Estetrol as estrogen in a combined oral contraceptive, from the first in-human study to the contraceptive efficacy

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ABSTRACT

Even though the use of combined oral contraceptive (COC) has numerous health benefits, it is associated with an increased risk of venous thromboembolism (VTE). Currently, the second generation COCs [ethinylestradiol (EE) with levonorgestrel (LNG)] are considered as the safest regarding the VTE risk but the androgenicity of LNG is responsible for undesirable side effects (acne, hirsutism and mood alteration) jeopardizing compliance. In the opposite, the use of less androgenic progestins or anti-androgenic progestins such as drospirenone (DRSP) is better tolerated but doubles the risk of VTE in comparison with EE/LNG. Replacing EE by a natural estrogen has been suggested to improve the VTE risk. Estetrol (E4) is a natural estrogen only produced by the human fetal liver. *In-vivo* and *in-vitro* fundamental studies suggest that E4 is safer than EE and estradiol (E2) on important estrogenic targets such as breast tissue and synthesis of liver proteins (responsible for hemostasis impairments associated with the use of estrogens). A vast clinical program has recently been conducted in order to evaluate the use of E4 as estrogen in a COC. A dose-finding program studied different combinations of E4 with DRSP or LNG. Ovulation inhibition, bleeding pattern, and tolerance were used to select the best E4-COC for further evaluation. All the E4-COCs tested were safe and capable of blocking ovulation. However, 15 mg E4 with 3 mg DRSP was associated with the best bleeding pattern and the highest tolerance. In addition, the changes in hemostasis parameters elicited by 15 mg E4/DRSP were significantly less pronounced than those recorded with EE/DRSP, and similar or even lower than those seen with the safe EE/LNG. This combination was therefore selected to be further evaluated in a Phase 3 program where it confirmed its excellent safety and contraceptive efficacy.

KEYWORDS

Combined oral contraceptive, estetrol, drospirenone.

Introduction

Although the progestin component of combined oral contraceptive (COC) is sufficient to ensure adequate ovulation inhibition, the addition of an estrogen is crucial to provide an acceptable bleeding pattern. Since the launch of the first COC in 1961, there has been a constant effort to develop new progestins in order to improve the safety and tolerability of the earliest combinations. Indeed, the androgenicity of the first progestins was held responsible of metabolic impairment (insulin resistance and deleterious effect on plasma lipid levels). It was also associated with a series of undesirable side effects, like weight gain, acne, oily hair, seborrhea, and hirsutism [1, 2]. Research in women's health has therefore focused on developing less androgenic compounds. The two last decades have even seen the advent of anti-androgenic progestins. One of them, drospirenone (DRSP), also displays anti-mineralocorticoid activity. Combined to EE, DRSP has been demonstrated to maintain blood pressure, slightly decrease body weight, improve acne and hirsutism, and improve premenstrual dysphoric disorder [3].

On the other side, only three different estrogens have been used in COC since 1961: the first one was the pro-drug mestranol rapidly replaced by its potent active form, ethinylestradiol (EE). Ethinylestradiol has remained the only estrogen used in COC during more than four decades. After initial unsuccessful attempts, estradiol (E2) was finally introduced into two COCs in the early 2010': in the form of the pro-drug E2 valerate in combination with dienogest (E2V/DNG) and in the form of E2 in combination with nomegestrol acetate [4, 5]. However, these E2-containing COCs are less prescribed as over 95% of combined hormonal contraceptive users still utilize an EE-containing product.

Estrogens (and particularly the potent EE) modify the synthesis of hepatic proteins, including those of haemostasis [6]. Hemostasis is a subtle balance between pro-coagulation, anti-coagulation and fibrinolysis. Estrogens alter this balance by decreasing natural anticoagulant and favouring pro-coagulation; this is the reason why venous thromboembolism (VTE) risk is increased in COC users [7] (Figure 1 A and B).

Decreasing the amount of EE in COC from > 75 to 20 mcg has undoubtedly decreased the incidence of VTE [8]. But epi-

