Cesarean Delivery and Risk of Intestinal Bacterial Infection

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Background. An individual’s intestinal bacterial flora is established soon after birth. Delivery by Cesarean section (c-section) deprives the newborn of colonization with maternal vaginal bacteria. We determined whether delivery by c-section is associated with an altered risk of infection with intestinal bacterial pathogens.


Results. During 14.0 million person-years of follow-up, 22,486 individuals were diagnosed with ≥1 intestinal bacterial infection. C-section was associated with a small increase in risk at age 1 to 2 years (IRR, 1.09; 95% confidence interval, 1.00–1.18) and at age 2 to <5 years (IRR, 1.08; 95% confidence interval, 1.00–1.17), but after age 5 years, there was no significant association. Assuming causality only 0.62% of intestinal bacterial infections were attributable to c-section.

Conclusions. Mode of delivery appears not to be a clinically relevant determinant of risk for intestinal bacterial infections. The possible impact of increasing frequencies of c-section on the overall burden of intestinal bacterial infections appears negligible.

The use of Cesarean deliveries (c-sections) has increased considerably over the past decades, in some countries now constituting up to 30% of all deliveries [1, 2]. Delivery by c-section leads to an altered bacterial colonization of the newborn’s intestine [3–7], which has been suggested to cause prolonged immunological immaturity [8–11] and susceptibility to various diseases [12, 13]. Because colonization patterns play important roles in tolerance induction, mucosa-associated barrier defense against pathogens, and in development and homeostasis of innate and adaptive immunity to pathogens [10, 14–16], increasing c-section practices may impact on susceptibility to infections with intestinal bacteria.

Two critical stages of intestinal colonization are in the days after birth and during weaning [17]. During intrauterine development, the fetal intestine is sterile, but as the infant becomes exposed to the maternal bacterial flora of the birth canal during vaginal delivery, the colonization process begins [17–20]. Within days, the intestinal tract becomes colonized by large numbers of Escherichia coli and streptococci, and with breastfeeding, there is succession of anaerobes (Bifidobacterium, Bacteroides, and Clostridium species) possibly associated with bifidobacterial growth factors in breast milk [21]. Formula-fed newborns have high numbers of Enterobacteriaceae, enterococci, and Bifidobacterium, Bacteroides, and Clostridium species [21]. In contrast, newborns delivered by c-section are not exposed to vaginal and fecal bacteria, and they often experience prolonged mother-infant separation, longer hospital stays, and delayed and shorter breastfeeding periods [22–24]—factors that have been suggested to delay or reduce colonization with beneficial probiotic bacteria (eg, lactobacilli, Bifidobacterium species, and Bacteroides...
species) or to favor outgrowth of unusual, potentially harmful bacterial strains [7]. It is yet unclear whether disturbances in the initial intestinal colonization have life-long implications for the composition of the intestinal bacterial flora [20, 25, 26].

Taken together, it is possible that an altered intestinal microflora following delivery by c-section might compromise the defense against intestinal pathogens, but these issues have received little epidemiological attention [13, 27]. Therefore, we took advantage of the Danish nationwide registries and investigated the risk of intestinal bacterial infections according to mode of delivery in a large cohort of mothers and infants in Denmark.

**METHODS**

**Study cohort and data sources.** A study cohort of 1.71 million singleton persons born during the period from 1 January 1973 through 4 April 2005 to Danish-born parents was established by linkage between the Medical Birth Registry, the Civil Registration System, the Integrated Database for Labor Market Research, and the Registry of Enteric Pathogens. The information is kept under the unique Danish personal identification number assigned to all Danish residents since 1 April 1968, thus ensuring precise and secure linkage of person-identifiable information between registers [28]. Since 1973, the Medical Birth Registry has contained computerized information about birth characteristics, including mode of delivery, which are required to be recorded shortly after birth [29]. Information about gestational age has been uniformly registered since 1977, and a distinction between elective and acute c-section has been possible since 1997. The Integrated Database for Labor Market Research contains longitudinal information about total income and number of persons living in each household in the entire Danish population from 1980 to the present. The Registry of Enteric Pathogens contains information on laboratory-confirmed positive intestinal bacterial infections in Denmark since 1991 [30–32].

