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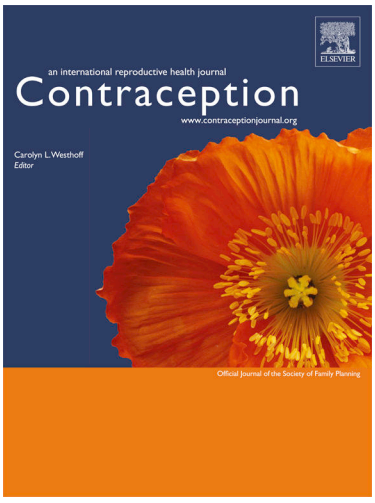

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Ethinyl Estradiol vs Estradiol Valerate in Combined Oral Contraceptives - Effect on Glucose Tolerance: A Randomized, Controlled Clinical Trial

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Disclosures

OH serves occasionally on advisory boards for Bayer, Gedeon Richter, HRA Pharma, and Vifor Pharma, and has lectured at educational events for Bayer, Gedeon Richter, and Sandoz. TP has served on advisory boards for Merck, Gedeon Richter, Roche, Astra Zeneca, Exeltis, MSD, Ferring, Finnish Medical Association, and Ajaton Terveys. The other authors report no conflict of interest.

Abstract

Objective

To compare the effects of two formulations of combined oral contraceptives (COCs), estradiol valerate (EV) and ethinyl estradiol (EE) combined with dienogest (DNG), and DNG-only, on glucose tolerance.

Study Design

We performed a randomized, controlled 9-week clinical trial. Inclusion criteria were: age 18–35 years, regular menstrual cycle (28±7 days), no polycystic ovaries, non-smoking, no contraindications for COC use and a 2-month wash-out from hormonal contraceptive use. The women were randomized to EV+DNG (n=20), EE+DNG (n=20), and DNG-only (n=19), and evaluated at baseline, at 4-5 weeks and 8-9 weeks of treatment. Study medications were used continuously for 63 days. Primary outcome measure was change in the whole-body insulin sensitivity index (Matsuda index) derived from the oral glucose tolerance test (OGTT) over the treatment period. Secondary outcome measures were area under curves (AUC) of glucose and insulin, homeostatic model assessment – insulin resistance (HOMA-IR) and Insulin Sensitivity Index (ISI).

Results

Fifty-nine women enrolled, and 56 women completed the study. The Matsuda index changed from baseline as follows (mean percentage change, mean change [95%CI]): DNG-only -12%, -1.45 [95%CI -3.22–0.325] *P*=0.10; EV+DNG +2.7%, -0.10 [-1.34–1.14] *P*=0.86; EE+DNG -5.5%, -1.02 [-

2.51–0.46] *P*=0.16, comparing the groups *P*=0.27. There were no clinically significant differences in glucose tolerance between the COC groups, but the DNG-only group showed an improvement in the 2-hour glucose levels (5.5 [95%CI 5.0-6.0] to 4.7 mmol/l [4.2-5.2], *P*=0.001).

Conclusion

We found no clinically significant differences between EV and EE combined with DNG and DNG-only on glucose tolerance in healthy, young, normal-weight women, indicating that these preparations appear close to neutral regarding glucose metabolism when used continuously for nine weeks.

Keywords: combined oral contraception; dienogest; ethinyl estradiol, estradiol valerate; glucose tolerance; oral glucose tolerance test

Trial registration number: EU Clinical trials register, EudraCT 2014-001243-20; ClinicalTrials.gov, NCT 02352090.

Implications

Combinations of both ethinyl estradiol and natural estradiol (estradiol valerate) with dienogest (DNG), as well as DNG-only, seem metabolically safe in young and healthy women in short-term continuous use.

1. Introduction

Combined oral contraceptives (COCs), used by millions of women worldwide, have been linked to worsened glucose tolerance [1–7]. Reduced glucose tolerance has been associated particularly with preparations containing high-dose ethinyl estradiol (EE) and androgenic progestins [8]. Our previous study on healthy, normal-weight women showed decreased glucose tolerance, worsened lipid profile, and elevated markers of chronic inflammation during the 9-week exposure to combined hormonal contraception regardless of the administration route [7]. Earlier studies have even linked the use of COCs with prediabetes and type 2 diabetes [9–11]. However, contradicting results have also been reported [12], and a recent meta-analysis concluded that hormonal contraceptive use has a limited effect on glucose metabolism in healthy, normal-weight women [13], although most included studies had limitations. To date, progestin-only preparations have shown either minor or no alterations in glucose tolerance [14–16].