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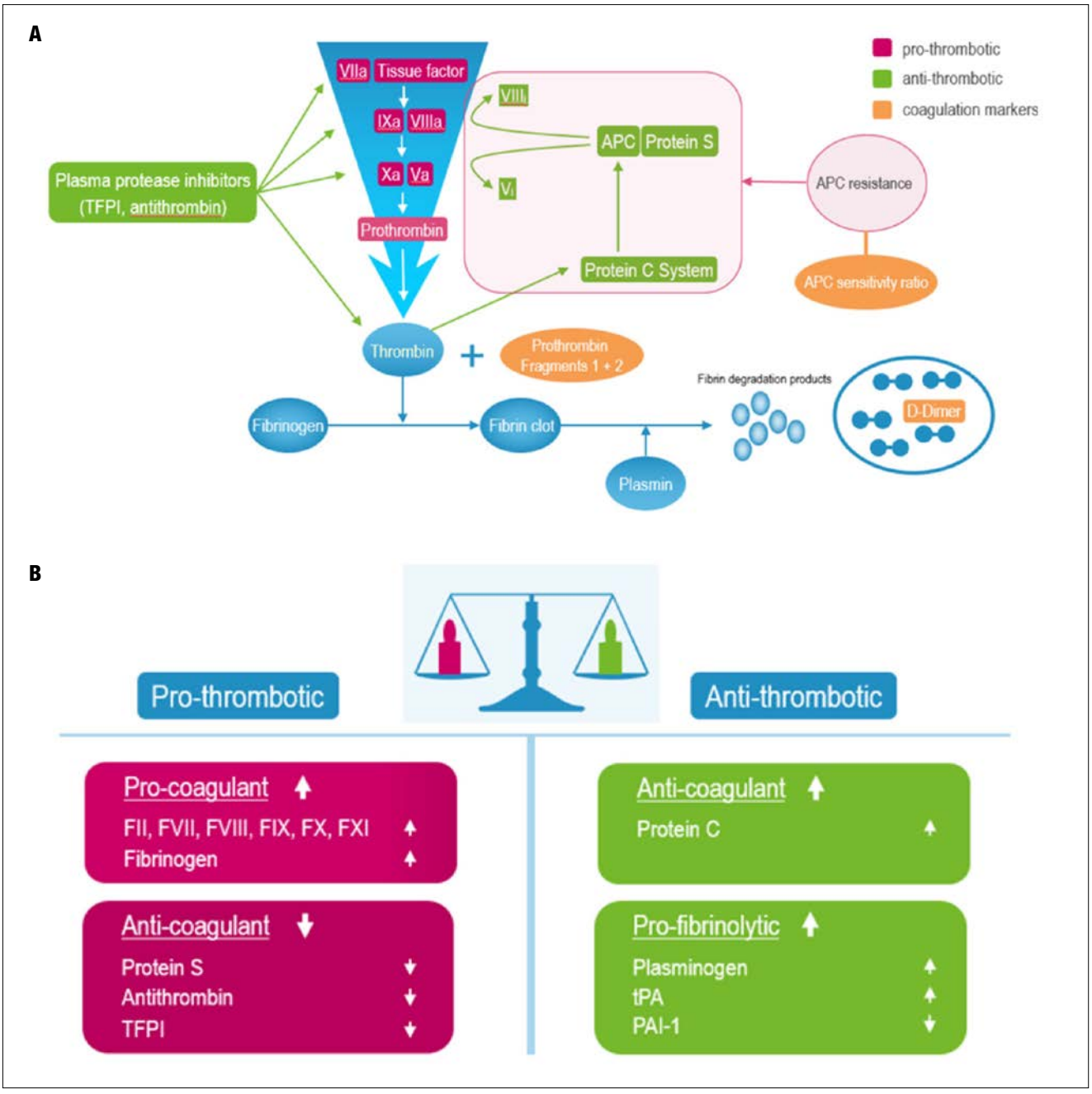
Figure 1 Global impact of estrogens or combined oral contraceptives on hemostasis (A) and resultant effects on hemostasis parameters considered as relevant for the evaluation of the risk of venous thromboembolism (B). Adapted from "Oral contraceptives and HRT: risk of thrombosis", Gialeraki A. *et al*, 2018, Clinical and Applied Thrombosis/Hemostasis, 24, p. 217. Copyright 2017 by The Author(s) (A) and from "APC resistance: biological basis and acquired influences", Castoldi E. & Rosing J., 2010, Journal of Thrombosis and Haemostasis, 8, p. 445. Copyright 2009 by International Society on Thrombosis and Haemostasis (B).



