Anesthesia for Cesarean Delivery and Learning Disabilities in a Population-based Birth Cohort

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Background: Anesthetics administered to immature brains may cause histopathological changes and long-term behavioral abnormalities. The association between perinatal exposure to anesthetics during Cesarean delivery (CD) and development of learning disabilities (LD) was determined in a population-based birth cohort.

Methods: The educational and medical records of all children born to mothers residing in five townships of Olmsted County, Minnesota from 1976–1982 and remaining in the community at age 5 were reviewed to identify those with LDs. Cox proportional hazards regression was used to compare rates of LD between children delivered vaginally and *via* CD (with general or regional anesthesia).

Results: Of the 5,320 children in this cohort, 497 were delivered *via* CD (under general anesthesia n = 193, and regional anesthesia n = 304). The incidence of LD depended on mode of delivery ($P = 0.050$, adjusted for sex, birth weight, gestational age, exposure to anesthesia before age 4 yr, and maternal education). LD risk was similar in children delivered by vagina or CD with general anesthesia, but was reduced in children receiving CD with regional anesthesia (hazard ratio = 0.64, 95% confidence interval 0.44 to 0.92; $P = 0.017$ for comparison of CD under regional anesthesia compared to vaginal delivery).

Conclusion: Children exposed to general or regional anesthesia during CD are not more likely to develop LD compared to children delivered vaginally, suggesting that brief perinatal exposure to anesthetic drugs does not adversely affect long-term neurodevelopmental outcomes. The risk of LD may be lower in children delivered by CD whose mothers received regional anesthesia.

THE short- and long-term effects of obstetric anesthetic techniques on behavior and development of the neonate, infant, and child have been of long-standing interest. It is clear that these techniques may at least transiently affect some aspects of newborn behavior.[1–7] However, the impact of obstetric analgesia and anesthesia on long-term outcomes in the absence of concurrent

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events such as fetal asphyxia is not known. Studies evaluating the association between perinatal and environmental characteristics and childhood behavioral outcomes have suggested that operative or instrumented deliveries *per se* are not linked to childhood behavioral disorders or abnormalities in cognitive, verbal, or reading functioning,[8–12] but these studies do not specifically evaluate the impact of anesthesia and analgesia.

In the peripartum period, children may be exposed to anesthetic and analgesic drugs that are administered to the mother. Exposure of fetal or neonatal animals (including primates) to anesthetics can cause histopathological changes in their brains, even after single, relatively brief administration.[13–19] These changes may be associated with a diminished capacity to retain learned behavior[20] and abnormal social behaviors resembling disorders in the autism spectrum.[21] However, the significance of these findings to humans is not clear. We recently demonstrated that repeated, but not single, exposure to anesthesia before the age of 4 yrs is associated with an approximately twofold increase in the incidence of learning disabilities (LD).[22] Our data could not distinguish whether exposure to anesthesia itself increases the risk of LD, or whether the need for anesthesia represents a marker for unidentified confounders that promote LD. Although the lack of effect of a single anesthetic exposure on the incidence of LD in infants and young children is reassuring,[22] it is still possible that even brief exposure of the less mature neonatal brain to anesthesia might have neurotoxic effects.[23]

Using the same unique population-based birth cohort described in our recent study[22] we sought to determine if an association exists between fetal exposure to anesthesia during Cesarean delivery (CD) and the subsequent development of LD in a birth cohort of children. On the basis of our recent report,[22] we hypothesized that brief fetal exposure to anesthetics during CD would not increase the risk for LD.

Materials and Methods

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards (both Rochester, Minnesota) approved this study. A birth cohort of children born in Rochester, Minnesota identified in previously published work[24–28] formed the basis of the current study. All children born between January 1, 1976 and December 31, 1982 to mothers residing at the time of delivery in

