Published in final edited form as:
Anesth Analg. 2011 June ; 112(6): 1424–1431. doi:10.1213/ANE.0b013e3181f2ecdd.

Neuraxial Labor Analgesia for Vaginal Delivery and Its Effects on Childhood Learning Disabilities

Randall P. Flick, M.D., M.P.H.[*,1], **KunMoo Lee, M.D.**[§,1,¥], **Ryan E. Hofer, B.A.**[¶,5], **Charles W. Beinborn, SRNA**[‖,2], **Ellen M. Hambel, SRNA**[‖,2], **Melissa K. Klein, SRNA**[‖,2], **Paul W. Gunn, M.D.**[§,1], **Robert T. Wilder, M.D., Ph.D.**[†,1], **Slavica K. Katusic, M.D.**[†,3], **Darrell R. Schroeder, M.S.**[*,4], **David O. Warner, M.D.**[‡,1], and **Juraj Sprung, M.D., Ph.D.**[‡,1]

[1]Department of Anesthesiology College of Medicine, Mayo Clinic, Rochester, MN 55905

[2]Nurse Anesthesia Program, Department of Health Sciences College of Medicine, Mayo Clinic, Rochester, MN 55905

[3]Department of Health Sciences Research, Division of Epidemiology College of Medicine, Mayo Clinic, Rochester, MN 55905

[4]Department of Health Sciences Research, Division of Biostatistics, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN 55905

[5]Mayo Clinic Mayo Medical School College of Medicine, Mayo Clinic, Rochester, MN 55905

Abstract

Background—In prior work, children born to mothers who received neuraxial anesthesia for cesarean delivery had a lower incidence of subsequent learning disabilities compared with vaginal delivery. The authors speculated that neuraxial anesthesia may reduce stress responses to delivery, which could affect subsequent neurodevelopmental outcomes. To further explore this possibility, we examined the association between the use of neuraxial labor analgesia and development of childhood learning disabilities in a population-based birth cohort of children delivered vaginally.

Methods—The educational and medical records of all children born to mothers residing in five townships of Olmsted County, MN from 1976-1982 and remaining in the community at age 5 years were reviewed to identify those with learning disabilities. Cox proportional hazards regression was used to compare the incidence of learning disabilities between children delivered vaginally with and without neuraxial labor analgesia, including analyses adjusted for factors of either potential clinical relevance or that differed between the two groups in univariate analysis.

Results—Of the study cohort, 4684 mothers delivered children vaginally, with 1495 receiving neuraxial labor analgesia**.** The presence of childhood learning disabilities in the cohort was not associated with use of labor neuraxial analgesia (adjusted hazard ratio 1.05, 95% C.I. 0.85 to 1.31, P = 0.63).

Corresponding Author: Juraj Sprung, M.D., Ph.D., Department of Anesthesiology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Phone: (507) 255-3298 / Fax: (507) 255-6463; sprung.juraj@mayo.edu**.** .
[*]Assistant Professor
[†]Associate Professor
[‡]Professor
[§]Resident/Fellow
[‖]Student in Nurse Anesthesia Program
[¶]Medical Student
[¥]Visiting from the Department of Anesthesiology, Paik Hospital, College of Medicine, Inje University, Busan, South Korea

No conflicts of interest

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Conclusion—The use of neuraxial analgesia during labor and vaginal delivery was not independently associated with learning disabilities diagnosed before age 19 years. Future studies are needed to evaluate potential mechanisms of the previous finding indicating that the incidence of learning disabilities is lower in children born to mothers *via* cesarean delivery under neuraxial anesthesia compared to vaginal delivery.

Introduction

How perinatal events affect short- and long-term neonatal outcomes is a topic of long-standing interest. It has been reported that maternal opioid administration during labor and anesthetic management during delivery may transiently affect neonatal behavior; however, most of these reports were not well controlled for confounding variables.[1-4] The potential long-term effects of labor anesthesia and analgesia on human development are unknown.

Learning disabilities (LD) are problems with one or more of the basic psychological processes involved in understanding or in using spoken or written language, which may manifest itself in an imperfect ability to listen, think, speak, read, write, spell or do mathematical calculations. We recently reported that the incidence of LD diagnosed before age 19 years was lower in a population-based birth cohort of children delivered of mothers who received neuraxial anesthesia for cesarean delivery compared to both children delivered vaginally and children delivered *via* cesarean delivery with general anesthesia.[5] The potential mechanism for this surprising finding is not known, but we speculated that it could relate to differences in maternal and fetal stress among the delivery techniques, based the on suggestion that the stress of labor may cause long-lasting behavioral effects in children.[6] Studies in animal models also find an association between peripartum stress and long-term behavioral outcomes.[7-10] Elective cesarean delivery more effectively attenuates fetal and maternal hormonal stress responses compared with vaginal delivery.[11] In our prior study, the use of neuraxial anesthesia for cesarean delivery (most of which were scheduled in nonlaboring women) could have suppressed the stress responses and improved long-term neurobehavioral outcomes.[5] However, this was an observational study involving many factors that were not controlled and thus is best interpreted as hypothesis-generating. Although prolonged antepartum maternal stress has been linked to adverse neurobehavioral outcomes in children,[12,13] it is less certain whether a single stress episode, such as one that occurs during labor and delivery, could contribute to long-lasting neurobehavioral outcomes.[6,14,15] In particular, whether peripartum stress plays a role in the development of LD is not known.

