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DRUG EVALUATION

Drospirenone and estetrol: evaluation of a newly approved novel oral contraceptive

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ABSTRACT

Introduction: Estetrol (E4) is a native estrogen produced only by the fetal liver during pregnancy. E4 is the first new estrogen to be used in hormonal contraception since the introduction of oral contraceptives in 1960. Ethinyl estradiol, the most commonly used estrogen in oral contraceptives today, increases the risks of thromboembolism and has other significant hepatic impacts, which induce important drug–drug interactions. On the other hand, Phase 2 E4 characterization studies demonstrated that E4 has negligible impacts on liver, breast, and vascular endothelium due to its distinct tissue selectivity. Combined with drospirenone (DRSP), E4 offers an improved safety profile for oral contraception.

Areas covered: This paper briefly highlights the unique pharmacokinetic and pharmacodynamic features of E4. The efficacy, safety, and tolerability results from the Phase 2 and 3 studies of the E4/DRSP pill are discussed to provide the reader with a thorough understanding of E4 and information to use when counseling potential users.

Expert opinion: The estetrol/drospirenone oral contraceptive is effective and well tolerated and provides good cycle control. In the future, estetrol may be the estrogen of choice if subsequent evidence verifies that it reduces the risks associated with current estrogens, such as venous thromboembolism and drug–drug interactions.

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1. Introduction

The current rate of high unintended pregnancy in the United States is alarming, especially as rates of maternal mortality and severe maternal morbidity are rising and access to pregnancy termination is being reduced [1,2]. Combined oral contraceptives (COCs) are often discontinued or used inconsistently, due, in part, to concerns about their health risks and side effects [3–5]. A new oral contraceptive with estetrol (Box 1) (E4) and drospirenone (DRSP) may be able to reduce those risks while maintaining efficacy [6,7].

2. Overview of the market

In the US, there are over 90 combined oral contraceptives (COCs), 3 transdermal contraceptive patches, and 3 vaginal contraceptive rings.

The hormonal composition of pills has evolved over time to reduce risks and side effects. Progestins provide most of the contraceptive activity; estrogen provides endometrial stability for cycle control and offsets progestin-induced estrogen deficiencies [8,9]. Ethinyl estradiol (EE) is the estrogen used in almost 99% of all modern COCs because it is highly resistant to hepatic metabolism and is able to support the endometrium with once-daily administration. However, EE greatly increases the hepatic synthesis of proteins affecting coagulation, fibrinolysis, and hypertension, which raises the risks of venous thromboembolism (VTE), myocardial infarction, and stroke [10,11]. Doses of EE have been reduced over time to decrease these risks. Progestins contribute to thrombosis only indirectly through their impacts on estrogen stimulation of hepatic protein synthesis [4,12,13]. Traditionally, large clinical trials have been needed to study VTE risk as it is a relatively infrequent event. Some progress has been made by utilizing a weaker estrogen. In one clinical trial an oral contraceptive with the native estrogen (estradiol (E2)) showed lower VTE rates than any of the EE-containing formulations, except for those with LNG [14,15]. Estrogens also induce melasma, breast proliferation, hypertension and drug-drug interactions especially those mediated through the cytochrome P450 activity. These observations underscore the need for improvement in estrogens for oral contraception and the potential that more selective native estrogens may have to meet that need.

3. Introduction of product

This new oral contraceptive with estetrol and drospirenone (Nextstellis®) is approved in the United States. It is also marketed as Dovelis®, Lydisilka® and with other names in the European Union, Canada, and Australia. It has 24 active pills, each containing 14.2 mg of anhydrous estetrol (15 mg monohydrate) and 3 mg of drospirenone, followed by four placebo tablets [16,17].

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Article highlights

- Estetrol (E4), the first new estrogen for contraception since the introduction of the pill in 1960, is a unique, native, long-acting, tissue-selective estrogen with desirable metabolic impacts.
- Combined with drospirenone, the contraceptive efficacy of E4 is good, with total PI in The North American study sites of 2.65 pregnancies/100 woman-years, rates that are not increased in women with higher BMIs.
- E4 has negligible hepatic impacts and does not interact with cytochrome P450 enzymes, so drug–drug interactions are minimized. DRSP does have slight hepatic effects and does rely on cytochrome P450 enzymes for clearance.
- E4/DRSP pills provide reliable cycle control, favorable bleeding patterns, and high user satisfaction supported by the low discontinuation rates (9.1%) seen in the clinical trials for treatment-related adverse events and by the high satisfaction scores on survey.

Box 1. Drug Summary Box.

Drug Name: Estetrol/Drospirenone
Indication: Oral contraception
Posology and route of administration: Recommended dosage is one oral tablet taken once daily in 28-day cycles at the same time every day.

