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Inhaled Nitric Oxide Use in Preterm Infants in California Neonatal Intensive Care Units

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Abstract

Objective—To describe inhaled nitric oxide (iNO) exposure in preterm infants and variation in Neonatal Intensive Care Unit (NICU) use.

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Conflict of Interest

The University of California Davis has received compensation from Ikaria, Inc for consulting work performed by Dr. Steinhorn. Dr. Steinhorn has also participated in clinical trials funded by Actelion and United Therapeutics. Dr. Van Meurs has attended scientific advisory boards, the costs of travel were paid by Ikaria, Inc. Dr. Van Meurs has also participated in inhaled nitric oxide clinical trials supported and funded by Ikaria, Inc. The remaining authors have indicated no financial disclosures.

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Study Design—This was a retrospective cohort study of infants, 22–33+6/7 weeks gestational age (GA), during 2005–2013. Analyses were stratified by GA and included population characteristics, iNO use over time and hospital variation.

Result—Of 65 824 infants, 1 718 (2.61%) received iNO. Infants, 22–24+6/7 weeks GA, had the highest incidence of iNO exposure (6.54%). Community NICUs (n = 77, median hospital use rate 0.7%) used less iNO than regional NICUs (n = 23, median hospital use rate 5.8%). In 22–24+6/7 week GA infants the median rate in regional centers was 10.6% (hospital IQR 3.8%–22.6%).

Conclusion—iNO exposure varied with GA and hospital level, with the most use in extremely premature infants and regional centers. Variation reflects a lack of consensus regarding the appropriate use of iNO for preterm infants.

Introduction

Evidence from randomized controlled trials supports the use of inhaled nitric oxide (iNO) for respiratory failure in term infants.[1] However, the efficacy of iNO for the preterm population has not been established. A variety of indications for iNO have been studied in preterm infants including selective use in the first three days of life for infants with poor oxygenation, routine use in intubated preterm infants, and later use in infants with an elevated risk of bronchopulmonary dysplasia.[2] Several publications over the last five years, including the 2011 National Institutes of Health (NIH) Consensus Statement and a report from the 2014 American Academy of Pediatrics (AAP) Committee on Fetus and Newborn, concluded that the available data do not support routine use of iNO in preterm infants.[2, 3, 4, 5, 6]

iNO was first approved for use in term and late preterm (or as referred to at that time, “near-term”) neonates in 1999 and the first AAP statement regarding iNO was published in 2000.[7] The use of iNO in preterm infants has increased since that time. Clark et al described iNO use in neonates between 2000 and 2008 across the Pediatrix Neonatal Intensive Care Unit (NICU) network and reported a six-fold increase in iNO use in infants less than 34 weeks, with an eight-fold increase in infants from 23 to 26 weeks gestational age (GA).[8] Another study examined the variation in iNO use across children’s hospitals, and found that 7.2% of infants less than 34 weeks were exposed to iNO with marked variation in use, from 0.5% to 26.2%, across hospitals.[9] A report from the National Institute of Child Health and Development (NICHD) Neonatal Research Network (NRN) showed lower rates of iNO use in preterm babies, but similar variability (0.4% to 21.9%) among academic centers and a significant decrease in use after the 2010 Consensus Statement.[10] However, a recent publication from the Pediatrix NICU network reported increased use from 5.03 to 6.19%, in infants born at 23 to 29 weeks from 2009 to 2013.[11]

Despite the current recommendations, preterm infants continue to be exposed to iNO. However, our understanding of which infants are more likely to be exposed to iNO and in which hospital settings iNO is utilized is not well described. This information is essential for developing clinical guidelines, planning further multi-center clinical trials and assessing the feasibility of conducting such trials. Our objective was to perform a population-based study

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stratified by gestational age to examine the patterns of iNO use in preterm infants 22 to 33+6/7 weeks GA during the time period 2005 to 2013.

