

Paracetamol preceding very preterm birth: Is it safe?

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Abstract

Introduction: The use of paracetamol for pain relief in pregnancy is common. However, the influence of paracetamol on the perinatal adaptation of high-risk infants has not been studied. These data are important for safety, since another inhibitor of prostaglandin synthesis is harmful to infants born very preterm and increases serious morbidity. We studied whether the use of paracetamol had an adverse influence on neonatal adaptation and the outcomes of infants during the first hospitalization.

Material and Methods: We studied the patient records of high-risk mothers and their infants born before 32 weeks of gestation for multiple variables over a period of 84 months in Oulu University Hospital, a regional tertiary care hospital caring for high-risk deliveries and providing neonatal intensive care. In a matched cohort setting, the exposition was defined as paracetamol use <24 h before childbirth. The controls had consumed no paracetamol up to 1 week before delivery. Infants with major anomalies were excluded. The primary outcome was defined as the need for early interventional treatments for the preterm infants. Outcomes during the first hospitalization were also studied.

Results: Altogether, 170 fetuses from 149 mothers were exposed to paracetamol during the study period. The control population, delivering during the same period, consisted of 118 non-exposed fetuses from 104 mothers. Among them, the mothers were pairwise matched according to their medications, amniotic fluid leakage time, clinical infections, and delivery mode. After matching, 72 mothers/group remained, resulting in 88 paracetamol-exposed infants and 85 controls. No perinatal adverse reactions were detected. There were no differences in either circulatory support during the first postnatal day or in the risk for major diseases during the first hospitalization. Paracetamol-exposed infants needed fewer acute delivery room therapies (51.1% vs. 65.9%, mean difference -14.89; 95% confidence interval -0.29 to -0.003). Maternal total paracetamol dose in the 1 week before delivery correlated positively with Apgar scores.

Conclusions: Antenatal paracetamol given within 24 h before birth had no adverse effects on extremely or very preterm infants. The long-term safety of paracetamol and

Abbreviation: NICU, neonatal intensive care unit

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the potential acute benefits for preterm infants during perinatal transition remain to be proven in larger, prospective settings.

KEYWORDS

acetaminophen, Apgar scores, blood pressure, pain therapy, premature infant, respiratory support

1 | INTRODUCTION

Paracetamol (acetaminophen) is used worldwide as an over-the-counter drug for pain relief.¹ It is considered safe within the recommended doses and is not contraindicated, even during pregnancy.² Despite its wide usage, only a few studies about neonatal outcomes after fetal intrauterine exposure to paracetamol are available.³⁻⁵ Conversely, maternal indomethacin medication is associated with serious adverse reactions in neonates, including fetal ductus arteriosus contraction, severe intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and necrotizing enterocolitis.⁶⁻⁸ A systematic review reported that maternal opioid use was associated with lower umbilical artery pH and a higher need for postnatal tactile stimulation in neonates.⁹ Severe fetal consequences are well known for some maternal medications, whereas others (e.g., corticosteroids, magnesium infusions, antibiotics, and antiarrhythmic medications) have been used during pregnancy for the treatment or prevention of fetal or neonatal diseases.^{10,11}

Although the precise molecular mechanisms of action remain unknown, paracetamol inhibits the peroxidase subcomponent of the prostaglandin synthase enzyme and decreases prostaglandin synthesis.^{12,13} Recent studies reported that paracetamol crossed the placental barrier via passive diffusion.^{4,14} It had fetal hemodynamic effects, and even contracted ductus arteriosus, which decreases cerebral oxygenation when persistent in extremely or very preterm infants.^{15,16} Some epidemiological and experimental data on paracetamol use during pregnancy have associated it with possible long-term adverse effects on offspring, raising questions about its safety.^{17,18} However, several recent studies did not support these results.^{19,20} For all this, paracetamol is emerging as a new treatment for patent ductus arteriosus in extremely or very preterm infants with hardly any adverse reactions reported.^{21,22} Despite promising results with the administration of paracetamol after very premature birth, acute paracetamol effects on newborn preterm infants after maternal administration just before spontaneous or elective premature birth have not been studied.

