Journal Club

Maintenance fluconazole therapy for vulvovaginal candidiasis. Sobel JD, Wiesenfeld HC, Martens M, Danna P, Hooton TM, Rompalo A, *et al*. *N Engl J Med* 2004; **351**: 867–883 and editorial in the same issue

Uncomplicated isolated episodes of vulvovaginal candidiasis (VVC) affect most women at some point in their lives, with almost half experiencing two or more episodes.[1] Topical vaginal, oral single-dose, or short-course azole therapy is usually effective in this situation.[1,2] Recurrent VVC (R-VVC) is much less common, affecting around 5% of women. As pointed out in Eschenbach's editorial,[3] this accounts for many medical consultations in women of all ages who suffer the miserable symptoms of recurrent vulval itching and soreness, vaginal discharge and associated dyspareunia. Despite the unpleasant symptoms, VVC is not a cause of substantial morbidity or mortality and as such it is understudied and poorly understood, and it follows from this that management is not evidence-based.[2]

In this paper, Sobel and colleagues evaluate an open-label induction programme (three oral doses of 150 mg fluconazole 3 days apart) followed 2 weeks later by randomisation to either monthly oral 150 mg fluconazole or placebo for 6 months. The subjects were followed up for a further 6 months. The patients enrolled had severe symptoms of mycologically proven recurrent VVC with acute candidal vaginitis and four documented episodes in the previous year. Exclusion criteria included the known risk factors for R-VVC of pregnancy (also a contraindication for oral therapy)[1,2] and HIV seropositivity but interestingly not diabetes (2% of those in the fluconazole and 5% in the placebo group were diabetic), and the reasons for this are not explained.

This is a large study with 494 women initially enrolled and 373 included in the intent to treat analysis. Obviously, during a year-long study, a significant number of patients will be lost to follow-up or drop out, and 126 in the fluconazole and 137 in the placebo groups completed the 12 months. The primary endpoint was the number of women in clinical remission, and the secondary endpoint, mycological outcome. Unsurprisingly, those in the treatment arm did significantly better, with 90.8% recurrence free at 6 months compared to 35.9% in the placebo arm (relative risk in placebo arm 2.53; 95% CI 2.20–3.17, $p<0.001$). Mycological eradication was 82.1% and 28.2% and adverse events 2.9% and 1.2% in the treatment and placebo arms, respectively. No fluconazole resistant strains were isolated at all. During the following 6 months' observation, significantly more clinical and mycological relapses were experienced by the treatment arm, but at the end of the 6 months, 42.9% remained clinically cured as compared to 21.9% in the placebo group.

This study establishes a successful induction and maintenance regime for R-VVC with a well-tolerated, convenient oral regime. As pointed out in both the paper's discussion and Eschenbach's editorial[3], the high rates of recurrence following withdrawal of therapy both in this study and in clinical practice indicate that the optimum duration of secondary prophylaxis of R-VVC is unknown, and the induction–maintenance regime often requires repeating. The lack of resistance found to fluconazole used in this way was reassuring. The importance of good genital skincare and ruling out other genital infections (both at time of presentation and, if appropriate, at recurrence) are not discussed at all. These points are crucial to good management, as is investigating possible predisposing conditions including diabetes and HIV infection.

References
1 *CDC Guidelines on the Management of Vulvovaginal Candidiasis*. http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00050909.htm.
2 *National Guideline on the Management of Vulvovaginal Candidiasis*. Clinical Effectiveness Group (British Association for Sexual Health and HIV). http://www.bashh.org/guidelines/2002/candida%2006%2001.pdf.
3 Eschenbach DA. Chronic vulvovaginal candidiasis. *N Engl J Med* 2004; **351**: 851852.

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Safety of a new oral contraceptive containing drospirenone. Heinemann LA, Dinger J. *Drug Saf* 2004; **27**: 1001–1018

This review looks at the safety of Yasmin® [ethinylestradiol 30 µg/drospirenone 3 mg (EE/DRSP)]. Clinical phase studies showed this combined oral contraceptive (COC) to be highly effective in preventing pregnancy and to have a good safety profile. Clinical trials are not usually sufficiently powered to detect rare adverse events such as venous thromboembolism (VTE) to enable comparison with other COCs. This review sets out to look at data from the clinical development programme, postmarketing surveillance and spontaneous worldwide reporting, as well as information from other sources.

