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Intrauterine Hyperoxemia and Risk of Neonatal Morbidity

Nandini Raghuraman, MD, MS, Lorene A. Temming, MD, Molly J Stout, MD, MSCI, George A. Macones, MD, MSCE, Alison G. Cahill, MD, MSCI, and Methodius G. Tuuli, MD, MPH
Department of Obstetrics and Gynecology, Washington University School of Medicine in St. Louis, St. Louis, MO

Abstract

Objective—To test the hypothesis that intrauterine hyperoxemia is associated with an increased risk of neonatal morbidity.

Methods—This was a secondary analysis of a prospective study of singleton, non-anomalous deliveries at or beyond 37^o weeks at an institution with universal umbilical cord gas policy from 2010 to 2014. The primary outcome was a composite of neonatal morbidity including neonatal death, meconium aspiration syndrome, intubation, mechanical ventilation, hypoxic-ischemic encephalopathy, and hypothermic therapy. Intrauterine hyperoxemia was defined as cord venous PO₂ 90th percentile of the cohort. Adjusted relative risks (aRR) were estimated for neonatal morbidity controlling for confounders. Analysis was performed for the entire cohort and stratified by the presence of acidemia defined as umbilical artery pH<7.1.

Results—Of 7,789 patients with validated paired cord gases, 106 (1.4%) had the composite neonatal morbidity. There was no difference in composite neonatal morbidity in patients with and without intrauterine hyperoxemia in the entire cohort (1.5% vs 1.3%, aRR 1.5, 95% CI 0.9–2.7). The rate of acidemia was not significantly different in the two groups (1.9% vs 1.8%, aRR 1.5, 95% CI 0.9–2.5). In stratified analysis, there was evidence of effect modification (p for interaction <0.001), with a significant association between intrauterine hyperoxemia and neonatal morbidity in the presence of acidemia (41.2% vs 21.4%, aRR 2.3, 95% CI 1.1–3.5), but not in its absence (0.8% vs 1.0%, aRR 1.0, 95% CI 0.5–2.2).

Conclusion—Intrauterine hyperoxemia, compared with normoxemia, is associated with a small, but significantly increased risk of neonatal morbidity in academic neonates.

Introduction

Maternal oxygen administration is a ubiquitously used intrapartum intervention to address concerning fetal heart rate tracing (FHT) patterns. This form of intrauterine resuscitation is often performed for FHT patterns that are thought to be associated with fetal hypoxemia or

Corresponding author: Nandini Raghuraman MD MS, Washington University School of Medicine, 660 S. Euclid Avenue, 5th floor Maternity Building, St. Louis, MO 63110; raghuramann@wudosis.wustl.edu, Telephone (314) 362 7300.

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acidemia(1). The theoretical benefit of maternal hyperoxygenation is to increase oxygen delivery to the fetus via the umbilical cord vein, thereby reducing adverse outcomes related to fetal asphyxia.

Although animal and human studies have shown increased umbilical venous oxygen content and alleviation of fetal heart rate decelerations with maternal hyperoxygenation(2–5), there is a paucity of data linking hyperoxygenation to improved neonatal outcomes(6). Moreover, there are potential harmful effects of hyperoxygenation via free radical production (4). Hyperoxygenation in the setting of neonatal resuscitation has been shown to increase the risk of neonatal morbidity (6–11). Due to these findings, the American Academy of Pediatrics now recommend initial neonatal resuscitation with room air rather than supplemental oxygen(12, 13). The detrimental outcomes associated with hyperoxygenation at time of neonatal resuscitation demand a closer look at the safety of intrauterine fetal oxygen exposure.

We tested the hypothesis that intrauterine hyperoxemia is associated with an increased risk of neonatal morbidity by investigating the relationship between high fetal umbilical cord venous oxygen content at time of birth and neonatal outcomes. We were particularly interested in the relationship between neonatal morbidity and hyperoxemia in the setting of acidemia.

Materials and Methods

This was a secondary analysis of a large prospective cohort study at a tertiary care center with a universal cord gas policy from 2010 to 2014. This study was approved by the Washington University School of Medicine Human Research Protection Office.