the five Olmsted County, Minnesota, townships within Minnesota Independent School District No. 535 (the Rochester public school system) were identified through computerized birth certificate information obtained from the Minnesota Department of Health, Division of Vital Statistics (n = 8,548). To ascertain vital status (still living in Rochester, moved, or deceased) for each member of the birth cohort during the 1995–1996 school year, we used resources available from the Rochester Epidemiology Project,[29] Minnesota Independent School District No. 535, the Reading Center/Dyslexia Institute of Minnesota (Rochester, Minnesota), and the Minnesota Department of Health (Rochester, Minnesota) were utilized. Children who left Olmsted County before age 5 yrs (*i.e.*, moved or died, n = 2,830) were not included in the final study cohort.[24] Through the Rochester Epidemiology Project, all diagnoses and surgical procedures recorded at all Rochester medical facilities are indexed for automated retrieval. This index expedites retrieval of the unit (or dossier) medical record, which includes the history of all encounters in the hospital, community and ambulatory medical and social services, emergency department, outpatient clinics, and home visits as well as laboratory and psychological test results from birth until patients no longer reside in the community. Through a contractual research agreement, all public schools (19 primary, 3 junior high, 3 high schools) and nonpublic (12 primary, 10 junior high, 4 high schools) gave permission to access their richly documented cumulative educational records for every child from this birth cohort. Under a second research agreement, permission was obtained to access the resources of the privately owned Reading Center/Dyslexia Institute of Minnesota, the only private tutoring agency in the community during the years relevant to this study. The Reading Center/Dyslexia Institute of Minnesota files included a pool of some 3,000 evaluations and outcomes of tutorial instruction that spanned nearly 50 yr. Thus, the overall strategy in identifying all children in this cohort with LD employed multiple sources of information (school, medical, and Reading Center/Dyslexia Institute of Minnesota records) and relied on a richly documented history of any learning/behavior concerns, information of educational intervention, and individually administered test results.

Identification of Learning Disabilities

The details of LD ascertainment have been described in previously published reports examining the epidemiology of LD.[25,26,28] To summarize, all school, medical, and Reading Center/Dyslexia Institute records were reviewed by trained personnel who used detailed data abstraction protocols, seeking evidence for reported learning difficulties. Based on the initial review, potential LD was identified in 1,510 children (26% of all 5,718 children in the birth cohort). The results of individually administered intelligence quotient (IQ, primarily age-appropriate Wechsler scales) and achievement (primarily Woodcock-Johnson tests) tests, medical, educational, and socioeconomic information were abstracted. Research criteria using an average of two individually administered IQ and three individually administered achievement tests were then applied to these children to diagnose reading, written language, and math LD. Children were classified as having LD if they met criteria according to at least one of three standard formulae. In each of the following formulae, X is equal to the study subject's IQ score, and Y represents the predicted standard score from the achievement test. The regression formula–Minnesota, $Y < 17.40 + 0.62 X$, is issued by the Minnesota Department of Education.[30] Children classified as having LD by this formula had standard scores in academic achievement that were more than 1.75 SD below their predicted standard score from an individually administered measure of cognitive ability (IQ). The value 0.62 represents the correlation between IQ and achievement used in the formula from the state of Minnesota. The discrepancy nonregression method was used in Minnesota Independent School District No. 535 before 1989 and included the school years of the children in the birth cohort. By using this approach, differences between standard scores on measures of intelligence and measures of achievement that were believed to be important varied by grade as follows: (1) kindergarten to third grade, 15 or more standard score points difference, with achievement lower; (2) fourth to sixth grade, 19 or more points difference, achievement lower; and (3) seventh to twelfth grade, 23 or more points difference. Finally, the low-achievement method ($X \geq$ 80 [aptitude] and $Y \leq 90$ [achievement]) represents a recent concept in identifying LD independent of measured cognitive ability, assuming that cognitive ability is at least in the low average range.[31] Children meeting the criteria before age 19 for at least one of the three LDs (reading, written language, and math disorders) using IQ and achievement scores obtained within the same calendar year were identified as LD cases regardless of presence or absence of any comorbid conditions.[25,26,28]

Other Variables

We identified all children who were delivered *via* CD under general or regional anesthesia using the Mayo Clinic and Olmsted County Medical Center Surgical Information Retrieval Systems. For mothers who delivered with CD, the following information was abstracted: American Society of Anesthesiologists physical status classification, urgency of CD (elective, emergent), type of anesthesia (general or regional, defined as epidural or spinal anesthesia), agents used (inhalational, intravenous, local anesthetics) and duration of anesthesia. Duration of anesthesia was defined as follows: (1) general anesthesia as the time from administration of induction agent to delivery of the child; (2) spinal anesthesia as the time

from injection of neuraxial local anesthetic until the delivery; and (3) epidural anesthesia as the time from the first epidural administration of drug (which could be a labor epidural) until delivery of child. If a failed regional anesthetic required conversion to general anesthesia, for the purpose of analyses, the anesthetic was classified as general anesthesia, and the duration was recorded as time from administration of induction agent to delivery.