In the present study, we evaluated the effects of antenatal paracetamol exposure on infants' delivery room rescue therapies. Paracetamol was used for pain and discomfort within 24h before preterm births. The paracetamol-exposed fetuses and nonexposed controls were studied for perinatal transition characteristics. We hypothesized that maternal paracetamol for treatment of discomfort shortly before the delivery of extremely or very preterm infants may not have adverse effects on the fetus or the newborn. The primary

Key message

In pregnancy, paracetamol and its potential toxic products enter the fetal compartment and may be harmful to the fetus and the newborn. In the present matched cohort study, preterm paracetamol-exposed infants had no excess of early adverse events or serious morbidities during hospitalization.

outcome was defined as the need for any acute rescue treatments, i.e., surfactant administration, adrenalin injections, inotrope infusions, and/or fluid boluses, in the delivery room. This outcome was chosen to reflect responses to birth stress when an immature fetus is exposed to effective inhibition of prostaglandin synthesis.^{7,8} Secondary outcomes included neonatal morbidities during neonatal intensive care unit (NICU) stay and at discharge from hospital, and death up to 1 year of age.

2 | MATERIAL AND METHODS

We screened extremely and very preterm infants (birth weight ≤ 1500 g and/or length of gestation $<32+0$ weeks) born between January 2012 and December 2018 in the tertiary-level perinatal center, Oulu University Hospital Delivery Unit, and treated in the NICU of Oulu University Hospital, Oulu, Finland, for maternal in-hospital paracetamol use before delivery (Figure 1). We obtained clinical data, paracetamol administration details, and outcomes for study mothers and infants from hospital patient databases (Esko 4.0, Northern Ostrobothnia Healthcare District, Oulu Finland; iPANA 13.0, CSAM Finland Oy, Oulu, Finland) and the NICU patient database (CCC Clinisoft, GE Healthcare Finland, Helsinki, Finland) that were collated in Microsoft Access 2016 MSO (Microsoft Corporation).

The indications for maternal paracetamol use were pain, discomfort, or fever $>38^{\circ}\text{C}$. Every single dose of orally and intravenously administered paracetamol that the pregnant mothers received on the hospital ward during the week preceding premature births, documented by the midwives, was retrieved from the individual patient records (AL, OA). The paracetamol dose was 500–1000mg up to four times daily as needed. The study group inclusion criteria were delivery of infants with gestational age $<32+0$ weeks and antenatal, maternal, intravenous, or oral administration of paracetamol within