Dosage: Each cycle consists of 24 active tablets, containing 14.2 mg E4 (equivalent to 15 mg estetrol monohydrate) and 3 mg DRSP, and 4 inert (placebo) tablets.
Mechanism of action:
It prevents pregnancy primarily by suppressing ovulation, and thickening cervical mucus.
Pivotal Trials:

- Creinin MD, Westhoff CL, Bouchard C, et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. Contraception. 2021;104(3):222–228.
- Gemzell-Danielsson K, Apter D, Zatik J, et al. Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022;129(1):63–71.
- Jensen JT, Kaunitz AM, Achilles SL, et al. Pooled efficacy results of estetrol/drospirenone combined oral contraception phase 3 trials. Contraception. 2022;116:37–43.

4. Introduction of compounds

4.1. Estetrol

Estetrol (E4) is a natural estrogen such as estrone (E1), estradiol (E2), and estriol (E3) and is distinguished by having a fourth hydroxyl group at position 15-α (Figure 1). It is synthesized from E2 and E3 in vivo by the fetal liver starting at 9 weeks gestational age [18,19]. Its physiologic role is not clear, but E4 is abundant in both the fetal and maternal compartments. At term, maternal levels reach concentrations of 1.2 ng/mL and fetal levels are 12 to 19 times higher; E4 disappears entirely after delivery [12,20,21]. For this pill, E4 is synthesized from commercially available soy estrone with 99.9% purity [22,23].

4.2. Drospirenone

Drospirenone (DRSP) is an analog of spironolactone with both anti-mineralocorticoid and antiandrogenic activities, which increase the contraindications to the pill's use (i.e. adrenal insufficiency, renal failure, and chronic use of drugs predisposing to hyperkalemia) but add clinical applications [24,25]. Drospirenone is currently used in three other pill formulations. The 3 mg dose of DRSP is metabolically equivalent to 25 mg spironolactone.

5. Chemistry of the compounds

The chemical structures of estetrol and drospirenone, as portrayed in the product labeling, are displayed in Figure 1 [24].

6. Pharmacodynamics

The product labeling for E4/DRSP reports the pharmacodynamic effects of 'combined hormonal contraceptives' and emphasizes that the estrogen-related contraindications and warnings it cites for this formulation are the same as for EE-containing pills [24].

However, the estetrol is significantly different from EE [12,21]. E4 has high bioavailability (90%) and long half-life (28 h), but it has weak affinity for estrogen receptors (ERs). E4's potency is 100-fold lower than E2, which accounts for its milligram (not micrograms) dosing [17,19]. E4 has low impacts on breast tissue; similarly E4 has neglibile effects on hepatic functions reflected in hemostatic biomarkers, glucose levels, lipids, and the renin-angiotensin-aldosterone system [23,26,27]. E4 has only minor effects on CYP450 enzymes, which minimizes drug–drug interactions [28–31]. The metabolites of E4 have little or no estrogenic activity [31]. Biomarkers for bone resorption (C-telopeptide) and bone formation (osteocalcin) are lower with the use of E4 in a dose-related fashion [29,32]. E4 has weak interactions with glucocorticoids, progesterone, and testosterone receptors [28].

All other native and synthetic estrogens are known to bind to and act as agonists at all estrogen receptors (all alpha and beta receptors) [9,20,33]. Estetrol has a very low binding affinity to any estrogen receptors (ERs). Contrary to other estrogens, selective estrogen receptor modulators (SERMS) and antiestrogens, E4 has a higher binding to ERα than to ERβ, and its binding to ERα is selective; it has different effects on the ERα membrane receptor than on the ERα nuclear membrane [28]. Estetrol is an agonist to ERα nuclear receptors, which are predominantly found on endometrial cells, vaginal epithelium, and osteoclasts [34]. However, at doses found in this oral contraceptive, E4 is devoid of membrane ERα activity. E4 is antagonistic to -E2 induced stimulation of membrane ERα, especially in breast and hepatic tissues [20]. In fact, estetrol blocks the estradiol-induced proliferation of both normal and malignant breast cells [26]. Both the United States Food and Drug Administration (FDA) and the European Medication Agency (EMA) have recognized that although E4 has receptor selectivity, it is not a selective estrogen receptor modulator (SERM) but is a New Active Substance (NAS) [20,33,35,36].

