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REVIEW ARTICLE

The impact of hormonal contraceptives containing estradiol, estradiol valerate, and estetrol on liver proteins, lipids, glucose, blood pressure, and bone. A literature review

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ABSTRACT

Objective: We investigated the metabolic profile induced by contraceptives containing body-identical oestrogens.

Methods: A literature search was made for articles on contraceptives with oestradiol/nomegestrol acetate (E2/NOMAc), oestradiol valerate/dienogest (E2V/DNG), estetrol/drospirenone (E4/DRSP) and metabolic parameters.

Results: The three formulations induced a similar, slight but significant increase of liver proteins. Levels of angiotensinogen were measured only during E4/DRSP, and were significantly increased ($p < 0.05$). Scanty data indicate a neutral effect of the three formulations on blood pressure. Lipids and lipoproteins were not modified by E2/NOMAc and E2V/DNG, while triglycerides slightly but significantly increased ($p < 0.05$) during E4/DRSP. Fasting glucose was unaffected by any association while fasting insulin increased during E2/NOMAc and E2V/DNG. Data were not reported for E4/DRSP. Insulin resistance was increased by E4/DRSP and not by E2V/DNG. Bone turnover was tested only in users of E2V/DNG. Markers of bone formation did not change while markers of bone absorption decreased. Bone mineral density (BMD) did not change after 6 months of E2V/DNG and after 2 years of E2/NOMAc. No data on BMD is available for users of E4/DRSP.

Conclusions: The three contraceptive formulations exert a similar, almost neutral effect on metabolism and blood pressure. Only a slight increase of triglycerides and a decrease of insulin sensitivity emerged with the use of E4/DRSP. The few data on bone, suggest a neutral effect of E2V/DNG and E2/NOMAc. There is no data evaluating the effect of the contraceptive association of E4/DRSP on bone.

Abbreviations: ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; BMD: Bone mineral density; CBG: Cortisol-binding globulin; DNG: Dienogest; DRSP: Drospirenone; E1: Oestrone; E2/NOMAc: Oestradiol plus nomegestrol acetate; E2: Oestradiol; E2V/DNG: Oestradiol valerate plus dienogest; E2V: Oestradiol valerate; E4/DRSP: Estetrol plus drospirenone; E4: Estetrol; EE: Ethinylestradiol; ER: Oestrogen receptor; HbA1c: Glycated haemoglobin A1c; HDL: High-density lipoprotein; HOMA-IR: Homeostasis model assessment of insulin resistance; LDL: Low-density lipoprotein; NOMAc: Nomegestrol acetate; OGTT: Oral glucose tolerance test; SHBG: Sex hormone-binding globulin; TBG: Thyroxine-binding globulin; VTE: Venous thromboembolism

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Introduction

For many years, combined hormonal contraceptives have contained an association of a progestin, usually an androgenic progestin, and an oestrogen, firstly mestranol, and then ethinylestradiol (EE). In the early ages, the interest was mainly focused on creating a contraceptive that was acceptable and effective in preventing pregnancies. The conservation of monthly menstrual periods was perceived as an important

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point to meet the woman desire, and it was obtained by designing a 21/7 day regimen of administration. Doses of both EE and progestin molecules were kept high to guarantee the contraceptive efficacy and a good cycle control.

Contraceptives were used by an increasing number of women of different civilised countries, and concomitantly to their widespread use, side effects emerged along with an increased risk of cardiovascular events [1]. Initially, an increased rate of arterial events became evident, namely myocardial infarction and stroke [2–4], and then of venous thromboembolism (VTE) [5,6]. Studies [1] reported dose-dependent negative effects of EE-based contraceptives on angiotensinogen, blood pressure, and coagulation, and of the associated androgenic progestin on lipid and glucose metabolism. Substitution of strong androgenic with less androgenic, non-androgenic, or antiandrogenic progestins reduced the negative effect on metabolism but increased the risk of VTE [1]. To avoid the increased risk of VTE, indications were given to use contraceptives with EE and androgenic progestins, like levonorgestrel, norethisterone, or norgestimate [7], the possible negative effect of these progestins on metabolism or arterial vessels being considered less important or negligible [7]. Reduction of EE doses or changes of the oestrogen component were also searched.

Body-identical oestrogens were introduced to overcome the critical balance between the risk and benefits associated with the use of contraceptives containing EE and androgenic progestins. In comparison to EE-based contraceptives, the formulation with oestradiol valerate (E2V) showed a very limited, if any, impact on body proteins [8]. Indeed, body-identical oestrogens emerged to exert minimal effect on coagulation and VTE risk [1,9–12], androgenic progestin being unnecessary to mitigate their effects. Ultimately this translated into a more neutral impact on women's metabolism [1].

