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Prenatal Low-Dose Aspirin and Neurobehavioral Outcomes of Children Born Very Preterm

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KEY WORDS

acetylsalicylic acid, neuroprotection, periventricular leukomalacia, follow-up, neurologic disabilities

ABBREVIATIONS

EPIPAGE—Etude Epidemiologique des Petites Ages Gestationnels
SEH—subependymal hemorrhage
IVH—intraventricular hemorrhage
WMI—white matter injury
LDA—low-dose aspirin
MPC—mental processing composite
PS— propensity score
aOR—adjusted odds ratio
CI— confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: Aspirin given to the mother in high-risk pregnancies seems to produce a moderate reduction of several different risks such as preeclampsia; delivery before 37 weeks of gestation; and fetal growth restriction.

WHAT THIS STUDY ADDS: A low dose of prenatal aspirin treatment was not associated with adverse neonatal or long-term outcomes.

abstract

FREE

OBJECTIVE: Low-dose aspirin (LDA) given during pregnancy may alter brain development in very preterm infants. We report the short- and long-term outcomes of very preterm infants according to LDA treatment.

PATIENTS AND METHODS: Data were from the Etude Epidemiologique des Petites Ages Gestationnels (EPIPAGE) cohort study, which included all infants born before 33 weeks of gestation in 9 French regions in 1997. This study was restricted to 656 children who were born to 584 women with an obstetric history of placental vascular disease or with chronic hypertension or renal or autoimmune diseases. The main outcome measures were mortality, cerebral lesions, and outcome at 5 years of age, which were measured by a diagnosis of cerebral palsy; behavioral difficulties, which were assessed with the Strength and Difficulties Questionnaire; and cognitive impairment, which was measured by the mental processing composite scale of the Kaufman Assessment Battery for Children (an IQ-equivalent measure of cognitive ability in 2 dimensions: sequential and simultaneous processing scores).

RESULTS: LDA treatment was administered to 125 of 584 (21%) mothers and was not significantly associated with mortality, cerebral lesions, cerebral palsy, or global cognitive impairment of the children at 5 years of age. The proportion of low simultaneous processing scores (<70) was lower in the group with LDA (7% vs 19% without LDA; $P = .04$). This association was not significant after adjustment for propensity score, prognostic factors, and social class (adjusted odds ratio [aOR]: 0.59 [95% confidence interval (CI): 0.17–2.06]). LDA treatment was associated with a reduction, at the limit of significance, in total behavioral difficulties (aOR: 0.44 [95% CI: 0.19–1.02]) and hyperactivity (aOR: 0.43 [95% CI: 0.17–1.05]).

CONCLUSIONS: LDA was not associated with adverse neonatal or long-term outcomes. Moreover, the results suggest that LDA may be associated with a reduction in neurobehavioral difficulties. More research is needed to assess the effects of aspirin alone or combined with other neuroprotective agents. *Pediatrics* 2010;125:e29–e34

