Birth mode of delivery in the modern delivery ward - indication improves understanding of childhood asthma

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Almqvist, Catarina; Rejnö, Gustaf

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Birth mode of delivery in the modern delivery ward – indication improves understanding of childhood asthma

Authors

Almqvist C, MD, PhD[1,2]

Rejnö G, MD[1,3]

Affiliations

[1]Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet

[2]Dept of Women's and Children's Health, Astrid Lindgren Children's Hospital, Karolinska University Hospital

[3]Department of Obstetrics and Gynaecology, Södersjukhuset (Stockholm South General Hospital)

Stockholm, Sweden

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Short title

Birth mode of delivery in the modern delivery ward

Corresponding author

Associate Professor Catarina Almqvist
Department of Medical Epidemiology and Biostatistics and
Lung and Allergy Unit, Astrid Lindgren Children's Hospital;
PO Box 281, Karolinska Institutet
SE-171 77 Stockholm
SWEDEN
T +46 (0)8 524 86193
F +46 (0)8 31 49 75
catarina.almqvist@ki.se

Birth mode of delivery may affect outcomes such as asthma and allergic disease in children many years later. Recent meta-analyses have reported a 20% increase in the subsequent risk of asthma in children delivered by Caesarean section (CS) (1, 2) and a moderate risk increase for allergic rhinitis and asthma (3). Some recent papers have reported children born with CS to have an increased risk of asthma (4-6) whereas others found no such associations (7-10). Two recent papers have examined the difference in effect between emergency and elective CS on asthma outcomes (11, 12). Some have also examined the association between instrumental delivery (forceps and vacuum extraction) and the risk of asthma and allergy (13-15).

The choice of birth mode of delivery is made based on maternal characteristics and anticipated paediatric outcomes. It is also related to choice/preference of the pregnant mother/couple as well as local practice. Obstetricians assess the choice of CS / VD / forceps and vacuum extraction based on timing, progress and the degree of foetal distress. Normally a spontaneous vaginal delivery is considered the safest mode of delivery for both mother and child. The choice of emergency procedures (instrumental vaginal delivery or emergency CS) is based on many factors such as maternal compliance, degree of foetal stress and progress of labour. If labour must end promptly, vaginal instrumental delivery 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. The choice of forceps or vacuum extraction in an instrumental delivery is mainly based on local practise and the physician's familiarity with the methods (16). There is evidence of higher maternal morbidity in forceps delivery and higher risks of neonatal cephalohaematoma and retinal haemorrhages in vacuum extraction delivery. Vacuum extraction is contraindicated with face presentation and forceps can be used for the after-coming head of the breech and in the rare situations where maternal effort is impossible or contraindicated (17). 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). Emergency CS is normally chosen 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 vaginal delivery (instrumental or spontaneous) is not an option (18). The rates of forceps and vacuum extraction delivery along with elective CS show a large variation in different countries. In Sweden, the rate of caesarean section (CS) is approximately 17% (10% emergency and 7% planned), 8% of all children are born with vacuum extraction and 0.2% with forceps, whereas for example Scotland and Israel have higher rates of instrumental deliveries.

Mechanisms for the presumed association between instrumental delivery or CS and subsequent asthma and allergy has been referred to a modified intestinal microflora in those unexposed to the vaginal flora, according to the "hygiene hypothesis" (19). It has also been recently been shown by Schlintzig et al that DNA-methylation is higher in infants delivered by CS than in those vaginally delivered (20). However, parts of the association between CS and risk of asthma in offspring may be explained by the underlying *indications* for CS (21, 22). 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. Figure 1 visualises microflora exposure and delivery complication in relation to risk of impaired outcome. In non-instrumental VD, the foetus is exposed to microflora and 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 (20) may also be relevant in instrumental deliveries, although an instrumental delivery may be more similar to VD than CS. Thus, future studies could assess the difference between VD, CS and instrumental deliveries on mechanisms such as microflora exposure, epigenetic changes and stress mediators and subsequent childhood outcomes.

