Obstetric Anesthesiology - Behavioral and neuropsychological outcomes in children after exposure to labor epidural analgesia

Oliver Isik[1], Shaqif Junaid, Ling Guo, Deven Lackraj, Ruth Landau[2], Caleb Miles, Craig Pennell, Britta von Ungern Sternberg, Andrew Whitehouse, Guohua Li[3], Caleb Ing[2]

Columbia University Vagelos College of Physicians & Surgeons[1] Columbia University Irving Medical Cente[2] Columbia University[3]

Introduction: The potential effect of labor epidural analgesia (LEA) on child neurodevelopment is still being investigated. An association between mothers who receive LEA and later development of autism spectrum disorder in their children was reported,[1] while several subsequent studies reported either no association or slightly elevated risks that could be explained by unmeasured confounding.[2-4] This study explores the association between maternal LEA and child behavioral and neuropsychological assessments, accounting for a wide range of sociodemographic and perinatal variables.

Methods: This study evaluates participants from the Raine Study, a multigenerational birth cohort of children born between 1989 and 1992 in Perth, Australia. Children born via vaginal delivery from a singleton pregnancy were included for analysis. The primary outcome was the Child Behavior Checklist (CBCL) evaluated at age 10, with higher scores indicating more behavioral problems. To adjust for confounding, 73 sociodemographic and clinical covariates were identified. Multiple imputation was used to impute any missing covariate data. To account for differences in children exposed to LEA, the predicted probability of LEA exposure conditional on all covariates was calculated and applied to Inverse Probability of Treatment Weights (IPTW). We aimed for standardized differences in covariate means below 0.1 following IPTW. To account for missing outcome data, censoring conditional on all covariates and exposure status was calculated and applied to Inverse Probability of Censoring Weights (IPCW). As a primary analysis, the association between LEA and CBCL scores was evaluated using linear regression with IPTW and IPCW. Three secondary analyses were performed. The risk of clinical deficit based on LEA exposure was evaluated using modified Poisson regression with IPTW and IPCW, where clinical deficits were defined as CBCL scores above 60.[5] In mothers who received LEA, a multivariable linear regression evaluated the association between duration of LEA exposure and CBCL scores. Where significant score differences were observed, mediation analysis evaluated the role of fever during labor requiring antibiotics and oxytocin for augmentation of labor.[6] The same analyses were applied to secondary outcomes: Clinical Evaluation of Language Fundamentals (CELF), Peabody Picture Vocabulary Test (PPVT), McCarron Assessment of Neuromuscular Development (MAND), Raven's Colored Progressive Matrices (CPM), Symbol Digit Modality Test (SDMT), and Autism Spectrum Quotient (AQ). AQ was assessed between child ages 19 and 20; other assessments were evaluated at age 10. Higher AQ scores indicate more autistic tendencies, whereas for other secondary outcomes, higher scores indicate better performance.

Results: Of 2180 children included for analysis, 850 (39.0%) were exposed to LEA (Figure 1). Covariates for exposed and unexposed children were evaluated, with a subset of covariates displayed in Table 1. Appropriate balance in all covariates following IPTW is displayed in Figure 2. For the primary outcome, LEA-exposed children had higher (worse) scores on the CBCL Total (+1.66 points; 95% confidence interval [CI] 0.49, 2.83; $p = 0.006$), Internalizing (+1.33; 95% CI 0.20, 2.45; $p = 0.021$), and Externalizing (+1.26; 95% CI 0.18, 2.34; $p = 0.022$) assessments. Exposure was not associated with an increased risk for clinical deficit (Table 2), nor was increased LEA duration associated with CBCL performance (Table 3). Fever and oxytocin for augmentation of labor did not mediate observed increases in CBCL scores. Regarding the secondary outcomes, while exposed children had worse scores in some of the outcomes (Table 2), increased LEA exposure duration was not associated with worse scores (Table 3). Fever and oxytocin for labor augmentation also did not mediate the observed differences.

Conclusions: Children exposed to LEA performed worse on the CBCL assessment at age 10 but had no increased risk for clinical deficit, suggesting a lack of clinical significance in the observed differences. Differences were seen in some secondary outcomes, but are small and should be interpreted with caution. It should be noted that higher concentrations of local anesthetic were used in the era that these epidurals were performed. That longer LEA duration and thus exposure to higher doses of local anesthetic was not associated with worse scores may argue against toxicity of local anesthetic medications.

References: 1. JAMA Pediatr. 2020; 174 (12): 1168-1175.

