

long-term eradication, will minimise drug side effects and antibiotic resistance, but with the least possible upset to schooling, work and family life. Getting there will require every CF centre to participate in multicentre trials and the timely application of evidence to clinical practice. Who will join the ELITE?

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Is postmenopausal HRT a risk factor for adult-onset asthma?

A E Tattersfield

Adult onset asthma is often progressive¹ and the cause of considerable morbidity. Some asthma developing de novo in adults can be attributed to environmental factors, such as occupational sensitizers. When such an association is recognised, asthma can often be prevented, so searching for aetiological factors is well worthwhile. Hormone replacement therapy (HRT) may be one such factor.

Postmenopausal HRT was used widely until recently, being seen as the way for women not only to appear more youthful and glamorous following the menopause but also to be healthier. Various observational studies had suggested a reduced risk of diseases such as osteoporosis, heart disease and possibly dementia. However, when the results of prospective studies became available the picture was, alas, rather less positive. Not only did these studies fail to confirm many of the alleged

benefits of HRT, they suggested or confirmed important adverse effects including an increased risk of breast cancer, ovarian cancer, venous thrombo-embolism, heart disease, cognitive decline and, more recently, mortality from lung cancer.^{2–8} Should late-onset asthma be on this list?

Cross-sectional studies have shown an association between the use of HRT and a diagnosis of asthma and asthma symptoms.^{9–11} The studies have varied in design and in how asthma was diagnosed, but the findings have been fairly consistent in showing a modest association between HRT use and reported asthma, with ORs ranging from 1.38 to 1.57.^{9–11} The associations with symptoms and asthma medication were of similar magnitude.^{9–11} Two studies found the strongest association in never smokers^{9 11} and two showed an interaction with body mass index (BMI), in that the effects of HRT were seen largely in women with a low BMI.^{9 10} Having a high BMI per se was associated with asthma,⁹ but there was no additional effect from HRT in these more overweight women. Cross-sectional studies have limitations, and

none of these studies looked at the type of HRT used, nor did they distinguish between new-onset and established asthma.

Data from the large US Nurses Health Study were published in 1995¹² and 2004.¹³ This was the first prospective study to look at the relationship of postmenopausal hormone use to the development of new cases of physician-diagnosed asthma, using biennial questionnaires to determine HRT use. The analyses covered a quarter¹² and half¹³ a million person-years of follow-up, respectively, with some overlap for the middle period. Both analyses showed an increased risk of developing asthma in association with current use of HRT, and this was similar for oestrogen alone and oestrogen/progestin preparations. The increased risk with unopposed oestrogen showed a dose–response relationship in the first study.¹² In the more recent study, by Barr *et al*,¹³ the rate ratio for newly diagnosed asthma amongst current users of oestrogen only was 2.29 (95% CI 1.59 to 3.29), and this tended to be greater in women with a low BMI. HRT was not a risk factor for developing chronic obstructive pulmonary disease.¹³

This issue of *Thorax* contains a further prospective study, from Romieu *et al* (see page 292), looking at the relationship of HRT use to new-onset asthma amongst postmenopausal women in the E3N study, a cohort of 98 995 French women using

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a health insurance plan that covers predominantly teachers.¹⁴ The analysis is based on 57 664 women who said at the time of the menopause that they had never had asthma, and who had adequate follow-up data. The women were aged 40–65 years when the study was initiated in 1990, and data on medical history, menopausal status and aspects of lifestyle were obtained subsequently from two-yearly self-completed questionnaires. Recent use of HRT was observed for 56% of person study years, with 11.2% of women taking oestrogen alone as last treatment and most of the remainder a combination of oestrogen and some form of progestogen. A third of the 19% of women who had had a hysterectomy had taken oestrogen alone.