In the latest formulations of COCs, EE has been replaced with natural 17β-estradiol (E_2) or its ester, estradiol valerate (EV) [8]. Existing data suggest that COCs containing EV or E_2 have a milder effect on glucose tolerance than do COCs containing EE [17–19]. However, in previous comparative studies EE and EV have been combined with different progestins, which hampers the interpretation of the results.

In this study, we compared the effects of COCs containing EE and EV with the same anti-androgenic progestin, dienogest (DNG), and DNG-only on glucose tolerance. This design provided an opportunity to specifically evaluate the effect of the estrogen component of COCs on insulin sensitivity. Based on the existing evidence, we hypothesized that EV would influence blood

glucose and insulin levels less than EE, and that the DNG-only preparation would not affect these parameters [20,21].

2. Material and Methods

2.1 Study Design and Participants

This randomized, open-label, nine-week controlled, investigator-initiated clinical trial was conducted between April 2015 and January 2018 in an outpatient setting at Helsinki and Oulu University Hospitals, Finland. The study protocol was approved by the Finnish Medicines Agency (FIMEA) and registered in the European Union Clinical Trials Register (EudraCT identifier code: 2014-001243-20) and on the Clinical Trials register (ClinicalTrials.gov, NCT 02352090). Ethics Committee of Helsinki University Hospital approved the study, and the study protocol was also approved by the Ethics Committee of Oulu University Hospital, Finland. All participants signed an informed consent form.

Primary outcome was defined as change in the whole-body insulin sensitivity index (Matsuda index, derived from OGTT) between EE and EV groups. Secondary outcomes were area under the curve (AUC) of glucose and insulin, homeostatic model assessment – insulin resistance (HOMA-IR) and Insulin Sensitivity Index (ISI). DNG-only group was included to dissect the influence of the estrogen.

The inclusion criteria were: 18–35 years old, normal weight (BMI 19–24.9 kg/m^2), regular menstrual cycle (28±7 days), no polycystic ovaries in transvaginal ultrasound or polycystic ovary

syndrome (PCOS) defined by the revised Rotterdam criteria [22], normal blood pressure (<140/90 mmHg), non-smoking, no drug or alcohol abuse, no pregnancy or lactation, no general contraindications to hormonal contraceptive use, and good general health (i.e. no chronic disease or regular medications). A wash-out period of two months without hormonal contraceptive use was required prior to entering the study. Altogether, 77 healthy Caucasian women volunteered for the study and were assessed for eligibility (Figure 1). The study included three study visits. At Visit 1 preceding randomization, all women were clinically examined (by AH, TP, or OH) including measurements of height, weight, waist and hip circumference, blood pressure as well as gynecological examination, transvaginal ultrasound and fasting blood tests including OGTT. In addition, the study participants filled in a questionnaire regarding general and gynecological health and medication. Visit 2 after at 4-5 weeks (29-35 days) of treatment included clinical measurements and fasting blood samples. Visit 3 at the end of the study at 8-9 weeks (57-63 days) included clinical measurements, transvaginal ultrasound and blood tests including OGTT.

The three treatment groups were as follows: Group 1—EV+DNG 1–2 mg/2–3 mg (*Qlaira®* day 1-5 EV+DNG 2 mg/2 mg, day 6–21 EV+DNG 2 mg/3 mg); Group 2—EE+DNG 0.03 mg/2 mg (*Valette®* day 1–21 EE+DNG 0.03 mg/2 mg, day 22–28 placebo); Group 3—DNG-only 2 mg (*Visanne®* day 1–28 DNG 2 mg). *Qlaira®* and *Visanne®* were manufactured by Bayer AG, Germany, and *Valette®* by Jenapharm, Germany (Bayer AG). Original preparation packages were altered to match hormonal contents as well as possible. Seven tablets were removed from all packages (all placebo and some active tablets), leaving a total of 21 tablets in each (Figure2). Baseline assessment took place on cycle days 1–5, and study preparations were commenced on the following day (cycle days 2–6) after having confirmed normal baseline OGTT. Study medications

were used continuously without breaks for 63 (21x3) days. We instructed women to use barrier contraception during the study period.