Per institutional protocol, umbilical cord gases were collected for every patient by trained technicians. Both arterial and venous blood samples are obtained from a clamped segment of cord immediately after delivery and analyzed in the hospital laboratory using the ABL800 benchtop gas analyzer (Radiometer). The coefficient of variation of the partial pressure of oxygen (PO₂) using this analyzer ranges from 1.9–2.9%. All singleton, term, non-anomalous deliveries with validated and paired venous and arterial cord gases were eligible. Patient with unpaired and unvalidated cord gases were excluded. Paired cord gases were validated by confirming that the arterial cord pH was at least 0.02 lower in the artery than the vein(14, 15).

Information regarding maternal demographics, antenatal care, labor outcomes, cord gas values, and neonatal diagnoses were collected from medical records by trained research staff. The primary outcome was a composite of neonatal morbidity that included neonatal death, hypoxic ischemic encephalopathy, need for hypothermia treatment, intubation, mechanical ventilation, and meconium aspiration syndrome.(14, 16) When neonates had more than one morbidity only one was counted per patient. Given the wide and skewed range of oxygen content in the umbilical cord(17) we defined hyperoxemia as cord venous PO₂ 90th percentile (39 mmHg) of the cohort. Coincidentally this cut-point is consistent with the upper range of published normal values of umbilical venous PO₂.(18)

Baseline characteristics of patients with and without fetal umbilical cord hyperoxemia were compared using χ^2 or Fisher exact test, Mann-Whitney U test, or Student t test as appropriate. Multivariable logistic regression was used to adjust for confounders. Potential confounders were selected on the basis of biologic plausibility, risk factors that have been identified in the literature for the various outcomes, and results of univariable and stratified analyses. Backwards elimination was used to reduce the number of variables in each model. Variables were included in the final model if they had at least a 10% effect on the magnitude of the odds ratio associated with the primary exposure. Model fit for the final model was assessed with the Hosmer-Lemeshow goodness-of-fit test (19). Because the frequency of the primary outcome was >10% in some subgroups and odds ratios would overestimate the relative risks, we estimated adjusted relative risks using the method proposed by Zhang et al. (20)

Analysis was performed for the entire cohort and was then stratified by the presence of acidemia defined as umbilical artery pH < 7.1. We included an interaction term in the logistic regression model to test for effect modification by acidemia on the relationship between hyperoxemia and neonatal morbidity. This test assessed whether the magnitude of the association between hyperoxemia and neonatal morbidity significantly differed in acidemic and non-acidemic neonates. The original prospective cohort study from which our sample was obtained did not contain information on intrapartum oxygen supplementation. We conducted additional chart review to abstract data on intrapartum oxygen supplementation for the acidemic cohort.

We included all consecutive patients meeting inclusion criteria; no *a priori* sample size estimation was performed. All tests were 2-tailed with $P < 0.05$ considered significant. STATA Version 12.1 (STATA Corp., College Station, TX) was used to perform all analyses.

Results

A total of 8,580 deliveries occurred during the study period. Of these, we excluded 791 for missing validated or paired cord gases, leaving 7,789 for analysis. In all, 907 (11.6%) had cord venous PO_2 90th percentile (Figure 1). Composite neonatal morbidity was diagnosed in 106 (1.4%) neonates. Intubation (68.9%), mechanical ventilation (45.3%), and hypothermic therapy (37.7%) were the most common outcomes (Table 1).

Baseline characteristics of patients with fetal umbilical cord hyperoxemia were compared to those without hyperoxemia. Patients with fetal hyperoxemia were more likely to be younger, African American, smoke cigarettes, and have hypertension. Cesarean delivery, cesarean for the specific indication of non-reassuring fetal status, and intrapartum maternal fever were less common in the hyperoxemic group. There was no difference in BMI or diabetes between groups. Although patients with fetal hyperoxemia had slightly higher mean umbilical cord arterial pH compared to those without hyperoxemia (7.28 ± 0.07 versus 7.27 ± 0.06 , $p < 0.01$), there was no significant difference in the proportion with acidemia (umbilical arterial pH < 7.1) between the groups (Table 2).

