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## Prenatal nutrition and asthma: hope or hype?

Seif O Shaheen

David Barker's "fetal origins" hypothesis has changed the way we think about the aetiology of adult onset diseases, such as coronary heart disease and type 2 diabetes.<sup>1</sup> Underpinning the epidemiological evidence are recent animal data which suggest that fetal programming of these diseases by prenatal nutrition may be mediated through epigenetic mechanisms.<sup>2</sup> If adult onset disease is partly programmed in utero, it seems even more plausible that the prenatal environment influences the inception of asthma, which may first manifest in infancy. A number of exposures during pregnancy have been implicated<sup>3–5</sup> and, although data are conflicting, associations with birth anthropometry prompted speculation that prenatal nutrition might programme fetal lung and immune development leading to asthma and atopy.<sup>6</sup> Given that the diet of pregnant mothers has clearly changed considerably while asthma has been rising, the notion that it might be modified as a strategy for the primary prevention of asthma has considerable appeal.<sup>7</sup> This has perhaps been reinforced by recent disappointments with dietary interventions aimed at secondary prevention of adult asthma.<sup>8</sup>

### NUTRIENTS, FOODS OR DIETARY PATTERNS?

Trying to measure prenatal nutrition presents a major challenge for epidemiologists. Estimating maternal dietary intake in pregnancy, usually using a semiquantitative food frequency questionnaire on one occasion, leads to considerable exposure misclassification, and fetal nutrition will depend, not just on maternal intake, but also on nutrient absorption by the mother, placental transfer and fetal demand. Nutrients measured in maternal blood during pregnancy may be useful to validate dietary intake, and biomarkers measured in umbilical cord blood, cord tissue or deciduous tooth enamel may estimate fetal exposure more precisely. Furthermore, biomarkers may be the best way to capture the overall status of nutrient exposures such as vitamin D which are not exclusively determined by diet.

Initial epidemiological interest focused on the antioxidant hypothesis,<sup>9</sup> and birth cohort studies have reported associations between wheezing in early childhood and low prenatal selenium status,<sup>10,11</sup> and low maternal intakes of vitamin E and zinc.<sup>12–14</sup> Following the observation of a link between low maternal intake of vitamin D and early wheezing,<sup>15,16</sup> it has been proposed that vitamin D deficiency in pregnancy is the main cause of the asthma epidemic in the West.<sup>17</sup> However, given that asthma was not common during the industrial revolution when rickets was rife in cities, this idea would appear to give, at

best, an incomplete account of the rise in asthma. Low intakes of apples and fish in pregnancy have also been associated with an increased risk of wheezing, asthma and other atopic outcomes in the offspring.<sup>18–20</sup>

One disadvantage of studying multiple nutrients and foods is that many are highly correlated with each other, making it difficult to disentangle independent effects. Another is that analysis of multiple exposures and outcomes inevitably leads to numerous statistical comparisons. An alternative approach is to relate dietary patterns to disease outcomes. This has the advantage of reducing a large number of dietary measurements down to a small number of overall features of diet which are uncorrelated. Dietary patterns can be derived either by data driven methods such as principal components analysis or by defining a priori scores, as has been used to describe a "Mediterranean" diet. In this issue of *Thorax*, Chatzi and colleagues<sup>21</sup> have examined relations between adherence to a Mediterranean diet in pregnancy and wheeze and atopic outcomes in the offspring in a relatively small birth cohort in Menorca (*see page 507*). A high diet score was negatively associated with persistent wheeze, atopic wheeze and atopy at 6.5 years of age although, as the score was condensed into two categories, it is not possible to determine whether there are "dose response" relations that would favour a causal interpretation. In fact, when the score was analysed as a continuous variable, only one of the three associations remained significant. A key component of a Mediterranean diet is fish, and it would be of interest to know to what extent the apparent effect of a Mediterranean diet on atopic outcomes was explained by a high intake of fish in pregnancy, as the latter was shown to be negatively associated

