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The association between antenatal indomethacin exposure and persistent pulmonary hypertension of the newborn in extremely preterm infants

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The study aimed to investigate the association between antenatal indomethacin exposure and persistent pulmonary hypertension of the newborn (PPHN) in extremely preterm infants. A retrospective cohort study was conducted involving extremely preterm infants admitted from January 2022 to May 2024. Neonates were categorized into the indomethacin group and the control group based on the antenatal indomethacin exposure. The primary outcome focused on the incidence of PPHN, while secondary outcomes encompassed the incidence of moderate to severe bronchopulmonary dysplasia (BPD), mortality, respiratory distress syndrome (RDS) ≥ stage III, hemodynamically significant patent ductus arteriosus (hsPDA), spontaneous intestinal perforation (SIP), intraventricular hemorrhage (IVH) ≥ grade III, surgical necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP) ≥ stage 3. Among the 203 included neonates, there were 68 neonates in the indomethacin group and 135 neonates in the control group. A significant association was observed between antenatal indomethacin exposure and the incidence of PPHN in extremely preterm infants (OR, 6.435; 95% CI, 1.263–32.795; *P* = 0.031). Among the secondary outcomes, the incidence of pneumothorax in indomethacin group was higher than that in the control group (OR,10.635; 95% CI,1.217–92.94, *P* = 0.029). There were no significant differences between the two groups in the incidence of other secondary outcomes (*P* > 0.05 for all). Antenatal indomethacin exposure was found to be associated with PPHN in extremely preterm infants. Therefore, careful consideration and comprehensive assessment were necessary when using indomethacin during pregnancy. Determining the optimal timing for its administration was crucial to minimize the risk of PPHN in this vulnerable population.

Keywords Indomethacin, Extremely preterm infant, Persistent pulmonary hypertension of the newborn

Abbreviations

BPD	Bronchopulmonary dysplasia
CI	Confidence interval
GDM	Gestational diabetes
hsPDA	hemodynamically significant patent ductus arteriosus
ICP	Intrahepatic cholestasis of pregnancy
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NRN	Neonatal research network
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PMA	Postmenstrual age

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PPHN	Persistent pulmonary hypertension of the newborn
PPROM	Preterm premature rupture of membranes
PS	Pulmonary surfactant
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity

Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), effectively inhibits prostaglandin synthesis, thereby reducing preterm uterine contractions and delaying delivery[1]. A meta-analysis has shown that indomethacin could postpone preterm delivery for a duration ranging from 48 h to 7 days[2]. Furthermore, according to the 2015 National Institute for Health and Care Excellence (NICE) guidelines, indomethacin has proven more effective than other tocolytic agents in prolonging pregnancy[3].

However, the use of indomethacin requires careful consideration due to its potential adverse effects on both the fetus and neonates, particularly during the third trimester of pregnancy[4,5]. As pregnancy progressed from the second to the third trimester, there was an estimated 33% increase in the expected levels of indomethacin in the fetal blood plasma[6]. Fetal exposure to indomethacin escalated as pregnancy advanced. Therefore, the U.S. Food and Drug Administration (FDA) advises against the administration of antenatal indomethacin after 30 weeks of pregnancy. Atephen et al.[7] has demonstrated that the ductus arteriosus and pulmonary vessels become more sensitive to antenatal indomethacin exposure as the pregnancy progressed. Several studies have indicated a potential association between antenatal indomethacin exposure and persistent pulmonary hypertension of the newborn (PPHN). Prolonged ductal constriction can elevate right ventricular pressure, resulting in irreversible changes in the pulmonary vasculature and persistent pulmonary hypertension in neonates[8–11]. A literature review conducted by Katarina Dathe et al.[12] highlighted the scarcity of recent research on the effects of indomethacin exposure during the second trimester of pregnancy on neonates. Additionally, routine echocardiography for fetuses exposed to indomethacin during this period was not standard practice, making it difficult to detect certain complications promptly. Therefore, it is essential to investigate whether antenatal indomethacin exposure during the second trimester poses risks to extremely preterm infants. The aim of our study was to analyze the association between antenatal indomethacin exposure and PPHN in this vulnerable population.

Methods

Study design

This retrospective single-center cohort study was conducted at the Neonatal Intensive Care Unit (NICU) of the Women's Hospital, School of Medicine, Zhejiang University, including extremely preterm infants with a gestational age of less than 28 weeks between January 1, 2022 and May 10, 2024.

