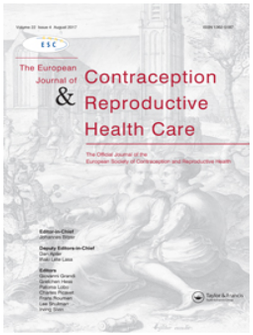

The European Journal of Contraception & Reproductive Health Care

ISSN: 1362-5187 (Print) 1473-0782 (Online) Journal homepage: http://www.tandfonline.com/loi/iejc20

Estradiol in hormonal contraception: real evolution or just same old wine in a new bottle?

Giovanni Grandi, Fabio Facchinetti & Johannes Bitzer

To cite this article: Giovanni Grandi, Fabio Facchinetti & Johannes Bitzer (2017) Estradiol in hormonal contraception: real evolution or just same old wine in a new bottle?, The European Journal of Contraception & Reproductive Health Care, 22:4, 245-246, DOI: 10.1080/13625187.2017.1372571

To link to this article: https://doi.org/10.1080/13625187.2017.1372571

Published online: 13 Sep 2017.

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE, 2017
VOL. 22, NO. 4, 245–246
https://doi.org/10.1080/13625187.2017.1372571

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Estradiol in hormonal contraception: real evolution or just same old wine in a new bottle?

The first combined hormonal contraceptive (CHC) was introduced in 1960 by Gregory Pincus [1] composed by an oral estrogenic and progestin component mestranol and norethinodrel, respectively.

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 [2]. The EE doses were gradually decreased up to 15 μg. At the same time, numerous different generations of progressively weaker androgenic and even anti-androgenic progestins were tested in order to have products that better fits individual needs. The replacement of EE with estradiol (E2), the estrogen naturally secreted by the granulosa cells of the human ovary, was difficult because of the failure to achieve a satisfactory bleeding control [3].

The first oral preparation, composed of the quadriphasic combination of estradiol valerate (E2V) and dienogest (DNG), was marketed in 2009 in Europe and US in by Bayer HealthCare (Leverkusen, Germany) (Europe: Qlaira®, Klaira®; USA: Natazia®) [4]. A few years later in 2012 another monophasic combined hormonal contraceptive composed by micronized 17-β estradiol and nomegestrol acetate (NOMAc) was introduced in the European market by Teva Pharmaceutical Industries Ltd. (Petah Tiqwa, Israel) (Zoely®) [5]. These preparations combine progestins with a strong action on the endometrium and progestational activity, like DNG and NOMAc, with E2V or E2. The recent introduction of a new particular progestin, called nestorone (NES), a potent 19-nor-progesterone derivative when given parenterally via sustained release formulations, has opened new horizons in the non-oral release of E2 [6]. Among synthetic progestins, NES has the highest antiovulatory activity and a neutral metabolic profile, associated with no androgenic activity. NES is not active orally but it is rapidly absorbed through the skin and the mucosal epithelium. Combinations of E2 and NES are extensively under investigation using an advanced transdermal deliver gel contraceptive [7] and by transvaginal route.

Theoretically, products containing E2 should be associated with less cardiovascular events in comparison to those containing EE [8]: indeed, the impact of these new preparations on secondary minor metabolic end-points, such as lipid and glucose metabolism [9–13], the hemostatic system [9,10,14] and blood pressure [15] seems milder than that caused by EE-based ones. However, population data were missing.

Recently, the International Active Surveillance study 'Safety of Contraceptives: role of Estrogens' (INAS-SCORE) [16,17] investigated the cardiovascular risks and the effectiveness associated with the use of the CHC containing E2V/DNG compared to other EE-based ones in a routine clinical setting. A cohort of more than 50,000 new users between Europe and USA was actively monitored for up to five years for the occurrence of rare or unexpected adverse outcomes possibly related to CHC exposure. This study showed a significant reduction of about 60% venous thromboembolic events (VTE) and of about 50% serious cardiovascular events in E2V/DNG group in comparison to other EE-based CHCs as a whole [16]. The difference in risk with respect to EE/LNG containing CHCs was only a trend and did not reach statistical significance. This will need still a larger study. There is however proof of non inferiority thus providing best available safety with different progestogenic properties compared to LNG combinations.

The contraceptive failure rate was 0.5 and 1.9 events/100 women years in Europe and in USA, respectively, mainly due to differences in compliance and body mass index (BMI) [17]. Furthermore, E2V/DNG showed a statistically significant halved risk of contraceptive failure rates compared to other EE-based CHCs, maintained after accounting for potential confounders such as age, parity and smoking [17]. This effect is probably due to the longer estrogen phase and reduced hormone-free period with E2V/DNG (26 + 2 vs. the traditional 21 + 7) that can provide better contraceptive efficacy, as already shown with other formulations [18,19]. The spontaneous pregnancy rate after stopping the different CHCs was similar [17].

