

Low-Dose Aspirin in Pregnancy: Maternal and Neonatal Aspirin Concentrations and Neonatal Prostanoid Formation

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ABSTRACT. *Objective.* To evaluate maternal and neonatal plasma concentrations of acetylsalicylic acid and salicylic acid and the neonatal endogenous prostanoid formation during low-dose aspirin prophylaxis (LDA; 100 mg daily) in pregnant women.

Methods. Concentrations of acetylsalicylic acid and salicylic acid in maternal plasma after at least 4 weeks of LDA ($n = 14$) and in umbilical cord plasma of newborns after maternal LDA ($n = 7$) were determined by gas chromatography–mass spectrometry. Platelet and renal formation of thromboxane A_2 and the formation of prostaglandin E_2 and prostacyclin were evaluated in vivo by quantification of index metabolites in plasma and urine by gas chromatography–mass spectrometry in neonates after maternal LDA ($n = 14$) and in a control group.

Results. In the pregnant women, acetylsalicylic acid and salicylic acid concentrations rapidly increased after ingestion of LDA. Acetylsalicylic acid was completely eliminated within 4 hours, whereas salicylic acid was detected with low concentrations at 18 and 21 hours after dosing. In the neonates, acetylsalicylic acid was not detected. Salicylic acid was detected in 1 infant only. Platelet thromboxane A_2 formation in the newborn infants was significantly suppressed but recovered within 2 to 3 days after discontinuation of LDA. Renal thromboxane A_2 formation and the formation of prostaglandin E_2 and prostacyclin were not affected by LDA.

Conclusion. In pregnant women who are treated with LDA, acetylsalicylic acid is not completely inactivated in the portal circulation but reaches the uteroplacental circulation and exerts antiplatelet effects in the fetus and newborn. *Pediatrics* 2003;111:e77–e81. URL: <http://www.pediatrics.org/cgi/content/full/111/1/e77>; low-dose aspirin, prostanoids, newborn infant, mass spectrometry.

ABBREVIATIONS, LDA, low-dose aspirin; Tx, thromboxane; PG, prostaglandin; GC-MS, gas chromatography–mass spectrometry.

Treatment of pregnant women with low-dose aspirin (LDA) for prevention of preeclampsia has been investigated extensively during the past years. Routine administration of LDA is not justified in women identified by clinical and historical risk factors.^{1,2} LDA, however, may be beneficial in small subgroups of high-risk women or if treat-

ment is started very early or at a higher dose.^{3–7} In addition to its use in preeclampsia, LDA is under investigation for the prevention of other pregnancy complications.^{8,9}

The main effect of LDA is inhibition of platelet thromboxane (Tx) A_2 formation by irreversible acetylation of platelet cyclooxygenase.¹⁰ The formation of prostaglandins (PGs) and prostacyclin is only marginally affected.¹¹ Acetylsalicylic acid crosses the placenta.¹² The ingestion of aspirin in antiinflammatory doses by pregnant women has been associated with an increased risk of fetal and neonatal hemorrhage.^{13,14} So far, plasma levels of acetylsalicylic acid have not been measured in newborns after maternal LDA. Only a few investigations have addressed the effect of LDA on the fetal and neonatal formation of platelet TxA_2 . Both impaired^{15–18} and unimpaired^{19,20} formation of platelet TxA_2 has been demonstrated. Most of these investigations^{15–18,20} measured the capacity of platelets to form TxA_2 ex vivo, which is greater than the actual in vivo formation,²¹ whereas the neonatal endogenous formation of Tx, PGs, and prostacyclin after maternal LDA has not been evaluated.

The present study was designed to determine maternal and neonatal plasma levels of acetylsalicylic acid and salicylic acid during LDA treatment in women at risk for pregnancy-induced hypertension. In the neonates, the inhibition and recovery of platelet TxA_2 formation, the renal TxA_2 formation, and the formation of prostacyclin and PGE_2 were evaluated in vivo.

