Received: 26 January 2020 | Revised: 28 April 2020 | Accepted: 29 April 2020

DOI: 10.1111/apa.15338

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Preeclampsia was a risk factor for pulmonary interstitial emphysema in preterm infants born ≤32 weeks of gestational age

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Abstract

Aim: This study determined the prenatal and postnatal risk factors for pulmonary interstitial emphysema (PIE) in preterm infants born at up to 32 weeks of gestational age (GA) and their contribution to severe complications.

Methods: We studied 179 preterm infants, who had undergone chest X-rays during the first five days of life at Justus Liebig University Giessen, Germany, between 2016 and 2017. Of these, 33 were retrospectively classified as PIE and 146 as non-PIE. The PIE cases were also matched with 33 non-PIE cases by GA and gender. Risk factors were identified by univariate analyses and multivariable logistic regression.

Results: Previously known risk factors for pulmonary interstitial emphysema were confirmed, including GA and birthweight and the associations with adverse outcomes like intraventricular haemorrhage and mortality. We identified preeclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome as additional risk factors for PIE (P = .027), and lung impairment was associated with respiratory distress syndrome (P = .001), higher maximum inspired oxygen (P = .014) and needing surfactant (P = .006).

Conclusion: Preeclampsia and HELLP syndrome were identified as possible additional risk factors for PIE in preterm infants. These conditions should be included in future studies, to identify preterm infants at risk of PIE straight after birth.

KEYWORDS

air leak, pulmonary interstitial emphysema, prematurity, preeclampsia, mechanical ventilation

Abbreviations: BPD, bronchopulmonary dysplasia; FiO_2, fractional inspired oxygen concentration; GA, gestational age; HELLP, haemolysis, elevated liver enzymes and low platelet count; IUGR, intrauterine growth restriction; PIE, pulmonary interstitial emphysema; RDS, respiratory distress syndrome; VEGF, vascular endothelial growth factor.

1 | INTRODUCTION

Pulmonary interstitial emphysema (PIE) is an air leak syndrome, and it is one of the most severe respiratory complications to affect preterm infants. It is characterised by the dissection of the interstitial or perivascular lung tissue, which results in air being trapped along the bronchovascular system. This leads to overdistension, decreased compliance and restricted gas exchange.[1-3] The radiological characteristics of PIE are either cyst-like or linear radiolucencies radiating from the pulmonary hilum to the surface of the lung, and these may be aggravated by the development of pneumomediastinum, pneumothorax or pneumopericardium.[4,5] Chest radiography is the diagnostic gold standard for PIE, and lung ultrasound is a useful and non-invasive follow-up tool.[6] PIE typically affects extremely low birthweight infants who are mechanically ventilated with respiratory distress syndrome (RDS), but it has also been reported in non-invasive ventilated or non-ventilated infants.[2,7] It can occur unilaterally or bilaterally and is classified as local or diffuse and acute or persistent PIE.

The incidence of PIE ranges from 5% to 40%, in extremely low birthweight infants, despite advances in neonatal medicine. These include the established use of antenatal corticosteroids, avoiding mechanical ventilation, the introduction of new, and more gentle, modes of ventilation[8] and the application of postnatal surfactant application. PIE has been associated with higher mortality and high rates of severe morbidities that are common in premature infants, such as intraventricular haemorrhage and bronchopulmonary dysplasia (BPD).[5,9,10] Other suggested risk factors for PIE include the prenatal use of magnesium sulphate,[11] higher ventilation parameters, increased tidal volumes and higher fractions of inspired oxygen (FiO_2).[12] However, one study reported that infants who developed pulmonary interstitial emphysema during the first days after birth had lower Apgar scores in the delivery room and needed increased ventilator settings and FiO_2, increased rates of intubation and more frequent surfactant. These findings suggest a pulmonary predisposition for PIE as early as birth.[3] This assumption has been further strengthened by reports of PIE occurring during non-invasive ventilatory support.[2]

The aim of this study was to determine any associations between a number of other prenatal and postnatal risk factors and the occurrence of PIE. These included any diabetes during pregnancy, preeclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, intrauterine growth restriction (IUGR), the use of antenatal corticosteroids, male gender and multiple birth. All of these conditions are known to increase the risk of preterm infants developing bronchopulmonary dysplasia (BPD) and long-term pulmonary sequelae.[13,14]

Key Notes

- This study focused on 179 preterm infants, who had undergone chest X-rays during the first five days of life, to determine the prenatal and postnatal risk factors for pulmonary interstitial emphysema (PIE).
- We identified preeclampsia and haemolysis, elevated liver enzymes and low platelet count syndrome as additional risk factors in infants with PIE.
- In addition, lung impairment was associated with respiratory distress syndrome, higher maximum inspired oxygen and needing surfactant.