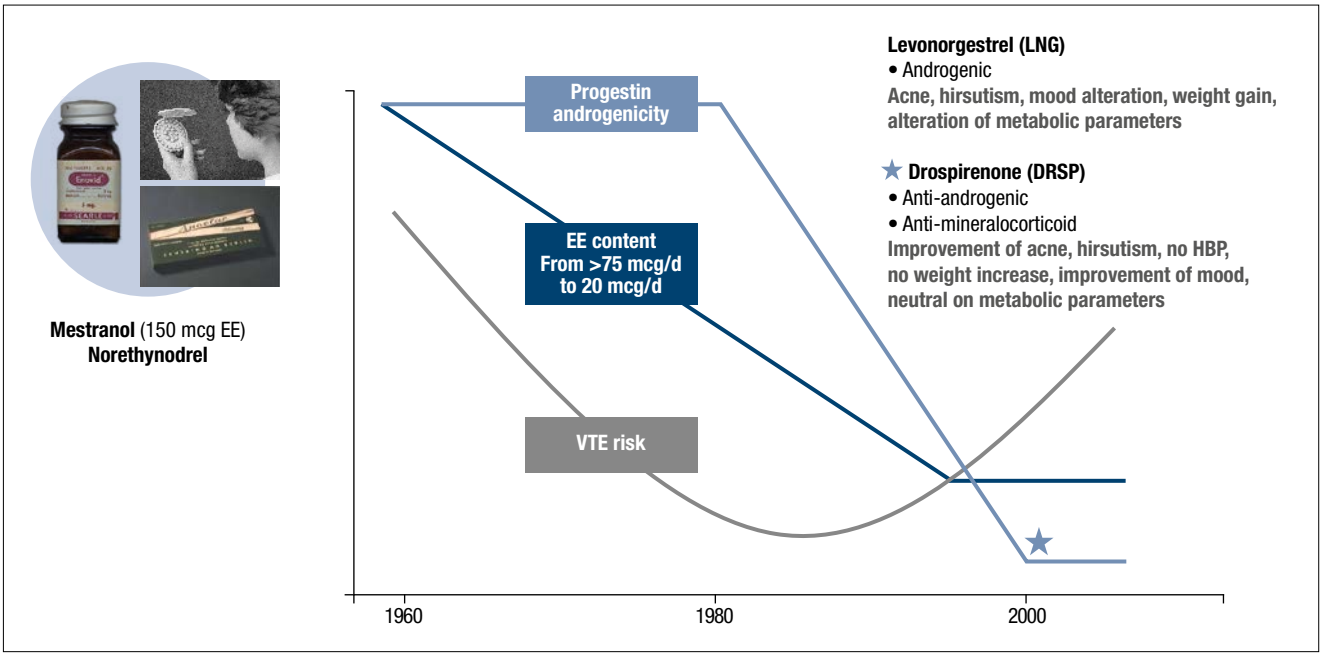
demiological studies have shown that the combination of less androgenic/anti-androgenic progestins, even to low dose of EE, has re-enhanced the incidence of VTE, because the resultant estrogenicity of these combinations is higher with these progestins than with the androgenic ones [9, 10] (Figure 2).

A further decrease in EE content is associated with a barely acceptable bleeding pattern.

In general, the lower dose estrogen pills (20 mcg or less) are associated with higher unscheduleld bleeding episodes which could increase discontinuation rate [11]. Therefore, the other option was to replace EE by an estrogen with less impact on coagulation. This is the reason why E2 was introduced in COCs. The current E2-containing COCs try to minimize the incidence of unscheduled bleeding but the bleeding pattern differs from the EE-COCs as 15-25% of users present with occasional amenorrhea [12, 13]. Currently, studies are still necessary to confirm the lower VTE incidence with these preparations.

No new estrogen has been introduced since 1943 but a vast clinical program has recently been conducted to evaluate the potential of estetrol (E4) as estrogen in a COC. The goal of this article is to summarize the current published knowledge on E4 and on the first E4-based COC.

Figure 2 Evolution of combined oral contraceptives composition from 1960 to 2000: in association with the androgenic progestin levonorgestrel, a progressive decrease in ethinylestradiol (EE) content from 150 to 20 mcg/day has permitted a decrease of the risk of venous thromboembolism (VTE). Development of less/anti-androgenic progestin in the 1980s has decreased the androgenic side effects of COCs but combinations of these progestins even to low dose EE were associated with a new increase of the VTE risk.



What is estetrol?

The natural estrogen family encompasses 4 estrogens differing on the number of hydroxyl groups: estrone (E1), estradiol E2, estriol (E3) and the less known, estetrol (E4). Estetrol, a four hydroxylated estrogen, was discovered at the Karolinska Institute (Sweden) in 1965 by Egon Diczfalusy and co-workers in the urines of pregnant women [14]. Its synthesis starts from E2 and necessitates the activity of two enzymes (16- and 15α-hydroxylase) only present in the liver of the human fetus [15]. Estetrol crosses the placenta and is detectable in the mother's blood from the first weeks of pregnancy onwards. The concentration in E4 increases throughout the pregnancy in both mother and fetus and, at term, is on average 12 times higher in the child plasma than in the mother plasma: mean concentrations (standard deviation) of 9,034 (2,968) pg/ml and 723 (290) pg/ml, respectively. Short after birth, the enzymes necessary to its synthesis are not active anymore, explaining why the concentration in E4 decreases rapidly in the new-born plasma [16].

In the first decade following its discovery, E4 was extensively studied as it was hoped to be a good marker of fetal well-being. However, the high inter-subject variability precluded its use in this context and research was abandoned in the early 1980's. The molecule was then forgotten until recently, when the need of developing more physiologic estrogenic compounds became crucial [17].

