baseline BP ≥130/85 mmHg and one or more additional cardiovascular risk factors, 1.6% (95% CI 0%–3.3%) discontinued for hypertension.

Conclusions: Among > 1400 study participants with cardiovascular risk factors using estetrol/drospirenone, only three (0.2%) discontinued for hypertension, all of whom had high-normal baseline BP and at least one other risk cardiovascular risk factor.

Implications: Estetrol/drospirenone use demonstrates excellent cardiovascular tolerance in study participants with normal and high-normal blood pressure, even in those with cardiovascular risk factors. The very low rate of hypertension, even when cardiovascular risk factors were present, provides evidence to warrant clinical trials of estetrol/drospirenone in patients with hypertension desiring contraception.

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☆ Conflicts of interest: MDC has received speaking honoraria from Gedeon Richter, Mayne, and Organon, has stock options with Femasys, and has consulted for Curai, Estetra SRL (including support for medical oversight of this trial), Medicines360, and Organon. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Chemo Research SL, Femasys, Medicines360, Merck, Sebela, and Sumitomo Pharma. JMF was a board member for Mithra, the company that initially developed the study product for contraception, and received financial support for the supervision of this study. KGD is ad hoc advisory board member and speaker for Organon (MSD), Bayer, Exelgyn, Actavis, Gedeon Richter, Mithra, Exeltis, Ferring, Natural Cycles, Azanta, Gynuity, Obseva MedinCell, Cirqle, Addeira and HRA-Pharma. She is a member of the ICCR, Population council and Director of a WHO collaborating center for research in Human Reproduction. She is an investigator of ongoing NICHD male contraception trial. NCF is an employee of Estetra SRL, a wholly owned subsidiary of Gedeon Richter PLC. AK has taken part in sponsored educational activity and served on advisory boards for pharmaceutical companies including Bayer, Merck and Exeltis. UG was a senior consultant at Mithra Pharmaceuticals, the company that initially developed the study product for contraception. JD is the director and founder of Qualiblood, a contract research organization that received funding from Mithra Pharmaceuticals and Fuji Pharma. He also reports personal fees from Daiichi Sankyo, Diagnostica Stago, Gedeon Richter, Portola, Roche, and Roche Diagnostics.

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1. Introduction

Since the initial regulatory approval of oral contraceptives in the 1960s, continued developments of the estrogen and progestogen components have improved tolerability and safety profiles while maintaining efficacy [1]. Most combined oral contraceptives (COCs) contain ethinyl estradiol (EE) as the estrogenic component. Over the last 60 years, EE dose has been significantly reduced, primarily to limit adverse events. Still, EE even at very low doses can cause serious cardiovascular complications, especially in patients with risk factors [2]. Because most COC users have low absolute cardiovascular risk, the benefits of EE-COC typically outweigh the associated risks [3].

Significant cardiovascular risk factors include hypertension, smoking, age > 35 years, high body mass index (BMI), and diabetes mellitus [4]. Hypertension is the leading global risk factor for cardiovascular disease and a neglected health burden in women [5]. When cardiovascular risk factors are present in patients desiring oral contraception, clinicians must carefully evaluate the risk-benefit ratio of EE-containing COCs [6].

Estetrol is a native estrogen recently introduced for clinical use with drospirenone as a COC. Estetrol has a molecular mode of action distinct from other estrogens with significantly less impact on the liver and metabolic and hemostasis parameters compared to EE/drospirenone or EE/levonorgestrel COCs [7]. Additionally, estetrol does not stimulate renal water retention through the renin-angiotensin-aldosterone system (RAAS), a potentially important differentiator for blood pressure (BP) impact and overall cardiovascular risk [8–10].

Because of these differences, we compared adverse event rates in participants with and without cardiovascular risk factors and assessed discontinuation rates for cardiovascular adverse events in the phase 3 estetrol/drospirenone clinical trials.

2. Materials and methods

We performed a secondary analysis of data from two parallel multicenter, open label, single arm, phase 3 clinical trials that assessed the contraceptive efficacy and safety of estetrol/drospirenone, one in Europe and Russia (EU/RU, NCT02817828) and one in the US and Canada (US/CAN, NCT02817841) [11,12]. Prior to enrollment, each investigational center obtained ethics approval and participants provided written informed consent.