2 | MATERIAL AND METHODS

2.1 | Study design

This was a retrospective case-control study that focused on 226 preterm infants who were born at up to 32 weeks of gestational age (GA) and were discharged from the neonatology unit of the Justus Liebig University of Giessen, Germany, between 2016 and 2017. All received chest X-ray examinations during the first 5 days of life. The exclusion criteria included no chest X-ray being available and prenatal interventions like foetal paracentesis. We also excluded infants with lower urinary tract obstructions, spina bifida, congenital heart defects, apart from patent ductus arteriosus, atrial septum defects, hypoplasia or sequestration of the lung, syndromal disease or oesophageal atresia.

After the exclusion criteria were applied, we had 179 infants left in the study (Figure 1). All the cases were retrospectively classified by a neonatologist and a paediatric radiologist using an independent double-blinded study design, and any differences of opinion were jointly resolved. This classification showed that 33 of the cases had PIE and 146 did not. The PIE cases were classified as unilateral or bilateral and subdivided in central, global or lobar manifestations (Figure 2). The first X-ray available was used to grade RDS.[15] To compensate for important confounders of pulmonary RDS severity, each of the 33 PIE cases was matched with a non-PIE case by the closest GA and gender (Figure 1, Appendix S1). A number of perinatal variables were retrieved from the medical notes. These included the infant's clinical characteristics, their birthweight, GA and gender. We also collected data on any IUGR, premature rupture of the membranes, histologically proven chorioamnionitis, preeclampsia/HELLP syndrome,[16,17] gestational diabetes, type I diabetes, antenatal corticosteroids, HELLP, maternal age, multiple pregnancy and Apgar scores at one and five minutes. The factors that were considered with regard to postnatal respiratory support included the following: severe RDS (grades III-IV), invasive mechanical ventilation, applied as assist controlled or synchronised intermittent positive pressure ventilation, maximum ventilator settings during the first 24 hours of life. We also included less invasive surfactant administration, if the preterm infant was on non-invasive ventilatory support at the time of surfactant application; otherwise, it was given via the endotracheal tube. Postnatal corticosteroids were separated into early for the first seven days of life and late if it was beyond that point. The selected outcome parameters were intraventricular haemorrhage (grade III-IV), BPD,[18] necrotising enterocolitis, focal intestinal perforation, retinopathy of prematurity and mortality.

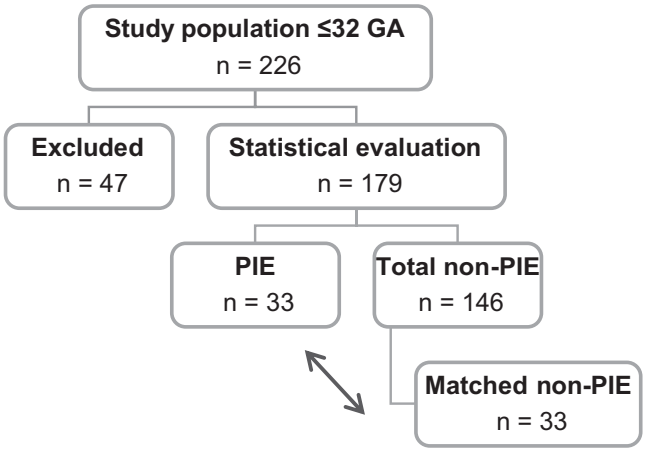

FIGURE 1 Study design. Flowchart of the study population and analysed subgroups

2.2 | Statistical analysis

The statistical analyses were performed using R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). The demographics in Table 1 are shown as medians and interquartile ranges. The absolute and relative frequencies of the parameters are given for counted data. Comparisons were carried out using the using Wilcoxon rank-sum test for unpaired, unmatched, metric data and the Wilcoxon signed-rank test for matched metric data. Fisher's exact test was used for unmatched categorical data, and conditional logistic regression was used for matched data. To control for possible confounders, multivariable conditional logistic regression was performed with PIE as the dependent variable and preeclampsia or HELLP, birthweight, multiples, antenatal corticosteroids and severe RDS as the independent variable (Table 2). Statistical significance was defined as a P value of <.05. Appendix S1 provides a detailed description of the complete statistical analysis, including the confidence intervals and the area under the curve.

