Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California

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abstract

BACKGROUND AND OBJECTIVES: There are limited epidemiologic data on persistent pulmonary hypertension of the newborn (PPHN). We sought to describe the incidence and 1-year mortality of PPHN by its underlying cause, and to identify risk factors for PPHN in a contemporary population-based dataset.

METHODS: The California Office of Statewide Health Planning and Development maintains a database linking maternal and infant hospital discharges, readmissions, and birth and death certificates from 1 year before to 1 year after birth. We searched the database (2007–2011) for cases of PPHN (identified by *International Classification of Diseases, Ninth Revision* codes), including infants ≥34 weeks' gestational age without congenital heart disease. Multivariate Poisson regression was used to identify risk factors associated with PPHN; results are presented as risk ratios, 95% confidence intervals.

RESULTS: Incidence of PPHN was 0.18% (3277 cases/1 781 156 live births). Infection was the most common cause (30.0%). One-year mortality was 7.6%; infants with congenital anomalies of the respiratory tract had the highest mortality (32.0%). Risk factors independently associated with PPHN included gestational age <37 weeks, black race, large and small for gestational age, maternal preexisting and gestational diabetes, obesity, and advanced age. Female sex, Hispanic ethnicity, and multiple gestation were protective against PPHN.

CONCLUSIONS: This risk factor profile will aid clinicians identifying infants at increased risk for PPHN, as they are at greater risk for rapid clinical deterioration.

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WHAT'S KNOWN ON THIS SUBJECT: Persistent pulmonary hypertension of the newborn results from the failure to transition from fetal to postnatal circulation and presents with respiratory failure. It is a condition with varying underlying etiologies and pathophysiology, resulting in persistent elevation of pulmonary vascular resistance.

WHAT THIS STUDY ADDS: This is the first population-based study describing incidence, etiologies, and risk factors of persistent pulmonary hypertension of the newborn. Multiple independent risk factors are established, and late preterm infants are identified as a group at increased risk for this condition.

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Successful transition from intra- to extrauterine life involves a rapid decrease in pulmonary vascular resistance with concomitant increase in pulmonary blood flow and decreased shunting across the foramen ovale and ductus arteriosus.[1,2] The failure to transition from fetal to postnatal circulatory pattern is called persistent pulmonary hypertension of the newborn (PPHN), a disease with different underlying etiologies causing persistent elevation of pulmonary vascular resistance.[1,2] Although these etiologies have been characterized into 3 pathophysiological categories, there is considerable overlap in etiology for any single condition. Broadly, the etiologies are (1) abnormally constricted pulmonary vasculature (eg, sepsis, meconium aspiration syndrome [MAS], or respiratory distress syndrome [RDS]), (2) hypoplastic vasculature (eg, congenital diaphragmatic hernia [CDH]), and (3) remodeled pulmonary vasculature (eg, idiopathic PPHN, MAS).[1–3]

In a previous multicenter study, the overall incidence of PPHN was estimated to be 1.9 per 1000 live births, with wide variability across referral centers.[4] Mortality has been reported at 12% to 29%.[4,5] More recent randomized trials evaluating inhaled nitric oxide (iNO) for treatment of PPHN report a lower overall mortality (7%–15%), although none showed decreased mortality with iNO.[6–8] To the best of our knowledge, previous work examining incidence, mortality, and underlying causes in infants with PPHN has been from single or multicenter studies. Single-center or multicenter cohort studies of incidence and outcomes are problematic because of referral bias.

Several case-control studies have identified antenatal and perinatal risk factors for PPHN,[9–12] often with conflicting results likely due to small sample size (n = 31–377), which limits power to adjust for covariates/confounders and may identify spurious relationships due to incomplete adjustment. Given the current paucity of epidemiologic information of PPHN, we conducted a large population-based epidemiologic study of PPHN by using a California birth cohort. This dataset allowed us to explore incidence, etiologies, mortality, and risk factors, accounting for multiple covariates, in late preterm and term infants who develop PPHN.

TABLE 1 ICD-9-CM Codes for Underlying Causes of PPHN

Disease	ICD-9 code
CDH	
Anomalies of diaphragm	756.6
Congenital anomalies of respiratory tract	
Agenesis, hypoplasia, and dysplasia of the lung	748.5
Other anomalies of lung	748.6
Other respiratory anomaly	786.09
Other anomalies of larynx, trachea, and bronchus	748.3
Congenital cystic lung	748.4
MAS	
Meconium aspiration with respiratory symptoms	770.12
Infection	
Septicemia of newborn	771.81
Bacteremia of newborn	771.83
Other infections specific to the perinatal period	771.89
SIRS	995.9
Severe sepsis	995.92
Infective pneumonia acquired prenatally	770.0
Pneumonia	486
RDS	
Respiratory distress syndrome	769
Other identified causes	
Birth asphyxia	768.5–7, 768.9
Cystic kidney disease	753.1
Hydrops fetalis	778.0
Interstitial emphysema	770.2
Leukemia	208.9
Polycythemia	776.4
Renal agenesis and dysgenesis	753.0
Trisomy 21	758.0

CDH, congenital diaphragmatic hernia; MAS, mecondium aspiration syndrome; RDS, respiratory distress syndrome; SIRS, systemic inflammatory response syndrome.

METHODS

The study cohort was drawn from a birth cohort database maintained by the California Office of Statewide Health Planning and Development that contained 1 781 156 live births from 2007 to 2011. This database includes detailed information on infant characteristics derived from hospital discharge records (neonatal and readmissions), linked to birth and death certificates, from birth to 1 year of age. The database has been used in multiple studies examining birth and neonatal outcomes.[13–19] Gestational age (GA, best obstetric estimate), birth weight, demographic factors, and maternal diagnoses (from 1 year before birth) are included. Diagnosis and procedure codes are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

Infants born at ≥34 0/7 weeks' GA with ICD-9-CM codes 747.83 (persistent fetal circulation), 416.0 (primary pulmonary hypertension), or 416.8 (other secondary pulmonary hypertension) present in the birth hospitalization record were categorized as PPHN cases. Birth

hospitalization is defined as the hospitalization from birth to initial discharge, including transfer to another hospital, if present. These codes have identified infants with PPHN in large administrative databases, validated by a high positive predictive value (PPV) when compared with primary medical record review.[20,21]

Infants with major congenital heart disease were excluded; infants with minor cardiac defects associated with the diagnosis of PPHN, or diagnosed in its evaluation (eg, ventricular septal defect [VSD], atrial septal defect [ASD], and patent ductus arteriosus [PDA]) were included (ICD-9-CM codes 745–747.4, except 7.45.4–7.45.6, 747).