The study adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Women's Hospital, School of Medicine, Zhejiang University (Approval No. IRB-20240312-R). Due to its retrospective nature, the requirement for informed consent was waived by the Ethics Committee of the Women's Hospital, School of Medicine, Zhejiang University. Our dedicated Ethics Committee supervised the research process, ensuring its standardization and the confidentiality of patients' information.

Inclusion criteria for neonates were as follows: (1) gestational age less than 28 weeks and (2) admission to the NICU within 1 h after birth. Neonates were excluded based on the following criteria: (1) presence of multiple congenital anomalies, (2) congenital structural heart disease, (3) severe inherited metabolic disease, or (4) incomplete clinical data.

This study aimed to provide a comprehensive analysis of extremely preterm infants admitted to the NICU, focusing on their clinical characteristics and outcomes. By carefully selecting participants based on specific inclusion and exclusion criteria, the study ensured a robust dataset for accurate and reliable findings.

Data collection

The data were collected for two groups, including antenatal complications and neonatal demographic data. The primary outcome was the incidence of PPHN. The secondary outcomes included the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (PMA), as defined by the Neonatal Research Network (NRN) in 2019[13] or death in hospital, respiratory distress syndrome(RDS) ≥ stage III diagnosed by chest X-ray[14], hemodynamically significant patent ductus arteriosus (hsPDA)[15], spontaneous intestinal perforation (SIP), pulmonary hemorrhage, pneumothorax, congenital pneumonia, intraventricular hemorrhage (IVH) ≥ grade III[16], surgical necrotizing enterocolitis (NEC)[17] and retinopathy of prematurity (ROP) ≥ stage 3[18]. To assess the time to closure of PDA after treatment, an ultrasound was routinely performed 24 to 48 h after the last dose of each treatment course[15].

Diagnosis of PPHN[19,20]: Neonates with refractory hypoxemia that could not be attributed to pulmonary diseases and met one or more of the following criteria: (1) Echocardiographic evidence: an estimated peak systolic pulmonary artery pressure > 35 mmHg or exceeding two-thirds of the systemic systolic pressure, indicated by the presence of tricuspid regurgitation and/or right-to-left/bidirectional shunting at the ductus arteriosus and/or foramen ovale level; (2) Preductal and postductal oxygen saturation gradient ≥ 5% or preductal and postductal arterial oxygen partial pressure difference ≥ 10mmHg.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20.0 was used for statistical analyses. Data were presented as mean and standard deviation or median and interquartile range depending on their distribution. Baseline characteristics and other relevant material information between the indomethacin group and control group were compared using independent sample t-tests for normally distributed variables and Mann-Whitney tests for non-normally distributed variables. The chi-square test and Fisher's exact test were used for categorical variables. The

odds ratio (OR) and 95% confidence interval (CI) were presented to explore maternal and neonatal outcomes. *P* value < 0.05 was considered to be statistically significant.

Results

Demographic data of neonates and maternal complications

A total of 203 neonates with a gestational age between 24^{+1} weeks and 27^{+6} weeks and a birth weight between 410 g and 1280 g were included in our study (Fig. 1).There were 68 neonates in the indomethacin group(Antenatal indomethacin administration: Initial dose:50–100 mg, then 25 mg every 6 h until contractions ceased, orally). Their gestational ages ranged from 24^{+4} weeks to 27^{+5} weeks and their birth weights ranged from 460 g to 1260 g. There were 135 neonates in the control group. Their gestational ages ranged from 24^{+1} weeks to 27^{+6} weeks and their birth weights ranged from 410 g to 1280 g.

There were no significant differences in gestational age, birth weight, gender, mode of delivery, oligohydramnios, Apgar score at 1 and 5 min, multiple births, intrauterine distress, blood gas pH at admission, blood gas lactate at admission, surfactant use at admission and respiratory support at admission between the two groups ($P > 0.05$, all). The details were shown in Table 1.

There were also no significant differences in maternal complications, such as gestational hypertension, placenta previa, placental abruption, ICP, GDM, PPROM, pathological chorioamnionitis and mycoplasma infection ($P > 0.05$, respectively). The details were shown in Table 2.

Neonatal complications

Primary outcomes: The incidence of PPHN was significantly elevated in the indomethacin group compared to the control group (OR, 6.44; 95% CI, 1.26–32.80, $P = 0.031$).

