Intermittent Hypoxemia in Infants Born Late Preterm: A Prospective Cohort Observational Study

Logan Zane John Williams, BMedSc(Hons)[1], David McNamara, PhD[2], and Jane Marie Alsweiler, PhD[1,2]

Objective To determine if late preterm infants are at increased risk of intermittent hypoxemic events compared with term infants.

Study design Prospective, cohort, observational study of late preterm infants ($34^{0/7}$-$36^{6/7}$ weeks gestational age) and term infants ($39^{0/7}$-$41^{6/7}$ weeks gestational age). Overnight pulse oximetry recordings were performed on days 2-3 after birth, at term equivalent age, and at 45 weeks postmenstrual age. The primary outcome was the frequency of intermittent hypoxemic events per hour (desaturation ≥10% below the preceding baseline SpO_2) on the oximetry recording on days 2-3 after birth. Data were analyzed by the Student *t* test and general linear mixed model.

Results Eighty-five infants were enrolled (late preterm n = 43; term infants n = 42). On days 2-3 after birth, late preterm infants had more intermittent hypoxemic events than term infants (events per hour, mean ± standard error of the mean, 2.5 ± 1.2 vs 1.0 ± 1.2; $P < .0001$). On mixed model analysis, late preterm infants had a higher frequency of intermittent hypoxemic events at term equivalent age, which decreased to a similar frequency as in term infants by 45 weeks postmenstrual age (events per hour; term equivalent age, late preterm: least squares mean, 3.7 [95% CI, 2.7-5.1] vs term: least squares mean, 1.7 [95% CI, 1.2-2.3]; 45 weeks postmenstrual age, late preterm: least squares mean, 1.5 [95% CI, 1.1-2.1] vs term: least squares mean, 1.9 [95% CI, 1.4-2.6]; $P < .0005$).

Conclusions Late preterm infants are at greater risk of intermittent hypoxemia than term infants soon after birth. We speculate that preventing intermittent hypoxemia in late preterm infants may improve neurodevelopmental outcomes. *(J Pediatr 2019;204:89-95).*

Late preterm infants ($34^{0/7}$-$36^{6/7}$ weeks gestational age)[1] constitute 83% of the preterm population and approximately 6% of all infants born annually worldwide.[2] Recently, it has become apparent that late preterm infants have higher rates of mortality,[3] cerebral palsy,[4,5] developmental delay,[6] and behavioral disorders[7] compared with term infants (>37 weeks gestational age). There are currently no prophylactic treatments available for late preterm infants proven to improve their long-term neurodevelopmental outcomes. Antenatal betamethasone administration in pregnant women at risk of late preterm delivery improves short-term respiratory outcomes in infants born late preterm, but increases the incidence of hypoglycemia,[8] which may worsen long-term neurodevelopmental outcomes.[9]

Intermittent hypoxemia is common in very and extremely preterm infants, particularly in the second to sixth weeks after birth[10] and after cessation of caffeine treatment.[11] Suboptimal lung function, as well as impaired respiratory control, in preterm infants during early postnatal life may contribute to intermittent hypoxemia.[12,13] Extremely preterm infants who have more prolonged intermittent hypoxemic events are at an increased risk of neonatal morbidity and late death or disability at 18 months corrected age.[14] In children with sleep-disordered breathing, intermittent hypoxemic episodes have also been associated with neurodevelopmental impairment,[15] with improvement in behavior and functioning after adenotonsillectomy.[16]

Currently, it is unknown if late preterm infants are at increased risk of intermittent hypoxemia. If late preterm infants are at increased risk of intermittent hypoxemia, this condition may impair their neurodevelopmental outcomes and is potentially modifiable with caffeine treatment. The aim of this study was to determine if late preterm infants are at increased risk of intermittent hypoxemic events compared with term infants.

