Metabolic impact of combined hormonal contraceptives containing estradiol

Giovanni Grandi, Antonella Napolitano & Angelo Cagnacci

To cite this article: Giovanni Grandi, Antonella Napolitano & Angelo Cagnacci (2016): Metabolic impact of combined hormonal contraceptives containing estradiol, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2016.1190832

To link to this article: http://dx.doi.org/10.1080/17425255.2016.1190832

Accepted author version posted online: 17 May 2016.
Published online: 01 Jun 2016.

Submit your article to this journal

Article views: 28

View related articles

View Crossmark data
Metabolic impact of combined hormonal contraceptives containing estradiol

Giovanni Grandi, Antonella Napolitano and Angelo Cagnacci

Department of Obstetrics Gynecology and Pediatrics, Obstetrics and Gynecology Unit, Azienda Ospedaliero Universitaria Policlinico of Modena, Modena, Italy

1. Introduction

The introduction in the 1960s of the birth control pill as an effective and coital-independent method of contraception was one of the most important public health milestone of the last century. Its introduction has been followed by many positive consequences, such as decrease of unsafe abortion, maternal morbidity and mortality, and a net benefit in long-term risk of general mortality [1]. Reducing health-related risks is an important hallmark in the field of women’s health care of modern society. This topic is of primary interest for drugs used in contraception that are usually prescribed to healthy women with the only purpose of avoiding an unintended pregnancy [2]. Therefore, the ideal contraceptive would be the one that with a similar efficacy eliminates, or largely reduces, the risk of harm. Unfortunately, risk can never be fully predicted and managed, and there is always an element of uncertainty [3].

Nowadays, combined hormonal contraceptives (CHCs) are the most used methods of contraception in the more developed regions of the world, with a mean percentage of use of 18% of married women between 15 and 49 (about 29 million of women). These figures are still low and further strongly reduced in the more populated, regions of the world, with a mean percentage of use of 7% of engaged women between 15 and 49 (about 71 million of women) [4]. Risk associated with CHCs use may have a detrimental impact in the diffusion of this type of contraception, and products that have a limited or no impact on woman metabolism are urgently needed.

The metabolic effect of a CHC can be modulated by the type and dose of both the estrogen and the progestin contained in the preparation [5]. Over the last 55 years, the traditional pill has constantly evolved. After the early attempts with mestranol, the use of ethinyl estradiol (EE) became predominant for decades until a few years ago. The EE doses were gradually reduced up to 15 µg. At the same time, numerous different generations of progestins were tested in order to have products that better fit individual needs. Replacement of EE with estradiol (E2), the estrogen naturally secreted by the human ovaries, was really tricky because of the failure to achieve a satisfactory level of bleeding control [6]. This important step was only possible in recent years when particular endometrial-focused progestins, such as dienogest (DNG) and nomegestrol acetate (NOMAc), were introduced into the market.

Theoretically, natural estrogens may have fewer metabolic effects than synthetic ones, leading to an improved safety of these compounds. The main aim of the present paper is to provide an overview of available data regarding the metabolic impact of new E2-based CHCs in comparison to traditional EE-based CHCs.

2. Body

This is a narrative review paper: it includes all available data on the metabolic impact of CHCs containing E2 published in English up to December 2015. The searches were performed...
in January 2016. Relevant papers were identified through a search of the literature using PubMed with the keywords ‘metabolism’ in combination with ‘estradiol’ and ‘contraceptive’. We retrieved and assessed potentially relevant articles and checked the reference lists of all papers of interest to identify additional relevant publications. Only publications, in English language in press or published, were considered. We did not consider abstracts and case reports. Outcomes were considered a modification of the metabolic variable of interest during the first months of treatment with these preparations. The preliminary research matched about 8100 papers. Studies that were not pertinent to the outcomes of interest were not considered in the narrative review process. The final reference list consisted of 74 papers. Data will largely be presented in chronological order, depending on the topic.

### 2.1. Chemistry and metabolism

The term ‘estradiol’ derives from estrα-, from Greek ὑστρός (oistros, literally meaning ‘inspiration or verve’) and -diol, a suffix indicating that this is a type of alcohol bearing two hydroxyl groups.