To assign an underlying cause to cases with >1 condition, the following hierarchy for assigning the primary etiology was chosen based on the likelihood of the condition to be associated with PPHN: CDH, other congenital malformations of the respiratory system, MAS, infection/sepsis, and RDS (ICD-9-CM codes listed in Table 1). Records of the cases without ICD-9-CM codes consistent with any of these 4 conditions were searched for other ICD-9 codes associated with PPHN (Table 1). If any of these codes were found, the infant was classified as "other"; the remaining individuals were considered to have "idiopathic" PPHN.

Infants with CDH or other respiratory or renal malformations were excluded from the risk factor analysis. Clinical characteristics were chosen based on risk factors identified in previous studies[9–11]: GA, sex, fetal growth (small for gestational age [SGA, birth weight <10th percentile], large for gestational age [LGA, birth weight >90th percentile], and adequate for gestational age [AGA]).[22] Maternal diabetes (preexisting and gestational), prepregnancy BMI, maternal hypertension, preeclampsia, asthma, smoking, illicit drug abuse or addiction (as a marker for cocaine/amphetamine use), mental illness (as a marker for antidepressant use), age, parity, multiple gestation, oligohydramnios, premature rupture of membranes (PROM), chorioamnionitis, and mode of delivery. To assess risk associated with maternal race/ethnicity (self-report from the birth certificate) independent of socioeconomic status, we evaluated the following sociodemographic factors: insurance status at delivery, urban versus rural county of residence (from Federal Information Processing Standard [FIPS] codes: most urban [1–2], moderately rural [3–4], and most rural [5–6]), maternal and paternal educational attainment, and extent of prenatal care (classified as adequate, intermediate, and inadequate according to the adequacy of prenatal care utilization [APNCU] index[23]). The directed acyclic graph gives a conceptual framework for potential relationships among risk factors, mediators, and covariates (Fig 1).[10–12,20,24–37]

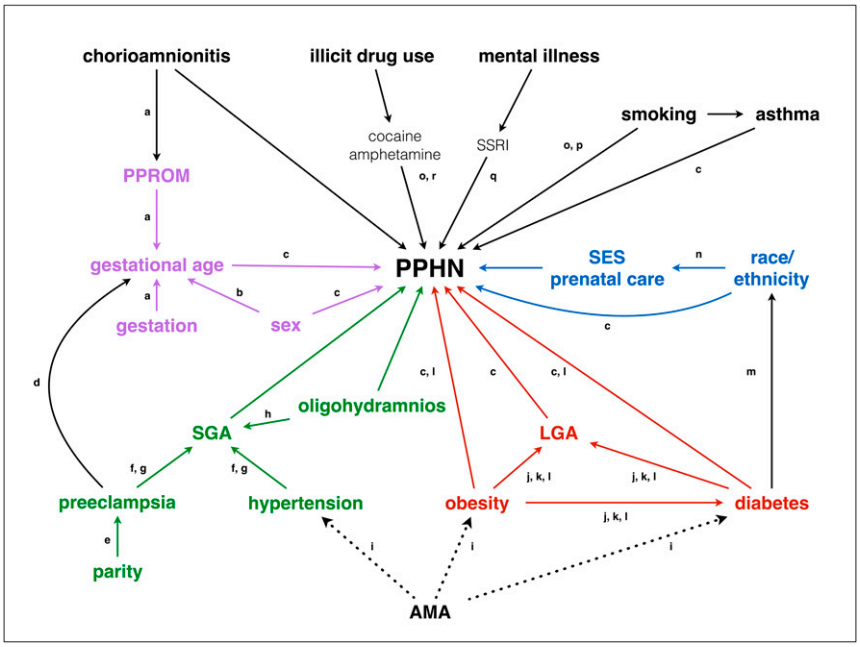

FIGURE 1

Directed acyclic graph for different risk factors for PPHN. a: Goldenberg et al 2008,[24] b: Peelen et al 2016,[25] c: Hernandez-Diaz et al 2007,[10] d: Shih et al 2003,[26] e: Long et al 1979,[27] f: Srinivas et al 2009,[28] g: Kaufmann 2003,[29] h: Magann et al 2011,[30] i: Cleary-Goldman et al 2005,[31] j: Metzger et al 2008,[32] k: Mitanchez et al 2014,[33] l: Radaelli et al 2003,[34] m: Ferdinand and Nassar 2015,[35] n: Blumenshine et al 2010,[36] o: Bearer et al 1997,[12] p: Van Marter et al 1996,[11] q: Huybrechts et al 2015,[20] r: Tseng et al 2014.[37] AMA, advanced maternal age; PPROM, preterm premature rupture of membranes; SES, socioeconomic status; SSRI, selective serotonin reuptake inhibitor.

We performed sensitivity analyses for potential outcome misclassification. As PPV for PPHN diagnosis by ICD-9 codes was higher in infants who were not transferred from the birth hospitals,[21] we restricted the analysis to infants who were either not transferred or had a PPHN diagnosis in both birth and transfer hospital records. To evaluate potential associations between risk factors and the severity, we restricted the outcome to severe PPHN, defined as a diagnosis of PPHN in the presence of a procedure code for positive pressure ventilation (procedure codes 96.70 and 93.90).

Associations are presented as crude (univariate) and adjusted risk ratios (RR) with 95% confidence intervals (CI). Poisson regression was used to

adjust for multiple covariates. The final multivariate model included all covariates. Kaplan-Meier curves were generated to compare mortality by underlying etiology of PPHN; hazard ratios with 95% CI were calculated. All analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC). The study protocol, by using de-identified data, was approved by the institutional review board of the Health and Human Services Agency of the State of California.