Fundamental research shows that E4 behaves differently than EE and E2

Animals and *in vitro* studies have revealed that E4 is able to dose-dependently block ovulation, to exert a proliferative activity on the endometrium and on the vaginal epithelium, to decrease vasomotor symptoms, to restore bone mineral density, to protect against atherosclerosis, and to confer vasorelaxation [18-24]. These characteristics are shared with the other estrogens like E2 and EE. However, unlike these estrogens, different studies have shown that E4 estrogenic activity is much weaker on breast tissue (either normal or cancerous) and on liver [25-28].

This distinct profile of E4 is probably best explained by its interaction with estrogen receptors (ERs). In the cells, estrogens act via two types of ERs: ERα and ERβ. Estetrol has a 5 fold higher affinity for ERα than for ERβ [29]. The ERs are either located in the cell membrane and in the cell nucleus. Estrogens classically activate both membrane and nuclear receptors. This is not the case of E4: like the other estrogens, it activates the nuclear receptor but it antagonizes the membrane receptor and, consequently, the response to E4 will differ from that of the other estrogen in functions of the target tissue. This could explain the weak effect of E4 on certain target tissues (e.g. the liver and the breast) *versus* its full estrogenic potential on other tissues (uterus, vagina, hypothalamus-pituitary-ovarian axis, brain, bone) [23, 30, 31].

First administration of exogenous E4 in human

The two first studies in which exogenous E4 was administrated in humans were carried on in post-menopausal women. The most important information retrieved in these trials was that E4 is safe up to 100 mg as a single dose and up to 40 mg when administrated during 28 consecutive days. Estetrol appeared to exert a dose-proportional anti-gonadotropic activity as well as a dose-proportional proliferative activity on the endometrium. Vaginal maturation index of these post-menopau-

sal participants was also clearly improved, even with an oral dose as low as 2 mg E4. It was neutral on lipids and glucose metabolism and a first preliminary evaluation of its effect on vasomotor symptoms suggested a positive effect [32-35].

Selecting the appropriate dose

The ideal COC is safe and well-tolerated, able to block the ovulation in 100% of users, and associated with an acceptable bleeding pattern, i.e. minimal incidence of breakthrough bleeding episodes (also called unscheduled bleeding) and presence of monthly withdrawal bleeding (also called scheduled bleeding). A robust dose-finding program was conducted with E4 in order to achieve all these goals before moving to a large Phase 3 program. In the dose-finding program, different doses of E4 (from 5 mg to 20 mg) were combined to either 150 mcg LNG or 3 mg DRSP.

Ovulation inhibition with E4-containing combinations

The capacity of E4-COCs to block the ovulation was evaluated in a first randomized, controlled trial [36]. The participants had confirmed ovulatory cycles (defined as the presence of ultrasonographic sign of ovulation between day 9 and day 24 of the cycle before starting the treatment, followed by a rise in progesterone level ≥16 nmol/l), were below 35 years of age, without contraindications to COC use. They were randomized to either 5 mg E4/DRSP (n= 17), 10 mg E4/DRSP (n=19), 5 mg E4/LNG (n=18), 10 mg E4/LNG (n=17), 20 mg E4/LNG (n=18), or to 20 mcg EE/DRSP (YAZ®, used as comparator). Treatment lasted 3 cycles of 28 days each and all the COCs were administrated in a 24-4 days regimen.

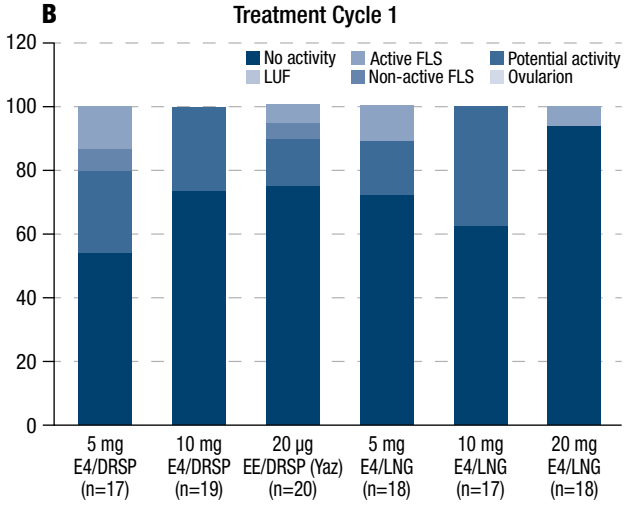
The method used to evaluate the ovarian activity in this study was the Hoogland Score, considered as the state-of-the art method for this purpose [37]. The Hoogland Score is a combination of three parameters, namely the maximal ovarian follicular size obtained by transvaginal ultrasonography, the maximal levels of serum E2 and the maximum level of serum progesterone. The results are reported in the Hoogland scoring system (Figure 3 A). A Hoogland score of 1 is indicative of low ovarian activity while a score of 6 indicates the presence of ovulation. Naturally, the goal of a COC is to have a maximum of treated women presenting a low Hoogland score.