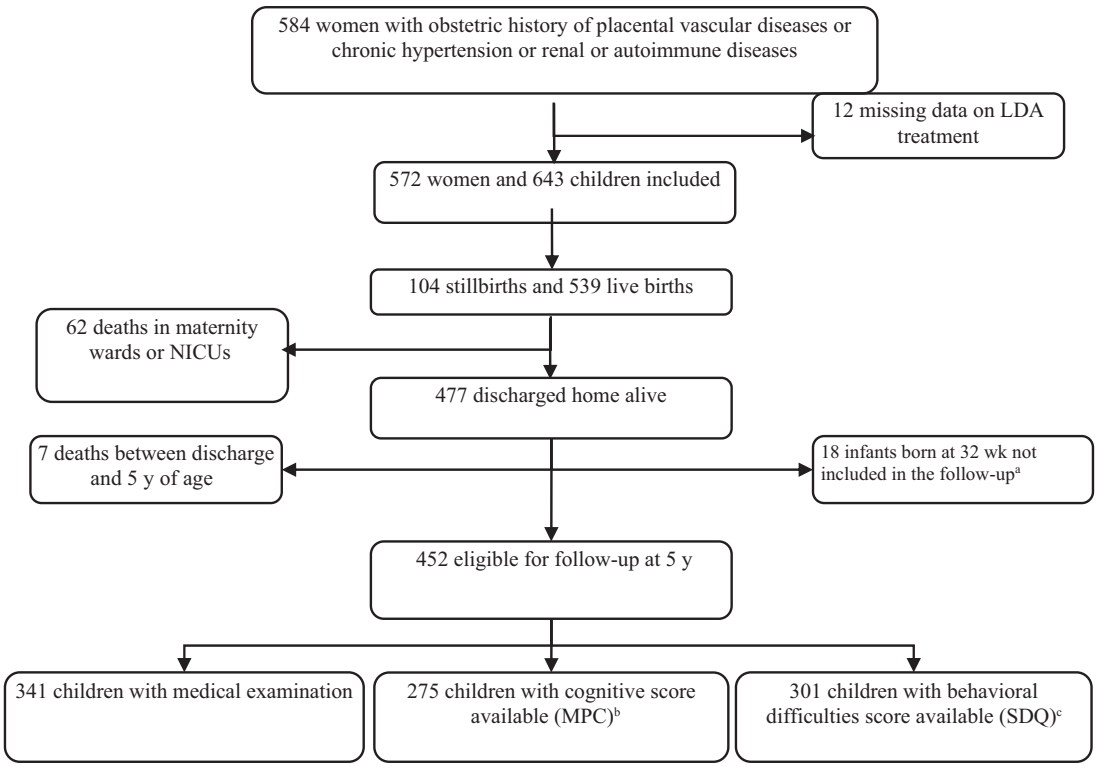

FIGURE 1

An overview of the study group. [a] Follow-up was proposed at hospital discharge for all infants who survived except in 2 regions where follow-up was randomly proposed to half of the infants who were born at 32 weeks of gestation; [b] MPC indicates mental processing composite of the K-ABC; [c] SDQ indicates strengths and difficulties questionnaire.

Learning to protect the preterm brain is a challenging priority in view of the disturbingly high rate of long-term neurosensory, cognitive, and behavioral disabilities in very preterm infants.[1] A large number of studies have examined the multifactorial origin of cerebral lesions (subependymal/intraventricular hemorrhages [SEH/IVH]) and white matter injuries [WMIs]) and later neurodisabilities, which involve acute/subacute ischemic/inflammatory antenatal or perinatal events combined with deprivation of placental hormonal or growth factors caused by preterm birth.[2] Aspirin given to the mother in high-risk pregnancies may cross the placenta.[3] Aspirin is well tolerated by the fetus and seems to produce a moderate reduction of several different risks (preeclampsia, delivery before 37 weeks of gestation, and fetal growth restriction) without increasing infant bleeding.[4] Nevertheless, the long-term effects of aspirin on preterm children are unknown. Aspirin inhibits cyclooxygenase 1 (COX 1) and COX 2. Because COX 2 plays a role in the dendritic arborization involved in the developing areas that are responsible for cognitive function in the human brain, its inhibition could be deleterious.[5] Conversely, aspirin may reduce the risk to vulnerable fetuses of IVH and WMI by stopping and resolving inflammation,[6] blocking the apoptotic nuclear factor κB,[7] scavenging free radicals,[8] or decreasing the propensity of the germinal matrix to hemorrhage after a high expression level of COX.[9] In the present observational population-based study, we aimed to assess the relations between low-dose aspirin (LDA) administered to women during pregnancy and the neurodevelopmental and behavioral abilities of 5-year-olds born before 33 weeks of gestation.