RESULTS

Population Characteristics

In this population-based cohort, the incidence of PPHN was 1.8 per 1000 live births (0.18%). The incidence in late preterm infants (34–36 weeks' GA) was highest at 5.4 per 1000 live births, compared with term infants at 1.6 per 1000 live births. The incidence of severe PPHN defined by need for positive pressure ventilation was 1.2 per 1000 live births (0.12%). Mortality in the first year of life was 7.6% for all infants with PPHN and 10.7% for infants with severe PPHN. Table 2 shows additional population characteristics.

Underlying Causes and Cause-Specific Mortality

The most common etiology for PPHN in this cohort was infection/sepsis (30.0%) (Table 3). In late preterm infants, infection/sepsis (42.7%), RDS (19.7%), and congenital anomalies of the respiratory system (9.2%) were more commonly associated with PPHN than in term infants (Table 3). One-year mortality was highly dependent on underlying etiology, highest in infants with other congenital anomalies of the respiratory system (32%), followed by CDH (25.0%), "other" (8%), and RDS (6.9%). Infants with underlying infection had a mortality of 6.2%.

TABLE 2 Baseline Characteristics of the Population

	Any PPHN	No PPHN
	n (%)	*n* (%)
	3277	1 777 879
GA, wk		
Mean GA (SD)	38.4 (1.8)	39.9 (1.4)
<37 wk	522 (15.9)	97 003 (5.5)
≥41 wk	324 (9.9)	141 622 (8.0)
Birth weight		
Mean birth weight, g (SD)	3318.3 (680.4)	3358.2 (483.8)
SGA	437 (13.3)	150 596 (8.5)
LGA	459 (14.0)	141 095 (7.9)
Mode of delivery		
Cesarean	1895 (57.8)	568 481 (32.0)
Race		
White not Hispanic	893 (27.3)	464 125 (26.1)
Hispanic	1492 (45.5)	882 498 (49.6)
Black	197 (6.0)	62 694 (3.5)
Asian	456 (13.9)	249 443 (14.0
Other	239 (7.3)	119 119 (6.7)
Sex		
Girls	1362 (41.6)	867 221 (48.8)
Gestation	1915 (58.4)	910 651 (51.2)
Singleton	3229 (98.5)	1 740 770 (97.9)
Twin	48 (1.5)	36 579 (2.1)
Multiple	530 (0.0)	0 (0.0)
Maternal education, y		
<12	821 (25.1)	446 160 (25.1)
12	812 (24.8)	414 016 (23.3)
>12	1514 (46.2)	853 334 (48.0)
Paternal education, y		
<12	752 (23.0)	422 614 (23.8)
12	834 (25.5)	423 340 (23.8)
>12	1290 (39.4)	749 628 (42.2)
Payment for delivery		
Private insurance	1566 (47.8)	876 120 (49.3)
Public insurance	1530 (46.7)	805 832 (45.3)
Self-pay	68 (2.1)	40 729 (2.3)
Other	101 (3.1)	52 608 (3.0)
FIPS code		
1–2, most urban	2522 (77.0)	1 357 687 (76.4)
3–4	682 (20.8)	385 818 (21.7)
5–6, most rural	56 (1.7)	23 510 (1.3)
Parity		
Nulliparous	1391 (42.5)	693 726 (39.0)
Prenatal care visits[a]		
Adequate	2206 (67.3)	1 233 257 (69.4)
Intermediate	333 (10.2)	184 908 (10.4)
Inadequate	637 (19.4)	309 001 (17.4)
Oligohydramnios	188 (5.7)	46 483 (2.6)
PROM	207 (6.3)	81 020 (4.6)
Chorioamnionitis	182 (5.6)	36 854 (2.1)
VSD	313 (9.6)	6904 (0.4)
ASD	971 (29.6)	10 684 (0.6)
PDA	1345 (41.0)	11 345 (0.6)
Maternal age, y		
<18	74 (2.3)	48 262 (2.7)
18–34	2421 (73.9)	1 389 770 (78.2)
>34	782 (23.9)	339 774 (19.1)
Maternal diabetes		
Any	465 (14.2)	149 785 (8.4)
Preexisting	121 (3.7)	15 857 (0.9)
Gestational	393 (12.0)	140 099 (7.9)
Maternal BMI[b]		

TABLE 2 Continued

	Any PPHN	No PPHN
	n (%)	*n* (%)
Underweight	97 (3.0)	67 501 (3.8)
Normal weight	1301 (39.7)	845 575 (47.6)
Overweight	782 (23.9)	418 827 (23.6)
Obese	776 (23.7)	298 823 (16.8)
Mental illness	97 (3.0)	31 579 (1.8)
Smoking during pregnancy	172 (5.3)	58 017 (3.3)
Illicit drug use	44 (1.3)	11 400 (0.6)
Maternal asthma	103 (3.1)	38 448 (2.2)
Hypertension		
Preexisting	50 (1.5)	14 515 (0.8)
Gestational	76 (2.3)	35 151 (2.0)
Preeclampsia	145 (4.4)	50 081 (2.8)
Mortality[c]	248 (7.6)	2258 (0.1)
Days to discharge home		
<7	567 (17.3)	1 690 290 (95.1)
7–14	954 (29.1)	37 316 (2.1)
15–29	651 (19.9)	9410 (0.5)
30–59	318 (9.7)	2517 (0.1)
≥60	193 (5.9)	2340 (0.1)
Undetermined/death before discharge	594 (18.1)	36 006 (2.0)
Positive pressure ventilation	2216 (67.6)	30 270 (1.7)
Transfer <7 d	1440 (43.9)	15 075 (0.9)

AGA, adequate for gestational age; ASD, atrial septal defect; CPAP, continuous positive airway pressure; FIPS, federal information processing system; GA, gestational age; LGA, large for gestational age; PROM preterm premature rupture of membranes; SGA, small for gestational age; VSD, ventricular septal defect.

[a] According to the APNCU index.

[b] Underweight: BMI <18.5; normal weight: BMI 18.5–24.9; overweight: BMI 25.0–29.9; obese: BMI ≥30.0.

[c] Mortality: death in the first year.

