Asthma and atopy

# Asthma and atopy: endocrine or metabolic conditions?

L Forbes

## New perspectives on the relationship between asthma or allergy and female sex hormones

Female sex hormones seem to have something to do with asthma and allergy. You might think this is a bit vague, but the research on this so far doesn't merit anything stronger. Women of reproductive age are more likely to be admitted to hospital for asthma than men.[1] Intrigued by this, people have studied the link between asthma or allergy and markers of female sex hormone levels—for example, time of menstrual cycle, menopause, pregnancy, hormonal contraceptives, hormone replacement therapy, maternal parity, and age at menarche—but the overall picture remains confused. The results of the studies are inconsistent, with no unifying pattern of effects of hormones. Three recent studies in *Thorax*, two in this issue[2 3] and one published in June this year,[4] have added some new pieces to the jigsaw puzzle and a new perspective on the problem.

Brenner *et al*[2] looked at menstrual variation in asthma symptoms. We have recognised for a long time that some women get worse asthma symptoms at certain times of the month. Surveys of asthma outpatient clinics suggest that about a third of women experience worse symptoms just before and during their periods,[5–7] although the figure would probably be lower in community based surveys. A few researchers have shown that peak expiratory flows[5 6] or bronchial responsiveness[8] vary over the menstrual cycle, but others have shown no such variation.[9 10] As with the premenstrual syndrome, exactly what it is about the different phases of the menstrual cycle that might exacerbate asthma is not known. Could it be absolute levels of oestrogens or progesterone, relative levels, changes in levels, or something else altogether? In the absence of an answer from looking at oestrogen and progesterone levels, research into the pathophysiology of the premenstrual syndrome has looked at other endocrine systems: renin-angiotensin-aldosterone, 5-hydroxytryptamine and gamma aminobutyric acid, among others.[11]

The study by Brenner *et al*[2] thickens the plot further: in 800 women (all premenopausal and not taking the contraceptive pill) attending the emergency room for asthma, more attended just before or during their periods (as expected), but a high proportion also attended just before they ovulated. The differences were fairly small: 27% attended during days 26 to 4 and 28% during days 5 to 11, compared with 25% during days 12 to 18 and 21% during days 19 to 25. A preovulatory increase in asthma emergency attendances has been noted before in a smaller study of 288 women, in which 33% attended during days 5 to 11 and only 21% during days 26 to 4.[12] In terms of gonadal hormone levels, the perimenstrual phase of the menstrual cycle is broadly characterised by fairly low levels of oestradiol and progesterone and the preovulatory phase by rising levels of oestradiol.

This line of enquiry is interesting not just because of the therapeutic implications for women with asthma that varies over the menstrual cycle, but because of the clues it leaves about the aetiology of asthma. Aetiology was the focus of the two other studies. Maitra *et al*[3] examined associations between maternal age at menarche (early menarche being a marker of higher oestrogen levels in adulthood) and asthma and atopy in offspring, the hypothesis being that oestrogen exposure in utero might influence the later development of these conditions. An analysis of data from the Avon Longitudinal Study of Parents and Children, it found no association between maternal age at menarche and asthma (based on parental questionnaire responses) or atopy (based on parental questionnaire responses and positive skin prick tests to common aeroallergens) at age 7. This conflicts with the findings of an analysis of a Finnish birth cohort which found that maternal late menarche was associated with a lower prevalence of atopy at age 31, but there was no association between later menarche in the birth cohort members themselves and atopy at age 31, nor any association between maternal age at menarche and asthma.[13]

The study by Svanes *et al*[4] published in the June issue of *Thorax* examined the association between irregular menstruation and asthma and atopy in women. A community based postal questionnaire survey of over 8000 Northern European women aged 25–42 found that women with irregular periods were about 50% more likely to have asthma or asthma symptoms and about 30% more likely to report hay fever than those who said they had regular periods. The increase in risk was not explained by asthma medication, which may influence levels of sex hormones.[14]

This is a new and interesting finding. The association was strong and fairly consistent across the different participating countries. The women were young, so menopause is unlikely to explain it, and it is unlikely that breastfeeding is common enough at any one time to have any effect. One of the difficulties of interpreting the association is that women with irregular periods may attend for health care advice more often, so may be more likely to have received a diagnosis of asthma or hay fever; however, in the study, irregular menstruation was also associated with symptoms of asthma. Another difficulty is that women with ''irregular menstruation'' were defined as premenopausal (that is, had had a period in the last 6 months), were non-pregnant and not taking oral contraceptives or hormone replacement therapy, and had answered ''no'' to the question: ''Do you have regular menstrual periods?'', the assumption being that this meant that they had irregular periods—probably reasonable, but that wasn't quite what the question asked.

