Association of Cesarean Delivery with Childhood Hospitalization for Infections Before 13 Years of Age

Nathalie Auger, MD, MSc, FRCPC[1,2,3,5], Safiya Soullane, MDc[4], Thuy Mai Luu, MD, MSc, FRCPC[6,8], Ga Eun Lee, MScPH[1,2], Shu Qin Wei, MD, PhD[2,8], and Caroline Quach, MD, MSc, FRCPC[7,8]

Objectives To determine the association between cesarean delivery and childhood infections up to 13 years of age.

Study design We conducted a longitudinal cohort study of 731 803 children born between 2006 and 2016 at all hospitals in the province of Quebec, Canada. We followed children born by cesarean, operative vaginal, and nonoperative vaginal delivery up to 13 years of age. Outcomes included hospitalization for otitis media, respiratory, infectious enteritis, and other infections. We estimated hazard ratios with 95% CIs for the association between mode of delivery and childhood infections, adjusted for patient characteristics.

Results At age 3-4 years, cesarean delivery was associated with a 1.07-fold greater risk of otitis media (95% CI, 1.03-1.11), a 1.15-fold greater risk of respiratory infection (95% CI, 1.09-1.22), and a 1.13-fold greater risk of infectious enteritis (95% CI, 1.03-1.25) compared with nonoperative vaginal delivery. However, operative vaginal delivery was associated with these same outcomes. Both cesarean and operative vaginal delivery were more strongly associated with infection hospitalization before age 1 year, but associations disappeared after 5 years.

Conclusions Cesarean delivery is associated with infection hospitalization before but not after age 5 years. However, associations were also present for operative vaginal delivery, which suggests that mechanisms other than exposure to maternal vaginal flora explain the relationship. *(J Pediatr 2021;231:178-84)*.

Infections are a leading cause of hospitalization in childhood,[1,2] and a large body of work suggests that cesarean delivery is a risk factor.[3-9] Infants born by cesarean are thought to have a higher risk of infection because they do not pass through the birth canal and are not exposed to the same microbial flora as infants born vaginally.[10] Cesarean delivery results in suboptimal colonization of the gastrointestinal tract at birth,[11] with fewer and less diverse beneficial bacterial species in the microbiome.[12] Perturbations in gut microbiota may hamper immune responses against pathogens.[13] Under the extended hygiene hypothesis, colonization by maternal vaginal and intestinal flora during delivery is important for the normal development of immunity in infants.[11]

Current studies suggest that cesarean delivery may be associated with respiratory and gastrointestinal infections in childhood.[3-9] Cesarean delivery is associated with respiratory syncytial virus infection and bronchiolitis in children aged <2 years,[5,7] respiratory and intestinal infections in children aged <6 years,[3,8,9] and laryngitis and gastroenteritis in children up to age 18 years.[4,6] However, mounting evidence is challenging the role of the extended hygiene hypothesis in acquiring infections. A number of studies suggest that operative vaginal delivery also may be associated with childhood infections, to a similar extent as cesarean delivery.[14,15] These findings do not align with the extended hygiene hypothesis, because operative vaginal delivery involves passage through the birth canal and exposure to maternal microbial flora. To better delineate the role of cesarean delivery in childhood infections, we assessed the extent to which mode of delivery influences the risk of infectious diseases in children up to age 13 years.

Methods

We conducted a retrospective longitudinal cohort study of 731 803 children born between 2006 and 2016 in hospitals of the province of Quebec, Canada. The cohort includes the majority of children in Quebec, as most deliveries occur in the hospital. We extracted birth discharge summaries and future childhood hospitalizations from the Maintenance and Use of Data for the Study of Hospital Clientele registry. Each discharge summary contains clinical and demographic information, validated using algorithms with high coding accuracy.[16] Diagnoses are coded using the *International Classification of Diseases and Procedures, Tenth Revision* and the Canadian Classification of Health Interventions (**Table I**; available at www.jpeds.com). Infants are matched with their mothers in the registry.

From the [1]University of Montreal Hospital Research Centre; [2]Institut national de santé publique du Québec; [3]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University; [4]Faculty of Medicine, McGill University; [5]Department of Social and Preventive Medicine, School of Public Health, University of Montreal; [6]Department of Pediatrics, University of Montreal; [7]Department of Microbiology, Infectious Diseases, and Immunology, University of Montreal; and [8]Sainte-Justine Hospital Research Center, Montreal, Quebec, Canada

Funded by the Canadian Institutes of Health Research (PJT-162300, to N.A.) and the Fonds de recherche du Québec-Santé (34695, to N.A.). The study sponsors were not involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.12.036

In this study, we used health insurance numbers to follow the children over time from birth until study end on March 31, 2019. We identified admissions for infections up to age 13 years. We excluded 2712 infants who died at birth; 10 114 twins, triplets, or quadruplets; and 48 961 preterm infants.

Mode of Delivery

The main exposure measure was cesarean delivery, operative vaginal delivery, or nonoperative vaginal delivery. Following the extended hygiene hypothesis, we grouped planned and emergency cesarean delivery together, as neither involves usual exposure to maternal vaginal or intestinal flora. Similarly, we grouped forceps and vacuum under operative vaginal delivery, as passage through the birth canal is common to both. We used nonoperative vaginal delivery, or births that were spontaneous or by induction, as the reference. We expected that under the extended hygiene hypothesis,[15] both operative and nonoperative vaginal delivery would have a lower risk of infection compared with cesarean delivery.

Childhood Infections

The main outcome measure included a range of infectious diseases associated with hospitalization in children. We included otitis media, respiratory (acute upper respiratory, tonsillitis, influenza, bronchiolitis, bronchitis, pneumonia), infectious enteritis, central nervous system (meningitis, encephalitis), infectious nephritis, carditis (endocarditis, myocarditis, pericarditis), osteomyelitis and septic arthritis, impetigo, infections of the integument, septicemia, perinatal infections (before age 28 days), and other infections. We also included vaccine-preventable infections, defined as diphtheria, tetanus, whooping cough, *Haemophilus influenzae*, *Streptococcus pneumoniae*, meningococcal infection (invasive or not), measles, mumps, rubella, varicella, rotavirus, poliomyelitis, hepatitis A, and hepatitis B.