Mortality was lowest for infants with MAS and idiopathic PPHN (3.9% and 2.9%, respectively). After adjustment for GA, the hazard ratio for mortality was increased for all etiologies except MAS and RDS, compared with the idiopathic group: 11.3 (95% CI 6.6–19.2) for anomalies of the respiratory system, 9.6 (95% CI 5.6–16.2) for CDH, 2.8 (95% CI 1.5–5.3) for "other," 1.9 (95% CI 1.1–3.2) for infection, 1.8 (95% CI 0.9–3.5) for RDS, and 1.4 (95% CI 0.8–2.5) for MAS (Fig 2).

Risk Factors

In crude and adjusted analyses (Table 4), birth at 39 to 40 weeks' gestation had the lowest risk of PPHN, whereas late preterm infants (34–36 weeks' GA) had the highest risk of PPHN (adjusted RR 3.7, 95% CI 3.3–4.2). Girls were at lower risk than boys (adjusted RR 0.8, 95% CI 0.7–0.8). Both SGA and LGA infants had a higher risk of PPHN (adjusted RR 1.6, 95% CI 1.5–1.8, and 1.8, 95% CI 1.6–1.9, respectively). Maternal obesity and diabetes (gestational

TABLE 3 Etiology of PPHN According to GA

	GA, wk				
	All	34–36	37–38	39–40	≥ 41
	n (%)	n (%)	n (%)	n (%)	n (%)
Etiology	3277	522	936	1495	324
CDH	200 (6.1)	21 (4.0)	67 (7.2)	101 (6.8)	11 (3.4)
Other congenital anomalies of respiratory system	155 (4.7)	48 (9.2)	37 (4.0)	59 (4.0)	11 (3.4)
Agenesis of the lung	81 (2.5)	38 (7.3)	21 (2.2)	19 (1.3)	3 (0.9)
Other lung anomaly	11 (0.3)	3 (0.6)	0 (0.0)	7 (0.5)	1 (0.3)
Other respiratory anomaly	69 (2.1)	9 (1.7)	16 (1.7)	37 (2.5)	7 (2.2)
MAS[a]	799 (24.4)	30 (5.7)	126 (13.5)	476 (31.8)	167 (51.5)
Infection[b]	982 (30.0)	223 (42.7)	302 (32.3)	400 (26.8)	57 (17.6)
RDS	231 (7.1)	103 (19.7)	79 (8.4)	42 (2.8)	7 (2.2)
Other identified causes	264 (8.1)	26 (5.0)	114 (12.2)	110 (7.4)	14 (4.3)
Birth asphyxia	16 (0.5)	1 (0.2)	6 (0.6)	8 (0.5)	1 (0.3)
Cystic kidney	6 (0.2)	2 (0.4)	0 (0.0)	3 (0.2)	1 (0.3)
Cystic lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydrops fetalis	9 (0.3)	6 (1.1)	3 (0.3)	0 (0.0)	0 (0.0)
Interstitial emphysema	53 (1.6)	4 (0.8)	19 (2.0)	24 (1.6)	6 (1.9)
Neonatal leukemia	2 (0.1)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Polycythemia	33 (1.0)	0 (0.0)	14 (1.5)	16 (1.1)	3 (0.9)
Renal agenesis	2 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Hypoxic-ischemic encephalopathy	29 (0.9)	4 (0.8)	11 (1.2)	12 (0.8)	2 (0.6)
Trisomy 21	144 (4.4)	11 (2.1)	73 (7.8)	58 (3.9)	2 (0.6)
Idiopathic	646 (19.7)	71 (13.6)	211 (22.5)	307 (20.5)	57 (17.6)

[a] A total of 407 infants with MAS also had infection, 42 infants with MAS also had RDS, and 123 infants with MAS also had infection and RDS.

[b] A total of 351 infants with infection also had RDS.

TABLE 4 Crude and Adjusted RRs and 95% 95% CIs for the Association Between Selected Characteristics and PPHN (n = 2902)

	Crude RR (CI)	Adjusted RR (CI)
Gestational age, wk		
34–36	3.6 (3.3–4.1)	3.7 (3.3–4.2)
37–38	1.3 (1.2–1.5)	1.3 (1.2–1.4)
39–40	Reference	Reference
≥41	1.7 (1.5–1.9)	1.5 (1.3–1.7)
Sex		
Boys	Reference	Reference
Girls	0.7 (0.7–0.8)	0.8 (0.7–0.8)
Race		
White not Hispanic	Reference	Reference
Hispanic	0.9 (0.8–0.9)	0.8 (0.7–0.9)
Black	1.7 (1.4–2.0)	1.3 (1.1–1.6)
Asian	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Other	1.0 (0.9–1.2)	0.9 (0.8–1.1)
Birth weight		
AGA	Reference	Reference
SGA	1.7 (1.5–1.9)	1.6 (1.5–1.8)
LGA	2.2 (2.0–2.4)	1.8 (1.6–2.0)
Maternal Diabetes		
None	Reference	Reference
Preexisting	4.5 (3.7–5.5)	2.8 (2.3–3.4)
Gestational	1.7 (1.5–1.9)	1.3 (1.2–1.5)
Maternal BMI[a]		
Underweight	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Normal weight	Reference	Reference
Overweight	1.2 (1.1–1.3)	1.1 (1.0–1.2)[b]
Obese	1.7 (1.6–1.9)	1.3 (1.2–1.5)
Hypertension		
None	Reference	Reference
Preexisting	1.9 (1.4–2.6)	1.0 (0.8–1.4)
Gestational	1.2 (0.9–1.5)	0.8 (0.7–1.1)
Preeclampsia		
None	Reference	Reference
Any	1.7 (1.4–2.0)	0.9 (0.7–1.0)
Maternal asthma		
No	Reference	Reference
Yes	1.4 (1.1–1.7)	1.1 (0.9–1.4)
Smoking during pregnancy		
No	Reference	Reference
Yes	1.6 (1.4–1.9)	1.3 (1.1–1.6)
Illicit drug use		
No	Reference	Reference
Yes	2.3 (1.7–3.1)	1.3 (0.9–2.0)
Mental illness		
No	Reference	Reference
Yes	1.7 (1.4–2.1)	1.1 (0.9–1.5)
Maternal age, y		
<18	0.8 (0.6–1.0)	0.9 (0.7–1.2)
18–34	Reference	Reference
>34	1.4 (1.2–1.5)	1.2 (1.1–1.3)
Parity		
Nulliparous	1.1 (1.1–1.2)	1.2 (1.1–1.3)
Multiparous	Reference	Reference
Mode of delivery		
Vaginal	Reference	Reference
Cesarean	3.0 (2.8–3.2)	2.6 (2.4–2.8)
Gestation		
Singleton	Reference	Reference
Multiple	0.7 (0.5–1.0)[b]	0.3 (0.2–0.3)
Oligohydramnios	1.9 (1.6–2.2)	1.4 (1.2–1.6)
PROM	1.4 (1.2–1.6)	1.0 (0.9–1.2)
Chorioamnionitis	2.9 (2.4–3.3)	2.3 (1.9–2.7)