The authors offer two hypotheses to explain the association. The first is that the disturbance of sex hormones associated with irregular menstruation might cause asthma. What that disturbance might be is not clear. Women have irregular periods for a variety of reasons: for several months after stopping hormonal contraceptives or breastfeeding, injected or intrauterine contraceptives, eating disorders, weight gain, hard sports training, psychological disturbance, fibroids, endometriosis, and endocrine disorders including polycystic ovary syndrome, diabetes and thyroid disease. To my knowledge there is no known pattern of sex hormone disturbance common to all these.

The second hypothesis is more interesting and offers a much needed new perspective on the relationship between female sex hormones and asthma and, indeed, the aetiology of asthma.

Polycystic ovary syndrome, probably the most common endocrine cause of irregular menstruation and the most common form of anovulatory infertility,[15] is associated with insulin resistance which, like the metabolic syndrome, is a strong risk factor for cardiovascular disease.[16] The authors suggest that asthma, allergy, and menstrual irregularity caused by polycystic ovary syndrome may have insulin resistance in common. This might fit in with the as yet unexplained association between asthma and obesity, which is particularly strong in women,[17] and between lung function and insulin resistance.[18] Could asthma be another manifestation of the metabolic syndrome? Could something in early life influence the development of asthma, allergy, and insulin resistance?

Women with polycystic ovary syndrome have high circulating levels of androgens, polycystic ovaries on ultrasound imaging, oligo- or anovulatory cycles and, usually, oligo- or amenorrhoea.[19] The precise diagnostic criteria are considered contentious, although the prevalence is estimated to be as high as 5–10% of women of reproductive age.[20] Are these women more likely to have asthma or atopy? Women with infertility were more likely to have used asthma medication before age 21 in a case-control study.[21]

These studies add more chapters to the rather jumbled story of female sex hormones and asthma and allergy. The hypothesis put forward by Svanes and colleagues—that asthma and allergy share a common aetiology with metabolic syndrome which may be related to early life influences on insulin resistance—is attractive, suggesting a new metabolic line of enquiry for researchers trying to identify the causes of asthma. It may also help identify what female sex hormones have to do with asthma—if anything.

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Correspondence to: Dr L Forbes, Consultant in Public Health Medicine, Wandsworth Primary Care Trust, Lupin Ward, Jasmine Tower, Springfield Hospital, 61 Glenburnie Road, London SW17 7DJ, UK; Lindsay.forbes@swlondon.nhs.uk

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Passive smoking and asthma exacerbation

# Passive smoking and asthma exacerbation

**J Britton**

## Further evidence to advance the public, political, and legal process towards effective public protection from the effects of passive and active smoking

Cigarette smoke is a toxic mixture containing around 4000 different chemicals including a range of carcinogens, irritants, and toxins.[1] It is therefore no surprise that inhaling cigarette smoke, either actively as a cigarette smoker or passively through exposure to exhaled and sidestream smoke from other smokers, is bad for health.[1] In fact, active smoking kills more people in economically developed countries than any other preventable cause, and currently accounts for over 100 000 deaths (or about 20% of all deaths) each year in the UK.[2] Worldwide the annual death total is currently close to 5 million.[3] Passive smoking is also a major problem, causing at least 12 000 deaths each year in the UK,[4] or about 2% of the current annual total, and probably a similar proportion in other developed countries. On these figures alone it should be clear that we have sufficient evidence to conclude that preventing exposure to cigarette smoke, either active or passive, should be a fundamental priority of all clinical and public health practice. We already know what the main health effects of smoking are, or in relation to passive smoking, are likely to be. So do we need more research defining the adverse effects of passive smoking in still greater detail?

The answer to this question is that we do, and primarily to inform, support, or otherwise enhance the political process towards effective tobacco control. While governments continue to prevaricate over the implementation of simple public health measures to reduce smoking incidence and encourage smoking cessation, new evidence can help tobacco control lobbyists and supporters both inside and outside the government and health services to press for change. New