Favorable hemostatic effects were reported in two Phase 2 dose-finding comparative studies of low-dose

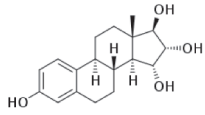
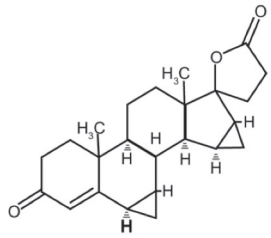
	Estetrol	Drospirenone
Chemical structure	15-hydroxyethryol or estra-1,3,5(10)-trien-3, 15-16,17-tethrol 	(6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)–1,3',4',6,6a,7,8,9,10,11,12,13/4,15,15a, 16-hexadecohydro10-13-dimethylspiro-[17H-dicyclopropa-[6,7:15,16]cyclopenta [a]phenathrene-17,2'(5H)-furan]-3,5',(2H)-dione) 
Molecular formula	$C_{18}H_{24}O_4H_20$	C24H30O3
Molecular weight	322.4 g/mol or 304.4g/ mol anhydrous	366.5 g/mol

Figure 1. Chemistry of the compounds.

E4/DRSP pills [30,37,38]. In those trials, E4/DRSP pills with current doses were compared to EE/DRSP pills. E4/DRSP users had significantly smaller changes from baseline in all the parameters of procoagulation, anticoagulation, and fibrinolysis than did EE/DRSP users. The EPT-based activated protein C (APC) resistance, which has been used as a functional test of thrombogenicity of COCs, increased 30% with E4/DRSP compared to a 165% increase seen with EE/LNG and a 219% increase with EE/DRSP ($p < 0.05$) [37]. In another trial comparing the thrombograms (which measure the synergistic hemostatic changes induced by pills) of E4 and EE-containing pills, only E4/DRSP had mean thrombogram within the reference interval. This strongly suggests that E4/DRSP has more neutral impacts on hemostasis [38,39].

In the pooled analysis of the Phase 3 clinical trials, E4/DRSP showed no clinically significant mean changes from baseline values of fasting glucose, glycated hemoglobin (HbA1C), or lipids [17,40]. The impact of E4 was studied in a six-month trial comparing E4/DRSP to EE/DRSP pills; triglycerides increased only 24% with E4/DRSP compared to a 65.3% increase seen with EE/DRSP. Increases in angiotensinogen, cortisol-binding globulin, and thyroxin-binding globulin were also significantly lower for E4/DRSP [41].

7. Pharmacokinetics

7.1. Estetrol

E4 is rapidly absorbed orally; median Tmax is 0.5 h with a range of 0.5 to 2 h followed by a rapid distribution. When taken with a high-fat meal, the Cmax for E4 is reduced, but its total absorption, is not [24,31]. Oral bioavailability of E4 is 90% [42]. E4 does not bind to sex hormone-binding globulin (SHBG) or increase its production by human HepG2 cells; this is a unique characteristic of E4 compared to other estrogens [43]. Moderate binding to plasma proteins is observed within the 46–50% range [24,43]. E4 is an end-stage product of estrogen metabolism so, in contrast to other estrogens, it is not converted into other active metabolites, such as E1, E2, or E3. Instead, E4 undergoes extensive Phase 2 UGT metabolism to form glucuronide conjugates that are devoid of estrogenic activity [18]. The elimination half-life of E4 is 27 h (24–32), which exceeds that of natural estrogens and is comparable to EE. The E4 is excreted 69% in the urine as a ring D monoglyceride and 22% in the feces unaltered [24].

7.2. Drospirenone

The median time to Cmax of DRSP is 1.0 h. When taken with a high-fat meal, Cmax is reduced to 75%, but the area-under-the-curve is unchanged. In plasma, DRSP is 95–97% bound to protein (primarily albumin). The half-life of DRSP is 34 h. DRSP is metabolized by cytochrome P4503A4. Drospirenone is excreted 38% into urine and 44% into feces [24,31].

8. Clinical efficacy

8.1. Phase 2 studies

An early Phase 2 trial demonstrated that doses as low as 5 and 10 mg of E4 in combination with DRSP 3 mg could efficiently suppress ovulation from the first treatment cycle in all subjects; ovulation returned approximately 17 days after the last treatment day [24,44]. A follow-up Phase 2 dose-finding study

showed that the combination of 15 mg E4 with 3 mg DRSP was most effective in terms of bleeding patterns and cycle control and was chosen as the formulation for Phase 3 clinical trials [45].

8.2. Phase 3 clinical trials for E4 15 mg/DRSP 3 mg

Two prospective, multicenter, open-label, single-arm, Phase 3 studies evaluated the efficacy of this formulation. The North American study involved 70 sites in the US and 7 in Canada. The European/Russia study had 69 sites [16,17].

The subjects were healthy, heterosexually active women, aged 16–50 years, with regular spontaneous menstrual cycles and body mass index ≤35 kg/m^2. The World Health Organization's (WHO) Category 3 or 4 conditions for COC use were exclusionary, as were medications or supplements that increase hepatic metabolism. The demographic features of each study population are displayed in Table 1.