3 | RESULTS

There were 226 preterm infants born at up to 32 weeks of gestation who were available for the analysis. Of these, 179 infants met the inclusion criteria and were included in the statistical evaluation (Figure 1). The subjects' demographic data are summarised in Table 1, and the total data set can be found in Appendix S1. The incidence of PIE in the study cohort was 18.4%, and the infants that we included had a median GA of 28.7 (range 26.1-30.7) and birthweight of 0.99kg (range 0.76-1.44) with a balanced gender distribution.

The detailed radiological classification showed that there were 63.6% unilateral cases and 36.4% cases with bilateral PIE. Focusing on the parameters of respiratory support within the first 24 hours of life enabled us to consider the early effects on postnatal manifestation. Just under a third (32.9%) of the preterm infants underwent invasive mechanical ventilation, with a median positive end-expiratory pressure of 6.0 cmH_2O and a peak inspiratory pressure of 16.5 cmH_2O. The majority (63.7%) received surfactant, while 82.6% of the mothers were treated with antenatal corticosteroids, which is standard treatment for this high-risk population. When the PIE and non-PIE cases were compared, this showed that the established risk factors for PIE, including GA and birthweight, were associated with the known outcomes of death and intraventricular haemorrhage. In addition, severe BPD and retinopathy of prematurity continued to present as complications following PIE (Table 2). Important parameters for calculating risks for outcomes after preterm birth, like antenatal corticosteroids, maternal age, any diabetes during pregnancy or multiple births, did not continue to pose risk factors for PIE. However, there was a trend towards a higher incidence of preeclampsia and HELLP in the PIE group. Therefore, we decided to carry out further evaluations of preeclampsia and HELLP as risk factor for PIE by using a matched-pairs analysis. Because the incidence of PIE correlates with RDS severity, we excluded the main confounding factors of GA and gender. The matched-pairs analysis showed that preeclampsia and HELLP syndrome were the only statistically significant maternal risk factor (P = .0499) in the conditional logistic regression model. In contrast, other important contributors to pulmonary distress, like chorioamnionitis and maternal diabetes, did not have any impact on the incidence of PIE in our study. A conditional logistic regression model that included the predictors of birthweight, multiple births, severe RDS and antenatal corticosteroids confirmed that preeclampsia and HELLP syndrome were independent predictors of PIE (P = .027) (Appendix S1). When it came to the severity of pulmonary sequelae, maximum postnatal fraction of inspired

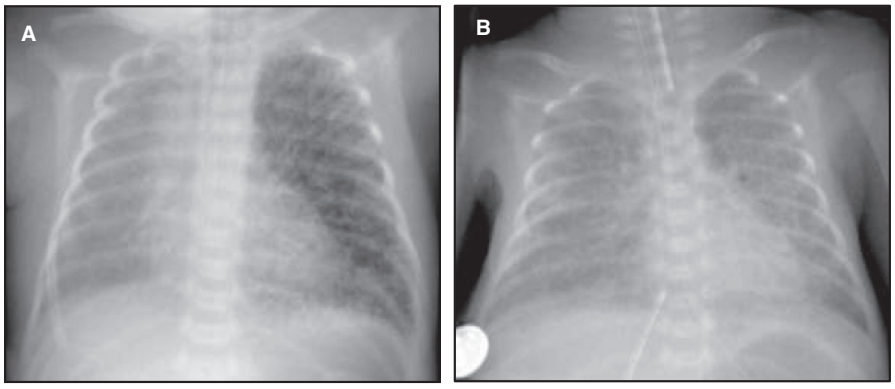

FIGURE 2 Example of chest X-ray with PIE. Anterior-posterior chest X-ray with diagnosed PIE (A, unilateral left; B, bilateral)

