Brain damage in preterm newborns and maternal medication: The ELGAN Study

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Abstract

Objective—To evaluate the association between maternal medication use during pregnancy and cerebral white matter damage and cerebral palsy (CP) among very preterm infants.

Study Design—This analysis of data from the ELGAN Study included 877 infants born <28 weeks gestation. Mothers were interviewed, charts reviewed, placentas were cultured and assessed histologically, and children evaluated at 24 months corrected age. A diagnostic algorithm classified neurologic findings as quadriparetic CP, diparetic CP, hemiparetic CP, or no CP.

Results—After adjustment for the potential confounding of disorders for which medications might have been indicated, the risk of quadraparetic CP remained elevated among the infants of mothers who consumed aspirin (OR=3.0, 95% CI 1.3,6.9) and non-steroidal anti-inflammatory medications (NSAIDs) (OR=2.4, 95% CI 1.04,5.8). The risk of diparetic CP was also associated with maternal consumption of an NSAID, but only if the consumption was not approved by a physician (OR=3.5, 95% CI 1.1,11.0)

Conclusion—The possibility that aspirin and NSAID use in pregnancy could lead to perinatal brain damage cannot be excluded.

Medical Subject Headings

Cerebral palsy; cerebral white matter damage; preterm

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INTRODUCTION

Some obstetricians prescribe aspirin for recurrent miscarriage in the setting of antiphospholipid antibody syndrome [1], and to reduce the risk of preeclampsia [2, 3], while others have used indomethacin, a non-steroidal anti-inflammatory medications (NSAID), to stop preterm uterine contractions or as a tocolytic to prevent preterm delivery[4].

In response to a 2007 survey conducted by the American College of Obstetricians and Gynecologists, only 28% of clinicians considered aspirin safe for first trimester consumption, while only 31% considered ibuprofen safe; in contrast, 94% considered acetaminophen safe [5]. Most research on drug safety has focused on fetal malformations,. Due to the association of inflammatory phenomena and markedly preterm birth, and the relationships between preterm birth and brain damage [6–8], we sought to determine if there is an association between over the counter NSAIDs and perinatal brain damage in these infants born well before term. Maternal consumption of NSAIDS to reduce symptoms of inflammatory processes may indicate the existence of such processes which might themselves contribute to brain damage, or they may independently lead to brain damage. [9–12].

In this paper, we assess to what extent maternal consumption of medications often used to minimize symptoms of inflammation and infection are associated with white matter lesions recognized on neonatal cranial ultrasound scans. We also assess the extent to which these medications are associated with cerebral palsy (CP) subtypes two years later.

MATERIALS and METHODS

The ELGAN Study

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs (the acronym for Extremely Low Gestational Age Newborns) [13]. During the years 2002–2004, women who delivered before the 28th post-menstrual week at 14 participating institutions in 11 cities in 5 states were asked to enroll in the study. The enrollment and consent processes were approved by the institutional review boards of the participating institutions.

Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. 1,249 mothers of 1,506 infants consented. Approximately 260 women were either missed or did not consent to participate. Of the 1,205 infants who survived to age two, 1,056 (88%) had a neurologic examination at approximately 24-months corrected age. Fully 877 children had complete information on variables of interest and are the subjects of our analyses.

Demographic and pregnancy variables

After delivery, a trained research nurse interviewed each mother in her native language about her socio-demographic, anthropometric, reproductive, and medical history (e.g., conditions and medications) using a structured data collection form. The mother's report of her own characteristics and exposures during pregnancy, as well as the sequence of events leading to delivery were taken as valid, even when her medical record provided discrepant information. Women who acknowledged consuming a medication were questioned as to whether the medication was taken under the direction of her physician; these responses were tabulated.

Shortly after the mother's discharge, the research nurse reviewed the maternal chart using a second structured data collection form. The medical record was relied on for establishing the validity of events whose occurrence followed maternal admission to hospital.

