

Article

# Cardiopulmonary ultrasound patterns of transient acute respiratory distress of the newborn: a retrospective pilot study

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## SUPPLEMENTAL MATERIAL

### MATERIAL AND METHODS

**Definitions of the prenatal collected data are as follows:**

- diabetes in pregnancy as defined by NICE guidelines in presence of a fasting plasma glucose level of 5.6 mmol/liter or above or a 2-hour plasma glucose level of 7.8 mmol/liter or above [1], or preexisting diabetes [2]. Type of diabetes was recorded
- Gestational disorders of pregnancy were defined according to the American College of Obstetricians and Gynecologists (ACOG) guidelines [3]: preexisting or gestational hypertension, defined by the new onset of hypertension (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg) at  $\geq 20$  weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction, preeclampsia refers to the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or postpartum in a previously normotensive patient, HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count); chronic hypertension (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg) before 20 weeks gestation
- “Intrauterine Inflammation or Infection or both” also known as “Triple-I syndrome” was defined as the presence of intrapartum fever with at least one of the following items: fetal tachycardia ( $> 160$  bpm for more than 10 minutes), maternal WBC  $> 15,000$  in absence of corticosteroid treatment, purulent fluid from the cervical canal and biochemical or microbiologic amniotic fluid results consistent with microbial invasion of the amniotic cavity. Instead, a clinically documented fever with a temperature measured orally higher than  $39.0^{\circ}\text{C}$  or  $102.2^{\circ}\text{F}$  once or  $38.0^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$  twice was defined as isolated maternal fever [4].
- Intrauterine growth restriction (IUGR) was defined as a weight below the 10th percentile at fetal ultrasound [5].
- Fetal heart monitoring: intrapartum fetal heart health monitoring with non-invasive electronic monitoring classified in three categories: category 1 (normal) when fetal heart rate (FHR) baseline is between 110 and 160 bpm with moderate FHR variability (6 to 25 bpm) and absence of late, variable, or prolonged FHR decelerations; category 3 (pathological) if there are sinusoidal pattern, absent baseline FHR variability or recurrent late decelerations, recurrent variable decelerations, bradycardia; category 2 (indeterminate) FHR tracing does not meet criteria for either category I or III [6].