Age and education (less than 12 yr [some high school education], 12 yr [high school graduate], and more than 12 yr [any postsecondary education]) for both mother and father were recorded from both school records and birth certificates. Pregnancy complications were abstracted from birth certificates, including pregnancy-induced hypertension, preeclampsia, and eclampsia, hemorrhage during pregnancy, premature rupture of membranes, abnormalities of placenta or fetus. Information obtained for each child included sex, the number of births (multiple or single), gestational age at birth, birth weight, and complications of labor and delivery (need for induced labor and method of induction, hemorrhage during delivery, fetopelvic disproportion, dystocic position of the fetus, prolonged labor, and umbilical cord compression). APGAR scores (Appearance, Pulse, Grimace, Activity, Respiration) at 1 and 5 min were available only for children born 1980–1982 (n = 1,635).

Statistical Analysis

The primary outcome for the current analysis was LD based on individually administered IQ and academic achievement test scores using any of the three standard formulae for determining the presence of reading, written language, or math LDs. The primary risk factor of interest for this investigation was the association of LD and exposure to CD under either general or regional anesthesia. Analyses were performed to compare demographic, pregnancy and delivery complications, and parental characteristics across delivery modes (vaginal, CD with general anesthesia, CD with regional anesthesia) using analysis of variance (ANOVA) for continuous variables and the chi-square test (or Fisher exact test) for categorical variables. Individuals were followed from birth until the date they first met the LD criteria using any of the three standard formulas. Cumulative incidence rates of LD were calculated according to the method of Kaplan and Meier, with data censored at the initial occurrence of emigration, death, last follow-up date, or the age of 19 yr. Proportional hazards regression was used to assess whether anesthetic exposure at birth was a risk factor for LD. Both unadjusted and adjusted analyses were performed. For the adjusted analyses the covariates were selected *a priori* on the basis of previous work[24–27] and included gestational age (no more than 31 weeks, 32–36 weeks, 37 weeks or more), sex (male, female), birth weight (less that 2,500 g, 2500 g or

more), maternal education (some high school, high school graduate, any college), and number of anesthesia exposures before the age of 4 (0, 1, 2, or more).[22] To supplement these planned analyses, additional *post hoc* analyses were performed, eliminating children who were exposed to anesthesia after birth and before age 4 (a factor shown in previously published work to increase the risk of LD in children receiving multiple anesthetics),[22] and also eliminating all children who were delivered by emergency CD. An additional *post hoc* adjusted analysis included additional covariates for all characteristics that were found to differ significantly across delivery groups. These additional covariates included maternal age (no more than 19 yr, 20–34 yr, 35 yr or more), paternal education (some high school, high school graduate, any college), complications of pregnancy (none *vs.* any), induction of labor (no *vs.* yes), and complications of labor and delivery (none *vs.* any). Although APGAR scores were found to differ significantly across delivery modes, these scores were not used as covariates in this analysis because they were only available for neonates born between 1980 and 1982; they are, therefore, missing for 69% of the cohort. In all adjusted analyses, only those individuals for whom complete covariate information was available were included. Results were summarized by using hazard ratio estimates and corresponding 95% confidence intervals (CI). In all cases, two-tailed *P* values less than 0.05 were considered to be statistically significant. Analyses were performed using SAS statistical software (version 9.1; SAS Institute, Inc., Cary, NC).

