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Citation

Panneflek, T. J. R., Kuypers, K. L. A. M., Polglase, G. R., Hooper, S. B., Akker, T. van den, & Pas, A. B. te. (2022). Effect of clinical chorioamnionitis on breathing effort in premature infants at birth: a retrospective case-control study. *Archives Of Disease In Childhood. Fetal And Neonatal Edition*, 108(3), 280-285. doi:10.1136/archdischild-2022-324695

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Effect of clinical chorioamnionitis on breathing effort in premature infants at birth: a retrospective case–control study

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Received 26 July 2022

Accepted 15 November 2022

Published Online First

23 November 2022

ABSTRACT

Rationale Antenatal inflammation, usually associated with chorioamnionitis, is a major cause of premature birth. As inflammation could depress respiratory drive, we have examined the effect of clinical chorioamnionitis (CCA) on spontaneous breathing in premature infants at birth.

Methods Infants with CCA born <30 weeks' gestation were matched with control infants based on gestational age (± 6 days), birth weight (± 300 g), antenatal corticosteroids, sex and general anaesthesia. The primary outcome was breathing effort, assessed as minute volume (MV) of spontaneous breathing. We also measured tidal volume (Vt), respiratory rate (RR) and apnoea in the first 5 min and additional physiological parameters in the first 10 min after start of respiratory support.

Results Ninety-two infants were included (n=46 CCA infants vs n=46 controls; median (IQR) gestational age 26⁺⁴ (25⁺⁰–27⁺⁶) vs 26⁺⁶ (25⁺¹–28⁺³) weeks). MV and Vt were significantly lower (MV: 43 (17–93) vs 70 (31–119) mL/kg/min, p=0.043; Vt: 2.6 (1.9–3.6) vs 2.9 (2.2–4.8) mL/kg/breath, p=0.046), whereas RR was similar in CCA infants compared with controls. Incidence of apnoea was higher (5 (2–6) vs 2 (1–4), p=0.002), and total duration of apnoea was longer (90 (21–139) vs 35 (12–98) s, p=0.025) in CCA infants. CCA infants took significantly longer to reach an oxygen saturation >80% (3:37 (2:10–4:29) vs 2:25 (1:06–3:52) min, p=0.016) and had a lower oxygen saturation at 5 min (77 (66–92) vs 91 (68–94) %, p=0.028), despite receiving more oxygen (62 (48–76) vs 54 (43–73) %, p=0.036).

Conclusion CCA is associated with reduced breathing effort and oxygenation in premature infants at birth.

INTRODUCTION

Most premature infants require respiratory support at birth, as their breathing is often insufficient to aerate their lungs and establish effective pulmonary gas exchange unassisted.¹ This respiratory support is provided non-invasively and primarily focuses on supporting spontaneous breathing via continuous positive airway pressure (CPAP). However, positive pressure ventilation is applied when infants are apnoeic.² Effective non-invasive ventilation requires a patent larynx for air to enter the lungs, but evidence indicates that when an infant's breathing is intermittent or absent, the larynx is mainly closed and only opens during a spontaneous breath.³ As a closed larynx during apnoea

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Antenatal inflammation, usually associated with chorioamnionitis, is a major cause of premature birth.
- ⇒ Chorioamnionitis is associated with diminished fetal breathing in animals and an increased need for respiratory support in premature infants at birth.

WHAT THIS STUDY ADDS

- ⇒ Clinical chorioamnionitis is associated with reduced spontaneous breathing and oxygenation at birth.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Clinicians should be aware that chorioamnionitis likely depresses breathing at birth, and infants affected by chorioamnionitis might therefore be at a higher risk of requiring respiratory support at birth.

hampers the effectiveness of respiratory support, spontaneous breathing should be stimulated and supported in infants requiring assistance at birth.^{1,4}

Apnoea occurs more often in premature infants than in term infants due to their immature respiratory control centres,⁵ especially when they become hypoxic due to an inability to aerate their lungs.^{1,6} Similarly, inflammation also depresses respiratory drive,^{7–10} which is thought to be mediated by an increase in proinflammatory cytokines and prostaglandin E₂ (PGE₂) levels, acting directly on respiratory control centres in the medulla oblongata and nucleus tractus solitarius.^{7–11} The most prevalent form of inflammation affecting premature infants is chorioamnionitis, defined as antenatal inflammation of the fetal membranes and umbilical vessels.¹² Infants affected by chorioamnionitis require more respiratory support at birth, which might be associated with the aforementioned inflammatory-mediated respiratory depression.^{13–16}

Although studies have investigated the association between chorioamnionitis and respiratory support, the effect of chorioamnionitis on measurable breathing effort at birth is unknown. Therefore, we aimed to evaluate the effect of clinical chorioamnionitis (CCA) on spontaneous breathing in premature infants. We hypothesised that CCA would reduce breathing effort (i.e. minute volume



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To cite: Panneflek TJR, Kuypers KLAM, Polglase GR, et al. *Arch Dis Child Fetal Neonatal Ed* 2023;**108**:F280–F285.