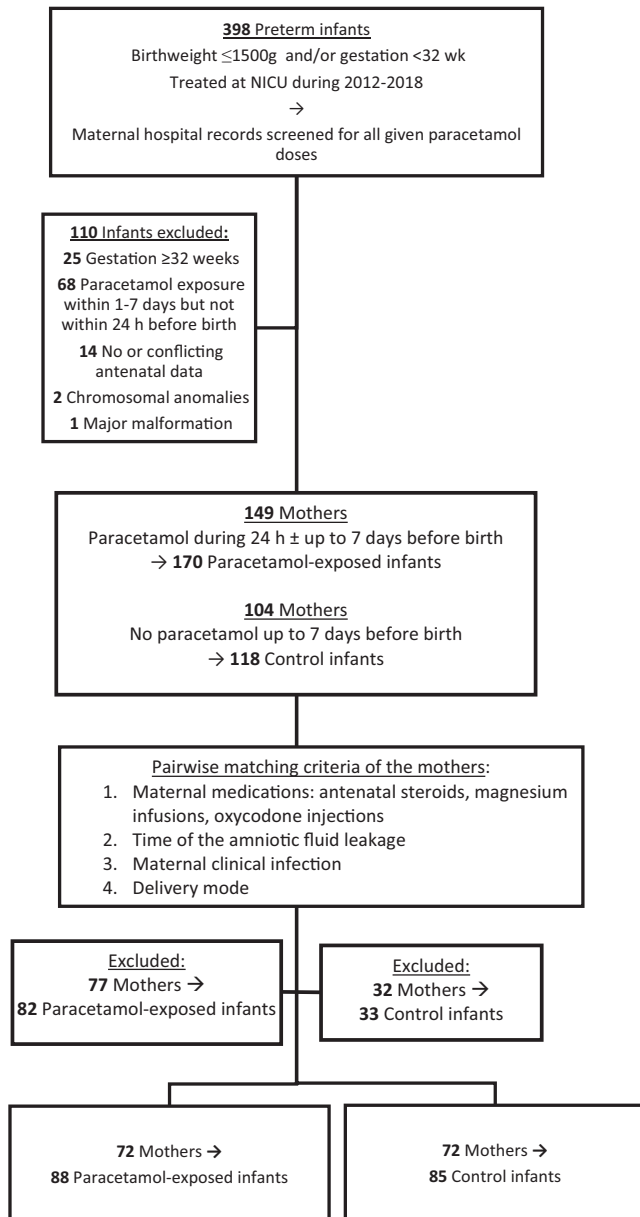


FIGURE 1 Flowchart of the study patient data. NICU, neonatal intensive care unit; wk, week.

24 h before birth (Figure 1). The control group consisted of preterm infants born at <32+0 weeks whose mothers were not exposed to antenatal paracetamol use for 7 days preceding birth according to hospital records. We excluded infants who were exposed to paracetamol 1–7 days before delivery but not during the 24 h before birth. This was because the paracetamol half-life is 1–4 h in adults. We assumed that if mothers had received paracetamol >24 h before the preterm birth, we would no longer be able to detect the potential effects of paracetamol or separate them from some of the acute effects of other drugs or diseases. In addition, we excluded from analysis all infants born with severe malformations or chromosomal defects and those with conflicting or unavailable antenatal data.

We collected data on paracetamol preparations, including the number of doses given on the hospital ward, each dosage of the

drug, the total in-hospital paracetamol doses per patient, and the administration time points for up to 7 days preceding delivery. Time from the last paracetamol dosage to childbirth was also recorded. We collected the following data from the mothers' patient files: pregnancy complications (diabetes, hypertensive disorders, preterm prelabor rupture of membranes, chorioamnionitis, placental abruption); maternal diagnoses; the use of antenatal intramuscular betamethasone and magnesium infusions; delivery mode; pain treatments, including local anesthesia (paracervical, pudendal, epidural, and spinal anesthesia), nitrous oxide, and oxycodone injections. The hospital unit does not use sedative analgesics for pain relief during pregnancy; however, rare obligatory instances may arise where the drug of choice is oxycodone. Magnesium infusion for neuroprophylaxis was intended at $\leq 31 + 6$ gestational weeks, with two doses of antenatal betamethasone given before preterm delivery (gestation 22 + 5 to 34 + 6 weeks) and a single booster dose in case of inevitable delivery before 32 gestation weeks after more than a week from the first course. Similarly, we collected accurate birth details of the infants, such as the length of gestation, birth time, birth weight, pH and base excess from the umbilical artery at birth, and Apgar scores. For blood gas analysis, the umbilical cord is double-clamped, the vessels are identified, and the blood is withdrawn from the vein and one of the umbilical arteries. The Finnish Current Care Guidelines on Newborn Resuscitation were followed, including the use of adrenaline and other therapies.²³ According to this evidence-based guideline, the indication for adrenaline use in the delivery room is bradycardia (pulse <60/min) not responding to adequate respiratory support, i.e., intubation, ventilation, surfactant, and supplemental oxygen. For resuscitation of extremely or very preterm infants, adrenaline can be used as endotracheal fluid boluses through the intubation tube or as intravenous injections. We recorded the following neonatal outcomes after birth as secondary outcomes: the need for adrenaline, fluid boluses, and surfactant for delivery room resuscitation, blood pressure measurements in the NICU, the need for circulatory support (medications and fluid resuscitation up to 24 h of age), the highest fraction of supplemental oxygen and highest mean airway pressure (cmH₂O) measured, paracetamol medication, diagnoses (patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotising enterocolitis) during the hospital stay, and mortality up to 1 year of age.^{24–26} The first measured blood pressure was defined as the first reading identified in the NICU database.