The clinical circumstances that led to preterm delivery were operationally defined using data from the maternal interview and data abstracted from the medical record [14]. Each mother/infant pair was assigned to the category that described the primary reason for preterm delivery.

Gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval, intrauterine insemination, or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

To describe fetal growth, we used the birth weight Z-score, defined as the number of standard deviations the infant's birthweight was above or below the median weight of infants at the same gestational age in a standard data set.[15]

Placenta variables

Placentas were handled in a sterile manner from time of collection to biopsy. Eighty-two percent of the samples were obtained within 1 hour of delivery. The microbiologic procedures are described in detail elsewhere [16]. Briefly, the frozen samples were allowed to thaw at room temperature, a portion approximately 1 cm squared was removed and weighed, then diluted 1:10 with sterile phosphate buffered saline (PBS), homogenized and aliquots plated on selective and non-selective media, including pre-reduced brucella-base agar with 5% sheep blood enriched with hemin and vitamin K_1, tryptic soy agar with 5% sheep blood, chocolate agar, and A-7 agar. After incubation, the various colony types were enumerated, isolated and identified by established criteria [17].

In keeping with the guidelines of the 1991 CAP Conference [18], representative sections were taken from all abnormal areas as well as routine sections of the umbilical cord and a membrane roll, and full thickness sections from the center and a paracentral zone of the placental disc. After training to minimize observer variability, study pathologists examined the slides for histologic characteristics listed on a standardized data form they helped create [19, 20]. Placental inflammation consisted of any of the following: inflammation of the chorionic plate of grade 3 (neutrophils up to amnionic epithelium) or stage 3 (>20 neutrophils/20x), moderate/severe chorioamnionitis (numerous large or confluent foci of neutrophils), inflammation of umbilical cord (neutrophils in perivascular Wharton's jelly). Infarcts were searched for, while syncytial knots in the chorionic villi were scored as increased or not.

Protocol cranial ultrasound scans

Routine scans were performed by technicians at all study hospitals using digitized high frequency transducers (7.5 and 10 MHz). Ultrasound scans included the six standard quasi-coronal views and five sagittal views using the anterior fontanel as the sonographic window. [21] The three sets of protocol scans were defined by the postnatal day on which they were obtained (1: days 1–4; 2: days 5–14; 3: day 15-week 40). After creation of a manual and data collection form, efforts to minimize observer variability included conference calls to discuss aspects of images prone to different interpretations.[22] Templates of multiple levels of ventriculomegaly were included in the manual. All ultrasound scans were read by two independent readers, each at a separate institution, who were not provided clinical

information. The images, usually as electronic images on a CD imbedded in the software eFilm Workstation™ (Merge Healthcare/Merge eMed, Milwaukee, WI), were sent to a sonologist at another ELGAN study institution for a second reading. The eFilm program allowed the second reader to see what the first reader saw, and provided options to zoom and alter gains. When the two readers differed in their recognition of moderate/severe ventriculomegaly or an echolucent (hypoechoic) lesion, the films were sent to a third (tie-breaking) reader who did not know what the earlier readers reported.

Cerebral palsy diagnosis

To standardize neurological examinations at all sites, a stand-alone, multimedia-training video/CD-ROM was developed, based on elements of a standard neurological exam.[23] The video/CD-ROM program had audiovisual teaching sequences, voice-over commentary, graphics and text to organize the training and amplify key teaching points. The training video provided instruction in the proper method of performing each item of the examination and illustrated all possible findings. Additionally, the CD contained 6 sets of 20 video clips for inter-observer testing purposes. Repeated testing resulted in 96% agreement with the gold-standard pediatric neurologist assessment.

A diagnostic algorithm that assigned children to CP sub-types demonstrated how an experienced pediatric neurologist might go about making a CP diagnosis in a young child [24].

Data analysis

We evaluated the hypothesis that very preterm newborns whose mother consumed an NSAID or acetaminophen during pregnancy were not at increased or decreased risk of white matter lesions recognized on neonatal cranial ultrasound scans or of a CP sub-type at age 2 years. Although aspirin is an NSAID, we evaluated aspirin separately from other NSAIDs.