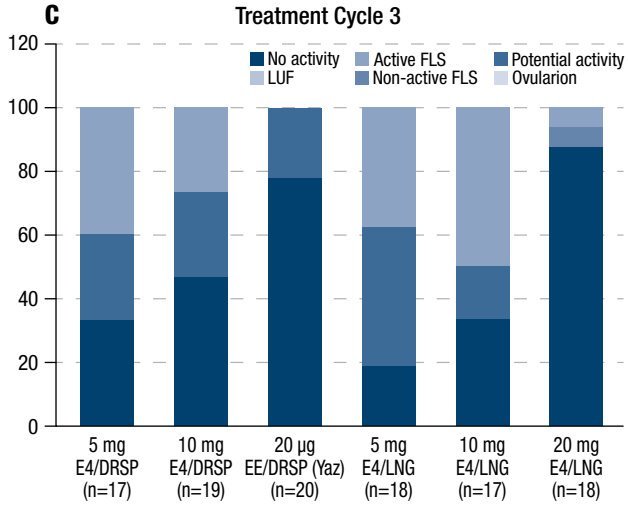
The results are displayed in Figure 3 B and C. No ovulation

Figure 3 Ovulation inhibition according to the Hoogland score (A). Hoogland scores obtained during cycle 1 (B) and cycle 3 (C) with the different combinations tested during the trial. Results are expressed in percentage of participants. E2, estradiol; FLS: follicle-like structure; LUF: luteinized unruptured follicle; E4, estetrol; DRSP, drospirenone; EE, ethinylestradiol; LNG, levonorgestrel. Reprinted from "Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: Results of a phase II dose-finding pilot study", by I. Duijkers *et al*, 2015, The European Journal of Contraception and Reproductive Health Care, 20, p. 476. Copyright 2015 by The European Society of Contraception and Reproductive Health. Reprinted with permission.

A

Score	Activity	Follicle size (nm)	E2		Progesterone	
			nmol/L	pg/mL	nmol/L	pg/mL
1	No activity	≤ 10	-	-	-	-
2	Potential activity	> 10	-	-	-	-
3	Non activity - FLS	> 13	≤ 0.1	≤ 27.2	-	-
4	Active FLS	> 13	> 0.1	> 27.2	≤ 5	≤ 1.57
5	LUF	> 13, persisting	> 0.1	> 27.2	> 5	> 1.57
6	Ovulation	> 13, ruptured	> 0.1	> 27.2	> 5	> 1.57





occurred in any group which demonstrates that, like EE, once combined to a progestin, E4 exerts an optimal contraceptive action. The residual ovarian activity (i.e. the endogenous ovarian production of estrogen) appeared to decrease with increasing doses of E4 and was optimal when doses of E4 above 10 mg were administrated. It is well documented in the literature that achieving a profound ovarian function inhibition with a COC is beneficial since it allows for a better bleeding pattern and decreases the incidence of side effects like headache and breast tenderness [38-40]. Therefore, it was decided to continue the program with doses of 20 mg E4 and to evaluate also an intermediate dose between 10 mg and 20 mg, i.e. 15 mg.

Bleeding pattern with E4-containing combinations

The bleeding pattern was assessed in a second randomized controlled study conducted with 15 mg E4 and 20 mg E4 combined to either 3 mg DRSP or to 150 mcg LNG [13]. The active comparator in this study was E2V/DNG (Qlaira®), selected because, at the time of the study, it was the only COC containing a natural estrogen. The participants (healthy women, below 50 years of age, without contraindications to COC use) were treated for 6 consecutive cycles. There were between 73 and 77 volunteers per group.