For the entire cohort, there was no difference in composite neonatal morbidity between those with and without fetal hyperoxemia (1.9% versus 1.8%, aRR 1.5, 95% CI 0.9–2.5). However, in the stratified analysis among those with acidemia, hyperoxemia was associated with a significantly higher risk of the composite neonatal morbidity among acidemic neonates (41.2% versus 21.4%, aRR 2.3, 95% CI 1.1–3.5). There was no difference in neonatal morbidity between those with and without hyperoxemia among non-acidemic neonates (0.8% versus 1.0%, aRR 1.0, 95% CI 0.5–2.2). The test of interaction confirmed that the magnitude of the association between hyperoxemia and neonatal morbidity was significantly different in acidemic compared with non-acidemic neonates (P for interaction <0.001) (Table 3)

On further analysis of the acidemic cohort, there were no significant differences in clinical characteristics including mode of delivery, prolonged labor, and cesarean for non-reassuring fetal status between acidemic fetuses with and without hyperoxemia. (Table 4) There was also no difference in median arterial pH [7.07 (IQR 7.01, 7.09) versus 7.04 (IQR 7.01, 7.09), $P=0.71$], base excess [-11.1 mEq/L (-12.8 , -9.3) versus -10.8 mEq/L (-13 , -9.4), $P=0.92$], or PCO₂ [83 mmHg (78, 90) versus 88 mmHg (76, 93) $P=0.96$] between those with and without hyperoxemia. Frequency of oxygen supplementation in the acidemic cohort was high, and not different between those with and without hyperoxemia (80.0% versus 90.1%, $P=0.22$). The median duration of oxygen supplementation was not different between acidemic patients with and without hyperoxemia (230 versus 175 minutes, $P=0.19$). There was no statistically significant difference between groups when duration of oxygen supplementation was assessed categorically (Table 5). Finally, in sensitivity analysis where we included only patients who had oxygen supplementation, there was a significantly higher risk of neonatal morbidity in the setting of acidemia and hyperoxemia compared with acidemia without hyperoxemia (41.7% versus 21.1%, aRR 2.6; 95% CI 1.1 – 3.9).

Discussion

In this large prospective cohort, we found no difference in morbidity between neonates with and without hyperoxemia. However, the risk of neonatal morbidity varied depending on the presence of acidemia with a small, but significantly increased risk of adverse neonatal outcomes with hyperoxemia in the setting of acidemia, but not in its absence.

An increase in adverse outcomes has also been observed in clinical trials evaluating intrauterine oxygen exposure. In a trial of 56 laboring women randomized to oxygen or room air for at least 30 minutes before delivery, Nesterenko et al found that more infants in the oxygen group required delivery room resuscitation.(21) A similar trial by Thorp et al comparing oxygen to room air in the second stage of labor revealed that babies in the oxygen group were four times more likely to have umbilical artery pH values <7.20 and that duration of oxygen exposure had an inverse relationship with cord arterial pH.(22) In a double-blinded trial of room air versus oxygen during elective cesarean delivery, Khaw et al demonstrated that oxygen was associated with increased maternal and umbilical cord levels of malondialdehyde, a marker of free radical activity and oxidative stress.(4) However, none of these studies directly related fetal hyperoxemia to clinical neonatal outcomes and did not stratify on the basis of acidemia.