TABLE 1 Demographics of 179 infants with and without PIE included in the study

Variables	Data shown as median (interquartile range) or n (%)
Birth weight (kg)	0.99 (0.76-1.44)
Gestational age (weeks)	28.71 (26.14-30.71)
Maternal age	31.00 (28.00-35.00)
Male	89 (49.72)
Multiple birth	75 (41.90)
Intrauterine growth restriction	32 (17.88)
Preeclampsia or HELLP	27 (15.08)
Diabetes (gestational/type I)	15 (8.38)
Antenatal corticosteroids	147 (82.58)
Premature rupture of the membranes	59 (33.15)
Chorioamnionitis	30 (17.86)
Invasive mechanical ventilation	59 (32.96)
Surfactant	114 (63.69)
Postnatal corticosteroids (early)	8 (4.47)
Postnatal corticosteroids (late)	15 (8.38)
Pulmonary interstitial emphysema	33 (18.44)
Bronchopulmonary dysplasia (36 wk of postmenstrual age)	62 (34.64)
Intraventricular haemorrhage (III°-IV°)	15 (8.38)
Necrotising enterocolitis	2 (1.12)
Focal intestinal perforation	8 (4.47)
Retinopathy of prematurity	49 (27.84)
Death	12 (6.70)

Abbreviation: HELLP, haemolysis, elevated liver enzymes and low platelet count.

oxygen (FiO_2) was higher in the PIE group (P = .014), according to the Wilcoxon signed-rank test. Conditional logistic regression also showed that this was the case for the number of severe RDS cases (P = .007) and the need for surfactant (P = .0281). The matched-pairs analysis in the conditional logistic regression model confirmed that the higher incidence of intraventricular haemorrhage was a relevant complication following PIE (P = .0499). As birthweight plays a substantial role in calculating outcome parameters in preterm infants, we also analysed the total cohort in a stepwise univariate multivariable regression model, starting with birthweight and then adding GA, gender, multiple births, severe RDS and antenatal corticosteroids. The calculated cut-off for the strongest effect for preeclampsia and HELLP syndrome was a birthweight of 790g based on these findings: birthweight ≤ 790g (P = .008) versus birthweight ≥ 790g P = .054 (Appendix S1). These data suggest that immature preterm infants had an increased predisposition for PIE if their mothers had maternal preeclampsia or HELLP syndrome.

4 | DISCUSSION

Pulmonary interstitial emphysema is a potentially life-threatening condition following premature birth. Understanding the aetiopathogenesis of this pulmonary disease is crucial if we are to develop better treatment strategies for PIE cases that have not yet fully established themselves. Prenatal steroids and postnatal surfactant replacement have been reported to independently reduce mortality, the severity of RDS and air leaks in preterm infants.[19] A high percentage of our PIE cases were treated with antenatal corticosteroids and surfactant administration and therefore did not impact on the incidence of PIE. Moreover, the timing of surfactant administration played a fundamental role. In our study cohort, surfactant application was standardised at FiO_2 > 30%-40%. It is unclear whether mechanical ventilation or oxygen supply is the main drivers in the aetiology of PIE or whether early PIE is the reason for invasive mechanical ventilation, FiO_2 requirements and the need for surfactant administration. Only half of the PIE cases in our study underwent invasive mechanical ventilation during the first 24 hours of life, and the match-pairs analysis showed that ventilator settings had no significant impact on the incidence of PIE. Moreover, our cohort contained preterm infants with PIE who had not received invasive ventilation until they developed PIE and this finding has previously been described in low birthweight twins.[2] Conversely, anatomical and functional airway characteristics in the early course of severe RDS are different and may predispose infants to developing PIE.[20] Our data highlight the strong association between the development of PIE and RDS and between PIE and the well-known risk factors linked to immaturity, namely GA and birthweight.[3,5] Our results also underline that a postnatal predisposition to severe pulmonary disease severity was reflected by the need for higher supplemental oxygen and more frequent application of surfactant. Previous studies had already reported that using higher oxygen levels to resuscitate extremely premature infants had increased oxidative stress and the incidence of BPD.[21] Another study suggested that higher oxygen needs during resuscitation were an independent risk factor for PIE.[3] Furthermore, PIE development has been related to impaired oxygenation and ventilation efficiency and the oxygenation index during the development of PIE has been shown to be a predictor for death or BPD.[22] Our matched-pairs analysis took all the known major contributing factors to PIE into consideration, such as birthweight, GA and gender. The matching procedure focused on the main confounders of gestational age and gender, because prematurity is the main risk factor for developing air leaks, especially for PIE,[23] and male gender has been associated with consistently worse pulmonary outcomes.[24] Once we excluded those confounding factors, the new, and only relevant, maternal risk factors for PIE were revealed as preeclampsia and HELLP syndrome. It had already been reported that BPD was increased in infants exposed to preeclampsia.[25] Placental structural abnormalities related to IUGR and preeclampsia have also been strongly associated with foetal growth restriction, and studies have linked antenatal stress with poor respiratory outcomes.[26] Marked elevations of the soluble, endogenous vascular endothelial