We did not know the specific indication for each medication consumed although we collected information regarding disorders of pregnancy that might have prompted their use. Our including antibiotics among the drugs consumed allows us to explore the contribution of confounding by indication [25]. In essence, if consumption of an NSAID was merely a marker of antenatal inflammation, and not in itself a brain-damaging exposure, then the risks of brain damage following NSAID exposure could be compared to the risks of brain damage following antibiotic consumption.

Similarly, we included acetaminophen among the drugs of interest because it provides symptomatic relief comparable to that provided by NSAIDs, but unlike NSAIDs, acetaminophen has no known anti-inflammatory capabilities. Consequently, comparing the risks of brain damage following NSAID consumption to the risks following acetaminophen consumption allows an assessment of the potential contribution of diminishing inflammation.

In this sample, multi-fetal gestations did not have a higher risk of any CP diagnosis. Data were therefore analyzed with the infant, rather than the mother, as the unit of analysis. Thus, a mother of twins was counted twice, once for each newborn. Additional analyses to determine the effect of including multiple infants from the same mother on variance estimates did not significantly influence our findings.

We created Tables I through IV to help identify potential confounders. For example, were women who consumed a medication more likely to have an inflamed placenta than women who did not?, And similarly, were the newborns who developed ventriculomegaly more likely to have an inflamed placenta than infants who did not? We calculated the probabilities

(Fisher's exact test) that column percents on the same line in adjacent columns occurred randomly.

We created multivariable logistic regression models to identify the contribution of maternal medication consumption to the infant's risk of brain damage. We selected variables as potential confounders if they were associated with both the exposure and the outcome in our data with probabilities .30 [26]. We used multinomial (i.e., polytomous or polychotomous) logistic regression to model the risk of the CP-subtype diagnosis because these diagnoses are mutually exclusive and each is compared to the same referent group of children without any CP diagnosis. The contributions of relevant variables are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Results are presented overall and stratified by physician approval, in an effort to address the potential for confounding by indication.

RESULTS

Maternal demographic characteristics of medication consumption (Table I)

Overall, 25.9% of women in our sample consumed an antibiotic, 5.6% consumed aspirin, 7.2% consumed a NSAID, and 50.4% consumed acetaminophen during pregnancy. Compared to their peers, women who were prescribed an antibiotic during pregnancy were more likely to identify as Black, single, receiving Medicaid, and having a history of vaginitis or a urinary tract infection. Women who consumed aspirin reported a lower prevalence of being single, and receiving Medicaid than women who did not consume aspirin. Women who consumed other NSAIDs were more likely to identify as Black, single, receiving Medicaid, smoking, having less than a high school education, ingesting an antibiotic and having a history of vaginitis during pregnancy than women who did not consume other NSAIDs. Compared to women who did not consume acetaminophen during pregnancy those who did reported a higher prevalence of consuming an antibiotic, and having a fever during pregnancy. Women who were prescribed antibiotics during pregnancy were more likely to be black, single, on Medicaid and to have had a history of vaginitis or a urinary tract infection (UTI). Women who had taken aspirin were less likely to be single or on Medicaid tha those who did not take aspirin. Women who had taken other NSAIDS were more likely to be black, single, on Medicaid, and to have less than a high school education. In addition they were more likely to have ingested antibiotics and to have had a history of vaginitis than those who did not take other Women who had taken acetaminophen had also more commonly taken an antibiotic during pregnancy and to have had a fever.

Delivery-related characteristics associated with medication consumption (Table II)

Women who consumed an antibiotic and who consumed aspirin during pregnancy each reported a higher prevalence of cervical insufficiency than their counterparts. The placentas of women who consumed aspirin had a lower prevalence of Mycoplasma but a higher prevalence of histologic inflammation than the placentas of women who did not consume aspirin. The placentas of women who took other NSAIDs had a higher prevalence of infarct than the placentas of women who did not take NSAIDS.