The observed interaction between acidemia and hyperoxemia on neonatal morbidity is biologically plausible and may be attributable to hypoxia-reoxygenation injury. Fetal acidemia occurs when hypoxia causes a shift from aerobic to anaerobic metabolism. The hydrogen ions produced by anaerobic metabolism in this setting overwhelm the buffer capacity of the fetus resulting in a fall in pH.(23) Subsequent reoxygenation results in calcium influx at a cellular level that increases substrate availability for the enzyme xanthine oxidase, a generator of free radicals.(6, 24, 25) The buildup of free radicals then triggers cellular damage and subsequent injury to fetal organs including the brain and lungs.(10, 26) In addition, the decreased cerebral blood flow associated with hyperoxia can further amplify the severity of reperfusion injury.(27) This is supported by studies of neonatal resuscitation which showed an increased risk of neonatal mortality, retinopathy of prematurity, and bronchopulmonary dysplasia when resuscitation was performed with 100% oxygen rather than room air.(8, 10, 28) Furthermore, hyperoxemia at the time of resuscitation is associated with impaired neonatal inspiratory responses attributed to hyperoxemia-related oversaturation of peripheral chemoreceptors.(9) Although neonatal hyperoxemic injury may differ in pathophysiology from that of intrauterine hyperoxemia, the potential harm of excess fetal oxygen exposure must be carefully evaluated. We found that patients with hyperoxemia were less likely to have cesareans for non-reassuring fetal tracings. This is consistent with prior studies linking increased umbilical venous oxygen content with alleviation of fetal decelerations. However, although fetal heart tracings may improve as a result of hyperoxygenation, it may not improve neonatal outcomes.(3, 29) Although we did not assess the diagnosis of chorioamnionitis, we observed a lower proportion of patients with intrapartum maternal fever in the hyperoxemia group. We suspect that the relationship between chorioamnionitis, fetal heart tracings, and oxygen administration is complex and cannot account for changes in placental regulation that may occur secondary to inflammation and infection.

The large prospective cohort design is a strength of this study. The large sample size enabled us to stratify our analysis by acidemia, which revealed evidence of interaction. The universal cord gas collection and objective validation of cord gas values allowed for accurate, generalizable estimates of cord venous content and reduced the potential for selection bias.

There are limitations that should be considered. We defined hyperoxemia by umbilical venous PO_2 90th percentile without reference to whether the patients received supplemental oxygen. The lack of oxygen supplementation data for the entire cohort limits our ability to directly link hyperoxemia with oxygen administration. However, prior studies have demonstrated an association between maternal hyperoxygenation and increased umbilical vein PO_2 . (5, 29). Among the acidemic cohort for which we had data on oxygen supplementation, we found high frequency of oxygen supplementation. Although the overall frequency of oxygen supplementation was not significantly different between the acidemic subgroups with and without hyperoxemia, the median duration of oxygen supplementation was nominally higher in the subgroup with hyperoxemia (230 versus 175 min., $P=0.19$) and there was a tendency towards a higher proportion of patients in the hyperoxemia group receiving oxygen for greater than 6 hours compared to the normoxic group. These differences may not be statistically significant due to the limited sample size of the acidemic cohort. It is possible that fetal acidemia triggers changes in villous oxygen absorption,

independent of maternal oxygen administration, that account for the observed changes in neonatal morbidity. However, in sensitivity analysis limited only to patients who received oxygen, and thus hyperoxemia associated with oxygen administration, we observed a similarly increased risk of neonatal morbidity in the setting of acidemia and hyperoxemia compared with acidemia without hyperoxemia.

The use of a composite neonatal outcome measure may also be seen as a weakness. This was necessary for adequate statistical power to perform detailed analysis, which would not be possible if the relatively rare individual outcomes were used. Moreover, we used an established composite with carefully selected components of neonatal morbidities that are directly or indirectly linked to intrauterine hypoxia.(14, 16) Finally, although we used appropriate statistical methods to control for confounders, there is the possibility of residual confounding by unmeasured factors.

In conclusion, this study demonstrates a small, but significantly increased risk of neonatal morbidity with intrauterine hyperoxemia in the presence of acidemia. Since intrauterine resuscitation is commonly used for suspected fetal acidemia, this finding calls for a closer look at the safety of liberal and prolonged oxygen administration for intrapartum management of suspected fetal acidemia. While these findings are insufficient to recommend practice change, they support the need for further studies including an ongoing randomized trial comparing outcomes associated with intrauterine resuscitation using oxygen or room air.

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Précis

Intrauterine hyperoxemia, compared with normoxemia, is associated with a small, but significantly increased risk of neonatal morbidity in acidemic neonates.

Figure 1.
Flow chart of study population. PO₂, partial pressure of oxygen.