Secondary outcomes: There were no significant differences in pulmonary hemorrhage, moderate to severe BPD, mortality, hsPDA, SIP, IVH ≥ grade III, surgical NEC, congenital pneumonia, RDS ≥ stage III, early-onset sepsis and ROP ≥ stage 3 ($P > 0.05$, respectively). In comparison to the control group, a significantly higher incidence of pneumothorax was observed in the indomethacin group (OR, 10.635; 95% CI, 1.217–92.94, $P = 0.029$). The details were shown in Fig. 2.

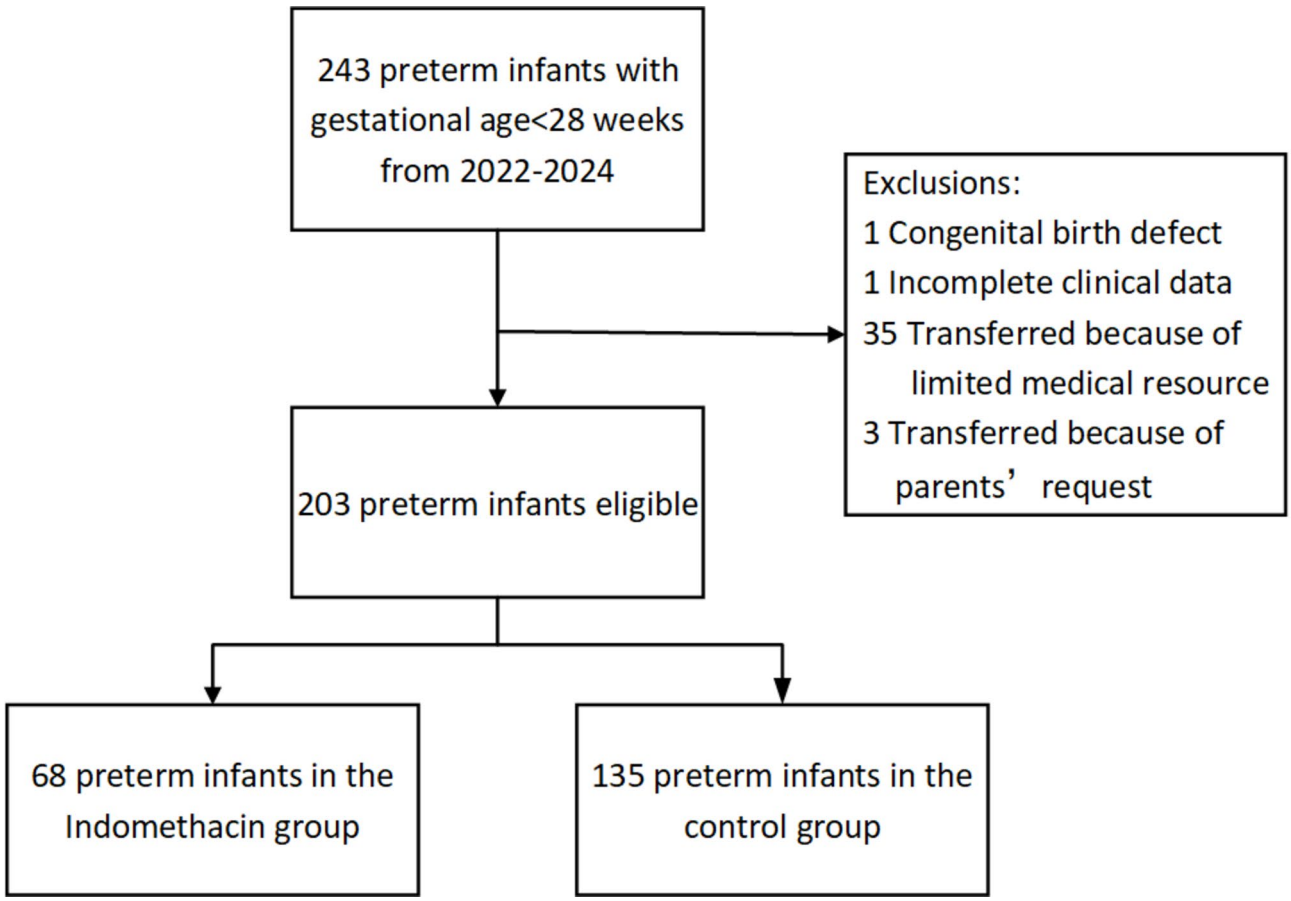

Fig. 1. Flowchart.

