

**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.<sup>1</sup> 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.

Reviewed by **Bruno Rushforth**, MChB, DFRSH General Practice Specialty Registrar, *Outwood Park Medical Centre, Wakefield, UK*

**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 regimens.

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Qlaira if aggravation, exacerbation or new risks appear. No epidemiological studies on the effects of estradiol/estradiol valerate containing COCs exist. All of the following warnings and precautions are derived from clinical and epidemiological data of ethinylestradiol-containing COCs. Whether these warnings apply to Qlaira is unknown. Some studies suggest an association between COCs and an increased risk for venous and arterial thromboembolism. Risk for venous thrombosis associated with COCs increases with: age, family history of VTE, immobilisation, major surgery, any leg surgery, major trauma, obesity. There is an increased risk of VTE with any COC use compared to no COC use. The risk is highest in the first year of COC use but still much lower than that associated with pregnancy. VTE can be fatal. The risk of VTE during Qlaira use is currently unknown. Risk for arterial thrombosis or a cerebrovascular accident increases with: age, smoking, family history of arterial thromboembolism, obesity, dyslipoproteinaemia, hypertension, migraine, valvular heart disease, atrial fibrillation. Advise users to contact a doctor at first sign of possible thrombosis (e.g. chest or limb pain, breathlessness, numbness etc.). If thrombosis suspected or confirmed, stop COC use; consider increased risk during the puerperium. Diabetes, systemic lupus erythematosus (SLE), haemolytic uraemic syndrome (HUS), chronic inflammatory bowel disease and sickle cell disease are associated with increased risk of vascular events. Stop medication immediately if increase in frequency/severity of migraine, significant hypertension, or pregnancy occurs. Some studies suggest increased risk of cervical and breast cancer associated with COC use. Hepatic tumours have been reported with isolated cases of life-threatening haemorrhage. Possible increase in risk of pancreatitis if presence or family history of hypertriglyceridaemia. Certain conditions may occasionally occur or deteriorate: cholestatic jaundice and/or pruritus, gall stones, porphyria, SLE, HUS, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss, depression, epilepsy, Crohn's disease, ulcerative colitis, chloasma. Stop COC use if recurrence of pregnancy or sex-steroid related jaundice or cholestasis – related pruritus occurs. Angioedema may be induced or exacerbated in women with hereditary angioedema. Acute or chronic disturbances in liver function may occur. If this happens stop COC use until markers of liver function return to normal. Chloasma may occur. If tendency to chloasma present, advise avoidance of sun/uv radiation. Contains not more than 50 mg lactose per tablet, which should be considered for patients with intolerance to certain sugars. Include personal and family medical history and physical examination as part of assessment prior to treatment. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications and warnings. The frequency and nature of examinations should be based on established practice guidelines and adapted to the individual woman. Investigate bleeding irregularities that occur after regular cycles. Certain conditions, such as cardiac or renal dysfunction and diabetes during initial usage, require strict medical supervision. **Interactions:** Interaction with specific drugs will necessitate additional non-hormonal contraceptive measures. Qlaira may affect the metabolism of other medicines. Lab tests may be affected. The prescribing information of concomitant drugs should be consulted to identify potential interactions. **Pregnancy and lactation:** Qlaira should not be used during pregnancy or recommended during lactation. **Effects on ability to drive and use machines:** Qlaira has no influence on the ability to drive or use machines. **Undesirable effects:** Common - Headache (including tension headache), abdominal pain (including abdominal distension), acne, amenorrhea, dysmenorrhea, intracyclic bleeding (metrorrhagia), breast discomfort, weight increase. Serious side effects of CI/Warnings and Precautions – in addition hypertension, cervical dysplasia, migraine, uterine leiomyoma, genital hemorrhage, presumed ocular histoplasmosis syndrome, ruptured ovarian cyst. In addition to the above mentioned adverse reactions, erythema nodosum, erythema multiforme, breast discharge and hypersensitivity have occurred under treatment with ethinylestradiol-containing COCs (although these symptoms were not reported during the clinical studies performed with Qlaira, the possibility that they also occur under treatment cannot be ruled out). Other side effects - Prescribers should consult the SmPC in relation to other side effects. **Overdose:** There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in case of taking an overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** £25.18 per 3 x 28 tablets. **MA Number(s):** PL 00010/0576. **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** January 2009.

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**Adverse events should be reported. Reporting forms and information can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). Adverse events should also be reported to Bayer Schering Pharma. Tel: 01635 563500, Fax: 01635 563703, Email: [phdsguk@bayer.co.uk](mailto:phdsguk@bayer.co.uk)**