Epidural analgesia administered for labor decreases markers of both maternal and fetal stress such as cortisol.[11,14,16] If fetal stress played a role in the observed differences in the incidence of LD among delivery methods in our previous study, we speculated that neuraxial labor analgesia might also affect long-term outcomes after vaginal delivery. The purpose of this study was to test the hypothesis that the incidence of LD is lower in children whose mothers received neuraxial labor analgesia for vaginal delivery compared with those whose mothers did not.

Methods

The Mayo Clinic and Olmsted Medical Center IRBs (both located in Rochester, Minnesota) approved this study. In compliance with Minnesota law (Minnesota Statute 144.335 [Subd. 3a. (d)]), only data from patients who provided research authorization for the use of their medical records were included in the study. A birth cohort of children born in Rochester, MN identified in prior work by the authors [17-23] formed the basis of the present study, and we have previously summarized the methods used to collect these data.[5,24] Thus the cohort used for this study represents a subset of the cohort analyzed previously.[5,22,24,25]

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 comprising the Rochester public school system were identified through computerized birth certificate information (N = 8548). Vital status (still living in Rochester, moved, or deceased) was determined for each member of the birth cohort during the 1995–1996 school year through the Rochester Epidemiology Project.[26] Children who left Olmstead County before age 5 years (i.e., moved or died, N = 2830) were not included in the final study cohort.[17] Through the Rochester Epidemiology Project, all diagnoses and surgical procedures recorded at all Rochester medical facilities are indexed for automated retrieval. Through a contractual research agreement, all public (19 primary, 3 junior high, 3 high schools) and nonpublic (12 primary, 10 junior high, 4 high schools) 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. Thus, the overall strategy for identifying all children in this cohort with LD used multiple sources of information that provided 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 prior reports examining the epidemiology of LD.[17,18,20-23] 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 1510 children (26% of the birth cohort, n = 5,718). 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 formulas. In each of the following formulas, X is equal to the study subject's IQ score, and Y represents the predicted standard score from the achievement test. 1) The regression formula–Minnesota ($Y<17.40+ 0.62X$) is issued by the Minnesota Department of Education.[27] 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. 2) 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, aptitude and measures of test achievement that were believed to be important varied by grade as follows: (1) kindergarten-3rd grade, 15 or more standard score points difference, with achievement lower; (2) 4th-6 th grade, 19 or more points difference, achievement lower; and (3) 7th -12 th grade, 23 or more points difference. 3) Finally, the low-achievement method [$X\geq80$ (aptitude) and $Y\leq90$ (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.[28] Children meeting the criteria before age 19 years for at least one of the three LD (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. Children with moderate/severe mental retardation (IQ < 50) were excluded from the cohort.

Other variables

We identified all children within the cohort who were delivered vaginally. The following information was abstracted from the anesthesia records: use of neuraxial analgesia during labor and delivery (epidural or spinal), other regional blocks used during labor (e.g., pudendal and paracervical nerve blocks), and the use of opioids, benzodiazepines, and any adjuvant inhaled anesthetics. Age and education [<12 years (some high school education), 12 years (high school graduate), and >12 years (any post-secondary education)] for both mother and father were recorded from school records and birth certificates. Pregnancy complications were abstracted from the birth certificates, including preeclampsia and eclampsia, hemorrhage during pregnancy, premature rupture of membranes, and abnormalities of the placentation. Information obtained for each child included sex, gestational age at birth, birth weight, induced labor, instrumental vaginal delivery (forceps or vacuum extraction), complications of labor and delivery (hemorrhage during delivery, feto-pelvic disproportion, dystocia [abnormal fetal position that slowed labor progression), prolonged labor, umbilical cord compression, birth trauma and intrauterine hypoxia], and Apgar scores at 5 min (these data were gathered from the labor and delivery “check list” entered by the delivering obstetrician). Finally, we reviewed requirements for neonatal resuscitation immediately after delivery and admission to the neonatal intensive care unit.