Results

Between 1976 and 1982, there were 8,548 children born in the five Olmsted County, Minnesota, townships within Independent School District No. 535, and 5,718 of these children still resided in the community at 5 yr of age. Of these, 19 children were diagnosed with severe mental retardation and were excluded, as were 342 children who denied research authorization for the use of their medical records. An additional 37 children were excluded because the mother denied research authorization for use of their medical records or the charts were missing. Therefore, the cohort consisted of 5,320 children. Of these, 497 children were delivered *via* CD, 193 with general anesthesia and 304 with regional anesthesia. Most general anesthetics included sodium thiopental, nitrous oxide, and potent inhalational anesthetics (table 1).

Several demographic and birth characteristics differed among groups (tables 2 and 3). Notably, children delivered *via* CD under general anesthesia had lower mean birth weight, lower gestational age, and lower APGAR scores at 1 and 5 min, were more likely to weigh less than 2,500 g, and were more likely to have a gestational

Table 1. Anesthetic Agents Used for Cesarean Delivery during General Anesthesia among Children in the 1976–1982 Rochester, Minnesota Birth Cohort

	n
Intravenous agents*	
Sodium thiopental	189
Ketamine	2
Inhalational agents	
Enflurane	15
Halothane	105
Isoflurane	6
Methoxyflurane	42
Nitrous oxide	191

* Data were missing for one patient.

age less than 37 weeks (table 2). Their mothers were also more likely to experience complications of pregnancy and delivery such as hemorrhage and eclampsia/preeclampsia (table 3). For children delivered by CD, an emergency indication was more common among those whose mothers received general anesthesia (68%, n = 131) compared to CD under regional anesthesia (31%, n = 93; $P < 0.001$). Median duration of epidural analgesia/anesthesia (see Materials and Methods for definitions) was 63.5 min (interquartile range 52–82), spinal anesthesia was 21 min (interquartile range 15.5–28), and general anesthesia was 14 min (interquartile range 8–23).

A Priori *Analyses*

Within the cohort, 921 children were diagnosed with LD before age 19 yr. The cumulative incidence of LD among those who were delivered by vagina was 20.8% (95% CI 19.5–22.0%) compared with 19.4% (95% CI 13.2–25.1%) for those whose mothers received a general

anesthesia for a CD, and 15.4% (95% CI 11.0–19.7%) for those whose mothers received a regional anesthetic for CD. With proportional hazard regression, not adjusting for covariates, the incidence of LD did not differ significantly when compared across the three modes of delivery (overall $P = 0.135$). However, the CI for the hazard ratio comparing those delivered *via* CD with regional anesthesia with those delivered vaginally did not include unity (hazard ratio = 0.73, 95% CI 0.53–0.99; $P = 0.046$ for pairwise comparison of CD with regional anesthesia compared to vaginal delivery; fig. 1 and table 4), suggesting a lower risk of LD in the former. After adjusting for sex, birth weight, gestational age, exposure to anesthesia between ages 0 and 4, and maternal education (factors determined *a priori*) a similar pattern of results was observed (overall comparison across the three delivery modes $P = 0.050$; hazard ratio = 0.64, 95% CI 0.44–0.92; $P = 0.017$ for pairwise comparison of CD under regional anesthesia compared to vaginal delivery).

Post Hoc *Analyses*

The analysis was repeated after eliminating children who were exposed to anesthesia after birth and before age 4 yr, with similar findings (overall comparison across the three delivery modes $P = 0.076$; hazard ratio = 0.63, 95% CI 0.42–0.94; $P = 0.024$ for pairwise comparison of CD under regional anesthesia compared to vaginal delivery). A similar pattern was also observed after eliminating all children who were delivered by emergency CD (overall comparison across the three delivery modes $P = 0.171$; hazard ratio = 0.68, 95% CI 0.44–1.06; $P = 0.086$ for pairwise comparison of CD under regional anesthesia compared to vaginal delivery) and from a multivariable analysis that included additional covariates for other characteristics found to differ across delivery modes