The primary efficacy outcome was the 13-cycle Pearl Index (PI) for subjects ≤35 years of age. All pregnancies conceived within 7 days of the last pill intake were included. Only at-risk cycles were counted; cycles without coitus or with any use of any other contraceptive were excluded. Secondary efficacy endpoints were the method failure PI and Kaplan-Meyer life table analyses for total and method failures with 95% confidence intervals (CIs).

The North American efficacy study, which was used for the FDA approval, included 1674 women (12,763 at-risk cycles). Based on 26 in-treatment pregnancies, the Pearl Index (PI) was 2.65 pregnancies per 100 woman-years (95% CI 1.73–3.88) [17]. The total pooled PI for all study sites, which reflects the pregnancies seen in 2,837 women (26,455 cycles) was 1.52 pregnancies per 100 woman-years (95% CI 1.04–2.16) [40,46]. See Table 2. Factors associated with lower efficacy are shown in Table 3 [40,46]. Importantly, a multivariable analysis of the pooled population did not find any association between BMI >30 kg/m^2 and efficacy of E4/DRSP [46]. A secondary analysis of adherence and pregnancy rates found that PIs were low (1%) when women missed no pills or followed instructions when they did miss pills [47].

Table 1. Demographic variables of study populations in the North American, the EU/Russian study sites, and the Pooled analysis.

	Study Sites					
	North American[1]		EU/Russia[2]		Pooled Analysis[3]	
Age at enrollment (years)	16–35	36–50	18–35	36–50	16–35	36–50
Number enrolled	1674	190	1353	200	3027	390
Mean age (years)	25.8	40.6	25.5	41.3	25.4	41.4
Mean BMI (kg/m^2)	25.8	27.0	22.9	23.7	24.5	25.3
% >30	22.5	29.5	5.5	7.0	14.9	18.0
% Caucasian	70.1	66.3	98.6	98.6	82.8	82.9
% Black/African American	19.5	22.6	0.6	0.5	11.0	11.3
% nulligravid	58.7	13.7	74.0	8.5	64.7	11.0
% current smoker	13.3	0	18.2	0	15.5	0
% never smoked	75.4	83.2	77.8	91.5	76.5	87.4

Table 2. Primary and secondary pregnancy rates for efficacy Populations.

Number of At-Risk Cycles	North American[1] 12,763	EU/Russian[2] 13,692	Pooled[3] 26,455
Total pregnancy PI (95% CI)	2.65 (95% CI 1.73–3.88)	0.47 (0.15–1.11)	1.52 (1.04–2.16)
Method failure PI (95% CI)	1.43 (95% CI 0.78–2.39)	0.29 (0.06–0.83)	.84 (.49–1.34)
*Cumulative 13-cycle failure (95% CI)	2.06 (95% CI 1.40–3.04)	0.45 (0.19–1.09)	1.28 (.83–1.73)
*Cumulative method 13-cycle failure (95% CI)	1.18 (95% CI 0.69–2.01)	0.28 (0.09–0.86)	.73 (.38–1.08)

Table 3. Risk factors for higher failure rates.

Risk Factor	Groups Compared	Hazard Ratios (95% CI) North American	Hazard Ratios (95% CI) Pooled Studies
Younger age (years)	16–25 vs. 26–35	2.41 (1.05–5.54)	2.37 (1.09–5.15)
Race	Black vs. White	3.41 (1.32–7.45)	4.61 (1.97–1.80)
Parity	$P \geq 1$ vs. $P = 0$	4.15 (1.65–10.46)	3.61 (1.56–8.38)
Compliance	<99% vs. ≥99%	3.17 (1.45–6.93)	4.21 (2.04–8.66)

9. Safety and tolerability

9.1. Bleeding patterns

Bleeding patterns strongly influence pill continuation. In the Phase 3 studies, abnormal *bleeding* was defined as any bleeding needing sanitary protection; *spotting* did not. The bleeding patterns from those trials are displayed on Table 4. Overall, bleeding was predictable; 87.2–90.4% of women had scheduled bleeding/spotting events each cycle. Amenorrhea was more frequent with higher BMIs [16,45,48].

9.2. Safety

Study-drug-related adverse events (AEs) were reported by 28.9% of participants in the North American study [17]. The most frequent study-related adverse events were metrorrhagia (4.4%) and headache (3.5%). The mean increase in BMI at study completion was 0.4 ± 1.7 kg/m^2 [17] Pooled treatment-related adverse events from all sites in the Phase 3 trials are displayed on Table 5. Over 93% of AEs were rated by the participants as mild to moderate in severity. Hyperkalemia or increased potassium levels were seen in seven women; five of them were determined to be treatment-related, but only one subject discontinued study medication [40]. There were three treatment-related serious adverse events (SAEs), including worsening depression (no drug discontinuation), ectopic pregnancy, and lower extremity VTE. One death, which was determined not to be related to the study drug, occurred from a prescription drug overdose. Based on the one VTE event that occurred in 3,417 participants, the VTE annual incidence from the pooled analysis of Phase 2 and 3 trials was 3.66/10,000 women-years, which is within the range of VTE rates seen in nonpregnant women using no hormonal contraception [40].