E2 (Figure 1), or more precise 17β-estradiol ([8R,95,13S,14S,17S]-13-methyl-6,7,8,9,11,12,14,15,16,17-deca- hydrocyclopenta[alphenanthrene-3,17-diol], is the primary female sex steroid hormone.

One milligram of oral micronized E2 results in plasma concentrations of E2 and estrone (E1) that are 30–50 and 150–300 pg/mL, respectively. Conversely, 1 mg of percutaneous or transdermal E2 results in plasma concentrations of E2 and E1 that are around 44 and 53 pg/mL, respectively. The vaginal route achieves a far higher E2/E1 ratio in comparison, with a daily dosage of 0.5 mg resulting in levels of 250 and 130 pg/mL, respectively [7,8] (Table 1).

E2 valerate (E2V) is the synthetic ester, specifically the 17-pentanoyl ester, of E2. Upon absorption, regardless of the route of administration, E2V behaves as a prodrug, being cleaved by esterases in blood plasma and the liver into E2 and valeric acid. E2V is virtually identical to E2 in pharmacokinetics and exactly identical in pharmacodynamics and clinical practice. One milligram of E2V is equivalent to 0.76 mg of E2 (Table 1). E2 has a lower oral bioavailability than EE and is metabolized at a faster rate due to the absence of the 17α-ethyl group, which prevents fast metabolism by 17β-hydroxysteroid dehydrogenase of the EE molecule [9]. E2 is metabolized extensively in the liver and the intestinal mucosa, entering the systemic circulation, mostly as E1, E1 sulfate, and E1 glucuronide. The direct effect of EE on the liver for some protein synthesis, such as sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG), and angiotensinogen, is up to 500–600 times greater than E2 [10].

The progestins currently associated with E2 in CHCs are NOMAc in a monophasic 24 + 4 and DNG in a quadriphasic (days 1–2: 3 mg E2V, days 3–7: 2 mg E2V + 2 mg DNG, days 8–24: 2 mg E2V + 3 mg DNG, days 25–26: 1 mg E2V, and days 27–28: placebo) regimen.

NOMAc is a 19-norpregestosterone progestin with high activity for the progesterone receptor, a weak antiandrogenic effect but with no binding to estrogen, glucocorticoid, or mineralocorticoid receptors. At dosages of 1.5 mg/day or more, it effectively suppresses ovulation in women of reproductive age [11], as known for a long time [12,13]. Because of its strong endometrial efficacy, its high antigonadotropic activity, and long elimination half-life (about 50 h), the contraceptive efficacy of its association with E2 is maintained even when dosages are missed. In this particular 24 + 4 regimen, cyclical endometrial stability can be achieved similarly during CHC containing EE.

DNG is a 19-nortestosterone progestin with a high endometrial efficacy, widely used as a monotherapy to treat endometriosis for its strong direct antiproliferative and anti-inflammatory effects on endometrium [14]. It presents a short plasma half-life of about 10 h, a high oral bioavailability (of >90%), and a potent antiandrogenic associated with no glucocorticoid and no mineralocorticoid activity. Administration of E2V and DNG in a quadriphasic fashion for 26 out of 28 days allows an optimal contraceptive efficacy and cycle control [15].

### Table 1. Serum concentrations of E2 and E1 and the E2/E1 ratio during the daily administration of 1 mg of E2 by oral, transdermal/percutaneous, and vaginal route.

<table>
<thead>
<tr>
<th>Serum concentrations</th>
<th>Oral route</th>
<th>Vaginal route</th>
<th>Transdermal/percutaneous route</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>E1</td>
<td>E2/E1 ratio</td>
<td>E2</td>
</tr>
<tr>
<td>Daily 1 mg E2 (equivalent to 1.31 mg of E2V)</td>
<td>30–50 pg/mL</td>
<td>150–300 pg/mL</td>
<td>0.1–0.2</td>
</tr>
</tbody>
</table>
2.2. Lipid metabolism

Lipids are biomarkers correlated with the risk for cardiovascular disease, even if it is not clear whether CHCs-induced modifications of lipid metabolism do really translate in clinically significant effects on the risk of cardiovascular diseases [16]. Initial investigations demonstrated that users of high-dose oral contraceptives experienced a marked increase in serum triglycerides and total cholesterol [17,18]. Over the years, the gradual reduction of the EE dose has reduced their impact on lipid metabolism [19].

