Synthetic vs Natural Estradiol in Combined Oral Contraception (SYLVI study)

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Publications:

Haverinen A, Kangasniemi M, Luiro K, Piltonen T, Heikinheimo O, Tapanainen JS. Ethinyl estradiol vs estradiol valerate in combined oral contraceptives - Effect on glucose tolerance: A randomized, controlled clinical trial. Contraception. 2021 Jan;103(1):53-59. doi: 10.1016/j.contraception.2020.10.014. Epub 2020 Oct 21. PMID: 33098852.

Found at: https://www.contraceptionjournal.org/article/S0010-7824(20)30384-X/fulltext

Kangasniemi MH, Haverinen A, Luiro K, Hiltunen JK, Komsi EK, Arffman RK, Heikinheimo O, Tapanainen JS, Piltonen TT. Estradiol Valerate in COC Has More Favorable Inflammatory Profile Than Synthetic Ethinyl Estradiol: A Randomized Trial. J Clin Endocrinol Metab. 2020 Jul 1;105(7):dgaa186. doi: 10.1210/clinem/dgaa186. PMID: 32303765.

Found at: https://academic.oup.com/jcem/article-abstract/105/7/e2483/5821528?redirectedFrom=fulltext

Study protocol

Title

Synthetic vs.Natural Estrogen in Combined Oral Contraceptives – Effects on Insulin Sensitivity, Inflammation, Coagulation and Endometrium. A Comparison with a Progestin-only Preparation. A Randomized Clinical Trial.

Abbreviated title

SYLVI-study

Research group

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Research centers

The trial sites are in Helsinki Kätilöopisto Hospital or Naistenklinikka Hospital and in Oulu, Oulu University Hospital.

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Oulu University Hospital: Kajaanintie 50, 90200 Oulu, Finland

Background

The latest formulations of combined oral contraceptives (COC) are based on natural estradiol (E2) or its ester estradiol valerate (EV) and antiandrogenic, "fourth generation" progestins. Conventional COCs, consisting of synthetic ethinyl estradiol (EE) and different progestins, are known to have a negative effect on insulin sensitivity, lipid profile and markers of chronic inflammation. Furthermore, conventional COCs induce a change in hemostasis to a more prothrombotic state, contributing to the most feared adverse event of COCs, venous thromboembolism. This new estradiol based COCs might have a reduced metabolic impact, due to a decreased influence on hepatic metabolism and the pharmacological properties of antiandrogenic progestins. Previous comparative trials on the metabolic effects of COCs have in general been done with preparations containing different doses of EE and E2 combined with different types of progestins which hampers with the interpretation of the estrogen components effects.

Aim

The aim of the study is to compare the metabolic effects of natural estradiol and synthetic ethinyl estradiol used in combined oral contraception in healthy, young women.

Objectives

The objective of the study is to evaluate the effects of estradiol valerate (EV) combined with dienogest (EV+DNG) compared with ethinyl estradiol (EE) combined with dienogest (EE+DNG) on glucose metabolism, inflammation, coagulation activity and other biomarkers. A dienogest-only (DNG) preparation will be included in the study as an active control.

Hypothesis

We hypothesize that the EV+DNG preparation will influence glucose tolerance, biomarkers of chronic inflammation and coagulation activity less than the EE+DNG preparation. The DNG-only preparation will not affect these variables.

Outcome measures

Primary Outcome Measure

- A change in Matsuda index (whole body sensitivity index) from baseline to nine weeks

Secondary Outcome Measures

- Coagulation biomarkers
- Lipids and markers of chronic inflammation
- Possibility to ad hoc studies on other biomarkers
- Bleeding diary, QAL questionnaires
- Proliferation markers of the endometrium

Study design

This is a nine-week, non-blinded, three parallel-group, active-control clinical randomized trial. Enrollment will begin after between April 2015 in Helsinki University and Oulu University hospitals.

Study treatments

We will compare the effects of the following hormonal preparations on metabolical biomarkers:

- 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 will altered to match for hormonal contents. Seven tablets will be removed from all packages (all placebo and some active tablets), leaving a total of 21 tablets in each. Study medications will be used continuously without breaks for 63 (21x3) days.

Day	1 2 3 4 5	6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
EV+DNG	EV 2 mg + DNG 2 mg	EV 2 mg + DNG 3 mg
EE+DNG	EE 0.03 mg + DNG 2 mg	
DNG	DNG 2 mg	

Figure 1. Hormonal contents of the study preparations

Study participants

Based on the sample size calculation 48 women are needed to find the anticipated difference in Matsuda Index. We aim to enroll 60 women to account for possible discontinuation or losses to follow up. Voluntary women will be recruited by advertisements in hospital intranet, magazines directed to students, flyers in applied science schools and by direct e-mails to student organizations.

Inclusion criteria

- 18-35 years
- Regular menstrual cycle (28 +/- 7 days)
- Normal weight (body mass index 19-24.9)
- No regular medications or chronic disease
- Non-smoking

- Two-month wash-out from hormonal contraceptive use
- Polycystic ovary syndrome

Exclusion criteria

- Contraindications for oral contraceptive use (World Health Organization medical eligibility criteria for contraceptive use)
- Pregnancy
- Lactation
- Drug or alcohol abuse
- Finings in gynecological
- High blood pressure (>140/90 mmHg)
- Disturbance in glucose tolerance

Protocol

Eligible women will be clinically examined before randomization. Anthropometric measurements include; height, weight, hip and waist circumference. Additionally, we measured blood pressure and women underwent a gynecological exam including sonography. We screened women for polycystic ovary syndrome (clinical diagnosis) according to Rotterdam criterion and disturbances in carbohydrate metabolism according to WHO by two-hour glucose tolerance test and excluded women with signs of either.