Table 2. Sex and Birth Characteristics of Children in the 1976–1982 Rochester, Minnesota Birth Cohort (n = 5,320)*

| Variable	Vaginal Delivery (n = 4,823)	Cesarean Delivery with General (n = 193)	Cesarean Delivery with Regional (n = 304)	P Value
Sex				0.15
Female	2,321 (48%)	99 (51%)	131 (43%)	
Male	2,502 (52%)	94 (49%)	173 (57%)	
Number at birth				< 0.001
Single	4,752 (99%)	181 (94%)	287 (94%)	
Twin	71 (1%)	12 (6%)	17 (6%)	
Birth weight, g	3,477 ± 528.0	3,248 ± 779	3,453 ± 609	< 0.001
Birth weight				< 0.001
< 2,500 g	178 (4%)	31 (16%)	16 (5%)	
≥ 2,500 g	4,635 (96%)	162 (84%)	288 (95%)	
Gestational age, weeks	40.1 ± 2.0	39.3 ± 3.2	39.6 ± 2.2	< 0.001
Gestational age				< 0.001
< 31.9 weeks	30 (1%)	8 (4%)	3 (1%)	
32 to 36.9 weeks	241 (5%)	27 (15%)	23 (8%)	
≥ 37 weeks	4,250 (94%)	145 (81%)	264 (91%)	
APGAR score at 1 minute†	8.0 ± 1.3	6.8 ± 1.7	7.4 ± 1.8	< 0.001
APGAR score at 5 minutes†	9.2 ± 0.7	8.6 ± 1.0	8.8 ± 0.9	< 0.001

* Birth weight was missing for 10 (0.2%), and gestational age was missing for 329 (6.2%).   † Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores were only available children born in 1980–1982 (n = 1,360).

Table 3. Maternal and Paternal Characteristics, Complications of Pregnancy, and Labor among Children in the 1976–1982 Rochester, Minnesota Birth Cohort (n = 5,320)*

Variable	Vaginal Delivery (n = 4,823)	Cesarean Delivery with General (n = 193)	Cesarean Delivery with Regional (n = 304)	P Value
Age of mom at birth, yr	26.4 ± 4.7	26.7 ± 5.2	27.8 ± 4.8	< 0.001
Mother's education				0.003
Some high school	292 (7%)	10 (6%)	10 (4%)	
High school graduate	1,511 (34%)	74 (43%)	75 (28%)	
Any college education	2,609 (59%)	90 (52%)	185 (69%)	
Father's education				0.007
Some high school	192 (5%)	11 (7%)	3 (1%)	
High school graduate	1,282 (31%)	49 (30%)	66 (25%)	
Any college education	2685 (65%)	101 (63%)	192 (74%)	
Complications of pregnancy				
Hemorrhage	22 (0%)	20 (10%)	6 (2%)	< 0.001
Premature rupture of membranes	16 (0%)	0 (0%)	0 (0%)	0.44
Abnormalities of placenta	13 (0%)	3 (2%)	4 (1%)	< 0.001
Preeclampsia/eclampsia	108 (2%)	22 (11%)	11 (4%)	< 0.001
Urgency status				< 0.001
Elective		62 (32%)	211 (69%)	
Emergency		131 (68%)	93 (31%)	
Induction of labor				< 0.001
None	3,734 (77%)	152 (79%)	263 (87%)	
Method not indicated	50 (1%)	2 (1%)	2 (1%)	
Amniotomy or rupture of membrane	85 (2%)	0 (0%)	0 (0%)	
Drug induction	792 (16%)	37 (19%)	35 (12%)	
Amniotomy plus drug induction	132 (3%)	1 (1%)	4 (1%)	
Other methods	30 (1%)	1 (1%)	0 (0%)	
Complications of labor and delivery				
Hemorrhage	23 (0%)	13 (7%)	1 (0%)	< 0.001
Fetopelvic disproportion	45 (1%)	26 (13%)	32 (11%)	< 0.001
Dystocic position of fetus	328 (7%)	49 (25%)	82 (27%)	< 0.001
Prolonged labor of other origin	383 (8%)	32 (17%)	37 (12%)	< 0.001
Umbilical cord complication	48 (1%)	5 (3%)	9 (3%)	0.001
Birth trauma	25 (1%)	1 (1%)	1 (0%)	0.90
Intrauterine hypoxia	2 (0%)	0 (0%)	0 (0%)	0.90

* Mother's education was missing for 464 (8.7%), and father's education was missing for 739 (13.9%).