Covariates

We used a directed acyclic graph to identify potential confounders (dagitty.net/mxWjvjo). Confounders included parity (0, 1, ≥2), maternal age at delivery (<20, 20-24, 25-29, 30-34, ≥35 years), maternal morbidity (hypertensive disorders of pregnancy; type 1, 2, and gestational diabetes; illicit drug, tobacco, and alcohol use), infant sex, congenital anomaly, socioeconomic deprivation (most deprived one-fifth of the population, least deprived, unknown), place of residence (rural, urban, unknown), and time period (2006-2009, 2010-2013, 2014-2016). Socioeconomic deprivation was based on a neighborhood measure of income, employment, and education.[17]

Data Analyses

We assessed the distribution of maternal and infant characteristics according to mode of delivery. We computed the incidence of infection hospitalization per 1000 person-years and the cumulative incidence at 13 years. Using Cox proportional hazards regression models, we estimated hazard ratios and 95% CIs for the association between mode of delivery and infection hospitalization in models adjusted for confounders. We accounted for siblings who shared the same mother using robust sandwich estimators. Follow-up time was measured in days from birth until the first hospitalization for infection, death, or study end. We censored children who were never hospitalized for infection. We accounted for death from noninfectious causes as a competing event that prevented children from developing infections.

To assess the association between mode of delivery and infections at different ages, we examined hazard ratios for children at <1, 1-2, 3-4, and 5-13 years. In sensitivity analyses, we determined whether including preterm and multiple births in the analysis altered the associations. We conducted the analysis using SAS version 9.4 for Windows (SAS Institute). We obtained an ethics waiver from the Institutional Review Board of the University of Montreal Hospital Centre, because data were encrypted and patients could not be identified.

Results

Among 731 803 infants with 4 654 995 person-years of follow-up, 163 466 (22%) were born by cesarean delivery and 72 136 (10%) by operative vaginal delivery (**Table II**; available at www.jpeds.com). Cesarean delivery was more frequent in women with nulliparity, those with morbidity, and those aged ≥30 years. Operative vaginal delivery was more frequent in nulliparous women.

The incidence of any childhood infection hospitalization was higher for cesarean (41.8 per 1000 person-years) and operative vaginal delivery (40.7 per 1000 person-years) than nonoperative vaginal delivery (38.3 per 1000 person-years) (**Table III**). A similar trend was apparent for otitis media, upper respiratory infections, and infectious enteritis. However, there was little evidence that cesarean and operative vaginal delivery led to a higher rate of hospitalization for meningitis, encephalitis, nephritis, carditis, and other serious infections.

The cumulative incidence of infection hospitalization for both cesarean and nonoperative vaginal delivery indicated that most of the excess risk of infection occurred before age 5 years (**Figure**). The gap between cesarean and nonoperative vaginal delivery changed little after 5 years. Similarly, the gap between operative and nonoperative vaginal delivery did not vary after 5 years. This pattern was present for otitis media, respiratory infection, and infectious enteritis. By age 13 years, there were 277.4 infection hospitalizations per 1000 children for cesarean delivery (95% CI, 274.9-279.8) and 277.6 for operative vaginal delivery (95% CI, 273.9-281.2), compared with 262.3 for nonoperative vaginal delivery (95% CI, 260.9-263.7).

Cesarean delivery was associated with the risk of infection hospitalization, but so was operative vaginal delivery (**Table IV**). In adjusted regression models, cesarean

Table III. Mode of delivery and incidence of infection hospitalization by site

Type of infection	Total infections	Cesarean delivery		Operative vaginal delivery		Nonoperative vaginal delivery	
		No. of infections	Incidence per 1000 person-years (95% CI)	No. of infections	Incidence per 1000 person-years (95% CI)	No. of infections	Incidence per 1000 person-years (95% CI)
Any infection	182 923	42 553	41.8 (41.6-42.1)	18 736	40.7 (40.3-41.1)	121 634	38.3 (38.1-38.4)
Otitis media	94 319	22 192	19.2 (19.0-19.3)	9624	18.4 (18.2-18.6)	62 503	17.5 (17.4-17.6)
Respiratory	80 550	18 625	16.0 (15.9-16.1)	7676	14.5 (14.3-14.7)	54 249	15.1 (15.0-15.2)
Acute upper respiratory	36 233	8519	6.92 (6.84-7.01)	3710	6.68 (6.56-6.80)	24 004	6.34 (6.29-6.38)
Tonsillitis	3910	908	0.71 (0.68-0.74)	408	0.71 (0.67-0.75)	2594	0.66 (0.65-0.68)
Influenza	5778	1291	1.01 (0.98-1.04)	545	0.95 (0.90-0.99)	3942	1.01 (0.99-1.02)
Bronchiolitis	26 995	6307	5.09 (5.02-5.17)	2100	3.73 (3.64-3.82)	18 588	4.89 (4.85-4.93)
Bronchitis	2954	711	0.56 (0.53-0.58)	278	0.48 (0.45-0.52)	1965	0.50 (0.49-0.51)
Pneumonia	29 250	6733	5.42 (5.34-5.49)	2769	4.93 (4.83-5.04)	19 748	5.18 (5.13-5.22)
Infectious enteritis	19 056	4524	3.61 (3.55-3.67)	2027	3.59 (3.50-3.68)	12 505	3.24 (3.21-3.28)
Central nervous system	2177	473	0.37 (0.35-0.39)	191	0.33 (0.30-0.36)	1513	0.39 (0.37-0.40)
Meningitis	1849	397	0.31 (0.29-0.33)	151	0.26 (0.24-0.29)	1301	0.33 (0.32-0.34)
Encephalitis	360	88	0.07 (0.06-0.08)	41	0.07 (0.06-0.08)	231	0.06 (0.05-0.06)
Nephritis	12 277	2718	2.15 (2.10-2.20)	1183	2.08 (2.01-2.15)	8376	2.16 (2.13-2.19)
Carditis	212	57	0.04 (0.04-0.05)	29	0.05 (0.04-0.06)	126	0.03 (0.03-0.04)
Osteomyelitis and septic arthritis	1191	269	0.21 (0.20-0.22)	130	0.23 (0.20-0.25)	792	0.20 (0.19-0.21)
Integument	8209	1803	1.42 (1.38-1.45)	818	1.43 (1.37-1.48)	5588	1.43 (1.41-1.45)
Septicemia	1555	343	0.27 (0.25-0.28)	157	0.27 (0.25-0.30)	1055	0.27 (0.26-0.28)
Perinatal	20 042	5007	4.02 (3.95-4.08)	2555	4.57 (4.47-4.68)	12 480	3.25 (3.21-3.28)
Vaccine-preventable	5389	1240	0.97 (0.94-1.01)	534	0.93 (0.89-0.98)	3615	0.92 (0.91-0.94)
Other infection	15 216	3569	2.83 (2.76-2.89)	1481	2.60 (2.51-2.70)	10 166	2.62 (2.59-2.66)