METHODS

Patients and Control Subjects

Pregnant women and their newborn infants were included in the study when the women had been treated with 100 mg of aspirin daily for prevention of preeclampsia. The women started LDA prophylaxis at 14 to 33 (median: 20) gestational weeks. Because of anesthesiological concerns, LDA was discontinued before the expected parturition to preserve the possibility of performing an epidural anesthesia, which was considered to be otherwise associated with an increased risk of hemorrhage. Therefore, the number of days from discontinuation of LDA to delivery differed between the newborns. This procedure enabled us to evaluate the relationship between alterations in neonatal prostanoid formation and the number of days without LDA. Because 21% of women in LDA trials are noncompliers,²² urinary excretion of 2,3-dinor- TxB_2 , reflecting platelet TxA_2 formation,²³ was measured while the women were still treated with LDA and was compared with the urinary excretion of 2,3-dinor- TxB_2 in healthy pregnant women matched for gestational age (± 10 days). Only newborn infants of mothers with complete inhibition of

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2,3-dinor-TxB₂ excretion were evaluated further. In the pregnant women, plasma concentrations of acetylsalicylic acid and salicylic acid were measured after at least 4 weeks of LDA treatment. In a subgroup of newborns, concentrations of acetylsalicylic acid, salicylic acid, and 11-dehydro-TxB₂, which reflects the in vivo formation of platelet TxA₂,²³ were determined in umbilical cord blood. In all newborns, urinary excretion of index metabolites of platelet (2,3-dinor-TxB₂) and renal (TxB₂) TxA₂ formation²³ and the formation of PGE₂ (PGE₂ and 7 α -hydroxy-5,11-diketotetranorprostate-1,16-dioic acid)²⁴ and prostacyclin (6-keto-PGF_{1 α}) and 2,3-dinor-6-keto-PGF_{1 α})²⁵ were measured during the first days of life. Plasma 11-dehydro-TxB₂ and urinary prostanoid metabolites were also measured in healthy, age-matched (± 2 days) term infants who were born after an uneventful pregnancy. The concept of assessing the in vivo formation of TxA₂, PGE₂, and prostacyclin by measuring index metabolites in plasma or urine has been evaluated in adults^{23–25} and does therefore not necessarily apply to newborns. Newborns, however, generate the same metabolites that reflect the in vivo generation of the respective primary prostanoids in adults.²⁶ Consequently, index metabolites have been used successfully to investigate the generation of TxA₂ by neonatal platelets^{15,16,18,19} and to clarify the role of prostanoids in various diseases of newborns.^{27–32} The local ethics committee for clinical studies approved the study protocol. Informed consent was obtained from all mothers.

Sample Collection

Umbilical cord blood was collected with a large-bore cannula into ice-cold tubes containing indomethacin in a 3.8% sodium citrate solution immediately after clamping of the umbilical cord. The sample was immediately centrifuged at 4°C and 1000 g. The plasma was frozen at -80°C . Urine was collected over a period of 24 hours in the women. In the newborns, urine was collected in a urine bag for infants over a period of 3 to 13 (median: 10) hours. The urine bag was connected to a container in a refrigerator. During the collection period, the urine was kept at 4°C. After the collection period, the volume was determined and an aliquot was stored at -80°C until analysis.

Analytical Methods

The methods for quantification of prostanoids in urine and plasma by gas chromatography–mass spectrometry (GC-MS) have been previously developed in our laboratory and have been described elsewhere.^{33,34} Quantification of acetylsalicylic acid and salicylic acid was accomplished as follows. Deuterated salicylic acid was prepared by a bromine-deuterium exchange reaction.³⁵ The obtained [3,5-²H₂]salicylic acid was converted by an acetylation reaction with [²H₆]acetic anhydride and [²H₂]SO₄ to the corresponding [²H₅]acetylsalicylic acid. The deuterated standards contain 2.4% (salicylic acid) and 0.9% (acetylsalicylic acid) non-deuterated material. Standard solutions of [3,5-²H₂]salicylic acid and [²H₅]acetylsalicylic acid in ethanol were stored at -80°C . Plasma (500 μL) was spiked with 500 ng of [²H₂]salicylic acid and 500 ng of [²H₅]acetylsalicylic acid. A total of 1.5 mL of 0.06 M sodium phosphate buffer, 1.5 mL of 0.05 M tetrabutyl-ammonium hydrogensulfate (phase-transfer catalyst), 10 μL of pentafluorobenzyl bromide (reagent), and 2 mL of dichloromethane as extracting solvent were added. Under vigorous stirring for 10 minutes, the mixture was allowed to form the pentafluorobenzyl derivatives of salicylic acid and acetylsalicylic acid. After centrifugation, the organic phase was evaporated to dryness under nitrogen. The residue was resuspended in 1 mL of hexane, and 1 mL of water was added. After mixing for 30 seconds and centrifugation with $1000 \times g$ for 5 minutes, the hexane phase was taken and dried under a gentle stream of dry nitrogen. The sample was dissolved in 20 μL of ethyl acetate. One microliter of this solution was injected into the GC-MS/MS system. GC-MS/MS analysis was conducted on a Finnigan MAT TSQ45 GC-MS (Finnigan MAT, Bremen, Germany). GC separation was performed on a fused silica capillary column (DB-5; 20 m \times 0.25 mm internal diameter, film thickness 0.25 μm ; J&W, Carlo Erba, Hofheim, Germany) in splitless mode at an inlet pressure of 100 kPa. The GC oven temperature program was as follows: the initial temperature of 100°C was held for 2 minutes then increased at 25°C/min to 280°C and at 10°C/min to 310°C. This temperature was held for 2 minutes. Mass spectrometer conditions were as follows: GC injector temperature 250°C, interface temperature 290°C, methane