Amongst the 57 664 women there were 569 incident cases of asthma over the 12 years of the study (1.15/1000 women/year).¹⁴ Overall there was a small increased risk of asthma developing amongst recent users of HRT, of borderline statistical significance (HR 1.2 (95% CI 0.98 to 1.46)). The risk of a new diagnosis of asthma was, however, increased amongst women who reported taking oestrogen alone as their last treatment, with a HR of 1.54 (95% CI 1.13 to 2.09). This increased risk amongst oestrogen users was seen mainly in women who had never smoked (HR 1.8 (95% CI 1.15 to 2.8)) and in women who had a history of allergic disease prior to asthma onset (HR 1.86 (95% CI 1.18 to 2.93)). There was no increased risk for new asthma onset for women taking oestrogen/progestogen preparations overall, although amongst non-smokers and people with previous allergic disease there was a small increase, of borderline statistical significance. Higher BMI was associated with an increased risk of asthma, but the effects of HRT on the risk of developing asthma did not vary with BMI.

The data from the current study by Romieu *et al*¹⁴ are broadly in keeping with the prospective US Nurses Study^{12 13} for women taking unopposed oestrogen, with an OR for recent users in the French study¹⁴ of 1.67, compared with rate ratios of 1.42¹² and 2.29¹³ for current users in the US studies. The main difference between the two studies is that combined oestrogen/progestogen preparations were associated with a similar risk of developing asthma to oestrogen alone in the US studies^{12 13} but with no increased risk in the French study,¹⁴ apart from subgroups of non-smokers and people with previous allergic disorders. The finding that being overweight is a risk factor for developing

asthma is in keeping with several previous studies,^{15–18} but the findings of an interaction between BMI and the effects of HRT have been less consistent.^{9–14}

Differences in outcome between cross-sectional and longitudinal studies are not too surprising, but the reason for the different findings for combined oestrogen and progestin preparations between the two large prospective studies is a bit more puzzling since they were of similar size and both collected data prospectively. The French teachers studied by Romieu *et al*¹⁴ were considerably less likely to take unopposed oestrogens than the nurses in the US study¹³ (11.2% vs 44%) and they had a lower median BMI. Both studies were prospective but observational rather than randomised controlled trials, and so the possibility of bias due to residual confounding cannot be excluded. The reasons why women choose to take or not take HRT, and which preparation, are complex and likely to be affected by social factors, educational attainment, availability and medical advice. The differences between the two studies may reflect differences in the population studied or the type or dose of HRT used. Despite the large numbers and long follow-up (around half a million years in both studies), some of the analyses are based on fairly small numbers because the number of new cases of asthma is relatively small. Furthermore, categorising HRT is inevitably untidy and very much larger numbers would be needed to try to disentangle the effects of the different preparations, formulations and doses used, and which are likely to differ between countries and could well have affected study outcomes. If, for example, oestrogen was the main driver of the increase in asthma with progestogens having a modifying effect, differences in the relative doses of oestrogen and progestogens might explain the differences in outcome between the two studies. Understanding the mechanism underlying the effects of oestrogen and progestogens in the lung might help but, as Romieu *et al*¹⁴ discuss, these are complicated, with oestrogen, for example, having actions that could be either proinflammatory or anti-inflammatory.

So what can we conclude from these studies? Unopposed oestrogen appears to be associated with an increased risk of developing asthma, and this risk appears to be greater in non-smokers and women with a history of allergic disease. There is less agreement about the risk of asthma associated with combined oestrogen/progestogen preparations and the role of

a low BMI in enhancing this risk, which might relate to differences in the nature and dose of the oestrogen and progestogens used in the combination product in different studies. The two most recent prospective studies^{13 14} provide some estimate of the likely risk of asthma from HRT in postmenopausal women and, although this may not be seen as being as serious as some of the adverse effects associated with HRT, it adds to the downside when women consider the pros and cons of hormone treatment.

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Improved survival in COPD: reasons for hope

Douglas W Mapel

Not long ago treatment of chronic obstructive pulmonary disease (COPD) was viewed with a sense of nihilism.¹ Patients were chronically and irreversibly debilitated. Treatments brought only brief palliative relief, and most had serious side effects. Worst of all, many patients were hopelessly addicted to nicotine, and the frustration of watching patient after patient continue to destroy their lungs in spite of their warnings caused many doctors to give up on even diagnosing the disease. Sceptics could point to the relative lack of efficacy of inhaled steroids in COPD. Cynics could question the motives of those who want to help persons who have destroyed their own health.

