The association between caesarean section and asthma or allergic disease continues to thrill

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The rate of caesarean section (CS) has increased in developed countries, and is now the most common surgical procedure in women of reproductive age. According to The World Health Organisation, CS is indicated in up to 15% of deliveries, yet the majority of developed countries currently exceeds this recommendation (1). This suggests that it is especially the rate of elective (pre labour) CS without a clear medical indication that has increased rather than emergency CS.

Birth mode of delivery may affect outcomes such as asthma and allergic disease in children many years later. Previous meta-analyses have reported a moderate (20%) risk increase of allergic rhinitis and asthma in children delivered by CS (2), but no association with atopic dermatitis/eczema (3). More recent studies linking risk of asthma to mode of delivery have examined the roles of emergency (after onset of labour) versus elective CS (pre labour) (4-6), instrumental use (forceps or vacuum extraction) at vaginal delivery (VD) (7), or performed sophisticated sibling analyses (5, 6). Most of these aspects are reviewed in Pyrhönen et al, as they further extend the literature in a study recently published in Acta Paediatrica (8).

Pyrhönen et al aimed to further elucidate the association between CS and occurrence of allergic manifestations (food allergy, pollen allergy, hay fever, atopic eczema and asthma) in a group of 1-4 year old children (8). The target population (N=4779) was identified from the Finnish nationwide population register. Questionnaire data on 3181 participants was merged with allergy test results (skin prick tests, IgE antibodies and open food challenges). While consistent with a null hypothesis, their negative (non-significant) findings on the association between CS and any allergic manifestation or positive test results for food, pollen or animal allergens also need to be considered in the context of limited power (not enough participants) and methodological issues (study design and definition of exposures and outcomes). Among

the strengths of the study were objective markers for several allergic outcomes. While authors also emphasize the representativeness of the sample, there should be some concern for participation bias and selection for blood testing as well as potential recall bias for perinatal data. It would further have been very interesting to see mode of delivery explored in greater detail (VD, emergency and elective CS as well as instrumental delivery). Potential shortcomings aside, it is very important that negative findings such as these are reported (published) to add to the growing body of literature on this far from resolved topic.

The choice of birth mode of delivery is made based on maternal characteristics and anticipated paediatric outcomes. It is also related to choice and preference of the pregnant mother/couple as well as local practice. Obstetricians assess the mode of delivery based on timing, progress and the degree of foetal distress. Normally a spontaneous VD is considered the safest mode of delivery for both mother and child. The choice of emergency procedures (emergency CS or instrumental VD) is based on many factors such as maternal compliance, degree of foetal stress and progress of labour. If labour must end promptly, instrumental VD is the best choice if the cervix is fully dilated and the foetal head is in a good position. Otherwise an emergency CS is normally the fastest and safest way of delivering when there are signs of foetal distress or when elective CS has been decided but the woman has gone into labour before the planned procedure and VD (instrumental or spontaneous) is not an option. An elective CS is chosen for maternal reasons (e.g. extreme fear of labour) or a combination of maternal and foetal reasons (e.g. malpresentation, two or more previous CS or multiple gestation).

A few recent studies have distinguished between elective CS and emergency CS. Among 37,171 children in the Norwegian Mother and Child Cohort Study, children delivered by CS

had an increased likelihood of current asthma at 36 months of age (relative risk 1.17, 95% confidence interval (CI) 1.03-1.32), with similar findings among children delivered by emergency and elective CS. Two studies based on the Swedish national health registers have shown an increased risk of asthma in children born with CS however with differing and conflicting results for emergency and elective CS (5, 6). Mechanisms to explain the association between birth mode of delivery and subsequent asthma or atopy could involve confounders such as maternal smoking, socioeconomic status or family history of asthma. Sibling studies therefore provide an excellent opportunity to study the association between CS and asthma independent of shared (familial) environmental and genetic factors. Full siblings share approximately half of their segregating genes, some intrauterine exposures, maternal factors and early environment. In addition, siblings may be discordant regarding mode of delivery. Traditionally, if associations seen in a cohort of siblings remain in sibling control analyses, this is taken to indicate that factors specific to each individual (such as exposure to vaginal flora or the indication for mode of delivery) are involved in the underlying causal pathways. Conversely, if the relationships changes in the sibling control analyses, this would indicate an influence from factors common to the siblings (such as maternal factors). Such conclusions however, also require careful consideration of the potential influence of measurement error and individual (non-shared) confounders (9). Pyrhönen et al had too few siblings to perform this type of control analyses however both studies based on the Swedish national health registers had negative findings in older children after sibling control (5, 6), consistent with a lack of causal association between CS and childhood asthma.

Potential mechanisms for the presumed associations between CS and subsequent asthma or allergic disease were recently reviewed by Cho et al (10). In line with the “hygiene hypothesis” the intestinal microflora may be modified in those unexposed to the vaginal flora.

It has also been suggested that DNA-methylation is higher in infants delivered by CS than in those vaginally delivered, and differences in immune biomarkers, gene expression and stress following CS compared to vaginal birth have also been proposed (10). However, all or parts of the association between CS and risk of asthma could also be explained by the underlying *indications* for CS. These could be related to choice of elective CS (anxious mother, anthropometric measures, or obstetric history), emergency situations (prematurity, prolonged parturition or foetal asphyxia) or subsequent diagnoses including early respiratory stress.

If vaginal microflora and/or epigenetics play a role in the association between CS and asthma in the offspring, some guidance should be obtained from the difference in effect after VD, instrumental VD, and elective or emergency CS. In non-instrumental VD the foetus is exposed to microflora, there is no excessive stress for the mother and normally no abnormal stress on the foetus (although there are cases of unexplained asphyxia also in normal VD). In instrumental VD the foetus is also exposed to microflora and the indication can be stress in mother, foetus or both. In emergency CS there may be exposure to vaginal microflora if a failed forceps/vacuum extraction delivery requires a CS, if there is sign of intraamniotic infection and theoretically also if the amniotic membranes are ruptured. Both maternal and/or foetal stress may be involved. For elective CS there is normally no microflora exposure, no maternal and no foetal stress. Epigenetic changes such as those related to CS may also be relevant in instrumental deliveries, although an instrumental delivery may be more similar to VD than CS. Thus, future studies could help shed light on the potential differences between VD, CS and instrumental deliveries on mechanisms such as microflora exposure, epigenetic changes and stress mediators and subsequent childhood outcomes.

In conclusion, negative findings on the association between CS and allergic manifestations displayed in the Pyrhönen paper appear consistent with recent reports from larger cohorts including sibling controls. Further investigations on the long-term effects of emergency and elective CS may include all types of mode of delivery in a systematic survey to characterize the nature of immune response and gene expression over time, and to measure potentially confounding genetic and environmental factors appropriately.

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