Maternal demographic characteristics associated with indicators of brain damage (Table III)

Children who developed quadriparetic CP were more likely to have prenatal exposure to an antibiotic, aspirin, and other NSAIDs. Children who developed diparetic CP were also more likely than others to have been exposed to a non-aspirin NSAID.

Delivery-related characteristics associated with indicators of brain damage (Table IV)

Children who developed ventriculomegaly or an echolucent lesion were more likely than others to have been delivered following preterm labor and less likely to have been born to women who had preeclampsia or placenta abruption. Children who developed an echolucent lesion, quadriparetic CP, or diparetic CP were more likely than others to have had a placenta that was more likely to be infected aerobe or an anaerobe. Only children who developed diparetic CP were more likely have had a placenta that harbored Mycoplasma species. The placentas of children who developed an echolucent lesion or developed diparetic CP were more likely to be inflamed than the placentas of other children.

Risks of indicators of brain damage associated with drug exposures (Table V)

After adjusting for potential confounders (identified at the bottom of Table V), none of the four drug exposures were associated with increased risk of cerebral white matter damage, or of hemiparetic CP. Children were at increased risk of quadriparetic CP if exposed to aspirin (OR=3.0, 95% CI, 1.3–6.9) and if exposed to other NSAIDs (OR=2.4, 95% CI 1.04–5.8). The risk of diparetic CP was increased only among children whose mother consumed an NSAID without approval from a medical care provider (OR=3.5, 95% CI 1.1–11.0).

COMMENT

The purpose of this analysis was to examine the relationship between maternal medication use and the risk of cerebral white matter damage and CP diagnosis among children born before the 28th post-menstrual week. We found that the risk of quadriparetic and diparetic CP was elevated among infants whose mother consumed NSAIDs during pregnancy, even after adjustment for potential confounders. To our knowledge, we are the first to identify these associations in a well characterized population, with a large sample of extremely low gestational age infants.

Aspirin and other NSAIDs might be surrogates for pregnancy correlates that increase the risk of CP diagnoses. Alternatively, these drugs might contribute to fetal brain damage. We consider both possibilities.

In this sample, gravidas who consumed aspirin were more likely than other women to have had a placenta that was inflamed and harbored an anaerobe, while women who consumed other NSAIDs were more likely than others to have had vaginitis during the pregnancy. These observations prompt the view that consumption of NSAIDs in our sample is merely a surrogate for inflammatory phenomena capable of damaging the fetal brain, and not in the causal chain. Despite our efforts to minimize such confounding, we recognize that residual confounding may have occurred, and therefore might account for some of what we found.

In contrast to our findings, a recent study found that low dose aspirin was not significantly associated with cerebral lesions or CP among infants born before 33 weeks gestation [27]. Additionally, the randomized CLASP study found that antenatal aspirin had no effect on neurologic outcomes [28].

The basic science literature provides support for brain-damaging effects of NSAIDs, as well as for brain-protection effects. By decreasing the availability of anti-inflammatory cytokines IL-4 and IL-10 [10]. NSAIDs have the potential to exacerbate inflammation. In addition, ibuprofen significantly increased the size of the cerebral infarct in a rat model of stroke [11] while, indomethacin increased the proportion of animals displaying neuronal damage in a rat model of cerebral hypoperfusion [12].

In contrast, NSAIDs might be beneficial. Prostaglandin synthesis results in compounds that have the capacity to exacerbate brain-damaging processes [27,31,32,33]. By virtue of their ability to interfere with prostaglandin synthesis, NSAIDs have the capacity to minimize such potential damage. NSAIDs also have the capacity to diminish damage associated with excitotoxicity [36]. In humans, low-dose aspirin given prenatally to women with a history of placental vascular disease was not followed by an increased risk of brain damage in the very preterm newborn, and the reduced risk of neurobehavioral outcomes approached statistical significance [27].