The last decade has seen the introduction of new treatments for COPD, which in turn have brought a new perspective and sense of energy.¹ It is not uncommon in medicine that the discovery of new treatments results in a surge of new interest in a disease. Many examples of this phenomenon are notable in recent history: sleep apnoea, pulmonary hypertension and erectile dysfunction are but a few. The release of the long-acting anticholinergic drug tiotropium, the approval of combined long-acting β_2 agonist/corticosteroid inhalers for COPD, development of new nebulised agents and release of innovative medications for nicotine addiction have provided us with new effective tools for COPD. Advocacy groups for COPD have multiplied and grown worldwide. In countries where it is allowed, direct-to-consumer drug advertising has introduced hundreds of millions of lay persons to the term 'COPD', and has educated doctors and patients alike that there are effective new treatments that can

reduce chronic respiratory symptoms and improve lung function.

An important dimension of COPD outcomes research that is lacking is evidence that treatment also improves survival. Survival is a big motivator. Patients are willing to tolerate expensive treatments with horrible side effects if they believe that they will improve their survival (eg, chemotherapy for cancer). Doctors will screen for asymptomatic diseases if they believe that finding them will improve the patient's chances of survival (eg, elevated cholesterol). The US Preventive Services Task Force recommended against using spirometry to screen for COPD in part due to the lack of evidence that pharmacological treatments affect hospitalisations or all-cause mortality.²

In this issue of *Thorax*, Almagro *et al* (*see page 298*) provide new evidence that modern management of COPD patients does improve survival.³ They compared the long-term survival of patients admitted for a COPD exacerbation in one hospital during the period from October 1996 to May 1997 (n=135) with that of patients with COPD admitted to the same hospital from June 2003 to September 2004 (n=181). Unadjusted 3-year mortality decreased from 47.4% to 38.7% (p<0.05). The cohorts were very similar in terms of demographics, and while the earlier group had a slightly worse airflow obstruction (forced expiratory volume in 1 s (FEV₁) % predicted 41.4% vs 45.1%), the latter group had worse oxygenation (partial pressure of oxygen (P_{O₂}) at discharge 70 vs 63) and more severe dyspnoea. After adjustment for multiple clinical factors, the relative risk of death was 0.70, which did not quite reach the definition of statistical significance (95% CI 0.47 to 1.05). Nevertheless, in a relatively small population, this is an impressive survival difference. Mortality was significantly decreased among the patients with COPD who also had

concomitant heart failure or cancer, suggesting that management of co-morbidities may have had as much to do with the improved survival as increased use of long-acting β_2 agonists and tiotropium at hospital discharge.

The Almagro study is obviously limited by the factors that affect any historical study design, including the potential for selection biases and possibility of inadequate adjustment for confounders. Also, the study is not conclusive proof that better cancer and heart failure care or better respiratory drugs are the causes of the improved survival, even though there were substantial changes in their utilisation between these two time periods. On the other hand, the features of a relatively consistent patient population, similar prevalence of co-morbidities and treatment in one hospital system provide some reassurance that the risks for selection and treatment biases were minimised. Despite the shortcomings, the message for the providers and patients in this hospital and similar systems is clear: we can improve survival in COPD, and that is very exciting news.

Smoking cessation for those who are still smoking and oxygen therapy for those who are chronically hypoxaemic are still the only treatments clearly proven to improve survival in COPD.⁴ Only one randomised clinical trial for treatment of COPD, the TORCH study, has ever been designed with survival as the primary end point, and it missed its statistically defined definition of a significant difference by the narrowest of margins (observed p value 0.052).⁵ The UPLIFT study of tiotropium in moderate and severe COPD found a survival benefit, but survival was a secondary end point and thus it has not received much attention.⁶ Also, in UPLIFT the statistical significance was observed at the end of the protocol-defined 4-year treatment period (p=0.034), but not 30 days thereafter (p=0.086), which is a perplexing observation that raises questions about withdrawal from treatment. The INSPIRE study was a direct comparison of salmeterol plus fluticasone in a combined inhaler (SFC) versus the long-acting anticholinergic tiotropium in severe COPD, with exacerbations captured as the primary outcome.⁷ Both treatments had a similar impact on COPD

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