Table 1 Baseline characteristics

	CCA infants (n=46)	Controls (n=46)	P value (pairs)
Maternal			
Maternal age (years), mean±SD	31±7	29±5	N.S* (46)
Primiparity, n (%)	29 (63)	28 (60.9)	N.S† (46)
Caesarean delivery, n (%)	17 (37)	18 (39.1)	N.S† (46)
General anaesthesia, n (%)	4 (8.7)	4 (8.7)	N.S† (46)
Multiple pregnancy, n (%)	22 (47.8)	22 (47.8)	N.S† (46)
Antenatal corticosteroids two gifts†, n (%)	36 (78.3)	36 (78.3)	N.S† (46)
Fetal growth restriction, n (%)	6 (13)	6 (13)	N.S† (46)
pPROM, n (%)	29 (63)	12 (26.1)	0.002† (46)
Histological chorioamnionitis, n (%)	26 (56.6)	11 (23.9)	N.S† (21)
Missing data, n (%)	13 (28.3)	16 (34.8)	
Neonatal			
Gestational age (weeks), median (IQR)	26 ⁺⁴ (25 ⁺⁰ –27 ⁺⁶)	26 ⁺⁶ (25 ⁺¹ –28 ⁺³)	N.S‡ (46)
Birth weight (g), mean±SD	920±297	900±298	N.S* (46)
Small for gestational age, n (%)	3 (6.3)	2 (4.3)	N.S† (46)
Male, n (%)	16 (34.8)	16 (34.8)	N.S† (46)
Apgar score at 1 min, median (IQR)	4 (2–6)	4 (3–7)	N.S‡ (46)
Apgar score at 5 min, median (IQR)	7 (6–8)	8 (67–8)	N.S‡ (46)
Apgar score at 10 min, median (IQR)	8 (7–9)	9 (8–9)	N.S‡ (46)
Umbilical pH, median (IQR)	7.3 (7.1–7.4)§	7.3 (7.3–7.3)§	N.S‡ (27)

Umbilical pH represents the umbilical artery or vein pH.
 *Paired samples t-test.
 †Related samples McNemar test.
 ‡Related samples Wilcoxon signed-rank test.
 §Missing data comprised n=10 (27.1%) in both groups.
 CCA, clinical chorioamnionitis; N.S, non-significant p value; pPROM, prolonged premature rupture of the membrane.

of spontaneous breathing) and increase the risk of apnoea in premature infants at birth.

METHODS

A retrospective case–control study was performed in infants born between 23⁺⁶ and 29⁺⁶ weeks of gestation. All available resuscitation recordings of premature infants <30 weeks recorded at the Leiden University Medical Centre (LUMC) between January

2016 and December 2020 were analysed. Recordings were excluded if no respiratory function monitor (RFM) data were available. Data were collected from RFMs and electronic health records.

Chorioamnionitis was diagnosed based on the Triple I criteria, which differentiates between isolated fever ($\geq 38^{\circ}\text{C}$), suspected Triple I and confirmed Triple I.¹⁷ Suspected Triple I, that is, CCA, is diagnosed by maternal fever ($\geq 38^{\circ}\text{C}$) without a clear cause with one of the following: leucocytosis (white cell count $>15 \times 10^9/\text{L}$ in the absence of corticosteroids), fetal tachycardia (fetal heart rate (HR) >160 beats per minute for 10 min or longer) or purulent vaginal discharge from the cervical os.¹⁷ Confirmed Triple I is diagnosed when suspected Triple I is apparent, combined with histopathological evidence of inflammation in the placenta, fetal membranes or umbilical cord vessels or evidence of infection in the amniotic fluid (eg, positive gram stain, low glucose, high white cell count or positive amniotic fluid culture).¹⁷

Infants of pregnant women who fulfilled the criteria for suspected Triple I (CCA infants) were matched on a 1:1 ratio with infants of pregnant women who did not (controls). We matched using IBM Statistics SPSS V.25.0 (IBM Software, Chicago, Illinois, USA, 2016) and matchings were based on gestational age (± 6 days), birth weight (± 300 g), antenatal corticosteroids, sex and general anaesthesia.