	Indomethacin group $N=68$	Control group $N=135$	P-value*
Gestational age, wk, median (IQR)	26.9 (26.0-27.4)	26.9 (25.9–27.1)	0.656
Birth weight, g, (Mean ± SD)	869.0 ± 196.4	874.6 ± 192.9	0.846
Male, n (%)	40 (58.8)	71 (52.6)	0.400
Multiple birth, n (%)	31 (45.6)	47 (34.8)	0.136
SGA, n (%)	1 (1.5)	8 (5.9)	0.274
Intrauterine distress, n (%)	23 (33.8)	34 (25.2)	0.196
Cesarean section, n (%)	32 (47.0)	71 (52.6)	0.457
Oligohydramnios, n (%)	32 (47.1)	77 (57.0)	0.178
Intubation at birth, n (%)	26 (38.2)	47 (34.8)	0.632
1-min Apgar score, median (IQR)	6 (5–9)	8 (5–9)	0.103
5-min Apgar score, median (IQR)	9 (8–10)	9 (8–10)	0.158
surfactant use at admission, n (%)	57 (83.8)	105 (77.8)	0.311
Blood gas pH at admission, median (IQR)	7.2 (7.2–7.3)	7.2 (7.2–7.3)	0.914
Blood gas lactate at admission, median (IQR)	3.7 (2.7–4.7)	3.5 (2.5–5.7)	0.668
Invasive mechanical ventilation at admission, n (%)	30 (44.1)	52 (38.5)	0.443
Duration of invasive mechanical ventilation, day, median (IQR)	3 (0–16)	1 (0–11)	0.422
Duration of noninvasive respiratory support, day, median (IQR)	51 (41–69)	44 (35–63)	0.079
Duration of oxygen inhalation, day, median (IQR)	8 (0–20)	11 (1–22)	0.298
Duration of hospital, day, median (IQR)	89 (83–110)	96 (78–114)	0.473

Table 1. Demographic data of neonates in two groups. *SGA* small for gestational age. * Significant P value < 0.05.

	Indomethacin group $N=68$	Control group $N=135$	P-value*
Maternal age, year, (Mean ± SD)	31.6 ± 4.5	32.3 ± 4.5	0.312
Maternal education > 12 years, n (%)	46 (67.6)	87 (64.4)	0.65
Gestational hypertension, n (%)	7 (10.3)	25 (18.5)	0.129
Placenta previa, n (%)	1 (1.5)	1 (0.7)	1
Placental abruption, n (%)	22 (32.4)	29 (21.5)	0.092
ICP, n (%)	3 (4.4)	2 (1.5)	0.092
GDM, n (%)	6 (8.8)	23 (17.0)	0.114
PPROM, n (%)	18 (26.5)	53 (39.3)	0.071
Pathologic chorioamnionitis, n (%)	18 (26.5)	44 (32.6)	0.371
Mycoplasma infection, n (%)	53 (77.9)	104 (77.0)	0.885
Prenatal corticosteroid: Complete, n (%) Incomplete, n (%)	 41 (60.3) 12 (17.6)	 75 (55.6) 29 (21.5)	 0.520 0.521

Table 2. Maternal complications in two groups. *ICP* intrahepatic cholestasis of pregnancy, *GDM* gestational diabetes mellitus, *PPROM* preterm premature rupture of membranes. *Significant P value < 0.05.

The association between antenatal indomethacin exposure and PPHN

Among the 68 neonates exposed to antenatal indomethacin, six neonates developed PPHN. Their gestational ages ranged from 25^{+1} weeks to 27^{+6} weeks and their birth weights ranged from 700 g to 1050 g. For these six infants, the initial gestational age of antenatal indomethacin exposure occurred between 24^{+1} weeks and 26^{+1} weeks. Regarding the antenatal indomethacin treatment, four neonates received it for 2 days, one for 3 days, and the other for 5 days. The mean interval from the last dose of medication to delivery was 67.9 h. Among the six neonates with PPHN, five neonates required the therapy of nitric oxide inhalation (iNO) and two neonates required sildenafil. Tragically, two neonates died succumbed to severe PPHN and one neonate developed severe BPD. The detailed information was shown in Table 3.