2.2 Assessment of Glucose Metabolism

Glucose and insulin analyses were carried out in two laboratories (Huslab, Helsinki and Nordlab, Oulu) by accredited methods to ensure comparable results. Serum insulin was quantitated with an immunochemiluminescent assay on the LIAISON® XL analyser (DiaSorin, Saluggia, Italy) or with Siemens Advia Centaur (Simens Diagnostica, Erlangen, Germany). The detection limits of the assays were 0.2–0.6 mU/L and 0.5 mU/L, respectively. Blood glucose was measured photometrically using an enzymatic assay on the Roche Modular P800 (Roche Diagnostics, Mannheim, Germany) with a testing range of 0.1–41.6 mmol/L or with Siemens Advia Chemistry XPT (Siemens Diagnostica, Eralngen, Germany) with a testing range of 0.2–39.9 mmol/L.

A standard two-hour oral glucose tolerance test (OGTT, 75 g glucose load in 250 mL water) was performed after a 12-hour overnight fast at baseline and at nine weeks of treatment. Blood samples were drawn before the OGTT at 0 minutes and at 30 minutes, one hour, and two hours. Fasting plasma glucose and serum insulin levels were analyzed immediately. 2. At Visit 2, blood samples were drawn, and fasting glucose and insulin were analyzed. Glucose tolerance was defined according to World Health Organization (WHO) guidelines [23].

Several indices were derived from fasting glucose and insulin values, and from OGTT to evaluate glucose tolerance. Insulin and glucose areas under the curve ($AUC_{GLU/INS}$) were calculated using the trapezoidal method [24]. The total AUC values for glucose and insulin at baseline and at nine weeks were compared. The Matsuda index, a whole-body insulin sensitivity index, was calculated

as described by Matsuda and DeFronzo [25]. To estimate basal insulin sensitivity, and thus the degree of beta-cell deficiency and target-tissue sensitivity to insulin (i.e. insulin resistance), the homeostasis model assessment—insulin resistance (HOMA-IR) was calculated as previously described [26]. The insulin sensitivity index (ISI) was calculated from fasting glucose and insulin values (ISI_{0h} = fasting glucose/fasting insulin) and at 2 h from OGTT values (ISI_{2h} = glucose 2 h/insulin 2 h).

2.3 Power Calculation and Randomization

The power calculation was based on our previous study showing that Matsuda index decreases 23% (from 7.3 [±2.9] to 5.6 [±2.8]) during continuous use of COC containing EE over a period of nine weeks [7]. COCs containing EV have not been shown to affect glucose tolerance [17,18,21], and therefore our hypothesis was that the Matsuda index decreases significantly in the EE group, but remains unaffected in the EV and DNG-only groups [21]. We calculated the effect size, f = 0.25 (f as defined by Cohen), the significance level was set at <0.05 (the risk of α-error) and power at 0.8 (risk of 1-β error) [27]. To achieve a power of 0.8, 16 participants were required in each of the three groups. Sample size was calculated using the G*Power software (www.gpower.hhu.de). We aimed to enroll 60 women to allow for possible discontinuation or loss during follow-up.

The study subjects were allocated to the three parallel treatment groups by randomization in a 1:1:1 ratio and in blocks of six. The randomization list was produced by a statistician using a web-based randomizer (www.sealedenvelope.com) and kept in sealed

envelopes. Two research nurses allocated the women to treatment groups after eligibility had been established; 29 women were enrolled in Oulu and 30 in Helsinki.

2.4 Statistical Analysis

IBM SPSS version 25 for Mac iOS was used for all statistical calculations. The significance level was set at <0.05. Data are expressed as mean (±SD or 95%CI). Comparisons of baseline demographic characteristics among the three groups were performed using one-way analysis of variance (ANOVA).

Data was analyzed with one-way multiple measures ANOVA (analysis within group) and two-way multiple measures ANOVA (analysis between groups) and Bonferroni adjustments were used for multiple comparisons within the groups. The normality assumption was checked from residuals, and skewed variables were log-transformed ($AUC_{INSULIN}$, fasting insulin, HOMA-IR, ISI_{0h} and ISI_{2h}). The OGTT-derived values at 30 minutes, one hour, and two hours for glucose and insulin were compared from baseline to nine weeks within the group by paired-samples *t*-test or Wilcoxon's signed ranks test.