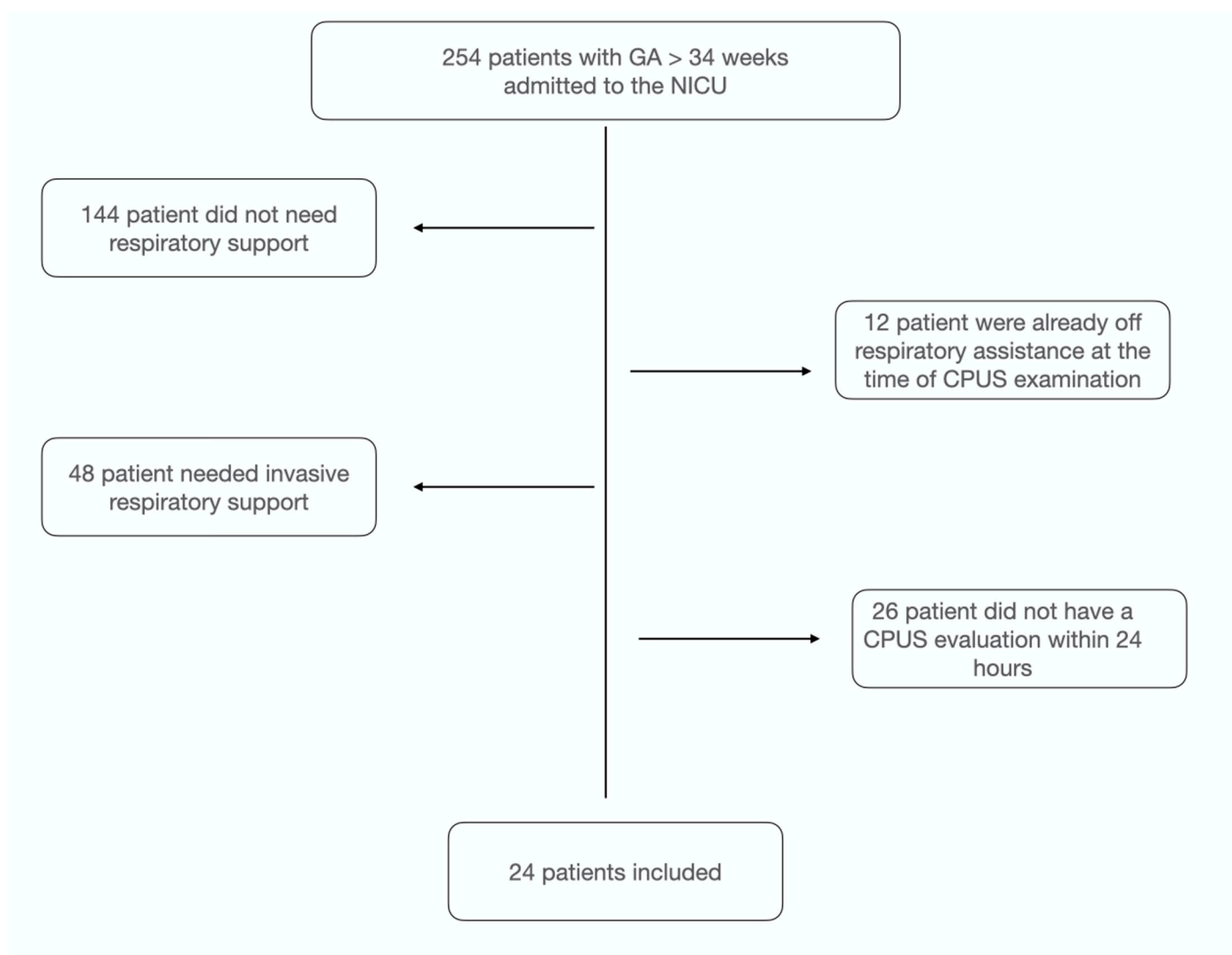
#### Placental histology

We retrospectively evaluated also placental histology. The presence of maternal vascular malperfusion (MVM) and chorioamnionitis on the placental histologies was defined according to the Amsterdam International Consensus criteria [7], and examined under the conventional microscope after hematoxylin and eosin staining. The placental pathologic findings involving maternal decidual vessels, reflecting abnormal spiral artery remodeling, and villous parenchyma, reflecting abnormalities in oxygenation and flow dynamics in the intervillous space, are summarized by the term MVM of the placental bed. MVM was defined by both macroscopic and microscopical placental findings. Macroscopic features include placental hypoplasia (with a weight and/or a thin cord

below 10th centile per gestational age), infarction and retroplacental hemorrhage. Microscopic findings include abnormalities of villous development, divided into distal villous hypoplasia and accelerated villous maturation. In case of chorioamnionitis (CA), we described the staging and grading of inflammation formulated in the Amsterdam International Consensus criteria. Preacute chorioamnionitis (stage 0) is characterised by neutrophils in the space beneath the chorionic plate. Early chorioamnionitis (stage 1) is defined by neutrophils limited to the chorion (chorionitis). Intermediate (stage 2) is distinguished by neutrophils within the chorionic or amniotic mesoderm.