9.3. Tolerability and satisfaction

In the North American study, 54.5% of all participants and 53.7% of the primary efficacy population completed 13 cycles; 10.1% of the subjects were discontinued due to treatment-related adverse events [17]. In a pooled analysis of all study sites, 64.5% of the subjects completed 13 cycles, and 9.9% discontinued prematurely due to treatment-related AEs (Table 5). Subject Satisfaction and Health-Related questionnaires were administered in the comparative Phase 2 trials. E4 15 mg/DRSP 3 mg scored better in the 'general feeling,' 'mood,' 'sexual life,' and 'overall effect' domains. Rates of satisfaction and predictions of future product use were also highest among E4/DRSP users [49].

10. Expert opinion

The new monophasic E4 15 mg/DRSP 3 mg oral contraceptive pill has demonstrated efficacy, good cycle control, safety, tolerability, and rapid return to fertility [40,46]. In the North American trials, the PI was 2.65 pregnancies/100 women-years [17]. This PI is comparable to other new hormonal contraceptive methods. All new contraceptive methods have generally had higher PIs than older formulations because of new Phase 3 study requirements (allowing only at-risk cycles in the denominator) and the availability of more sensitive and available pregnancy tests that raise the numerator. This so-called 'Creeping Pearl Index' phenomenon has been validated by the observation that pills approved in the 1980s with PIs of less than 1 pregnancy/100 woman-years have more recently had PIs greater than 3 pregnancies/100 woman-years when used in comparative clinical trials [50].

Table 4. Bleeding patterns.

	North American Sites	EU/Russian Sites	Pooled Analysis
Number of Women	1864	1553	3409
Scheduled bleeding			
% each cycle	82–87%	91.9–94.5%	87.2–9.4%
Median duration	4–5 days	4–5 days	4–5 days
Days spotting	2	2	
Unscheduled episodes			
Cycle 1	30.1%	23.5%	27.1%
Cycles 2–4	22.0%		2.6%
Cycles 5+	15–20%	16.0%	≤17.5%
Duration of episodes (median)	4 days	3	3–4
% spotting only	55.0%	<71.8%	66.5%
Discontinuation due to bleeding	2.5%	<3%	3%

Table 5. Prevalence of treatment-related adverse events and related premature discontinuation rates from Pooled analysis ($n = 3417$ participants).

Treatment-Related Adverse Events	% Participants Reporting	% Participants Discontinuing
Any bleeding abnormality	9.5	3.7
Acne	3.3	1.6
Dysmenorrhea	2.5	1.0
Weight gain	2.2	1.4
Low libido	<1	0.9
Mood disorder	3.2	1.2
Breast tenderness	4.0	1.6
Headache	3.2	1.1
VTE	0	0.0002

Estetrol is unique among all natural and synthetic estrogens. E4 has the longest half-life of all the native estrogens. E4 has selective tissue binding. It is agonistic on nuclear ERαs, which results in beneficial impacts on the endometrium, vagina, and bone. However, it is antagonistic on membrane ERαs, found predominantly in the breast and liver [51]. E4 blocks E2-stimulated proliferation of both benign and malignant breast tissue. E4 has negligible impacts on liver function. Changes in glucose metabolism, binding proteins, and lipids are minimal. There are few E4-induced drug–drug interactions. Importantly, E4/DRSP has exhibited reduced hemostatic effects. This is most profoundly demonstrated by the minimal effect it has on the most accurate biomarker of oral contraceptive-induced thrombosis (acquired resistance to APC) [37,38]. If regulatory authorities accept the recommendation from the International Society on Thrombosis and Haemostasis to use that test as an accurate predictor of thrombosis, the requirements for large-scale post-marketing studies to investigate VTE risk may be reduced. If not, large-scale Phase 4 trials will be needed to determine if E4/DRSP has the minimal effect on VTE/ATE risks seen in the clinical studies to date. If these trials also find that E4 is associated with low VTE rates similar to those seen in nonpregnant women not using estrogen-containing contraception, E4 may well be the preferred estrogen in future formulations and may reinvigorate interest in oral contraceptive use [52].

Tissue selectivity involving breast proliferation will be appealing to both users and prescribers. COCs with ethinyl estradiol have been associated with a small reversible increased risk of breast cancer (similar in magnitude to the risk posed by pregnancy). E4 may be able to remove the concerns women harbor for even that small an increase [22,26]. This may well enhance acceptance of consistent utilization of oral contraceptives.