The methods, including entry criteria and primary outcomes, have been previously reported [11–15]. Briefly, the trials enrolled healthy participants aged 18 to 50 years (EU/RU) or 16 to 50 years (US/CAN) to use estetrol 15 mg and drospirenone 3 mg for thirteen 28-day cycles. Pertinent to this secondary analysis, investigators excluded individuals with the following cardiovascular risk factors: smoking if ≥35 years old, BMI > 35.0 kg/m^2, hypertension (systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg), personal history of deep vein thrombosis or pulmonary embolism, current or planned prolonged immobilization, known or acquired thrombophilia or thrombogenic mutations, presence or history of arterial thromboembolism, complicated valvular heart disease, dyslipoproteinemia with current treatment, diabetes mellitus with vascular involvement or of more than 20-year duration, or use of BP or lipid-lowering medications. Investigators allowed participants with specific cardiovascular risk factors based on smoking (if < 35 years), age (> 35–50 years), BMI (≥30–35 kg/m^2), and BP (SBP ≥135 or DBP ≥85 mmHg) to participate [4].

Table 1
Participant cardiovascular risk factors at enrollment in phase 3 clinical trials with estetrol/drospirenone

Characteristic	Pooled trials (n = 3417)	EU/RU trial (n = 1553)	US/CAN trial (n = 1864)	p-value[a]
Age, years				
≤35	3027 (88.6)	1353 (87.1)	1674 (89.8)	0.02
> 35–50	390 (11.4)	200 (12.9)	190 (10.2)	
Body mass index, kg/m^2	24.6 ± 4.4	23.0 ± 3.5	25.9 ± 4.7	< 0.0001
< 30	2896 (84.8)	1464 (94.3)	1432 (76.8)	< 0.0001
30–35	521 (15.3)	89 (5.7)	432 (23.2)	
Blood pressure				
Normal[b]	3042 (89.0)	1354 (87.2)	1688 (90.6)	0.002
High-normal[c]	375 (11.0)	199 (12.8)	176 (9.4)	
Smoking (tobacco)[d]	468 (13.7)	246 (15.8)	222 (11.9)	< 0.0001
Cardiovascular risk factors[e]				
None	2007 (58.7)	937 (60.3)	1070 (57.4)	0.09
One	1101 (32.2)	509 (32.8)	592 (31.8)	0.53
Two	274 (8.0)	96 (6.2)	178 (9.6)	< 0.001
Three	35 (1.0)	11 (0.7)	24 (1.3)	0.12

CAN, Canada; EU, Europe; RU, Russia; US, United States.
Data presented as n (%) or mean ± standard deviation.
[a] Comparing EU/RU and US/CAN trial participants using Fisher exact tests.
[b] Systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg.
[c] Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg.
[d] Participants could not enroll if ≥35 years old and currently smoking.
[e] Risk factors: smoking (current smoker), age (> 35 years), body mass index (≥30 kg/m^2), and blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg); smoking with age > 35 years, SBP > 140 mmHg, or DBP > 90 mmHg were exclusionary.

Participants received pill packets with 28 tablets containing hormones for 24 days and a placebo for four days with instructions to take one pill daily. Follow-up visits occurred during cycles 2, 4, 7, and 10, and within three weeks of completing cycle 13. Visits included BP measurements, blood sampling for lipid profile assessment at a central laboratory, and reporting of adverse events. Research staff assessed BP as per their local clinic standard.

For this secondary analysis, we included all participants with at least one follow-up evaluation with a BP, lipid parameter or adverse event outcome. We evaluated participants for specific cardiovascular risk factors at enrollment (smoking, age > 35 years, BMI > 30 kg/m^2, SBP ≥130 mmHg, or DBP ≥85 mmHg) and compared adverse events during the trial leading to discontinuation in > 0.25% of all participants in those with and without cardiovascular risk factors and assessed discontinuation rates for cardiovascular adverse events. We performed Fisher exact tests using SAS version 9.4 (Cary, NC) with a $p \leq 0.05$ considered significant.

3. Results

A total of 3417 participants received study treatment in the phase 3 trials, 1553 in the EU/RU trial and 1864 in the US/CAN trial. Participant cardiovascular risk factors are presented in Table 1; 1410 (41.3%) had one or more cardiovascular risk factors. Participants reported similar prevalence of cardiovascular risk factors in the two trials, except for BMI ≥30 kg/m^2 which was lower in the EU/RU (5.7%) than the US/CAN (23.2%) trial, $p < 0.0001$. Participants in the EU/RU trial were less likely to have two or more risk factors (n = 107 [6.9%]) than the US/CAN trial (n = 202 [10.8%]), $p < 0.0001$. Overall, the EoT assessment occurred in 793 (23.2%) at six or fewer cycles and 2624 (76.8%) at seven to 13 cycles in the full study population.