While some may view CP as a homogeneous entity [34,35], we do not. In the ELGAN Study sample, the clinical correlates [24], as well as some antecedents differ among the three phenotypes [6 and 7]. Thus, our finding that maternal consumption of NSAIDs is associated with just one phenotype (*i.e.*, quadriparetic CP) is not surprising.

We recommend caution in drawing inferences based on our one study, as unpublished studies might have found that NSAID consumption by gravidas is not associated with any increase in perinatal brain damage.

Our study is subject to several limitations. Although our sample consisted of 877 newborns, it included only 88 children who developed ventriculomegaly, 59 with an echolucent lesion, 52 with an eventual diagnosis of quadriparetic CP, 31 with a diagnosis of diparetic CP, and only 16 considered to have hemiparetic CP. The second limitation is that as this is an observational study, we cannot distinguish between association and causation. Third, the consumption of a medication for a symptom that might have been associated with a disorder in the causal chain leading to perinatal brain damage makes our study prone to confounding by indication. Despite our best efforts to minimize this confounding, we might not have eliminated it entirely [25]. Perhaps equally important is our not having assessed the timing, indication, or dosage of over-the-counter medications.

On the other hand, our study has several strengths. First, we evaluated both sonographically-defined diffuse and focal perinatal brain damage, as well as multiple CP phenotypes. Second, attrition in the first two years was modest, with 88% of eligible children having a diagnostic neurologic examination. Third, we selected infants based on gestational age, not birth weight, in order to minimize confounding due to factors related to processes associated with fetal growth restriction (and the relative absence of inflammation) [29]. Fourth, we collected all of our data prospectively. Fifth, examiners were not aware of the medical histories of the children they examined, thereby minimizing "diagnostic suspicion bias"[30]. Sixth, we minimized observer variability as best we could in the interpretation of ultrasound scans [22], and the conduct of the neurologic exam [24]. Seventh, we used an algorithm to classify the CP phenotypes uniformly [23].

In conclusion, we found that maternal consumption of aspirin and NSAIDs during pregnancy were associated with increased risk of quadriparetic CP among infants born before the 28th post-menstrual week. Since, to our knowledge, we are the first to identify this association, we encourage others to search for confirmation or refutation of our findings.

Acknowledgments

Abbreviations

CP	Cerebral palsy
ELGAN	Extremely low gestational age newborn
NSAID	Non-steroidal anti-inflammatory medications

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Table I

Column percents of maternal demographic characteristics among consumers of 4 groups of drugs during pregnancy.

Maternal characteristic	Antibiotic		Aspirin		NSAID*		Acetaminophen		Row N
	Yes	No	Yes	No	Yes	No	Yes	No	
Antibiotic			37	29	39	29	36	24	262
Aspirin	7	5			8	5	5	6	49
NSAID*	10	6	10	7			6	8	64
Acetaminophen	60	46	45	51	44	51			442
Black	35	23	19	27	48	25	24	30	233
Hispanic	9	12	8	11	5	11	7	14	95
Maternal age <21	16	12	6	14	13	13	10	16	115
(yrs) >35	21	20	20	20	14	20	22	17	174
Primigravida	40	42	33	42	33	42	40	42	360
Education <12	49	40	35	43	58	42	39	47	373
(yrs) >16	26	38	38	34	14	36	33	36	300
Single	52	36	31	41	58	39	37	44	356
Medicaid recipient	50	33	29	39	63	37	36	40	337
Cigarette smoker	17	11	14	13	31	11	15	10	112
Pre-pregnancy BMI 30	23	20	22	21	25	20	22	19	180
Fever	11	4	2	6	9	6	8	4	54
Vaginitis	28	8	10	14	23	13	17	11	124
Urinary tract infection	42	3	14	15	16	15	16	14	131
Periodontal disease	2	2	2	2	3	2	2	3	19
Column N	262	615	49	828	64	813	442	435	877

*
NSAID = Non-steroidal anti-inflammatory medication

Column percents of delivery-related characteristics among consumers of 4 groups of drugs during pregnancy.