Methods

This was a prospective cohort observational study. The cases were late preterm infants born at Auckland City Hospital. The controls were the next term infant

D10	Desaturation ≥10% below the preceding baseline SpO_2 for ≥2 seconds
D3	Desaturation ≥3% below the preceding baseline SpO_2 for ≥2 seconds
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
SpO_2	Oxygen saturation

From the [1]Department of Paediatrics: Child and Youth Health, The University of Auckland; and [2]Newborn Services, Auckland City Hospital, Auckland, New Zealand

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($39^{0/7}$-$41^{6/7}$ weeks gestational age) born after the birth of a late preterm infant at Auckland City Hospital whose parents gave consent, matched for mode of delivery (vaginal delivery or caesarean delivery). At Auckland City Hospital, all infants born at less than 35 weeks gestational age, or with a birth weight of less than 2 kilograms, are admitted to the neonatal intensive care unit (NICU); infants born at $35^{0/7}$-$36^{6/7}$ weeks gestational age are admitted to the postnatal ward unless they require respiratory support. This study was approved by the Northern A Health and Disability Committee (15NTA169) and Auckland District Health Board (6868).

Inclusion criteria for late preterm and term infants were gestational age at birth of $34^{0/7}$-$36^{6/7}$ and $39^{0/7}$-$41^{6/7}$ weeks, respectively. Exclusion criteria were respiratory distress requiring respiratory support (including caffeine) at the time of the first overnight oximetry, multiple births (>2), major congenital abnormality, and admission to the NICU (term infants only). Eligible infants were identified postnatally using a prospectively maintained database. Written, informed consent from the parents was obtained for all participants.

Intermittent hypoxemic events were measured overnight using a Masimo Radical-7 pulse oximeter (Masimo Corp, Irvine, California), a motion-resistant oximeter with a short 2-second averaging time and a 2-second resolution. Overnight postductal oxygen saturation (SpO_2) was measured from either foot.

For all infants enrolled in the study, the initial overnight pulse oximetry recording was performed on days 2-3 after birth. For late preterm infants, overnight oximetry recordings were repeated weekly after the initial oximetry recording until term equivalent age (40 weeks postmenstrual age [PMA]), at term equivalent age, and at 45 weeks PMA. For term infants, an overnight oximetry recording was repeated at 45 weeks PMA. The overnight pulse oximetry was carried out at the location of the infant (Auckland City Hospital or the infant's home).

The overnight oximetry recording was downloaded using PROFOX oximetry software (version Masimo 2011.27D, PROFOX Associates Inc, Escondido, California). Sections of recording with poor signal quality were identified and removed by the PROFOX software. Only oximetry reports with a total time of 6 hours or longer of recorded data, after removal of recording with poor signal quality, were included in the analysis.

The primary outcome of the study was the frequency of intermittent hypoxaemia events defined by desaturation of 10% or more below the preceding baseline SpO_2 with a minimum duration of 2 seconds (D10), on the overnight oximetry recording performed on days 2-3 after birth. The secondary outcomes of the study were frequency of intermittent hypoxemic events defined by desaturation of ≥3% below the preceding baseline SpO_2 with a duration of ≥2 seconds ([D3]); duration of prolonged D10 events (intermittent hypoxemic event between ≥10 seconds and ≤3 minutes in duration); mean heart rate; mean SpO_2; and time spent at less than 90% SpO_2.

Hypoglycemia was defined as any blood glucose concentration of less than 2.6 mmol/L. The date of the first full enteral feed was the first 24 hours the infant received full enteral nutrition without intravenous nutrition. The date of first full oral feeds was the first 24 hours of fully tolerated feeds (breast milk, formula, or combination) without a nasogastric tube.

Statistical Analysis

In a randomized, controlled trial of caffeine to decrease the incidence of intermittent hypoxemic events, very preterm infants at 35 weeks PMA not treated with caffeine had a mean ± SD of 8.4 ± 8.4 intermittent hypoxemic events per hour.[11] At term, these infants had a mean of 3.0 ± 3.3 events per hour. Therefore, we determined that 82 infants (41 in each group) would allow us to detect a similar difference between late preterm infants and term infants at birth, with 80% power and 0.05 alpha.

Data were analyzed using JMP (version 12.0.0, SAS Institute Inc, Cary, North Carolina). Parametric data were analyzed with the Student *t* test. Nonparametric data were log transformed to approximate a standard distribution if possible and then back transformed. Nonparametric data that could not be log transformed were analyzed with Mann-Whitney *U* test. Categorical data were analyzed with the χ^2 test. Imputations were not made for missing data. Data are presented as mean ± standard error of the mean, median (IQR), or number (%).