chemical ionization gas pressure 50 Pa, electron energy 70 eV, emission current 0.2 mA, conversion dynode 3 kV, and electron multiplier 2000 V. Collision cell pressure was 0.2 Pa, and collision energy was 12 eV. The most intense ions in the upper mass region were [M+H]⁺ (salicylic acid, m/z 319 and ²H₂-salicylic acid, m/z 321), [M+H-(CH₂=C=O)]⁺ (acetylsalicylic acid, m/z 319), and [M+H-(C²H₂=C=O)]⁺ (²H₅-acetylsalicylic acid, m/z 322). These ions were chosen as parent ions for collisionally activated decomposition. In the collisionally activated decomposition spectra of all derivatives, only 3 daughter ions of the parent ion ([P]⁺) could be observed: [P-H₂O]⁺, [P-PFBOH]⁺, and PFB⁺. Of these, the most intense ion ([PFB]⁺) was used for quantification in the selective reaction monitoring mode. Because of the relatively high amount of undeuterated material in the deuterated internal standards, the detection limit was 30 ng/mL for both acetylsalicylic acid and salicylic acid. The assay was validated in the concentration range of 30 to 500 ng/mL. Acetylsalicylic acid was stable in plasma samples kept 1 hour at room temperature. During sample preparation, no shift from acetylsalicylic acid to salicylic acid was observed. The intra-assay accuracy was less than $\pm 10\%$ bias from the nominal concentration. The interassay precisions (day-to-day variability) were $<15\%$ (coefficient of variation) for acetylsalicylic acid and salicylic acid.

Statistical Analysis

Continuous data were assessed for normal distribution with normal plots and the Shapiro-Francia W test.³⁶ Nonparametric statistical methods were used because not all variables were normally distributed. Data were expressed as the median (25th, 75th percentiles) unless otherwise stated. The primary study parameters were urinary excretion of 2,3-dinor-TxB₂ and plasma concentrations of 11-dehydro-TxB₂ in the newborns. Urinary excretion of TxB₂ and of PGE₂ and prostacyclin index metabolites were secondary study parameters analyzed exploratively. Comparisons of the medians of 2 groups were performed by the Mann-Whitney U test. The relationship between continuous variables was analyzed by Spearman rank correlation. $P < .05$ was considered significant. All analyses were performed with use of StatView software 5.0 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

Fourteen newborn infants and their mothers were included in the study. The infants were born at 36 to 42 (median: 40) gestational weeks. Birth weight was 3455 g (3280 g; 3720 g). All infants were healthy. In particular, no hemorrhage or clinical signs of impaired platelet function were observed. Intracranial hemorrhage was excluded by cerebral ultrasound.

Plasma Concentration of Acetylsalicylic Acid and Salicylic Acid

In the pregnant women, plasma concentrations of acetylsalicylic acid and salicylic acid increased rapidly after ingestion of LDA (Fig 1). The highest plasma levels of acetylsalicylic acid (4210 ng/mL) and salicylic acid (7928 ng/mL) were measured after 30 and 75 minutes, respectively. Four hours after ingestion of LDA, acetylsalicylic acid was no longer detectable. Plasma concentrations of salicylic acid were 59 and 64 ng/mL after 18 and 21 hours, respectively. Plasma concentrations of acetylsalicylic acid and salicylic acid were measured in umbilical cord blood in a subgroup of 7 newborns. The infants' mothers had discontinued LDA 1 to 13 days (median: 3 days) before delivery. Acetylsalicylic acid was not detected in any of the samples. Salicylic acid (39 ng/mL) was detected in 1 infant. This infant's mother had discontinued LDA 1 day before delivery.