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 3 standard formulas for determining the presence of reading, written language or math LDs. The primary risk factor of interest for this investigation was the association between LD and exposure to neuraxial labor analgesia. Analyses were performed to compare demographic, pregnancy and delivery complications, and parental characteristics across 2 delivery analgesic regimens (no neuraxial block *vs.* neuraxial analgesia) using the Student’s two sample t-test for continuous variables and the chi-square test (or Fisher’s exact test) for categorical variables. Individuals were followed from birth until the date they first met the LD criteria using any of the 3 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 years. Proportional hazards regression was used to assess whether use of neuraxial analgesia was significantly associated with LD. Both unadjusted and adjusted analyses were performed. For the first adjusted analysis the following covariates were selected *a priori* based on previous work[17,18,22,29] and included gestational age (≤31 weeks, 32-36 weeks, ≥37 weeks), sex, birth weight (<2500 g, ≥2500 g), maternal education (some high school, high school graduate, any college), 5-min APGAR score, and number of anesthesia exposures before the age of 4 years (0, 1, 2 or more).[24] For the second adjusted analysis, in addition to factors included in the first analysis, we also included as covariates other factors that we deemed potentially relevant or were significantly ($P < 0.05$) different between the two groups in univariate analysis: use of forceps or vacuum extraction (any *vs* none), fetal presentation (cephalic *vs* all other presentations), dystocia, prolonged labor, birth trauma, inhaled analgesia during labor and delivery, supplemental regional blocks (pudendal and paracervical), systemic opioid analgesia, labor induction, neonatal resuscitation or admission to the neonatal intensive care unit after delivery, and maternal age. Proportional hazards assumptions were checked with the use of scaled Schoenfeld residuals. [30] Results were summarized using hazard ratio estimates and corresponding 95% confidence intervals. In all cases, two-tailed *P*-values less

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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 8548 children were born, and 5718 of these children still resided in the community at 5 years-of-age. Of these, 398 were excluded because of moderate/severe mental retardation (19 children) or because the parents denied research authorization (379 children). Of the 5320 children who were included in our previous report,[5] 4823 were delivered vaginally. Of these, 139 were excluded because the pertinent information from the mother's medical records regarding birth characteristics and/or neuraxial analgesia information were missing. Therefore, the present cohort consists of 4684 vaginal births (3189 births without neuraxial analgesia and 1495 with neuraxial analgesia, including 1274 epidural blocks and 221 spinal blocks).

Mothers who received neuraxial analgesia were older than those who did not; otherwise there were no differences in parent and child demographic characteristics (Table 1). The absolute rate of pregnancy complications was low, but mothers who received neuraxial analgesia were more likely to have had preeclampsia or eclampsia. The birth weights and gestational ages of the neonates were comparable between groups.

Use of neuraxial analgesia was associated with a higher frequency of cephalic presentation, induction of labor, and labor/delivery complications; the most common complication was prolonged labor (Table 2). Also, mothers who received neuraxial analgesia had an approximately four-fold higher rate of forceps- or vacuum- assisted deliveries. The median 5-min Apgar score was lower in the neuraxial analgesia group, but there was no difference in the rate of neonatal resuscitation or neonatal intensive care unit admission. Mothers who did not receive neuraxial analgesia were more likely to receive supplemental systemic opioid analgesia, paracervical and pudendal regional blocks, and inhaled anesthetics (mostly nitrous oxide or methoxyflurane) (Table 3). The percentage of children who underwent surgical procedures under the age of 4 years did not differ between those born to mothers who received neuraxial analgesia (89.3%, 8.5%, and 2.2% undergoing 0, 1, and 2 or more surgeries respectively) and those born to mothers who did not receive neuraxial analgesia (89.4%, 8.0%, and 2.6%; $P = 0.62$).

Within the cohort 818 children were diagnosed with LD before the age of 19 years. The cumulative incidence of LD at age 19 years among those who were delivered vaginally without neuraxial analgesia was 19.6 % (95% C.I. 18.1% to 21.1%) compared with 22.7% (95% C.I. 20.3% to 24.1%) for those whose mothers received an neuraxial analgesia. In the proportional hazard regression analysis, the unadjusted risk for LD was higher in children born to mothers who received neuraxial analgesia compared to those who did not (Table 4). However, after adjusting for covariates which were previously shown to be associated with LD, this risk was not significantly different between groups, nor was it different after further adjustment for additional peripartum maternal and child variables. To assess which of the additional covariates most attenuated the increased risk of LD associated with the use of neuraxial analgesia in the unadjusted analysis, a series of *post-hoc* analyses were performed. Each covariate was assessed individually by including it in a model along with neuraxial analgesia and the other covariates previously shown to be associated with LD. The largest reduction in the hazard ratio associated with neuraxial analgesia was found when "instrumented delivery" was included as an additional covariate. In the *post hoc* model which included this additional risk factor the hazard ratio for neuraxial analgesia was 1.09 (95% C.I. 0.91 to 1.31; $P = 0.35$).

Discussion

The pathogenesis of LD is poorly understood but likely involves a combination of genetic and environmental factors.[31,32] Human neurodevelopment is especially vulnerable to pharmacological and environmental insults[33,34] and the most sensitive period is between the third trimester of pregnancy to several years (3-4) after birth.[33] In animal models exposure to sedatives and anesthetics during the critical periods of rapid neural development may cause accelerated neuroapoptosis [35-39] associated with impaired learning and memory.[36,40]