Repeated measures across the 2 groups were analyzed by general linear mixed models. Nonparametric data were transformed into binomial data (≥25th or <25th percentile) and analyzed by generalized linear mixed model with logit link and binary distribution. The time period of measurement was included as a repeat measure, with late preterm birth and mode of delivery as explanatory variables. Initially, the interaction of being late preterm with time was included in the mixed model. If the interaction was significant, this was given as the analysis outcome. If the interaction was not significant, it was removed from the model and the effect of preterm birth and PMA are presented. Participant identification was included as a random effect. Least squares means and their 95% CI or ORs and their 95% CIs were produced as a measure of the effect size.

Weekly repeated measures in late preterm infants were analyzed by a standard least squares model with postnatal age at the time of the pulse oximetry as a repeat measure and gestational age at birth as an explanatory variable. The interaction of postnatal age and gestational age at birth was included in the model. Participant identification was included as a random effect. Birth weight, crown-heel length, and head circumference z-scores for gestational age and sex were calculated in reference to normative data.[17] Statistical significance was defined as $P < .05$.

Results

Between March and September 2016, a total of 85 infants were enrolled in the study (**Figure 1**). Parents of 6 infants (all late preterm) withdrew from the study after the first overnight recording. Maternal body mass index was higher in mothers of term infants, and more of these mothers were obese compared with the mothers of late preterm infants (**Table I**). Late

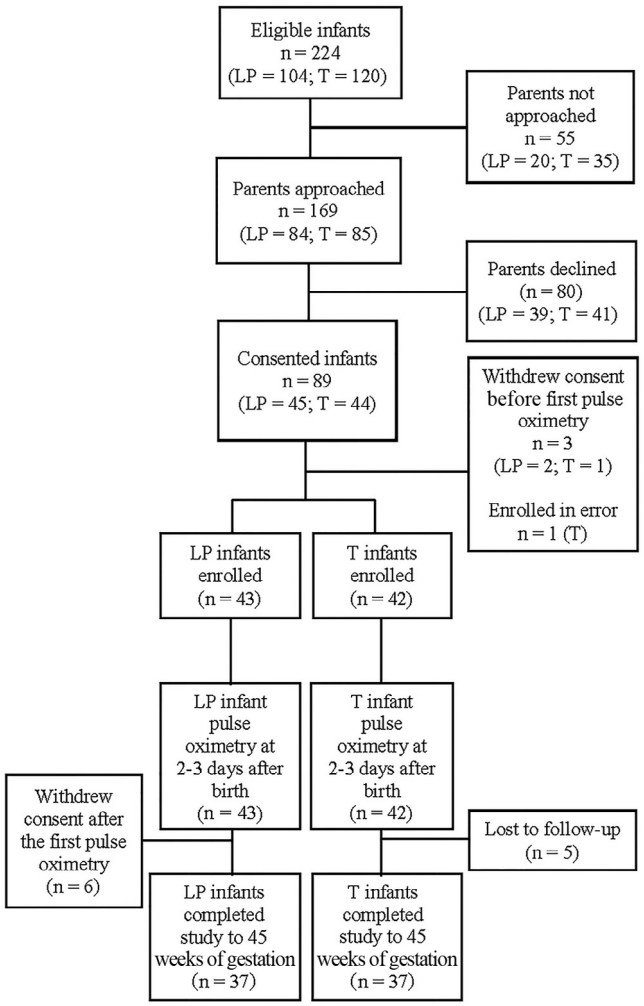

Figure 1. STROBE diagram of recruitment. *LP*, late preterm; *T*, term. One early term infant was enrolled in error (gestational age of $38^{1/7}$ weeks).

preterm infants had similar birthweight, crown-heel length, and head circumference z-scores to term infants (**Table I**). Late preterm infants were more likely to have hypoglycemia, jaundice requiring phototherapy, receive intravenous nutrition and nasogastric feeds, take longer to reach full sucking feeds, and to be discharged from hospital than term infants (**Table II**; available at www.jpeds.com).