PATIENTS AND METHODS

The Etude Epidemiologique des Petites Ages Gestationnels (EPIPAGE) cohort study included all stillbirths and live births between 22 and 32 completed weeks of gestation in 9 regions of France in 1997.[1] We restricted this study to 584 mothers (656 children) with an obstetric history of preeclampsia, fetal growth restriction, or fetal death or with chronic hypertension or renal or autoimmune diseases. Women with no information available about aspirin intake ($n = 12$) were excluded; thus, the analysis included data for the 572 remaining women and 643 infants. There were 104 fetal deaths and 62 neonatal deaths, and 477 infants were discharged from the hospital alive (Fig 1). Accordingly, 452 infants were eligible for follow-up at 5 years of age. Because 15 (3%) families refused follow-up and 96 (21%) were

lost to follow-up, the study included 341 children.

Data were recorded by using standardized questionnaires that were administered in maternity wards and neonatal units. LDA treatment was extracted from obstetrical records. We also collected information on maternal social class, gestational age, infant gender, birth weight, small-for-gestational-age status (birth weight below the 10th percentile for gestational age in weeks and gender among live-born infants), plurality, antenatal corticosteroid administration, and outcomes (ie, stillbirth, neonatal death, and SEH/IVH and WMI diagnosed by neonatal cranial ultrasonographic studies). WMI was defined by the presence of periventricular echolucency or hyperechoic images that persisted for >14 days without cyst formation; periventricular parenchymal hematoma, defined as a large unilateral hyperechoic area; or isolated ventricular dilatation with no associated IVH.

Assessment at 5 years of age was based on a standardized medical and neuropsychological examination.[1] Physicians recorded their neurologic assessment (tone, reflexes, posture, and movements). We used the definition of cerebral palsy that was proposed by the Surveillance of Cerebral Palsy in Europe network.[10] Cognitive outcome was assessed by the mental processing composite (MPC) scale of the Kaufman Assessment Battery for Children. The MPC score is a global IQ-equivalent measure of cognitive ability in 2 dimensions: a sequential score and a simultaneous processing score. Cognitive impairment was defined as an MPC score of <70. To assess behavioral difficulties, parents completed the Strength and Difficulties Questionnaire. This questionnaire was structured into 5 scores that explore hyperactivity, conduct problems, emotional symptoms, peer problems, and prosocial behavior. A global indicator of behavioral difficulties was obtained by adding the first 4 scores.[11] The cutoff points were defined such that approximately 10% of children born at term were considered to be at risk for behavioral problems.

The propensity-score (PS) method was used to reduce indication bias in assessing the relation between LDA and outcomes.[12,13] The PS can be defined as a patient's probability of receiving LDA conditional on his or her individual observed covariates. In our study, the PS was estimated by a multivariate model that included the following covariates: maternal age, parity, tobacco consumption, multiple pregnancy, infertility treatment, and region. We studied crude associations between LDA and outcomes and then the same associations after adjustment for PS in quintiles. The final models adjusted for major prognostic factors such as gestational age, infant gender, pregnancy complications, and antenatal corticosteroids and for cognitive development and behavior, educational level, and social class. To take into account the nonindependence of observations in multiple pregnancies, we used generalized estimating equation models to study factors associated with LDA treatment, to estimate PS, and to measure crude and adjusted associations between LDA treatment and outcomes. We used SAS software (SAS Institute, Inc, Cary, NC) for the statistical analysis. The French Data Protection Authority approved the study.

RESULTS

Of 584 women who had at least 1 indication for LDA treatment, 125 (21%) received LDA (LDA group) and 447 did not (no-LDA group). The mean (SD) and median duration of treatment were 12 (7) and 13 weeks, respectively.