3. Results

The flow chart of the study is shown in Figure 1. In the EV+DNG group, two subjects had not been fasting at Visit 2 sampling, and in the EE+DNG group, two subjects had either 30-minute or one-hour values missing during OGTT due to technical problems in the laboratory. In the EV+DNG group, two subjects had not fasted at Visit 2 (5 weeks), and thus only 18 subjects were included in analyses derived from fasting values in this group. The latter subjects in the EE+DNG group

were excluded from the baseline to nine weeks comparisons, as their corresponding indices could not be calculated.

The study groups were well-matched at baseline regarding their demographic characteristics (Table 1). The groups differed regarding body weight, but not body mass index or waist-to-hip ratio. Systolic blood pressure (BP) was higher in the EV+DNG and EE+DNG groups compared to the DNG-only group.

3.1 Oral Glucose Tolerance Test

The results of the OGTT are summarized in Table 2 and Figure 3. The primary outcome, the change in the Matsuda index, did not differ within or between the groups. Similarly, ISI_{2h} remained unchanged in all groups. In OGTT, only a few changes within the groups were significant. From baseline to nine weeks, significant change was observed in the DNG-only group for increased insulin at 30 minutes and decreased glucose at 2 h, as shown in Figure 3 and Table 2. The AUC_{GLU} and AUC_{INS} from baseline to nine weeks did not change in any of the study groups. A tendency towards an increased AUC_{INS} was found in all groups, but only minor changes were observed in the $AUC_{GLU.}$ We found no difference among the three groups when comparing for mean difference in the AUC_{GLU} and AUC_{INS}.

3.2 Fasting Values

The fasting variables describing glucose tolerance are presented in Table 2. Mean fasting glucose levels remained stable in all three groups from baseline to Visit 2 and Visit 3, and the mean change from baseline was not significant when comparing the three groups. Fasting insulin was

increased in both DNG-only and EE+DNG groups, but after Bonferroni adjusted paired comparisons, the treatment effect was significant only from baseline to Visit 2 but not to Visit 3 (Supplemental Table 1). HOMA-IR derived from the fasting values increased over the study period in the DNG-only and EE+DNG group Analyzed by paired comparisons, the change in the DNG-only group was significant from baseline to Visit 2 and from baseline to Visit 3. In EE+DNG group the change was significant from baseline to Visit 2 but not to Visit 3 (Supplemental Table 1). Insulin sensitivity index (ISI_{0h}) decreased in the DNG-only and EE+DNG groups. Paired comparisons showed a significant change from baseline to Visit 2 and Visit 3 in DNG-only group and in EE+DNG group from baseline to Visit 2 (Supplemental Table 1). No significant changes in fasting value indices of glucose tolerance were seen in the EV+DNG group. The difference between groups in the mean change from baseline in fasting Insulin, HOMA-IR and ISI_{0h} was not significant.

4. Discussion

No clinically significant changes were found in insulin sensitivity during this nine-week study when comparing COCs containing EV and EE, and DNG-only regimen.

A major strength of our study is that the study design allows a direct comparison between EE and EV, as the progestin component DNG was the same, with the DNG-only group as an active control. Yet the study has some limitations. Although the sample size was based on power calculations, the number of study subjects is still limited, and the follow-up time is relatively short. However, in our previous study using the same protocol and follow-up time, we were able to make important new observations [7]. Change in the Matsuda index was chosen as the

primary outcome measure, as it is considered one of the best indices for evaluating OGTT and glucose tolerance. Relatively small changes in Matsuda index (1.1 to 1.15) have been shown to be of clinical relevance, i.e. predicting progression to diabetes [28,29]. The homogeneity of the study subjects can be regarded as a strength or a limitation; the women were all Caucasian, slim, young, and healthy individuals with minimal prior risk of disturbances in glucose tolerance. Importantly, WHR and BMI remained stable during the study period in all groups, eliminating the potential effect of weight gain on glucose metabolism. The study protocol was non-blinded because the DNG-only preparation lacks indication for use as birth control. As commercial preparations were used, we could not completely match the hormonal contents of the study preparations; DNG dosing was higher (3 mg vs 2 mg) in the EV group for most of the study period (48 of 63 days; see Figure 2). This could affect our results in the EV group and alter differences between the groups. Differences between DNG-only, EV+DNG and EE+DNG groups were small and the confidence intervals calculated for the differences were narrow showing that we did not miss any large differences between these groups.