The study was based on existing data in national registries and databases and was approved by the Danish Data Protection Agency (j.nr. 2001–41-0576 and 2001–41-5326). Participants were not contacted during the study, so no written informed consent was required.

**Definition and categorization of variables.** Variables obtained in the Registry of Enteric Pathogens included laboratory-confirmed nontyphoidal *Salmonella* species, *Campylobacter* species, *Yersinia enterocolitica*, and other intestinal infection-causing bacteria (*Shigella* species and Shiga toxin–producing *E. coli*). Variables from the Medical Birth Registry included mode of delivery (vaginal vs c-section), gestational age (<32, 33–34, 35–36, and ≥37 weeks), birth weight (<2499, 2500–2999, 3000–3499, 3500–3999, and >4000 g), and maternal age (<19, 20–24, 25–29, 30–34, and ≥35 years). Information on gestational age was treated as missing for persons born during 1973–1976. Variables based on the Civil Registration System included vital status, age (0 to <1, 1 to <2, 2 to <5, 5 to <10, 10 to <20, and ≥20 years), sex, birth order (1 [for first born], 2, and ≥3), season of birth (October–March vs April–September), degree of urbanization (population density, <25, 25–349, 350–999, 1000–1999, and >2000 persons/km²), and county of residence (14 counties). A variable for average gross annual income for each individual was based on the Integrated Database for Labor Market research, and calculated as household income divided by number of adults in the household, scaled with a price index to make the income comparable over the study period, and then grouped into 5 levels of 100,000 Danish kroner (DKK) (~10,500 British Pounds and ~21,000 US dollars in 2008), with the highest level being >500,000 DKK.

**Statistical analyses.** Each person was observed from 1 January 1991 or date of birth, whichever came later, until 5 April 2005, emigration, death, or registered date of intestinal bacterial infection, whichever came first. Log-linear Poisson regression models were used to estimate incidence rate ratios (IRRs) for infection, according to mode of delivery. IRRs were adjusted for age, sex, birth order, season of birth, maternal age, average gross annual income, degree of urbanization, birth weight, and gestational age. An interaction term for calendar-year and county of residence was included to account for diagnostic and reporting differences between regional laboratories. We also assessed the potential association between gestational age and birth weight on one side and risk of intestinal bacterial infections on the other with adjustment for mode of delivery and all other variables. Maximum likelihood estimation of IRRs and 95% confidence intervals (CIs) was performed using the Genmod procedure in SAS software, version 8.02 (SAS Institute).

To evaluate the impact of c-section on the burden of intestinal bacterial diseases at the population level, we calculated the population attributable risk percent (PAR%) as follows: PAR% = 100 × [p × (RR – 1)]/(p × (RR – 1) + 1), where p is the proportion of newborns in the population who are delivered by c-section, and RR is the relative risk of intestinal bacterial infection associated with c-section. The PAR% can be considered as the proportion of all intestinal bacterial infections in the population that is theoretically preventable if all children were born by vaginal delivery.

**RESULTS**

The cohort included 1.71 million persons, of whom 1.49 million (87.44%) were born vaginally and 0.21 million (12.56%) were born by c-section. Overall, 22,486 individuals had a laboratory-confirmed intestinal bacterial infection during the 14.01 million person-years of follow-up between 1991 and 2005. Table 1 shows the IRRs of intestinal bacterial infection according to mode of delivery. Delivery by c-section compared
with vaginal delivery was associated with a small, but statistically significant increase in risk for intestinal bacterial infection overall (IRR, 1.05; 95% CI, 1.01–1.09). For specific infections, the IRR was significantly increased for Y. enterocolitica only (IRR 1.13; 95% CI, 1.01–1.25).