The impact of CHC on lipoprotein levels varies depending on the potency of the estrogen component and its counteraction by the androgenic potency of the progestin [20]. In general, the EE stimulus leads to a decrease of LDL and to an increase of both HDL and triglycerides [21,22]. Progestins with androgenic properties antagonized EE effects, in a dose and potentially related fashion, thus increasing LDL and decreasing HDL and triglycerides levels [21,23]. Accordingly, at similar EE doses, CHCs with less androgenic third-generations progestins demonstrate greater increases in HDL and triglycerides than other more androgenic formulations [24]. This impact is even more pronounced with the administration of EE-CHCs containing nonanandrogenic or antiandrogenic progestins, such as DNG [25], drospirenone (DRSP) [26], and chlormadinone acetate (CMA) [27–29].

The introduction of E2-based contraceptives has highly reduced the estrogenic potency of CHCs, avoiding significant effects on lipid metabolism. This impact was recently demonstrated in a prospective trial for the monophasic E2V/DNG in comparison to EE/CMA. E2V/DNG does not impact lipid metabolism [28]. HDL, LDL, total cholesterol/HDL, LDL/HDL ratio, Apo-A1, Apo-B, and Apo-B/Apo-A1 ratio remained unmodified after three cycles of treatment. These results are similar to what was recently reported in another study on 30 women treated for seven cycles in comparison to a triphasic regimen of EE/levonorgestrel (LNG) [30]. The absent modification of lipids observed during the administration of DNG in association of E2V can be interpreted as the noncapability of the weak estrogen E2V to modify lipoprotein profile. Indeed, when DNG is associated with a potent estrogen such as 30 µg of EE, it is not capable to antagonize the EE-induced increase of HDL, triglycerides, and Apo-A1 and the decrease of LDL [25].

Similarly, the E2/NOMAc combination does not induce changes in lipid metabolism. When it was compared to EE/LNG, they both give no change of total cholesterol (+1.3% with E2/NOMAc and +0.7% with EE/LNG), but the E2/NOMAc impact was significantly milder on HDL (1.6% vs. −13.1%), LDL (−0.5% vs. 6.8%), and triglycerides (7.5% vs. 17.0%) after six cycles [31]. The neutral impact of this preparation was recently confirmed in a smaller observational three-cycles pilot study in comparison to EE/CMA [29]. Since NOMAc does not give a modification of lipoproteins when given alone in a dose of 5 mg/day [32], the addition of a weak estrogenic component such as E2 does not change the impact on lipid metabolism.

Dyslipidemia is highly prevalent in the more developed world (about 33% of the population considering together
Although available data in a healthy population do not support a significant negative influence of CHCs on glucose and insulin homeostasis [34], their long-term use might increase the risk of diabetes, particularly in obese patients with severe insulin resistance [41]. E2-based CHC does not seem to negatively affect glucose and insulin metabolism.

2.4. Blood pressure

Hypertension, although adequately controlled by drugs, is a condition where the theoretical or proven risks of using CHCs generally outweigh the advantages according to the most important international guidelines [3].

Traditional CHCs containing 50 µg of EE or mestranol can induce an increase in mean systolic and diastolic office blood pressure (BP) of 14 and 8 mmHg, respectively, after 4 years of use [42] (Figure 2). Possibly, this increase of BP may increase cardiovascular morbidity, affecting life expectancy. Milder increases of about 4 to 5 mmHg office BP have been documented with CHCs containing lower EE doses [43–45] and confirmed by the few data performed with ambulatory 24-h BP monitoring [46,47]. Even the administration of EE-based hormonal contraceptives intravaginally induces an increase of 24-h BP of about 2 mmHg [48]. The clinical implication of this mild BP elevation in healthy normotensive women is unclear. The hypertensive effect of a CHC could depend on the hepatic activation of the renin–angiotensin–aldosterone system (RAAS) induced by the estrogen component, in a dose-dependent way [49]. The activation of the mineralocorticoid system causes sodium retention, plasma volume increase, and an increase in BP. This hypothesis seems to be confirmed by a study showing that the addition of the antimineralocorticoid progestin DRSP antagonized the EE effect and BP did not increase [50].