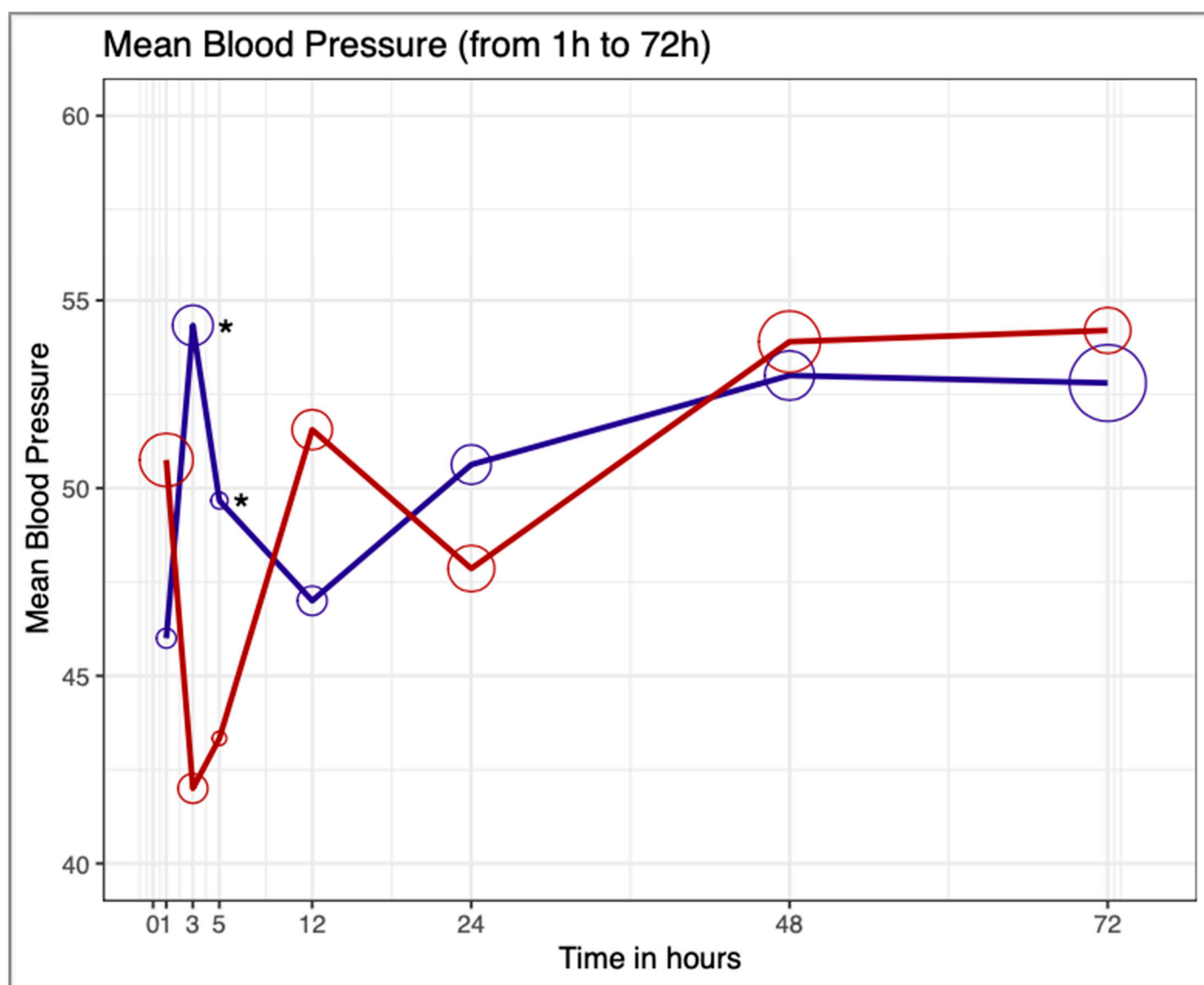
Advanced chorioamnionitis (stage 3) included inflammation of the chorioamniotic membranes with necrosis of amniotic epithelium or neutrophil necrosis. About grading we described severe if there were confluent polymorphonuclear leukocytes or with subchorionic

## FIGURES



**Figure S1. Patient population flow chart**

Abbreviations: gestational age (GA), neonatal intensive care unit (NICU), cardiopulmonary ultrasound (CPUS)



**Figure S2 Blood pressure trends.**

Blood pressure trends in infants with increased pulmonary vascular resistances (red line) and normal vascular resistances (blue line). Circles represent standard deviations