TABLE 2 Clinical characteristics, postnatal ventilatory support and outcome parameters of preterm infants with and without PIE and the matched cases subgroup drawn from the non-PIE sample

	PIE[a], n = 33	Total non-PIE[a], n = 146	*P* value	Matched non-PIE subgroup[a], n = 33	*P* value matched-pairs comparison
Clinical characteristics					
Birth weight (kg)	0.70 (0.58-1.16)	1.10 (0.83-1.46)	**.0002**	0.77 (0.62-1.07)	.0612
Gestational age (weeks)	27.29 (24.00-28.71)	29.00 (26.75-30.86)	**.0008**	27.00 (25.00-28.71)	.5994
Male	16 (48.48)	73 (50.00)	1.0000	16 (48.48)	not applicable
Apgar score (1 min)	7.00 (5.00-8.00)	8.00 (6.00-8.00)	.1026	7.00 (5.00-8.00)	.5542
Apgar score (5 min)	9.00 (7.00-9.00)	9.00 (8.00-9.00)	.4741	9.00 (8.00-9.00)	.8531
Maternal age	31.00 (27.00-35.00)	31.00 (28.25-35.00)	.8477	34.00 (28.00-35.00)	.4579
Multiple birth	15 (45.45)	60 (41.10)	.6981	13 (39.39)	.4843
Premature rupture of the membranes	12 (36.36)	47 (32.41)	.6852	13 (39.39)	.7633
Chorioamnionitis	8 (25.81)	22 (16.06)	.2029	8 (25.81)	1.0000
Preeclampsia or HELLP	8 (24.24)	19 (13.01)	.1119	1 (3.03)	**.0499**
Diabetes (gestational/type I)	3 (9.09)	12 (8.22)	1.0000	2 (6.06)	.5714
Antenatal corticosteroids	27 (81.82)	120 (82.76)	1.0000	29 (87.88)	.4843
Intrauterine growth restriction	8 (24.24)	24 (16.44)	.3166	7 (21.21)	.7394
Postnatal respiratory support					
Severe respiratory distress syndrome (III°-IV°)	17 (51.52)	26 (17.81)	**.0002**	4 (12.12)	**.0074**
Invasive mechanical ventilation	18 (54.55)	41 (28.08)	**.0069**	11 (33.33)	.0674
Days of invasive ventilation	2 (0.00-6.00)	0 (0.00-1.00)	**<.0001**	0.00 (0.00-8.00)	.9899
Positive end-expiratory pressure (cmH_2O)	6.00 (6.00-6.00)	6.00 (6.00-7.00)	.2834	6.50 (6.00-7.00)	.1056
Peak inspiratory pressure (cmH_2O)	19.00 (17.00-23.25)	16.00 (14.00-20.00)	**.0304**	16.00 (14.00-21.00)	.3963
Mean airway pressure (cmH_2O)	9.00 (9.00-10.00)	9.00 (8.00-9.88)	.3384	9.00 (9.00-10.00)	.2785
Fraction of inspired oxygen	50.00 (40.00-81.00)	39.00 (28.25-50.00)	**<.0001**	40.00 (25.00-55.00)	**.0143**
Surfactant	32 (96.97)	82 (56.16)	**<.0001**	23 (69.70)	**.0281**
Early postnatal corticosteroids	5 (15.15)	3 (2.05)	**.0060**	1 (3.03)	.1418
Late postnatal corticosteroids	6 (18.18.)	9 (16.16)	**.0360**	6 (18.18)	1
Outcome parameters					
Intraventricular haemorrhage	8 (24.24)	7 (4.79)	**.0015**	1 (3.03)	**.0499**
Bronchopulmonary dysplasia (36 wk postmenstrual age)	16 (48.48)	46 (31.51)	.0713	21 (63.64)	.1182
Severe bronchopulmonary dysplasia	12 (36.36)	18 (12.33)	**.0031**	10 (30.30)	.5299
Necrotising enterocolitis	0 (0.00)	2 (1.37)	1.0000	1 (3.03)	.9984
Focal intestinal perforation	3 (9.09)	5 (3.42)	.1655	1 (3.03)	.9985
Retinopathy of prematurity	15 (48.39)	34 (23.45)	**.0077**	19 (57.58)	.3719
Death	6 (18.18)	6 (4.11)	**.0103**	1 (3.03)	.9985