Contraceptives with body-identical oestrogens include the associations of micronized oestradiol (E2) and nomegestrol acetate (NOMAc), approved by the European Medicine Agency (EMA) in 2011, the association of E2V and dienogest (DNG), approved by EMA in 2009, and the association of estetrol (E4) and drospirenone (DRSP), approved by EMA in 2021 [10,12–14]. All formulations are devoid of EE and of androgenic progestins, but differ in various characteristics, such as the regimen of administration, the type and dose of the oestrogen component, and the type of progestin used. The present review is an exercise to evaluate the similarities and differences exerted by these three formulations on women's metabolism.

Methods

Articles were searched on PubMed and Scopus. The search included terms like 'estradiol', 'estetrol' 'drospirenone', 'dienogest' 'nomegestrol', 'contraception', 'contraceptive', 'sex hormone binding globulin', 'cortisol binding globulin', 'thyroxine binding globulin', 'angiotensinogen', 'blood pressure' 'metabolism', 'lipid', 'lipoprotein', 'glucose', 'insulin', 'bone', 'bone turnover', 'bone mineral density'. We retrieved only the data considering the use of the contraceptive associations with biodentical hormones, excluding all the data obtained in animals or by the single components in different period of the woman life. Only prospective studies documenting the changes of metabolic parameters after a variable period of time were included. Information regarding the modifications induced by the three formulations of high-density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, total cholesterol (T-Chol), triglycerides, glucose, insulin, response to an oral glucose tolerance test (OGTT), insulin resistance, angiotensinogen, blood pressure, sex hormone binding globulin (SHBG), cortisol binding globulin (CBG), thyroxine binding globulin (TBG), bone mineral density, and bone turnover were retrieved. When available, registration materials of the different contraceptives were consulted, and data of interest considered. Data were described as reported in the original articles and as standardised mean change (SMC) with 95\% confidence intervals (CIs). SMC normalise the data to a universal unit of measure and allows comparison of the effects among different studies and different factors. Treatment effects are easier to interpret, confidence intervals not including the 0 being considered as significant. When the available data were sufficient, a metanalysis was performed on SMC values to compare changes induced by the different contraceptive formulations.

Literature overview

Characteristics of the contraceptive associations

E2/NOMAc

E2/NOMAc is a monophasic association of micronized E2 1.5 mg and NOMAc 2 mg, administered in a 24/4 regimen. During absorption, E2 is rapidly metabolised to a weaker oestrogen, oestrone (E1) (4% of the oestrogenic potency of E2), whose circulating levels represent a buffer for E2, E1 being in equilibrium and reconverted to E2 [10,15]. Following the oral administration of E2, the ratio E1/E2 is about 5/1 [16]. E2 has a short half-life of 90 min [15,16]. It circulates free for 2%, bound to sex hormone binding globulin (SHBG) for 37%, and to albumin for the remaining 61%. The active part of the hormone is the one that circulates either free or bound to albumin.

NOMAc is a potent progestin derived from 19-norprogesterone. It is devoid of androgenic, glucorticoid, and mineralcorticoid activities and it exerts modest antiandrogenic activity. It has a half-life of 46–50 h. In blood, it is bound to albumin but not to SHBG. NOMAc inhibits ovulation at a daily dose of 1.5 mg/day [13,17].

E2v/dng

E2V/DNG is a quadriphasic contraceptive association containing E2V 3 mg alone in the first two days, E2V 2 mg/DNG 2 mg from day 3 to 7, E2V 2 mg/ DNG 3 mg from day 8 to 24, E2V 1 mg on day 25 and 26, and placebo on days 27 and 28. E2 reaches and maintains steady state levels in blood between days 3 and 24. Twenty-four hour exposure to E2 is similar on day 1 and day 24 [16]. The intestinal mucosa entirely absorbs E2V, and the cleavage of E2 and valeric acid takes place during absorption or hepatic first pass [16]. One mg of E2V corresponds to 0.76 mg of E2 [13]. E2 is rapidly metabolised to E1 during its absorption and in the liver, and levels of E1 exceeds those of E2 in a E1/E2 ratio of 5/1 [16]. E2 circulates free for 2%, bound to SHBG for 37% and to albumin for 61%. It has a half-life of 90 min [16]. E1 serves as a buffer for circulating E2 [15].