In the LUMC, respiratory support was provided by the Neopuff infant T-piece resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) via facemask (Neonatal Resuscitation Mask, Fisher & Paykel Healthcare Ltd). Respiratory support started with CPAP of 5–8 cm H₂O. In case of apnoea and/or bradycardia, initial inflations of 3–15 s and positive pressure ventilation with a frequency of 40–60 inflations per minute were given for which a positive end-expiratory pressure of 5–8 cm H₂O and a peak

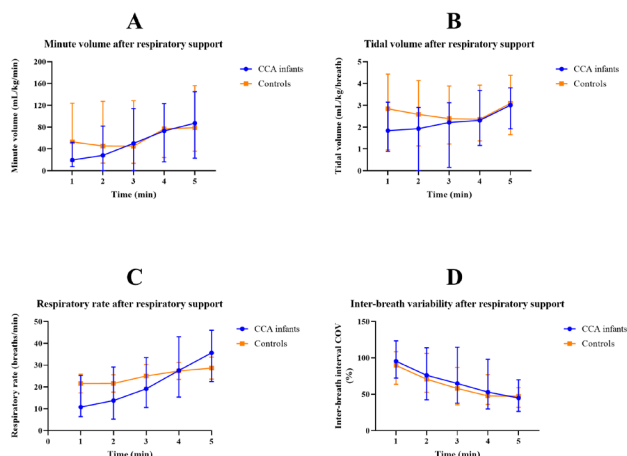


Figure 1 Breathing effort outcomes. Measurements of minute volume (A), tidal volume (B), respiratory rate (C) and coefficient of variation (COV) of the inter-breath interval (D) in controls and CCA infants with median group values and IQRs during the first 5 min after the start of respiratory support.

Table 2 Physiological parameters

	CCA infants (n=46)	Controls (n=46)	P value (pairs)
Respiratory parameters in the first 5 min after start of respiratory support			
Time until start of respiratory support (min), median (IQR)	0:59 (0:39–1:19)	1:02 (0:30–1:43)	0.769* (46)
Incidence of apnoea (n), median (IQR)	5 (1.8–6)	2 (1–4)	0.002* (46)
Duration per apnoea (s), median (IQR)	18.7 (14.8–24.2)	17.3 (13.0–22.7)	0.712* (37)
Total duration of apnoeas (s), median (IQR)	90.1 (21.3–138.9)	35.13 (11.7–97.7)	0.025* (46)
CPAP level (cm H ₂ O), median (IQR)	6.3 (5.7–7.4)	7.0 (6.2–7.9)	0.227* (45)
PIP level (cm H ₂ O), median (IQR)	25.3 (23.6–26.0)	24.4 (22.7–26.0)	0.985* (32)
Additional physiological parameters in the first 10 min after start of respiratory support			
Saturation (%), median (IQR)	76.3 (71.8–79.9)	78.4 (71.6–83.7)	0.121* (32)
Time until saturation >80% (min), median (IQR)	3:37 (2:10–4:29)	2:55 (1:06–3:52)	0.016* (32)
Saturation at 5 min after birth (%), median (IQR)	77 (66–92)	91 (68–94)	0.028* (29)
HR (bpm), median (IQR)	134.7 (122.1–148.4)	133.9 (119.8–141.9)	0.851* (33)
Time until heart rate >100 bpm (min), median (IQR)	0:56 (0:38–1:48)	1:26 (0:33–2:13)	0.501* (33)
Fraction of inspired oxygen (%), median (IQR)	61.9 (48.2–75.6)	54.1 (43.2–73.1)	0.036* (45)
The time until SpO ₂ >80% and HR>100 bpm is the time difference between the outcome of interest and start of respiratory support.			
*Related samples Wilcoxon signed-rank test.			
bpm, beats per minute; CCA, clinical chorioamnionitis; CPAP, continuous positive airway pressure; HR, heart rate; PIP, peak inspiratory pressure.			

inspiratory pressure (PIP) of 20–25 cm H₂O were used. The fraction of inspired oxygen (FiO₂) started at 0.3 and was titrated based on the 25 percentile of the Dawson nomogram.¹⁸ The infants' physiological measurements were collected in the first 10 min (min) after start of respiratory support in the delivery room using an RFM (Advanced Life Diagnostics, Weener, Germany) and the Polybench physiological software (Applied Biosignals, Weener, Germany). Pulmochart software (Applied Biosignals) allowed for a breath-by-breath analysis to calculate respiratory outcomes corrected for birth weight, and the analysis of physiological data was performed by one researcher (TJRP) blinded to the groups.

