Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Palombo-Kinne E, Schellschmidt I, Gräser T. *Contraception* 2009; **79**: 282–289

A recent Cochrane Review found that combined oral contraceptives (COCs) reduced acne lesion counts, severity grades and self-assessed acne compared to placebo.[1] However, differences in the comparative effectiveness of COCs with varying progestin types and dosages were less clear.

Ethinylestradiol (EE) and cyproterone acetate (CPA) is used as a hormonal treatment for acne, due to its anti-androgenic action. The *British National Formulary* (*BNF*) states that it can be a useful treatment option for women who also require oral contraception.

The authors of this study report on a drug company-funded, randomised, double-blind, three-arm study that recruited healthy women aged 16–45 years with mild to moderate facial acne from 65 centres in eastern Europe and the Russian Federation. Their aim was to determine whether a COC-containing dienogest (DNG) was superior to placebo and non-inferior to EE/CPA in the treatment of mild to moderate acne.

Participants were allocated to six cycles of treatment with: 0.030 mg EE/2 mg DNG (n = 530), 0.035 mg EE/2 mg CPA (n = 541) or placebo (n = 267). Primary outcome measures were the percentage change of inflammatory and total lesion counts, and the percentage of patients with improvements according to the Investigator Global Assessment.

The authors state that all primary analyses proved that EE/DNG was superior to placebo and non-inferior to EE/CPA (p<0.05). For total lesion count the percentage change (± SD) from baseline to cycle six was: –54.7 ± –26.3% (n = 515) for EE/DNG, –53.6 ± –27.5% (n = 528) for EE/CPA and –39.4 ± –33.6% (n = 259) for placebo.

Points to note include the fact that this study was concerned with treatment of mild to moderate acne, whereas the *BNF* states that EE/CPA is licensed for women with severe acne not responding to oral antibacterial treatment. In addition, an intention to treat analysis was not used. Although a statistically significant (p<0.05) difference was found between the means of all three primary outcome measures of the EE/DNG versus placebo arms, in favour of EE/DNG, given the large placebo effect it is unclear whether this equates with a clinically significant difference.

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Reference

1 Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. *Cochrane Database Syst Rev* 2007; (**1**): CD004425.

Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. von Hertzen H, Piaggio G, Wojdyla D, Marions L, My Huong NT, Tang OS, *et al;* WHO Research Group on Post-ovulatory Methods of Fertility Regulation. *Br J Obstet Gynaecol* 2009; **116**: 381–389

Presently the treatment regimen for termination of early pregnancy (less than 63 days gestation) in the UK comprises 200 mg mifepristone orally followed by 800 µg misoprostol vaginally 36–48 hours later. Although unlicensed, these are the guidelines from the Royal College of Obstetricians and Gynaecologists (2004) for regimens for inducing medical abortion. The mifepristone works to soften and dilate the uterine cervix and sensitise the myometrium prior to use of the prostaglandin analogue, misoprostol. Pharmacokinetic studies suggest that oral administration of 100 mg or higher single doses of mifepristone result in similarly efficacious serum concentrations. Data available regarding the interval between treatments suggest that the efficacy is highest when the interval is 48 hours. No research studies previously have investigated the time interval between doses, or the comparison of 100 mg with 200 mg doses of mifepristone.

This study had four treatment arms (mifepristone 100 mg orally followed by 800 µg misoprostol vaginally either 24 or 48 hours subsequently, and mifepristone 200 mg followed by 800 µg misoprostol after 24 or 48 hours) to which 2126 women were randomised, across 13 obstetric and gynaecology departments in nine countries. Through a thorough selection protocol almost equal numbers (with significant similarities for age, gravidity and previous terminations) were recruited to each arm across all sites; randomisation was achieved by utilisation of an international sequence produced by the World Health Organization in Geneva. The double-blind trial was well designed and powered with a low attrition rate (55 from 2181 women). Even those patients lost to follow-up are counted as failures of method when in fact they may have had complete abortions. Internal validity was achieved by randomisation and a required confidence interval of 95% for the difference in complete abortion rates – the margin of equivalence of 5% having been chosen using the researchers' clinical judgement. External validity was demonstrated as women were enrolled from several different populations and included clinicians with different levels of experience of medical abortions.

The primary outcome measure was efficacy of the treatment in inducing complete abortion in all arms. The study found that both doses and both administration intervals are equivalent when the gestational age is 49 days or less, and results were inconclusive when the gestational age is 50 days or more. The findings show similar efficacy for complete abortion with both mifepristone doses and both treatment intervals. Despite the maximal sensitivity of mifepristone administration previously being demonstrated at 36–48 hours before the prostaglandin analogue use, this study found the 24-hour interval to have lower failure rates than the 48-hour interval group. Also both mifepristone doses produced equivalent rates of failure to achieve complete abortion within each interval of misoprostol administration. Reports of side effects were lower in the 24-hour interval group, suggesting this regimen could be better tolerated and provide a more pleasant patient experience. Overall conclusions are that the dose of mifepristone could be lowered to 100 mg and the administration interval between that and 800 µg misoprostol could be shortened to 24 hours without detrimental effect when terminating early pregnancy. This could have many repercussions in termination service including reducing cost implications of higher doses and the provision of well-tolerated regimes.

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