(overall comparison across the three delivery modes P = 0.152; hazard ratio = 0.68, 95% CI 0.46 to 1.00; P = 0.052 for pairwise comparison of CD under regional anesthesia compared to vaginal delivery).
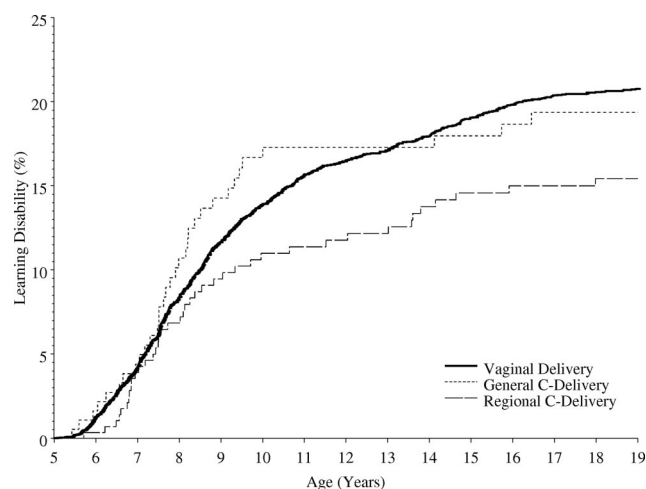
Fig. 1. Cumulative percentage of learning disabilities diagnosis (Kaplan-Meier estimates) shown separately for those that had vaginal delivery and *via* Cesarean delivery under general or regional anesthesia in the 1976–1982 Rochester, Minnesota birth cohort.

Discussion

The main finding of this study is that children exposed to general or regional anesthesia for CD are not more likely to develop LD compared to children delivered vaginally. An unexpected finding of this study was evidence suggesting that the risk of LD was lower in children delivered *via* CD under regional anesthesia compared with children delivered vaginally.

The potential long-term effects of anesthesia on central nervous system structure and function, especially exposure at the extremes of age, have attracted considerable recent interest on the basis of *in vitro* and animal data showing that these drugs can cause apoptosis and other degenerative changes when applied to the young (or aging) brain.[13–19] We recently published the first evidence that repeated, but not single, exposure to anesthesia and surgery in children (before age 4 yrs) is associated with an increased risk of LD by using a population-based birth cohort in Olmsted County, Minnesota.[22] This birth cohort provides several unique advantages. All these children resided in the same community, all attended public and private schools, and all received health care at one of two local facilities (Mayo Clinic and

Table 4. Effects of Mode of Delivery and Anesthetic Exposure on Risk for Developing Learning Disabilities among Children in the 1976–1982 Rochester, Minnesota Birth Cohort*

	Unadjusted			Adjusted		
	HR	95% CI	P Value	HR	95% CI	P Value
Type of delivery			0.135			0.050
Vaginal	1.00			1.00		
CD (general anesthetic)	0.97	0.68–1.37		0.88	0.59–1.31	
CD (regional anesthetic)	0.73	0.53–0.99		0.64	0.44–0.92	
Gestational age						0.314
≥ 37 weeks				1.00		
32–36 weeks				0.86	0.62–1.20	
≤ 31 weeks				0.50	0.18–1.39	
Birth weight						0.269
≥ 2500 g				1.00		
< 2500 g				1.24	0.85–1.81	
Gender						< 0.001
Female				1.00		
Male				1.66	1.44–1.93	
Anesthesia exposure < 4 yrs†						0.008
0				1.00		
1				1.04	0.82–1.34	
2 or more				1.80	1.25–2.61	
Mother's education						< 0.001
Any college education				1.00		
High school graduate				1.64	1.41–1.91	
Some high school				3.09	2.46–3.89	

* Analyses were performed using proportional hazards regression, with findings presented as hazard ratio (HR) and corresponding 95% confidence interval (CI). Mode of delivery was available for all 5,320 individuals (unadjusted analysis). Due to missing covariate information, only 4,553 individuals were included in the adjusted analysis. † Number of exposures to anesthesia under the age of 4 yr (excluding exposure during labor and delivery).

CD = Cesarean delivery.

