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

Statistical Analysis Plan

SYLVI- study

Power Calculation

The power calculation is based on our previous study showing that the Matsuda index decreases 23% (from 7.3 [±2.9] to 5.6 [±2.8]) during the use of COC containing EE for nine weeks 1. COCs containing EV have not been shown to affect glucose tolerance 2–4. Therefore we hypothesize that the Matsuda index decreases significantly in the EE group but remains unaffected in the EV and DNG-only groups 2. Based on this previous data, the effect size was estimated to be f = 0.25 (f as defined by Cohen). With the significance level set at <0.05 (the risk of a-error) and the desired power at 0.8 (risk of 1-b error), 16 participants were required in each of the three groups. We aimed to enroll 60 women to allow for possible discontinuation or loss during follow-up. We used the G*Power software (www.gpower.hhu.de) for the sample size calculation.

Randomization

The study subjects will be allocated to three parallel treatment groups by randomization in a 1:1:1 ratio and blocks of six. A statistician will produce the randomization list using a web-based randomizer (www.sealedenvelope.com). Two research nurses will allocate the women to the treatment groups after established eligibility.

Statistical Analysis

We will use IBM SPSS version 25 and 27 and Prism 9 (Graphpad) for Mac iOS for all statistical calculations. The significance level will be set at <0.05. Summarized data will be expressed as mean (±SD or 95%CI) or medians (ranges) as appropriate. The change from baseline will be described as mean (95%) or median (range) as applicable. Shapiro-Wilks test will test the normality of the data, and skewed variables will be log-transformed if needed. Comparisons of baseline demographic characteristics among the three groups will be performed using one-way analysis of variance (ANOVA). Repeated measures will be analyzed with one-way multiple measures ANOVA (analysis within-group) and two-way multiple measures ANOVA (analysis between groups) or the hierarchal linear mixed model. Corrections for multiplicity (Bonferroni) will be applied. Parametric and nonparametric counterparts will be used to compare the within-group changes for secondary outcomes. The between-group changes from baseline will be analyzed by ANOVA or Kruskal-Wallis test with post hoc tests.

1. Piltonen T, Puurunen J, Hedberg P, 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(10):3046-3056.
2. 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 Obs*. 2010;282(5):507-514. doi:10.1007/s00404-009-1301-z
3. 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(8):573-584. doi:10.2165/11590220-000000000-00000
4. 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(3):364-368. doi:10.1016/j.contraception.2012.09.003