A total of 275 overnight pulse oximetry recordings were included in the analysis (late preterm, n = 210 vs term, n = 65). There were no differences in the total valid sampling time between overnight pulse oximetry recordings for late preterm and term infants (mean ± standard error of the mean, 10.5 ± 0.2 hours vs 10.1 hours ± 0.3; $P = .91$). The majority of recordings were carried out at the participant's home (late preterm, 155/210 [74%]; term, 34/65 [52%]). Most overnight pulse oximetry recordings were done on infants sleeping supine (late preterm 207/210 [99%] vs term 63/65 [97%], $P = .35$). A total of 70 overnight pulse oximetry recordings (late preterm, n = 36; term, n = 34) were included in the analysis of intermittent hypoxemic events between late preterm and term infants at days 2-3 after birth.

Late preterm infants had a higher frequency of D10 events compared with term infants (mean ± standard error of the mean; 2.5 ± 1.2 events per hour vs 1.0 ± 1.2 events per hour; $P < .0001$) on overnight pulse oximetry at days 2-3 after birth. In a mixed model analysis, there was a significant decrease in D10 and D3 events between term equivalent age and 45 weeks PMA in late preterm infants, but not in term infants (**Table III**). There was no difference in the duration of D10 events between late preterm and term infants on overnight oximetry at days 2-3 after birth (late preterm, least squares means 21.9 [95% CI, 16.9-26.9] vs term, least squares means, 25.6 [95% CI, 20.8-30.5]; $P = .68$) or the mean SpO_2 at nadir for the D10 events (mean ± SD: late preterm, 84.6 ± 2.5% v 84.8 ± 3.5%; $P = .78$). At 40 weeks TEA, late preterm infants had a higher mean heart rate compared with term infants and this difference had resolved by 45 weeks PMA. From term equivalent age to 45 weeks PMA, the mean heart rate decreased in late preterm infants but increased in term infants (**Table III**).

Late preterm infants had an increase in the frequency of D10 and D3 events in the first 2 weeks after birth, followed by a decrease in the following 2 weeks (**Figure 2**). Gestational age at birth did not affect the change in frequency of intermittent hypoxemia in late preterm infants, with infants born at 34 weeks gestational age having a similar change with postnatal age to those born at 36 weeks of gestational (**Figure 2**).

Overall, there was an increase in SpO_2 with increasing PMA (term equivalent vs 45 weeks PMA, median, 98.6% [IQR, 97.1%-99.2%] vs median, 99.1% [IQR, 98.0%–99.5%]; $P = .002$). There was no difference between the late preterm and term groups in mean SpO_2 at days 2-3 after birth (median, 97.8% [IQR, 97.1%-98.3%] vs median, 97.9% [IQR, 96.7%-98.9%]; $P = .45$). Late preterm infants had a higher mean SpO_2 than term infants at term equivalent age (median, 98.8% [IQR, 98.4%-99.4%] vs median, 97.9% [IQR, 96.7%-98.9%]; $P < .005$). From term equivalent age to 45 weeks PMA late preterm infants had a lower proportion of mean SpO_2 of less than 97.5% (late preterm vs term, OR, 0.32 [95% CI, 0.11-0.94]; $P < .05$) and a lower proportion of time of less than 90% SpO_2 (late preterm vs term, OR, 0.32 [95% CI, 0.15-0.69]; $P < .005$).

Discussion

Late preterm birth has been associated with a higher incidence of neurodevelopmental impairment compared with birth at term, with no perinatal interventions that have been shown to improve long-term outcomes. Although there have been previous studies of intermittent hypoxemia that have included late preterm infants,[18,19] this study shows that late preterm infants have more intermittent hypoxemic events at birth and term equivalent age compared with term infants, and that these differences had resolved by 45 weeks PMA. The frequency of intermittent hypoxemic events in late preterm infants increased during the first 2 weeks after birth, and then decreased until 45 weeks PMA. A similar trend over time has been shown in