**Correspondence to:** Dr S O Shaheen, National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, Manresa Road, London SW3 6LR, UK; s.shaheen@imperial.ac.uk

with similar childhood outcomes in the same cohort.<sup>19</sup> Furthermore, although the main findings were not confounded by a Mediterranean diet in childhood, it is not clear whether they might partly be explained by high intakes of certain vegetables and fish, which were reported to have protective effects on atopic outcomes in previous cross sectional analyses of these children.<sup>22</sup> Dietary patterns in pregnancy are strongly socially determined,<sup>23</sup> and hence confounding of dietary effects by sociodemographic and lifestyle factors is a potential concern. It is therefore important to control for these factors as comprehensively as possible. For example, controlling for maternal smoking only as a binary variable may lead to residual confounding. Controlling for maternal asthma and atopy is useful as an indirect means of assessing whether avoidance of certain foods such as nuts and oily fish by allergic mothers might explain links between a low maternal intake of vitamins E and D, respectively, and a higher risk of atopic outcomes in the offspring.

#### TOO MUCH OF A GOOD THING?

In contrast with the data above on antioxidants and vitamin D, one birth cohort study has reported that a higher intake of raw sweet peppers and citrus fruit in late pregnancy was associated with an increased risk of sensitisation,<sup>20</sup> and in the Aberdeen cohort a higher intake of fruit and vitamin C intake in pregnancy was associated with an increased risk of early eczema.<sup>12</sup> While residual confounding by higher social class (associated with higher consumption of fruit, and with eczema), cannot be ruled out, this seems an unlikely explanation, as *negative* associations were seen between fish intake (also associated with higher social class) and eczema in the same cohorts.<sup>18, 20</sup> These findings are consistent with a recent hypothesis that antioxidants may *increase* the risk of asthma and allergic disease,<sup>24</sup> which is contrary to the currently accepted antioxidant-asthma paradigm. A small birth cohort study recently reported that higher blood levels of vitamin D in pregnancy were associated with an increased risk of asthma and atopy later in childhood,<sup>25</sup> and in a larger cohort, vitamin D supplementation in infancy was associated with an increased risk of later atopy and allergic rhinitis.<sup>26</sup> These data are in keeping with the original vitamin D hypothesis of Wjst and Dold, which argued that a higher intake of vitamin D might promote atopic disease.<sup>27</sup>

One way to reconcile the diverse findings for antioxidants and vitamin D, assuming that they have not arisen through chance, bias or confounding, is to speculate that maternal intake of antioxidants and vitamin D is a “double-edged sword”, with effects varying with phenotype. A higher intake may protect against early non-atopic wheezing, associated with small airways and viral infection, but may increase the risk of atopic outcomes. This model is reminiscent of some postnatal exposures, such as day care and endotoxin, which also have opposite effects on risks of early wheezing versus later atopic wheezing. If true, then supplementation with antioxidants or vitamin D in pregnancy would not be an appropriate strategy for the primary prevention of atopic asthma.

#### JUMPING THE GUN?

Despite the muddied waters described above, some investigators are eager to proceed with intervention studies,<sup>17</sup> and a trial of vitamin D supplementation in pregnancy is already planned in the UK, although not primarily with respiratory or atopic outcomes in mind. Intervention with a single nutrient has advantages over dietary modification. Nutrient supplementation may be more appealing to pregnant women, given that approximately 40% of adults in the UK take supplements. Also, a trial of this kind can be double blinded and placebo controlled. In order to maximise efficacy, and minimise adverse effects, initial screening of potential participants would seem prudent, so that only those with low blood nutrient levels are randomised. This would increase costs and is likely to require multiple study centres to recruit sufficient numbers of eligible women. A potential disadvantage of nutrient supplementation is that for a nutrient to have optimal biological action, it may need to be consumed with other nutrients in food, rather than in pill form. On the other hand, trying to improve the diet of pregnant women, even in the setting of a clinical trial, is a challenge, and simple advice may not be effective.<sup>28</sup>