DNG is a potent progestin derived from 19-nortestosterone, but for the presence of a cyanomethyl group in position C17alfa, has some properties of progesterone derivatives [16]. It lacks oestrogenic, glucocorticoid, mineralocorticoid, and androgenic properties and demonstrates a consistent antiandrogenic activity *in vivo* that is 40% that of cyproterone acetate [16,18]. DNG has a half-life of about 11 h and circulates bound to albumin (90%), but not to SHBG [16]. When given alone, it inhibits ovulation at the dose ≥ 2 mg [19].

E4/drsp

E4/DRSP is a monophasic association of E4 15 mg and DRSP 3 mg. E4 is a hormone produced by the human foetus in progressively higher quantities during the second half of pregnancy [20]. Once absorbed, it is not metabolised to other compounds by the liver, and it is excreted with urine (69%) and faeces (22%) in a conjugated form. In blood, it does not bind to SHBG and circulates free for 50% [21] with a half-life of 28 h [22]. E4 exhibits an oestrogenic potency 6% to 10% that of E2, and is characterised by a distinct receptor activity [20]. It acts as an agonist on nuclear oestrogen receptor (ER) alpha and beta, with a 5 times higher affinity for ER-alpha, and it acts as an antagonist on membrane ER-alpha.

DRSP is a derivative of spironolactone, lacking glucocorticoid and mineralocorticoid activities while demonstrating anti-mineralocorticoid and anti-androgenic activities. The anti-mineralocorticoid activity is 8 times higher than that of spironolactone [23], and the antiandrogenic activity is 30% that of cyproterone acetate [24]. Once absorbed, 95-97% of DRSP circulates bound to albumin and 3-5% is free. It does not bind to SHBG and has a half-life of 25–33 h [24,25]. DRSP completely inhibits ovulation at a dose of 3 mg/day when given alone or at a dose of 2 mg/day when given in association with EE [25].

Effect on inducible liver proteins

SHBG

Administration of E2/NOMAc, increased SHBG of about 60% after 3 months [26] and of 44% after 6 months of use ($p < 0.02$) [27,28].

Administration of E2V/DNG, increased SHBG of 45% after 6 months ($p < 0.01$) [29]. In another study, administration of E2V/DNG increased SHBG of 56% after 9 weeks ($p < 0.05$) [30], and of 62.7% after 6 months of use [31].

Administration of E4/DRSP, increased SHBG of 51% after 3 months and of 55% after 6 months of use ($p < 0.05$) [32].

A cross-sectional study found that levels of SHBG were similar among users of the 3 contraceptive formulations, and lower than those observed in users of EE-based associations [33].

The increase of SHBG induced by the 3 contraceptive associations is similar when data are expressed as SMC (Table 1).

CBG

Administration of E2/NOMAc increased CBG of about 27% after 6 months of use [27].

There is no data regarding the effect of E2V/DNG on CBG.

Administration of E4/DRSP, increased CBG of 36% after 3 months and of 40% after 6 months of use ($p < 0.05$) [32].

The increase of CBG induced by E2/NOMAc is similar to that induced by E4/DRSP when the data are expressed as SMC (Table 1).

TBG

Administration of E2/NOMAc was associated with an increase of TBG of about 21% after 6 months of use [27].

There is no data regarding the effect of E2V/DNG on TBG.

Administration of E4/DRSP was associated with an increase of TBG of 27% after 3 months and of 17% after 6 months of use ($p < 0.05$) [32].

The increase of TBG induced by E2/NOMAc is similar to that induced by E4/DRSP, when the data are expressed as SMC (Table 1).

Effects on angiotensinogen and blood pressure

No study has reported the modifications of angiotensinogen induced by the administration of E2/NOMAc or E2V/DNG. During E4/DRSP, angiotensinogen levels significantly increased of 50% after 3 months and of 70% after 6 months of treatment ($p < 0.05$) [32]. The increase induced by E4/DRSP of angiotensinogen is similar to that induced on SHBG or CBG (Table 1).

Table 1. Modifications of liver proteins observed during the administration of contraceptive associations containing micronized oestradiol and nomegestrol acetate (E2/NOMAc), oestradiol valerate and dienogest (E2V/DNG), or estetrol and drospirenone (E4/DRSP), expressed as standardised mean change (SMC) (95% confidence interval).