Overall, 336 participants (9.8%) had one or more adverse events leading to discontinuation, with 253 (7.4%) occurring at a rate of

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Table 2
TEAEs leading to discontinuation[a] without and with one or more cardiovascular risk factors[b] in phase 3 clinical trials with estetrol/drospirenone

TEAE	All participants (N = 3417)	No risk factors (n = 2007)	One risk factor (n = 1101)	Two risk factors (n = 274)	Three risk factors (n = 35)	p-value[c]
Menstrual flow complaints[d]	100 (2.92)	57 (2.84)	38 (3.45)	3 (1.09)	2 (5.71)	0.76
Acne	31 (0.91)	20 (1.00)	11 (1.00)	0	0	0.59
Mood altered or swings[e]	28 (0.82)	18 (0.90)	7 (0.64)	3 (1.09)	0	0.70
Loss or decrease of libido	21 (0.61)	12 (0.59)	7 (0.64)	2 (0.73)	0	1.00
Weight increased	15 (0.44)	6 (0.30)	5 (0.45)	4 (1.46)	0	0.19
Headache	13 (0.38)	9 (0.45)	4 (0.36)	0	0	0.58
Depression[f]	12 (0.35)	8 (0.40)	3 (0.27)	1 (0.36)	0	0.77
Breast complaints[g]	12 (0.35)	9 (0.44)	3 (0.27)	0	0	0.38
Migraine[h]	11 (0.32)	6 (0.30)	4 (0.36)	1 (0.36)	0	0.77
Anxiety or Panic Disorder[i]	10 (0.29)	5 (0.25)	5 (0.45)	0	0	0.75

TEAEs, treatment emergent adverse events.
Results presented as n (%).
[a] Includes TEAEs with discontinuation in > 0.25 % of all participants.
[b] Risk factors: smoking (current smoker), age (> 35 years), body mass index (> 30 kg/m^2), and blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg); smoking with age > 35 years, SBP > 140 mmHg, or DBP > 90 mmHg were exclusionary.
[c] Fisher exact test comparing participants with no risk factors and those with any risk factors.
[d] Includes preferred terms of menorrhagia, uterine hemorrhage, vaginal hemorrhage, menometrorrhagia, metrorrhagia, oligomenorrhea, menstruation irregular.
[e] Includes preferred terms of affect lability, mood altered, mood swings.
[f] Includes preferred terms of depression, depressed mood.
[g] Includes preferred terms of breast discomfort, enlargement, mass, pain, swelling, tenderness.
[h] Includes preferred terms of migraine, migraine with aura, migraine without aura.
[i] Includes preferred terms of anxiety, panic disorder, nervousness.

0.25% or greater for the overall population (Table 2). We found no difference in the incidences of any discontinuation reasons in participants without and with cardiovascular risk factors.

Six (0.18%) participants discontinued for a cardiovascular event including 2/2007 (0.10%) without and 4/1410 (0.30%) with cardiovascular risk factors, p = 0.24. The two participants without risk factors discontinued for vasculitis (occurred cycle 5) or palpitations (occurred cycle 8). One participant with one cardiovascular risk factor (BP 134/80 mmHg) discontinued after experiencing a lower leg venous thrombosis (occurred cycle 2). Three (0.09%) participants discontinued for hypertension, one participant with two baseline risk factors (BP 133/88 mmHg, and BMI 33.8 kg/m^2, occurred cycle 2) who had a discontinuation BP of 142/95, and two participants with three risk factors (BP 135/86 mmHg, BMI 33.9 kg/m^2 and smoker, occurred cycle 7; BP 104/88 mmHg, BMI 32.9 kg/m^2, and age 47 years, occurred cycle 3) who had discontinuation BPs of 130/90 and 136/104, respectively. The discontinuation rate for hypertension among the 375 participants with high-normal BP at baseline was 0.8% (95% CI 0%–1.7%) and among the 192 participants with high-normal BP at baseline and at least one additional cardiovascular risk factor was 1.6% (95% CI 0%–3.3%).