It was recently demonstrated that E2-CHCs induced no modification of 24-h systolic, diastolic, and mean BP, even when daytime or nighttime values were separately considered [51] (Figure 2). In this study, no differences between the associations E2V/DNG and E2/NOMAc were observed. The two progestins used, DNG and NOMAc, are devoid of antimineralocorticoid properties and would not have the capability to antagonize the activation of the RAAS consequent to an elevated estrogen stimulus on the liver. Consequently, the neutral impact on BP of the two E2-based CHC can only be explained by the reduced/irrelevant estrogen-induced activation of the RAAS in the liver. This neutral impact of E2-CHC had also been previously shown by office BP measurement [40,52].

2.5. Hemostasis

Appearance of deep venous thrombosis (DVT), with the subsequent risk of venous thromboembolism (VTE), is a possible but uncommon side effect associated with CHC use. The risk varies between CHCs, depending on the dose of EE [53,54], and at similar EE doses by the type of progestin [55]. The risk ranges from 5 to 12 cases per 10,000 women/year and compares with two cases of VTE per 10,000 women/year of women not using CHCs (data from European Medicines Agency [EMA], http://www.ema.europa.eu).

The prothrombotic effect of a CHC can be considered to be related to estrogenic potency of the formulation, that increases with the dose of estrogen, but decreases with increasing the antiestrogenic activity of the androgenic progestin associated. Progestins that can better counteract the effect of EE are those more androgenic such as LNG, norethisterone, or norgestimate. Use of CHCs containing EE and LNG is associated with five to seven cases of VTE each year per 10,000 women and are considered those with the lowest risk of VTE, and for this reason, the best comparator for hemostatic studies. There are a slew of hemostatic variables that can be used as markers of thrombotic risk that, according to the EMA [56], may reflect different pharmacological effects, possibly related.
to DVT-VTE risk. EE modifies estrogen-sensitive hemostatic factors and hepatic proteins, and these effects are modulated by androgenic progestins. Shortly after EE intake, procoagulants factors increase, and anticoagulants, in particular protein S, decrease. Due to the decreased protein S activity, a prothrombotic phenotype characterized by resistance to activated protein C (APC) develops. By contrast, intake of progestins increases the anticoagulant protein S and activates fibrinolysis, as the consequent higher levels of d-dimer and prothrombin fragment 1 and 2. In summary, accurate profiling of the hemostatic impact of a CHC should include measurement of the d-dimer, prothrombin fragment 1 and 2, acquired APC resistance, and protein S [57,58]. Production of the hepatic protein SHBG is enhanced by estrogen and reduced by androgenic progestin. For this reason, modification of SHBG was proposed as marker for predicting thrombotic risk in CHC users. Its levels are indeed correlated to changes in the APC sensitivity ratio, which is, in turn, correlated to the risk of DVT-VTE [59].

The decrease of the estrogenic potency and the shift to natural estrogens should reduce the prothrombotic effect of CHC preparation. At the moment, this effect has been evaluated, particularly for E2/NOMAc. This formulation was evaluated in comparison to two LNG-containing CHCs: EE 20 µg/LNG 100 mg and EE 30 µg/LNG 150 mg [31]. Mean changes in prothrombin fragments 1 and 2 and antithrombin levels were null during E2/NOMAc and significantly smaller than those induced by EE 20 µg/LNG 100 mg. Increases in free protein S levels and protein S activity still were lower with E2/NOMAc in comparison to EE 20 µg/LNG 100 mg. Mean changes in APC resistance increased with both treatments, but to a lesser extent with E2/NOMAc. In general, E2/NOMAc induced significantly less change on the overall activity of the coagulation system and on APC resistance, indicating a lower activation of coagulation [31,60]. D-dimer increased during EE 20 µg/LNG 100 mg treatment but decreased during E2/NOMAc. SHBG levels increased after the use of both CHCs, not significantly different between the two CHCs. However, the overall effect on SHBG levels was different between the two CHCs: in EE/LNG, it is the consequence of an increase induced by the EE component, counterbalanced by a decrease induced by the androgenic effects of LNG, while the effect of E2/NOMAc is due only to the effects of the E2 component, as NOMAc is not androgenic.