Mechanisms to explain the association between birth mode of delivery and subsequent asthma or atopy can also be related to confounders such as maternal smoking, socioeconomic status or family history of asthma, where sibling studies are most helpful to adjust for unmeasured familial confounding. Sibling studies provide an excellent opportunity to study the association between CS and asthma, controlling for shared (familial) environmental and genetic factors (12, 23). Siblings share half of their genes, some intrauterine exposures, maternal factors and early environment. In addition, siblings may be discordant regarding mode of delivery. If associations seen in a cohort of siblings remain in sibling control analyses, then 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 disappear or substantially diminish in sibling control analyses, then factors common to the siblings (such as maternal factors) may be involved.

In this issue of CEA, Hancox et al report on the associations between delivery with forceps assistance and development of atopy and asthma. The findings were that children born using forceps were more likely to have atopy at ages 13 (53% vs 44%) and 32 years (68% vs 59%). They were also more likely to have asthma at ages 13 (21% vs 11%) and 32 years (23% vs 16%). Except for asthma at age 13, these associations were not statistically significant after adjustment for confounding factors (24). In instrumental VD, the foetus is exposed both to microflora and the indication for mode of delivery can be stress in mother, foetus or both (Figure 1). As instrumental deliveries are commonly performed because of concern of

maternal and foetal health, a possible association between forceps delivery and risk of asthma in offspring may be explained by the underlying *indications* for mode of delivery. These could be related to maternal and foetal reasons (prematurity, prolonged parturition or foetal asphyxia) or subsequent diagnoses including early respiratory stress.

At the time subjects in the Hancox study were born (1972-73), assessment and surveillance of pregnancies and deliveries were very different from present practice. Cardiotocography was not routinely used until late 1970's and ultrasound surveillance initiated a decade later, so the indication for intervention may have been different from today. Child and public health care was also very different at the time, and some asthma cases at the time may not have developed asthma if treated with current management. The Dunedin cohort also had very few cases of CS (4.6%) or vacuum extraction (none) whereas the prevalence of forceps was 21%, which precludes the possibility to assess the difference in effect between forceps and other instrumental deliveries. Likewise, very few deliveries are performed with forceps in most countries. Nevertheless, although these interventions are now less common than caesarean births, it is important to know whether they are also associated with an increased risk of allergy because it helps to explain the mechanism of the association. If the real risk for developing asthma associated with caesarean delivery is due to confounding or difficult birth rather than non-vaginal delivery, there would be an increased risk of allergic disease with other obstetric interventions which the authors show here. This is also similar to previous findings (13, 15) but contrary to others (14).

The authors have chosen some confounders which are not entirely related to exposure and outcome such as (recall of) breast feeding and maternal smoking. Although they are both related to immunological development, there is no reason to expect an association between them and the exposure (forceps) and thus they are not really confounders by definition (25). Other confounders such as sex, parental atopy, head circumference, birth order, and

socioeconomic status did change the estimates and reduced most of the estimates to non-significant.

The association between mode of delivery and subsequent asthma or atopy and its possible mechanisms has recently been studied in a large dataset where vaginal delivery (VD) was analysed separate from vaginal instrumental delivery (forceps and vacuum extraction), CS subdivided into emergency CS and elective CS and unmeasured familial confounding taken into consideration using sibling controls. An increased risk of asthma medication in the group born by emergency CS, but not elective, suggests that there is no causal effect due to vaginal microflora. A more probable explanation should be sought in the indications for emergency CS (12).

Future studies based on large datasets with detailed information including sibling controls may have additional power to analyse the association between mode of delivery and asthma. Collection of objective markers of lung function and measures of allergic disease in siblings discordant for CS would also provide important data, as would information on maternal choice of delivery. The results will be even stronger if related to actual measures of intestinal microflora, or if measures of complications during delivery (maternal and children's diagnoses) are included. Instrumental delivery and/or caesarean section are normally chosen for good reasons. Since there seem to be long term implications, choice of delivery should be carefully considered. However, the most imminent potentially adverse delivery outcomes (such as foetal asphyxia) will always be the main target for prevention. This means that when considering new policies or recommendations for mode of delivery elective CS might be the only mode of delivery where changes are possible. This may give us further basis for public health advice and implementation.

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Figure

Figure 1. Diagram to illustrate microflora exposure and delivery indication or complication in relation to risk of impaired outcome where (+) denotes increased risk and (-) decreased risks.

	Medical complications	Exposure to vaginal microflora	Risk of asthma
VD, non-instrumental	-	+	-
VD, instrumental	+	+	(+)
Emergency CS	++	-	+
Elective CS	+	-	-