## TABLES

Table S1 - Characteristics of the Acute Respiratory Distress Phenotype Subgroups

Characteristics	Undefined (AND-U) (n=2)	Vascular (AND-v) (n=4)	Wet lung (AND-w) (n=4)	Vascular- wet lung (AND- vw) (n=4)	Vascular- RDS (n=2)	Consolidati on (AND-p) (n=6)	Vascular- consolidat ion (AND- vc) (n=2)	p-value
Maternal diabetes, n (%)	2 (100%)	0	1 (25%)	1 (25%)	0	0	0	0.628
Triple -I, n (%)	0	1 (25%)	3 (75%)	1 (25%)	1 (50%)	1 (16.7%)	1 (50%)	0.466
Placenta previa, n (%)	0	1 (25%)	0	0	0	1 (16.7%)	0	0.802
Fetal tachicardia, n (%)	1 (50%)	1 (25%)	1 (33.3%)	0	1 (50%)	2 (33.3%)	0	0.990
Maternal tachicardia, n (%)	0	0	0	0	0	1 (16.7%)	0	0.909
Maternal fever, n (%)	0	1 (25%)	0	1 (25%)	0	1 (16.7%)	0	0.925
Intrapartum antibiotics, n (%)	0	1 (25%)	2 (66.7%)	2 (50%)	2 (100%)	1 (16.7%)	0	0.241
Chorioamnionitis								0.478
No, n (%)	1 (50%)	2 (50%)	3 (75%)	1 (50%)	1 (50%)	5 (83.3%)	0	
Histological, n (%)	1 (50%)	1 (25%)	1 (25%)	1 (50%)	1 (50%)	0	2 (100%)	
Clinic, n (%)	0	1 (25%)	0	0	0	1 (16.7%)	0	
Placenta malperfusion, n (%)	1 (50%)	3 (75%)	1 (25%)	1 (25%)	2 (100%)	2 (33.3%)	2 (100%)	0.264
Gestational age (weeks), median (IQR)	40.4 (39.7- 41.1)	41 (35.8- 41.8)	37.5 (36- 40.3)	36.8 (36- 40.3)	38 (35.7- 39.3)	40.2 (39-41)	40.3 (39- 41.6)	0.729
Birth weight (grams), median (IQR)	3700 (3500- 3900)	3400 (2720- 3690)	3590 (3030- 4388)	2800 (2710- 3200)	3200 (2100- 4300)	3400 (3080- 3540)	3500 (3200- 3800)	0.453
Need for any kind of resuscitation at birth, n (%)	1 (50%)	3 (75%)	0	0	1 (50%)	4 (66.7%)	2 (100%)	0.072
Apgar at 1 minute, median (IQR)	7.5 (6-9)	5 (3.5-8)	9 (9-9)	9 (9-9)	6.5 (4-9)	7 (5-9)	5.5 (5-6)	0.153
Apgar at 5 minutes, median (IQR)	9 (8-10)	7.5 (6-9)	10 (10-10)	10 (10-10)	7.5 (5-10)	8 (7-9)	7.5 (7-8)	0.061
Amniotic fluid								0.126
Clear, n (%)	2 (100%)	1 (25%)	3 (100%)	4 (100%)	1 (100%)	1 (16.7%)	0	
Meconium stained, n (%)	0	3 (75%)	0	0	0	4 (66.7%)	2 (100%)	
Blood stained, n (%)	0	0	0	0	0	1 (16.7%)	0	

Maximum CRP (mg/dL) , median (IQR)	0.9 (0.9-0.9)	3 (0.5-5.4)	5.2 (1.6-6.5)	2 (1.4-3.5)	18.5 (5-30)	1.2 (0-2)	3.4 (3.-3.8)	0.001
Positive blood culture, n (%)	0	0	0	0	1 (50%)	0	0	0.550
Antibiotic therapy, n (%)	0	3 (75%)	3 (75%)	0	2 (100%)	1 (16.7%)	1 (50%)	0.055
Antibiotics duration (days), median (IQR)	0 (0-0)	3.5 (0.7-4)	3 (0.5-4.7)	0 (0-0)	8.5 (2-15)	0 (0-2)	1.5 (0-3)	
Length of stay (day), median (IQR)	11.5 (5-18)	8 (6-12)	9 (7-11)	4 (3-5)	14.5 (11-18)	4 (3.5-8)	6.5 (6-7)	0.094
Duration of CPAP (hours), median (IQR)	15 (0-30)	16 (0-60)	65 (13-78)	12 (0-60)	80 (58-102)	24 (8-32)	27 (5-49)	0.211
Duration of HFNC (hours), median (IQR)	115 (0-230)	3 (0-56)	1.5 (0-41.2)	0 (0-36)	6.5 (1-12)	0 (0-21)	0 (0-0)	0.266
Duration of NRS/low-flow oxygen (hours), median (IQR)	133 (30-236)	54 (8-92)	70 (55-84)	38 (25-66)	96.5 (88-105)	15.5 (4-59)	27 (5-49)	0.207
Maximum FiO2, median (IQR)	0.35 (0.30-0.40)	0.30 (0.30-0.38)	0.40 (0.26-0.55)	0.25 (0.30-0.35)	0.50 (0.50-0.50)	0.30 (0.26-0.45)	0.40 (0.40-0.40)	0.752
Surfactant administration via INSURE, n (%)	0	1 (25%)	1 (25%)	0	1 (50%)	1 (16.7%)	0	0.731
Hours of life at CPUS, median (IQR)	18 (10-22)	18 (10-21)	14 (6-22)	9 (5-19)	23.5 (23-24)	15 (5-26)	13 (2-24)	0.692
FiO2 at CPUS, median (IQR)	0.33 (0.27-0.39)	0.28 (0.28-0.38)	0.35 (0.24-0.50)	0.25 (0.30-0.35)	0.45 (0.40-0.50)	0.30 (0.24-0.40)	0.38 (0.36-0.40)	0.354