The association of E2V/DNG was compared with CHCs containing 30 or 40 µg of EE and various doses of LNG (50, 75, 125, or 150 mg) [30]. The absolute changes in prothrombin fragments 1 and 2 were not statistically different between E2V/DNG and EE 30 µg/LNG 150 mg [30]. A significantly smaller increase in d-dimer levels was evidenced for E2V/DNG in comparison to EE/LNG, although in both groups, mean levels remained within the reference interval [30]. No statistically significant differences were found between the two CHCs for protein S and APC resistance, although the mean APC sensitivity ratio showed a statistically significant greater increase in the EE/LNG group. Increases in the levels of SHBG were less marked in women who received E2V/DNG [30], but this result was not statistically different between treatment groups. In another single-center and randomized trial, similar SHBG levels and APC resistance in users of E2V/DNG and EE/LNG oral contraceptives were found, suggesting a similar thrombotic risk for both oral contraceptives [61].

The milder hemostatic biomarkers modification and possibly of DVT-VTE events during E2-based CHC use has to be confirmed in large clinical data.

### 2.6. Bone metabolism

Estrogens are one of the major regulatory factors of bone remodeling. All hypoestrogenic status of women is associated with a reduction in bone mineral density (BMD) and a subsequent increased risk of fracture. This effect is reversed or antagonized by hormone replacement therapy either in hypothalamic amenorrhea or in postmenopausal subjects. Evidence concerning the bone effects of CHCs is more conflicting. EE-CHCs has no impact on BMD when given during adulthood and could prevent the bone loss that occurs within the perimenopausal years [62,63]. To date, there is no evidence that past use of CHCs is associated with an increased or decreased risk of fracture, but CHC use might interfere with normal acquisition of bone peak [64]. If the effect of CHC on bone mass acquisition is dependent upon the dose of EE (low-dose vs. higher-dose compounds) is also presently unclear [65].

Literature data are mainly derived from studies having the effects on BMD or parameters of bone turnover, namely bone formation and bone resorption. These processes rely on the activity of osteoblasts (formation) and osteoclasts (resorption). Bone formation markers are products of active osteoblasts expressed during different phases of osteoblast development: the most used are total alkaline phosphatase, osteocalcin, and procollagen type I propeptides. Majority of bone resorption markers are degradation products of bone collagen, in particular hydroxyproline, 3-hydroxypropyridinium cross-links of collagen pyridoline (PYD) and deoxypyridoline (D-PYD), and cross-linked telopeptides of type I collagen that are derived from specific regions of the collagen type I molecule, namely the aminoterminal and the carboxyterminal (CTX) telopeptides.

To date, there are no trials showing that E2-CHC users have a different risk of fracture in women receiving EE-CHD or not taking any hormonal contraceptive. Di Carlo et al. found that urinary levels of PYD and D-PYD were significantly lower at 3 and 6 months of treatment with E2V/DNG in comparison with baseline values. Serum osteocalcin levels were somewhat, but not significantly, lower, and vertebral BMD did not differ from baseline [66]. A similar impact was confirmed by another independent trial in which a six-cycle treatment with E2V/DNG significantly decreased both serum osteocalcin and CTX levels [28]. In this study, the impact of E2V/DNG was similar to that exerted by a CHC containing 30 µg of EE and CMA.

The clinical effect of E2/NOMAc was evaluated in a large, prospective, randomized, open-label, comparative study [67]. After 2 years of treatment, E2/NOMAc had no clinically meaningful effect on BMD. The effect on BMD of E2/NOMAc was similar to the one observed during EE/LNG.

Although limited, these data indicate that estrogen-based CHCs exert effects on bone metabolism similar to EE-CHCs.
2.7. New horizons

An important step in the hormonal contraception technology is the introduction of parenteral routes of administration (intravaginal, subdermal, transdermal, injectable, or intrauterine) [5].