Table I. Maternal and neonatal baseline characteristics

	Late preterm (n = 43)	Term (n = 42)	*P* value
Maternal characteristics			
Age (y)	32.1 ± 0.8	30.3 ± 0.9	.14
Ethnicity			<.05
Māori	1 (2)	6 (14)	
Pacific Islander	7 (16)	5 (12)	
New Zealand European	13 (31)	20 (48)	
Asian	21 (49)	10 (24)	
South American	1 (2)	1 (2)	
Maternal diabetes			<.05
None	31 (82)	40 (95)	
Gestational	6 (16)	1 (2)	
Type I	0 (0)	0 (0)	
Type II	1 (3)	0 (0)	
Body mass index (kg/m^2)	22.8 (21.2-26.7)	26.2 (22.6-30.4)	<.05
Underweight	1 (3)	0 (0)	.13
Overweight	11 (30)	14 (33)	
Obese	3 (8)	12 (29)	
Smoking status			
Mother smoked	5 (13)	7 (17)	.59
Father smoked	5 (13)	10 (24)	.16
Mother smoked during pregnancy	0 (0)	4 (10)	<.05
Socioeconomic status (NZDep '13 decile)	6 (2-9)	6 (4-9)	.49
Multiple gestation	7 (16)	0 (0)	<.005
Presenting antenatal problem(s)			
Preterm prelabor rupture of membranes	9 (21)	0 (0)	<.0005
Preterm labor	14 (33)	0 (0)	<.0001
Hypertension in pregnancy	7 (17)	2 (5)	.08
Antepartum hemorrhage	8 (19)	1 (2)	<.01
Suspected intrauterine growth restriction	7 (17)	0 (0)	<.005
Antenatal glucocorticoids	12 (32)	0 (0)	<.0001
Mode of delivery			.93
Caesarean delivery	18 (42)	18 (43)	
Duration of stay (d)	6.6 (4.3-7.7)	3.2 (2.2-4.5)	<.0001
Neonatal characteristics			
Sex (female)	15 (35)	20 (48)	.23
Gestational age at birth (wk; late preterm/term)	35.4 ± 0.1	40.1 ± 0.1	<.0001
34/39	10 ± 23	17 ± 40	—
35/40	17 ± 40	17 ± 40	—
36/41	16 ± 37	8 ± 20	—
Birthweight			
Grams	2571 ± 66	3685 ± 78	<.0001
z-Score	0.0 ± 0.2	0.5 ± 0.2	.06
Birth crown-heel length			
Centimeters	47.4 ± 0.5	51.9 ± 0.4	<.0001
z-Score	0.1 ± 0.2	0.3 ± 0.2	.48
Head circumference			
Centimeters	32.8 ± 0.2	35.3 ± 0.3	<.0001
z-Score	0.1 ± 0.2	0.3 ± 0.2	.51
Small for gestational age	4 (9)	2 (5)	.41
Apgar score ≤7 (at 5 min)	6 (14)	0 (0)	<.01

For maternal body size, underweight was a body mass index of <18.5 kg/m^2, overweight a body mass index of 25.0-29.9 kg/m^2, and obese a body mass index of ≥30.0 kg/m^2. Socioeconomic status deciles (NZDep2013) were based on nine variables from the 2013 New Zealand census. Small for gestational age was a birthweight below the 10th percentile. Data are mean ± standard error of the mean, median (IQR), or n (%).

extremely preterm infants.[10] Intermittent hypoxemic events have been associated with neurodevelopmental impairment in extremely preterm infants.[14] However, intermittent hypoxemia was more frequent in extremely preterm infants compared with the frequency of intermittent hypoxemia in late preterm infants seen in this study.[14] It is unknown how frequent or severe intermittent hypoxemia needs to be before it is associated with poorer neurodevelopmental outcomes. However, it is possible that the treatment of late preterm infants to reduce the frequency of intermittent hypoxemia may improve their long-term outcome.

We found that the frequency of D10 and D3 events increased from birth to 2 weeks postnatal age, after which there was a decrease in frequency until 9-11 weeks postnatal age, and the same trend was seen in late preterm infants born at different gestational ages. These findings, along with other studies that show the frequency of intermittent hypoxemia decreases with increasing postnatal age,[11] suggest that the incidence of intermittent hypoxemic events after preterm birth is likely to be a function of postnatal maturation.[20]

Sleep state has a significant impact on respiratory function in infants and may also contribute to the frequency of

Table III. Intermittent hypoxemia events in late preterm and term infants at 40 and 45 weeks PMA

	40 weeks PMA		45 weeks PMA		
	Late preterm (n = 31)	Term (n = 34)	Late preterm (n = 32)	Term (n = 31)	*P* value
Frequency of intermittent hypoxemia events (events/h)					
D10	3.7 (2.7-5.1)	1.7 (1.2-2.3)	1.5 (1.1-2.1)	1.9 (1.4-2.6)	<.0005
D3	32.8 (25.9-41.4)	29.3 (23.5-36.6)	16.2 (12.6-20.7)	23.2 (18.1-29.7)	<.05
Mean HR (beats/min)	151.8 (148.4-155.2)	119.2 (115.9-122.4)	136.1 (133.1-139.1)	138.6 (135.7-141.6)	<.0001