The primary outcome was measurable breathing effort in the first 5 min after start of respiratory support. Breathing effort was defined as minute volume of spontaneous breathing and is the product of the average tidal volume per breath and the respiratory rate in this time period. Tidal volume (mL/kg/breath) was calculated during inspiration on CPAP with at least a peak flow rate of 0.3 L/min and mask leak <75%.¹⁹ In contrast, respiratory rate (breaths/min) included all spontaneous breaths made by infants independent of the type of respiratory support. Additional respiratory parameters were assessed in the first 5 min and consisted of: occurrence of apnoea, which is defined as a cessation of breathing for more than 10 s, inter-breath variability and CPAP and PIP levels. Physiological parameters were assessed in the first 10 min and included: HR, oxygen saturation (SpO₂) and fraction of inspired oxygen (FiO₂). Other outcomes comprised of: type of respiratory support given in the delivery room and

neonatal intensive care unit (NICU) and neonatal infection parameters (temperature at admission, white blood cell count, C-reactive protein levels and positive blood culture).

Collected demographics comprised maternal characteristics: maternal age, parity, mode of delivery, type of anaesthesia, multiple pregnancy, antenatal corticosteroids, fetal growth restriction, prolonged premature rupture of the membranes (pPROM) and Triple I criteria and neonatal characteristics: gestational age, birth weight, sex, Apgar scores and umbilical pH.

Statistical analysis

All data were analysed using IBM SPSS Statistics V.25.0. Categorical data were analysed by a related samples McNemar test and presented as n (%). Continuous data were assessed for normality by inspecting the histograms and using the Shapiro-Wilkinson test. Parametric data were analysed using a paired samples t-test presented as mean±SD and non-parametric data using a related samples Wilcoxon signed-rank test presented as median (IQR). The corresponding test is mentioned in the reporting table, and the percentage of missing data is noted. Two-sided p values <0.05 were considered significant.

RESULTS

Three hundred fifty-eight eligible infants were born in the LUMC between 2016 and 2020, of which 52 (15%) met the criteria of CCA. Based on the matching criteria, six CCA infants could not be matched, and we included 46 CCA infants and 46 controls. All maternal and neonatal baseline characteristics were similar between the groups, except for a higher incidence of pPROM in CCA infants (CCA infants vs controls: 29 (63%) vs 12 (26.1%), p=0.002) (table 1).

Respiratory parameters in the first 5 min after respiratory support

CCA infants had significantly lower minute volumes (42.9 (16.6–93.4) vs 70.1 (31.0–118.8) mL/kg/min, p=0.043, figure 1A) with lower tidal volumes (2.6 (1.9–3.6) vs 2.9 (2.2–4.8) mL/kg/breath, p=0.046, figure 1B) when compared with the control group. Respiratory rate and inter-breath variability were similar

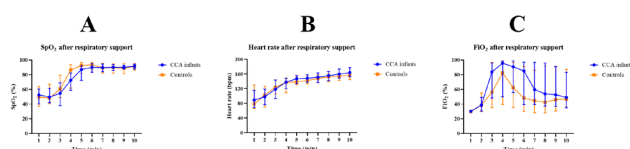


Figure 2 Physiological outcomes. Measurements of oxygen saturation (SpO₂ (A)), heart rate (HR (B)) and fraction of inspired oxygen (FiO₂ (C)) in controls and CCA infants with median group values and IQRs during the first 10 min after the start of respiratory support. CCA, clinical chorioamnionitis.

