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B Laubereau, B Filipiak-Pittroff, A von Berg, A Grübl, D Reinhardt, H E Wichmann, S Koletzko, for the GINI Study Group

Aims: To investigate the effect of caesarean section on gastrointestinal symptoms, atopic dermatitis, and sensitisation to nutritional allergens in infants.

Methods: A total of 865 healthy full term neonates with parental history of allergy participating in the prospective German Infant Nutritional Intervention Program (GINI) were exclusively breast fed during the first four months of life and had a one year follow up. Data were obtained by follow up visits at age 1, 4, 8, and 12 months, weekly diaries for the first six months, and measurement of total and specific IgE at birth and 12 months.

Results: Infants born by caesarean section (147/865, 17%) had a greater risk of diarrhoea (ORadj 1.46, 95% CI 1.022 to 2.10) and sensitisation to food allergens, both in adjusted (ORadj 2.06, 95% CI 1.123 to 3.80) and stratified analyses (by cord blood IgE). Caesarean delivery was not associated with colicky pain and atopic dermatitis.

Conclusion: Caesarean delivery might be a risk factor for diarrhoea and sensitisation in infants with family history of allergy. Further research in this area seems warranted as choosing caesarean section becomes increasingly popular.

Methods

Study design and subjects

We used data from a birth cohort of healthy full term neonates with a family history of allergy enrolled between 1995 and 1998 in two regions in Germany for the German Infant Nutritional Intervention Program (GINI). Newborns with severe congenital or metabolic diseases, or other medical conditions interfering with the study design, were excluded from enrolment. The study is described in detail elsewhere. Briefly this was a prospective randomised study to investigate the allergy preventive effect of three hydrolysed formulae compared to a conventional cows' milk formula. At birth all mothers were given uniform nutritional recommendations on feeding the child during the first year of life. Ethical reasons, study formulae were to be fed only when the recommended exclusive breast feeding for the first four months was not feasible. Follow up visits with structured interview and physical examination were scheduled for age 1, 4, 8, and 12 months. During the first six months mothers filled in weekly diaries on feeding and health status of the child. Blood samples for total IgE were obtained at birth (cord blood (CB)), and for specific IgE at 12 months of age. The sera were kept at −20°C until analysis. Contamination of IgA levels in cord blood samples with detectable IgE levels (>0.35 kU/l). This analysis is restricted to infants exclusively breast fed during the first four months of life with a one year follow up. Formula fed infants were excluded because the feeding regimen was heterogeneous and this group differed significantly from the exclusively breast fed group with respect to mode of delivery, compliance to the given feeding recommendations, and socioeconomic characteristics.

Abbreviations: CB, cord blood; CI, confidence interval; OR, odds ratio
Classification of exposure and outcomes
Caesarean section
Information on mode of delivery was copied by a physician from the child’s medical check up chart during the interview at age 1 month. Answer categories “spontaneous delivery” and “obstetrical extraction” were combined into “no caesarean section”.

Gastrointestinal symptoms
“Colicky pain” was based on parental reporting in both the interviews and the weekly diaries. It was assessed for the first four months only, as this was felt to be the clinically relevant period. “Diarrhoea” was based on parental reporting in the interviews up to age 4 months and 12 months respectively. Information from the diaries was not used as they were available for the first six months only.

Atopic dermatitis
Atopic dermatitis was defined using a computer algorithm based on (1) typical skin lesions assessed by the study physician; (2) reported itching and/or signs of scratching and/or treated with steroids/oral antihistamines; and (3) reported duration of at least 14 days without treatment and/or chronically relapsing. Case definition required all three criteria.

Atopic sensitisation to nutritional allergens
The RAST technique was used according to the manufacturer’s instructions (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden). Specific IgE were tested at age 12 months for major cows’ milk allergens (alpha-lactalbumin f76, beta-lactoglobulin f77, casein f78) and ovalbumin f1 and soybean f14. Atopic sensitisation at age 12 months was defined as at least one specific IgE ≥ RAST class 1 (levels ≥0.35 kU/l) if results for all five allergens were available.