.	N	3 months	p-value*	6 months	p-value*
SHBG			—		—
E2/NOMAc [27]	60	0.55 (0.27, 0.82)		0.62 (0.34, 0.89)	
E2V/DNG [30]	20	0.65 (0.17, 1.13)			
E4/DRSP [32]	38	0.93 (0.55, 1.31)		0.91 (0.53, 1.28)	
CBG			—		—
E2/NOMAc [27]	60	0.64 (0.37, 0.92)		0.64 (0.36, 0.92)	
E2V/DNG	—	—		—	
E4/DRSP [32]	38	0.78 (0.42, 1.14)		0.97 (0.58, 1.35)	
TBG			—		—
E2/NOMAc [27]	60	0.91 (0.61, 1.21)		0.83 (0.54, 1.13)	
E2V/DNG	—	—		—	
E4/DRSP [32]	38	0.25 (−0.07, 0.58)		0.48 (0.15, 0.82)	
Angiotensinogen			—		—
E2/NOMAc	—	—		—	
E2V/DNG	—	—		—	
E4/DRSP [32]	38	0.79 (0.42, 1.15)		1.04 (0.65, 1.43)	

Numbers in brackets indicate the reference in the manuscript. *Statistical comparison among treatments was possible only when sufficient data were available.

Both preclinical data [28] and one study using 24-hour ambulatory blood pressure monitoring indicated a neutral effect of E2/NOMAc on blood pressure [34].

A neutral effect of E2V/DNG on blood pressure was observed in one study monitoring ambulatory blood pressure [34].

Among individuals with at least one cardiovascular risk factor, the use of E4/DRSP induced hypertension in fewer than 2% of users [35]. Data published in abstract form [36] suggest a neutral effect of E4/DRSP on office blood pressure, and no information is available regarding its effect on ambulatory blood pressure (24-hour monitoring).

Effects on lipids and lipoproteins

The administration of E2/NOMAc did not significantly modify HDL-cholesterol, LDL-cholesterol, total cholesterol, triglycerides, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) [37,38] (Table 2).

The administration of E2V/DNG did not significantly modifiy HDL-cholesterol, LDL-cholesterol, total cholesterol, triglycerides, ApoA1, or ApoB [31,39] (Table 2).

The administration of E4/DRSP did not significantly modify HDL-cholesterol, LDL-cholesterol, or total cholesterol. ApoA1 increased of approximately 4% after 6 months ($p < 0.05$), and similarly, ApoB increased of about 4.5% after both 3 and 6 months ($p < 0.05$). Triglycerides increased of 10% and 24% after 3 and 6 months of treatment, respectively ($p < 0.05$) [32] (Table 2). Metanalysis of SMC data indicates that the increase of triglycerides observed after 3 months of E4/DRSP administration is significantly higher than that observed with the administration of the other 2 contraceptive associations ($p = 0.059$), and that a similar elevation is observed also after 6 months of treatment (Table 2 and Figure 1).

Effects on glucose and insulin metabolism

Administration of E2/NOMAc did not alter fasting glucose [38], the glucose and insulin response to an oral glucose tolerance test (OGTT), or HbA1c levels (Table 3) [37].

E2V/DNG did not alter fasting glucose, insulin resistance as assessed by HOMA-IR, or the insulin responses to an OGTT, while slightly increased fasting insulin and the glucose response to an OGTT

Table 2. Metanalysis of the modifications of lipids observed during the administration of contraceptive associations containing micronized oestradiol and nomegestrol acetate (E2/NOMAc), oestradiol valerate and dienogest (E2V/DNG), or estetrol and drospirenone (E4/DRSP), expressed as standardised mean change (SMC) (95% confidence interval).