Discussion

In our retrospective cohort study, we observed a notably elevated incidence of PPHN among extremely preterm infants exposed to antenatal indomethacin. This observation was particularly pronounced in neonates with smaller gestational age and lower birth weight. While the risks associated with antenatal indomethacin exposure during the third trimester are widely recognized, there is a paucity of research examining its link to PPHN in

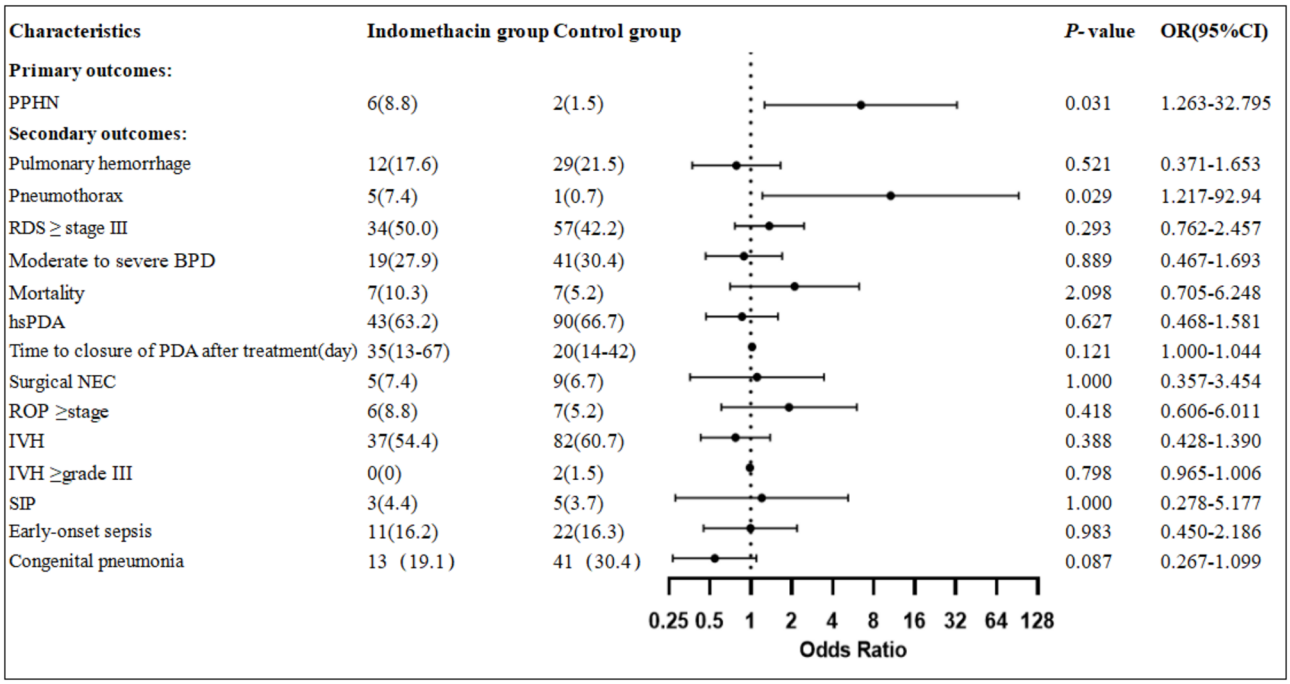

Fig. 2. Primary outcomes and secondary outcomes of neonates. *PPHN* persistent pulmonary hypertension of the newborn, *RDS* respiratory distress syndrome, *BPD* bronchopulmonary dysplasia, *hsPDA* hemodynamically significant patent ductus arteriosus, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *IVH* intraventricular hemorrhage, *SIP* spontaneous intestinal perforation. *Significant *P* value < 0.05.

Gestational age, wk, (Mean ± SD)	26.0 ± 0.8
Birth weight, g, (Mean ± SD)	807.5 ± 131.5
Initial gestational age of antenatal indomethacin exposure, wk, (Mean ± SD)	25.1 ± 0.8
Mean course of therapy, day, (Mean ± SD)	2.7 ± 1.2
Time of last medicine to delivery, hour, (Mean ± SD)	67.9 ± 46.8

Table 3. Comparison of neonatal outcomes in antenatal indomethacin exposure.

extremely preterm infants. Therefore, our study aimed to explore this association and enhance awareness for prompt intervention during pregnancy.