4. Discussion

Only three (0.09% of total population [N = 3417] and 0.2% of those with cardiovascular risk factors [n = 1410]) participants using estetrol/drospirenone developed for hypertension, all of whom had high-normal baseline BP and at least one other risk cardiovascular risk factor. Among the subgroup of participants with high-normal BP and at least one other risk cardiovascular risk factor, 1.6% discontinued for hypertension suggesting that this subgroup may warrant closer monitoring for BP changes with estetrol/drospirenone use, although most users will still not develop hypertension. Importantly, the likelihood of a patient with normal BP at baseline developing hypertension is relatively negligible. Similar analyses are needed for other COC products.

In the estetrol/drospirenone phase 3 trials, > 40% of participants had one or more cardiovascular risk factors, such as smoking (13.7%), age between 36 and 50 years (11.4%), BMI between 30 and 35 kg/m^2 (15.3%), and SBP ≥135 mmHg and/or DBP ≥85 mmHg (11.0%). In the US/CAN trial, more than 10% had 2 or more cardiovascular risk factors. This relatively high rate of participants with these risk factors occurred despite exclusion criteria were used that are consistent with the contraindications established by the World Health Organization and U.S. Centers for Disease Control and Prevention for EE- and estradiol-containing COCs [16,17], demonstrating that COC users today are not all “healthy” users.

Estrogens can activate the RAAS [18,19] by enhancing liver production of angiotensinogen, the substrate of renin [20,21]. The dose and type of estrogen impacts the extent of RAAS upregulation [8,22]. Even low EE doses and high estrogen levels during pregnancy stimulate angiotensinogen production, leading to elevated angiotensin II and aldosterone levels, causing salt and water retention. The subsequent vasoconstriction combined with water and salt retention may lead to extracellular volume expansion and slight increases in weight and BP [23], and a higher risk of acute cardiovascular complications [24]. Progesterone and drospirenone have high mineralocorticoid receptor affinity and are aldosterone antagonists. All other synthetic progestogens are devoid of substantial antimineralocorticoid effect and are unable to antagonize the salt-retaining effect of classical estrogens [23].

In a 10-year surveillance study with 59,150 participants, users of EE/drospirenone less frequently developed hypertension compared to EE/levonorgestrel users [25]. While two small studies from 1995 and 2009 (n = 20–72) with healthy EE/drospirenone users demonstrated a modest BP decrease of 1 to 6 mmHg with EE/drospirenone use for 6 to 12 months [26,27], multiple studies since 2010 have failed to show any significant benefit, including in healthy participants and those, with hypertension on antihypertensives or with polycystic ovarian syndrome [28–33]. No studies with EE/drospirenone have specifically evaluated patients with high-normal BP. The phase 2 trials with estetrol/drospirenone showed that this combination causes lower increase in angiotensinogen (+75%) than the EE/levonorgestrel (+170%) or EE/drospirenone (+207%) [2].

Research staff assessed BP per local clinic routine. Although these assessments lacked standardization seen in studies that focus on BP outcomes [4], the findings likely reflect common practice and provide high generalizability. Still, a significant limitation of this study is that all baseline BP evaluations are based on a single interaction and not multiple measurements to validate the values. We do not know if the three participants diagnosed with hypertension during the trials had multiple readings to confirm the diagnosis. Other limitations include that all cardiovascular risk factors are not accounted for, such as family history of hypertension and personal history of

hypertensive disorders in pregnancy. Although the studies included obese participants, the upper limit of BMI was 35 kg/m^2, so the findings may not be generalizable to patients with higher BMI.

In summary, these results show the excellent cardiovascular tolerance of estetrol/drospirenone in study participants with normal and high-normal BP, even in the presence of one or two cardiovascular risk factors. Currently, the Contraceptive Medical Eligibility Criteria and World Health Organization and U.S. Centers for Disease Control and Prevention Contraceptive Medical Eligibility Criteria both consider hypertension a condition for which the risks usually outweigh advantages of combined hormonal contraceptive use [16,17]. Although these study results do not prove overall safety for patients with hypertension, the very low rate of hypertension even in participants with baseline high-normal BP plus an additional cardiovascular risk factor provides the evidence needed to warrant estetrol/drospirenone trials in patients with hypertension to evaluate true clinical outcomes.

Author contributions

J.D.: writing – review & editing. N.C.F.: writing – review & editing, project administration, methodology, formal analysis, data curation. A.K.: writing – review & editing, investigation. J.M.F: writing – review & editing, writing – original draft, supervision, investigation, formal analysis, conceptualization. K.G.-D.: writing – review & editing, data curation. M.D.C.: writing – review & editing, writing – original draft, supervision, methodology, formal analysis, conceptualization. U.G.: writing – review & editing, project administration.

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