2.1 | Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 27 (IBM Corp). Preliminary analyses of the whole data indicated that some crucial baseline characteristics of the mothers were imbalanced between the two groups. Given the heterogeneity of maternal backgrounds, regression analysis was anticipated to be unsuitable, and the matched cohort setting was chosen to control for the potential confounding factors.^{27,28} Therefore, mothers in the present

selected population were matched pairwise according to the following criteria: (i) maternal medications, including (a) antenatal steroids, (b) magnesium infusions, and (c) oxycodone injections; (ii) duration of amniotic fluid leakage (≤ 24 or > 24 h before childbirth); (iii) delivery mode (vaginal or cesarian section); and (iv) maternal clinical infection/no signs of infection. The variables were analyzed using the independent-samples *t*-test, nonparametric Mann-Whitney U-test, Pearson's chi-squared test, Fisher's exact test, Pearson's bivariate correlation test, and Spearman's rho correlation test, as appropriate. Significance was set at $p < 0.05$.

2.2 | Ethical approval

In Finland, ethics boards do not process registry study plans; these studies are approved by local hospital administration officials. The medical directors of the Northern Ostrobothnia Hospital District and the Department of Children and Adolescence approved the present retrospective cohort study plan on August 30, 2012 (diary number 194/2012, amendment approved on October 10, 2018). As the data were captured from the hospital patient databases, the permission from hospital administration was inclusive, and no informed consents were required.

3 | RESULTS

Altogether, 398 very preterm infants were treated in the NICU of Oulu University Hospital between January 1, 2012 and December 31, 2018 (Figure 1). Of these, 170 fetuses, born to 149 mothers, were exposed to paracetamol within 24 h before birth; 123 mothers received only oral paracetamol, and 47 received either intravenous ($n = 30$) or both oral and intravenous paracetamol ($n = 17$). The 118 control fetuses, born to 104 mothers, were not exposed to any paracetamol for a period of at least 1 week before birth. An additional 110 infants did not meet the study inclusion criteria (Figure 1). After pairwise matching, 72 mothers remained in each group; accordingly, 88 paracetamol-exposed and 85 control infants were analyzed. Comparison of the paracetamol-exposed groups revealed that the excluded group of 82 infants had a lower frequency of intrauterine growth restriction, a higher frequency of singleton deliveries, and higher umbilical artery pH (Table S1).

The main characteristics of the pregnant women and the specifics regarding paracetamol administration are presented in Table 1. No differences were found in the incidences of diabetes or placental abruption, whereas mothers in the paracetamol group had more hypertensive disorders. There were no differences in the pain relief methods used in the deliveries. The number of multiple pregnancies and length of gestation did not differ between the two groups.

Perinatal and neonatal outcomes are presented in Tables 2 and 3. Infant birth weights and sex distributions were similar between groups (Table 2). The combined need for any delivery room treatments was lower in the paracetamol-exposed group than in

the control group (51.1% vs. 65.9%, mean difference -14.89 , 95% confidence interval [CI] -0.29 to -0.003). The umbilical artery pH and base excess and Apgar scores were similar. When tested in the subgroups based on the number of fetuses, these findings were the same in the singletons and in the twin/triplet A subgroup, whereas in the twin/triplet B and C subgroup, umbilical artery pH was higher in the paracetamol-exposed group. The Apgar scores did not differ in these subgroups. The first systolic and mean arterial pressures measured in the NICU did not differ (Table 3). During intensive care, the highest mean airway pressures were lower in the paracetamol-exposed infants than in the controls (Table 3). There were no differences in the numbers of infants needing any circulatory support, surfactant, or paracetamol. Antenatal exposure to paracetamol was not associated with any acute clinical adverse outcomes for the neonates (Table 3). There were no differences in severe neonatal morbidity or mortality up to 1 year of age.

Data from the excluded paracetamol-exposed infants ($n = 82$) were compared with those from the paracetamol-exposed group ($n = 88$). These data are presented in Table S1. Among these comparisons, the excluded infants were more often singletons, weighed more at birth, and had less intrauterine growth retardation. They also had higher umbilical arterial pH values, especially the A-twins/triplets.