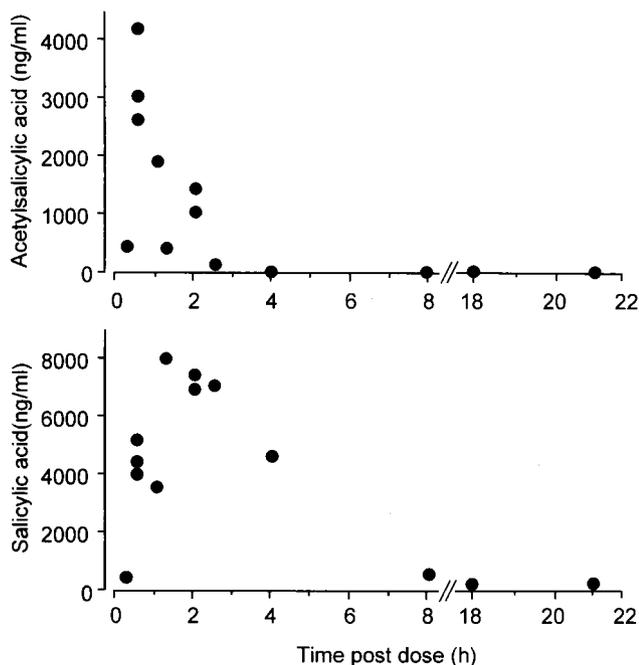


Fig 1. Plasma concentrations of acetylsalicylic acid and salicylic acid in pregnant women after at least 4 weeks of prophylaxis with LDA (100 mg/d).

Formation of Platelet TxA₂ in Pregnant Women During LDA

In all women, platelet TxA₂ formation was evaluated by measuring the urinary excretion of 2,3-dinor-TxB₂ 1 to 18 days (median: 6 days) before parturition and while the women were still taking LDA. Urinary excretion of 2,3-dinor-TxB₂ was lower in the pregnant women who had been treated with LDA as compared with healthy, untreated pregnant women (3.8 ng/h/1.73 m² [2.4 ng/h/1.73 m²; 5.4 ng/h/1.73 m²] vs 26.8 ng/h/1.73 m² [23.2 ng/h/1.73 m²; 31.6 ng/h/1.73 m²]; *P* < .0001). Urinary excretion rates of 2,3-dinor-TxB₂ of the 2 groups did not overlap (range: 2.0–7.1 and 11.1–53.3 ng/h/1.73 m² in the LDA and control groups, respectively). This indicates complete inhibition of platelet TxA₂ formation at the time of the investigation.

Formation of Prostanoids in the Newborn Infants

Plasma concentrations of 11-dehydro-TxB₂ were measured in umbilical cord blood of a subgroup of 7 newborns. The infants' mothers had discontinued LDA 1 to 13 days (median: 3 days) before delivery. Plasma 11-dehydro-TxB₂ correlated with the days without LDA (*r*² = 0.88, *r* = 0.94, *P* = .02; Fig 2) and was lower in the newborns after maternal LDA prophylaxis than in the control subjects (20.1 pg/mL [7.7 pg/mL; 42.6 pg/mL] versus 70.7 [42.4 pg/mL; 117.0 pg/mL]; *P* = .01; Fig 2). Urinary excretion of prostanoid metabolites was measured in all newborns. At the time of the investigation, the infants were 1 to 10 days old (median: 2 days) and the infants' mothers had discontinued LDA 1 to 17 days before (median: 5.5 days). Urinary 2,3-dinor-TxB₂ (platelet TxA₂ formation) was lower in the newborns after maternal LDA than in the control subjects (14.4 ng/h/1.73 m²