Methods

Study Population

The California Perinatal Quality Care Collaborative (CPQCC) prospectively collects data from greater than 90% of NICUs in California. At the time of this study, the CPQCC included 132 NICUs. During the study period, CPQCC eligibility criteria for data collection included: infants with birth weight between 401 and 1500 grams or gestational age between 22+0/7 and 29+6/7 weeks. For infants not meeting those criteria (i.e. those with birth weight > 1500 grams), data were collected for neonates with any of the following: non-invasive ventilation for more than four hours, intubation and ventilation for more than four hours, hyperbilirubinemia, early bacterial sepsis, surgery, acute transfer in or out of a NICU, and death. Infants with gestational age 30 weeks and greater would be included in the dataset if birth weight was < 1500 grams, or if they met other criteria such as ventilation, transfer, or death.

The California Children's Services (CCS) classifies NICUs into three levels which generally correspond to the AAP Level designations as follows: regional (tertiary) NICUs (similar to AAP Level IV) provide mechanical ventilation and a full range of pediatric medical and surgical subspecialty services for patients, and outreach services to surrounding hospitals; community NICUs (similar to AAP Level III) provide unrestricted care and ventilation to infants of all gestational ages and may have some availability of medical and surgical subspecialty services; intermediate NICUs (similar to AAP Level II) provide care to a variably restricted population, ventilate only up to a specified number of hours, and refer all complicated cases to a higher level of care.[12] There are some variations at the individual NICU level, as some community NICUs may not offer surgical services, and not all Intermediate NICUs are equivalent to AAP Level II.[13] However, the CCS designations have an advantage to AAP designations in that they are not self-reported, but regulated and approved by the state.

The study cohort included infants born between 22+0/7 to 33+6/7 weeks GA, during the period January 2005 to December 2013. Infants were assigned "year" according to the date of birth. Prior to applying exclusion criteria there were 69 428 infants in the cohort. Infants included in the cohort were born in CPQCC associated NICUs. To limit the possibility of errors in estimation of gestational age, infants who were outside the 1st or 99th percentile for birth weight for their gestation age were excluded.[14] There were 605 infants less than the 1st percentile representing 0.83% of the cohort and 118 infants greater than the 99th percentile representing 0.16% of the cohort. Infants with severe congenital anomalies or anomalies of unknown severity (n=405) were also excluded. Additionally, infants who died in the delivery room (n=2 440) and those who never received mechanical ventilation and died in the NICU (n=36) were excluded. The final cohort included 65 824 infants.

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Data Analysis

Inhaled NO use was defined as any documented iNO use at a CPQCC NICU. Information including age at initiation of use, iNO dose and duration of use were not available. Student's t test or chi-squared test was used, as appropriate, to compare maternal and neonatal characteristics between those who were or were not exposed to iNO. Variables examined included birth weight, gestational age, small for gestational age (those between the 1st and 10th percentile for weight), gender, multiple gestation, antenatal steroid exposure, mode of delivery (cesarean section or vaginal), Apgar scores, need for delivery room cardiopulmonary resuscitation (DR-CPR, defined as chest compressions and/or epinephrine administration), race, mortality in the first 12 hours of life and mortality prior to hospital discharge. Data collection was performed by trained data abstractors based on definitions from the CPQCC and Vermont Oxford Network.[15, 16]

Analysis was completed using SAS version 9.4 (SAS, Cary, NC). The cohort was stratified into gestational age subgroups. The subgroups were 22 to 24+6/7, 25 to 27+6/7, 28 to 30+6/7, and 31 to 33+6/7 weeks GA. Multivariable logistic regression was used to examine factors associated with iNO exposure. Variables included in the model were birth weight, gestational age, gender, singleton versus twin gestation, antenatal steroid exposure, receipt of DR-CPR, and care in a regional center. To determine rates of use over time, a frequency analysis was completed, stratified by GA. In order to examine variation of iNO use by hospital, iNO rates were calculated for the hospital level of care. Hospital level was assigned based on the most recent 2013 CCS designation. Non-CCS and intermediate level hospitals were excluded from the hospital variation analysis as their rates of eligible patients were low. Institutional Board Review approval was obtained through Stanford University.

