

## Occasional reviews

## Do exogenous oestrogens and progesterone influence asthma?

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Between 20% and 40% of women of childbearing age in the UK use hormonal contraceptives.<sup>1,2</sup> In a survey carried out in Oxfordshire in 1990 about 20% of women aged 45-64 years were taking hormone replacement therapy (HRT).<sup>3</sup> Around 5% of women of childbearing age in the UK have diagnosed asthma, and a higher proportion have asthma-like symptoms.<sup>4</sup> There is less information available about the prevalence of asthma in older women, but there is little doubt that it is a common problem in this age group also.

There are no special guidelines on the prescription of hormonal contraceptives or hormone replacement therapy to women with asthma. Should we be concerned about the effect of oestrogens and progesterone on the risk of developing asthma? Should women with asthma avoid hormonal contraceptives and HRT? Or could they have a therapeutic role? The prevalence of asthma and asthma-like symptoms is similar in adult men and women<sup>5</sup> but women have a higher risk of hospital admission for asthma than men.<sup>5</sup> While this may be due to differences in illness behaviour and thresholds for admission, it may be that women have more severe symptoms, which could be due to their endogenous or exogenous levels of sex hormones. A recent paper documented the rise in asthma prevalence over the last 30 years and noted the parallel increase in the use of the oral contraceptive pill, hypothesising that hormonal contraceptives might increase the risk of asthma in subsequently born children.<sup>6</sup> Could they also influence the risk of asthma in women themselves? A body of research that has attempted to explore the influence of exogenous oestrogen and progesterone on the incidence and severity of asthma is reviewed here.

There are theoretical reasons why oestrogens and progesterone might be expected to influence the clinical expression of asthma. Pregnancy is associated with changes in immune function.<sup>7</sup> Animal studies have shown that oestrogens have many effects on humoral and cellular immunity,<sup>8</sup> influence smooth muscle function,<sup>9</sup> and have effects on the cholinergic and adrenergic systems.<sup>10-12</sup> Prostaglandins, which have been implicated in the pathogenesis of asthma,<sup>13</sup> may be partially controlled by the levels of sex hormones.<sup>14,15</sup> However, it is not clear what these findings mean for women

considering taking hormonal contraceptives or oestrogen replacement therapy.

**Hormonal contraceptives**

Hormonal contraceptives reduce the magnitude of variations in oestrogen and progesterone over the menstrual cycle. If fluctuations in the levels of these hormones over the menstrual cycle cause cyclical variations in asthma severity, the idea that hormonal contraceptives might reduce their amplitude is plausible. Symptoms get worse in the perimenstrual part of the cycle in about a third of asthmatic women.<sup>16-18</sup> A prospective study of 182 asthmatic women of childbearing age followed for a year found that a significantly higher proportion were admitted to hospital in the perimenstrual phase (days 26 to 4) than in other parts of the cycle.<sup>19</sup> Are perimenstrual exacerbations and admissions to hospital directly due to the cyclical effects of hormones on the lung or to variations in the perception of, and response to, symptoms over the menstrual cycle? Several studies have demonstrated falls in peak expiratory flow rate (PEFR) in the perimenstrual parts of the cycle.<sup>16,17,20</sup> One study found an increase in bronchial hyper-responsiveness (BHR) in the luteal phase in a small group of women,<sup>21</sup> though three others of similar design have shown no such association.<sup>22-24</sup> Possible explanations for the negative findings of these three studies include the participation of a very small number of subjects and therefore low power to detect differences, the timing of measurements of BHR which may not have been those most likely to show differences, and the selection of subjects who did not experience clinical premenstrual exacerbations.

Whether cyclical variations in perceived asthma severity are due to fluctuations in circulating levels of oestrogen and progesterone matters because, if this is the case, exogenous hormones may have a therapeutic role in asthma. There are a number of published reports giving some evidence to support this idea. Beynon *et al* described three women with severe perimenstrual exacerbations accompanied by falls in PEFR who needed fewer corticosteroids and had no perimenstrual PEFR dips following the administration of regular intramuscular progesterone.<sup>25</sup> Two of them had already tried combined oral contraceptive pills before with

no improvement. A premenopausal woman with severe steroid dependent asthma for 10 years and a history of perimenstrual exacerbations experienced an improvement in symptoms after starting to take a combined oral contraceptive pill.<sup>26</sup>

In an uncontrolled study 14 women of child-bearing age with asthma, five of whom reported premenstrual worsening of symptoms, were given a daily oestrogen supplement (2 mg oestradiol) on days 23–28 of the cycle.<sup>20</sup> Compared with a previous cycle during which no exogenous hormone supplementation was given, the women had improved average symptom scores. However, the “before and after” design of this study means that we cannot rule out the possibility that the improvements occurred for some reason other than oestrogen supplementation.

There is further support for the idea that administration of exogenous hormones improves asthma severity from the study by Tan *et al* which showed an increase in BHR during the luteal phase of the menstrual cycle.<sup>21</sup> Of the 18 subjects in this study, nine were taking the oral contraceptive pill and no increase in BHR or reduction in PEFR was seen in these subjects during the luteal phase. The clinical significance of this finding is not clear because BHR is not always related to the severity of symptoms. In this study there were no significant differences in symptom scores and bronchodilator requirements between the luteal and follicular phases whether or not the women were taking the contraceptive pill. This may have been due to the fact that subjects were asked to give a daily symptom score of 0 to 3 which may have only a limited ability to detect subtle changes in symptoms. However, without clear evidence of a difference in clinically relevant indicators of severity of disease, we cannot conclude that the finding has any therapeutic implications for women with asthma.