To further investigate the factors affecting immediate newborn status after birth, we analyzed umbilical artery pH, base excess, and Apgar score correlations with the antenatal total paracetamol doses. Although no correlations were found with umbilical artery blood analyses, all Apgar scores were associated with maternal paracetamol use (Table 4).

4 | DISCUSSION

Antenatal administration of paracetamol within 24 h before extremely or very preterm births did not cause adverse effects when compared with infants without paracetamol exposure. Our results indicate it was not associated with neonatal or later excessive morbidities in preterm infants, implying adequate tolerance of the fetuses to maternal delivery-associated paracetamol use. Although these clinical associations may be explained by some confounders that remain unaccounted for in the present cohort, they do, most importantly, suggest that maternal consumption of paracetamol shortly before delivery is safe for preterm infants, whereas antenatal indomethacin, another non-sedative analgesic drug, is clearly harmful to immature infants.⁸

Maternal need for pain medication is obvious, but only a limited selection of preparations is available. Some maternal medications have been shown to have harmful effects on the offspring. A large meta-analysis confirmed increased risks for severe intracerebral hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia after antenatal indomethacin exposure.⁸ Another meta-analysis of maternal opioid treatment found that the umbilical artery pH and 5-min Apgar scores were lower and that the requirement for tactile stimulation of infants was higher upon opioid

TABLE 1 Maternal characteristics after pairwise matching

	Paracetamol exposure (n = 72)	Control group (n = 72)	p value
Any pregnancy complication, n (%)	48 (66.7)	37 (51.4)	0.062
Gestational diabetes or diabetes mellitus, n (%)	12 (16.7)	19 (26.4)	0.143
Pre-eclampsia and hypertensive disorders, n (%)	30 (41.7)	15 (20.8)	0.007
PPROM, n (%)	9 (12.5)	7 (9.7)	0.596
Time from PPRM until delivery, days, mean (SD)	4.1 (13.3)	3.4 (12.6)	0.749
Clinical and/or histological chorionamnionitis, n (%)	7 (9.7)	7 (9.7)	1.000
Placental abruption, n (%)	2 (2.8)	4 (5.6)	0.404
Multiple pregnancies, n (%)	15 (20.8)	15 (20.8)	1.000
Length of gestation, wk, mean (SD)	28.7 (2.2)	28.7 (2.2)	0.970
Spontaneous onset of labour ^a , n (%)	21 (29.2)	20 (27.8)	0.853
Vaginal delivery, n (%)	11 (15.3)	11 (15.3)	1.000
Caesarean section, n (%)	61 (84.7)	61 (84.7)	1.000
Elective, n (%)	5 (6.9)	9 (12.5)	0.256
Urgent, n (%)	49 (68.1)	49 (68.1)	1.000
Emergency, n (%)	7 (9.7)	3 (13.9)	0.187
Antenatal steroids, n (%)	71 (98.6)	71 (98.6)	1.000
Antenatal steroid doses, mean (SD)	1.79 (0.58)	1.72 (0.74)	0.530
Intravenous magnesium, n (%)	22 (30.6)	22 (30.6)	1.000
Intravenous magnesium dose, g, mean (SD)	12.8 (5.43)	12.0 (2.17)	0.532
Nitrous oxide inhalation, n (%)	5 (6.9)	4 (5.6)	0.747
Local anaesthesia ^b , n (%)	4 (5.6)	7 (9.7)	0.334
Oxycodone, n (%)	1 (1.4)	1 (1.4)	0.992
Intravenous paracetamol, n (%)	26 (36.1)	0	—
Per oral paracetamol only, n (%)	46 (63.9)	0	—
Paracetamol dose up to 24 h before childbirth, g, mean (SD)	1.43 (0.58)	0	—
Paracetamol, total in-hospital dose, g, mean (SD)	2.79 (2.38)	0	—
Time from the last paracetamol dose to birth, h, mean (SD)	8.31 (6.10)	NA	—

Abbreviations: PPRM, preterm prelabour rupture of membranes; NA, not applicable; SD, standard deviation; wk, week.