TABLE 4 Continued

	Crude RR (CI)	Adjusted RR (CI)
Maternal education, y		
<12	0.9 (0.8–1.0)[b]	1.0 (0.9–1.1)
12	Reference	Reference
>12	0.9 (0.8–1.0)[b]	0.9 (0.8–1.0)[b]
Paternal education, y		
<12	0.9 (0.8–1.0)[b]	0.9 (0.8–1.1)
12	Reference	Reference
>12	0.9 (0.8–1.0)[b]	0.9 (0.8–1.0)
Payment for delivery		
Private insurance	Reference	Reference
Public insurance	1.0 (1.0–1.1)	1.1 (1.0–1.2)
Self-pay	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Other	1.1 (0.8–1.3)	1.0 (0.8–1.3)
FIPS code		
1–2, urban	Reference	Reference
3–4, moderately rural	0.9 (0.9–1.0)	1.0 (0.9–1.0)
5–6, rural	1.2 (0.9–1.6)	1.2 (0.9–1.6)
Prenatal care[c]		
Adequate	Reference	Reference
Intermediate	1.0 (0.9–1.1)	1.1 (0.9–1.2)
Inadequate	1.1 (1.0–1.1)[b]	1.1 (1.0–1.3)[b]

Cases with CDH, congenital anomalies of the respiratory tract, and congenital renal anomalies are excluded from this analysis.
[a] Underweight: BMI <18.5 kg/m^2; normal weight: BMI 18.5–24.9 kg/m^2; overweight: BMI 25.0–29.9 kg/m^2; obese: BMI ≥30.0 kg/m^2.
[b] $P < .05$.
[c] According to the APNCU index.

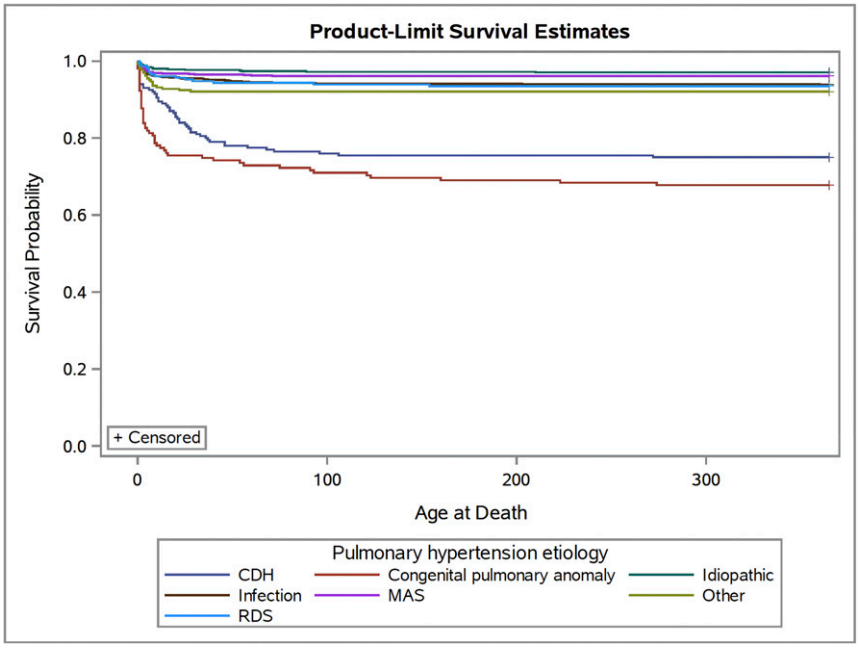

FIGURE 2
Kaplan-Meyer curve for cause-specific 1-year survival in late preterm and term infants with PPHN.

and preexisting) were independent risk factors in multivariate analysis (adjusted RR for maternal obesity 1.3, 95% CI 1.2–1.5; for preexisting maternal diabetes 2.8, 95% CI 2.3–3.4; and for gestational diabetes 1.3, 95% CI 1.2–1.5). Preeclampsia (crude RR 1.7, 95% CI 1.4–2.0) and maternal preexisting hypertension (crude RR 1.9, 95% CI 1.4–2.6) predicted PPHN in the crude analyses but not after multivariate adjustment.

Maternal asthma and smoking were both associated with PPHN in the crude analysis, but only smoking remained a significant risk factor after adjusting for asthma, a potential intermediate in the causal pathway of smoking and PPHN (RR 1.3, 95% CI 1.1–1.6) (Fig 1, Table 4).

Maternal Race/Ethnicity

In multivariate analysis adjusting for socioeconomic status and demographic factors, black race remained associated with an increased risk of PPHN (adjusted RR 1.3, 95% CI 1.1–1.5); Hispanic ethnicity was protective (adjusted RR 0.8, 95% CI 0.7–0.9) (Table 4). CDH and infection were less common among infants of black mothers (3.6% and 25.9%, respectively). Other malformations of the respiratory system were most prevalent in Hispanic infants (6%) and infection was most common among Asian infants with PPHN (32.9%). One-year mortality was highest in Hispanic infants (8.2%) and lowest in white infants (6.4%) (Table 5).