Results

During the study period there were 65 824 infants who met inclusion criteria. Across all subgroups, 22+0/7 to 33+6/7 weeks, 64 106 (97.39%) infants were not exposed to iNO and 1 718 (2.61%) were exposed to iNO. Incidence of iNO exposure was highest in the youngest GA cohort, with 401 infants (6.54%) receiving iNO at some point during their hospitalization. Exposure decreased with increasing gestational age: 4.64% for 25 to 27+6/7 weeks GA, 1.71% for 28 to 30+6/7 weeks GA, and 1.11% for 31 to 33+6/7 weeks GA. Characteristics of infants receiving iNO varied by GA (Table 1). Notably, in the 22 to 24+6/7 week cohort infants, those who received iNO were more likely to have higher birth weight and higher antenatal steroid exposure rates than those who did not receive iNO. However, the rates of delivery room resuscitation and mortality prior to discharge were not significantly different between those who did and did not receive iNO.

Findings differed somewhat for the 25 to 27+6/7 and 28 to 30+6/7 week GA cohorts. Infants who were exposed to iNO were more likely to have higher antenatal steroid exposure rates but lower birth weight, and be small for gestational age. Those infants who were exposed to iNO had significantly higher rates of delivery room resuscitation and mortality in both the first 12 hours of life and prior to hospital discharge. In the 31 to 33+6/7 week GA group, iNO exposure was more common in larger, older infants; however trends in resuscitation and

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mortality reflect those of the slightly younger infants, with increased DR-CPR and increased mortality.

Multivariable logistic regression was used to identify significant factors associated with iNO exposure for each GA subgroup. Receipt of DR-CPR was significantly associated with iNO in all subgroups except the 22–24+6/7 week cohort. Notably, care in a regional center was the most strongly associated characteristic across all cohorts (Table 2).

Analysis of rates of use over time across all centers revealed variable use over time by GA, with the most premature infants consistently the most exposed. In all cohorts there was increasing use from 2005 to 2007 and transient decreases after 2010. However, since 2012 increased use was observed in all groups except the 31 to 33+6 cohort (Figure 1).

There were 23 regional level NICUs and 77 community level NICUs included in the hospital variation analysis. Rates of iNO exposure varied significantly by hospital level of care, with infants cared for in regional NICUs receiving significantly more iNO across all gestational age cohorts. All regional NICUs used iNO on at least some of their preterm patients. The median iNO exposure rate for preterm infants at regional NICUs was 5.8% with an interquartile range (IQR) of 2.4% to 7.0% (Figure 2). The median iNO exposure rate for community NICUs across all cohorts was 0.7%, with 19 (25%) of community NICUs never using iNO during the study period. However, there remained variation in community NICUs across GA groups with the most exposure in the 22 to 24+6/7 cohort, IQR 0% to 4.3%, compared to the 31 to 33+6/7 cohort, IQR 0% to 0.9% (Figure 2).

Discussion

Premature infants, and particularly extremely premature infants, are exposed to iNO in California NICUs. While there was a transient decrease in iNO use after the 2010 NIH Consensus Statement, use subsequently increased after 2012 in nearly all GA cohorts. The reason for this is unclear, and subsequent trends will be interesting to explore further. Although iNO is available in both community and regional level NICUs, we observed more frequent use in regional centers across all GA cohorts, possibly because regional centers care for the sickest patients and often receive referrals from community NICUs. Across nearly all GA groups, those that received iNO were more likely to receive antenatal steroids, perhaps indicating that a decision to pursue intensive care prior to the delivery had been made. This was also consistent with the finding that those receiving DR-CPR were also more likely to receive iNO. The receipt of DR-CPR may also be a marker of severity of illness.