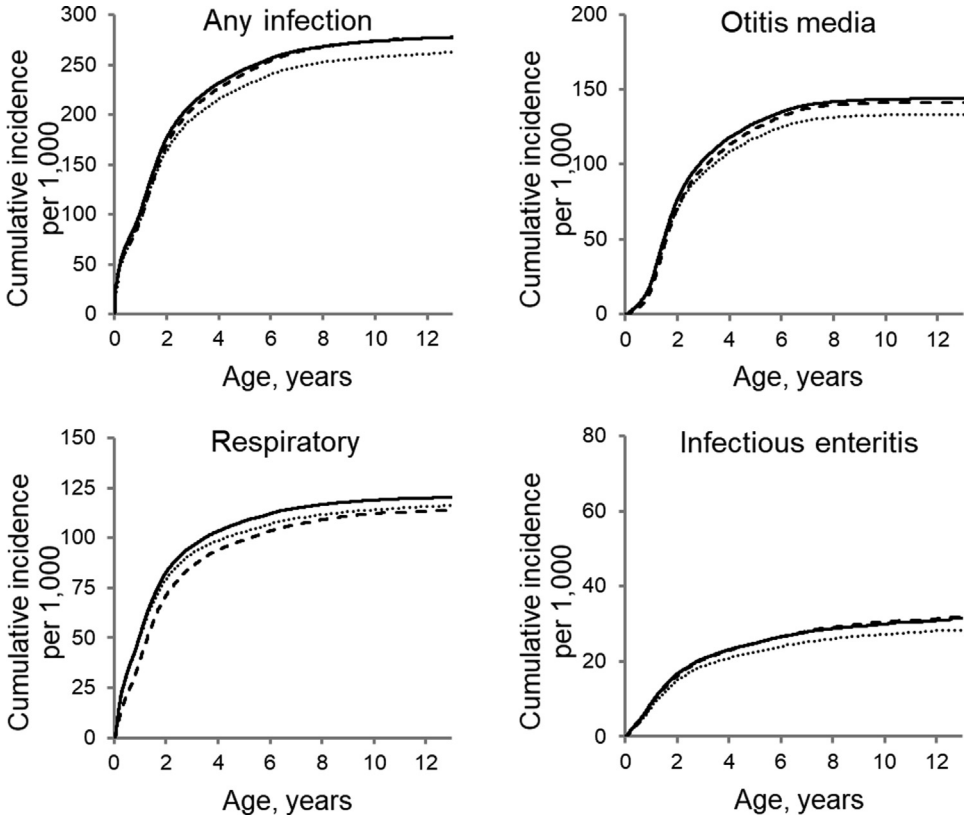

Figure. Cumulative incidence of infection hospitalization from birth to 13 years of age by mode of delivery. *Solid line*, cesarean delivery; *dashed line*, operative vaginal delivery; *dotted line*, nonoperative vaginal delivery.

delivery was associated with a 1.11-fold greater risk of any infection hospitalization (95% CI, 1.10-1.13) compared with nonoperative vaginal delivery. Cesarean delivery was associated with otitis, acute upper respiratory infection, bronchiolitis, bronchitis, pneumonia, and infectious enteritis. Cesarean delivery also was associated with carditis, perinatal infections, and vaccine-preventable infections. Operative vaginal delivery was just as strongly associated with all these infections. Moreover, operative vaginal delivery was associated with infectious nephritis.

The association between mode of delivery and infection hospitalization weakened with age (Table V). Compared with nonoperative vaginal delivery, cesarean delivery was associated with a 1.11-fold greater risk of any infection-related hospitalization before age 1 year (95% CI, 1.09-1.13), a 1.12-fold greater risk between 1 and 2 years (95% CI, 1.10-1.14), a 1.08-fold greater risk between 3 and 4 years (95% CI, 1.05-1.12), and a 1.00-fold greater risk between 5 and 13 years (95% CI, 0.96-1.04). Associations weakened with age for most types of infection. The same trend was present for operative vaginal delivery, although the association with infectious enteritis and nephritis continued past 5 years.

In sensitivity analyses when we included preterm and multiple births, associations between cesarean delivery and infection hospitalization persisted and became statistically significant for most types of infection. Associations for operative vaginal delivery were mostly unchanged.