HR, hazard ratio.
Intermittent hypoxemic events defined by desaturation of ≥10% (D10) or ≥3% (D3) below the preceding baseline SpO_2 with a minimum duration of 2 seconds. There was no effect of mode of delivery on any variable. The *P* value is for the interaction of being late preterm with time. Data are presented as least squares means (95% CI).

intermittent hypoxemia observed in late preterm infants. Active sleep is the predominant sleep state during early postnatal life, especially in preterm infants.[21] As infants grow older, the proportion of active sleep decreases and the proportion of quiet sleep increases.[22] Term infants have more desaturations in active sleep compared with quiet sleep in the first 6 months after birth.[23] This condition may be due to hypoventilation, low pulmonary oxygen stores, and increased oxygen consumption,[24,25] which are more likely to occur in active sleep[26-28] and may be a likely trigger for intermittent hypoxemic events.[29] Therefore, if late preterm infants spend more time in active sleep than term infants, this finding may explain the higher frequency of intermittent hypoxemic events in the late preterm infants. Also, late preterm infants may follow a similar trend in sleep architecture with age as term infants, which may explain the decrease in frequency of intermittent hypoxemic events with postnatal age. Further research is needed to determine sleep state changes over time in late preterm infants using polysomnography.

Currently, there is no consensus definition of intermittent hypoxemia for SpO_2 thresholds or the duration of the event. Previous studies of intermittent hypoxemia on neurodevelopmental outcomes have used various definitions of the duration of the event ranging from no minimum duration[15,30] to 60 seconds or greater.[14] In this study, we chose to use a short oximeter averaging time (2 seconds), with a minimum 2-second duration event time, to include brief episodes of intermittent hypoxemia in the analysis, because adverse effects of hypoxemia have been observed with even mild oxygen desaturation in children with obstructive sleep apnea.[31]

Although there was no difference in mean SpO_2 between the groups at days 2-3 after birth, late preterm infants had a higher mean SpO_2 at term equivalent age than term infants. This finding was probably due to the increase in mean SpO_2 with postnatal age; because late preterm infants had a postnatal age of 4-6 weeks at term equivalent age, they had a longer exposure to the postnatal environment, which gave them more time to increase their SpO_2 compared with term infants who were only 2-3 days old at the time of their term equivalent age recording. A previous study reported that infants born at 35-36 weeks of gestational spent less time with a SpO_2 of greater than 90% than infants born at 37-41 weeks of gestational over a 6-hour period in the first 48 hours after birth,[32] but the study potentially included preductal measurements (sensor on the hand or foot) in the late preterm cohort and not the term cohort (sensor on the foot).

Most of the late preterm infants were admitted to NICU and had a higher incidence of hypoglycemia, respiratory distress, and jaundice requiring phototherapy than term infants. These findings are consistent with retrospective database studies[3,33] and 1 prospective observational study.[34] Hypoglycemia,[9,35] respiratory disease,[36] and jaundice[37] have been associated with poor neurodevelopmental outcomes. Therefore, more than 1 management solution may be required to improve neurodevelopmental outcome in late preterm infants.[38]

A limitation of our study is that the term infants may not be fully representative of the population. Preterm birth is more likely in mothers of Māori ethnicity,[39] mothers with a higher body mass index,[40] and mothers who smoked during pregnancy.[41] However, in our study the mothers of the term infants were more likely to be obese, identify as Māori, and smoke than mothers of late preterm infants. At Auckland City Hospital, it is standard care for mothers and infants who are well after birth (vaginal and caesarean delivery) to be transferred to Birthcare (a primary care facility) for postnatal care, and mothers and term infants with perinatal complications such as postpartum hemorrhage or neonatal hypoglycemia, remain at Auckland City Hospital. Recruitment to this study, for both late preterm and term infants, was from Auckland City Hospital. It is possible that the term infants or their mothers recruited at Auckland City Hospital were more likely to have had a perinatal complication than the general population of term infants. If this was the case, these infants may not be representative of healthy term infants, and this study may have underestimated, rather than overestimated, the difference in intermittent hypoxemia between late preterm and term infants.