In prior work we reported that exposure to anesthesia before age 4 years was a risk factor for the development of LD in children receiving multiple, but not single, anesthetics.[24] Although the lack of association between a single anesthetic exposure and LD is reassuring,[24] it is still possible that a brief exposure of the neonatal brain to anesthetic during delivery might be neurotoxic. Therefore, we subsequently examined the association between neonatal exposure to anesthesia during cesarean delivery and the development of LD.[5] Children exposed to general anesthesia during cesarean delivery were not more likely to develop LD compared to children delivered vaginally. However, an unexpected finding was that the adjusted risk of LD was lower in children delivered *via* cesarean section under neuraxial anesthesia. The potential effects of anesthetic technique used during delivery on long-term neurodevelopmental outcomes in humans are not known. A single primate study examined the effects of bupivacaine administered *via* epidural to nonlaboring rhesus monkeys at term, and found no effects on learning, memory and attention domains at 1 year-of-age.[41] We speculated that our previous finding might be explained by a reduction in the labor and delivery stress with neuraxial anesthesia.[5]

Prenatal stress in animals may induce synaptic loss causing long-term learning abnormalities in offspring.[7,8,10] Human fetal stress during pregnancy and during the peripartum period can produce lasting organizational changes which can be associated with abnormal behaviors and altered cognitive and language development.[6,13,15,42-45] For example, children with a higher intensity of perinatal stressors may have an increased rate of attention deficit hyperactivity disorder,[46] as well as altered personality and depressive disorders.[13,47] The potential role of perinatal stress on development, specifically the incidence of LD, is not known. Perinatal stresses such as vaginal delivery and neonatal circumcision can alter endocrine markers of stress responses to painful stimuli that are detectable months after delivery,[6,14,15] and for the latter, local anesthetic for circumcision may modulate this response.[15] The mechanisms responsible may involve exposure of neural tissues to corticosteroids released during stress.[48-50] For example, a prospective randomized study on premature neonates found a positive association between immediate postdelivery week-long administration of dexamethasone and worse neurologic and motor function, cognition, and school performance at age 5.[51]

Labor and delivery are associated with significant stress. As assessed by cortisol levels, the intensity of maternal and fetal stress decreases from vaginal delivery with instrumentation, to unassisted vaginal delivery, and is least with cesarean delivery.[11,14,52] Combined spinal-epidural used during labor is associated with reduced umbilical cord cortisol concentrations independent of delivery mode. [14] Epidural anesthesia for cesarean delivery significantly reduces fetal cord blood cortisol levels compared with levels in infants born vaginally.[11] We speculated that if such reductions in stress mediated the favorable effects of cesarean delivery with neuraxial anesthesia on the incidence of LD observed in our prior study,[5] then labor neuraxial analgesia might have similar beneficial effects in children delivered vaginally. However, we found that the use of neuraxial analgesia does not have a protective effect on development of LD. Rather, before adjusting for covariates, labor neuraxial analgesia was found to be associated with a small, but statistically significant, increase in the risk of LD. This risk was no longer significant after inclusion of covariates previously shown to be associated with risk for LD,[5,24] and was further reduced in an expanded multivariable model that included numerous peripartum covariates. These findings suggest that the use of neuraxial analgesia *per se* likely does not have a significant impact on the development of LD, but rather, may be associated with other factors such as the need for instrumented delivery, that could affect the incidence of LD. Indeed, postpartum arterial cord cortisol levels are more elevated in neonates whose deliveries are assisted.[14]

Several factors could explain the lack of effect of neuraxial analgesia on incidence of LD. Although neuraxial analgesia can attenuate some measures of maternal stress responses,[11,16] its effects on neonatal stress responses are less clear. The effects of epidural labor analgesia on neonatal cortisol levels is not well-studied, with one small study finding no effect[11] and another larger study finding a decrease in cortisol levels.[14] We have no data regarding the quality of analgesia achieved by the neuraxial analgesia, and other analgesics were used in both groups. In addition, neuraxial analgesia does not prevent psychological stress associated with delivery, which may play a significant role in increasing stress hormones regardless of the level of pain control.[53] Thus, it is possible that there was little or no difference in the stress experienced by the neonates in the two groups. Also, it is possible that the high frequency of assisted deliveries in the neuraxial group may have increased fetal stress,[11,14,52] counterbalancing any beneficial stress-reducing effects of neuraxial analgesia that the mother might experience. Finally, it is possible that short but extreme neonatal stress during delivery plays no role in development of LD and cannot explain our prior results observed with neuraxial anesthesia during cesarean delivery.[5]

We have extensively discussed the limitations with both the birth cohort and this type of analysis.[5,24] Most importantly, in our multivariable analysis we adjusted for risk factors known to be associated with the risk of LD and covariates for several peripartum characteristics found to differ significantly between groups, and we found no significant association between the use of labor neuraxial analgesia and the incidence of childhood LD. However, we cannot exclude the possibility that other confounding variables which were not available in the present study could have affected our findings. Another limitation is that techniques used to provide neuraxial analgesia for labor and delivery during the study period differ from contemporary practice. These women received 0.25% bupivacaine as intermittent bolus only, compared with current practices which often use continuous infusions of low-dose local anesthetic solutions, frequently with opioids and combined spinal-epidural techniques. Finally, with 818 events observed in a total sample-size of 4,684 of whom 1,495 (32%) received neuraxial analgesia, and 3,189 (68%) who did not receive neuraxial analgesia, our study provided statistical power (two-tailed, alpha=0.05) of more than 80% to detect a hazard ratio, of 1.25. However, based on the upper limit of the 95% confidence interval for the hazard ratio we cannot exclude the possibility of smaller but significant effect sizes.

