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.2,3 Recurrent VVC (R-VVC) is much less common, affecting around 5% of women. As pointed out in Eschenbach’s editorial,1 this accounts for many medical consultations in women of all ages who suffer the miserable symptoms of recurrent vulval itching and/or redness, vaginal discharge, and associated dyspareunia. Despite the unpleasant symptoms, VVC is not a cause of substantial mortalities,2 nerve or sexual dysfunction, and R-VVC is well understood and poorly understood, and it follows from this that management is not evidenced based.3

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 drugs) and diabetes (2% of those in the fluconazole and placebo arms, respectively). No fluconazole events 2.9% and 1.2% in the treatment and placebo arms, respectively. No fluconazole patients were lost to follow-up or drop out, and 126 in the placebo arm (relative risk in placebo arm 9.29% lower than treatment arm). The study shows that management is not evidence based.2

Comparison of symptoms of mycologically proven recurrent VVC (also a contraindication for oral drugs) and diabetes (2% of those in the fluconazole and placebo arms, respectively). No fluconazole events 2.9% and 1.2% in the treatment and placebo arms, respectively. No fluconazole patients were lost to follow-up or drop out, and 126 in the placebo arm (relative risk in placebo arm 9.29% lower than treatment arm). The study shows that management is not evidenced based.2

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 any unexpected adverse outcomes that might be related to their use of oral contraceptives. Follow-up data for over 49,000 women were available for the review: 30.4% were using EE/DRSP, 27.9% levonorgestrel-containing OCs and 35.9% 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 rate 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 OCs. 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 contained no 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 unreported 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. Suspicions are heightened in people regarded as at increased risk. The difficulty in establishing a true rate for long-haul travel is a case in point. The increased case of diagnosis using d-dimer testing and the greater availability of imaging may help to establish more accurate current baseline 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:

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

Reference

Reviewed by Gill Wakley, MD, FFPM
Visiting Professor in Primary Care Development, Staffordshire University and Freelance GP, Writer and Lecturer, Abergavenny, UK


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 choice of intervention was randomised and each received 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 with a BMIs>30 or with a predisposition to VTE.

The results did not show that a brief intervention in a routine consultation improved knowledge about risk or changed 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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