There are studies, on the other hand, that suggest that exogenous sex hormones make asthma worse. Horan and Lederman described a 26 year old woman whose asthma improved when she stopped taking the oral contraceptive pill.<sup>27</sup> A study of seven asthmatic women using a randomised crossover design found that the administration of a single dose of 10 mg medroxyprogesterone during the early follicular phase was associated with a reduced lymphocyte  $\beta_2$  adrenoceptor binding density and a lower cyclic adenosine monophosphate response to isoprenaline.<sup>28</sup> Oestrogen administration had no effect on these measures. While this suggests that asthmatic women may experience reduced efficacy of  $\beta_2$  agonists when taking exogenous progesterone, the finding has not been confirmed in studies measuring clinical outcomes.

A recent study suggests that any effect of hormonal contraceptives on asthma severity is likely to be small.<sup>29</sup> In a survey of 461 women recruited from general practice registers who had been prescribed a bronchodilator in the previous two years and who responded “yes” to the question “Have you ever had asthma?”,

only 6% of the 389 women who had ever taken hormonal contraceptives reported that these had influenced their asthma symptoms; 4% reporting a worsening and 2% an improvement. The women who reported that hormonal contraceptives had made their asthma worse had slightly but significantly worse asthma, as measured by the Marks’ Asthma Quality of Life Questionnaire.<sup>30</sup> These findings suggest that hormonal contraceptives influence severity in only a small proportion of women with asthma, probably those with more severe symptoms. There was no difference in the Asthma Quality of Life Score between women currently taking hormonal contraceptives and those not. The power to detect even small differences in score was over 90%, and the score was shown to be a valid measure of severity, being strongly associated with other measures of severity such as use of inhaled steroids, number of days off work, number of visits to general practitioner, and whether admitted to hospital in the last six months.

This study is reassuring. It is unlikely that hormonal contraceptives influence symptom severity in most women with asthma. The effect on women with severe asthma, and especially those with premenstrual exacerbations, remains to be evaluated.

There are plans to measure the association between use of hormonal contraceptives and asthma in some of the centres participating in the second phase of the European Community Respiratory Health Survey, a multicentre survey of respiratory morbidity and risk factors in large representative samples of the adult population across Europe (Cecilie Svanes, personal communication). This study will have the advantage that BHR and atopy will be measured as well as symptoms.

### Hormone replacement therapy

In the absence of fluctuations in endogenous sex hormones in postmenopausal women, there are less convincing theoretical reasons to believe that hormone replacement therapy would improve asthma symptoms. A case report describes two postmenopausal women with poorly controlled asthma who had been dependent on oral corticosteroids for several years. In both cases the introduction of conjugated oestrogen therapy without the addition of progesterone was followed over the next few months by a remarkable improvement in symptoms and they were able to stop oral steroids.<sup>26</sup> However, another report describes a postmenopausal woman with chronic airflow obstruction whose symptoms got much worse with the introduction of oestrogen therapy with progesterone and which improved when it was stopped.<sup>31</sup>

An uncontrolled study of 15 postmenopausal women with asthma found a small but significant fall in mean PEFR and an increase in medication requirements 4–5 weeks after starting oestrogen replacement therapy without the addition of progesterone.<sup>32</sup> There was, however, no difference in general well being with regard to asthma reported by the subjects before and during treatment. The authors

concluded that there may be a subclinical worsening of asthma with oestrogen replacement therapy. The instrument used to measure symptom severity, however, may not have allowed the detection of subtle differences. In another uncontrolled study of 36 postmenopausal women without asthma taking oestrogen replacement therapy without the addition of progesterone, there was a reduction in the average maximal decrease in forced expiratory volume in one second after inhaling histamine at a concentration of 8 mg/ml.<sup>33</sup> This suggests that oestrogen replacement therapy is associated with an improvement in airway responsiveness in non-asthmatic women. The major drawbacks of both these studies are that the subjects were not blind to the administration of oestrogens and that there were no control groups. We cannot therefore assume any causal relationship, nor necessarily conclude that the effects of oestrogens are different in asthmatic and non-asthmatic women.

Epidemiological evidence for an influence of HRT on the risk of asthma, though not the severity, comes from the nurses' health study which followed up nurses without asthma for 582 135 woman-years.<sup>34</sup> The incidence of asthma in postmenopausal women was 1.1 per 1000 person-years. Having ever taken HRT was associated with an increased incidence of asthma after controlling for age, body mass index, smoking, and previous use of the oral contraceptive pill (incidence rate ratio 1.49, 95% confidence intervals 1.1 to 2.0). There was a dose-response relationship between asthma incidence and current dose of oestrogens and the duration of use. The association was present in women taking unopposed oestrogens and those taking oestrogens plus progesterone. One possible bias in this study may have been that women taking HRT may see doctors more often, increasing the probability of being diagnosed with asthma, but the association was still present when the analysis was restricted to women who reported a visit to a doctor in 1978. However, the possibility remains that there are other unmeasured and as yet not well understood differences between women who take HRT and those who do not that may have influenced the risk of developing asthma.

What are the implications for prescribers of hormonal contraceptives and HRT to women with asthma or at risk of developing asthma symptoms? There is no convincing evidence to suggest that hormonal contraceptives either exacerbate or improve asthma symptoms. We can therefore be reassured that any effect on women with relatively mild asthma, if present, is likely to be small. However, we cannot be sure about the effect on women with more severe symptoms or those with premenstrual exacerbations until it has been evaluated in controlled trials with outcomes that are relevant to people with asthma. Likewise, studies of HRT in postmenopausal women do not unequivocally demonstrate a causal relationship with either the severity or incidence of asthma. The possible risks of both hormonal contraceptives and HRT in women with or without asthma should be seen in the context

of their widely accepted benefits. At present there is not enough evidence to suggest any change to current prescribing practice.

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