Others have also reported that clinicians tend to use iNO in the most premature infants, thus they are the most likely to be exposed to iNO.[8] A variety of hypotheses have been suggested as to why the youngest infants are likely to have clinical presentations that may signal a potential benefit from iNO. Part of the answer may lie in the developmental biology of the fetal pulmonary vasculature. Fetal pulmonary vascular resistance is physiologically high during the canalicular stage, due to an overall paucity of the pulmonary vascular network and reduced cross sectional area of the immature pulmonary vascular bed. In fetal lambs, pulmonary blood flow does not increase in response to hyperoxia at 94–101 days gestation

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(68% gestation, equivalent to 27 weeks).[17] In human pregnancies, maternal hyper-oxygenation with 60% oxygen by face mask at 20–26 weeks gestation did not produce fetal pulmonary vasodilation.[18] These findings suggest a lack of sensitivity to oxygen and high pulmonary vascular resistance in early gestation, and could contribute to the higher use of iNO in extremely low birth weight infants in an attempt to achieve pulmonary vasodilation. This population is at higher risk for life-threatening respiratory failure.[2, 19] Some studies have shown short-term improvement in oxygenation; however at least one randomized controlled trial found that the most preterm infants are less likely to respond to iNO and may have higher rates of intracranial hemorrhage and death than infants treated without iNO. [2, 20, 21]

Although the mortality at 12 hours was lower in the iNO exposed 22 to 24+6/7 week GA infants, there was no difference in mortality prior to hospital discharge. It should be noted that the results at 12 hours may reflect infants dying very soon after delivery and not having an opportunity to receive iNO due to their acute deterioration, or infants for whom the care team and parents had come to a decision to transition to palliative care. Ultimately, there was no survival advantage observed for those who received iNO in this cohort. In the three older GA cohorts, iNO was associated with significantly higher rates of mortality, both in the first 12 hours of life and prior to discharge. Given that infants in these older cohorts who received iNO all had significantly lower Apgar scores and required significantly more delivery room resuscitation, specifically chest compressions and/or epinephrine, we speculate that the difference in mortality may reflect the severity of illness at time of birth and beyond, and not necessarily an effect of iNO exposure. Some iNO use may have occurred later in the hospital course for its potential effect of bronchopulmonary dysplasia and associated pulmonary hypertension, which is suggested by Ellsworth who reported 16–21% of use in infants 22–29 weeks GA was after 28 days of life.[11] We did not have data on the timing of iNO exposure.

There were changes in iNO use between 2005 and 2013, which could have been in part secondary to the increasing availability of iNO over time in both regional and community level NICUs. A recent report found a decrease in iNO use in 22 to 29 week GA infants in the NICHD NRN after 2010,[10] a change that was also seen across all GA cohorts in CPQCC NICUs. However, this was a transient phenomenon in the CPQCC NICUs, as evidenced by an increase in iNO use in three out of the four gestational age cohorts after 2012. This pattern of use closely parallels the recent study by Ellsworth in which a transient decrease was seen in 2011 followed by a significant increase in use in 2012 and 2013.[11] Data are not yet available for 2014 to determine if the most recent AAP Committee of Fetus and Newborn publication had an effect on iNO use in premature infants.

As captured by the studies by Truog and Stenger, there is marked variability in iNO use between centers, including large referral NICUs included in the NICHD NRN.[9, 10] Of the infants included in the analysis of hospital variation, 36 503 (61.5%) were cared for in community NICUs and the remaining 22 839 (38.5%) in regional NICUs. Despite the greater volume of preterm infants cared for in community NICUs, there was significantly less use of iNO than in regional centers. While this difference may be related to clinical acuity, it suggests that practice variation may be greatest at the referral centers, which is consistent with previous reports of significant hospital variation. In addition to variation in