A second limitation was that we did not perform weekly oximetry recordings in the term infants. An observational study of healthy term infants, with recordings in the first week repeated once at 2-4 weeks postnatal age showed that intermittent hypoxemia with an SpO_2 of less than 80% was more common in the second week of life.[42] Therefore, term infants may have a similar pattern of increasing intermittent hypoxemia in the weeks after birth, similar to those we found in late preterm infants. Further research is needed to determine the longitudinal changes in SpO_2 in full-term infants.

Caffeine has been shown to decrease the frequency of intermittent hypoxemic events in preterm infants after routine

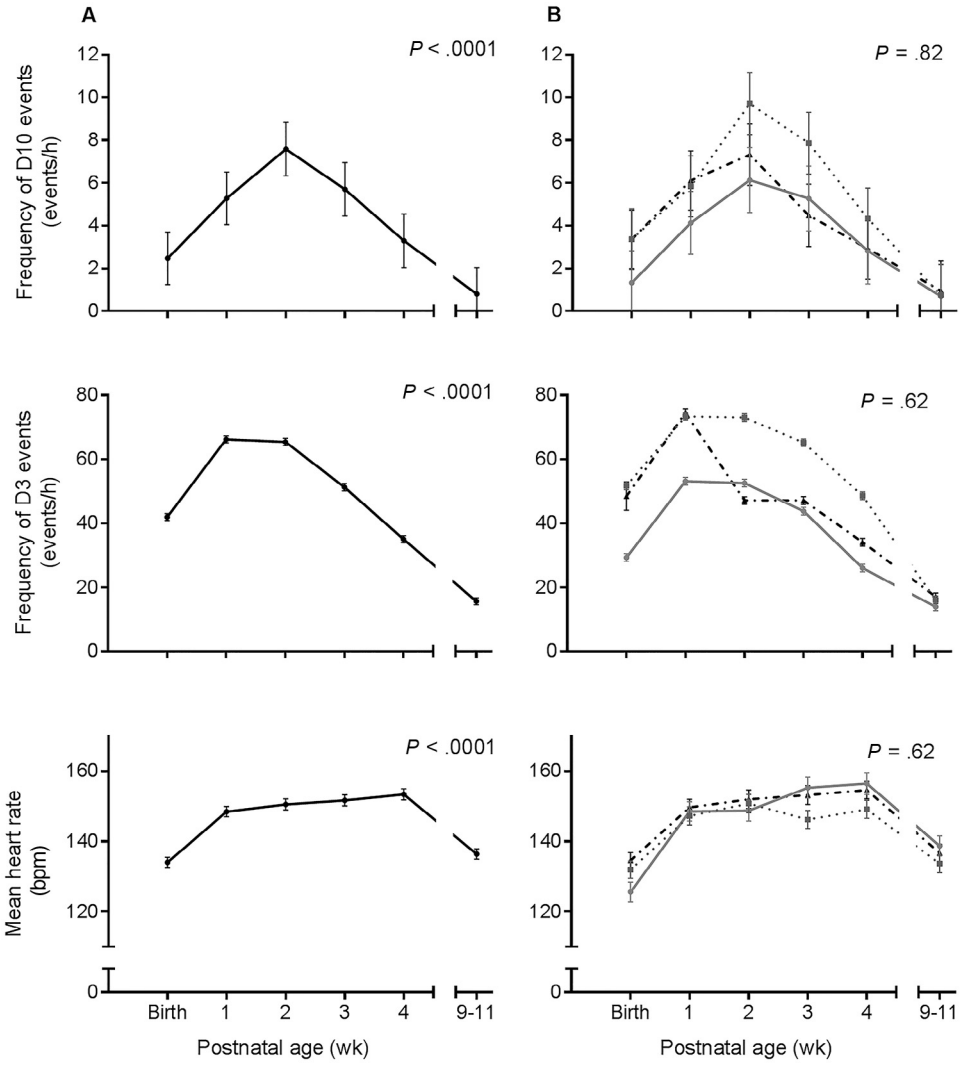

Figure 2. Frequency of intermittent hypoxemic events in late preterm infants in the first 9-11 weeks after birth. Data are combined on the left **A,** and presented by gestational age at birth on the right **B,** 34 weeks, *solid line*; 35 weeks, *dashed line, triangle*; 36 weeks, *dotted line*. Intermittent hypoxemic events defined by desaturation of ≥10% (D10, top) or ≥3% (D3, middle) below the preceding baseline SpO_2 with a minimum duration of 2 seconds. Data are least squares means ± standard error of the mean. *P* values; **A,** Effect of postnatal age. **B,** Effect of the interaction of postnatal age with gestational age at birth. Number of oximetry reports at each postnatal age: birth = 36; 1 week = 35; 2 weeks = 28; 3 weeks = 27; 4 weeks = 29; and 9-11 weeks postnatal age = 32 weeks.

caffeine therapy[11] and to improve neurodevelopmental outcomes of very and extremely preterm infants.[36,43] Further research is needed to determine if caffeine therapy in late preterm infant may reduce the frequency of intermittent hypoxemia, and to improve their neurodevelopmental outcomes.

Late preterm infants had more intermittent hypoxemia than term infants soon after birth. Future research is needed to determine the impact of intermittent hypoxemia on long-term neurodevelopmental outcomes in late preterm babies. ■