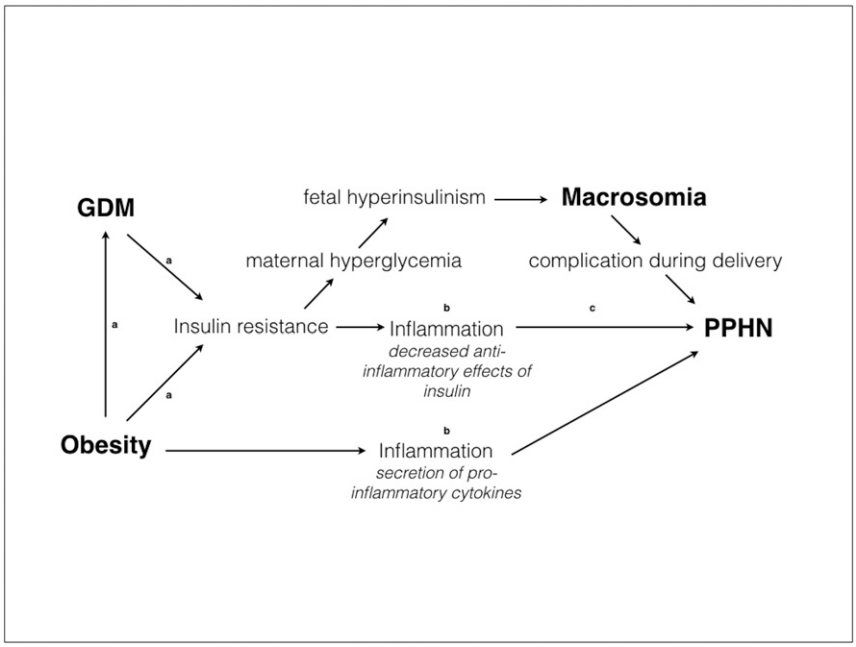

FIGURE 3
Potential causal relationship among obesity, gestational diabetes, macrosomia, and PPHN. a: Kahn et al 2006,[43] b: Dandona et al 2004,[44] c: Radaelli et al 2003.[34,45] GDM, gestational diabetes mellitus.

Sensitivity Analyses

Neither excluding transferred cases with the diagnosis of PPHN in only birth or transfer hospital record nor restricting the analysis to infants with more severe PPHN altered the risk factor profile (Supplemental Table 6).

DISCUSSION

In this population-based cohort of late preterm and term infants, the incidence of PPHN was 1.8 per 1000 live births. Interestingly, the incidence of PPHN in late preterm infants (34–36 weeks' GA) was highest at 5.4 per 1000 live births. The main underlying cause of PPHN was infection/sepsis. We observed a relatively low 1-year mortality of 7.6% for infants with PPHN that varied by etiology. Additional risks for PPHN (race/ethnicity, sex, fetal growth, and length of gestation, maternal diabetes, obesity, smoking, and advanced age) were established.

Although this is the largest and most complete population-based epidemiologic study to date on PPHN, similarities and differences between our studies and others should be noted. Walsh-Sukys and colleagues[4] provided important epidemiologic information from a multicenter study of 12 NICUs in the US-based Neonatal Research Network. This study examined 385 infants with PPHN and GA of 34 to 43 weeks and reports an overall incidence of 1.9 per 1000 live births, comparable to the incidence of 1.8 per 1000 live births reported in the current study. However, the definition of PPHN in the former study is based on more stringent criteria, similar to our definition of severe PPHN. For this more severely affected group, we report a lower incidence of PPHN (1.2/1000 live births) compared with the study of Walsh-Sukys and colleagues.[4] This difference may be attributable to the underlying study design. Multicenter studies can lead to referral bias for population-based epidemiologic measures as patients admitted to an institution may not fully represent the cases originated in the community in frequency or severity.[38,39] Further differences in study populations may have contributed to the difference in incidence estimates. For example, in the study by Walsh-Sukys et al,[4] the proportion of black infants was higher, but Hispanic ethnicity was not examined. The mortality rate for infants with severe PPHN in the current study was only slightly lower than the mortality rate reported in the study by Walsh-Sukys et al[4] (10.7% vs 12%, respectively). We report a lower overall mortality rate of 7.6% for all cases with PPHN, which is consistent with multicenter studies evaluating iNO (7%–15%).[6–8]

Although PPHN is often thought to be a disease of postterm infants, our study shows that late preterm infants are at highest risk of PPHN, and early term infants (37–38 weeks) are at higher risk compared with the reference group (39–40 weeks). The incidence of PPHN in this late preterm age group is much higher at 5.4 per 1000 live births and more likely to be due to RDS or infection than in term infants. Our data suggest that clinicians caring for late preterm infants should be aware of the increased risk in this patient group and monitor these infants for PPHN, as its early recognition may avert serious consequences.

The diagnosis of RDS might contribute to the higher risk for PPHN in late preterm infants: severe RDS causes hypoxic pulmonary vasoconstriction and is associated with PPHN.[40] However, female sex is protective against severe RDS because of advanced fetal pulmonary maturity,[41,42] which might explain the protective effect of female sex on PPHN after adjustment for multiple factors in our study (Fig 1).
In contrast, although black race is protective against RDS, our study confirms the previously identified elevated risk for PPHN in black infants,[9–11] suggesting that the increased susceptibility is not related

TABLE 5 Selected Characteristics Between Different Race/Ethnicities of Cases With PPHN