Discussion

In this study of 731 803 infants followed from birth up to age 13 years, cesarean delivery was associated with increased risks of hospitalization for infectious diseases compared with nonoperative vaginal delivery. Risks were elevated for otitis media, acute upper respiratory infection, pneumonia, infectious enteritis, and a range of other infections. Associations decreased with age, appearing most prominent before age 1 year and disappearing at around age 5 years; however, the same pattern of associations was present for operative vaginal delivery. The findings suggest that both cesarean and operative vaginal delivery are associated with the risk of infection in childhood, and that the extended hygiene hypothesis does not fully explain the relationship. Exposure to maternal microbial flora may not be the key factor contributing to the infection risk in children.

There have been few attempts to contrast cesarean delivery with operative vaginal delivery in previous literature. Most studies have focused on comparisons with vaginal delivery as a whole, without distinguishing operative vaginal births,[3-8] yet there are indications that operative vaginal delivery may be associated with childhood infections.[9,14,15] In a cohort study of 660 000 children aged up to 13 years, operative vaginal delivery was associated with a 1.1-fold greater risk of gastroenteritis compared with nonoperative vaginal delivery, and cesarean delivery was associated with a 1.3-fold greater risk of gastroenteritis.[14] An investigation of 491 590 infants followed until age 5 years found that operative vaginal delivery was associated with a 1.3-fold greater risk of respiratory infection and cesarean delivery was associated with a 1.4-fold greater risk of respiratory infection compared with spontaneous vaginal birth.[15] However, interventions that involve passage through the birth canal and expose infants to maternal vaginal flora should not be associated with infection under the extended hygiene hypothesis.

Table IV. Association of mode of delivery with infection hospitalization in children between birth and age 13 years

	Unadjusted, HR (95% CI)		Adjusted*, HR (95% CI)	
Type of infection	Cesarean delivery	Operative vaginal delivery	Cesarean delivery	Operative vaginal delivery
Any infection	1.08 (1.06-1.09)§	1.07 (1.05-1.08)§	1.11 (1.10-1.13)§	1.12 (1.11-1.14)§
Otitis media	1.09 (1.07-1.11)§	1.06 (1.04-1.08)§	1.12 (1.10-1.13)§	1.11 (1.09-1.14)§
Respiratory	1.05 (1.03-1.06)§	0.96 (0.94-0.99)‡	1.11 (1.09-1.13)§	1.09 (1.07-1.12)§
Acute upper respiratory	1.08 (1.06-1.11)§	1.06 (1.03-1.10)§	1.11 (1.09-1.14)§	1.13 (1.10-1.18)§
Tonsillitis	1.07 (0.99-1.16)	1.08 (0.97-1.20)	1.07 (0.99-1.16)	1.04 (0.94-1.16)
Influenza	1.00 (0.94-1.07)	0.95 (0.87-1.04)	1.03 (0.97-1.10)	1.03 (0.94-1.13)
Bronchiolitis	1.03 (1.00-1.06)†	0.77 (0.74-0.81)§	1.15 (1.11-1.18)§	1.03 (0.99-1.08)
Bronchitis	1.10 (1.01-1.20)†	0.97 (0.86-1.10)	1.19 (1.09-1.29)§	1.11 (0.98-1.26)
Pneumonia	1.04 (1.01-1.07)‡	0.96 (0.92-1.00)	1.10 (1.07-1.13)§	1.08 (1.03-1.12)§
Infectious enteritis	1.10 (1.07-1.14)§	1.11 (1.06-1.17)§	1.15 (1.11-1.19)§	1.11 (1.06-1.17)§
Central nervous system	0.95 (0.86-1.06)	0.87 (0.75-1.01)	0.98 (0.89-1.09)	0.99 (0.85-1.15)
Meningitis	0.93 (0.83-1.04)	0.80 (0.67-0.94)‡	0.97 (0.87-1.09)	0.94 (0.79-1.11)
Encephalitis	1.16 (0.91-1.49)	1.21 (0.87-1.69)	1.12 (0.87-1.43)	1.19 (0.84-1.67)
Nephritis	0.99 (0.94-1.03)	0.97 (0.91-1.03)	1.03 (0.99-1.08)	1.07 (1.00-1.14)†
Carditis	1.38 (1.01-1.89)†	1.58 (1.05-2.36)†	1.38 (1.00-1.89)	1.75 (1.15-2.66)‡
Osteomyelitis and septic arthritis	1.04 (0.90-1.19)	1.12 (0.93-1.35)	1.02 (0.88-1.17)	1.08 (0.89-1.30)
Integument	0.98 (0.93-1.04)	1.00 (0.93-1.08)	1.01 (0.96-1.07)	1.06 (0.99-1.15)
Septicemia	0.99 (0.88-1.12)§	1.02 (0.86-1.21)	0.98 (0.87-1.11)	1.04 (0.88-1.24)
Perinatal	1.22 (1.18-1.26)	1.42 (1.36-1.48)§	1.19 (1.16-1.23)§	1.36 (1.30-1.42)§
Vaccine-preventable	1.04 (0.98-1.12)	1.02 (0.93-1.11)	1.10 (1.03-1.18)‡	1.09 (1.00-1.20)
Other infection	1.07 (1.03-1.12)§	1.00 (0.95-1.06)	1.11 (1.07-1.15)§	1.05 (0.99-1.11)

*Associations are relative to nonoperative vaginal delivery, adjusted for parity, maternal age, maternal morbidity, infant sex, congenital anomaly, socioeconomic deprivation, place of residence, and time period.
†$P < .05$.
‡$P < .01$.
§$P < .001$.