In conclusion, the maternal use of neuraxial labor analgesia during labor and vaginal delivery in this population was not an independent risk factor for the subsequent development of childhood LD. Future studies are needed to evaluate potential mechanisms/ explanation of our previous findings that the incidence of LD is lower in children born to mothers *via* cesarean under neuraxial anesthesia compared to vaginal delivery.

Acknowledgments

We acknowledge the late Leonard T. Kurland, M.D. (Epidemiologist, Mayo Clinic, Rochester, Minnesota) for his vision in initiating the Rochester Epidemiology Project. We also thank Ms. Candice Klein, B.S. (Clinical Research Coordinator, Mayo Clinic, Rochester, Minnesota), Ms. Peg Farrell, R.N. (Data abstractor) and other members of the Learning Disability team for data collection; Independent School District #535; and the Reading Center/Dyslexia

Institute of Minnesota for their collaboration. We would also like to thank data analyst, Miss. Ashley Nadeau, B.A. (Statistical Program Analyst, Mayo Clinic Rochester, Minnesota). Finally we would like to thank the Anesthesia Clinical Research Unit, Mayo Clinic, Rochester, Minnesota (Cindy Medcalfe, R.N., Nora Feher, R.N., Melissa Passe, R.N., and Shonie Beunvenida, R.T.-research coordinator) for help in abstracting the data.

Funding Sources: Support was provided by the Department of Anesthesiology, College of Medicine, Mayo Clinic (Rochester, Minnesota, USA) and from research grants HD29745 and AR30582 from the National Institutes of Health (Bethesda, Maryland, USA).

References

1. Brackbill Y, Kane J, Manniello RL, Abramson D. Obstetric meperidine usage and assessment of neonatal status. Anesthesiology. 1974; 40:116–20. [PubMed: 4812708]
2. Scanlon JW, Brown WU Jr. Weiss JB, Alper MH. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology. 1974; 40:121–8. [PubMed: 4812709]
3. Abboud TK, Nagappala S, Murakawa K, David S, Haroutunian S, Zakarian M, Yanagi T, Sheikh-Ol-Eslam A. Comparison of the effects of general and regional anesthesia for cesarean section on neonatal neurologic and adaptive capacity scores. Anesth Analg. 1985; 64:996–1000. [PubMed: 4037398]
4. Mahajan J, Mahajan RP, Singh MM, Anand NK. Anaesthetic technique for elective caesarean section and neurobehavioural status of newborns. Int J Obstet Anesth. 1993; 2:89–93. [PubMed: 15636857]
5. Sprung J, Flick RP, Wilder RT, Katusic SK, Pike TL, Dingli M, Gleich SJ, Schroeder DR, Barbaresi WJ, Hanson AC, Warner DO. Anesthesia for cesarean delivery and learning disabilities in a population-based birth cohort. Anesthesiology. 2009; 111:302–10. [PubMed: 19602960]
6. Taylor A, Fisk NM, Glover V. Mode of delivery and subsequent stress response (Research Letter). Lancet. 2000; 355:120. [PubMed: 10675176]
7. Hayashi A, Nagaoka M, Yamada K, Ichitani Y, Miake Y, Okado N. Maternal stress induces synaptic loss and developmental disabilities of offspring. Int J Dev Neurosci. 1998; 16:209–16. [PubMed: 9785117]
8. Kapoor A, Matthews SG. Short periods of prenatal stress affect growth, behaviour and hypothalamo-pituitary-adrenal axis activity in male guinea pig offspring. J Physiol. 2005; 566:967–77. [PubMed: 15932885]
9. Schneider ML, Roughton EC, Koehler AJ, Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. Child Dev. 1999; 70:263–74. [PubMed: 10218255]
10. Griffin WC 3rd, Skinner HD, Salm AK, Birkle DL. Mild prenatal stress in rats is associated with enhanced conditioned fear. Physiol Behav. 2003; 79:209–15. [PubMed: 12834792]
11. Vogl SE, Worda C, Egarter C, Bieglmayer C, Szekeres T, Huber J, Husslein P. Mode of delivery is associated with maternal and fetal endocrine stress response. BJOG. 2006; 113:441–5. [PubMed: 16489937]
12. Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. Neurosci Biobehav Rev. 2005; 29:237–58. [PubMed: 15811496]
13. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav Immun. 2005; 19:296–308. [PubMed: 15944068]
14. Miller NM, Fisk NM, Modi N, Glover V. Stress responses at birth: determinants of cord arterial cortisol and links with cortisol response in infancy. BJOG. 2005; 112:921–6. [PubMed: 15957993]
15. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet. 1997; 349:599–603. [PubMed: 9057731]
16. Abboud TK, Sarkis F, Hung TT, Khoo SS, Varakian L, Henriksen E, Noueihed R, Goebelsmann U. Effects of epidural anesthesia during labor on maternal plasma beta-endorphin levels. Anesthesiology. 1983; 59:1–5. [PubMed: 6305238]
17. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Potential influence of migration bias in birth cohort studies. Mayo Clin Proc. 1998; 73:1053–61. [PubMed: 9818038]

18. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Incidence of reading disability in a population-based birth cohort, 1976-1982, Rochester, Minn. Mayo Clin Proc. 2001; 76:1081–92. [PubMed: 11702896]
19. Katusic SK, Colligan RC, Beard CM, O'Fallon WM, Bergstralh EJ, Jacobsen SJ, Kurland LT. Mental retardation in a birth cohort, 1976-1980, Rochester, Minnesota. Amer J Ment Retard. 1996; 100:335–44. [PubMed: 8718989]
20. Barbaresi W, Katusic S, Colligan R, Weaver A, Pankratz V, Mrazek D, Jacobsen S. How common is attention-deficit/hyperactivity disorder? Towards resolution of the controversy: results from a population-based study. Acta Paediatr Suppl. 2004; 93:55–9. [PubMed: 15176722]
21. Barbaresi WJ, Katusic SK, Colligan RC, Pankratz VS, Weaver AL, Weber KJ, Mrazek DA, Jacobsen SJ. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. Arch Pediatr Adolesc Med. 2002; 156:217–24. [PubMed: 11876664]
22. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Math learning disorder: incidence in a population-based birth cohort, 1976-82, Rochester, Minn. Ambulatory Pediatrics. 2005; 5:281–9. [PubMed: 16167851]
23. Katusic SK, Colligan RC, Weaver AL, Barbaresi WJ. The forgotten learning disability: epidemiology of written-language disorder in a population-based birth cohort (1976-1982), Rochester, Minnesota. Pediatrics. 2009; 123:1306–13. [PubMed: 19403496]
24. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009; 110:796–804. [PubMed: 19293700]
25. St Sauver JL, Katusic SK, Barbaresi WJ, Colligan RC, Jacobsen SJ. Boy/girl differences in risk for reading disability: potential clues? Amer J Epidemiol. 2001; 154:787–94. [PubMed: 11682360]
26. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc. 1996; 71:266–74. [PubMed: 8594285]
27. SLD Companion Manual. Revision ed. Minnesota Educational Series; Roseville: 1998.
28. Fletcher J, Shaywitz S, Shankweiler D, Katz L, Liberman I, Stuebing K, Francis D, Fowler A, Shaywitz B. Cognitive profiles of reading disability: comparisons of discrepancy and low achievement definitions. J Educ Psychol. 1994; 86:6–23.
29. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Case definition in epidemiologic studies of AD/HD. Ann Epidemiol. 2005; 15:430–7. [PubMed: 15967390]
30. Therneau, TM.; Grambsch, PM. Modeling survival data: extending the cox model. Springer-Verlag; New York: 2000.
31. McGrath LM, Pennington BF, Willcutt EG, Boada R, Shriberg LD, Smith SD. Gene x Environment interactions in speech sound disorder predict language and preliteracy outcomes. Dev Psychopathol. 2007; 19:1047–72. [PubMed: 17931434]
32. Pennington BF, McGrath LM, Rosenberg J, Barnard H, Smith SD, Willcutt EG, Friend A, Defries JC, Olson RK. Gene X environment interactions in reading disability and attention-deficit/hyperactivity disorder. Dev Psychol. 2009; 45:77–89. [PubMed: 19209992]
33. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000; 108(Suppl 3):511–33. [PubMed: 10852851]
34. Middaugh LD, Dow-Edwards D, Li AA, Sandler JD, Seed J, Sheets LP, Shuey DL, Slikker W Jr. Weisenburger WP, Wise LD, Selwyn MR. Neurobehavioral assessment: a survey of use and value in safety assessment studies. Toxicol Sci. 2003; 76:250–61. [PubMed: 12915715]
35. Olney JW, Young C, Wozniak DF, Ikonomidou C, Jevtovic-Todorovic V. Anesthesia-induced developmental neuroapoptosis. Does it happen in humans? Anesthesiology. 2004; 101:273–5. [PubMed: 15277906]
36. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003; 23:876–82. [PubMed: 12574416]