Statistical analysis
Multiple logistic regression analyses were used to determine association of caesarean section with outcomes, adjusting for a fixed set of risk factors (sex, parental history of allergy, birth order, pet keeping). Further potential confounding factors (gestational age, cord blood IgE, maternal age at birth, birth weight, smoking before pregnancy, parental education) were included in the final model if the effect estimate of caesarean section on the outcome was changed by more than 10%. Uniform models were chosen each for OR for CB-IgE <0.35 kU/l versus ≥0.35 kU/l was performed. The positive association between mode of delivery and sensitisation to any of the five nutritional allergens persisted in the strata (crude OR for CB-IgE <0.35 kU/l: 3.50, 95% CI 1.2 to 10.5; and for CB-IgE ≥0.35 kU/l: 2.2, 95% CI 0.66 to 7.2), although confidence intervals were wide due to small numbers in the strata.

DISCUSSION
In this cohort of 865 healthy neonates we found that infants born by caesarean section had a higher risk for diarrhoea and sensitisation to nutritional antigens during the first year of life compared to vaginally born infants.

Caesarean section, gut flora, and development of the immune system
Our results are in line with a current hypothesis that the gut flora very early in life plays an important role for the immune response and that circumstances associated with caesarean section alter or delay “normal” colonisation of the gut micro flora of the infant. This alteration could be due to different factors. The colonisation of vaginally delivered newborns is influenced by the mother’s vaginal, intestinal, and perianal flora, whereas infants delivered by caesarean section are colonised with bacteria from the hospital environment. Moreover in the latter group “rooming in” is less common and prophylactic use of perioperative antibiotics is highly recommended. Each factor by itself may adversely affect the development of the infant’s gut flora.

Reports on the clinical significance of the microbiological findings in infants born by caesarean section are scarce and conflicting with respect to gastrointestinal symptoms. A study in 168 infants from the neonatal intensive care unit in Turku, Finland, reported caesarean section and prematurity to be significant risk factors for C perfringens in stool, which was associated with the occurrence of gastrointestinal symptoms like flatulence, distended abdomen, diarrhoea, and blood in stool. In contrast, in 64 healthy term infants born at the same hospital no differences were found between infants born by caesarean section (n = 30) and vaginally (n = 34) with respect to flatulence, abdominal distension,
bowel habits, and colicky crying within the first two months of life in spite of differences found for the gut flora. These studies were both confined to a selected group of children from one hospital. It was shown previously that certain environmental circumstances may influence the development of the infant’s gut flora. This unwanted effect of one

Table 1 Characteristics of the study population (n = 865) by mode of delivery

<table>
<thead>
<tr>
<th>Caesarean section</th>
<th>Yes</th>
<th>No</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Female sex</td>
<td>70/147</td>
<td>47.6</td>
<td>363/718</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>17/147</td>
<td>11.6</td>
<td>84/718</td>
</tr>
<tr>
<td>2500–2999</td>
<td>82/147</td>
<td>55.8</td>
<td>412/718</td>
</tr>
<tr>
<td>3000–3699</td>
<td>48/147</td>
<td>32.7</td>
<td>222/718</td>
</tr>
<tr>
<td>&gt;3700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>&lt; 51</td>
<td>49/147</td>
<td>33.3</td>
</tr>
<tr>
<td>52–53</td>
<td>49/147</td>
<td>33.3</td>
<td>245/718</td>
</tr>
<tr>
<td>&gt;53</td>
<td>49/147</td>
<td>33.3</td>
<td>215/718</td>
</tr>
<tr>
<td>Head circumference ≥37 cm</td>
<td>18/129</td>
<td>14.0</td>
<td>73/640</td>
</tr>
<tr>
<td>Gestational age (completed week)</td>
<td>&lt; 41</td>
<td>134/147</td>
<td>91.2</td>
</tr>
<tr>
<td>&gt;41</td>
<td>13/147</td>
<td>8.8</td>
<td>24/717</td>
</tr>
<tr>
<td>Age mother at birth (y)</td>
<td>&lt; 30</td>
<td>32/146</td>
<td>21.9</td>
</tr>
<tr>
<td>30–34</td>
<td>77/146</td>
<td>52.7</td>
<td>389/715</td>
</tr>
<tr>
<td>&gt;34</td>
<td>37/146</td>
<td>25.3</td>
<td>135/715</td>
</tr>
<tr>
<td>Birth order: firstborns</td>
<td>100/146</td>
<td>68.5</td>
<td>372/717</td>
</tr>
<tr>
<td>&gt;1</td>
<td>46/147</td>
<td>31.5</td>
<td>345/717</td>
</tr>
<tr>
<td>Cord blood available</td>
<td>67/147</td>
<td>45.6</td>
<td>488/718</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>22/147</td>
<td>15.0</td>
<td>99/718</td>
</tr>
<tr>
<td>Maternal history of allergy</td>
<td>104/147</td>
<td>70.8</td>
<td>503/717</td>
</tr>
<tr>
<td>Both parents history of allergy</td>
<td>50/147</td>
<td>34.0</td>
<td>240/718</td>
</tr>
</tbody>
</table>