Study flow

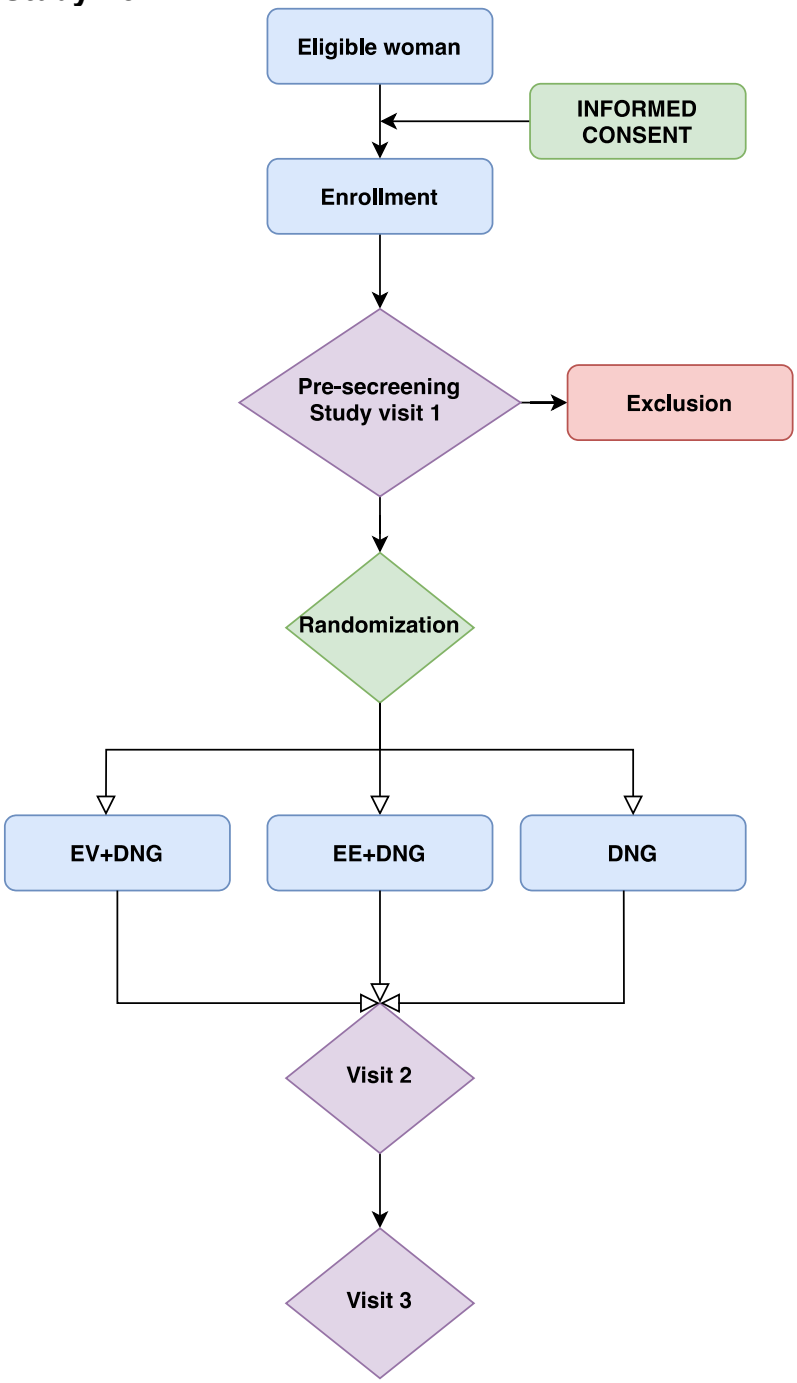

Figure 2 Study flow

Screening visit/Study Visit 1 – Baseline, before treatment

In early menstrual cycle (cycle day 1-5) study preparations will be commenced on the following day (cycle days 2–6).

- Gynecological exam, including vaginal ultrasound
- Endometrial sample
- Anthropometric measures, 2h-oralglucose tolerance test, blood samples for biomarkers
- Blood pressure measurement
- Filling out questionnaires

Study Visit 2 – 5th week of treatment

- Anthropometric measures, blood samples for biomarkers
- Blood pressure measurement

Study Visit 3 – 9th week of treatment

- Gynecological exam, including vaginal ultrasound
- Endometrial sample
- Anthropometric measures, 2h-oralglucose tolerance test, blood samples for biomarkers
- Blood pressure measurement
- Returning bleeding diary
- Filling out questionnaires

Financial plan

This study is investigator-initiated and will not receive any financial sponsoring from the pharmaceutical industry. The study will be financed by the University of Helsinki and Oulu research funds, the Academy of Finland, Svenska Kulturfonden, The Finnish Medical Society, Finska Läkaresällskapet and Eemil Aaltonen Foundation.

Ethical Considerations

- All participants are insured by the patient insurance during this study.
- All adverse events will be reported. Serious adverse events it will be reported to FIMEA (the Finnish Medicines Agency) and the participant will discontinue the study medication.
- Participation in this study is based on informed consent.
- This study will be conducted in accordance with the Declaration of Helsinki.
- The study protocol is approved by the Independent Ethics Committees of Helsinki and Oulu University Hospitals and permission to conduct the study was given by both hospitals.

Registration

The study will be registered in the www.clinicaltrials.org and Eudra-CT databases.

Results

The results of this study will be reported according to CONSORT guidelines.