*Abbreviations:* Intrauterine growth restriction (IUGR), non invasive respiratory support (NRS), continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC), C-reactive protein (CRP)

Table S2 - Characteristics of the **Vascular/not Vascular** Phenotype Subgroups

Characteristics	Normal PVR (n=12)	Increased PVR (n=12)	p-value
Maternal diabetes, n (%)	1 (8.3%)	1 (8.3%)	1
Triple I, n (%)	4 (33.3%)	4 (33.3%)	1
Fetal tachicardia, n (%)	4 (36.4%)	2 (16.7%)	0.549
Maternal tachicardia, n (%)	1 (11.1%)	0	1
Maternal fever, n (%)	1 (10%)	2 (18.2%)	1
Intrapartum antibiotics, n (%)	3 (30%)	5 (41.7%)	0.903
Chorioamnionitis			0.140
No, n (%)	9 (75%)	4 (33.3%)	
Histology, n (%)	2 (16.7%)	6 (55.6%)	
Clinic, n (%)	1 (8.3%)	2 (11.1%)	
Placenta malperfusion, n (%)	4 (33.3%)	8 (66.7%)	0.071
Gestational age (weeks), median (IQR)	40 (37.2-41)	39.5 (35.8-42.5)	0.932
Birth weight (grams), median (IQR)	3480 (3300-3740)	3230 (2700-3700)	0.160
Need for any kind of resuscitation at birth, n (%)	5 (41.7%)	6 (50%)	1
Apgar at 1 minute, median (IQR)	9 (6.2-9)	6 (5-9)	0.347
Apgar at 5 minutes, median (IQR)	9.5 (8-10)	8 (7-10)	0.347
Amniotic fluid			0.574
Clear, n (%)	6 (54.4%)	6 (50%)	
Meconium stained, n (%)	5 (36.4%)	6 (50%)	
Blood stained, n (%)	1 (9.1%)	0	
Maximum CRP (mg/dL), median [IQR]	1.8 (0.7-5)	2.8 (1.4-4.7)	0.264
Positive blood culture, n (%)	0	1 (16.7%)	1
Antibiotic therapy, n (%)	4 (33.3%)	6 (50%)	0.679
Antibiotics duration (days), median (IQR)	0 (0-3.5)	1 (0-3.8)	0.59
Length of stay (days), median (IQR)	7 (4-11)	6 (6-11)	0.746
Duration of CPAP (hours), mean (IQR)	28.5 (3-51)	28 (0-67)	0.775



Duration of HFNC (hours), mean (IQR)	0 (0-41)	0 (0-10.5)	0.367
Duration of NRS/low-flow oxygen (hours), median (IQR)	48 (13-85)	49 (25-85)	0.692
Maximum FiO <sub>2</sub> , median (IQR)	0.35 (0.29-0.40)	0.35 (0.30-0.40)	0.875
Surfactant administration via INSURE, n (%)	2 (16.7%)	2 (16.7%)	1
Hours of life at CPUS, median (IQR)	15 (7.2-23.5)	18 (6.2-22.5)	0.977
FiO <sub>2</sub> at CPUS, median (IQR)	0.33 (0.28-0.40)	0.34 (0.28-0.38)	0.833

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*Abbreviations:* Intrauterine growth restriction (IUGR), non invasive respiratory support (NRS), continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC), C-reactive protein (CRP)