Regarding the effects of COCs containing EE on glucose metabolism, results remain conflicting, although a tendency towards worsened insulin sensitivity has been reported [30]. Although several studies have addressed the metabolic effects of EE, only a few studies have evaluated the effects of COCs containing EV on glucose tolerance. Two earlier comparative studies on COCs containing EV or natural estradiol (E_2) found less influence on glucose tolerance compared with preparations containing EE. As EV is metabolized to and exerts its biological effects through E_2, we can regard them as analogues in this context [8]. A study comparing EV+DNG with EE+levonorgestrel (LNG) reported that the AUC_{GLU} and AUC_{INS} in OGTT remained

stable with EV+DNG over seven cycles, whereas during EE+LNG use the AUC_{INS} was slightly increased [18]. However, only descriptive statistics were given. In a comparison of EE+LNG with E_2+nomegestrol acetate (NOMAC) for six cycles, the effect of E_2+NOMAC preparation was neutral, whereas EE+LNG decreased glucose tolerance [19]. In our previous study with EE+desogestrel (DSG), we found decreased glucose tolerance [7]. The present study did not show clinically significant changes in glucose tolerance in the EE+DNG group. This may reflect the different properties of the progestin component. DNG, used in this study, is considered a hybrid progestin being derived from the estrane group with a 17-α-cyanomethyl group. In contrast, DSG belongs to the gonanes, also derived from the 19-nortestosterone, and there is evidence of residual androgenic activity, which may play role in reducing glucose tolerance [31]. Other mechanisms by which progestin in COCs can modulate the action of estrogen include extending the half-life of insulin, increasing the receptor binding of insulin, and increasing pancreatic insulin secretion [32,33]. Furthermore, steroids may also alter the secretion and regulation of the counter-regulatory hormones, such as cortisol, growth hormone, adrenalin and glucagon, opposing the effects of insulin [34].

In this study, the DNG-only preparation resulted in increased fasting insulin and 30-minute insulin (data not shown) during OGTT, reflecting an early response to glucose stimulation. Moreover, HOMA-IR was elevated and ISI_{0h} decreased. These observations are in agreement with a previous study reporting an elevation in early-phase insulin response during intravenous glucose tolerance test during the use of DNG-only [20]. However, the clinical relevance of this possibly enhanced early insulin secretion remains uncertain, as despite their wide clinical use since 1990, few studies have been published on the metabolic effects of COCs containing DNG

[35]. In a study investigating DNG in treatment of endometriosis, the use of DNG-only preparation was not associated with worsened insulin sensitivity when evaluated by fasting glucose, insulin levels, and HbA1c [21]. The metabolically favorable profile of DNG was also reflected in the present study by the improvement of the 2-h glucose value in OGTT. DNG is the only nortestosterone derivative with no androgenic, but an antiandrogenic potency, which could account for its metabolically favorable profile also in combination with an estrogen [36]. Compared to other antiandrogenic progestins, for instance chlormadinone and drospirenone, DNG is the most antiandrogenic and has about 40% of the potency of cyproterone acetate, the most potent antiandrogenic progestin [37]. DNG has no affinity for sex hormone-binding protein (SHBG), and hence it does not displace testosterone or estradiol from binding SHBG or increase the free fractions of these hormones [36]. Moreover, it has a low hepatic impact and does not alter serum SHBG levels, therefore, it is unlikely that DNG would counteract the effects of EE or EV via changing levels of SHBG [38].

In conclusion, both EV and EE in combination with DNG as well as DNG-only, had no clinically significant effects on insulin sensitivity in young, healthy, normal-weight women after nine weeks of continuous use. Both combinations of estrogen (EE/EV) and DNG seem neutral regarding glucose metabolism. Although these findings are reassuring considering the large scale worldwide use of COCs, further studies on populations at higher risk are needed.