The transdermal contraceptive technology guarantees effective drug absorption and delivery of relatively constant serum hormone concentrations. The need to use transdermal patches or other devices, rather than taking oral tablets, may be beneficial in terms of perceived convenience and compliance. On the other hand, the idea of contraceptive vaginal rings derives from the capacity of steroids to slowly diffuse at a constant rate through bio-compatible silicone elastomers combined with the capability of the vaginal epithelium to rapidly absorb them into the circulation [68]. There are only two vaginal rings currently available on the market. One releases 120 µg of etonogestrel and 15 µg of EE/day, and it is approved for use over a 3-week period; the other is a progesterone-releasing vaginal ring (10 mg/day) designed for use by breastfeeding women [5].

The advantage to use E2 instead of EE in parenteral methods of hormonal contraception derives from the purpose of avoiding the effects of first-pass metabolism in the liver of E2 from a nonoral delivery route. The recent introduction of a new particular progestin, called nestorone (NES), has opened new horizons in this field as well. NES (16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-dione) formerly referred to as ST 1435, is a potent 19-nor-progesterone derivative when given parenterally through sustained release formulations [69]. Among synthetic progestins, it has the highest antiovulatory activity, a neutral metabolic profile, and no androgenic or estrogenic activity. Therefore, it seems to represent an attractive option for the use with E2. NES is not active orally but is rapidly absorbed through the skin and the mucosal epithelium. Combinations of NES and E2 are extensively under investigation using an advanced transdermal delivery gel contraceptive. Preliminary evaluations of this method at three different doses (1.5 mg NES/0.5 mg E2, 3 mg NES/1.0 mg E2, and 4.5 mg NES/1.5 mg E2) show no effect on serum SHBG during the first cycle of use [70], with minor side effects. The same combination is under evaluation also for the vaginal route. A clinical trial is investigating a new vaginal delivery system made of silicone rubber, containing NES and E2. The investigators planned to evaluate three different combinations that contain a fixed dose of NES and escalating doses of E2 (75, 100, or 200 µg/day) as the basis for selecting a vaginal ring for a larger contraceptive efficacy trial [ClinicalTrials.gov Identifier: NCT02626208].

3. Conclusions

In CHC, the replacement of EE with E2 was really tricky because of the failure to achieve a satisfactory bleeding control. E2-based CHC became possible after the availability of particular progestins with a high endometrial potency. E2 was extensively tested in association with NOMAc in a monophasic 24 + 4 and its ester E2V in association with DNG in a quadriphase 26 + 2 oral regimen. The impact on lipid metabolism and the hemostatic system of these preparations seems to be milder than that of EE-based CHCs. E2-based CHCs are neutral on carbohydrate metabolism and BP, and on markers of bone metabolism, they exert an effect similar to EE-based CHCs. The preliminary parenteral use of E2, both transdermal and vaginal, seems to be promising, in particular after the introduction of a specific progestin with a high antiovulatory activity, such as NES.

Metabolic data reinforce the general perception that CHCs containing E2 are safer than those containing EE. Nevertheless, these conclusions cannot be drawn until real strong data on clinical events are available.

The major limitation of this review is its narrative design: these types of studies tend to be mainly descriptive, do not involve a systematic search of the literature, and thereby often focus on a subset of studies in an area chosen based on availability or author selection. Thus, narrative reviews while informative can often include an element of selection bias.

Another important limitation of the present review is the lack of studies comparing E2 versus EE associated with the same types and similar doses of progestin. Indeed, the progestin component impacts independently metabolic parameters, so a real comparison will be really feasible when large, randomized trials within a single cohort comparing E2 and EE associated to the same progestin will be performed. For these reasons, these conclusions should be taken with caution and confirmed in future investigations.

4. Expert opinion

The best contraceptive is the one that fulfills women’s needs, with acceptable side effects and possibly at an affordable price in different settings. However, even today, millions of women/couples still have no access to contraceptive methods, and around 50% of pregnancies are unintended, irrespective of the woman’s social class, age, marital status, ethnicity, or whether the woman lives in a developed or developing country. The development of a new contraceptive method, especially if it is hormonal, presents a challenge to researchers and to pharmaceutical companies.