I would argue, however, that new supplementation trials in pregnancy aimed at the primary prevention of asthma may be premature, for two reasons. Firstly, we should be cautious about safety. In the case of antioxidant vitamins, there is evidence of increased adult mortality associated with vitamin supplement use,<sup>29</sup> and a recent trial of prenatal vitamin C and E supplementation in pregnancy, aimed at reducing

pre-eclampsia risk, found that, compared with placebo, vitamin supplementation increased the risk of low birth weight.<sup>30</sup> The teratogenic risks of a high vitamin A intake in pregnancy are well known,<sup>31</sup> but we know little about possible risks to the fetus of vitamin D supplementation in pregnancy.<sup>32</sup> An observational study found that a higher intake during early pregnancy of cod liver oil, a rich source of vitamin A and vitamin D, was associated with an increased risk of hypertensive disorders.<sup>33</sup> Secondly, I believe that more convincing data are needed to strengthen the case for prenatal interventions, a view echoed by others.<sup>34</sup> A number of different approaches could be used. Follow-up of birth cohorts beyond 5 years, with detailed assessment of asthma phenotypes, may clarify whether higher intake of antioxidants and vitamin D in pregnancy is associated with an increased risk of atopy, and would allow a clearer assessment of potential confounding by childhood diet. Also, for birth cohorts which have collected DNA from mothers and/or children, genetic epidemiology provides an opportunity to strengthen causal inference, either through a Mendelian randomisation approach<sup>35</sup> or by identifying a priori interactions between maternal nutrient intake and relevant gene polymorphisms. Another neglected approach is to identify existing randomised trial cohorts which were set up to study the impact of nutritional interventions in pregnancy on other disease outcomes. If the interventions are of interest, and follow-up and assessment of respiratory and atopic outcomes in the offspring is feasible, then this would be more cost effective than conducting a trial *de novo*, especially if the case for the latter is weak given existing observational data. Finally, studies in animals would be a useful adjunct to epidemiological research in this area in order to confirm or refute causal links and to clarify underlying mechanisms.

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## Aspirin and asthma: barking up the right tree?

Andrew A Clayton, Douglas L Forrester, Alan J Knox

According to World Health Organization estimates, 300 million people worldwide suffer from asthma. It is the most common chronic condition in childhood and continues to impose a high burden of morbidity and mortality in adulthood; over 250 000 people are thought to have died from asthma in 2005. In the UK 5.2 million people are currently receiving treatment for asthma.

There has been an apparent increase in incidence over recent years, at least in children and adolescents. Data in adults are more sparse but suggest that incidence

increases slightly with age, albeit to a level much lower than that in children.<sup>1</sup> The aetiology of asthma at all ages is still not fully understood although environmental allergens, immunological and genetic factors are all known to contribute. In this issue of *Thorax* Kurth *et al*<sup>2</sup> report interesting post hoc data from the Women's Health Study which suggest that assignment of 100 mg aspirin on alternate days reduces the relative risk of newly reported diagnosis of asthma in otherwise healthy adult women (*see page 514*).

The first descriptions of aspirin-like medication come from the time of Hippocrates when the bark of the white willow was used as an antipyretic agent. In the 1700s its use is again described to treat "ague" (fever).<sup>3</sup> The active compound was extracted and purified during the 1800s. Most physicians associate aspirin with its

ability to precipitate or worsen asthma symptoms. Aspirin-sensitive asthma is in fact a distinct clinical syndrome. Bayer released aspirin onto the market in 1899 as an analgesic and antipyretic agent.<sup>3,4</sup> It became clear soon after this that aspirin ingestion could lead to severe asthma attacks. The clinical triad of aspirin sensitivity, asthma and nasal polyps was first described by Widal *et al* in 1922.<sup>5</sup> This was further characterised by Samter and Beers in 1968, leading to the diagnostic label of "Samter's triad".<sup>6</sup> Typically, these patients develop symptoms 2–3 h after ingestion of aspirin, characterised by bronchospasm, profuse rhinorrhoea, conjunctival injection, periorbital oedema and generalised flushing. Studies estimate the prevalence of aspirin sensitivity among individuals with asthma at 5–20%.<sup>7,8</sup> These patients usually develop perennial rhinitis in their third decade followed by asthma and aspirin sensitivity a few years later.

The mechanism of these effects is thought to involve disordered arachidonic acid metabolism. Evidence suggests that a reduction in cyclo-oxygenase-1-derived prostaglandin E<sub>2</sub> production<sup>9–11</sup> and increased levels of leucotrienes<sup>12–14</sup> are both important.

Faculty of Medicine and Health Sciences, Centre for Respiratory Research, Nottingham City Hospital, Nottingham, UK

**Correspondence to:** Professor A J Knox, Faculty of Medicine and Health Sciences, Centre for Respiratory Research, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; alan.knox@nottingham.ac.uk