Table 2 shows age-specific IRRs of intestinal bacterial infection according to mode of delivery. Overall, c-section was associated with a small, but statistically significant increase in risk for intestinal bacterial infection at ages 1 to <2 years (IRR, 1.09; 95% CI, 1.00–1.18) and 2 to <5 years (IRR, 1.08; 95% CI, 1.00–0.17). The age-specific IRR was not significantly increased for any specific infection, except for infections at age 1 to <2 years with Shigella species or Shiga toxin–producing E. coli (IRR, 1.33; 95% CI, 1.06–1.66).

In an additional analysis restricted to subjects born since 1997, the age-specific IRRs for infections with Salmonella or Campylobacter species were not significantly different between those born after acute and planned c-sections (for Salmonella infection, P = .47 for age 0 to <5 years and P = .19 for age >5 years; for Campylobacter infection, P = .26 for age 0 to <5 years and P = .64 for age >5 years).

Neither birth weight (IRR for <2499 g, 0.93 [95% CI, 0.85–1.01]; IRR for 2500–2999 g, 0.97 [95% CI, 0.93–1.02]; 3000–3499 g was the reference; IRR for 3500–3999 g, 0.98 [95% CI, 0.94–1.01]; IRR for >4000 g, 0.97 [95% CI, 0.93–1.02]) nor gestational age (IRR for <32 weeks, 1.03 [95% CI, 0.87–1.21]; IRR for 33–34 weeks, 0.95 [95% CI, 0.85–1.06]; IRR for 35–36 weeks, 1.03 [95% CI, 0.96–1.11]; >37 weeks was the ref-

### Table 1. Incidence Rate Ratios (IRRs) for Bacterial Intestinal Infection, According to Mode of Delivery, Denmark, 1991–2005

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>All</th>
<th>Salmonella species</th>
<th>Campylobacter species</th>
<th>Yersinia enterocolitica</th>
<th>Othera</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>PYRS</td>
<td>IRR (95% CI)</td>
<td>No. of cases</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>19,351</td>
<td>12.23</td>
<td>1 (reference)</td>
<td>7211</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>3135</td>
<td>1.78</td>
<td>1.05 (1.01–1.09)</td>
<td>1161</td>
<td>1.05 (0.99–1.12)</td>
</tr>
</tbody>
</table>

**NOTE.** The study cohort included all singleton persons who were born after 1972 and to Danish-born parents. IRRs are adjusted for birth weight, gestational age, age, sex, birth order, season of birth, maternal age, average gross annual income, degree of urbanization, and the interaction term calendar-year × county of residence. CI, confidence interval; PYRS, person-years at risk (in millions).

* Includes Shigella species and Shiga toxin–producing Escherichia coli.

### Table 2. Age-Specific Incidence Rate Ratios (IRRs) for Bacterial Intestinal Infection, According to Mode of Delivery, Denmark, 1991–2005

<table>
<thead>
<tr>
<th>Infection and mode of delivery</th>
<th>IRR (95% CI), by age at bacterial intestinal infection, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to &lt;1</td>
</tr>
<tr>
<td>All infections</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>1.09 (0.96–1.23)</td>
</tr>
<tr>
<td>Salmonella infection</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.14 (0.95–1.35)</td>
</tr>
<tr>
<td>Campylobacter infection</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.05 (0.92–1.34)</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.22 (0.86–1.74)</td>
</tr>
<tr>
<td>Other infectiona</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>0.88 (0.56–1.37)</td>
</tr>
</tbody>
</table>

**NOTE.** The study cohort included all singleton persons who were born after 1972 and to Danish-born parents. IRRs are adjusted for birth weight, gestational age, age, sex, birth order, season of birth, maternal age, average gross annual income, degree of urbanization, and the interaction term calendar-year × county of residence. CI, confidence interval. 