*P value for x^2 test.
†Self reported asthma and/or allergic rhinitis and/or atopic dermatitis and/or food allergy and/or urticaria.

Table 2 Association between caesarean delivery and gastrointestinal symptoms, atopic dermatitis, and sensitization in infants exclusively breast fed for four months

<table>
<thead>
<tr>
<th>Caesarean section</th>
<th>Yes</th>
<th>No</th>
<th>Yes versus no; odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Any colicky abdominal pain</td>
<td>41/146</td>
<td>28.2</td>
<td>246/713</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>63/147</td>
<td>42.9</td>
<td>311/717</td>
</tr>
<tr>
<td>&lt;4 months</td>
<td>5/145</td>
<td>3.5</td>
<td>10/714</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>22/147</td>
<td>15.0</td>
<td>80/716</td>
</tr>
<tr>
<td>Bloody/mucous diarrhoea</td>
<td>84/147</td>
<td>57.1</td>
<td>347/713</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;4 months</td>
<td>10/145</td>
<td>6.9</td>
<td>27/715</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>25/147</td>
<td>17.2</td>
<td>84/706</td>
</tr>
<tr>
<td>Non-concomitant diarrhoea*</td>
<td>4/144</td>
<td>2.8</td>
<td>8/714</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>14/145</td>
<td>9.7</td>
<td>36/715</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>31/147</td>
<td>21.4</td>
<td>118/707</td>
</tr>
<tr>
<td>Atopic dermatitis &lt;12 months</td>
<td>13/147</td>
<td>8.8</td>
<td>69/716</td>
</tr>
<tr>
<td>Sensitisation at 12 months</td>
<td>9/105</td>
<td>8.6</td>
<td>22/522</td>
</tr>
</tbody>
</table>

*Diarrhoea that did not accompany flu-like disease or other infection.
†Odds ratio adjusted for: 1sex, parental history of allergy, birth order, pets in household; 2sex, parental history of allergy, birth order, pets in household, age mother at birth >30 years; 3sex, family history of atopic dermatitis, birth order, pets in household.
‡RAST class 1: alpha-lactalbumin f76 and/or beta-lactoglobulin f77 and/or casein f78.
*RAST class 1: alpha-lactalbumin f76 and/or beta-lactoglobulin f77 and/or casein f78 and/or soy bean f1 and/or hen’s egg f14.
specific setting was avoided in our study by the large sample of children born in several hospitals in two regions of Germany. Adjustment for study area and perinatal centres did not change our results (data not shown).