Table S3 - Characteristics of the lung phenotype groups

Characteristics	Normal n=6	Wet lung n=8	RDS n=2	Consolidation n=8	p-value
Maternal diabetes, n (%)	0	0	2 (28.6%)	0	0.23
Triple I, n (%)	1 (16.7%)	4 (100%)*	1 (14.3%)*	2 (28.6%)	0.03
Placenta previa, n (%)	1 (16.7%)	0	0	1 (14.3%)	1
Fetal tachicardia, n (%)	2 (33.3%)	1 (25%)	1 (14.3%)	2 (28.6%)	0.92
Maternal tachicardia, n (%)	0	0	0	1 (14.3%)	1
Maternal fever, n (%)	1 (16.7%)	1 (25%)	0	1 (14.3%)	0.33
Intrapartum antibiotics, n (%)	3 (50%)	3 (75%)	2 (28.6%)	2 (28.6%)	0.45
Chorioamnionitis					
No, n (%)	3 (50%)	4 (50%)	1 (50%)	4 (57.1%)	1
Histology, n (%)	2 (33.3%)	4 (50%)	1 (50%)	3 (28.6%)	
Clinic, n (%)	1 (16.7%)	0	0	1 (14.3%)	
Placenta malperfusion, n (%)	4 (66.7%)	2 (50%)	2 (28.6%)	4 (57.1%)	0.63
Gestational age (weeks), median (IQR)	40.7 (38.3-41)	37.5 (36-2-40.3)	37.6 (36-41)	40 (39-41)	0.524
Birth weight (grams), median (IQR)	3510 (3097-3787)	3590 (2860-4388)	2900 (2790-3550)	3380 (3170-3500)	0.654
Need for any kind of resuscitation at birth, n (%)	4 (66.7%)	0§	1 (14.3%)*	6 (75%)*§	0.01
Apgar at 1 minute, median (IQR)	5.5 (4.5-9)	9 (9-9)	9 (9-9)	6 (5-7)	0.058
Apgar at 5 minutes, median (IQR)	8 (6,7-9.2)*	10 (10-10)*†	10 (10-10)§	8 (7-8)†§	0.017
Amniotic fluid					
Clear, n (%)	3 (50%)	4 (100%)§	7 (100%)*§	0*	0.001
Meconium stained, n (%)	3 (50%)	0	0*	6 (85.7)*	
Blood stained, n (%)	0	0	0	1 (14.3%)	
Maximum CRP (mg/dL), median (IQR)	1.5 (0.5-5)	5.2 (3.6-6.5)	1.7 (0.6-10)	1.92 (0.9-3)	0.722
Positive blood culture, n (%)	0	0	1 (50%)	0	0.813
Antibiotic therapy, n (%)	3 (50%)	3 (37%)	2 (100%)	2 (25%)	0.633
Antibiotics duration (days), median (IQR)	1.5 (0-4)	3 (0.5-4.7)	0 (0-2)	0 (0-3)	0.929
Length of stay (days), median (IQR)	8 (5.7-14.2)	8 (6.2-9.8)	7 (3.5-14)	4 (4-7)	0.415
Duration of CPAP (hours), median (IQR)	15 (0-41)	38 (0-78)	54 (0-72)	28 (11-41)	0.574
Duration of HFNC (hours), median (IQR)	3 (0-112)	1.5 (0-41.2)	0 (0-12)	0 (0-0)	0.440
Duration of NRS/low-flow oxygen (hours), median (IQR)	54 (22.5-132)	70 (35-84)	54 (24-88)	20 (5-50)	0.506
Maximum FiO <sub>2</sub> , median (IQR)	0.30 (0.30-0.40)	0.40 (0.32-0.55)	0.30 (0.21-0.50)	0.40 (0.30-0.40)	0.526
Surfactant administration via INSURE, n (%)	1 (16.7%)	1 (12.5%)	1 (50%)	1 (12.5%)	1
Hours of life at CPUS, median (IQR)	18 (10-22)	14 (7-22)	20 (5-24)	3 (13-24)	0.798
FiO <sub>2</sub> at CPUS, median (IQR)	0.28 (0.27-0.36)	0.35 (0.32-0.50)	0.30 (0.21-0.45)	0.35 (0.38-0.40)	0.523

*Abbreviations:* Intrauterine growth restriction (IUGR), non invasive respiratory support (NRS), continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC), C-reactive protein (CRP). \*§: symbols represent significance among groups. Two groups with the same symbol are significant among each other

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