^aIncludes patients with prelabour rupture of membranes.

^bIncludes paracervical, pudendal, epidural, and spinal anaesthesia.

exposure.⁹ Paracetamol has been used as a well-tolerated option before delivery despite the lack of studies on intrauterine exposure and its acute effects on the perinatal transition. In the present study, prenatally administered paracetamol decreased the combined need for delivery room treatments (Table 2). This finding is of borderline significance (risk ratio 0.83; 95% CI 0.65–1.07) and must be carefully interpreted. However, antenatal paracetamol exposure was not associated with harmful effects for the extremely or very preterm infants as compared with those reported after maternal indomethacin or opioid treatment. Total doses of antenatal paracetamol varied

markedly during the week before delivery (range 1–13 g/patient; Table 1) but did not result in increased neonatal morbidities, e.g., circulatory compromise or intracerebral hemorrhage (Tables 2 and 3).

During pregnancy, the paracetamol mechanism of action, via pharmacokinetics of maternal and placental units, may impact the fetal compartment in ways that have not yet been studied.¹⁰ In recent studies, paracetamol crossed the placental barrier via passive diffusion.^{4,14} Perinatal asphyxia is predicated by fetal acidosis, determined by umbilical cord pH and/or Apgar scores at birth.^{29,30} The twin/triplet B and C subgroup, prone to low umbilical artery pH and perinatal asphyxia,

TABLE 2 Neonates' characteristics and perinatal and acute neonatal outcomes

	Paracetamol-exposed (n = 88)	Control group (n = 85)	p value	Differences (95% CI)
Gestation at birth, wk, mean (SD)	28.6 (2.3)	28.7 (2.1)	0.834	
Birth weight, kg, mean (SD)	1.19 (0.4)	1.19 (0.4)	0.962	
Birth weight Z-score, mean (SD)	-0.76 (1.40)	-0.68 (1.75)	0.737	
Small for gestational age ^a , n (%)	16 (18.2)	21 (24.7)	0.333	
Females, n (%)	40 (45.5)	40 (47.1)	0.832	
Singletons, n (%)	57 (64.8)	57 (67.1)	0.751	
Twin/triplet A, n (%)	15 (17.0)	16 (18.8)	0.501	
Twin/triplet B, n (%)	14 (15.9)	12 (14.1)	0.859	
Triplet C, n (%)	2 (2.3)	0	0.493	
Umbilical arterial pH, mean (SD)	7.272 (0.073)	7.249 (0.097)	0.110	0.023 (-0.005 to 0.050)
Singleton	7.261 (0.076)	7.244 (0.107)	0.347	0.02 (-0.02 to 0.05)
Twin/triplet A	7.293 (0.070)	7.284 (0.059)	0.714	0.01 (-0.04 to 0.06)
Twin/triplet B and C	7.300 (0.058)	7.231 (0.074)	0.036	0.06 (0.005 to 0.12)
Umbilical arterial base excess, mean (SD)	-4.3 (6.1)	-4.7 (3.9)	0.635	0.42 (-1.34 to 2.19)
Singleton	-4.6 (5.2)	-4.7 (4.1)	0.878	0.15 (-1.83 to 2.14)
Twin/triplet A	-5.3 (10.3)	-4.7 (3.5)	0.865	-0.57 (-7.49 to 6.34)
Twin/triplet B and C	-2.1 (3.3)	-4.6 (3.6)	0.128	2.49 (-0.79 to 5.77)
Apgar 1 min, mean (SD)	5.9 (2.3)	5.4 (2.2)	0.135	0.51 (-0.16 to 1.18)
Apgar 5 min, mean (SD)	6.4 (2.1)	6.3 (2.0)	0.665	0.14 (-0.48 to 0.75)
Apgar 10-15 min, mean (SD)	7.4 (1.6)	7.4 (1.6)	0.850	0.05 (-0.45 to 0.54)
5 min Apgar <7, n (%)	40 (45.5)	40 (47.1)	0.776	-1.60 (-0.16 to 0.13)
Adrenaline at delivery room, n (%)	2 (2.3)	3 (3.5)	0.622	-1.20 (-0.06 to 0.04)
Fluid bolus at delivery room, n (%)	1 (1.1)	2 (2.4)	0.540	-1.30 (-0.05 to 0.03)
Surfactant treatment, n (%)	44 (50.0)	55 (64.7)	0.051	-14.70 (-0.29 to -0.001)
Surfactant doses, median (range)	1 (1-3)	1 (1-4)	0.766	-0.10 (-0.37 to 0.18)
Surfactant, total dose, mg/kg, mean (SD)	171.2 (80.7)	156.7 (104.1)	0.467	-12.34 (-50.23 to 25.54)
Primary outcome: delivery room treatments, combined, n (%)	45 (51.1)	56 (65.9)	0.049	-14.80 (-0.29 to -0.003)