Olmsted County Medical Center), making it possible to review all available medical and educational records. These records, combined with rigorous definitions of LD,[25,26,32] made it possible to perform a population assessment of a clinically significant outcome that plausibly reflects the learning abnormalities observed in animal model after anesthesia.[13–19] Availability of nearly complete data from birth records made it possible to control for several important confounders known to affect the frequency of LD (sex, gestational age, birth weight, repeated exposure to anesthesia, and maternal education).

It is clear that the newborn may be at least transiently affected by anesthetics and analgesics administered during labor and delivery.[3,33–35] For example, the use of opioids for labor analgesia is associated with neonatal respiratory depression. In contrast to these short-term effects, there are only a few studies that attempt to assess the effect of mode of delivery on long-term child neurodevelopment. The Collaborative Perinatal Project[8] found that school achievement of 26,760 children, measured by standardized test of intelligence, did not differ between children delivered vaginally or *via* CD; however, this study did not examine the method used to provide anesthesia and used standardized group rather than individually administered tests of achievement. McGee *et al.*[9] compared "normal spontaneous delivery" *versus* "other than normal spontaneous delivery" (rotation, CD,

forceps, etc.) and found no effect on behavioral maturation at age 7 yrs as defined by standardized test of intelligence and other behavioral domains. McBride *et al.*[11] did not find any deleterious effect of mode of delivery (various types of forceps delivery *vs.* elective CD *vs.* spontaneous delivery) on developmental outcomes in children at age 5 yrs (compared by standardized IQ tests). Pasamanick *et al.*[10] found no difference in behavioral disorders between children delivered by "serious operative procedures" (CD, forceps, breech extraction, internal version, and extraction) compared to children delivered vaginally, although there were only a few CD in this study.[10] In all of these studies, the type of anesthesia used for CD was not reported.

There are very few animal studies that could provide insight into potential effects of obstetric anesthesia and analgesia on neonatal outcome. Rizzi *et al.*[19] found that 4 h of maternal exposure to isoflurane caused neuroapoptosis of the fetal guinea pig brain; however, this is a much longer exposure than during typical CD. Therefore, this may not be applicable model to a term human fetus. Golub *et al.*[36] examined the role of epidural anesthesia administered to primates on long-term infant behavior. Monkeys at term received either epidural bupivacaine or saline during induced vaginal delivery. At 1 yr, infant monkeys born of mothers receiving bupivacaine did not exhibit abnormalities or specific cognitive deficits in learning, memory, or attention, although some

earlier phases of behavioral development were affected.[36] Again, this study likely has limited applicability to our findings, other than suggesting a lack of deleterious long-term effects attributable to absorbed bupivacaine on the term fetus.

The fact that CD in our study was not associated with an increased risk of LD is consistent with these findings, and it is reassuring regarding any concern that the brief exposure to general anesthesia during CD could adversely affect learning. This lack of adverse effect occurred despite the presence of several potential risk factors in the CD deliveries with general anesthesia, including an increased frequency of prematurity and emergent delivery. What was not expected was the apparent decrease in risk associated with regional anesthesia for CD, which persisted after adjustment for known risk factors for LD.

Given the lack of relevant animal data to suggest a potential mechanism, we can only speculate. One potential factor that could be relevant is the stress response to labor and delivery. The perinatal period is critical to subsequent behavioral development and stress responses during that period play a significant factor in developmental outcomes.[37] Perinatal stress has been associated with synaptic loss resulting in learning abnormalities in animals[38] and maladaptive responses in humans and animals.[37,39-44] Labor and vaginal delivery in humans is associated with a significant increase in the levels of stress hormones such as epinephrine, norepinephrine, and cortisol.[40] Evidence is accumulating that exposure of the developing human brain to stress can produce lasting organizational changes that can lead to a variety of abnormal behaviors in later life (hyperactivity, hyperreactivity, decreased cognition, etc).[37] For example, an increased frequency of attention deficit hyperactivity disorder has been linked to the presence of peripartum stressors.[45] Anesthesia and analgesia during labor and delivery may reduce the level of stress. CD performed under epidural anesthesia decreases stress hormone levels in both the mother and fetus compared with vaginal delivery (both with and without labor epidural analgesia),[40,46] and it significantly decreases these levels compared with elective CD performed under general anesthesia.[47] It is not known whether the stress response accompanying vaginal delivery and CD with general anesthesia is of sufficient intensity and duration to affect subsequent neurodegeneration. If so, CD with regional anesthesia could inhibit the stress response sufficiently to potentially affect long-term outcome. We emphasize that this is a speculation that depends on several assumptions; this result should be regarded as generating hypotheses that can be tested in future studies.