	White Not Hispanic	Hispanic	Black	Asian	Other
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sample	893	1492	197	456	239
PPHN cause					
CDH	59 (6.6)	96 (6.4)	7 (3.6)	22 (4.8)	16 (6.7)
Congenital pulmonary anomaly	34 (3.8)	89 (6.0)	8 (4.1)	16 (3.5)	8 (3.4)
MAS	163 (18.3)	416 (27.9)	64 (32.5)	99 (21.7)	57 (23.9)
Infection	243 (27.2)	471 (31.6)	49 (25.9)	150 (32.9)	69 (28.9)
RDS	101 (11.3)	83 (5.6)	11 (5.6)	20 (4.4)	16 (6.7)
Other identified causes	86 (9.6)	102 (6.8)	8 (4.1)	42 (9.2)	26 (10.9)
Idiopathic	207 (23.2)	235 (15.8)	50 (25.4)	107 (23.5)	47 (19.7)
Gestational age, wk					
34–36	172 (19.3)	233 (15.6)	26 (13.2)	59 (12.9)	32 (13.4)
37–38	269 (30.1)	431 (28.9)	51 (25.9)	125 (27.4)	60 (25.1)
39–40	371 (41.6)	679 (45.5)	92 (46.7)	235 (51.5)	118 (49.4)
≥41	81 (9.1)	149 (10.0)	28 (14.2)	37 (8.1)	29 (12.1)
Birth weight					
SGA	78 (8.7)	228 (15.3)	27 (13.7)	68 (14.9)	36 (15.1)
LGA	133 (14.9)	212 (14.2)	40 (20.3)	39 (8.6)	35 (14.6)
Mode of delivery					
Cesarean	479 (53.6)	906 (60.7)	126 (64.0)	239 (52.4)	145 (60.7)
Sex					
Boys	530 (59.4)	864 (57.9)	118 (59.9)	260 (57.0)	143 (59.8)
Girls	363 (40.7)	628 (42.1)	79 (40.1)	196 (43.0)	96 (40.2)
Gestation					
Singleton	865 (96.9)	1483 (99.4)	195 (99.9)	450 (98.7)	236 (98.7)
Twin	28 (3.1)	9 (0.6)	2 (1.0)	6 (1.3)	3 (1.3)
Maternal education, y					
<12	46 (5.2)	675 (45.2)	33 (16.8)	1 (4.6)	47 (19.7)
12	200 (22.4)	419 (28.1)	56 (28.4)	85 (18.6)	52 (21.8)
>12	629 (70.4)	374 (25.1)	94 (47.7)	339 (74.3)	78 (32.6)
Paternal education, y					
<12	30 (3.4)	655 (43.9)	18 (9.1)	15 (3.3)	34 (14.2)
12	234 (26.2)	404 (27.1)	57 (28.9)	89 (19.5)	50 (20.9)
>12	560 (62.7)	263 (17.6)	67 (34.0)	326 (71.5)	74 (31.0)
Payment for delivery					
Private insurance	636 (71.2)	410 (27.5)	78 (39.6)	322 (70.6)	120 (50.2)
Public insurance	209 (23.4)	996 (66.8)	109 (55.3)	107 (23.5)	109 (45.6)
Self-pay	9 (1.0)	41 (2.8)	2 (1.0)	11 (2.4)	5 (2.1)
Other[a]	35 (3.9)	40 (2.7)	7 (3.6)	15 (3.3)	4 (1.7)
FIPS code					
1–2	622 (69.7)	1147 (76.9)	177 (89.9)	381 (83.6)	195 (81.6)
3–4	222 (24.9)	328 (22.0)	19 (9.6)	73 (16.0)	40 (16.7)
5–6	40 (4.5)	11 (0.7)	1 (0.5)	0 (0.0)	4 (1.7)
Parity					
Nulliparous	393 (44.0)	573 (38.4)	95 (48.2)	228 (50.0)	102 (42.7)
Multiparous	500 (56.0)	919 (61.6)	102 (51.8)	228 (50.0)	134 (56.1)
Prenatal care visits[b]					
Adequate	638 (71.4)	982 (65.8)	120 (60.9)	312 (68.4)	154 (64.4)
Intermediate	96 (10.8)	153 (10.3)	17 (8.6)	47 (10.3)	20 (8.4)
Inadequate	136 (15.3)	308 (20.6)	49 (24.9)	87 (19.1)	57 (23.9)
Oligohydramnios	43 (4.8)	100 (6.7)	10 (5.1)	23 (5.3)	11 (4.6)
PROM	78 (8.7)	83 (5.6)	7 (3.6)	34 (7.5)	5 (2.1)
Chorioamnionitis	35 (3.9)	79 (5.3)	18 (9.1)	38 (8.3)	12 (5.0)
Minor cardiac defect					
VSD	62 (6.9)	193 (12.9)	7 (3.6)	33 (7.2)	18 (7.5)
ASD	263 (29.5)	460 (30.8)	55 (27.9)	122 (26.8)	71 (29.7)
PDA	342 (39.3)	627 (42.0)	83 (42.1)	204 (44.7)	89 (37.2)
Maternal age, y					
<18	10 (1.1)	45 (3.0)	9 (4.6)	2 (0.4)	8 (3.4)
18–34	640 (71.7)	1128 (75.8)	155 (78.7)	329 (72.2)	169 (70.7)
>34	243 (27.2)	219 (21.4)	33 (16.8)	125 (27.4)	62 (25.9)

TABLE 5 Continued

	White Not Hispanic	Hispanic	Black	Asian	Other
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Maternal diabetes					
Any	85 (9.5)	236 (15.8)	32 (16.2)	74 (16.3)	38 (15.9)
Preexisting	31 (3.5)	63 (4.2)	9 (4.6)	10 (2.2)	8 (3.4)
Gestational	64 (7.2)	201 (13.5)	28 (14.2)	69 (15.1)	31 (13.0)
Maternal BMI[b]					
Underweight	24 (2.7)	28 (1.9)	6 (3.1)	36 (7.9)	3 (1.3)
Normal weight	447 (50.1)	464 (31.1)	60 (30.5)	245 (53.7)	85 (35.6)
Overweight	190 (21.3)	404 (27.1)	45 (22.8)	85 (18.6)	58 (24.3)
Obese	176 (19.7)	428 (28.7)	55 (27.9)	48 (10.5)	69 (28.9)
Mental illness	46 (5.2)	29 (1.9)	10 (5.1)	2 (0.4)	10 (4.2)
Smoking during pregnancy	67 (7.5)	49 (3.3)	19 (9.6)	16 (3.5)	21 (8.8)
Illicit drug use	16 (1.8)	16 (1.1)	8 (4.1)	0 (0.0)	4 (1.7)
Maternal asthma	39 (4.4)	38 (2.6)	13 (6.6)	6 (1.3)	7 (2.9)
Hypertension					
Preexisting	19 (2.1)	19 (1.3)	3 (1.5)	5 (1.1)	4 (1.7)
Gestational	14 (1.6)	42 (2.8)	9 (4.6)	7 (1.5)	4 (1.7)
Preeclampsia	38 (4.3)	63 (4.2)	16 (8.1)	13 (2.9)	15 (6.3)
Mortality[c]	57 (6.4)	122 (8.2)	15 (7.6)	35 (7.7)	19 (8.0)
CPAP or mechanical ventilation	596 (66.7)	1018 (68.2)	132 (67.0)	307 (67.3)	163 (68.2)

ASD, atrial septal defect; CPAP, continuous positive airway pressure; FIPS, federal information processing system; GA, gestational age; LGA, large for gestational age; PROM, preterm premature rupture of membranes; SGA, small for gestational age; VSD, ventricular septal defect.