Table 3 Respiratory support and neonatal infection parameters

	CCA infants (n=46)	Controls (n=46)	OR (95% CI)	P value (pairs)
Respiratory support in the delivery room and NICU				
Initial inflations received, n (%)	41 (89.1%)	36 (78.3%)	2.25 (0.69 to 7.31)	0.267* (46)
Positive pressure ventilation received in the delivery room, n (%)	35 (76.1%)	32 (69.6%)	1.43 (0.54 to 3.75)	0.629* (46)
Positive pressure ventilation duration in the first 5 min after respiratory support (min), median (IQR)	2:17 (1:11–3:12)	1:52 (1:02–2:52)		0.954* (24)
Intubation in delivery room, n (%)	12 (26.1%)	5 (10.9%)	3.33 (0.92 to 12.11)	0.092* (46)
Caffeine administration in the delivery room, n (%)	27 (58.7%)	28 (60.9%)	0.9 (0.37 to 2.21)	1.000* (45)
Missing data, n (%)	1 (2.2%)	0 (0%)		
Surfactant administration in the NICU, n (%)	28 (60.9%)	31 (67.4%)	0.79 (0.36 to 1.73)	0.69* (46)
Intubation in the NICU, n (%)	18 (39.1%)	26 (56.5%)	0.38 (0.14 to 1.08)	0.096* (46)
Neonatal infection parameters				
Temperature at admission, median (IQR)	37.0 (36.6–37.4)	36.5 (35.9–36.9)		0.003† (46)
Neonatal leukocytosis‡, n (%)	5 (10.9%)	3 (6.5%)	1.67 (0.40 to 6.97)	0.480* (40)
First WBC count (10 ⁹ /L)‡, median (IQR)	8.3 (6.48–13.81)	9.19 (5.04–11.93)		0.946† (40)
Highest WBC count (10 ⁹ /L)‡, median (IQR)	11.2 (7.2–21.2)	10.8 (7.9–17.1)		0.375† (40)
First CRP (mg/L)§, median (IQR)	2.4 (0.8–11.1)	1.4 (0.5–3.6)		0.172† (33)
Highest CRP (mg/L)§, median (IQR)	4.7 (1.0–14.8)	1.4 (0.5–3.6)		0.044† (33)
Culture proven early-onset sepsis¶, n (%)	1 (2.2%)	0 (0%)		1.000* (40)

*Related samples McNemar test.

†Related samples Wilcoxon signed-rank test.

‡Missing data comprised n=3 (6.5%) in both groups.

§Missing data comprised n=3 (6.5%) in CCA infants and n=10 (21.7%) in the control group.

¶Missing data comprised n=2 (4.3%) in CCA infants and n=4 (8.7%) in the control group.

CCA, clinical chorioamnionitis; CRP, C-reactive protein; NICU, neonatal intensive care unit; WBC, white blood cell.

between the groups (21 (15–32) vs 24 (17–33) *breaths/min*), $p=0.996$, figure 1C; 74.39 (55.5–92.4) vs 70.9 (58.2–86.2) %, $p=0.350$, figure 1D), while apnoea occurred more frequently in the CCA infants (5 (2–6) vs 2 (1–4), $p=0.002$) with a longer total duration of apnoea (90.1 (21.3–138.9) vs 35.1 (11.7–97.7) s, $p=0.025$) (table 2).

Additional physiological parameters in the first 10 min after respiratory support

Time to reach a $\text{SpO}_2 > 80\%$ was significantly longer and SpO_2 at 5 min after birth was significantly lower in CCA infants (3:37 (2:10–4:29) vs 2:25 (1:06–3:52) *min:sec*, $p=0.016$; 77 (66–92) vs 91 (68–94) %, $p=0.028$), despite requiring higher FiO_2 levels (63.2±16.8 vs 56.1±18.6%, $p=0.015$) to reach this target compared with control infants. The groups showed no differences in SpO_2 , HR and time until HR > 100 beats per minute (table 2 and figure 2).

Respiratory support in the delivery room and NICU

There were no statistical differences in non-invasive respiratory support received in the delivery room and NICU; however, CCA infants were more often intubated in the delivery room (12 (26.1%) vs 5 (10.9%), $p=0.092$), while controls were more often intubated in the NICU (18 (39.1%) vs 26 (56.5%), $p=0.096$), but this failed to reach statistical significance (table 3).

DISCUSSION

This retrospective case-control study has shown that infants exposed to CCA in utero have a significantly reduced breathing effort with lower tidal volume and a higher incidence and longer periods of apnoea compared with controls. In addition, they took longer to increase oxygenation levels above 80% and were more poorly oxygenated at 5 min after birth, despite receiving higher levels of supplemental oxygen. This suggests

that chorioamnionitis adversely impacts respiratory function in premature infants at birth.

Our measurements confirm and extend observations in previous studies reporting qualitative assessments of respiratory function in infants from mothers with chorioamnionitis.^{13–15} While they had no RFM data, these studies observed less spontaneous breathing and a greater need for both oxygen supplementation and invasive ventilation in the delivery room for infants affected by chorioamnionitis.^{13–15} These findings are consistent with the lower breathing effort and oxygenation observed in our study.