Limitations

Our study has several limitations beyond those inherent in any study that employs a retrospective approach. We have previously argued that LD is a relevant outcome to search for evidence of anesthetic-induced neurodegeneration in population-based studies,[22] but we cannot exclude that injury may occur that does not result in LD or, conversely, that LD is not a consequence of any injury that may occur. Study of the relationship between perinatal factors such as delivery mode and subsequent behavioral development is complicated by the multiple confounding factors that can affect development. For example, Pasamanick and Knobloch[48] introduced a theory of the continuum of reproductive casualty to describe the spectrum of factors that can affect fetal and neonatal brain and cause behavioral abnormalities, including perinatal factors (such as complications of pregnancy) and various socioeconomic and environmental conditions during early childhood. Although we included adjustor variables in our *a priori* analysis for those factors known to affect the risk of LD (such as prematurity), we cannot exclude the possibility that other unrecognized factors may be responsible for the observed differences, such as those related to the decision to perform elective CD with regional anesthesia. Data regarding many characteristics of those experiencing vaginal deliveries was not abstracted, such as the use of labor epidural analgesia, which could be relevant. We did perform additional *post hoc* adjusted analyses, which included covariates for several peripartum characteristics found to differ significantly across groups. The findings from these models remained consistent (albeit with varying levels of statistical significance) and revealed comparable point estimates, suggesting a decreased likelihood of LD with CD under regional anesthesia *versus* vaginal delivery. However, it should be noted that all of these models were performed using the same dataset; therefore, the consistency in results should not be interpreted as an independent validation of the study findings.

This birth cohort has been the subject of previously published reports describing the epidemiology of LD, and exhaustive efforts were made as a part of this work to obtain as complete case ascertainment of LD as possible, as previously discussed.[25,26,28] Information on all children in this cohort was gathered from three independent sources: school folders, medical records, and records at a local tutoring/reading center. All school records were examined page by page for each of the 5,718 children for even subtle signs of learning or behavior problems, including any kind of notation indicating that teachers, parents, or anyone else had concerns about the child's school or learning performance. Some of the children in the cohort might have had learning or performance difficulties that were not recorded in the

school record; therefore, the medical and Reading Center/Dyslexia Institute of Minnesota records of all children were searched for any indication of concerns about a learning or behavior problem. Comparison of our cumulative rates of reading disability is consistent with published prevalence estimates by Shaywitz *et al.*,[49] suggesting the validity of our ascertainment methods.

Another limitation relates to the birth cohort study design, which can be biased due to migration from the community. However, in a previously published analysis of this cohort, comparison of children who left the community before age 5 and those who stayed after age 5 indicated that the children included in the study are representative of the entire birth cohort.[24] Also, this cohort was almost exclusively composed of Caucasian children, which may limit the generalizability of these results to other populations.[29] The incidence of CD in this series is comparable with other reports from this era[50,51] but considerably less than in contemporary practice,[52] and it is not known how these potential changes in the indications for CD may affect these results. Finally, although potent inhalational agents were used in many of the mothers receiving general anesthesia for CD, the most commonly used agents (halothane and methoxyflurane) are no longer in widespread clinical use.

Summary

Children exposed to general or regional anesthesia during CD are not more likely to develop LD compared to children delivered vaginally, suggesting that brief perinatal exposure to anesthetic drugs does not adversely affect long-term neurodevelopmental outcomes. Rather, the risk of LD appears to be lower in children delivered by CD whose mothers received regional anesthesia. We caution that such a result from an observational study can only be viewed as hypothesis-generating and needs to be confirmed (or refuted), especially considering the possibility that undergoing CD with regional analgesia is simply a marker for unidentified confounders that may explain the differential risk for LD between groups. We propose the hypothesis that regional anesthesia for CD attenuates the neonatal stress response to vaginal delivery that in turn has significant effects on later neural development. Future studies are needed to evaluate this hypothesis.

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