

Cesarean section changes neonatal gut colonization



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Background: Delivery by means of cesarean section has been associated with increased risk of childhood immune-mediated diseases, suggesting a role of early bacterial colonization patterns for immune maturation.

Objective: We sought to describe the influence of delivery method on gut and airway colonization patterns in the first year of life in the Copenhagen Prospective Studies on Asthma in Childhood₂₀₁₀ (COPSAC₂₀₁₀) birth cohort.

Methods: Seven hundred children from the COPSAC₂₀₁₀ birth cohort participated in this analysis. Fecal samples were collected at age 1 week, 1 month, and 1 year, and hypopharyngeal aspirates were collected at age 1 week, 1 month, and 3 months and cultured for bacteria. Detailed information on delivery method, intrapartum antibiotics, and lifestyle factors was obtained by personal interviews.

Results: Seventy-eight percent of the children were born by means of natural delivery, 12% by means of emergency cesarean section, and 9% by means of elective cesarean section. Birth by means of cesarean section was significantly associated with colonization of the intestinal tract by *Citrobacter freundii*, *Clostridium* species, *Enterobacter cloacae*, *Enterococcus faecalis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* at age 1 week, whereas colonization by *Escherichia coli* was associated with natural birth. At age 1 month, these differences were less prominent, and at age 1 year, they were not apparent, which was confirmed by means of multivariate data-driven partial least squares analyses. The initial airway microbiota was unaffected by birth method.

Conclusion: Delivery by means of cesarean section was associated with early colonization patterns of the neonatal gut

but not of the airways. The differences normalized within the first year of life. We speculate that microbial derangements, as indicated in our study, can demonstrate a possible link between delivery by means of cesarean section and immune-mediated disease. (*J Allergy Clin Immunol* 2016;138:881-9)

Key words: Cesarean section, microbiota, bacteria, parturition immune diseases

We recently reported delivery by means of cesarean section as a shared risk factor for several immune-mediated diseases in the child, suggesting the early bacterial colonization pattern as an important environmental factor for health and disease.¹

The diversity of the human microbiome is established in early life,² and it has been hypothesized that the composition of the gut might have the ability to affect immune maturation of the host and that inappropriate exposure might lead to asthma and allergy and other immune disorders.³⁻⁷ Similarly, early-life bacterial composition in the respiratory tract has been associated with asthma development, perhaps because of a local epithelial modulation leading to chronic inflammation.^{8,9}

The healthy embryo is believed to be sterile, obtaining the first bacteria from the maternal birth canal and intestinal tract during natural birth. Early colonization patterns can be affected by mode of delivery and even within types of cesarean section because the patterns can differ according to delivery by means of elective or emergency cesarean section.¹⁰ Furthermore, it is common practice to use intrapartum antibiotics during the procedure, which might also lead to long-term microbial derangements.¹¹

The objective of this study was to analyze the effects of delivery mode on the colonization patterns of both the intestinal tract and airways during the first year of life of the children from the Copenhagen Prospective Studies on Asthma in Childhood₂₀₁₀ (COPSAC₂₀₁₀) birth cohort. We hypothesized that colonization patterns differ with delivery type and also within subtypes of cesarean sections because the first encounter with the external environment varies among these.

METHODS

Ethics

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen (H-B-2008-093) and the Danish Data Protection Agency (2008-41-2599). We are aware of and comply with recognized codes of good research practice, including the Danish Code of Conduct for Research Integrity. We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice, as defined in the European Union's Directive on Good Clinical Practice, the International Conference on Harmonisation's good clinical practice guidelines, and the Helsinki Declaration. We follow national and international rules on the processing of personal data, including the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate.

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Abbreviations used

aOR: Adjusted odds ratio
 COPSAC: Copenhagen Prospective Studies on Asthma in Childhood
 LV: Latent variable
 PLS: Partial least squares

Study population

The novel COPSAC₂₀₁₀ cohort is an ongoing Danish cohort study of 738 unselected pregnant women and their 700 children followed from pregnancy week 24 in a protocol previously described in detail¹² based on the COPSAC₂₀₀₀ birth cohort study.^{8,13,14} Data validation and quality control follow the guidelines for good clinical practice. Data were collected during visits to the clinical research unit and stored in a dedicated online database. The data were double-checked against source data and subsequently locked.

Delivery method

Information on delivery method was obtained at the COPSAC clinic 1 week after birth and validated against data from the Danish Medical Birth Registry. Children were categorized according to the type of delivery as natural delivery, emergency cesarean section, or elective cesarean section. Emergency cesarean section was defined as a spontaneous birth turning into a cesarean section and elective cesarean section was defined as induced birth without rupture of the membranes. The delivery method was analyzed both as a dichotomized variable (natural birth vs cesarean section) and categorized as natural birth, emergency cesarean section, and elective cesarean section.

