

EDITORIAL

Clinical and Experimental Allergy

Birth by caesarean section and asthma

This editorial discusses the findings of the paper in this issue by Thavagnanam et al. [5], pp . . .

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The prevalence of asthma and atopic disease in westernized countries has increased markedly over the last 30 years [1], although the cause for the increase remains unclear. Amongst the most attractive suggestions is the hygiene hypothesis, which proposes that decreased exposure to environmental agents, including bacteria early in life as a result of modern hygiene practice, shifts immune development towards an allergic phenotype.

There has been a concurrent increase in westernized countries of birth by caesarean section [2]. Numerous studies (although not all) have reported that the incidence of asthma is higher following caesarean section, and it has been suggested that a proportion of the increase in asthma can be explained by the increase in birth by caesarean section. Birth by caesarean section is associated with altered development of infant intestinal flora [3], and maturation of intestinal flora is associated with subsequent development of allergic diseases [4]. As delivery by caesarean section results in decreased exposure at birth to maternal environmental pathogens, it is postulated that this shifts the immune response to an allergic phenotype as predicted by the hygiene hypothesis, thus increasing the risk of development of asthma. So could some of the increase in the prevalence of asthma be due to the increase in birth by caesarean section, and does this add further support to the hygiene hypothesis?

In this edition of *Clinical and Experimental Allergy*, Thavagnanam et al. [5] report a meta-analysis of studies investigating the association between caesarean section and subsequent development of asthma. They identified 23 studies, the majority of which were of cohort design. To counter heterogeneity between studies, the authors used a random effects model to provide a more conservative odds ratio (OR) estimate. When all 23 studies were included there was significant heterogeneity, but this was no longer

significant when the analysis was restricted to the 20 studies where asthma diagnosis was ascertained in childhood. It is reassuring that the ORs did not change markedly between 1.22 [95% confidence interval (CI) 1.14, 1.29] for all studies and 1.20 (95% CI 1.14, 1.26) for asthma diagnosis ascertained in childhood. Their study suggests a 20% increase in the risk of asthma following birth by caesarean section, but that the magnitude of effect is unlikely to fully explain the worldwide increase in prevalence of asthma.

However neither asthma nor the indications for birth by caesarean section are discreet entities. There is recognition that there are at least two different wheezing phenotypes in childhood, and that the aetiology of transient early wheezing and atopic asthma are markedly different. Transient early wheezing is thought to reflect structural differences in airway calibre with maternal smoking a major risk factor; while atopic asthma is mediated by IgE, and personal and family history of allergic disease is more important. Similarly caesarean section may need to be performed as an emergency, but increasingly is performed for social or lifestyle reasons [6]. Thus a criss-crossing of biologically plausible explanations for the association between birth by caesarean section and subsequent development of asthma can be proposed depending on the wheezing phenotype and indication for caesarean section. It is noteworthy however that there is much less evidence of a relationship between birth by caesarean section and the development of atopy or other allergic diseases [7–9], suggesting that the association might be mediated through an effect on airway calibre.

Meta-analysis can only determine strength of association, and can give no indication of causality or of the possible direction of the effect. There are differences in the changes in asthma prevalence and rate of caesarean section, and numerous potential confounding variables that could contribute to the reported association. The sharp rise in asthma prevalence appears to have accelerated from the 1970s, but it is likely that the increase has now plateaued [10], and might actually be decreasing

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[11]. In contrast the rate of caesarean section increased from the 1970s, but fell slightly during the early 1990s. Since then the rate has increased further due to a combination of increased rate of primary caesarean section, but also a sharp fall in the rate of vaginal birth after caesarean section [2]. Currently 23% of infants are born by caesarean section in the UK [12], and nearly 30% in the US [2].

Pre-maturity, inter-uterine growth retardation (IUGR), and pre-natal smoking are all possible confounders that are closely linked. Pre-term infants and those born with IUGR are more likely to be born by caesarean section, and these infants have an increased risk of developing asthma [8]. Although a number of studies investigating the association between asthma and birth by caesarean section adjusted for low birth weight [7, 9, 13–15], birth weight might be an insensitive marker of differential growth retardation compared with head circumference or ponderal index at birth, which might be more closely linked to the development of an allergic phenotype [16]. Maternal smoking during pregnancy is associated with an increased rate of birth by caesarean section, pre-term birth [17, 18] and significantly decreased birth weight [18]. Both pre-natal smoking and subsequent maternal smoking during infancy is associated with an increased risk of pre-school wheezing. Although a number of studies in the meta-analysis [7, 9, 13–15] adjusted for maternal smoking, the relationship is likely to be complex. Breastfed babies have decreased risk of atopic disease due to presumed immunomodulatory effects from human milk [19], and women who give birth by caesarean section have reduced rates of breastfeeding [20].

If the relationship between birth by caesarean section and asthma is directly causative, there are potential causes in both directions. Asthma in the mother is a risk factor for many adverse maternal complications of pregnancy [21, 22]. In a case control study of over 10 000 pregnant women with singleton births, asthma in the mother was associated with increased risk of pre-eclampsia, placenta praevia and caesarean delivery; while the newborn infants were more likely to be pre-term, of low birth weight, small for gestational age and an increased frequency of congenital anomalies [21].

Transient tachypnoea of the newborn (TTN) is a condition where retained lung fluid following birth results in respiratory distress, and is significantly more likely in the newborn infants of asthmatic mothers [23, 24]. During labor the mature lung switches from active fluid and chloride ion secretion to active sodium and fluid absorption. TTN is most common following caesarean section where labor has not occurred – so the risk is greatest following elective caesarean section, particularly if less than 39 weeks gestation [25]. In a case controlled study over 13 000 term infants, TTN was an independent risk factor for developing asthma even after adjustment for

delivery by caesarean section (OR 1.5, 95% CI 1.13–1.99) [26]. The risk of TTN following elective caesarean section at term is significantly decreased through the administration of exogenous corticosteroids before delivery [27], suggesting either corticosteroid up-regulation of epithelial channels or increased surfactant production. It is unknown whether administration of exogenous corticosteroids before delivery changes the risk of subsequent development of asthma.

The meta-analysis reported by Thavagnanam is important in that quantifies the strength of relationship between birth by caesarean delivery and subsequent development of asthma [5]. It cannot determine cause, but the absence of evidence for an association with the development of other allergic disorders argues against an immunomodulatory effect, and thus is not supportive of hygiene hypothesis. Birth by caesarean section continues to increase, with rates of over 50% are being reported in some Latin American countries [28]. It will be important to track any changes in prevalence of asthma and allergic diseases in these countries.

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