Lower breathing effort in CCA infants was caused by lower tidal volume and a higher incidence of apnoea. This indicates that central inhibition of the aforementioned respiratory control centres by inflammatory mediators like PGE_2 may be the primary cause for the transient negative effect on tidal volume and apnoea, as these centres regulate depth and rate of inspiration.¹¹ Furthermore, this would explain why the inhibitory effects of CCA regressed over time (ie, higher tidal volume and respiratory rate; figure 1). PGE_2 is metabolised in the lung and an increase in pulmonary blood flow following lung aeration could increase PGE_2 metabolism, which would reduce the PGE_2 -mediated central inhibition and allow for the observed lower incidence of apnoea and higher tidal volume over time.^{6 20 21} However, whether or not lung aeration leads to such an increase in PGE_2 clearance is unknown. Moreover, other factors, such as increasing FiO_2 and oxygenation and changing adenosine levels (also known inhibitor of breathing) could also have contributed to the increase in spontaneous breathing over time in CCA infants.^{1 22} Changes to pulmonary function caused by chorioamnionitis, such as lung inflammation and decreased diaphragmatic contractility, may also contribute to the reduction in breathing effort.^{23–25} However, as minute volume and tidal volume were only transiently lower in CCA infants, the contribution of lung

inflammation and decreased diaphragmatic contractility is likely to be minimal, because presumably, their effects on pulmonary function should be sustained.^{23–25}

As CCA infants took significantly longer to reach an $\text{SpO}_2 > 80\%$ and their SpO_2 was lower at 5 min after birth, despite receiving higher FiO_2 levels, we found that chorioamnionitis also adversely affected oxygenation, which is in line with previous studies.^{13–14} This is likely caused by reduced breathing effort, which delays lung aeration and reduces the surface area available for gas exchange. In compensation, higher inspired oxygen tensions were required to increase the O_2 concentration gradient for O_2 diffusion and reach the same level of oxygen uptake across the lung.^{6–26} Nonetheless, in spite of increased oxygen tensions, oxygenation did not rise equally in both groups, which suggests that chorioamnionitis also reduces the oxygen exchange capacity in the lung.

While this study is a case-control study, we used a blinded (to outcome) approach to carefully match CCA affected infants 1:1 with control infants ensuring comparable criteria relevant to breathing effort, using a similar approach as previously described.^{27–28} In addition, individual patient data were also analysed blinded to the group and so, while not ideal, the risk of bias was minimised as much as possible. Lastly, the Triple I criteria have a sensitivity and specificity of 71% and 41%, respectively, for confirmed Triple I, indicating neither very specific nor sensitive criteria.²⁹ Nevertheless, they are currently recommended by the National Institute of Child Health and Human Development for detection of chorioamnionitis.^{17–30}

We consider that this study can be used as a rationale for further studies focused on factors regulating spontaneous breathing in premature infants at birth. A large proportion (40%) of premature infants are born due to antenatal inflammation, which could inhibit spontaneous breathing and reduce oxygenation at birth, as observed in our study.^{31–32} As such, caregivers may need to focus greater attention on stimulating spontaneous breathing and expect to give higher oxygen supplementation at birth in infants exposed to chorioamnionitis prenatally. Experimental studies investigating the temporal influence of perinatal factors associated with inflammation (eg, prostaglandins and adenosine) on spontaneous breathing during the cardiopulmonary transition would benefit our understanding of how respiratory support could be improved at birth.

CONCLUSION

In this study, we observed that CCA was associated with reduced breathing effort and oxygenation in premature infants at birth. Clinicians should be aware of the possible effect of chorioamnionitis on respiratory function and the importance of improving and stimulating spontaneous breathing in these infants at birth.

Twitter Arjan B te Pas @None

Acknowledgements We acknowledge the efforts of Hylke Salverda, who assisted in automatic data analysis and abstract formation in this study.

Contributors All authors contributed to the conception and design of the study; TJRP and KLAMK contributed to data acquisition and data management; TJRP, KLAMK and ABtP contributed to data analysis; all authors were involved with the data interpretation; TJRP contributed to the draft formation; KLAMK, GRP, SBH, TvdA and ABtP contributed to revising the draft formation. TJRP accepts full responsibility as guarantor for the finished work, conduct of the study and overall content. As guarantor, TJRP had access to the data, and controlled the decision to publish. All authors approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The medical ethics committee of Leiden, Den-Haag and Delft (METC LDD) approved the study protocol (approval number G21.080), issued a statement of no objection for conducting this study and waived the need to obtain informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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