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who gets treated with iNO, there is also likely to be variation in the indications for use, including the timing of use, for prevention, rescue, or for later use in bronchopulmonary dysplasia. Our study was limited by lack of data on timing of iNO initiation, duration, or indication for use. In a recent study, Kinsella found that iNO delivered noninvasively to premature infants was a safe treatment but did not decrease the incidence or severity of BPD, reduce the need for mechanical ventilation or alter the clinical course.[22] Although the impact of iNO to reduce BPD in some specific groups of preterm infants has been studied and published, the clinical benefit is not clear.[6]

Specific reports of iNO use at a large geographically-defined population level have been lacking. The extremely preterm cohort is one that is well captured by the CPQCC, and our data are an accurate representation of practices throughout a large state that cares for more than 12% of the births in the United States. While the strengths of this study include the fact that it is a population-based dataset, after 30 weeks GA the CPQCC did not always collect data on infants unless there was an indication for critical care, as captured by specified clinical criteria. Thus, while the total number of infants beyond 30 weeks GA who received iNO is accurate, the actual percentage exposed is potentially less than is reported in this study as the denominator would be larger if it captured all infants of this GA.

This study provides important information about iNO use and practice patterns across a large, diverse population cared for in a wide variety and large number of NICUs in the state of California. While a 65% reduction was noted over a similar time period in the academic NICUs of the NICHD NRN, similar changes were not observed in California NICUs. Currently, global “off label” use of iNO for any duration of “treatment” of preterm infants less than 34 weeks GA is not supported by published literature, nor by recent reviews of these data, nor is it FDA approved. [2,4] Although iNO is approved for the full term infant, further study would be needed to establish a new indication(s) for specific populations of preterm infants. Although there have been ongoing trials on iNO use for preterm infants, it may be beneficial to initiate a national collaboration in Investigational New Drug (IND) Research trial(s), which would provide rigorous study of new neonatal indications to determine safety and efficacy.

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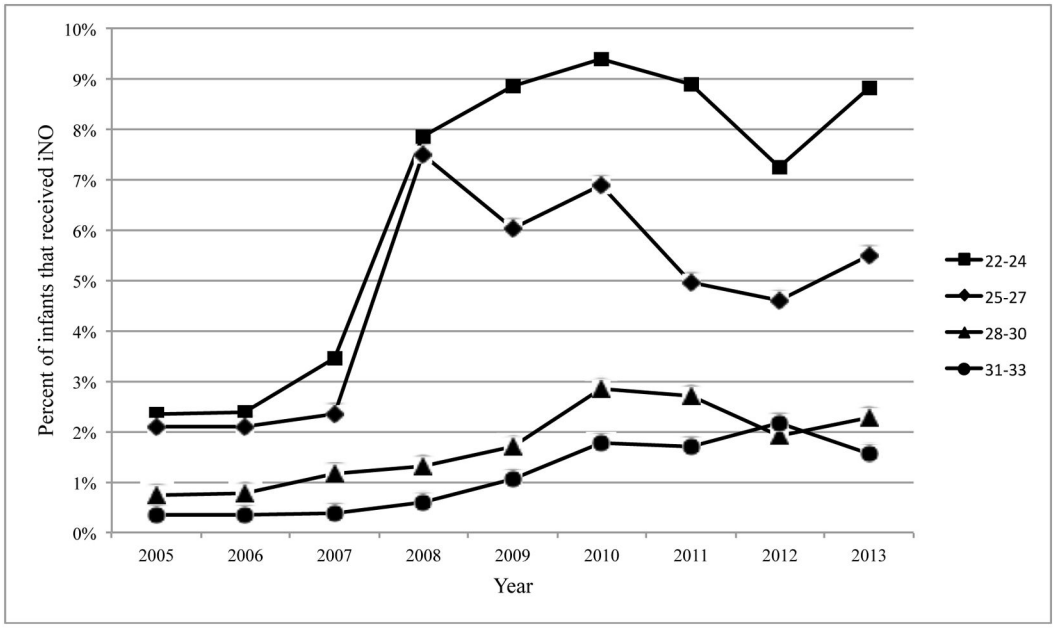

Figure 1.
Rates of iNO exposure from 2005 to 2013 stratified by gestational age.