Characteristics of the study population
Confounding by different health status at birth, gestational age, heredity of allergy, and different feeding patterns was minimised by choosing a homogeneous study population. High risk pregnancies leading to emergency caesarean sections were excluded. All infants had a positive family history for allergic diseases and had parents with similar educational level. Mothers were uniformly instructed to avoid feeding strong nutritional allergens during the first year of life. Formula fed infants differed significantly from exclusively breast fed infants with respect to mode of delivery, compliance to the given feeding recommendations, and socioeconomic characteristics (data not shown). The formula fed infants were excluded from the analysis because this group was heterogeneous when comparing the caesarean section born infants with the vaginally delivered infants with respect to many characteristics. Moreover we felt that early infant nutrition might strongly interfere with the outcomes. We considered it beyond the data to control for the impact of infant nutrition in this group because the type, the quantity, and the timing of first introduction of formula milk and of solid food varied considerably (data not shown).

Diarrhoea
It cannot be established whether the episodes of diarrhoea with mucous, sometime blood stained stools in our study population were of infectious origin, or whether they were caused by a mild allergic colitis, which we and others\(^1\) increasingly observe in exclusively breast fed infants. However, a recent study from Sweden reported a significant increase of hospital admissions for gastroenteritis in children born by caesarean section compared to children born by vaginal delivery,\(^18\) which is in agreement with our results.

Sensitisation
Apart from diarrhoea as a measure of short term effects of an abnormal gut flora we found a remarkably higher rate of sensitisation to nutritional allergens, especially hen's egg, which was the main allergen in our study. Specific IgE to nutritional allergens, sensitisation to nutritional allergens in infants born by caesarean section. Specific IgE to nutritional allergens, especially hen's egg, which was the main allergen in our study, has been shown to be positively associated with later sensitisation to aeroallergens, the development of asthma, and severity of atopic dermatitis.\(^14\) It is uncertain whether our findings also indicate a long term effect. The postnatal gut flora seems to be important for the development of oral tolerance and the immune response to allergens,\(^11, 24\) thus an abnormal colonisation might predispose to allergic manifestations later in life.\(^13\) The role of cord blood IgE as a predictor of later sensitisation is still under discussion.\(^25, 26\) The fact that cord blood was missing more often after caesarean section was due to logistic reasons, which should not bias our results. However, to our surprise infants born by caesarean section had raised cord blood IgE levels more often than vaginally delivered infants. This finding, which could not be explained by parental or mother's history of asthma or other allergic diseases, smoking habits, or educational level, contradicts previous results of a large German birth cohort study.\(^24\) Contamination with maternal blood, which is a major concern, was excluded by non-detectable IgA levels. Older gestational age and birth order have been reported to have an influence on cord blood IgE,\(^25, 26\) and thus may have played a role. However, controlling for cord blood IgE did not change the risk estimate for caesarean section; neither did stratification by cord blood IgE status.

Allergic diseases
Several recent studies focused on the association between caesarean delivery and allergic diseases, mainly asthma. A positive association with asthma was reported in five studies,\(^6, 8, 18, 27\) while no association was found in two.\(^28, 29\) Atopic dermatitis was investigated in two studies,\(^7, 27\) and allergic rhinitis in four,\(^4, 7, 27, 29\) and no association was found for any of them. However, controlling for confounding factors such as prematurity, feeding pattern early in life, or allergic diseases in the parents was often poor. In our study we also did not find an association between caesarean section and atopic dermatitis (AD) during the first year of life, which is the major period for clinical manifestation of AD. We could not investigate asthma and allergic rhinitis, as the children were too young for these outcomes. As the birth cohort is followed, we will be able to extend our analysis on these outcomes in the future.

Conclusion
We found an association between caesarean delivery and diarrhoea and sensitisation in infants with a family history of allergy. Further research in this subject seems warranted as choosing caesarean section becomes increasingly popular.

ACKNOWLEDGEMENTS
We would especially like to thank all children and families for participation in the study, the obstetric units to allow the recruitment procedure, and the GINI team for excellent work.

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1. O'Connell MP, Lindow D. Caesarean section controversy. Further research is needed on why rates of caesarean section are increasing. BMJ 2000;320:1074.