Note: Statistical significance was defined as $P < .05$.

P values for unmatched data were calculated using Fisher's exact test for count data and the Wilcoxon rank-sum test for metric data.

P values for matched data were calculated using conditional logistic regression for count data and the Wilcoxon signed-rank test with continuity correction for metric data.

Abbreviation: HELLP, haemolysis, elevated liver enzymes and low platelet count.

[a]Data shown as medians (interquartile ranges) or numbers (percentages).

growth factor (VEGF) receptor-1 inhibitor, have been reported in the blood and amniotic fluid samples of mothers with preeclampsia. Decreased VEGF and increased soluble VEGF receptor-1 levels have also been strongly associated with BPD in tracheal fluid samples from preterm infants with a low gestational age.[27-30] These findings underline the connection between alveolar and vascular lung development.

They also show that imbalanced circulating proangiogenic and antiangiogenic factors could impair vasculogenesis in foetal lungs, leading to early disruption in lung maturation. Hypothetically, the preeclamptic intrauterine environment causes a primary insult in the developing foetal lung, predisposing it to further postnatal damage, including PIE. Infants born following preeclampsia are more susceptible to further lung impairment and need intensive treatment for respiratory stability. Preeclampsia has been recognised as a risk factor for RDS and BPD.[27] The association between preeclampsia and PIE has never been assessed, but is in line with the outcomes reported by those studies.

Although the sample size of our study did not allow us to assess the associations between preeclampsia and BPD, it was sufficient to show an association between preeclampsia or HELLP and PIE. Our analyses clearly indicate the need to include preeclampsia and HELLP syndrome in future calculations, in order to identify high-risk infants directly after birth. A limitation of our study was that there are no uniform criteria for the radiological diagnosis of PIE, and some cases represent a kind of a grey zone of cystic or linear radiolucencies in the interstitium radiating from the hilum. Moreover, there could be more unknown factors that have not been taken into consideration. The incidence of PIE could also be influenced by other important, unmeasured prenatal and postnatal risk factors related to the mother or the preterm infant. The possible lack of generalisability of the present study findings to other populations or other study settings should be taken into account when interpreting the findings. Due to the small study cohort, our data only suggest that there was a trend towards an association between preeclampsia or HELLP and PIE. It is important not to overestimate the possible importance of the findings, as further studies are needed to confirm and enhance the risk factors for PIE. The strengths of this study were the short study period of two years, which ensured uniform prenatal and postnatal treatment strategies and the radiological assessment by two independent, blinded experts. Future large-scaled studies on risk factors for PIE should include preeclampsia and HELLP to confirm their impact on its incidence.

5 | CONCLUSION

Preeclampsia and HELLP syndrome were identified as possible additional risk factor for PIE and should be taken into account in future risk calculations. Infants who are delivered early due to preeclampsia and HELLP syndrome need to receive improved treatment approaches that are dedicated to preventing PIE.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Behnke J, Windhorst A, Oehmke F, et al. Preeclampsia was a risk factor for pulmonary interstitial emphysema in preterm infants born ≤32 weeks of gestational age. *Acta Paediatr*. 2021;110:134–140. https://doi.org/10.1111/apa.15338