Samples for bacterial culture

Fecal samples were collected 1 week, 1 month, and 1 year after birth either at the research clinic or by the parents at home by using detailed instructions. Hypopharyngeal aspirates from children were collected at the research clinic 1 week, 1 month, and 3 months after birth, with a soft-suction catheter passed through the nose into the hypopharynx, as previously described in detail.⁸ All samples were cultured within 24 hours at Statens Serum Institut by using standard methods on nonselective and selective media (SSI Diagnostica, Hillerød, Denmark). Blood agar plates (5% horse blood) and chocolate agar plates (including lysed blood cells) were used for general culturing. These were incubated aerobically at 37°C for 18 to 20 hours, whereas the blood agar and chocolate agar plates were incubated under microaerophilic conditions (5% CO₂, 3% H₂, 5% O₂, and 87% N₂) at 37°C for 48 hours. Subsequently, microbial identification was performed according to growth on selective media, characteristics of colonies, and cellular morphology. All bacteria identifications were confirmed biochemically by using VITEK 2 (BioMérieux, Marcy-L'Étoile, France). No bacterial quantification was performed. The isolates were all characterized at the species level. We used a cutoff value of greater than 2% of children colonized at a given time point for a species to be represented in the analyses.

Environmental factors

Information on maternal age at birth, asthma, and smoking during pregnancy; education; household income; antibiotics in pregnancy; pre-eclampsia; gestational diabetes; parity; antibiotics given to the child after birth; hospitalization of the child after birth; household pets; number of older children in the home; and duration of exclusive breast-feeding was obtained during the scheduled visits to the COPSAC clinic.

Intrapartum antibiotics

Information on intrapartum antibiotics was obtained by means of interview 1 week after birth and validated against birth records from hospitals.

Statistical analysis

ANOVA or the χ^2 test was used for analyzing simple associations in the cohort's baseline characteristics regarding differences in birth method and prenatal, perinatal, social, and lifestyle-related variables. With conventional statistics, the associations between cesarean section and bacterial species at different time points were analyzed by using logistic regression. Estimates were expressed as odds ratios with corresponding 95% confidence limits, with the children born naturally as the reference group. A significance level of .05 was used in all types of analysis.

The complementary data-driven pattern analysis was conducted by using partial least squares (PLS) regression based on colonization of the 57 most common bacterial species with at least 5 colonized children during the 3 sample time points. Score plots of the latent variables (LVs) were used to investigate differences in overall bacterial colonization patterns between the children with or without cesarean section. A single 3-way PLS model described the bacterial colonization patterns over time by using children, bacterial species, and sample time points as the 3 dimensions. Only children with complete data at all 3 sample time points were included in the analysis ($n = 597$). In a separate PLS model to discriminate between children born by means of natural delivery or by means of elective or emergency cesarean section, 1-week fecal colonization was used. Associations between PLS components and method of delivery were quantified by using the area under the receiver operating characteristic curve.

Data processing was conducted with SAS version 9.4 for Windows (SAS Institute, Cary, NC) and MATLAB R2013a v. 8.1.0.604.

RESULTS**Demographics**

In the COPSAC₂₀₁₀ birth cohort of 700 children, 78% (549) were born by means of natural delivery, 12% (85) by means of emergency cesarean section, and 9% (66) by means of elective cesarean section. A lower number of children born by means of emergency cesarean section attended the 1-week visit compared with those born by means of the other delivery types, which resulted in a lower prevalence of completed fecal and tracheal samples in this group. Fecal samples were obtained and cultured from 92% (645) of all children at 1 week, 96% (672) at 1 month, and 93% (652) at 1 year of age. Tracheal samples were obtained and cultured from 90% (633) of all children at 1 week, 96% (673) at 1 month, and 95% (664) at 3 months of age.

All mothers giving birth by means of cesarean section received intrapartum antibiotics versus only 13% ($n = 72$) of mothers having a natural birth. We observed a higher gestational age among the children born naturally (mean, 40.0 weeks) compared with children born by means of emergency cesarean section (mean, 39.3 weeks) and elective cesarean section (mean, 39.0 weeks). Mothers of children born by means of emergency cesarean section were more often primiparous (76%) compared with mothers of children born by means of natural delivery (44%) and elective cesarean section (24%). Twenty-seven percent of children born by means of emergency cesarean section were hospitalized after birth compared with 11% of those born by means of elective cesarean section and 9% after natural delivery. The duration of exclusive breast-feeding also tended to differ though only borderline significant; natural delivery (mean, 105.4 days), emergency cesarean section (mean, 88.4 days), and elective cesarean section (mean, 103.5 days; [Table I](#)). Therefore all analyses were adjusted for gestational age, parity, hospitalization, and duration of exclusive breast-feeding.

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