* Includes Shigella species and Shiga toxin–producing Escherichia coli.
ference) was associated with risk of intestinal bacterial infections overall. These findings did not change materially in analyses of IRRs restricted to each of the specific intestinal bacterial infections.

Assuming a causal association and using values of $P = .1256$ for the proportion of persons delivered by c-section in the study cohort and the overall RR of 1.05, as obtained in Table 1, the proportion of all intestinal bacterial infections in Denmark during the study period that were theoretically attributable to c-section was <1% (PAR%, 0.62%).

**DISCUSSION**

In a large cohort of Danes, we found that individuals delivered by c-section were at an overall 5% increased risk of intestinal bacterial infections compared with vaginally delivered peers, a finding that was restricted to infections in children aged ≤5 years. Identification of such a small increase as being statistically significant relied entirely on the very strong statistical power of our national cohort study and is hardly compatible with any clinically relevant increased susceptibility toward such infections among persons delivered by c-section. Moreover, at the population level, our estimate that <1% of all intestinal bacterial infections in Denmark may be attributable to c-section adds to the overall impression that mode of delivery has little impact, if any, on the risk of acquiring these infections.

Theoretically, however, we can not exclude that delivery by c-section may somehow induce a transient increased susceptibility to intestinal bacterial infections in the first years of life, but it appears more likely that other unmeasured factors may somehow explain the observed pattern. For instance, differences may exist in women’s attitudes toward breast-feeding that may be associated with the mode of delivery they experienced; if children delivered by c-section are less frequently breast-fed than children born vaginally [33], this might contribute to their slight excess of intestinal bacterial infections in the first years of life. A more general health disadvantage of infants born by c-section might also account for the excess risk, because c-section babies are often challenged by cord compression, placenta praevia, and other neonatal complications. We did, however, not observe significant differences in risk estimates after elective versus acute c-section. At any rate, our study excludes c-section as a cause of persistently increased susceptibility toward intestinal bacterial infections beyond the first few years of life.

To our knowledge this is the first study to relate mode of delivery to risk of infections caused by specific intestinal pathogens. In a Swedish study, ~20,000 childhood cases of hospitalized gastroenteritis were studied using nationwide registries of births and hospital discharges for the period 1985–1996 [13]. The authors reported c-section to be associated with a 30% increase in the risk of gastroenteritis among children aged >1 year. A German study of 865 infants with parental predisposition to allergy reported c-section to be associated with 2-fold increased risk of parent-reported diarrhea [27]. Neither of the 2 studies had information on the underlying cause of gastroenteritis or diarrhea.

The present study had several advantages. We used information on laboratory-confirmed intestinal infections from patients admitted to hospitals, as well as from patients whose stool samples had been examined during treatment in outpatient settings. We adjusted the IRR for several potential confounding factors previously associated with both c-section and the risk of intestinal bacterial infection. Furthermore, we included only individuals born to Danish parents, because Danish citizens of foreign descent are at an increased risk of intestinal bacterial infections [34], and ethnicity might influence obstetric intervention [35].

We also report on the risk of intestinal bacterial infections according to gestational age and birth weight. Like children born by c-section, preterm babies have been reported to have an altered intestinal microflora. Their intestinal colonization might be delayed due to, for example, the use of antibiotics and isolation in incubators, which are more frequently needed after preterm delivery [3, 36, 37]. However, we found no significant association between gestational age or birth weight and the subsequent risk of intestinal bacterial infections overall.

In conclusion, if at all causal the observed weak association of c-section with risk of intestinal bacterial infections restricted to the first few years of life suggests that mode of delivery is not a determinant of major clinical importance. At the population level, the possible impact of increasing frequencies of cesarean section on the overall burden of intestinal bacterial infections appears to be negligible.

**References**

7. Hallstrom M, Errola E, Vuento R, Janas M, Tammela O. Effects of mode of delivery and necrotising enterocolitis on the intestinal mi-