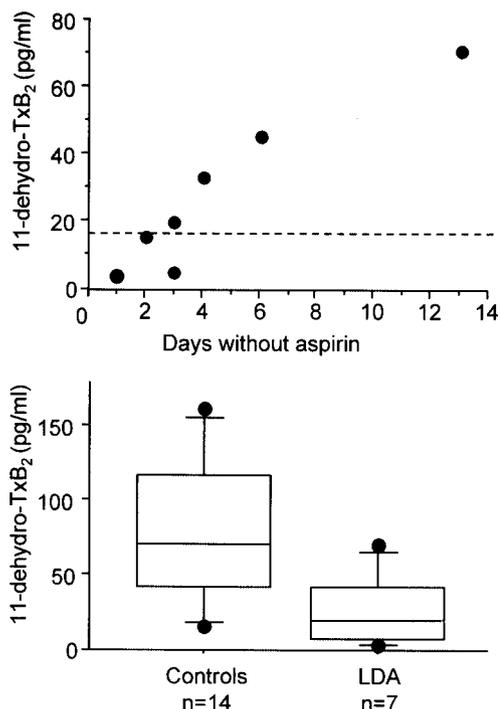


Fig 2. Concentration of 11-dehydro-TxB₂ reflecting in vivo platelet thromboxane A₂ formation in umbilical cord blood of newborns after maternal LDA prophylaxis. The infants' mothers had discontinued LDA 1 to 13 days before delivery. 11-dehydro-TxB₂ correlated with the days without LDA aspirin (*r*² = 0.88, *r* = 0.94, *P* = .02; top) and was lower in the newborns after maternal LDA than in the control subjects (*P* = .01; bottom). The broken line in the top panel indicates the fifth percentile of the control group.

[10.1 ng/h/1.73 m²; 19.6 ng/h/1.73 m²] vs 21.4 ng/h/1.73 m² [17.8 ng/h/1.73 m²; 32.7 ng/h/1.73 m²]; *P* = .02). 2,3-Dinor-TxB₂ was weakly correlated with the days without LDA (*r* = 0.52, *P* = .06). Urinary TxB₂ excretion (mainly renal TxA₂ formation) was not different between the 2 groups (3.7 ng/h/1.73 m² [1.5 ng/h/1.73 m²; 6.0 ng/h/1.73 m²] vs 4.6 ng/h/1.73 m² [2.8 ng/h/1.73 m²; 8.6 ng/h/1.73 m²]; *P* = .34). Neither the urinary excretion of PGE₂ and 7 α -hydroxy-5,11-dioxo-tetranor-prosta-1,16-dioic acid (formation of PGE₂) nor the urinary excretion of 6-keto-PGF_{1 α} and 2,3-dinor-6-keto-PGF_{1 α} (formation of prostacyclin) was affected by maternal LDA prophylaxis (data not shown).

DISCUSSION

We found an inhibition of platelet TxA₂ formation in neonates of pregnant women who had been treated with 100 mg of aspirin daily. Both acetylsalicylic acid and salicylic acid were detected in the plasma of the pregnant women in considerable amounts. At birth, plasma acetylsalicylic acid was below the detection limit in all newborns, and salicylic acid was detected in a very low concentration in 1 infant only.

Plasma concentrations of acetylsalicylic acid and salicylic acid measured in the present investigation largely agree with published pharmacokinetic data of both compounds in healthy adults^{10,37} and in pregnant women after a single aspirin dose.³⁸ It has been assumed that during LDA prophylaxis in preg-

nant women only very little acetylsalicylic acid reaches the uteroplacental circulation and may subsequently be transported across the placenta into the fetal compartment because acetylsalicylic acid is almost completely inactivated in the portal circulation.²⁰ The results of the present investigation, however, definitely indicate that the fetus is exposed to acetylsalicylic acid and salicylic acid during LDA prophylaxis in pregnancy.

Ex vivo studies indicate that acetylsalicylic acid readily crosses the placenta.¹² The placental transfer of salicylic acid has been demonstrated in vivo.^{39,40} After chronic ingestion of acetylsalicylic acid in anti-inflammatory doses, plasma concentrations of salicylic acid are higher in the newborn infants than in the mothers because the protein binding of salicylic acid is considerably higher in neonatal than in maternal plasma.^{39,40} Newborn infants mainly eliminate salicylic acid by conversion to the glycine and glucuronic acid conjugates.⁴⁰ The capacity of these pathways is very low, and elimination of salicylic acid by newborn infants is, therefore, much slower than in adults with a half-life of approximately 4 to 11 hours.⁴⁰ Against this background, salicylic acid might accumulate in the fetus and might therefore be detectable in the neonate. In the newborns studied, however, salicylic acid was detected with a very low concentration in umbilical cord blood in only 1 infant, whose mother had ingested the last aspirin dose 1 day before delivery. This suggests that the concentration of salicylic acid in the fetus is actually very low during maternal LDA. On the basis of a neonatal to maternal plasma salicylic acid concentration ratio of 1.6³⁹ and a maternal trough level of salicylic acid of approximately 50 ng/mL as suggested by the present study, an estimate of the resulting fetal plasma concentration of salicylic acid is <100 ng/mL.