Table V. Association between mode of delivery and infection hospitalization by age group*

Mode/Type of infection	<1 y, HR (95% CI)	1-2 y, HR (95% CI)	3-4 y, HR (95% CI)	≥5 y, HR (95% CI)
Cesarean delivery				
Any infection	1.11 (1.09-1.13)§	1.12 (1.10-1.14)§	1.08 (1.05-1.12)§	1.00 (0.96-1.04)
Otitis media	1.17 (1.12-1.21)§	1.13 (1.10-1.15)§	1.07 (1.03-1.11)§	1.03 (0.97-1.09)
Respiratory	1.14 (1.11-1.17)§	1.09 (1.06-1.12)§	1.15 (1.09-1.22)§	0.95 (0.88-1.02)
Infectious enteritis	1.18 (1.11-1.26)§	1.12 (1.06-1.18)§	1.13 (1.03-1.25)‡	1.14 (1.03-1.26)†
Central nervous system	0.89 (0.77-1.02)	1.15 (0.87-1.51)	1.03 (0.75-1.40)	1.02 (0.78-1.35)
Nephritis	0.98 (0.92-1.03)	1.16 (1.06-1.28)‡	1.19 (1.01-1.42)†	1.17 (0.98-1.39)
Carditis	1.67 (1.03-2.70)†	1.13 (0.52-2.46)	1.04 (0.42-2.59)	1.23 (0.56-2.70)
Osteomyelitis and septic arthritis	0.70 (0.45-1.10)	1.14 (0.93-1.39)	1.01 (0.71-1.45)	0.97 (0.73-1.28)
Integument	1.01 (0.88-1.16)	1.06 (0.96-1.17)	1.01 (0.87-1.16)	0.99 (0.86-1.14)
Septicemia	1.10 (0.93-1.31)	0.91 (0.70-1.17)	0.65 (0.43-1.00)	0.76 (0.51-1.13)
Vaccine-preventable	1.13 (1.02-1.25)†	1.10 (0.99-1.21)	1.01 (0.82-1.25)	1.08 (0.85-1.38)
Other infection	1.12 (1.05-1.19)§	1.12 (1.05-1.20)‡	1.07 (0.96-1.19)	0.98 (0.88-1.09)
Operative vaginal delivery				
Any infection	1.07 (1.04-1.11)§	1.12 (1.10-1.15)§	1.07 (1.02-1.12)‡	1.07 (1.01-1.12)†
Otitis media	1.14 (1.07-1.21)§	1.14 (1.10-1.17)§	1.06 (1.01-1.12)†	1.03 (0.95-1.11)
Respiratory	1.05 (1.00-1.09)†	1.12 (1.08-1.16)§	1.16 (1.07-1.25)§	1.08 (0.99-1.18)
Infectious enteritis	1.12 (1.03-1.23)†	1.08 (1.00-1.16)†	1.12 (0.99-1.28)	1.22 (1.07-1.40)‡
Central nervous system	0.82 (0.65-1.04)	1.27 (0.87-1.86)	1.01 (0.67-1.53)	1.04 (0.72-1.49)
Nephritis	1.04 (0.96-1.13)	1.15 (1.00-1.31)†	0.81 (0.61-1.07)	1.36 (1.07-1.72)†
Carditis	2.89 (1.61-5.21)§	0.92 (0.27-3.10)	1.10 (0.33-3.68)	0.77 (0.22-2.65)
Osteomyelitis and septic arthritis	1.23 (0.74-2.05)	1.11 (0.84-1.47)	0.97 (0.58-1.63)	1.02 (0.70-1.47)
Integument	1.09 (0.90-1.32)	1.05 (0.90-1.22)	1.11 (0.91-1.35)	0.98 (0.80-1.19)
Septicemia	0.93 (0.71-1.21)	1.08 (0.76-1.52)	1.17 (0.71-1.94)	0.97 (0.59-1.58)
Vaccine-preventable	1.09 (0.93-1.28)	1.07 (0.93-1.23)	1.05 (0.77-1.42)	1.29 (0.95-1.76)
Other infection	1.04 (0.95-1.15)	1.04 (0.94-1.14)	1.03 (0.88-1.20)	1.00 (0.86-1.16)

*Associations are relative to nonoperative vaginal delivery, adjusted for parity, maternal age, maternal morbidity, infant sex, congenital anomaly, socioeconomic deprivation, place of residence, and time period.
†$P < .05$.
‡$P < .01$.
§$P < .001$.

Therefore, our results suggest that a lack of exposure to vaginal flora might not explain the association between cesarean delivery and childhood infections.

The extended hygiene hypothesis proposes that cesarean delivery may have a lifelong impact on immune development,[18] but most analyses limit follow-up to age 2, 5, or 6 years.[3,5,7,9,15] The handful of studies with data beyond 6 years focused on associations over the entire duration of follow-up, even though age-specific data are needed to confirm the extended hygiene hypothesis.[4,6,14] These studies suggest that cesarean delivery is associated with laryngitis, gastroenteritis, and lower respiratory infections in children aged 0-18 years.[4,6,14] Associations at different ages were not investigated. In 1 of the few studies that considered changes over age, cesarean delivery was associated with infectious enteritis before but not after 5 years.[8] The investigators did not examine other infectious outcomes, but our results suggest that associations with almost all infections weaken or disappear after 5 years. Therefore, we found little support for the notion of a lifelong impact in the extended hygiene hypothesis.

According to the extended hygiene hypothesis, children born by cesarean have a suboptimal gut microbiome because they bypass the maternal vaginal microbiota.[19] Colonization by maternal flora in the birth canal is believed to promote diversity of the infant's microbiome, needed for normal immune development.[18,19] Previous studies have reported that infants born vaginally have a more diverse microbiota until age 6 months, including *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* species known to inhibit proinflammatory cytokine production, promote mucosal barrier function, and limit pathogen invasion.[20] Infants born by cesarean are more likely to be colonized by harmful organisms such as *Clostridioides difficile*; however, differences in gut microbiota have not been found in all studies.[20] Moreover, there is little support for the effectiveness of postnatal vaginal seeding, the practice of transferring maternal vaginal fluids to a neonate following cesarean delivery.[19]

In addition, such factors as breastfeeding may be more protective against childhood infections than maternal microbial exposure in the birth canal.[21] Cesarean and operative vaginal delivery are associated with impaired lactation and shorter breastfeeding duration.[19,22] Delayed breastfeeding and early cessation may hinder the passive transfer of maternal antibodies and disrupt neonatal microbiota composition.[23] A large multicenter study found that breastfeeding may be the most significant factor associated with the composition of neonatal gut microbiota.[24] Longer breastfeeding duration is associated with increased gut microbial diversity and beneficial commensal organisms.[21] Therefore, it is plausible that any birth intervention that impedes breastfeeding may be associated with early childhood infections.