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Author contributions

The study was designed by JST and OH in collaboration with TP and AH. JST and OH obtained funding for the study and AH, MK, TP, KL, OH and JST contributed to the data collection. The results were analyzed by AH, JST, OH, KL and TP. AH wrote the first draft of the manuscript; AH, AH, MK, TP, KL, OH and JST contributed to revision and approved the final version of the manuscript. JST, OH, and TP supervised the project.

References

[1] Cagnacci A, Ferrari S, Tirelli A, Zanin R, Volpe A. Insulin sensitivity and lipid metabolism with oral contraceptives containing chlormadinone acetate or desogestrel: a randomized trial. Contraception 2009;79:111–6.

[2] Godsland IF, Crook D, Worthington M, Proudler AJ, Felton C, Sidhu M, et al. Effects of a low-estrogen, desogestrel-containing oral contraceptive on lipid and carbohydrate metabolism. Contraception 1993;48:217–27.

[3] Watanabe RM, Azen CG, Roy S, Perlman JA, Bergman RN. Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. J Clin Endocrinol Metab 1994;79:1277–83.

[4] Skouby SO, Endrikat J, Düsterberg B, Schmidt W, Gerlinger C, Wessel J, et al. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 ug ethinyl estradiol combined with 100 ug levonorgestrel. Contraception 2005;71:111–7.

[5] Endrikat J, Klipping C, Cronin M, Gerlinger C, Ruebig A, Schmidt W, et al. An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 ug ethinyl estradiol and 100 ug levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables. Contraception 2002;65:215–21.

[6] Lüdicke F, Gaspard UJ, Demeyer F, Scheen A, Lefebvre P. Randomized controlled study of the influence of two low estrogen dose oral contraceptives containing gestodene or desogestrel on carbohydrate metabolism. Contraception 2002;66:411–5.

[7] Piltonen T, Puurunen J, Hedberg P, Ruokonen A, Mutt SJ, Herzig KH, et al. Oral, transdermal and vaginal combined contraceptives induce an increase in markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weight women: A randomized study. Hum Reprod 2012;27:3046–56.

[8] Sitruk-Ware R, Nath A. Characteristics and metabolic effects of estrogen and progestins contained in oral contraceptive pills. Best Pract Res Clin Endocrinol Metab 2013;27:13–24.

[9] Deleskog A, Hilding A, Stenson C-G. Oral contraceptive use and abnormal glucose regulation in Swedish middle aged women. Diabetes Res Clin Pract 2011;92:288–92.

[10] Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, et al. Oral contraceptive use and the risk of Type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. Diabetologia 1992;35:967–72.

[11] Rosenthal AD, Shu XO, Jin F, Yang G, Elasy TA, Li Q, et al. Oral contraceptive use and risk of diabetes among Chinese women. Contraception 2004;69:251–7.

[12] Gaspard U, Scheen A, Endrikat J, Buicu C, Lefebvre P, Gerlinger C, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. Contraception 2003;67:423–9.

[13] Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Cochrane Database Syst Rev 2014;4.

[14] Oderich CL, Wender MCO, Lubianca JN, Santos LM, de Mello GC. Impact of etonogestrel-releasing implant and copper intrauterine device on carbohydrate metabolism: a comparative study. Contraception 2012;85:173–6.

[15] Kahn HS, Curtis KM, Marchbanks PA. Effects of injectable or implantable progestin-only contraceptives on insulin-glucose metabolism and diabetes risk. Diabetes Care 2003;26:216–25.

[16] Morin-Papunen L, Martikainen H, McCarthy MI, Franks S, Sovio U, Hartikainen AL, et al. Comparison of metabolic and inflammatory outcomes in women who used oral contraceptives and the levonorgestrel-releasing intrauterine device in a general population. Am J Obstet Gynecol 2008;199.

[17] De Leo V, Fruzzetti F, Musacchio MC, Scolaro V, Di Sabatino A, Morgante G. Effect of a new oral contraceptive with estradiol valerate/dienogest on carbohydrate metabolism. Contraception 2013;88:364–8.

[18] Junge W, Mellinger U, Parke S, Serrani M. Metabolic and haemostatic effects of estradiol valerate/dienogest, a novel oral contraceptive. Clin Drug Investig 2011;31:573–84.

[19] Ågren UM, Anttila M, Mäenpää-Liukko K, Rantala ML, Rautiainen H, Sommer WF, et al. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol in comparison to one containing levonorgestrel and ethinylestradiol on markers of endocrine function. Eur J Contracept Reprod Heal Care 2011;16:458–67.