	N	3 months	p-value*	N	6 months	p-value*
Tot Cholesterol			**0.653**			—
E2/NOMAc [37,38]	80	−0.15 (−0.4, 0.1)		60 [37]	0.01 (−0.24, 0.27)	
E2V/DNG [39]	30	0.07 (−0.42, 0.56)		30 [31]	−0.16 (−0.52, 0.2)	
E4/DRSP [32]	38	0.01 (−0.31, 0.33)		38 [32]	0.25 (−0.07, 0.58)	
HDL-Cholesterol			**0.861**			—
E2/NOMAc [37,38]	80	−0.04 (−0.26, 0.18)		60 [37]	0.09 (−0.17, 0.34)	
E2V/DNG [39]	30	0.02 (−0.47, 0.51)		30 [31]	0 (−0.36, 0.36)	
E4/DRSP [32]	38	0.07 (−0.25, 0.39)		38 [32]	0.1 (−0.22, 0.42)	
LDL-Cholesterol			**0.728**			—
E2/NOMAc [37,38]	80	−0.09 (−0.31, 0.13)		60 [37]	−0.11 (−0.36, 0.15)	
E2V/DNG [39]	30	−0.01 (−0.5, 0.48)		30 [31]	−0.36 (−0.73, 0.01)	
E4/DRSP [32]	38	0.06 (−0.26, 0.38)		38 [32]	0.04 (−0.28, 0.36)	
Triglycerides			**0.059**			—
E2/NOMAc [37,38]	80	−0.12 (−0.39, 0.14)		60 [37]	0.05 (−0.21, 0.3)	
E2V/DNG [39]	30	0.04 (−0.45, 0.53)		30 [31]	0.27 (−0.09, 0.64)	
E4/DRSP [32]	38	0.45 (0.12, 0.78)		38 [32]	0.59 (0.25, 0.94)	
Apolipoprotein-A1			**0.366**			—
E2/NOMAc [37,38]	80	0.01 (−0.21, 0.23)		60 [37]	0.08 (−0.17, 0.33)	
E2V/DNG [39]	16	0.05 (−0.44, 0.54)				
E4/DRSP [32]	38	−0.25 (−0.58, 0.07)		38 [32]	0.2 (−0.12, 0.52)	
Apolipoprotein-B			**0.991**			—
E2/NOMAc [37,38]	80	0.1 (−0.24, 0.43)		60 [37]	0.03 (−0.22, 0.28)	
E2V/DNG [39]	16	0.09 (−0.4, 0.58)				
E4/DRSP [32]	38	0.13 (−0.19, 0.45)		38 [32]	0.23 (−0.09, 0.56)	

Numbers in brackets indicate the reference as cited in the manuscript. *Statistical comparison was possible only when sufficient data were available.