Breastfeeding may be particularly important for preterm infants who are born by cesarean and have less developed immune systems.[9,19] Breastfeeding preterm or multiple newborns may be challenging.[25] Preterm infants face barriers to breastfeeding, such as maternal separation, dysphagia, and ineffective suck.[26] When we included preterm and multiple births in the analysis, both cesarean and operative vaginal delivery were more strongly associated with pediatric infectious

hospitalization. Thus, it is possible that breastfeeding makes an important contribution to the association between cesarean delivery and infection.

The infant microbiome also may be altered by antibiotics.[19] In a study of 198 term infants, intrapartum antibiotic prophylaxis before cesarean and vaginal delivery was associated with depletion of *Bacteroides* and *Parabacteroides* and overgrowth of *Enteroccocus* and *Clostridium*.[27] It is common practice to use antibiotics short term to rule out sepsis[28] and for management of respiratory distress syndrome after cesarean or operative vaginal delivery.[29,30] Antibiotics in the perinatal period may be an additional factor that contribute to the association of cesarean delivery with childhood infection.

Intrapartum epigenetic changes have been raised as an alternative hypothesis.[19] The hypothesis proposes that stress hormones produced during vaginal birth trigger epigenetic remodeling of genes that program immune responses.[18,31] Abnormal levels of stress hormones during cesarean and operative vaginal delivery are thought to disrupt epigenetic priming of immune-related genes.[18] This hypothesis stems from evidence that labor duration is associated with DNA methylation patterns in hematopoietic stem cells.[32] However, the extent to which the epigenetic hypothesis may be more important for pediatric infections than breastfeeding or other patient characteristics remains to be demonstrated.

This study was subject to limitations. We had data on serious infections that required hospital treatment but not on mild uncomplicated infections treated in outpatient settings. In particular, we were able to capture a high proportion of patients with complicated or recurrent otitis media. We had less power for the analysis of infections after age 5 years, as the frequency of hospitalization decreases with age. We did not know the medical indication for cesarean or operative vaginal delivery and could not eliminate the possibility of confounding. Although we adjusted for several covariates, we did not have data on unmeasured characteristics, such as antibiotic or probiotic use; breastfeeding; daycare attendance; immunization status; paternal characteristics; maternal infections including HIV, group B streptococcus, hepatitis C virus, and other congenital infections; genetic factors; and ethnicity. We adjusted for maternal substance use, but underreporting is possible. Although we had neighborhood measures of socioeconomic deprivation, misclassification may be present, as we lacked individual level measures of income and education. Our findings are representative of a large region in a country with universal healthcare, but generalizability to areas with other demographics is uncertain.

Cesarean delivery is associated with the risk of infection hospitalization before age 5 years of age but not later. However, operative vaginal delivery was also associated with infection hospitalization before age 5 years, suggesting that pathways other than exposure to maternal vaginal and intestinal flora are involved. Although more data are needed to confirm these findings, patients may be reassured that cesarean delivery is not the underlying reason for the elevated risk of childhood infection, and that regardless of pathways, the excess risk disappears at age 5 years. ■

Submitted for publication Sep 10, 2020; last revision received Nov 9, 2020; accepted Dec 15, 2020.

Reprint requests: Nathalie Auger, MD, Institut national de santé publique du Québec, 190 Cremazie Blvd E, Montreal H2P 1E2, QC, Canada. E-mail: nathalie.auger@inspq.qc.ca

References

1. Canadian Institute of Health Information. Inpatient hospitalization, surgery and newborn statistics, 2017-2018. https://www.cihi.ca/sites/default/files/document/dad-hmdb-childbirth-quick-stats-2017-2018-en-web.xlsx. Accessed March 5, 2020.
2. Witt WP, Weiss AJ, Elixhauser A. Overview of hospital stays for children in the United States, 2012: Statistical Brief 187. Healthcare Cost and Utilization Project (HCUP). https://www.hcup-us.ahrq.gov/reports/statbriefs/sb187-Hospital-Stays-Children-2012.jsp. Accessed May 26, 2020.
3. Christensen N, Søndergaard J, Christesen HT, Fisker N, Husby S. Association between mode of delivery and risk of infection in early childhood: a cohort study. Pediatr Infect Dis J 2018;37:316-23.
4. Wainstock T, Walfisch A, Shoham-Vardi I, Segal I, Sergienko R, Landau D, et al. Term elective Cesarean delivery and offspring infectious morbidity: a population-based cohort study. Pediatr Infect Dis J 2019;38:176-80.
5. Kristensen K, Fisker N, Haerskjold A, Ravn H, Simões EAF, Stensballe L. Caesarean section and hospitalization for respiratory syncytial virus infection: a population-based study. Pediatr Infect Dis J 2015;34:145-8.
6. Kristensen K, Henriksen L. Cesarean section and disease associated with immune function. J Allergy Clin Immunol 2016;137:587-90.
7. Moore HC, de Klerk N, Holt P, Richmond PC, Lehmann D. Hospitalisation for bronchiolitis in infants is more common after elective Caesarean delivery. Arch Dis Child 2012;97:410-4.
8. Bager P, Simonsen J, Ethelberg S, Frisch M. Cesarean delivery and risk of intestinal bacterial infection. J Infect Dis 2010;201:898-902.
9. Bentley JP, Simpson JM, Bowen JR, Morris JM, Roberts CL, Nassar N. Gestational age, mode of birth and breastmilk feeding all influence acute early childhood gastroenteritis: a record-linkage cohort study. BMC Pediatr 2016;16:55.
10. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107:11971-5.
11. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol 2011;38:321-31.
12. Montoya-Williams D, Lemas DJ, Spiryda L, Patel K, Carney OO, Neu J, et al. The neonatal microbiome and its partial role in mediating the association between birth by Cesarean section and adverse pediatric outcomes. Neonatology 2018;114:103-11.
13. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. Nat Med 2016;22:713-22.
14. Håkansson S, Källén K. Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis. Clin Exp Allergy 2003;33:757-64.
15. Peters LL, Thornton C, de Jonge A, Khashan A, Tracy M, Downe S, et al. The effect of medical and operative birth interventions on child health outcomes in the first 28 days and up to 5 years of age: a linked data population-based cohort study. Birth 2018;45:347-57.
16. Landry JS, Croitoru D, Menzies D. Validation of ICD-9 diagnostic codes for bronchopulmonary dysplasia in Quebec's provincial health care databases. Chronic Dis Inj Can 2012;33:47-52.
17. Auger N, Quach C, Healy-Profitós J, Dinh T, Chassé M. Early predictors of Guillain-Barré syndrome in the life course of women. Int J Epidemiol 2018;47:280-8.
18. Dahlen HG, Downe S, Wright ML, Kennedy HP, Taylor JY. Childbirth and consequent atopic disease: emerging evidence on epigenetic effects based on the hygiene and EPIIC hypotheses. BMC Pregnancy Childbirth 2016;16:4.
19. Stinson LF, Payne MS, Keelan JA. A critical review of the bacterial baptism hypothesis and the impact of Cesarean delivery on the infant microbiome. Front Med (Lausanne) 2018;5:135.
20. Rutayisire E, Huang K, Liu Y, Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. BMC Gastroenterol 2016;16:86.