[20] Nikschick S, Köhler G, Männchen E. Carbohydrate Metabolism during Treatment of Endometriosis with the Progestin Dienogest. Exp Clin Endocrinol Diabetes 2009;94:211–4.

[21] Schindler AE, Henkel A, Moore C, Oettel M. Effect and safety of high-dose dienogest (20 mg/day) in the treatment of women with endometriosis. Arch Gynecol Obstet 2010;282:507–14.

[22] Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks

related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.

[23] Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabet Med 1998;15:539–53.

[24] Matthews J, Altman D, Campbell M, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5.

[25] Matsuda M, DeFronzo RA. Insulin Sensitivity Indices Obtained From Oral Glucose Tolerance Testing. Diabetes Care 1999;22:1462–70.

[26] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.

[27] Faul F, Erdenfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavorial, and biomedical sciences. Behav Res Methods 2007;39:175–91.

[28] De Mello VDF, Lindström J, Eriksson J, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Sundvall J, et al. Insulin secretion and its determinants in the progression of impaired glucose tolerance to type 2 diabetes in impaired glucose-tolerant individuals: The Finnish diabetes prevention study. Diabetes Care 2012;35:211–7.

[29] Ram J, Snehalatha C, Selvam S, Nanditha A, Shetty AS, Godsland IF, et al. The oral disposition index is a strong predictor of incident diabetes in Asian Indian prediabetic men. Acta Diabetol 2015;52:733–41.

[30] Wiegratz I, Stahlberg S, Manthey T, Sänger N, Mittmann K, Palombo-Kinne E, et al. Effects of Combined Oral Contraceptive Ethinylestradiol (30 μg) and Dienogest (2 mg) on Carbohydrate Metabolism During 1 Year of Conventional or Extended-Cycle Use. Horm Metab Res 2010;42:358–63.

[31] Sitruk-Ware R. Pharmacological profile of progestins. Maturitas 2008;61:151–7.

[32] Kojima T, Lindheim SR, Duffy DM, Vijod MA, Stanczyk FZ, Lobo RA. Insulin sensitivity is decreased in normal women by doses of ethinyl estradiol used in oral contraceptives. Am J Obstet Gynecol 1993;169:1540–4.

[33] Godsland IF, Walton C, Felton C, Proudler A, Patel A, Wynn V. Insulin resistance, secretion, and metabolism in users of oral contraceptives. J Clin Endocrinol Metab 1992;74:64–70.

[34] Verberne AJM, Sabetghadam A, Korim WS. Neural pathways that control the glucose

counterregulatory response. Front Neurosci 2014;8.

[35] Schwarz S, Onken D, Schubert A. The steroid story of Jenapharm: From the late 1940s to the early 1970s. Steroids 1999;64:439–45.

[36] Ruan X, Seeger H, Mueck AO. The pharmacology of dienogest. Maturitas 2012;71:337–44.

[37] Teichmann A. Pharmacology of Estradiol valerate/dienogest . Climacteric 2003;6:17–23.

[38] Kuhl H. Comparative pharmacology of newer progestogens. Drugs 1996;51:188–215.

Figure legends

Figure 1

CONSORT Flow chart of the study. Three women discontinued the study: one in the EE+DNG group due to minor non-specific side effects; and two in the DNG-only group, one due to general malaise, and one due to mood changes. Consequently, 56 women completed the study and were included in the analyses (EV+DNG n=20, EE+DNG n=19, DNG n=17).

Figure 2

Hormonal contents and dosing of the study medications.

DNG, dienogest; EE, ethinyl estradiol; EV, estradiol valerate

Figure 3

Results of oral glucose tolerance test at baseline and after nine weeks of treatment (mean, ±SD). Glucose and insulin plasma concentrations during 2-h OGTT after nine weeks of treatment with EV+DNG, EE+DNG, or DNG. Comparisons at different time points within the groups were performed using paired samples T-test or the nonparametric Wilcoxon signed ranks test. *P*-values represent differences between baseline and nine weeks within the groups. Differences in the AUC values between baseline and 9-weeks were not significant within all study groups.

AUC, area under the curve; DNG, dienogest; EE, ethinyl estradiol; EV, estradiol valerate; OGTT, oral glucose tolerance test.