2. JAMA Pediatr. 2021; 175 (7): 698-705.

3. JAMA. 2021; 326 (12): 1170-1177.

4. JAMA. 2021; 326 (12): 1178-1185.

5. Anesth Analg. 2021; 133 (3): 595-605.

6. Neonatology. 2020; 117 (3): 259-270.

Figure 1. Study flow with inclusion and exclusion criteria.

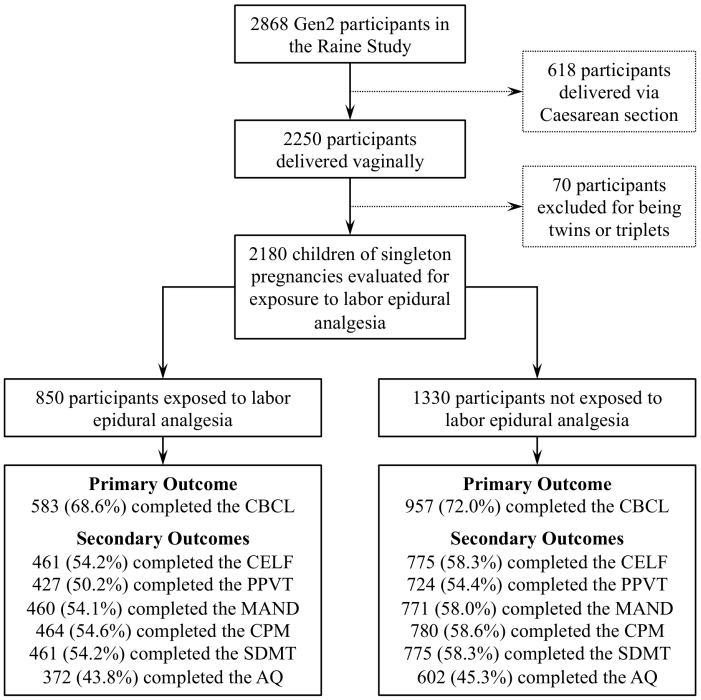

Figure 2. Standardized mean differences (SMD) in covariates for each imputed dataset before and after inverse probability of treatment weighting.

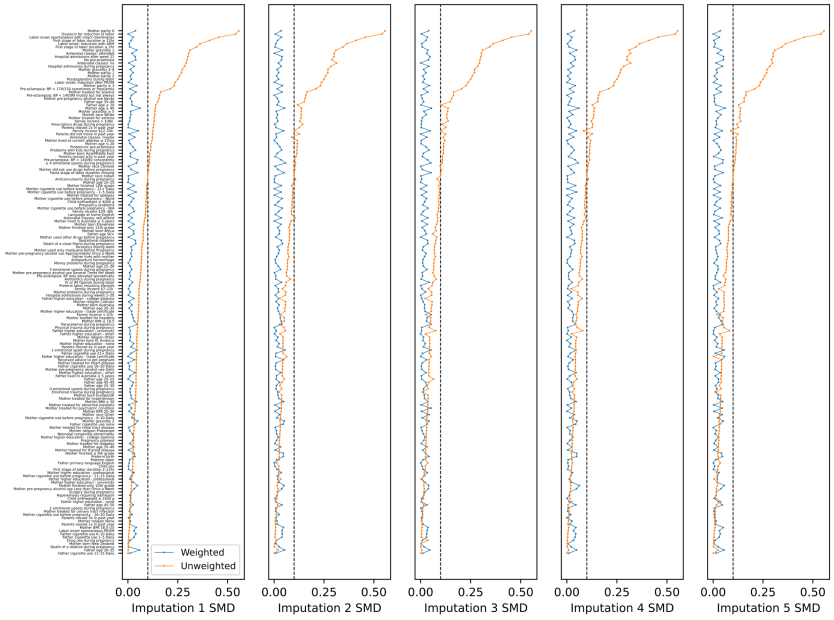

Table 1. Selected sociodemographic and clinical covariates in exposed and unexposed study participants.