21. van den Elsen LWJ, Garssen J, Burcelin R, Verhasselt V. Shaping the gut microbiota by breastfeeding: the gateway to allergy prevention? Front Pediatr 2019;7:47.
22. Leung GM, Lam TH, Ho LM. Breast-feeding and its relation to smoking and mode of delivery. Obstet Gynecol 2002;99(5 Pt 1):785-94.
23. Georgountzou A, Papadopoulos NG. Postnatal innate immune development: from birth to adulthood. Front Immunol 2017;8:957.
24. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 2018;562:583-8.
25. Whitford HM, Wallis SK, Dowswell T, West HM, Renfrew MJ. Breastfeeding education and support for women with twins or higher order multiples. Cochrane Database Syst Rev 2017;2:CD012003.
26. Briere CE, McGrath J, Cong X, Cusson R. An integrative review of factors that influence breastfeeding duration for premature infants after NICU hospitalization. J Obstet Gynecol Neonatal Nurs 2014;43:272-81.
27. Azad MB, Konya T, Persaud RR, Guttman DS, Chari RS, Field CJ, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. Br J Obstet Gynaecol 2016;123:983-93.
28. Patel K, Konduru K, Patra AK, Chandel DS, Panigrahi P. Trends and determinants of gastric bacterial colonization of preterm neonates in a NICU setting. PLoS One 2015;10:e0114664.
29. Santa Cruz Breim MC, de Mattos Segre CA, Lippi UG. Morbidity in neonates according to the mode of delivery: a comparative study. Einstein (São Paulo) 2010;8:308-14.
30. Moresco L, Calevo MG, Bruschettini M. Antibiotics for the management of [suspected] transient tachypnea of the newborn. Cochrane Database Syst Rev 2018;9:CD012872.
31. Schlinzig T, Johansson S, Stephansson O, Hammarström L, Zetterström RH, von Döbeln U, et al. Surge of immune cell formation at birth differs by mode of delivery and infant characteristics—a population-based cohort study. PLoS One 2017;12:e0184748.
32. Almgren M, Schlinzig T, Gomez-Cabrero D, Gunnar A, Sundin M, Johansson S, et al. Cesarean delivery and hematopoietic stem cell epigenetics in the newborn infant: implications for future health? Am J Obstet Gynecol 2014;211:502.e1-8.

50 Years Ago in *The Journal of Pediatrics*

Recognizing Familial Thyroid Dysgenesis

Orti E, Castells S, Qazi QH, Inamdar S. Familial thyroid disease: lingual thyroid in two siblings and hypoplasia of a thyroid lobe in a third. J Pediatr 1971;78:675-7.

In 1971, Orti et al described thyroid dysgenesis in 3 siblings. Two siblings had a lingual thyroid, and the third had a hypoplastic thyroid lobe. Other family members did not have thyroid disorders. The authors recognized that normal thyroid development may be genetically controlled, and that inherited defects could lead to abnormal thyroid development.

Thyroid dysgenesis, the failure of normal thyroid gland development, is the most common cause of primary congenital hypothyroidism and occurs in 1 in 3000 infants.[1] During embryogenesis, the thyroid gland primordium develops from the foregut endoderm, near the base of the tongue. These cells migrate from the pharyngeal floor through the anterior midline of the neck. The thyroid is connected to the pharynx by the thyroglossal duct during descent. The nascent thyroid reaches below the thyroid cartilage by week 7 of embryonic development and is completely formed by week 10.[2] Disruption of these developmental steps can lead to thyroid dysgenesis.

Most cases of thyroid dysgenesis occur sporadically, but the authors correctly recognized familial forms. Thyroid dysgenesis is attributed to genetic mutations in 2%-5% of cases.[3] Over the past 2 decades, several genes involved in thyroid gland development have been identified, including PAX8, NKX2-1, FOXE1, NKX2-5, GLIS3, JAG1, and CDCA8 (BOREALIN). Partial inactivation of the TSHR gene can also present with thyroid hypoplasia. Many of these genes are associated with developmental abnormalities in other organs as well. Familial thyroid dysgenesis often shows an autosomal dominant mode of inheritance with incomplete penetrance and variable disease expressivity.