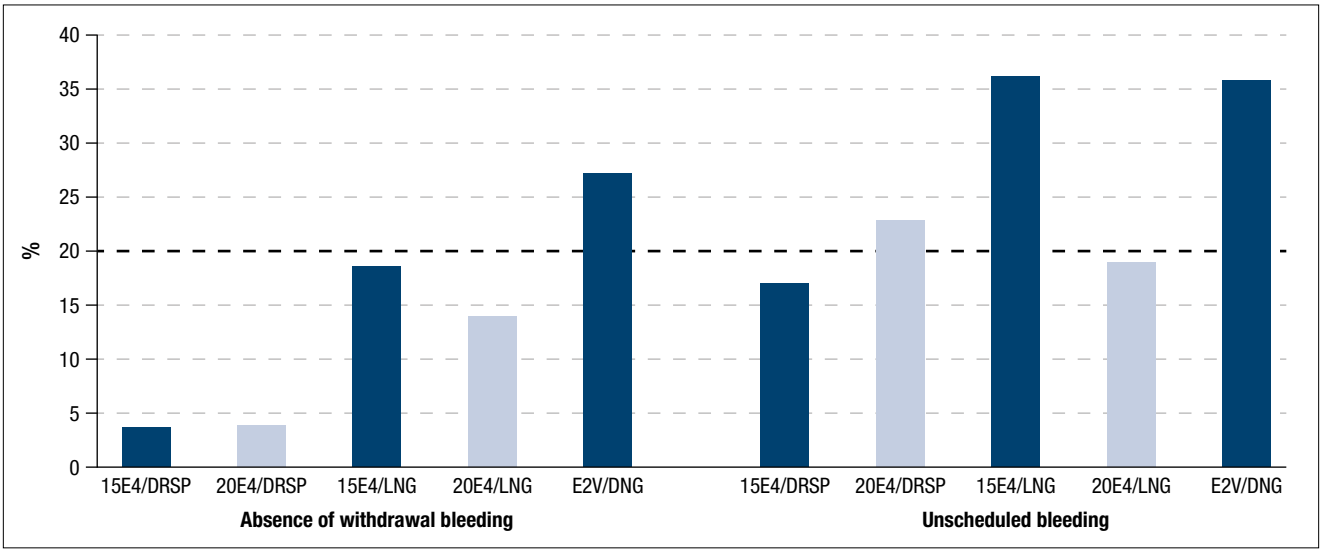
The purpose of the study was to find a dosing combination with no more than 20% absence of withdrawal bleeding and no more than 20% unscheduled intracyclic bleeding in cycle 6. Figure 4 displays the results. Interestingly, the marketed comparator E2V/DNG did not achieve the objective as, at cycle 6, 47.8% of the women presented unscheduled intracyclic bleeding and 27.1% of the women did not present withdrawal bleeding. In the opposite, two E4-combinations achieved the objective, namely 15 mg E4/DRSP and 20 mg E4/LNG. In the below section, we further describe the determinants used to select 15 mg E4/DRSP over 20 mg E4/LNG as final dose for the phase 3 program.

Safety and well-being associated with E4-containing combinations

Combined oral contraceptives are intended for a healthy population and, therefore, maintaining good health and well-being of the users is essential. It has also a direct influence on the compliance to the drug and thus, the contraceptive efficacy. The adverse events (AEs) recorded with the different E4-COCs during the above described studies were identical to those seen with the comparator (and common to all COCs) [36]. The incidence of drug-related AEs was usual for this type of studies, and appeared to be the lowest with the 15 mg E4/DRSP and the E2V/DNG combinations (25.3% and 23.1%, respectively) *versus* 41.3% in the 20 mg E4/DRSP, 35.0% in the 15 mg E4/LNG, and 45.5% in the 20 mg E4/LNG [13]. The second study, with its 6-cycle duration and its quite large population for a phase 2 study in this therapeutic area, was the occasion to closely document the well-being, tolerability and acceptance of the different combinations tested [41]. All the data converged to the superiority of the 15 mg E4/DRSP over the 20 mg E4/LNG combination:

1) the number of completers was the highest in the 15 mg E4/DRSP group (91.1%, *versus* the lowest for 20 mg E4/LNG with 70.1%).
2) A questionnaire was used in this study to evaluate subject's satisfaction and well-being. Well-being with E4/DRSP combinations was statistically significantly better than with E4/LNG combinations: OR (95% CI) 2.00 (1.13; 3.53) and 1.93 (1.06; 3.56) for 15 and 20 mg E4, respectively, and comparable to E2V/DNG. Again, the largest proportion of treatment satisfaction was reported for 15mg E4/DRSP (73.1%, *versus* the lowest for 15 mg E4/LNG with 50.6%).
3) The number of women willing to continue with the assigned study treatment was the highest in the 15mg E4/DRSP group (82.1%) and the lowest for 20mg E4/LNG (58.3%).

Figure 4 Percentage of subjects with absence of withdrawal bleeding and presence of unscheduled bleeding in each treatment group in cycle 6 (Per Protocol population). Absence of withdrawal bleeding and occurrence of unscheduled intracyclic bleeding ≤20% after six treatment cycles was set as a limit (dotted bar). DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel. Reprinted from "Bleeding pattern and cycle control with estetrol-containing combined oral contraceptives: results from a phase II, randomised, dose-finding study (FIESTA)", by D. Apter *et al*, 2016, Contraception, 94, p. 366. Copyright 2016 by Elsevier Inc. Reprinted with permission.



Increased body weight under COC intake remains an important fear of the patients and has been described as one of the determinants for compliance [42]. Due to its anti-mineralocorticoid activity, DRSP is known to have a positive effect on body weight as it counteracts the water retention effect induced by the estrogen.