Although acetylsalicylic acid concentrations were high in the pregnant women, the drug was not detected in any of the newborn infants studied 24 hours or more after the last maternal LDA. The concentrations of acetylsalicylic acid in the systemic and uteroplacental circulation of pregnant women, however, obviously result in substantial amounts of acetylsalicylic acid that cross the placenta and exert antiplatelet activity in the fetus. This assumption is confirmed by the analysis of the endogenous prostanoid formation in the newborn infants, which demonstrates the typical pattern of prostanoid formation during LDA treatment. The formation of platelet TxA₂ is selectively inhibited, whereas the renal TxA₂ formation and the formation of PGE₂ and prostacyclin are not affected. The inhibition of platelet TxA₂ formation cannot be ascribed to the placental transfer of salicylic acid, because even the administration of high doses of salicylic acid (1200 mg daily) has no effect on platelet TxA₂ formation.⁴¹ Benigni et al¹⁵ demonstrated that treating pregnant women with 60 mg of aspirin daily resulted in a 63% reduction of the ex vivo capacity of neonatal platelets to release TxA₂ in umbilical cord blood. Valcamonico et al¹⁸ and Regan et al¹⁶ obtained similar results. The ex vivo capacity of platelet TxA₂ formation, however, is considerably

greater than the actual in vivo biosynthetic rate.²¹ We therefore measured the plasma 11-dehydro-TxB₂ concentration and the urinary 2,3-dinor-TxB₂ excretion. Both compounds reflect the in vivo formation of platelet TxA₂.^{21,23} Thus, maternal LDA inhibits the actual in vivo formation of TxA₂ in the fetus and neonate.

Plasma 11-dehydro-TxB₂ was clearly lower in the newborns after maternal LDA than in the control subjects. The difference between the 2 groups was less pronounced with respect to urinary 2,3-dinor-TxB₂ excretion. The different inhibition of platelet TxA₂ formation as assessed by plasma 11-dehydro-TxB₂ and urinary 2,3-dinor-TxB₂ is probably attributable to the shorter period of time that elapsed since the last ingestion of aspirin by the mothers in the newborns with analysis of plasma 11-dehydro-TxB₂ (median: 3 days) as compared with the newborns with analysis of urinary 2,3-dinor-TxB₂ (median: 5.5 days). The correlation between plasma 11-dehydro-TxB₂ in umbilical cord blood and the days without LDA indicates rapid recovery of platelet TxA₂ formation. Already 2 to 3 days after the infants' mothers had ingested the last aspirin dose, plasma 11-dehydro-TxB₂ in the newborns exceeded the fifth percentile of plasma 11-dehydro-TxB₂ in the control subjects (Fig 2). Valcamonico et al¹⁸ and Benigni et al¹⁵ demonstrated recovery of the ex vivo capacity to form platelet TxA₂ in neonates after LDA within 4 and 5 days. These findings are consistent with the idea that inhibition of platelet TxA₂ formation by aspirin is attributable to irreversible acetylation of platelet cyclooxygenase and will recover with the production of unaffected platelets. The results also indicate that during LDA and until 2 to 3 days after the last aspirin dose, platelet function may be impaired in the fetus and newborn infant.

Inhibition of platelet TxA₂ formation in the fetus and neonate as observed in the present study may be clinically relevant. Ingestion of aspirin in analgesic or anti-inflammatory doses a few days before delivery is associated with bleeding complications in the newborn infant.^{13,14} In contrast, major hemorrhage was not observed in the large number of infants who were born after LDA prophylaxis in pregnancy.^{1,42,43} In adults, inhibition of the capacity to form TxA₂ must be virtually complete (>95%) before Tx-dependent platelet activation is influenced in vivo.^{44,45} Neither the previously published studies^{15,16,18} nor the findings of the present study support the assumption of complete inhibition of fetal or neonatal platelet TxA₂ formation by LDA in pregnancy when aspirin doses up to 100 mg daily are used. It has been suggested that a higher aspirin dose might possibly be more effective in the prevention of preeclampsia.^{4,46,47} Considering, however, the inhibition of platelet TxA₂ formation already present in the neonates after 100 mg of aspirin daily and the dose-dependent decline of platelet TxA₂ formation when aspirin doses of 20 to 325 mg/d are ingested,¹¹ increasing the aspirin dose will result in a more pronounced inhibition of platelet TxA₂ formation, which may be associated with an increased risk of fetal and neonatal hemorrhage.

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