The bone-sparing properties of E4 may also make this a preferred formulation for adolescents who are accruing bone mineral density.

Creinin et al. have demonstrated how important the correct use of pills – either daily utilization or daily intake of pills or adherence to practices to correct for missed pills – is to maintaining low failure rates with E4/DRSP [47]. This emphasizes the need to ensure that users completely understand what to do when they forget doses. It also emphasizes the need to reduce barriers to women's acquisition of adequate supplies of oral contraception. Legislation in many states enables women to be dispensed 13 cycles of pills at once to minimize pill discontinuation, unintended pregnancies, and abortion rates [53]. Prescribers should routinely write for 13 cycles to be dispensed at once and let the patient decide how many packs she wants to take with her [54].

There are many forces at play that may slow the rapid uptake of this potentially safer pill, especially in the United States. Many third-party payors currently only cover the costs of generic formulations. However, the federal government has drafted guidance clarifying their interpretation of the provisions of the Affordable Care Act to say that insurers must cover the total costs of all contraceptive options – branded or generic.

If there is a requirement for large-scale post-marketing clinical trials to investigate the claim of lower VTE rates, it will take years of study (not to mention millions of dollars). This delay will dampen the enthusiasm for the product in the near term and may not translate into increased use when the final results are announced.

In the meantime, the cycle control offered by E4/DRSP makes it a candidate for extended cycle use. Clinical trials will be needed to learn what the bleeding patterns are when offering several months of uninterrupted active pills, but these are relatively short-term studies. If there is no significant unscheduled bleeding with extended cycle use, this would offer users of E4/DRSP pills the health and quality of life benefits that attend the avoidance of the scheduled bleeding episodes.

Many studies have shown the great potential E4 has for control of premenopausal and menopausal symptoms including vasomotor symptoms, genitourinary complaints, and osteoporosis without increasing the perceived risk of breast cancer [22,26]. This may be important to perimenopausal women at risk for unintended pregnancy. The role E4 may play in menopausal hormone therapy may not be directly related to premenopausal women, but we witnessed that when the adverse finding of the Women's Health Initiative findings raised concern about health risk of postmenopausal hormonal therapy, many younger women generalized those concerns to include premenopausal hormone use. It will be interesting to see if good news from the use of E4 in menopause will have positive impacts on the image of hormonal contraception.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. UNFPA State of the World Population 2022, Seeing the unseen: the case for action in the neglected crisis of unintended pregnancy. [cited 2023 May 18]. Available from: https://www.unfpa.org/sites/default/files/pub-pdf/EN_SWP22%20report_0.pdf.
2. Hoyert DL. Maternal mortality rates in the United States 2021; NCHS Health E-Stats. 2023. doi: 10.15620/cdc:124678