Note: Differences for neonatal outcomes are variable units (95% CI) or %-units (95% CI). Abbreviations: CI, confidence interval; SD, standard deviation; wk, week.

^aSmall for gestational age definition: birth weight below -2 SD of the mean birth weight, adjusted for the length of gestation and sex.

had a better pH upon paracetamol exposure (Table 2). Interestingly, antenatal paracetamol exposure dose correlated with Apgar scores (Table 4). Although no causality was shown, the result may suggest clinical importance, requiring further studies.

Paracetamol, as a reducing agent, is involved in prostaglandin synthesis and peroxidase activity.³¹ The toxic metabolism product of paracetamol, N-Acetyl-p-benzoquinone imine, interferes with mitochondrial respiration.³² According to a recent ischemic stroke model, paracetamol may have had a neuroprotective role.³³ Decreased nociception potentially also decreases oxygen uptake.³⁴ Although paracetamol at low doses has experimentally been shown to have a protective effect in the brain, there is no evidence that its effect on the central nervous system decreases oxygen requirements.³⁵

Whether paracetamol may have an oxygen-sparing effect on intrauterine tissue without causing energy deficiency remains unknown.

After entry to the NICU, both the treated and the control infants received similar amounts of intravenous paracetamol for treatment of pain and discomfort during early neonatal ventilation (Table 3). This likely increased the closure of the ductus arteriosus and contributed to the cardio-respiratory stability of extremely and very preterm infants.^{22,36} At present, data are insufficient to suggest, besides the paracetamol-induced closure of ductus arteriosus, whether the drug has an additional direct effect on tissue oxygen metabolism after birth.

The present matched cohort study has limitations. To control the known biases causing a maternal need for paracetamol, we matched

TABLE 3 Neonatal outcomes during NICU stay and long-term outcomes of the infants

	Paracetamol-exposed (n = 88)	Control group (n = 85)	p value
First systolic arterial pressure, mmHg, mean (SD)	43.8 (12.5)	42.8 (9.9)	0.545
First mean arterial pressure, mmHg, mean (SD)	34.8 (9.1)	34.8 (8.9)	0.988
Need for medications for circulatory support at NICU, n (%)	20 (22.7)	26 (30.6)	0.242
Adrenaline injection, n (%)	0	3 (3.5)	0.075
Dopamine infusion, n (%)	20 (22.7)	25 (29.4)	0.316
Dobutamine infusion, n (%)	5 (5.7)	5 (5.9)	0.955
Noradrenaline infusion, n (%)	2 (2.3)	0	0.162
Milrinone infusion, n (%)	0	1 (1.2)	0.308
Intravenous hydrocortisone, n (%)	2 (2.3)	0	0.162
Ringer infusion, n (%)	12 (13.6)	9 (10.6)	0.539
Transfusion, n (%)	8 (9.1)	8 (9.4)	0.942
Fresh frozen plasma, n (%)	5 (5.7)	9 (10.6)	0.237
Highest fraction of supplemental oxygen, mean (SD)	0.38 (0.21)	0.42 (0.22)	0.226
Highest mean airway pressure, cmH ₂ O, mean (SD)	13.8 (3.6)	15.0 (3.1)	0.039
Paracetamol, first 24 h, n (%)	68 (77.3)	63 (74.1)	0.628
Paracetamol dose, first 24 h, mg/kg, mean (SD)	39.8 (6.0)	40.4 (6.8)	0.545
Paracetamol during the NICU stay, n (%)	79 (90.0)	71 (83.5)	0.227
Paracetamol, total NICU dose, mg/kg, mean (SD)	320 (445)	248 (255)	0.238
Patent ductus arteriosus, n (%)	12 (13.6)	8 (9.0)	0.385
Bronchopulmonary dysplasia, grades 2–3, n (%)	5 (5.7)	7 (8.2)	0.509
Intraventricular hemorrhage, grades 3–4, n (%)	6 (6.8)	4 (4.7)	0.552
Necrotizing enterocolitis, stage 3, n (%)	3 (3.4)	0	0.086
Death, up to 1 year of age, n (%)	3 (3.4)	1 (1.2)	0.329