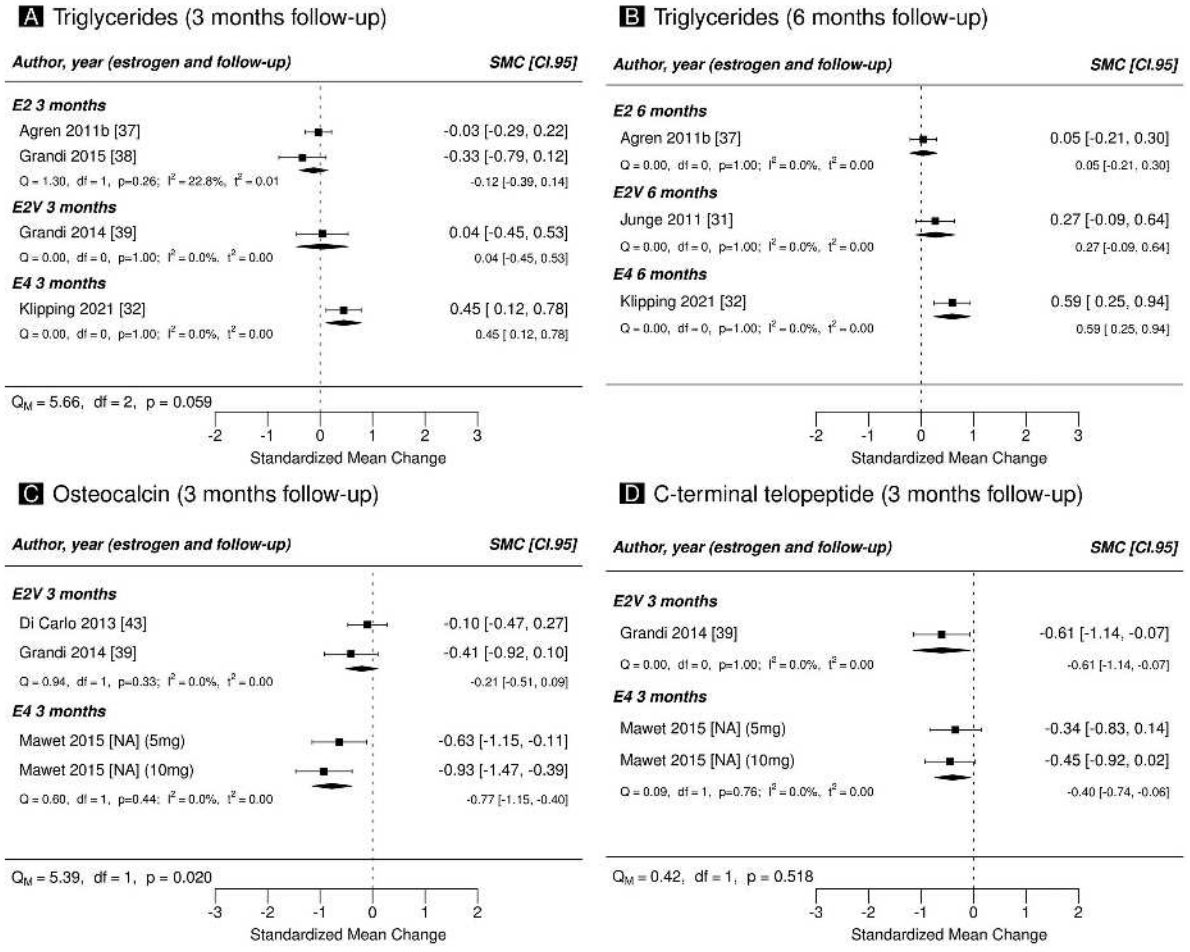

Figure 1. Metanalysis of the modifications of triglycerides (panel A and B) and the marker of bone formation osteocalcin (panel C) and of bone absorption C-terminal telopeptide (panel D), induced by the administration of the different contraceptive association containing micronized oestradiol and nomegestrol acetate (E2/NOMAc), oestradiol valerate and dienogest (E2V/DNG), or estetrol and drospirenone (E4/DRSP).

[39,40] (Table 3). Only a single study performed in women with polycystic ovary syndrome, reported that E2V/DNG reduces fasting insulin and insulin resistance measured by HOMA-IR, and the insulin and glucose response to an OGTT [41].

Administration of E4/DRSP increased fasting insulin and insulin resistance, as indicated by HOMA-IR, but it did not affect the glucose response to an OGTT [32] (Table 3).

Effects on bone turnover and bone mineral density (BMD)

No study has evaluated the effect of E2/NOMAc on markers of bone turnover.

The administration for 3 months of E2V/DNG to 16 women significantly reduced markers of bone absorption (CTX from 0.61 ± 0.32 to 0.35 ± 0.25 ng/ml;($p < 0.001$), and to a lesser extent markers of bone formation (osteocalcin from 12.0 ± 4.5 to 9.6 ± 3.0 mcg/ml; $p < 0.05$) [39]. Another study showed that the administration for 6 months of E2V/DNG to 30 women, significantly decreased ($p < 0.05$) the markers of bone absorption, urinary pyridinoline (from 33.2 ± 5.2 to 24.6 ± 4.6 mmol/mmolCr) and deoxypyridinoline (from 8.1 ± 1.1 to 5.8 ± 0.9 mmol/mmolCr), without modifying the marker of bone formation osteocalcin (from 6.8 ± 0.7 to 6.7 ± 0.7 ng/ml) [43], as previously reported [44]. No data are currently available on the effect of commercially available dosages of E4/DRSP, i.e., E4 15 mg/DRSP 3 mg, on the markers of bone turnover. There are data obtained with the association of E4 given in daily doses of 5 or 10 mg associated with DRSP 3 mg [45]. The results indicate a reduction of bone reabsorption (CTX) independent on the dose and similar to that observed with E2V/DRSP, but also a significant decrease of bone formation (osteocalcin) that at the metanalysis was not documented with E2V/DNG (Figure 1).

Table 3. Modifications of glucose-insulin parameters observed during the administration of contraceptive associations containing micronized oestradiol and nomegestrol acetate (E2/NOMAc), oestradiol valerate and dienogest (E2V/DNG), or estetrol and drospirenone (E4/DRSP), expressed as standardised mean change (SMC) (95% confidence interval).

	N	3 months	p-value*	6 months	p-value*
Glucose			**0.486**		—
E2/NOMAc [38]	15	−0.04 (−0.55, 0.47)			
E2V/DNG [39–41]	36	−0.25 (−0.8, 0.29)			
E4/DRSP [32]	38	0.28 (−0.04, 0.61)		0.31 (−0.02, 0.63)	
Insulin			**0.909**		—
E2/NOMAc	—	—		—	
E2V/DNG [39–41]	36	0.48 (0.05, 0.91)			
E4/DRSP [32]	38	0.44 (0.11, 0.78)		0.44 (0.1, 0.77)	
HOMA-IR			**0.671**		—
E2/NOMAc	—	—		—	
E2V/DNG [39–41]	36	0.34 (−0.23, 0.91)			
E4/DRSP [32]	38	0.54 (0.2, 0.88)		0.53 (0.19, 0.87)	
Glucose AUC OGTT			—		—
E2/NOMAc [37]	60	0.04 (−0.21, 0.3)		−0.08 (−0.33, 0.17)	
E2V/DNG [40]	20	0.78 (0.28, 1.28)			
E4/DRSP [32]	38	−0.04 (−0.36, 0.28)		0.11 (−0.21, 0.43)	
Insulin AUC OGTT			—		—
E2/NOMAc [37]	60	0.12 (−0.14, 0.37)		0.07 (−0.18, 0.33)	
E2V/DNG [40]	20	0.25 (−0.2, 0.69)			
E4/DRSP	—	—		—	