The rate of LDA treatment was significantly higher for women who were primiparous or nonsmokers or who had infertility treatment, hypertension, or small-for-gestational-age status at birth (Table 1). Although stillbirth was less frequent in the LDA group, this association was no longer significant after adjustment for PS (Ta-

TABLE 1 LDA Treatment According to Maternal and Pregnancy Characteristics ($N = 656$ Children)

	Children, *n*	%	*P*
Maternal age at birth, y			.51
<25	67	16	
25–34	398	22	
≥35	173	20	
Social class of family			.41
High	150	25	
Medium	133	23	
Low	313	19	
Maternal level of education			.06
University	106	25	
Secondary school, second part	92	30	
Secondary school, first part	296	19	
Primary school or no school	66	15	
Parity			.001
Primiparous	62	31	
1–2	385	24	
>2	194	12	
Multiple pregnancy			.03
No	513	23	
Yes	130	14	
Infertility treatment			.005
No	577	20	
Yes	52	37	
Smoking during pregnancy			<.001
No	316	27	
Yes	216	13	
Gestational age at delivery, wk			.73
24	15	13	
25	31	10	
26	39	18	
27	62	23	
28	59	20	
29	54	22	
30	99	23	
31	118	25	
32	166	19	
Pregnancy complications			<.001
Hypertension or SGA	288	36	
PPROM or IPL and other	348	9	

SGA indicates small for gestational age; PPROM, preterm premature rupture of membranes; IPL, idiopathic preterm labor.

TABLE 2 Perinatal Data and Neurologic and Behavioral Outcomes at 5 Years of Age According to LDA Treatment

	No LDA group, *n* (%)	LDA group, *n* (%)	*P*	OR (95% CI)
Neonatal outcomes				
Stillbirth	508 (16)	135 (11)	.07	0.59 (0.33–1.05)
				0.66 (0.35–1.25)[a]
				0.97 (0.23–4.14)[b]
Neonatal death	419 (11)	120 (13)	.70	1.13 (0.61–2.11)
				1.04 (0.52–2.07)[a]
				1.05 (0.46–2.37)[c]
SEH/IVH	393 (21)	113 (22)	.86	1.05 (0.63–1.73)
				1.28 (0.73–2.25)[a]
				1.35 (0.72–2.54)[c]
White matter injury	394 (18)	113 (21)	.40	1.24 (0.74–2.09)
				1.39 (0.78–2.47)[a]
				1.42 (0.76–2.68)[c]
Neurologic and behavioral outcomes at 5 y				
Cerebral palsy	257 (5)	84 (5)	.81	0.87 (0.28–2.70)
				1.02 (0.31–3.34)[a]
				1.12 (0.28–4.45)[c]
MPC score < 70	205 (21)	70 (13)	.25	0.63 (0.29–1.38)
				0.99 (0.39–2.52)[a]
				0.85 (0.32–2.29)[d]
Sequential processing score < 70	205 (15)	70 (11)	.56	0.78 (0.34–1.81)
				0.89 (0.33–2.39)[a]
				0.78 (0.27–2.29)[d]
Simultaneous processing score < 70	205 (19)	70 (7)	.04	0.36 (0.14–0.96)
				0.60 (0.19–1.89)[a]
				0.59 (0.17–2.06)[d]
Total behavioral difficulties	228 (27)	73 (12)	.008	0.36 (0.17–0.77)
				0.52 (0.24–1.12)[a]
				0.44 (0.19–1.02)[d]
Hyperactivity	228 (23)	73 (11)	.03	0.42 (0.19–0.91)
				0.45 (0.20–1.00)[a]
				0.43 (0.17–1.05)[d]
Conduct problems	228 (14)	73 (7)	.09	0.42 (0.15–1.16)
				0.65 (0.18–2.39)[a]
				0.73 (0.18–2.94)[d]
Emotional symptoms	228 (20)	73 (15)	.33	0.69 (0.33–1.46)
				0.85 (0.36–1.97)[a]
				0.69 (0.29–1.65)[d]
Peer problems	228 (23)	73 (15)	.25	0.65 (0.32–1.34)
				0.70 (0.32–1.53)[a]
				0.83 (0.36–1.91)[d]
Prosocial behavior problems	228 (21)	73 (12)	.07	0.49 (0.23–1.06)
				0.62 (0.25–1.51)[a]
				0.57 (0.21–1.51)[d]