[a] Underweight: BMI <18.5 kg/m^2; normal weight: BMI 18.5–24.9 kg/m^2; overweight: BMI 25.0–29.9 kg/m^2; obese: BMI ≥30.0 kg/m^2.

[b] According to the APNCU index.

[c] Mortality: death in the first year.

to lung maturity after adjustment for prematurity and maternal factors (Fig 1). In contrast to the findings of Hernández-Díaz and colleagues,[10] in our study, Asian infants were not at increased risk for PPHN. Given the large percentage of Hispanic births in California, we were able to demonstrate that Hispanic ethnicity was protective against PPHN, but did not result in decreased mortality. Further studies should focus on potential underlying causes explaining these differences.

Perturbed fetal growth due to maternal factors has been implicated as an important contributor to PPHN (Fig 1). Although macrosomia, diabetes, and maternal obesity are interrelated, we found them to be independent risk factors for PPHN. Diabetes and maternal obesity have been associated with multiple poor pregnancy outcomes in studies on fetal macrosomia[32,33]; however, their independent association with PPHN has been inconsistent.[10,11] Potential causal links between maternal obesity, gestational diabetes, macrosomia, and PPHN mediated through inflammation are shown in Fig 3.[34,43,44] This proinflammatory environment can affect fetal lung development.[34] Thus, there is good rationale that these factors might lead to PPHN. Additionally, maternal hyperglycemia leads to upregulation of fetal insulin and macrosomia, which is associated with delivery complications attributed to fetal macrosomia,[33] some of which (hypoxia-ischemia) can lead to the development of PPHN. By adjusting for gestational diabetes and macrosomia, we quantified the effect of obesity mediated through inflammation and insulin resistance without overt diabetes on PPHN. Similarly, by adjusting for obesity and macrosomia, we quantified the effect of gestational diabetes mediated through inflammation on PPHN. Previous studies did not distinguish between the effects of gestational and preexisting diabetes on PPHN, yet we find the strongest association with preexisting diabetes, possibly reflecting a chronic proinflammatory state with a stronger effect on fetal lung maturation.

This study identified SGA as a newly recognized risk factor for PPHN not previously reported in case-control studies. SGA is commonly used as a proxy for intrauterine growth restriction from placental dysfunction impairing nutrient and oxygen delivery to the fetus. There is evidence for a strong link between placental dysfunction, preeclampsia, and maternal hypertension (Fig 1).[28,29] However, after adjusting for covariates, these 2 risk factors were not associated with PPHN. This suggests that the association between SGA and PPHN is mediated through a different mechanism, possibly via decreased pulmonary alveolar and vessel growth or pulmonary artery endothelial cell dysfunction (Fig 1).[46]

Maternal smoking and asthma have been implicated as risk factors for PPHN because both conditions can cause fetal hypoxemia.[10,12] Bearer and colleagues[12] found increased cotinine (nicotine metabolite) levels in infants with PPHN compared

with controls. However, they and others failed to show a statistically significant association between PPHN and maternal smoking, with limited power and potential underreporting of smoking.[10,11] In our analysis, smoking is a significant risk factor in the crude and multivariate analysis. The crude RR for smoking quantifies the total effect of smoking on PPHN, by adjusting for asthma, the RR represents the effect not mediated through asthma (Fig 1). Although Hernández-Díaz and colleagues[10] report asthma as a risk factor for PPHN, they did not adjust for maternal smoking status, which acts as a potential confounder in this relationship. Alternatively, in this administrative dataset, maternal asthma might be underreported, as the rates of asthma are low compared with contemporary population-based US estimates.[47]

A major strength of this study is its large sample size. With 3277 cases of PPHN, we investigate multiple concurrent risk factors without concerns for multiple comparison testing. Population-based data allow us to present RRs that are more intuitive to clinicians than odds ratios presented in case-control studies.[48,49] Additionally, this study was not restricted to infants treated in referral centers. The greatest challenge using administrative data are correct ascertainment of the diagnosis. We used the same ICD-9 codes as Huybrechts et al,[20] who report a somewhat higher incidence of PPHN of 2.1 per 1000 live births, but they included cases with major CHD. However, we cannot exclude that either cases have been missed based on ICD-9 codes used or that ICD-9 codes for PPHN have been overused, and infants without PPHN were labeled as PPHN cases. Future population-based studies may determine whether our data reflect contemporary mortality rates in the post-iNO era.

Some misclassification of risks may have occurred given that we could explore only factors reported by ICD-9 codes.[50] For example, there is no information on maternal medication use by which to assess the effect of maternal antidepressant use on PPHN. We were also not able to evaluate the effect of emergent versus planned cesarean delivery, the use of extracorporeal membrane oxygenation, and the timing of sepsis/infection. However, sensitivity analyses excluding infants with milder PPHN and infants with the lowest PPV for PPHN[21] showed limited differences in risk factors. This strengthens the validity of our results, despite our potential study limitations.

In conclusion, in this large, population-based study, we found that fetal environmental, developmental, and genetic effects are likely important in the development of PPHN, across the spectrum of etiologies. In contrast, socioeconomic factors play a minor role as risks for PPHN.

The expanded profile of risk factors may help clinicians identify infants at higher risk for PPHN, as these infants are at increased risk for rapid clinical deterioration. Further, these data may be used to better understand the underlying pathophysiology of PPHN, which may help identify targeted therapies and prevention strategies.

ABBREVIATIONS

AGA: adequate for gestational age
APNCU: adequacy of prenatal care utilization
ASD: atrial septal defect
CDH: congenital diaphragmatic hernia
CI: confidence interval
FIPS: Federal Information Processing Standard
GA: gestational age
ICD: *International Classification of Diseases, Ninth Revision*
iNO: inhaled nitric oxide
LGA: large for gestational age
MAS: meconium aspiration syndrome
PDA: patent ductus arteriosus
PPHN: persistent pulmonary hypertension of the newborn
PPV: positive predictive value
PROM: premature rupture of membranes
RDS: respiratory distress syndrome
RR: risk ratio
SGA: small for gestational age
VSD: ventricular septal defect

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