OGTT: oral glucose tolerance test; AUC: area under the curve; HOMA-IR: homeostatic model assessment of insulin resistance.
Numbers in brackets indicate the reference as cited in the manuscript. *Statistical comparison was possible only when sufficient data were available.

In preclinical studies the administration of E2/NOMAc did not affect bone mineral density (BMD) [28] and the administration of E2/NOMAc to 56 women aged 20 to 35 years for 2 years did not modify BMD [42].

The administration of E2V/DNG for 6 months also did not affect BMD [43].

There are no data on the effect of the contraceptive association E4/DRSP on BMD.

Discussion

Few studies have investigated the metabolic impact of contraceptives containing body-identical oestrogens, most research being concentrated on efficacy, cycle control, side effects, and coagulation. The post-authorization safety studies on E2V/DNG [46,47] and E2/NOMAc [11,12] documented the safety profile mainly on VTE and, to a lesser extent, on arterial thrombosis of these formulations. Due to the more recent introduction on the market, the post-authorization safety study for E4/DRSP is presently ongoing [48].

Most metabolic modifications associated with the use of hormonal contraceptives depend on the balance between the oestrogenic and the androgenic stimuli exerted on the liver [1]. Contraceptives with body-identical hormones do not contain androgenic progestin capable of counteracting the effect of oestrogens, but the oestrogenic stimulus is weaker than that exerted by EE. Some considerations may indicate a different oestrogenic stimulus exerted by the 3 formulations containing body-identical oestrogens. E2 is given in a single constant dose of 1.5 mg for 24 days, while E2V is administered in 3 different doses ranging from 1 to 3 mg for 26 days. E4 has a lower potency than E2 but is given in quantities that are 10 times higher than E2 [20]. Furthermore, in comparison to E2, E4 does not bind to SHBG [21], has a longer half-life (28 h vs 90 min) [16,22], is not converted to weaker oestrogens, like E1 [15], has a preferential affinity for nuclear ER-alpha, and acts as an antagonist on membrane ER-alpha [20].

Besides these important differences, the analysis of the data indicates that the stimulus exerted by these 3 contraceptive formulations on oestrogen-inducible liver proteins is similar. The increase of SHBG is similar among the 3 formulations, and the rise of CBG and TBG induced by E2/NOMAc is similar to that exerted by E4/DRSP. Modification of angiotensinogen was not documented with E2/NOMAc and E2V/DNG. Angiotensinogen was increased by E4/DRSP [32] to an extent similar to the other liver proteins, but this does not seem to be associated with an increase of blood pressure probably for the anti-mineral corticoid properties of the associated progestin DRSP [49]. Few preclinical [28] clinical [32,35,36] and 24-h ambulatory blood pressure evaluations [34] indicate that the contraceptive

associations of E2/NOMAc and E2V/DNG do not significantly modify blood pressure. These findings contrast with contraceptives containing EE, which elevate blood pressure in a dose-dependent manner [13], except for those that include DRSP as progestin [49].

E2/NOMAc and E2V/DNG induce subtle non-significant modification of lipids and lipoproteins. E4/DRSP slightly and similarly increases ApoA1 and ApoB, to an extent that was not significant at metanalysis (Table 2). Triglycerides were significantly increased only by the administration of E4/DRSP [32], a modification usually associated with the administration of oestrogen with a high oestrogenic activity like EE [13]. The increase induced by E4/DRSP is minimal but yet it may suggest caution in conditions of already elevated levels of triglycerides.