In line with this, in the 6-cycle study conducted with E4-combinations, the number of women with a 2 kg or more weight loss was higher in the E4/DRSP groups than in the E4/LNG groups; again, the 15 mg E4/DRSP group was associated with the highest proportion of women loosing at least 2 kg (36.7% at cycle 6 *versus* 13.0% in the 15 mg/LNG group).

Impact on the hemostasis, endocrine and metabolic parameters

For almost two decades, several large retrospective epidemiologic studies have shown that the so-called third generation COCs (e.g. EE/desogestrel, EE/gestodene) and fourth generation COCs (EE/DRSP) are associated with a 1.5 to 2 fold higher risk of developing a VTE in comparison with second generation combinations (EE/LNG) [43]. In consequence, some guidelines now recommend the use of EE/LNG as first line therapy when prescribing a COC to a new user, and to switch to another combination only in case of unwanted side effects.

Although epidemiologic studies encompassing several thousands of subjects are still considered necessary to estimate the risk of VTE with a COC, increasing evidence suggests that the changes seen in specific hemostasis parameters may be considered a reliable method to estimate this risk. Therefore, per European Medicine Agency's guidelines, changes in a series of hemostasis parameters should be evaluated during the development of a new COC. Among these parameters, literature suggests that there is a good correlation between the epidemiological estimation of the risk of VTE and the changes induced by COC in the levels of sex hormone binding globulin (SHBG), a marker of liver estrogenicity, and of activated protein C resistance measured using the endogenous thrombin potential (ETP-based APCr) [7, 44-47].

A preliminary assessment of the changes in hemostasis parameters induced by E4-COCs was conducted during the 3-cycle study described above. The hemostasis changes observed in the 5 mg E4/DRSP, 10 mg E4/DRSP and the active comparator (EE/DRSP, YAZ®) were published by Kluft and co-workers [48].

A second randomized, controlled study was conducted with the final dosage (15 mg E4/DRSP) to evaluate the changes in the hemostasis parameters after 3 and 6 treatment cycles. Two active comparators were used in this study: 30 mcg EE/LNG (i.e. a second generation COC, considered as the safest combination on the VTE risk) and 20 mcg EE/DRSP (i.e. a fourth generation COC) [49].

Table 1 summarizes the results obtained in both studies. The data are expressed as percentage change of the median values from baseline to the end of treatment cycle 3. We selected the markers that are considered as the most relevant to estimate the VTE risk of a combination. In general, the parameters were not or minimally impacted by the E4/DRSP COCs. Although the hemostasis changes seemed dose-proportional with the E4 dose, the effect of the highest dose (15 mg E4) remained small and largely lower than those recorded with the use of EE/DRSP. In line with the results of other studies, EE/LNG had a moderate effect on the hemostasis parameters. It is to note however that the changes induced by this second generation COC were generally more marked than those seen with the E4/DRSP combinations. E4-COCs minimally impact SHBG and ETP based-APCr (expressed as normalized APCr sensitivity ratio, nAPCsr): the 15 mg E4/DRSP combination increases both levels by 51.5% and 39.5%, respectively. In contrast, EE/DRSP increases SHBG and nAPCsr by more than 230% and 200%, respectively. Sex hormone binding globulin was increased by 67% and nAPCsr by 165% in the EE/LNG group. The differ-

Table 1 Change from baseline to treatment cycle 3 in the most relevant surrogate markers of the venous thromboembolism risk associated with a combined oral contraceptive. The results are expressed as percentage change of the median values. The data between brackets are either the interquartiles 1 and 3 (*) or the minimum and maximum values (**). * Kluft C. *et al* (2017, p. 143). ** Douxfils J. *et al* (2020, p. 399).

	Marker of estrogenicity	Global functional coagulation test	Markers of coagulation inhibition		Markers of ongoing coagulation	
	SHBG	APC resistance, ETP-based (nAPCsr)	Protein C activity	Protein S activity	D-dimer	Prothrombin fragment 1+2
5 mg E4/DRSP*	0 (-10; 25)	5 (-7; 29)	-1 (-12; 2)	7 (1; 16)	-26 (-52; -8)	-23 (-32; -17)
10 mg E4/DRSP*	43 (29; 76)	-1 (-13; 54)	-1 (-9; 6)	3 (-4; 17)	-26 (-43; -6)	-3 (-24; 14)
15 mg E4/DRSP**	51.5 (-23; 132)	39.5 (-19; 117)	1 (-14; 32)	1 (-22; 33)	0 (-36; 219)	7 (-39; 73)
20 mcg EE/DRSP study 1*	281 (213; 362)	175 (96; 248)	11 (7; 25)	-27 (-33; -20)	27 (1; 54)	63 (31; -93)
20 mcg EE/DRSP study 2**	239 (128; 608)	229 (91; 781)	19.5 (-9; 46)	-26 (-41; -6)	0 (-46; 93)	47.5 (-6; 187)
30 mcg EE/LNG**	67 (-10; 313)	165 (33; 496)	12 (-11; 34)	2 (-32; 59)	0 (-65; 59)	62 (2; 125)

SHBG, sex hormone binding globulin; APC, activated protein C; ETP, endogenous thrombin potential; nAPCsr, normalized APC sensitivity ratio; E4, estetrol; DRSP, drospirenone; LNG, levonorgestrel

ence in nAPCsr between 15 mg E4/DRSP and EE/LNG was statistical significance.