Abbreviation: NICU, neonatal intensive care unit; SD, standard deviation.

TABLE 4 Mean Apgar scores (SD) and their correlations to the total doses of maternal in-hospital paracetamol use, i.e., the antenatal paracetamol exposures

Postnatal age	Paracetamol-exposed group (n = 88)			Control group (n = 85)	
	Apgar scores	Correlation coefficient to paracetamol dose	p value	Apgar scores	Apgar score absolute differences
1 min	5.9 (2.3)	0.223 ^a	0.037	5.4 (2.2)	0.5
5 min	6.4 (2.1)	0.284 ^a	0.007	6.3 (2.0)	0.1
10–15 min	7.4 (1.6)	0.250 ^b	0.022	7.4 (1.6)	0

Abbreviations: SD, standard deviation.

^aPearson's correlation.

^bSpearman's correlation.

the mothers of preterm infants pairwise using multiple criteria. Data for the excluded infants are shown in Table S1. Despite these efforts, one difference between the treated and control populations emerged: hypertensive disorders (Table 1). However, complete matching may lead to overmatching and sampling bias so is not advisable. Therefore, we allowed this factor to remain as it usually does not require pain therapy, so it remains a possible confounding factor. The number of infants exposed to hypertensive disorders was higher in the study group, rather implying a greater need for treatment. Because of matching, we needed to perform numerous comparisons that increased the risk of type I errors.³⁷ However, because the main

aim was to investigate the potential adverse effects, we did not perform adjustments for multihypothesis testing. Despite the matching, unrecognized confounders may ultimately influence findings. For instance, we do not know about spontaneous and nonreported maternal paracetamol use before delivery; however this was not anticipated to be very frequent. Our study used data on paracetamol consumption before the delivery, based on recordings made by the midwives. These notes are more accurate than retrospective patient self-reports, which are associated with recall bias. Time spent in hospital is another confounding factor, but we tried to control this by matching the pregnancy complications associated with more

frequent paracetamol use. Furthermore, all the study mothers were in the hospital for ≥ 24 h before the birth. Finally, the patient population was relatively small; however, the power was calculated to be sufficient to reveal an acute circulatory effect of paracetamol during the perinatal transition. Medication was used on demand, and no prospective dosing scheme or randomization setting was used.

5 | CONCLUSION

In the present matched cohort study, no neonatal adverse reactions to antenatal paracetamol were apparent during premature perinatal transition. Taking into account all the limitations of the present study, an association was found between Apgar scores and maternal total in-hospital paracetamol dose. Whether this is a chance finding or causal, prospective, randomized trials are required to elucidate whether delivery-associated paracetamol administration for mothers benefits the fetuses and extremely and very preterm infants without adverse effects.

AUTHOR CONTRIBUTIONS

AL wrote the first draft of the article and acquired, analyzed, and interpreted the data. TS participated in the data interpretation and paper revision and supervised the study. MV participated in the study conception and design, interpreted the data, and critically revised the paper. MH participated in the study conception and design, analyzed and interpreted the data, critically revised the paper, and supervised the study. OA participated in the study conception and design, acquired, analyzed, and interpreted the data, critically revised the paper, and supervised the study. All authors approved the final version for publication and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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