[a] Adjusted for PS.
[b] Adjusted for PS, cause of preterm birth, and gender.
[c] Adjusted for PS, cause of preterm birth, antenatal corticosteroids, gestational age, and gender.
[d] Adjusted for PS, social level, maternal level of education, cause of preterm birth, antenatal corticosteroids, gestational age, and gender.

ble 2). There was no significant association between LDA and any neonatal outcome. The cerebral palsy rate at 5 years of age did not differ according to LDA treatment (Table 2), nor did the rate of low MPC or low sequential processing scores (<70). The rate of simultaneous processing scores of <70 was significantly lower in the LDA group than in the no-LDA group (7% vs 19%; $P = .04$), but not after adjustment for PS, prognostic factors, and social class (adjusted odds ratio [aOR]: 0.59 [95% confidence interval (CI): 0.17–2.06]). Results showed a reduction at the limit of significance in total behavioral difficulties (aOR: 0.44 [95% CI: 0.19–1.02]) and hyperactivity (aOR: 0.43 [95% CI: 0.17–1.05]) associated with LDA treatment after adjustment for PS and prognostic factors.

DISCUSSION

Our analysis is based on a large population-based study of very preterm infants who were born after antenatal corticosteroids and surfactant became widely available. We were able to assess 5-year outcomes of these children and their association with LDA treatment; at the age of 5 years, cerebral palsy, cognitive impairment, and known behavioral difficulties may predict long-term outcomes.[14] However, 25% of the children were not assessed at the age of 5 years, and the rate of loss to follow-up was higher in the no-LDA group compared with the LDA group (27% vs 16%). The higher rate of loss to follow-up in the no-LDA group may have been caused by better outcomes compared with the LDA group; parents of children with better outcomes may be less likely to return for the follow-up examination. However, most studies have found that children who were lost to follow-up had worse outcomes. Therefore, the higher rate of loss to follow-up in the no-LDA group may have resulted in an underestimation of neurodevelopmental impairments in the no-LDA group.[15–18] Hence, loss to follow-up is unlikely to explain the associations that were found between LDA treatment and a lack of behavioral difficulties. It is difficult to control for indication bias in observational studies with standard analytical methods. Our approach, based on the PS method for improving control for indication bias[12,13] and additional adjustment for major prognostic factors, minimizes the likelihood of

attributing an effect to LDA caused by other factors.

We found no adverse effects that were associated with aspirin: fetal exposure to LDA did not increase rates of fetal/neonatal mortality, neonatal cerebral damage, or brain-development disorders. Although LDA exerts antiplatelet effects in fetuses and newborns, which could promote neonatal bleeding,[4] our study found no difference between the groups in rates of SEH/IVH and WMI. Moreover, our findings were consistent with those of Valcamonico et al[19] and the PARIS Collaborative Group meta-analysis.[20] A trend toward a decrease in stillbirth was observed. Stillbirth or infant deaths were reported to be less common in the PARIS study, but the results did not reach statistical significance.[20] LDA did not seem to affect rates of either cerebral palsy or global cognitive impairment, which are perhaps the most severe sequelae of preterm birth.[14] However, LDA was associated with a decrease, although not significant, in some specific cognitive and behavioral dysfunctions, with associated ORs of 0.5 to 0.6. These observations are important in view of the range of overlapping cognitive, executive, and behavioral problems that are found in very preterm children. These dysfunctions affect natural development processes and educational requirements for children who are born preterm, who are more likely than children born at term to be enrolled in special education classes.[21,22]

CONCLUSIONS

To our knowledge, this is the first study to examine the effects of LDA in such a homogenous population of very preterm newborns. We found that antenatal LDA was not associated with adverse neonatal or long-term outcomes. Moreover, the results of our study suggest that LDA may be associated with a reduction in neurobehavioral difficulties. However, these results should be interpreted with caution and need to be confirmed. Other studies are urgently needed to confirm the clinical potential of aspirin use during pregnancy, because few neuroprotective agents have been identified.

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