In this review, we have shown that hormonal contraceptives containing E2 instead of EE are associated with fewer metabolic effects. However, before proposing them as the gold-standard in the field of CHCs, many weak points of this review must be taken into account. For this reason, as long as the clinical studies are still ongoing, health authority guidelines indicate that the same warnings and contraindications given with CHCs containing EE are warranted for preparations containing E2. These should also be considered for legal reasons. The pharmaceutical companies responsible for the development and marketing of these products are also concerned about selection bias, as it is possible that at-risk patients will be more likely to be prescribed the new alternative CHCs. In postmarketing observational trials, this may represent a bias leading to a false increased rate of events, because of the high-risk population included.

In this review, we have shown the neutral metabolic impact of CHCs containing E2 currently on the market (E2V/DNG and E2/NOMAc), but what is different between the two
preparations is also a matter of debate. In relation to the reported Pearl Index, the two CHCs are similarly effective. However, these data refer to their correct use. Unfortunately, the real use of every hormonal contraceptive, especially an oral one, does not correspond to the correct use. More than 30% of women may miss a pill at least once in a blister. In the case of a missed tablet, management of a quadruphasic regimen may be a problem, much less so when a monophasic association with a longer half-life and stronger antigonadotropic progestin is used [71]. From this point of view, E2/NOMAc should be safer for contraception even if one pill is missed; even two missed pills during days 8–17 of the cycle did not lead to more pregnancies [71]. Women should be informed about this issue in the contraceptive counseling phase. In addition, we know very little about how these two associations comparatively behave in improving symptoms of reproductive age, such as dysmenorrhea, endometriosis [29,72–74], heavy menstrual bleeding [15], or PCOS [40].

The use of E2 by parenteral routes of administration, though still at the embryonic stage, seems promising for future widespread methods of contraception.

In conclusion, it is important to avoid prescribing CHCs to women at elevated risk of DVT-VTE, according to the WHO Medical Eligibility Criteria for Contraceptive Use [3]. Women who have a higher risk of DVT-VTE due to smoking, obesity, or family history should undergo a personal risk assessment and be advised appropriately. The hormonal contraceptives with the lowest DVT-VTE risk are the progestin-only pills. For those women at a low baseline risk of DVT-VTE, the attempt to minimize the risk of DVT-VTE associated with the use of CHCs can be further optimized by selecting the preparation with the mildest metabolic impact to further reduce the residual risk currently observed with the use of modern CHCs.

It is easy to become enthusiastic for newer CHCs formulations. E2-based formulations appear to be the CHCs of the future generations, but before this possibility becomes true, extensive epidemiological studies on strong outcomes are necessary.

In the meantime, we may be enough confident that they are not more harmful than EE-based CHCs and that they can be effectively used for contraception.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as • of interest
** of considerable interest


• A simple milestone to guide the prescribers of contraceptives worldwide.


• Desogestrel is the most used progestin in hormonal contraception. This paper explores its multiple modes of administration.


• The first experiences with E2 in hormonal contraception.


**A large, randomized, open-label trial that directly compares the six-cycle treatment with E2/NOMAc versus EE/LNG.**


**What is the effect of hormonal contraceptives on glucose metabolism? A meta-analysis of the current available evidence.**


**Combined oral contraceptives and cardiovascular risk.**


41. Yildiz BO. Approach to the patient: contraception in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2015;100:794–802.


**Historical impact on blood pressure of oral contraceptives containing old types of estrogenic component.**


**Oral contraceptives containing E2 do not modify 24-h blood pressure.**


58. Leth I, Chabbert-Buffet N, Jamin C, et al. Haemostatic and metabolic impact of estradiol pills and drospirenone-containing ethinylestradiol pills vs. levonorgestrel-containing ethinylestradiol pills: a
A complete review of the specific topic.


A large, double-blind, randomized trial that compares the hemostatic effects of E2NOMAc versus EE/LNG.


Bone metabolism and hormonal contraception.


A randomized, open-label trial comparing the effect of E2 versus EE on bone metabolism after 2 years of treatment.