Delivery characteristic	Antibiotic		Aspirin		NSAID*		Acetaminophen		Row N
	Yes	No	Yes	No	Yes	No	Yes	No	
Delivery indication									
Preterm labor	47	45	53	45	39	46	46	44	396
pPROM	19	22	14	22	23	21	21	21	185
Preeclampsia	13	14	6	14	11	14	15	13	120
Abruption	10	12	6	11	13	11	10	12	97
Cervical Insufficiency	8	4	14	4	6	5	4	6	43
Fetal Indication	3	4	6	4	8	4	4	4	36
Gestational age 23–24	23	19	29	20	25	20	23	17	178
(wks) 25–26	41	47	43	46	47	45	43	48	399
Birth weight Z-score < −2	5	6	0	6	5	6	5	6	45
Placenta bacteriology									
Aerobe	31	31	35	31	30	31	30	32	271
Anaerobe	26	30	37	28	22	29	29	29	251
Mycoplasma	14	8	0	11	16	10	11	9	89
Placenta histology									
Any inflammation[†]	42	38	59	38	41	39	39	40	344
Infarct	16	19	16	18	27	17	20	16	155
Increase syncytial knots	22	21	22	21	19	21	20	22	182
Column N	262	615	49	828	64	813	442	435	877

*
NSAID = Non-steroidal anti-inflammatory medication

[†]
Inflammation of the chorionic plate (grade 3, severity 3), moderate/severe chorioamnionitis, inflammation of umbilical cord (grade 3), and/or neutrophilic infiltration of the fetal vessels in the plate

Table III

Column percents of maternal demographic characteristics among women who gave birth to a child who developed an ultrasound indication of cerebral white matter damage or cerebral palsy.

Maternal characteristic	Cerebral White Matter Damage				Cerebral Palsy			
	Ventriculomegaly		Echolucent Lesion		Quadriparesis	Diparesis	Hemiparesis	None
	Yes	No	Yes	No				
Antibiotic	25	30	27	30	43	29	13	29
Aspirin	10	5	12	5	17	3	0	5
NSAIDs[*]	7	7	10	7	15	13	0	7
Acetaminophen	53	50	44	51	47	48	56	51
Black	28	27	34	26	26	39	44	26
Hispanic	10	11	17	10	8	3	19	11
Maternal age <21	9	14	14	13	9	10	13	14
(yrs) >35	26	19	15	20	19	26	6	20
Primigravida	39	41	25	42	32	32	31	42
Education <12	33	44	42	43	38	48	31	43
(yrs) >16	36	34	22	35	30	23	25	35
Single	39	41	41	41	36	48	44	41
Medicaid recipient	32	29	41	38	45	52	19	38
Cigarette smoker	11	13	15	13	16	16	0	13
Pre-pregnancy BMI 30	20	21	15	21	21	17	27	21
Fever	8	6	12	6	6	3	13	6
Vaginitis	17	14	17	14	25	19	19	13
Urinary tract infection	11	15	20	15	17	13	6	15
Periodontal disease	3	2	3	2	2	3	0	2
Column N	88	789	59	818	53	31	16	777

[*] NSAID = Non-steroidal anti-inflammatory medications

Table IV

Column percents of delivery-related characteristics among women who gave birth to a child who developed an ultrasound indication of cerebral white matter damage or cerebral palsy.