Table 1

Composite neonatal morbidity (n=106/7789 = 1.4%)

Component	n	%
Intubation	73	68.9
Mechanical ventilation	48	45.3
Hypothermia treatment	40	37.7
Hypoxic encephalopathy	33	31.1
Meconium aspiration syndrome	22	20.8
Neonatal death	4	3.8

Table 2

Baseline demographics of study cohort

Demographic	Entire Cohort (n=7789)	Venous PO ₂ 90 th %ile* (n=907)	Venous PO ₂ < 90 th %ile (n= 6882)	P-value
Maternal Age (years)	26 ± 5.9	25 ± 5.6	26 ± 6.0	<0.001
Race				<0.001
African American	5085 (65.8)	717 (79.2)	4368 (64.0)	
Caucasian	1744 (22.6)	122 (13.5)	1622 (23.8)	
Hispanic	552 (7.1)	38 (4.2)	514 (7.5)	
Other	350 (4.5)	28 (3.1)	322 (4.7)	
BMI (kg/m ²)	32.3 ± 7.4	32.5 ± 7.6	32.3 ± 7.3	0.35
Obese	4424 (56.8)	525 (57.9)	3899 (56.7)	0.48
Gestational age, weeks	39 ± 1.21	39 ± 1.24	39 ± 1.21	0.04
Nulliparous	3320 (42.6)	288 (31.8)	3032 (44.1)	<0.001
Maternal fever >38.1 C	358 (4.6)	21 (2.3)	337 (4.9)	<0.001
Mode of delivery				<0.001
Spontaneous vaginal	6033 (77.5)	787 (86.8)	5246 (76.2)	
Operative vaginal	373 (4.8)	37 (4.1)	336 (4.9)	
Cesarean	1383 (17.8)	83 (9.2)	1300 (18.9)	
Cesarean indication of non-reassuring fetal status	1118 (14.4)	86 (9.5)	1032 (15.0)	<0.001
Smoking	1085 (13.9)	149 (16.4)	936 (13.6)	0.02
Illicit drug use	901 (11.6)	124 (13.7)	777 (11.3)	0.04
Alcohol	86 (1.1)	11 (1.2)	75 (1.1)	0.75
Diabetes	120 (1.5)	7 (0.8)	113 (1.6)	0.05
Hypertension	372 (4.8)	58 (6.4)	314 (4.6)	0.02
Birthweight (grams)	3249 ± 463	3229 ± 433	3252 ± 467	0.16
Umbilical arterial pH	7.3 ± 0.1	7.28 ± 0.07	7.27 ± 0.06	<0.01
Umbilical arterial pH <7.1	147 (1.9)	17 (1.9)	130 (1.9)	0.98
NICU admission	123 (1.6)	19 (2.1)	104 (1.5)	0.19
Oxytocin	5227 (67.1)	598 (65.9)	4629 (67.2)	0.42
Induction of labor	3438 (44.1)	407 (44.9)	3031 (44.0)	0.64
Prolonged 1 st stage [†]	336 (5.1)	48 (5.8)	288 (5.0)	0.33

Demographic	Entire Cohort (n=7789)	Venous PO ₂ 90 th %ile* (n=907)	Venous PO ₂ < 90 th %ile (n= 6882)	P-value
Prolonged 2 nd stage [†]	443 (6.6)	43 (5.2)	400 (6.8)	0.07

* 90th%ile Venous PO₂ is 39 mmHg

Data represents n(%) or mean ± standard deviation

[†] >95th percentile of first stage of labor: 15.3 hours for nulliparas and >12.8 hours for multiparas

[‡] >3 hours for nulliparous patients without epidurals, >4 hours for nulliparous patients with epidurals. >2 hours for multiparous patients without epidurals, >3 hours for multiparous patients with epidurals

Table 3Neonatal outcomes by cord venous O₂ content and acidemia

Outcome	Venous PO ₂ 90th%ile	Venous PO ₂ < 90th%ile	RR (95% CI)	Adjusted RR [†] (95%CI)	P for interaction
Entire cohort	N=907	N=6882			
Cord arterial pH <7.1	17 (1.9)	126 (1.8)	1.0 (0.7–1.6)	1.5 (0.9–2.5)	
Composite neonatal morbidity	14 (1.5)	92 (1.3)	1.1 (0.7–1.9)	1.5 (0.9–2.7)	
Acidemic cohort *	N=17	N=126			
Composite neonatal morbidity	7 (41.2)	27 (21.4)	2.2 (0.9–5.4)	2.3 (1.1–3.5)	<0.001
Non-acidemic cohort	N=890	N= 6756			
Composite neonatal morbidity	7 (0.8)	65 (1.0)	0.8 (0.4–1.7)	1.0 (0.5–2.2)	