37. Slikker W Jr. Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG, Wang C. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci. 2007; 98:145–58. [PubMed: 17426105]
38. Cattano D, Young C, Straiko MM, Olney JW. Subanesthetic doses of propofol induce neuroapoptosis in the infant mouse brain. Anesth Analg. 2008; 106:1712–4. [PubMed: 18499599]
39. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vockler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999; 283:70–4. [PubMed: 9872743]
40. Fredriksson A, Archer T, Alm H, Gordh T, Eriksson P. Neurofunctional deficits and potentiated apoptosis by neonatal NMDA antagonist administration. Behav Brain Res. 2004; 153:367–76. [PubMed: 15265631]
41. Golub MS, Germann SL. Perinatal bupivacaine and infant behavior in rhesus monkeys. Neurotoxicol Teratol. 1998; 20:29–41. [PubMed: 9511167]
42. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. Horm Res. 2003; 59:161–79. [PubMed: 12649570]
43. King S, Laplante DP. The effects of prenatal maternal stress on children's cognitive development: Project Ice Storm. Stress. 2005; 8:35–45. [PubMed: 16019596]
44. O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. Br J Psychiatry. 2002; 180:502–8. [PubMed: 12042228]
45. Laplante DP, Barr RG, Brunet A, du Fort G Galbaud, Meaney ML, Saucier JF, Zelazo PR, King S. Stress during pregnancy affects general intellectual and language functioning in human toddlers. Pediatr Res. 2004; 56:400–10. [PubMed: 15240860]
46. Zappitelli M, Pinto T, Grizenko N. Pre-, peri-, and postnatal trauma in subjects with attention-deficit hyperactivity disorder. Can J Psychiatry. 2001; 46:542–8. [PubMed: 11526811]
47. Checkley S. The neuroendocrinology of depression and chronic stress. Br Med Bull. 1996; 52:597–617. [PubMed: 8949260]
48. Schneider ML, Coe CL, Lubach GR. Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the infant primate. Dev Psychobiol. 1992; 25:427–39. [PubMed: 1336466]
49. Noguchi KK, Walls KC, Wozniak DF, Olney JW, Roth KA, Farber NB. Acute neonatal glucocorticoid exposure produces selective and rapid cerebellar neural progenitor cell apoptotic death. Cell Death Differ. 2008; 15:1582–92. [PubMed: 18600230]
50. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Dev Neurosci. 2009; 31:285–92. [PubMed: 19546565]
51. Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH, Tsai CH. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med. 2004; 350:1304–13. [PubMed: 15044641]
52. Gitau R, Menson E, Pickles V, Fisk NM, Glover V, MacLachlan N. Umbilical cortisol levels as an indicator of the fetal stress response to assisted vaginal delivery. Eur J Obstet Gynecol Reprod Biol. 2001; 98:14–7. [PubMed: 11516793]
53. Kramer MS, Lydon J, Seguin L, Goulet L, Kahn SR, McNamara H, Genest J, Dassa C, Chen MF, Sharma S, Meaney MJ, Thomson S, Van Uum S, Koren G, Dahhou M, Lamoureux J, Platt RW. Stress pathways to spontaneous preterm birth: the role of stressors, psychological distress, and stress hormones. Am J Epidemiol. 2009; 169:1319–26. [PubMed: 19363098]

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Parental Characteristics, Complications of Pregnancy and Child Characteristics at Birth

	No Neuraxial Block (N=3,189)	Neuraxial Block (N=1,495)	Total (N=4,684)	P value
Age of Mother at birth of child (y)	26.9 (4.7)	25.5 (4.4)	26.5 (4.7)	<0.001
Education level of Mother				0.21
Some High School	189 (6.4%)	89 (6.7%)	278 (6.5%)	
High School Graduate	1029 (35.0%)	431 (32.2%)	1,460 (34.1%)	
Any College	1,723 (58.6%)	818 (61.1%)	2,541 (59.4%)	
Education level of Father				0.62
Some High School	122 (4.4%)	62 (4.9%)	184 (4.6%)	
High School Graduate	844 (30.3%)	391 (31.1%)	1,235 (30.6%)	
Any college	1,816 (65.3%)	804 (64%)	2,620 (64.9%)	
Complications of pregnancy				
Hemorrhage	17 (0.5%)	4 (0.3%)	21 (0.4%)	0.21
Premature rupture of membranes	12 (0.4%)	4 (0.3%)	16 (0.3%)	0.55
Abnormalities of placentation	10 (0.3%)	2 (0.1%)	12 (0.3%)	0.26
Preeclampsia/eclampsia	53 (1.7%)	50 (3.3%)	103 (2.2%)	<0.001
Child sex				0.52
Female	1,549 (48.6%)	711 (47.6%)	2,260 (48.2%)	
Male	1,640 (51.4%)	784 (52.4%)	2,424 (51.8%)	
Birth weight (g)	3,474 (540)	3,485 (496)	3,478 (527)	0.98
Birth weight				0.11
< 2499 g	126 (4%)	45 (3%)	171 (3.7%)	
≥ 2500 g	3,056 (96%)	1,449 (97%)	4,505 (96.3%)	
Gestational Age at birth				0.07
<31.9 w	24 (0.8%)	4 (0.3%)	28 (0.6%)	
32-36.9 w	166 (5.6%)	67 (4.8%)	233 (5.3%)	
≥37 w	2,792 (93.6%)	1,336 (95.0%)	4,128 (94.1%)	

Data were complete for >99% of the study sample for all characteristics with the exception of gestational age which was missing for 295 (6.3%); mother's education missing in 405 (8.7%), and father's education in 645(13.8%). Values are mean (SD) or n (%).