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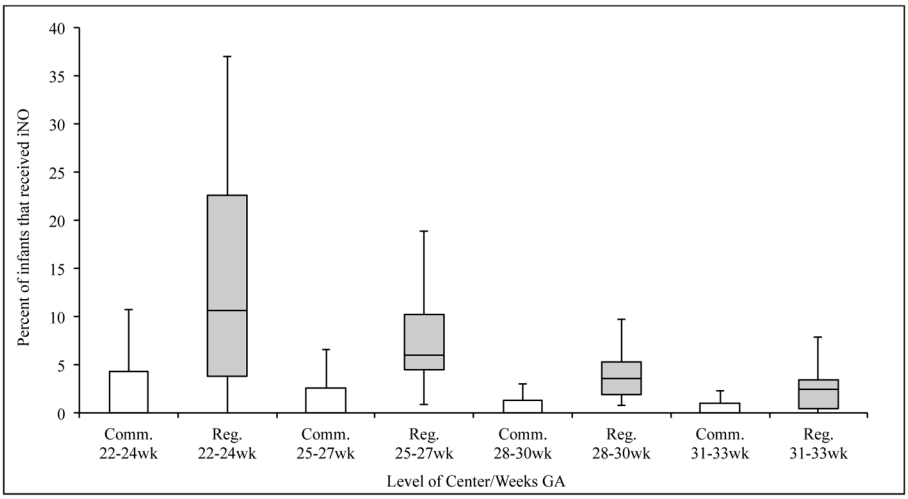

Figure 2.

Rates of iNO exposure by gestational age in community and regional NICUs. Comm, community; Reg, regional; wk, week; GA, gestational age.

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Table 1

Characteristics of infants stratified by gestational age who had exposure to iNO compared to infants who were not exposed to iNO.

	22–24+6/7			25–27+6/7		
n	**Any nitric 401**	**No Nitric 5733**	**P value**	**Any nitric 689**	**No Nitric 14157**	**P value**
BW (mean with SD)	659.3 (+/−117.9)	639.8 (+/−111.3)	<0.001	836.0 (+/−198.2)	887.4 (+/−188.0)	<0.001
GA (mean with SD)	23.7 (+/− 0.5)	23.6 (+/− 0.6)	<0.001	25.8 (+/−0.79)	26.1 (+/−0.82)	<0.001
SGA	5.24%	3.42%	0.057	7.26%	3.97%	<0.001
Male sex	56.36%	52.56%	0.141	58.78%	53.89%	0.012
Multiple birth	29.43%	23.77%	0.011	25.54%	22.68%	0.080
Antenatal steroids	80.35%	71.18%	<0.001	86.64%	81.03%	<0.001
Mode of delivery			<0.001			0.006
C-Section	68.00%	47.29%		75.47%	69.89%	
Vaginal	32.00%	52.71%		24.53%	30.11%	
1min APGAR (median with IQ)	3 (2–5)	3 (2–5)	0.806	4 (2–6)	5 (3–7)	<0.001
5min APGAR (median with IQ)	6 (5–8)	6 (4–8)	0.308	7 (5–8)	8 (6–8)	<0.001
Resuscitation (CC and/or Epi)	16.96%	19.94%	0.520	18.00%	9.37%	<0.001
Race			<0.001			<0.001
Non-Hispanic white	20.34%	15.46%		16.70%	13.59%	
Hispanic	34.24%	51.13%		33.21%	49.40%	
Non-Hispanic black	30.85%	22.54%		35.48%	25.13%	
Asian/PI	11.86%	7.77%		11.57%	9.03%	
Native American	0.34%	0.27%		0.38%	0.28%	
Other	2.37%	2.83%		2.66%	2.57%	
Mortality <12hrs (inc DR)	2.99%	7.37%	0.001	2.47%	1.13%	0.002
Mortality prior to discharge	39.40%	38.34%	0.673	27.72%	10.77%	<0.001