RR relative risk

* Acidemic defined as umbilical artery pH<7.1

† Adjusted for nulliparity, hypertension, and delivery mode

Bolded data represent statistically significant results

Table 4

Baseline demographics of academic cohort

Demographic	Acidemia* + Venous PO2 90 th %ile (n=17)	Acidemia* + Venous PO2<90 th %ile (n=126)	P-value
Maternal age	28 (19, 31)	28 (22, 33)	0.29
Race			
African American	12 (70.6)	78 (62.4)	0.75
Caucasian	4 (23.5)	34 (27.2)	
Hispanic	1 (5.9)	6 (4.8)	
Other	0 (0)	7 (5.6)	
BMI (kg/m ²)	33 (30, 41)	32 (27, 39)	0.56
Obese	12 (70.6)	77 (61.1)	0.45
Gestational age, weeks	39 (39,41)	39 (38,40)	0.13
Nulliparous	11 (64.7)	68 (54.0)	0.40
Maternal fever>38.1 C	1 (5.9)	9 (7.4)	0.85
Mode of delivery			
Spontaneous vaginal	8 (47.1)	32 (25.4)	0.17
Operative vaginal	1 (5.9)	15 (11.9)	
Cesarean	8 (47.1)	79 (62.7)	
Operative delivery (operative vaginal or cesarean)	9 (52.9)	94 (74.6)	0.06
Cesarean indication of non-reassuring fetal status	8 (47.1)	80 (63.5)	0.19
Smoking	2 (11.8)	12 (9.5)	0.77
Illicit drug use	2 (11.8)	9 (7.1)	0.50
Alcohol	0 (0)	0 (0)	–
Diabetes	0 (0)	10 (10.8)	0.28
Hypertension	2 (11.8)	22 (17.5)	0.56
Birthweight (grams)	3501 ± 118	3232 ± 43.9	0.04
NICU admission	6 (35.3)	25 (19.8)	0.15
Oxytocin	10 (58.8)	84 (66.7)	0.52
Induction of labor	7 (41.2)	62 (49.2)	0.53
Prolonged 1 st stage [†]	0 (0)	8 (11.1)	0.29

Demographic	Acidemia* + Venous PO2 90 th %ile (n=17)	Acidemia* + Venous PO2<90 th %ile (n=126)	P-value
Prolonged 2 nd stage [†]	0 (0)	9 (12.5)	0.26

* Umbilical artery pH<7.1

[†] >95th percentile of first stage of labor: 15.3 hours for nulliparas and >12.8 hours for multiparas

[‡] >3 hours for nulliparas without epidurals, >4 hours for nulliparas with epidurals. >2 hours for multiparas without epidurals, >3 hours for multiparas with epidurals

Data represents mean ± standard deviation, n(%), or median (interquartile range)

Table 5

Intrapartum oxygen supplementation in acidemic cohort

Intrapartum oxygen supplementation	Acidemia* + Venous PO2 90 th %ile n=15 [†]	Acidemia* + Venous PO2<90 th %ile n=121 [†]	P value
Any oxygen supplementation	12 (80.0)	109 (90.1)	0.22
Duration of oxygen supplementation (mins)	230 (119,381)	175 (68,290)	0.19
Oxygen 2 hours	14 (82.4)	86 (68.3)	0.28
Oxygen 3 hours	12 (70.6)	69 (54.8)	0.22
Oxygen 4 hours	11 (64.7)	55 (43.7)	0.10
Oxygen 5 hours	9 (52.9)	43 (34.1)	0.13
Oxygen 6 hours	8 (47.1)	31 (24.6)	0.05

* Umbilical artery pH<7.1

[†] Missing data for 2/17 in acidemia + venous PO2 90th percentile group and 5/126 in acidemia + venous PO2<90th percentile group

Data represent n (%) or median (interquartile range)