Although there has been growth in understanding the genes responsible for thyroid development, the greatest advancement in the diagnosis of congenital hypothyroidism over the past 50 years has been the role of universal newborn screening. The authors described 1 sibling with an intellectual disability owing to congenital hypothyroidism. Universal newborn screening, implemented in the early 1970s, has led to the prevention of intellectual disability due to severe congenital hypothyroidism and is a major achievement of preventive medicine.

Avani Ganta, MD
Lisa Swartz Topor, MD, MMSc
Division of Pediatric Endocrinology
Hasbro Children's Hospital & Warren Alpert School of Medicine of Brown University
Providence, Rhode Island

References

1. Mio C, Grani G, Durante C, Damante G. Molecular defects in thyroid dysgenesis. Clin Genet 2020;97:222-31.
2. Castanet M, Marinovic D, Polak M, Léger J. Epidemiology of thyroid dysgenesis: the familial component. Hormone Res Paediatr 2010;73:231-7.
3. Cherella CE, Wassner AJ. Congenital hypothyroidism: insights into pathogenesis and treatment. Int J Pediatr Endocrinol 2017;2017:11.

Table I. Diagnostic and procedure codes for exposures, covariates, and outcomes

Variables	*International Classification of Diseases Tenth Revision*/Canadian Classification of Health Interventions
Mode of delivery	
Cesarean delivery	5.MD.60
Operative vaginal delivery	5.MD.53, 5.MD.54, 5.MD.55
Maternal morbidity	
Preeclampsia	O11, O13, O14, O15
Preexisting and gestational diabetes	E10, E11, E13, E14, O24.5-O24.7
Substance use (illicit drugs, tobacco, alcohol)	F10-F19, K29.2, K70, K85.2, K86.0, K86.9, O35.4, O35.5, R78.0-R78.5, T40, T51.0, T65.2, X42, X45, X62, X65, Y12, Y15, Z50.2, Z50.8, Z58.7, Z71.4-Z71.6, Z72.0-Z72.2, Z86.40-Z86.42, Z86.48/5.AD.14.BK,6.AA.10.AD, 6.AA.10.CD, 7.SP.10.VA, 7.SP.10.VB, 7.SP.10.VK, 7.SP.60.VA, 7.SP.60.VB
Site of infection	
Otitis media	H65-H67
Respiratory	J00-J06, J09-J22
Acute upper respiratory	J00-J02, J04-J06
Tonsillitis	J03
Influenza	J09-J11
Bronchiolitis	J21
Bronchitis	J20
Pneumonia	J12-J18
Infectious enteritis	A00-A09
Central nervous system	A83-A87, A92.2, A92.3, B94.1, G00-G05
Meningitis	A87, G00-G03
Encephalitis	A83-A86, A92.2, A92.3, B94.1, G04, G05
Nephritis	N10-N12, N13.6, N16.0, N30, N34, N39.0
Carditis	I01, I30.0, I30.1, I30.8, I30.9, I32.0, I32.1, I33.0, I33.9, I38, I39, I40.0, I41.0, I41.1
Osteomyelitis and septic arthritis	M00, M01, M86
Integument	L00-L08
Septicemia	A40, A41, R57.2
Perinatal	P23, P35-P39, and other infections before 28 days
Vaccine-preventable	A08.0, A35-A37, A39, A40.3, A41.3, A49.2, A80, B01, B05, B06, B15, B16, B26, B91, B95.3, B96.3
Other	I00, and all remaining codes in sections A and B

Table II. Distribution of maternal and child characteristics according to mode of delivery

Characteristics	Cesarean delivery, n (%)	Operative vaginal delivery, n (%)	Nonoperative vaginal delivery, n (%)
Parity			
0	85 474 (52.3)	57 051 (79.1)	212 880 (42.9)
1	56 588 (34.6)	11 916 (16.5)	190 420 (38.4)
≥2	21 404 (13.1)	3169 (4.4)	92 901 (18.7)
Maternal age, y			
<20	2268 (1.4)	2008 (2.8)	12 423 (2.5)
20-24	16 434 (10.1)	11 220 (15.6)	72 077 (14.5)
25-29	48 155 (29.5)	26 406 (36.6)	170 940 (34.4)
30-34	58 341 (35.7)	22 244 (30.8)	165 102 (33.3)
≥35	38 268 (23.4)	10 258 (14.2)	75 659 (15.2)
Maternal morbidity*			
Yes	25 413 (15.5)	8081 (11.2)	55 405 (11.2)
No	138 053 (84.5)	64 055 (88.8)	440 796 (88.8)
Infant sex			
Male	87 012 (53.2)	40 530 (56.2)	246 380 (49.7)
Female	76 454 (46.8)	31 606 (43.8)	249 821 (50.3)
Congenital anomaly			
Yes	24 160 (14.8)	10 021 (13.9)	61 606 (12.4)
No	139 306 (85.2)	62 115 (86.1)	434 595 (87.6)
Socioeconomic deprivation			
Most deprived	31 926 (19.5)	13 388 (18.6)	97 303 (19.6)
Least deprived	124 803 (76.3)	55 568 (77.0)	378 004 (76.2)
Place of residence			
Rural	28 940 (17.7)	12 989 (18.0)	91 877 (18.5)
Urban	131 707 (80.6)	57 808 (80.1)	395 637 (79.7)
Time period			
2006-2009	61 697 (37.7)	29 048 (40.3)	191 185 (38.5)
2010-2013	49 957 (30.6)	21 631 (30.0)	155 294 (31.3)
2014-2016	51 812 (31.7)	21 457 (29.7)	149 722 (30.2)
Total	163 466 (100)	72 136 (100)	496 201 (100)

*Preeclampsia; type 1, 2, and gestational diabetes; and illicit drug, tobacco, and alcohol use.