	28–30+6/7			31–33+6/7		
n	**Any nitric 369**	**No Nitric 21172**	**P value**	**Any nitric 259**	**No Nitric 23044**	**P value**
BW (mean with SD)	1241.6 (+/−330.4)	1266.1 (+/−262.9)	0.077	1959.7 (+/−497.9)	1719.8 (+/− 393.6)	<0.001
GA (mean with SD)	28.8 (+/−0.8)	29.1 (+/−0.8)	<0.001	32.1 (+/−0.9)	32.0 (+/−0.8)	0.007

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n	28–30+6/7			31–33+6/7		
	Any nitric 369	**No Nitric 21172**	**P value**	**Any nitric 259**	**No Nitric 23044**	**P value**
SGA	10.30%	5.75%	<0.001	15.06%	22.00%	0.007
Male sex	58.54%	53.70%	0.065	62.16%	54.55%	0.014
Multiple birth	26.02%	27.44%	0.542	12.40%	29.77%	<0.001
Antenatal steroids	83.79%	82.00%	0.376	66.01%	70.50%	0.119
Mode of delivery			0.260			0.181
C-Section	77.17%	73.44%		74.90%	72.90%	
Vaginal	22.83%	26.56%		25.10%	27.10%	
1min APGAR (median with SD)	5 (2–7)	7 (5–8)	<0.001	5 (3–7)	7 (6–8)	<0.001
5min APGAR (median with SD)	7 (5–8)	8 (7–9)	<0.001	7 (5–8)	9 (8–9)	<0.001
Resuscitation (CC and/or Epi)	12.20%	4.28%	<0.001	13.51%	3.01%	<0.001
Race			0.065			0.978
Non-Hispanic white	10.37%	11.36%		8.86%	9.38%	
Hispanic	38.89%	45.58%		44.30%	45.30%	
Non-Hispanic black	37.78%	29.73%		34.18%	32.09%	
Asian/PI	11.11%	10.26%		9.49%	9.42%	
Native American	0.00%	0.27%		0.00%	0.28%	
Other	1.85%	2.80%		3.16%	3.53%	
Mortality <12hrs (inc DR)	2.71%	0.35%	<0.001	2.70%	0.31%	<0.001
Mortality prior to discharge	28.73%	2.73%	<0.001	25.48%	2.08%	<0.001

BW, Birthweight; GA, Gestational Age; SGA, Small for Gestational Age; CC, chest compressions; Epi, epinephrine; DR, Delivery Room; SD, Standard Deviation; IQ, Interquartile Range.

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Table 2

Factors associated with iNO exposure stratified by gestational age.

	22–24+6/7 aOR (95% CI)	25–27+6/7 aOR (95% CI)	28–30+6/7 aOR (95% CI)	31–33+6/7 aOR (95% CI)
Male	1.14 (0.92–1.41)	1.29 (1.10–1.52)	1.24 (0.99–1.53)	1.19 (0.92–1.54)
Singleton	0.76 (0.60–0.95)	0.89 (0.74–1.06)	1.08 (0.85–1.38)	2.45 (1.68–3.58)
Antenatal steroids	1.37 (1.06–1.78)	1.51 (1.20–1.89)	1.15 (0.87–1.53)	1.03 (0.79–1.36)
Recevied DR-CPR	0.92 (0.62–1.36)	1.94 (1.49–2.53)	2.00 (1.27–3.16)	2.06 (1.11–3.85)
Care in regional center	2.17 (1.76–2.68)	2.43 (2.08–2.85)	4.10 (3.29–5.10)	3.69 (2.84–4.78)

aOR, adjusted Odds Ratio; CI, Confidence Interval; DR-CPR, Delivery Room Cardiopulmonary Resusciation.