Indomethacin has been often used as a tocolytic therapy to prevent premature labor, primarily due to its role of prostaglandin synthesis, which plays a crucial part in regulating uterine contractions. Studies have demonstrated its effectiveness in delaying delivery and improving neonatal outcomes[2]. However, there are concerns regarding the potential risks associated with antenatal indomethacin exposure to neonates. These risks include an elevated chance of premature ductus arteriosus constriction, IVH, SIP, NEC, and periventricular leukomalacia[21–24]. In our study, we did not observe a significant relationship between antenatal indomethacin exposure and the neonatal outcomes previously reported by Balevic, et al.[1]. Notably, we identified an association between antenatal indomethacin exposure and the development of PPHN. Specifically, among the 68 extremely preterm infants exposed to antenatal indomethacin, six neonates (8.8%) developed PPHN. Levin et al.[25] postulated in 1987 that antenatal indomethacin exposure could affect the ductus arteriosus and pulmonary vasculature, which were linked to PPHN. Furthermore, a case report also suggested an association between antenatal indomethacin exposure and PPHN[10]. Taken together, these findings suggest that antenatal indomethacin exposure may potentially lead to the occurrence of PPHN.

Several studies suggested that the association between the incidence of PPHN and antenatal indomethacin exposure may be influenced by the duration of medication administration. The use of indomethacin can disrupt the delicate balance between pulmonary vascular resistance and ductus arteriosus constriction[26].Vermillion et al.[27] observed that neonates exposed to the medication for less than 72 h did not develop pulmonary hypertension. Rubaltelli et al.[28] identified five cases of pulmonary hypertension among 29 preterm infants were exposed to an extended courses of antenatal indomethacin treatment, which was consistent with the study by Besinger et al.[29].

Based on these findings, we hypothesize that the incidence of PPHN may be associated with the prolonged use of indomethacin. In our study, among the infants diagnosed with PPHN, only one mother received medication for approximately five days, while the remaining mothers underwent treatment for less than 72 h. However,

it is worth noting that the infant whose mother had a prolonged course of antenatal indomethacin treatment succumbed to severe PPHN. To validate the correlation between PPHN and the duration of medication use, further studies with larger sample sizes are warranted.

Some researchers have suggested that the incidence of PPHN associated with antenatal indomethacin exposure was influenced by the dosage of the medication. A case study reported that a preterm infant with gestational age of 27 weeks developed severe hypoxia and pulmonary hypertension shortly after birth. Subsequent analysis indicated a potential association with the dosage of antenatal indomethacin[10]. Donadono et al.[30] also found that neonates exposed to low dosage of indomethacin experienced minimal complications. It was particularly notable given that the half-life of indomethacin in preterm infants was five times longer compared to adults[31]. However, our study revealed that the infants with a gestational age of less than 28 weeks were at an elevated risk of developing PPHN, even when exposed to standard dosages of antenatal indomethacin. We hypothesized that this discrepancy in findings may be due to differences in gestational age, as the preterm infants in our study were at a lower gestational age.

The U.S. Food and Drug Administration (FDA) has cautioned that the administration of indomethacin during the second trimester of pregnancy should be done with care, primarily due to its potential impact on the newborn's renal function. Our research underscores the need for vigilance regarding the effects of the medication on pulmonary vasculature as well, which may provide valuable insights for medication use in clinical settings.

Limitation

Our study has demonstrated a notable association between antenatal indomethacin exposure and the incidence of PPHN in extremely preterm infants. However, it faces certain limitations. Primarily, the study was restricted by a small sample size, which prevented us from identifying whether antenatal indomethacin exposure was an independent risk factor for PPHN through multivariate analysis. Furthermore, we did not have access to data on the long-term outcomes of PPHN, which was crucial for a comprehensive understanding of the condition. Additionally, the low number of infants with PPHN who had been exposed to antenatal indomethacin limited our ability to conduct a detailed analysis of how factors such as the duration and dosage of the medication might impact the severity of PPHN. Therefore, further research is warranted to explore the relationship between the treatment regimen, including dosage and the incidence of PPHN more thoroughly.

Conclusion

Our research has revealed that antenatal indomethacin exposure elevated the risk of PPHN in extremely preterm infants. Therefore, extreme caution should be exercised when administering antenatal indomethacin, especially to infants who are at a higher risk of being born prior to 28 weeks of gestational age. This finding underscores the importance of careful consideration and potential alternative treatments to ensure the safety and well-being of these vulnerable infants.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chuncai Xu, Yingying Bao, Huanhuan Ding, Kaijian Wang and Qianyu Yang. The first draft of the manuscript was written by Chuncai Xu, Yingying Bao and Jiajun Zhu. All authors commented on previous versions of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was conducted at the NICU of the Women's Hospital, School of Medicine, Zhejiang University. It was approved by the Ethics Committee of Women's Hospital of Zhejiang University (reference: IRB-20240312-R). The human subjects were in accordance with the declaration of Helsinki.

Additional information

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