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Reprint requests: Jane Marie Alsweiler, PhD, Department of Pediatrics: Child and Youth Health, University of Auckland, PO Box 92019, Auckland Mail Centre, Auckland 1142, New Zealand. E-mail: j.alsweiler@auckland.ac.nz

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Table II. Neonatal morbidity in late preterm and term infants

	Late preterm (n = 43)	Term (n = 42)	*P* value
Duration of hospital stay (d)	8.5 (6.6-13.0)	2.7 (2.1-3.8)	<.0001
Admission to NICU	22 (58)	0 (0)	—
Reason(s) for admission to NICU	n = 22		
Preterm	11 (29)	—	—
Respiratory distress	6 (16)	—	—
Hypoglycemia	2 (5)	—	—
Intrauterine growth restriction	2 (5)	—	—
Tachycardia	1 (3)	—	—
Length of stay in NICU (d)	9.9 (2.9-14.2)	—	—
Hypoglycemia	17 (40)	2 (5)	<.0001
Treatment for hypoglycemia			
Oral dextrose gel	9 (21)	2 (5)	<.05
Formula	4 (9)	0 (0)	<.05
Intravenous dextrose	6 (14)	0 (0)	<.0001
Intravenous nutrition	16 (43)	0 (0)	<.0001
Time to full enteral feeds (d)	1.0 (1.0-4.0)	1.0 (1.0-1.0)	<.0001
Nasogastric tube inserted	34 (91)	0 (0)	<.0001
Time to full sucking feeds (d)	7.5 (5.0-11.8)	1.0 (1.0-1.0)	<.0001
Formula before discharge	31 (82)	13 (31)	<.0001
Indication for formula			
Hypoglycemia	2 (5)	1 (2)	.57
Feeding problems	29 (76)	6 (14)	<.0001
Mother's choice	2 (5)	5 (12)	.22
Temperature instability	32 (86)	18 (42)	<.0001
Hyperthermia	10 (27)	5 (12)	.09
Hypothermia	27 (73)	5 (12)	<.0001
Jaundice requiring phototherapy	11 (30)	0 (0)	<.0001
Duration of phototherapy (d)	1.7 (1.0-2.1)	—	
Respiratory distress			
Transient tachypnea of the newborn	5 (14)	0 (0)	<.01
Respiratory distress syndrome	3 (8)	0 (0)	<.05
Respiratory support	8 (22)	0 (0)	<.0005

Hypoglycemia was any blood glucose concentration of <2.6 mmol/L; temperature instability was any temperature of <36.6°C or >37.2°C after 4 hours of age; hypothermia was any temperature of <36.6°C after 4 hours of age; and hyperthermia was any temperature of >37.5°C after 4 hours of age. The date of the first full enteral feed was the first 24 hours the infant received full enteral nutrition without intravenous nutrition. The date of first full sucking feeds was the first 24 hours of fully tolerated feeds (breast milk, formula, or combination) without a nasogastric tube. Data are median (IQR) or n (%).