Hormonal contraceptives were originally designed to avoid unintended pregnancies giving the least possible side effects: with the important limitations of this observational study [16,17], its promising results indicate that the most serious and feared side effects during CHCs use (such as VTEs and other cardiovascular events) could be at least halved with the use of E2V/DNG, being associated with an almost doubled contraceptive efficacy. These results should be theoretically similar or even better for E2 and NOMAc [14], although population data are still lacking. If these results will be confirmed, these preparations could sign a real evolution in CHC technology over the next few years. This is especially true if combinations with E2 could be developed for transdermal or transvaginal applications thus theoretically lowering cardiovascular risk even more.

Disclosure statement

G. Grandi received honoraria for participation in advisory boards from Teva.

F. Facchinetti reports no conflicts of interest.

J. Bitzer received honoraria for lectures and participation in advisory boards from Bayer AG, Merck, Libbs, Actavis, Teva, Exeltis, Gedeon Richter, Boehringer-Ingelheim, Vifor, Lilly, Pfizer, HRA, Abbott, Mithra, Pierre Fabre and Aspen.

References

[1] Pincus G, Garcia CR, Rock J, et al. Effectiveness of an oral contraceptive. Science. 1959;30:81–83.

[2] Grandi G, Cagnacci A, Volpe A. Pharmacokinetic evaluation of desogestrel as a female contraceptive. Expert Opin Drug Metab Toxicol. 2014;10:1–10.

[3] Fruzzetti F, Bitzer J. Review of clinical experience with estradiol in combined oral contraceptives. Contraception. 2010;81:8–15.

[4] Mansour D. Qlaira: a 'natural' change of direction. J Fam Plann Reprod Health Care. 2009;35:139–142.

[5] Yang LP, Plosker GL. Nomegestrol acetate/estradiol: in oral contraception. Drugs 2012;72:1917–1928.

[6] Kumar N, Koide SS, Tsong Y, et al. Nestorone: a progestin with a unique pharmacological profile. Steroids. 2000;65:629–636.

[7] Brache V, Merkatz R, Kumar N, et al. A dose-finding, cross-over study to evaluate the effect of a Nestorone®/Estradiol transdermal gel delivery on ovulation suppression in normal ovulating women. Contraception. 2015;92:289–297.

[8] Grandi G, Napolitano A, Cagnacci A. Metabolic impact of combined hormonal contraceptives containing estradiol. Expert Opin Drug Metab Toxicol. 2016;12:779–787.

[9] Junge W, Mellinger U, Parke S, et al. Metabolic and haemostatic effects of estradiol valerate/dienogest, a novel oral contraceptive: a randomized, open-label, single-centre study. Clin Drug Investig. 2011;31:573–584.

[10] Ågren UM, Anttila M, Mäenpää-Liukko K, et al. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism. Eur J Contracept Reprod Health Care. 2011;16:444–457.

[11] Grandi G, Piacenti I, Volpe A, et al. Modification of body composition and metabolism during oral contraceptives containing nonandrogenic progestins in association with estradiol or ethinyl-estradiol. Gynecol Endocrinol. 2014;30:676–680.

[12] Grandi G, Napolitano A, Xholli A, et al. Effect of oral contraceptives containing estradiol and nomegestrol acetate or ethinylestradiol and chlormadinone acetate on primary dysmenorrhea. Gynecol Endocrinol. 2015;31:774–778.

[13] De Leo V, Fruzzetti F, Musacchio MC, et al. Effect of a new oral contraceptive with estradiol valerate/dienogest on carbohydrate metabolism. Contraception. 2013;88:364–368.

[14] Lete 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 literature review. Eur J Contracept Reprod Health Care. 2015;20:329–343.

[15] Grandi G, Xholli A, Napolitano A, et al. Prospective measurement of blood pressure and heart rate over 24 h in women using combined oral contraceptives with estradiol. Contraception. 2014;90:529–534.

[16] Dinger J, Do Minh T, Heinemann K. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. Contraception. 2016;94:328–339.

[17] Barnett C, Hagemann C, Dinger J, et al. Fertility and combined oral contraceptives - unintended pregnancies and planned pregnancies following oral contraceptive use - results from the INAS-SCORE study. Eur J Contracept Reprod Health Care. 2017;22:17–23.

[18] Dinger JC, Minh TD, Buttmann N, et al. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. Obstet Gynecol. 2011;117:33–40.

[19] London A, Jensen JT. Rationale for eliminating the hormone-free interval in modern oral contraceptives. Int J Gynaecol Obstet. 2016;134:8–12.

Giovanni Grandi

Azienda Ospedaliero-Universitaria Policlinico of Modena, Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Modena, Italy

grandi.gio@alice.it

Fabio Facchinetti

Azienda Ospedaliero-Universitaria Policlinico of Modena, Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Modena, Italy

Johannes Bitzer

Universitätsspital Basel, Department of Obstetrics and Gynecology, University of Basel, Basel, Switzerland and Editor-in-Chief, The European Journal of Contraception & Reproductive Health Care

Received 7 August 2017; accepted 23 August 2017