Delivery characteristic	Cerebral White Matter Damage				Cerebral Palsy			
	Ventriculomegaly		Echolucent Lesion					
	Yes	No	Yes	No	Quadriparesis	Diparesis	Hemiparesis	None
Delivery indication								
Preterm labor	57	44	59	44	49	55	75	44
pPROM	20	21	22	21	19	23	13	21
Preeclampsia	7	14	3	14	9	6	0	15
Abruption	7	12	2	12	4	10	13	12
Cervical Insufficiency	5	5	7	5	15	6	0	4
Fetal Indication	3	4	7	4	4	0	0	4
Gestational age 23–24	27	20	32	19	43	48	38	17
25–26 (wks)	48	45	44	46	34	23	44	47
Birth weight Z-score < −2	6	5	2	6	0	0	13	6
Placenta bacteriology								
Aerobe	39	30	44	30	43	65	25	29
Anaerobe	36	28	39	28	45	42	25	27
Mycoplasma	10	10	8	10	9	23	6	10
Placenta histology								
Any inflammation†	42	39	49	39	49	68	38	37
Infarct	10	19	19	18	25	13	13	18
Increase syncytial knots	17	21	15	21	21	13	6	22
Column N	88	789	59	818	53	31	16	777

† Inflammation of the chorionic plate (grade 3, severity 3), moderate/severe chorioamnionitis, inflammation of umbilical cord (grade 3), or neutrophilic infiltration of the fetal vessels in the plate

Table V

Odds ratios (and 95% confidence intervals) of the outcomes identified at the top of each column associated with the exposure on the left. Each multivariate model included its own set of potential confounders (listed below the table). Statistically significant odds ratios are bolded.

	Cerebral White Matter Damage		Cerebral Palsy *CP*		
	Ventriculomegaly *VM*	Echolucent Lesion *EL*	Quadriparesis	Diparesis	Hemiparesis
Antibiotic	0.8 (0.5, 1.3)	0.5 (0.2, 1.1)	1.5 (0.8, 2.8)	0.7 (0.3, 1.8)	0.3 (0.1, 1.3)
Aspirin – any	1.9 (0.9, 4.1)	2.2 (0.9, 5.4)	**3.0 (1.3, 6.9)**	0.5 (0.1, 4.1)	----
Aspirin – approved	1.6 (0.6, 4.0)	2.4 (0.9, 6.7)	**2.9 (1.1, 7.7)**	----	----
– not approved	3.2 (0.8, 13)	1.8 (0.4, 9.1)	3.3 (0.8, 14)	1.6 (0.2, 15)	----
NSAIDs * – any	1.0 (0.4, 2.4)	1.3 (0.5, 3.2)	**2.4 (1.04, 5.8)**	1.7 (0.5, 5.2)	----
NSAIDs * – approved	1.3 (0.4, 3.8)	1.2 (0.3, 4.2)	**3.0 (1.04, 8.5)**	----	----
– not approved	0.7 (0.2, 3.1)	1.4 (0.4, 4.9)	1.9 (0.5, 6.8)	**3.5 (1.1, 11)**	----
Acetamin§ – any	1.1 (0.7, 1.7)	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.8 (0.4, 1.7)	1.1 (0.4, 3.2)
Acetamin§ – approved	1.0 (0.6, 1.6)	0.6 (0.3, 1.1)	0.7 (0.4, 1.3)	0.9 (0.4, 2.0)	1.4 (0.5, 4.4)
– not approved	1.2 (0.7, 2.4)	1.1 (0.5, 2.3)	0.7 (0.3, 1.7)	0.7 (0.2, 2.4)	0.4 (0, 3.4)

*
NSAID = Non-steroidal anti-inflammatory medications

§
Acetamin = Acetaminophen

VM
List of ventriculomegaly-drug potential confounders: maternal age, maternal education, Medicaid, delivery indication, gestational age, placenta anaerobe, placenta infarct

EL
List of echolucent lesion-drug potential confounders: Black, Hispanic, primigravida, education, pre-pregnancy BMI, fever, vaginitis, urinary tract infection, delivery indication, gestational age, birth weight z-score, aerobe, anaerobe, placenta inflammation, increased syncytial knots in placenta

CP
List of CP-drug potential confounders: Black, primigravida, education, Medicaid, vaginitis, delivery indication, gestational age, birth weight zscore, aerobe, anaerobe, placenta Mycoplasma, placenta inflammation.