3. Kavanaugh ML, Pliskin E. Use of contraception among reproductive-aged women in the United States, 2014 and 2016. F S Rep. 2020;1(2):83–93.
4. Dragoman MV, Tepper NK, Fu R, et al. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet. 2018;141(3):287–294. doi: 10.1002/ijgo.12455
5. Simmons RG, Sanders JN, Geist C, et al. Predictors of contraceptive switching and discontinuation within the first 6 months of use among Highly Effective Reversible Contraceptive Initiative Salt Lake study participants. Am J Obstet Gynecol. 2019;220(4):376.e1–376.e12. doi: 10.1016/j.ajog.2018.12.022
6. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810. doi: 10.1136/bmj.k4810
7. Hagen AA, Barr M, Deczfalusy E. Metabolism of 17-BETA-OESTRADIOL-4-14-C in early infancy. Acta Endocrinol (Copenh). 1965;49:207–220.
8. Gallo MF, Nanda K, Grimes DA, et al. 20 μg versus >20 μg estrogen combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013;2013(8):CD003989.
9. Morimont L, Haguet H, Dogné JM, et al. Combined oral contraceptives and venous thromboembolism: review and perspective to mitigate the risk. Front Endocrinol. 2021;12:769187. doi: 10.3389/fendo.2021.769187
10. Bitzer J. Pharmacological profile of estrogens in oral contraception. Minerva Ginecol. 2011;63(3):299–304.
11. Hugon-Rodin J, Gompel A, Plu-Bureau G. Mechanisms in endocrinology: epidemiology of hormonal contraceptives-related venous thromboembolism. Eur J Endocrinol. 2014;171(6):R221–30. doi: 10.1530/EJE-14-0527
12. Fruzzetti F, Cagnacci A. Venous thrombosis and hormonal contraception: what's new with estradiol-based hormonal contraceptives? Open Access J Contracept. 2018;9:75–79.
13. Tepper NK, Whiteman MK, Marchbanks PA, et al. Progestin-only contraception and thromboembolism: a systematic review. Contraception. 2016;94(6):678–700. doi: 10.1016/j.contraception.2016.04.014
14. Reed S, Koro C, DiBello J, et al. Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism. Eur J Contracept Reprod Health Care. 2021;26(6):439–446. doi: 10.1080/13625187.2021.1987410
15. Heikinheimo O, Toffol E, Partonen T, et al. Systemic hormonal contraception and risk of venous thromboembolism. Acta Obstet Gynecol Scand. 2022;101(8):846–855. doi: 10.1111/aogs.14384
16. Gemzell-Danielsson K, Apter D, Zatik J, et al. Estetrol-drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022;129(1):63–71. doi: 10.1111/1471-0528.16840
17. Creinin MD, Westhoff CL, Bouchard C, et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. Contraception. 2021;104(3):222–228. doi: 10.1016/j.contraception.2021.05.002
    - **Excellent summary of clinical outcome of Phase III clinical trial in North America that found the cases for FDA labeling for the E4/DRSP pill.**
18. Schwers J, Eriksson G, Diczfalusy E. Metabolism of oestrone and oestradiol in the human foeto-placental unit at midpregnancy. Acta Endocrinol (Copenh). 1965;49(1):65–82. doi: 10.1530/acta.0.0490065
19. Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: a unique steroid in human pregnancy. J Steroid Biochem Mol Biol. 2008;110(1–2):138–143.
20. Abot A, Fontaine C, Buscato M, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor α modulation, uncoupling nuclear and membrane activation. EMBO Mol Med. 2014;6(10):1328–1346. doi: 10.15252/emmm.201404112
21. Coelingh Bennink F, Holinka CF, Visser M, et al. Maternal and fetal estetrol levels during pregnancy. Climacteric. 2008;11 Suppl (1):69–72.
    - **Early exploration of clinical applications for estetrol.**
22. Gérard C, Arnal JF, Jost M, et al. Profile of estetrol, a promising native estrogen for oral contraception and the relief of climacteric symptoms of menopause. Expert Rev Clin Pharmacol. 2022;15(2):121–137. doi: 10.1080/17512433.2022.2054413
23. Gérard C, Blacher S, Communal L, et al. Estetrol is a weak estrogen antagonizing estradiol-dependent mammary gland proliferation. J Endocrinol. 2015;224(1):85–95.
24. NEXTSTELLIS (drospirenone and estetrol tablets), for oral use. FDA product labeling. [cited from 2023 May 18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214154s000lbl.pdf
25. Motivala A, Pitt B. Drospirenone for oral contraception and hormone replacement therapy: are its cardiovascular risks and benefits the same as other progestogens? Drugs. 2007;67(5):647–655. doi: 10.2165/00003495-200767050-00001
26. Gallez A, Dias Da Silva I, Wuidar V, et al. Estetrol and mammary gland: friends or foes? J Mammary Gland Biol Neoplasia. 2021;26(3):297–308. doi: 10.1007/s10911-021-09497-0
27. Gérard C, Foidart JM. Estetrol: from preclinical to clinical pharmacology and advances in the understanding of the molecular mechanism of action. Drugs R D. 2023;23(2):77–92.
28. Coelingh Bennink HJ, Holinka CF, Diczfalusy E. Estetrol review: profile and potential clinical applications. Climacteric. 2008;11 Suppl 1:47–58.
29. Mawet M, Maillard C, Klipping C, et al. Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. Eur J Contracept Reprod Health Care. 2015;20(6):463–475. doi: 10.3109/13625187.2015.1068934
    - **Excellent summary of metabolic impacts of estetrol.**
30. Kluft C, Zimmerman Y, Mawet M, et al. Reduced hemostatic effects with drospirenone-based oral contraceptives containing estetrol vs. ethinyl estradiol. Contraception. 2017;95(2):140–147. doi: 10.1016/j.contraception.2016.08.018
    - **First study comparing hemostatic effects of two different estrogens in birth control pills while holding progestin constant.**
31. Lee A, Syed YY. Estetrol/Drospirenone: a review in oral contraception. Drugs. 2022;82(10):1117–1125.
32. Douxfils J, Gaspard U, Taziaux M, et al. Impact of estetrol (E4) on hemostasis, metabolism and bone turnover in postmenopausal women. Climacteric. 2023;26(1):55–63. doi: 10.1080/13697137.2022.2139599
33. Arnal JF, Lenfant F, Metivier R, et al. Membrane and nuclear estrogen receptor alpha actions: from tissue specificity to medical implications. Physiol Rev. 2017;97(3):1045–1087. doi: 10.1152/physrev.00024.2016
34. Fruzzetti F, Fidecicchi T, Montt Guevara MM, et al. Estetrol: a new choice for contraception. J Clin Med. 2021;10(23):5625.
35. Guivarc'h E, Buscato M, Guihot AL, et al. Predominant role of nuclear versus membrane estrogen receptor α in arterial protection: implications for estrogen receptor α modulation in cardiovascular Prevention/safety. J Am Heart Assoc. 2018;7(13):e008950. doi: 10.1161/JAHA.118.008950
36. Douxfils J, Morimont L, Gaspard U, et al. Estetrol is not a SERM but a NEST and has a specific safety profile on coagulation. Thromb Res. 2022;S0049-3848(22)00387–5.
37. Douxfils J, Klipping C, Duijkers I, et al. Evaluation of the effect of a new oral contraceptive containing estetrol and drospirenone on hemostasis parameters. Contraception. 2020;102(6):396–402. doi: 10.1016/j.contraception.2020.08.015
38. Morimont L, Jost M, Gaspard U, et al. Low thrombin generation in users of a contraceptive containing estetrol and Drospirenone.