There is a lack of precise data on insulin sensitivity measured by appropriate tools of investigation, i.e., the clamp or the minimal model method [50]. Insulin sensitivity was roughly evaluated by HOMA-IR on fasting blood samples of women using E2V/DNG and E4/DRSP, but not E2/NOMAc. Insulin sensitivity was not modified [39,40], or increased in one study [41] by E2V/DNG, while it was decreased by E4/DRSP [32]. The latter is consistent with the elevation of triglycerides reported with the administration of this contraceptive association [32], triglycerides being induced by insulin resistance and inducing insulin resistance [51]. The response of glucose to OGTT was not modified by the administration of E4/DRSP and unfortunately that of insulin was not reported. In the long-term a condition of insulin resistance may have detrimental metabolic and cardiovascular effects [51], and more specific studies to test insulin-glucose metabolism in users of E4/DRSP are worthy to be performed. None of the other 2 associations modified the response of insulin to an OGTT, but the response of glucose was slightly higher during E2V/DNG. However, one study performed in women with polycystic ovary syndrome documented that the use of E2V/DNG improves insulin sensitivity and reduces the response of insulin and glucose to an OGTT [41].

Data on bone metabolism are limited. Among the available contraceptive associations, only E2V/DNG has been studied in relation to markers of bone turnover. Findings indicate that bone turnover decreases, with markers of bone absorption showing a greater reduction than markers of bone formation. This pattern suggests the induction of a positive bone balance [39,43,44]. The neutral effect on bone mineral density (BMD) was documented after 6 months of E2V/DNG administration, a period too short to reach definitive conclusions, because any modification that bone can have in 6 months is within the coefficient of variation of the densitometric analysis [43]. A more appropriate evaluation was performed with E2/NOMAc, which, after 2 years of use, did not modify BMD of 56 women in reproductive age [42]. There is no data on the modification of bone markers or BMD induced by the administration of the contraceptive association E4/DRSP. Modifications of bone markers were investigated with the use of 5 and 10 mg E4 associated with DRSP 3 mg or 5, 10, and 20 mg E4 associated with levonorgestrel 150 mcg [45]. None of these associations is on the market as a contraceptive. The data obtained with these different combinations indicate that E4 induces a similar decrease of bone formation and bone absorption [45]. Interestingly, bone formation decreased significantly with all the associations of E4 and DRSP (3 mg) and not with those containing levonorgestrel (150 mcg), apart from the association E4 20 mg/levonorgestrel 150 mcg [44]. Accordingly, the effect of E4 on bone appears to be modulated by the associated progestin, DRSP being probably less advantageous than levonorgestrel [44]. The absence of clinical data on the effect exerted by E4 15 mg/DRSP 3 mg on women's bones is an important lack of knowledge that requires dedicated research to be fully evaluated.

Limitations

The present analysis included very few articles reporting scant evidence. Modifications of some parameters were not investigated with all three formulations, and some results were obtained after a different period of exposure to the compound. Accordingly, the attempt to compare the data is somewhat biased by these differences. In some studies, the modifications were reported only in a descriptive fashion without any inferential analysis. Yet the authors of these articles, in wording the description of the observed modifications, reported 'increase' or 'decrease' that we interpreted and herein reported as meaningful modifications of the parameter under consideration. These limitations were partially solved by changing the retrieved changes to SMC. Changes were considered significant when the SMC confidence interval

did not include the 0 value. Furthermore, when sufficient data were available SMC induced by the different associations were compared by metanalysis.

The age of women receiving E4/DRSP ranged between 18 and 50 years [32] while most of the metabolic data on E2/NOMAc or E2V/DNG were obtained in women 18 to 35 years of age [38–41]. Because of the superimposition of the age ranges we could not correct for this variable and is difficult to ascertain how much this may have influenced the results, for example the different modification of insulin resistance observed among the three contraceptive associations.

Conclusions

Contraceptives containing body-identical oestrogens and antiandrogenic progestin exhibit distinct pharmacokinetic and pharmacodynamic characteristics. Their oestrogenic effects on liver metabolism are comparable and almost neutral. The effects on triglycerides and insulin sensitivity with E4/DRSP seem to be less favourable compared to the other two formulations; however, the differences are minimal. Limited studies have assessed the effect of these contraceptive formulations on blood pressure. The limited data suggest a neutral influence on blood pressure. E2V/DNG and E2/NOMAc appear to have no harmful impact on bone; however, this conclusion is derived from markers of bone turnover and limited evidence regarding BMD. Currently, there is no evidence regarding the effect exerted by the E4/DRSP contraceptive association on bone health.

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Author contributions

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Ethical approval and consent to participate

The present study is exempt from ethical approval since this review only involves anonymous data, which has already been published.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data were extracted from previously published studies; thus, they are publicly available.

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