Table2

Labor, Delivery, and Birth Characteristics

	No Neuraxial Block (N=3,189)	Neuraxial Block (N=1,495)	Total (N=4,684)	P value
Presentation				<0.001
Cephalic	3,059 (96.9%)	1,475 (99.6%)	4,534 (97.7%)	
Other	99 (3.1%)	6 (0.4%)	105 (2.3%)	
Labor Induction				<0.001
No	2,619 (82.1%)	1,020 (68.2%)	3,639 (77.7%)	
Yes	570 (17.9%)	475 (31.8%)	1045 (22.3%)	
Forceps or Vacuum Used				<0.001
No	2695 (84.9%)	576 (38.7%)	3271 (70.2%)	
Yes	478 (15.1%)	911 (61.3%)	1389 (29.8%)	
Any labor/delivery complication				<0.001
Hemorrhage	15 (0.5%)	7 (0.5%)	22 (0.5%)	0.99
Fetopelvic disproportion	32 (1%)	11 (0.7%)	43 (0.9%)	0.37
Dystocia	187 (5.9%)	125 (8.4%)	312 (6.7%)	0.001
Prolonged labor	158 (5%)	212 (14.2%)	370 (7.9%)	<0.001
Umbilical cord compression	30 (0.9%)	17 (1.1%)	47 (1%)	0.53
Birth trauma	11 (0.3%)	14 (0.9%)	25 (0.5%)	0.01
Intrauterine hypoxia	1 (0%)	0 (0%)	1 (0%)	0.49
Apgar score at 5 min				<0.001
Mean (SD) Median (25^{th}, 75^{th})	9.4 (0.8) 9 (9, 10)	9.3 (0.8) 9 (9, 10)	9.3 (0.8) 9 (9, 10)	
Neonatal resuscitation after delivery				0.64
No	3,104 (97.8%)	1,449 (97.6%)	4,553 (97.7%)	
Yes	70 (2.2%)	36 (2.4%)	106 (2.3%)	
Neonatal Intensive Care Unit admission				0.35
No	3,136 (98.9%)	1,472 (99.2%)	4,608 (99%)	
Yes	35 (1.1%)	12 (0.8%)	47 (1%)	

For all characteristics date were complete for >99% of the study sample.

Values are n (%), mean (SD) or median (25^{th}, 75^{th} percentile).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Adjuvant Anesthetics and Analgesics Used During Delivery

	No Neuraxial block (N=3,189)	Neuraxial Block (N=1,495)	Total (N=4,684)	P-value
Inhaled analgesia				<0.001
No	2,681 (84.1%)	1,449 (96.9%)	4,130 (88.2%)	
Yes	508 (15.9%)	46 (3.1%)	554 (11.8%)	
Nitrous Oxide	192 (6.0%)	13 (0.9%)		
Methoxyflurane	266 (8.3%)	25 (1.7%)		
Methoxyflurane+Nitrous Oxide	43 (1.4%)	7 (0.5%)		
Other *	7 (0.2%)	1 (0.1%)		
Systemic opioid analgesia				0.002
No	2,455 (77.0%)	1,210 (80.9%)	3,665 (78.2%)	
Yes	734 (23.0%)	285 (19.1%)	1,019 (21.8%)	
Benzodiazepine				0.12
No	3,181 (99.7%)	1,487 (99.5%)	4,668 (99.7%)	
Yes	8 (0.3%)	8 (0.5%)	16 (0.3%)	
Paracervical block				0.004
No	2,906 (91.1%)	1,399 (93.6%)	4,305 (91.9%)	
Yes	283 (8.9%)	96 (6.4%)	379 (8.1%)	
Pudendal block				<0.001
No	687 (21.5%)	1,029 (68.8%)	1,716 (36.6%)	
Yes	2,502 (78.5%)	466 (31.2%)	2,968 (63.4%)	

* In "No neuraxial block" group: enflurane (n=1), nitrous oxide and enflurane (n=2), methoxyflurane and enflurane (n=1), halothane and nitrous oxide (n=1), the use of inhaled anesthetic indicated in medical records, but anesthesia record is missing (n=2). In "neuraxial" group: halothane and nitrous oxide (n=1).

Table 4

Association Between Neuraxial Labor Analgesia and Development of Learning Disabilities[¥]

Model	Hazard Ratio	95% Confidence Interval	P value
Unadjusted	1.19	1.03 – 1.37	0.02
Adjusted *	1.15	0.98 – 1.35	0.08
Adjusted †	1.05	0.85 – 1.31	0.63

¥Data were analyzed using proportional hazards regression. Three models were fit: 1) unadjusted; 2) adjusted for covariates known to be associated with learning disabilities (LD); and 3) adjusted for covariates known to be associated with LD, as well as additional peripartum maternal and child variables. For each model, the hazard ratio and corresponding 95% confidence interval for the association of neuraxial analgesia with LD is presented.

*Adjusted for gestational age (≤31 weeks, 32-36 weeks, ≥37 weeks), sex (male, female), birth weight (<2500 g, ≥2500 g), maternal education (some high school, high school graduate, any college), 5-min Apgar score, and number of anesthesia exposures before the age of 4 (0, 1, 2 or more).

†Adjusted for covariates included in initial adjusted model plus use of forceps or vacuum extraction, fetal presentation, dystocia, prolonged labor, birth trauma, use of any inhaled anesthetics during delivery, use of supplemental regional blocks, use of opioids, labor induction, delivery resuscitation or neonatal intensive care unit admission after delivery, and maternal age.