J Clin Endocrinol Metab. 2022;108(1):135–143. doi: 10.1210/clinem/dgac511
39. Hemker HC, Giesen P, Al Dieri R, et al. Calibrated automated thrombin generation measurement in clotting plasma. Pathophysiol Haemost Thromb. 2003;33(1):4–15. doi: 10.1159/000071636
40. Chen MJ, Jensen JT, Kaunitz AM, et al. Tolerability and safety of the estetrol/drospirenone combined oral contraceptive: pooled analysis of two multicenter, open-label phase 3 trials. Contraception. 2022;116:44–50. doi: 10.1016/j.contraception.2022.10.004
41. Klipping C, Duijkers I, Mawet M, et al. Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone. Contraception. 2021;103(4):213–221. doi: 10.1016/j.contraception.2021.01.001
42. Visser M, Holinka CF, Coelingh Bennink HJ. First human exposure to exogenous single-dose oral estetrol in early postmenopausal women. Climacteric. 2008;11(1):31–40.
43. Hammond GL, Hogeveen KN, Visser M, et al. Estetrol does not bind sex hormone binding globulin or increase its production by human HepG2 cells. Climacteric. 2008;11(1):41–46.
44. Duijkers IJ, Klipping C, Zimmerman Y, et al. Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: results of a Phase II dose-finding pilot study. Eur J Contracept Reprod Health Care. 2015;20(6):476–489.
45. Apter D, Zimmerman Y, Beekman L, et al. Bleeding pattern and cycle control with estetrol-containing combined oral contraceptives: results from a phase II, randomized, dose-finding study (FIESTA). Contraception. 2016;94(4):366–373.
46. Jensen JT, Kaunitz AM, Achilles SL, et al. Pooled efficacy results of estetrol/drospirenone combined oral contraception phase 3 trials. Contraception. 2022;116:37–43. doi: 10.1016/j.contraception.2022.07.009
47. Creinin MD, Jensen JT, Chen MJ, et al. Combined oral contraceptive adherence and pregnancy rates. Obstet Gynecol. 2023;141(5):989–994. doi: 10.1097/AOG.0000000000005155
48. Kaunitz AM, Achilles SL, Zatik J, et al. Pooled analysis of two phase 3 trials evaluating the effects of a novel combined oral contraceptive containing estetrol/drospirenone on bleeding patterns in healthy women. Contraception. 2022;116:29–36. doi: 10.1016/j.contraception.2022.07.010
49. Apter D, Zimmerman Y, Beekman L, et al. Estetrol combined with drospirenone: an oral contraceptive with high acceptability, user satisfaction, well-being and favorable body weight control. Eur J Contracept Reprod Health Care. 2017;22(4):260–267.
50. Trussell J, Portman D. The creeping Pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills? Contraception. 2013; 88(5):604–610. doi: 10.1016/j.contraception.2013.04.001
•• **Provides definitive understanding of forces underlying observed increases in Pearl Indices with newer hormonal contraceptives.**
51. Foidart JM, Desreux J, Lifrange E, et al. Hormone replacement therapy after breast cancer Yes…or no?. Rev Med Liege. 2003;58(2):77–82.
52. Gallez A, Blacher S, Maquoi E, et al. Estetrol combined to Progestogen for menopause or contraception Indication is neutral on breast cancer. Cancers (Basel). 2021;13(10):2486. doi: 10.3390/cancers13102486
53. Peasah SK, Kohli M, Munshi KD, et al. Twelve month oral contraceptive pill prescriptions: role of policy mandates on utilization. Explor Res Clin Soc Pharm. 2021;5:100094.
54. Gedestad I, Munnangi M, Chamberlin A, et al. Five years later: can women in Los Angeles County, California get adequate pill supplies?. Contraception. 2023;20:110294.