It includes an interesting report of the interim results from the European Active Surveillance (EURAS) Study. The EURAS Study is a multinational, controlled, prospective, postmarketing observational study of new users of EE/DRSP or other oral contraceptives (OCs). Women starting, or switching to, COCs are actively monitored for the occurrence of rare or unexpected adverse outcomes that might be related to their use of oral contraception. Follow-up data for over 49 000 women were available for the review: 30.4% were using EE/DRSP, 29.7% levonorgestrel-containing OCs and 39.9% other OCs. More women in the EE/DRSP cohort were obese (BMI>30) and had higher cholesterol levels. This might predict an increased risk of VTE.

A total of 205 VTE-like events were self-reported, but 163 of these events were not confirmed. Forty-two cases were confirmed as a definite VTE by imaging, or as a probable VTE by a non-imaging or clinical diagnosis. There were no significant differences between the cohorts in these interim reports (at 3 years). The review also points out that the risk of thrombotic events has previously been found to be higher in the first year of use of COCs and in people switching from one type to another. Trends for the EE/DRSP cohort were similar to those found for other COCs. Obese women (BMI>30) had a much greater risk of VTE than slim women. The review concluded that these interim results from the EURAS Study do not suggest that users of EE/DRSP are at any greater risk of VTE than users of other combinations.

There is a theoretical potential for hyperkalaemia to develop in some women who take an oral formulation containing DRSP, putting women at risk of arrhythmia. The clinical trial studies on EE/DRSP did not show any significant hyperkalaemia. Fifteen cases of raised levels of potassium have been reported in postmarketing surveillance but none of the levels were high enough for a risk of arrhythmia. The interim results from the EURAS Study showed no difference in rates of arrhythmia between the cohorts.

No increased risks of psychiatric conditions, fatalities or birth defects following the use of EE/DRSP were uncovered by the review.

The interim results from the EURAS Study may give rise to concern in that the incidence of VTE in all the cohorts of COC users was higher than has previously been reported for COCs. However, it is notoriously difficult to establish true baseline rates for VTE as many minor thrombotic events remain unreported and undiagnosed. Suspicion is heightened in people regarded as being at increased risk. The difficulty in establishing a true rate for long-haul travel is a case in point. The increased ease of diagnosis using d-dimer testing and the greater availability of imaging may help to establish more accurate current base rates for comparison in the future. The small absolute risks of VTE must be considered relative to other risks, such as road traffic accidents, that women in these age groups run.

NB. The most recent issue of the report from the Medicines and Healthcare products Regulatory Agency (MHRA) also comments on the early reports of higher numbers of episodes of VTE in users of Yasmin. This report from the Committee for Safety of Medicines points out that these early reports were derived from non-comparative data. The article concludes that prescribers should bear in mind that:

- all COCs increase the VTE rate
- the interim results from comparative studies suggest that the rates in users of Yasmin do not appear to differ from those in users of other COCs
- COCs should be prescribed with caution in people with a BMI>30 or with a predisposition to VTE.

Reference
1 Medicines and Healthcare products Regulatory Agency (MHRA). Combined oral contraceptives: venous thromboembolism. *Current Problems in Pharmacovigilance* 2004; **00**: 000–000.

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Randomized trial in family practice of a brief intervention to reduce STI risk in young adults. Proude EM, D'Este C, Ward JE. *Fam Pract* 2004; **21**: 537–544

Patients between the ages of 18 and 25 years completed a self-administered and confidential questionnaire in the waiting room of 20 participating practices before seeing a family practitioner for routine consultations. The patients were then randomised to receive usual care (the control group) or brief advice about safe sex, human immunodeficiency virus and hepatitis (the intervention group). Three months later, the patients were asked by post to complete a follow-up questionnaire to assess any changes in perception or behaviour about sexual risk.

A total of 312 patients completed the original baseline questionnaire and 237 of these agreed to receive a follow-up questionnaire. One hundred and fifty six (68%) returned the follow-up questionnaire. Self-reported use of condoms with a new partner and the assessment of the risk of unprotected sex with a new partner were similar in both the intervention and the control groups. There was significant change in the amount of knowledge about the risks of hepatitis in both the intervention and the control groups between the baseline and follow-up questionnaires. (Did the subjects talk to each other?)

The results did not show that a brief intervention in a routine consultation improved knowledge about risk or reduced risky behaviour. Given the competing demands on time in any consultation, this may not be a useful investment. It would seem to me that interventions are better targeted on the consultations where sexual activity is a natural part of the consultation.

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