These two studies included EE/DRSP as active comparator and were thus the first head-to-head comparison between EE and E4 on the hemostasis parameters. The results demonstrate accurately that the estrogen compound is the main responsible for the deleterious effect on hemostasis seen with COC.

This 3-arm study was also the occasion to assess the changes in a series of endocrine parameters (pituitary-ovarian axis, thyroid, prolactin, adrenal hormones, and androgens), lipids parameters (cholesterols and triglycerides) and glucose metabolism (glucose and insulin during oral glucose tolerance test). Results show that 15 mg E4/DRSP induces less pronounced changes in gonadotropins, cortisol, CBG, angiotensinogen, and tryglicerides levels compared to the two EE-containing products. The combination was neutral on cholesterol and glucose metabolism parameters [50].

Phase 3 program results

Contraceptive efficacy

The safety and the contraceptive efficacy of 15 mg E4/DRSP were confirmed in a large worldwide phase 3 program encompassing two studies, one conducted in North America (USA and Canada) and the other conducted in European countries and in Russia. Both studies had similar design and a duration of one year. The participants were healthy women below 50 years of age, with regular menstrual cycles and a BMI ≤ 35 kg/m².

The contraceptive efficacy was calculated in each study among women aged 16 to 35 years using the Pearl Index (PI) formulas. In the European/Russian study, an overall PI of 0.47 (95% CI: 0.15; 1.11) calculated among a total of 1,313 women was reported. The method-failure PI (i.e. excluding the user-failure pregnancies) was of 0.29 (95% CI: 0.06; 0.83) [51]. In the North American study, the overall and the method-failure PIs were of 2.65 (95% CI: 1.73; 3.88) and 1.43 (95% CI: 0.78; 2.39), respectively [52]. This difference between Europe/Russia and North America in terms of contraceptive efficacy is common in this type of study and is mainly attributed to socio-cultural differences influencing the compliance of the participants [53].

Bleeding pattern

In the European/Russian study, the incidence of unscheduled bleeding and/or spotting decreased from the 1st cycle (23% of the participants) to the last cycle of the study (13% of the participants) [51]. The mean duration of unscheduled episode was <0.5 day. Substantially similar bleeding pattern was seen in the North American study [52].

Conclusions

Estrogens moved from the field of physiology to the field of pharmacology more than 80 years ago. Progress has since been impressive both considering the chemistry of derivatives, their pharmacology and their indications. However no new natural estrogen has been introduced after 1943.

The use of less androgenic progestins, and particularly the use of the anti-androgenic and anti-mineralocorticoid DRSP, has significantly modified the contraceptive field. Indeed, the well-established non-contraceptive benefits of DRSP allowed for new therapeutic perspectives such as treatment of acne, improvement of premenstrual dysphoric disorder, stabilization of body weight and blood pressure, and an overall improvement for women suffering from lasting side effects associated with more androgenic progestins. However, epidemiological evidence suggests an increased VTE risk with EE/DRSP combinations. These data have been largely discussed in the scientific community but also in the lay press. Therefore, clinicians became reluctant to prescribe these COCs and, although well appreciated, users were no longer reassured by using these products. However, contraceptive efficacy largely relies on user compliance. Therefore, it is crucial to develop products associated with a high tolerance to ensure compliance.

This review summarizes the current knowledge on the use of E4 as estrogen in a COC. A vast clinical program (encompassing more than 3,500 women) has demonstrated that a combination of 15 mg E4 with DRSP is safe and well-tolerated, and confers a high contraceptive efficacy. The associated bleeding pattern appears better than the one seen with an E2-containing COC, and does not show any significant bleeding pattern differences *versus* EE/DRSP combinations. Fundamental studies had suggested a different behavior of E4 on important safety targets such as breast and hemostasis. The later has been confirmed in a well-conducted comparative clinical study which has demonstrated that 15 mg E4/DRSP leads to hemostasis changes similar (and sometimes even lower) than a second generation COC, currently seen as the safest combination regarding the VTE risk. However, these promising safety results should be confirmed in large epidemiological studies.

Combined oral contraception remains the most frequently used method for family planning in the developed countries but some fears and compliance issues show that there is still room for improving the currently available combinations. The results obtained so far with 15 mg E4/DRSP authorize to think that E4 could be the solution to the VTE issue associated with the use of EE/DRSP COCs.

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