	No LEA (%) *n* = 1330	**LEA (%) *n* = 850**
Parental Sociodemographic Characteristics		
Mother's age ≥ 35 years	166 (12.5)	85 (10.0)
Father's age ≥ 35 years	312 (23.5)	141 (16.6)
Mother's race White	1153 (86.7)	772 (90.8)
Mother native to Australia	775 (58.3)	518 (60.9)
Family income ≥ $24,000	673 (50.6)	456 (53.6)
Maternal Health Characteristics		
Treated for asthma	180 (13.5)	156 (18.4)
Treated for epilepsy	22 (1.7)	26 (3.1)
Treated for anemia	339 (25.5)	280 (32.9)
Maternal Antenatal Characteristics		
Mother primiparous	506 (38.0)	550 (64.7)
Attended antenatal classes	518 (38.9)	491 (57.8)
Hospital admission during pregnancy	243 (18.3)	258 (30.4)
Pre-eclampsia during pregnancy	240 (18.0)	260 (30.6)
Used prescription medications during pregnancy	215 (16.2)	184 (21.6)
Used paracetamol (acetaminophen) during pregnancy	150 (11.3)	113 (13.3)
Maternal Perinatal Characteristics		
Received prostaglandins during labor	31 (2.3)	66 (7.8)
Labor onset via induction of labor	355 (26.7)	418 (49.2)
Received oxytocin for induction of labor	198 (14.9)	322 (37.9)
Duration of first stage of labor ≥ 12 hours	43 (3.2)	125 (14.7)
Child Neonatal Characteristics		
Child Sex Male	666 (50.1)	436 (51.3)
Neonatal birthweight ≥ 4000 grams	107 (8.0)	92 (10.8)
Post-Exposure Mediators		
Received antibiotics for fever ≥ 37.4 °C during labor	11 (0.8)	58 (6.8)
Received oxytocin for augmentation of labor	56 (4.2)	212 (24.9)

Table 2. Score differences and relative risks of crossing a threshold for clinical deficit for primary and secondary outcomes. Each score and relative risk is adjusted by inverse probability of treatment weighting and inverse probability of censoring weighting.

Domain	Outcome	Adjusted Mean Score Difference		Adjusted Relative Risk of Clinical Deficit	
		Est. (95% CI)	*p*	aRR (95% CI)	*p*
Primary Outcome					
Behavior	CBCL Total	1.66 (0.49, 2.83)	0.006	1.12 (0.77, 1.62)	0.547
	CBCL Internalizing	1.33 (0.20, 2.45)	0.021	1.25 (0.88, 1.77)	0.209
	CBCL Externalizing	1.26 (0.18, 2.34)	0.022	1.07 (0.7, 1.63)	0.762
Secondary Outcomes					
Language	CELF Total	-1.05 (-2.81, 0.71)	0.242	1.04 (0.71, 1.52)	0.848
	CELF Receptive	-1.19 (-2.98, 0.60)	0.191	1.11 (0.75, 1.65)	0.588
	CELF Expressive	-0.19 (-1.97, 1.60)	0.837	1.04 (0.72, 1.5)	0.825
	PPVT	-0.82 (-2.21, 0.57)	0.245	1.14 (0.79, 1.65)	0.489
Motor	MAND	-1.72 (-3.34, -0.09)	0.038	1.44 (1.01, 2.06)	0.046
Cognition	CPM Total	-0.33 (-0.75, 0.08)	0.117	1.13 (0.79, 1.63)	0.498
	SDMT Written	-1.32 (-2.21, -0.44)	0.003	1.45 (1.02, 2.06)	0.037
	SDMT Oral	-1.55 (-2.72, -0.37)	0.010	1.54 (1.06, 2.24)	0.025
Autism	AQ	0.61 (-0.09, 1.30)	0.087	0.88 (0.38, 2.01)	0.759

Table 3. Score difference per additional hour of labor epidural analgesia exposure in children with recorded durations, adjusted by multivariable linear regression including all 73 covariates.

Domain	Outcome	Participants (%) *n* = 828	Adjusted score difference per additional hour of LEA	
			Est. (95% CI)	*p*
Primary Outcome				
Behavior	CBCL Total	573 (69.2)	0.08 (-0.25, 0.40)	0.632
	CBCL Internalizing	573 (69.2)	0.03 (-0.29, 0.36)	0.834
	CBCL Externalizing	573 (69.2)	0.09 (-0.21, 0.39)	0.562
Secondary Outcomes				
Language	CELF Total	454 (54.8)	0.68 (0.15, 1.21)	0.012
	CELF Receptive	456 (55.1)	0.78 (0.23, 1.34)	0.005
	CELF Expressive	454 (54.8)	0.48 (-0.05, 1.02)	0.077
	PPVT	420 (50.7)	0.16 (-0.25, 0.57)	0.456
Motor	MAND	453 (54.7)	-0.08 (-0.57, 0.41)	0.742
Cognition	CPM	457 (55.2)	0.05 (-0.08, 0.17)	0.493
	SDMT Written	455 (55.0)	0.07 (-0.19, 0.33)	0.600
	SDMT Oral	454 (54.8)	0.06 (-0.28, 0.40)	0.721
Autism	AQ	368 (44.4)	0.09 (-0.16, 0.34)	0.497