

ORIGINAL ARTICLE

Increased risk for respiratory distress among white, male, late preterm and term infants

JS Anadkat^{1,4}, MW Kuzniewicz^{2,3,4}, BP Chaudhari^{1,4}, FS Cole¹ and A Hamvas¹

¹Division of Newborn Medicine, The Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St Louis, MI, USA; ²Division of Neonatology, University of California, San Francisco, Department of Pediatrics, San Francisco, CA, USA and ³Division of Research, Northern California Kaiser Permanente, Oakland, CA, USA

Objective: To determine whether race/ethnicity and sex independently increase risk of respiratory distress syndrome (RDS) in late preterm and term infants.

Study Design: Using a cohort design, we studied the risk of RDS associated with race/ethnicity and sex in infants with gestational age (GA) 34 to 42 weeks born between 1 January 2000 and 31 December 2009 ($n = 286\,454$) within 12 hospitals in the Northern California Kaiser Permanente Medical Care Program.

Result: Male sex (adjusted odds ratio (aOR) 1.68; 95% confidence interval 1.45 to 1.93) and White race/ethnicity (vs Asians (aOR 0.57; 95% confidence interval 0.47 to 0.70), Blacks (aOR 0.66; 95% confidence interval 0.50 to 0.87), and Hispanics (aOR 0.76; 95% confidence interval 0.64 to 0.90)) independently increase risk for RDS regardless of GA. A GA <39 weeks, operative delivery, maternal diabetes, and chorioamnionitis also increased RDS risk in this cohort.

Conclusion: Male sex and White race/ethnicity independently increase risk for RDS in late preterm and term infants. Timing of elective delivery should acknowledge these risks.

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Keywords: neonatal respiratory; respiratory distress syndrome; late preterm infants; term infants

Introduction

Risk of neonatal respiratory distress syndrome (RDS) is inversely associated with gestational age (GA) owing to developmental delay in production of the pulmonary surfactant. In extremely premature (birth weight <1000 g, <27 weeks GA) and very premature (birth weight <1500 g, <32 weeks GA) infants, male sex, maternal

diabetes, White race, chorioamnionitis and operative delivery also increase risk and severity of RDS.^{1–6} However, the associations of sex and race/ethnicity with RDS risk have not been characterized in late preterm and term infants. When compared with term infants, late preterm infants (34^{0/7} weeks and 36^{6/7} weeks GA) have higher rates of RDS and other non-respiratory morbidities that often require technological and pharmacological interventions and prolonged hospital stays.^{7–17} Although preterm and late preterm birth rates have declined in the last 5 years, a substantial fraction of infants (12.3% in the United States) is still delivered before 37 weeks gestation, most of whom (70%) are late preterm infants.^{8,18} Term infants have increased risk of RDS through 39 weeks of gestation.² To determine whether race/ethnicity and sex independently increase risk of RDS in late preterm and term infants, we used a standardized diagnosis of RDS in a multihospital-based cohort of racially and ethnically diverse, late preterm and term infants from the Northern California Kaiser Permanente Medical Care Program (NC-KPMCP). We found that male sex and White race/ethnicity independently increase risk for RDS in late preterm and term infants.

Methods

Using a clinical information system employed at all NC-KPMCP facilities that links maternal and neonatal records and clinical records to multiple information systems (for example, laboratory and hospitalization data),^{19–22} we identified all live-born infants delivered at 12 NC-KPMCP facilities between 1 January 2000, and 31 December 2009 with a GA of 34 to 42 weeks ($n = 290\,355$). We excluded patients with unknown sex determination ($n = 14$), congenital heart disease ($n = 764$) and other major congenital defects ($n = 1574$). To avoid confusion with other conditions that may present with respiratory distress at birth, we excluded infants with a diagnosis of meconium aspiration syndrome ($n = 1950$) or culture-positive sepsis in the 1st four days of life ($n = 195$). Some infants met multiple exclusion criteria. The final analysis cohort consisted of 286 454 infants.

Correspondence: Dr JS Anadkat, Washington University in St Louis, 660 S. Euclid Ave., Campus Box 8116, St Louis, MO 63110, USA.

E-mail: anadkat_j@kids.wustl.edu

⁴These authors contributed equally to this work.

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Case definition was based on Vermont Oxford Network criteria for RDS (impairment in oxygenation and a chest radiograph consistent with RDS), or surfactant administration.²³ GA was entered as completed weeks of gestation from the obstetrical medical record and was based on last menstrual period, and

was confirmed or modified by fetal ultrasound. We classified infants as small for GA, appropriate for GA or large for GA based on birth weight and GA in comparison with the 10th and 90th percentiles of Fenton growth curves.²⁴ We determined mode of delivery (vaginal versus cesarean section) from maternal The International Classification of Diseases-9th revision procedure codes and the infant's medical record. Data regarding indications for cesarean section delivery was not available to be collected for analysis. We assigned multiplicity of gestation (singleton versus higher-order) based on infants' sharing the same maternal medical record number and maternal admission date to labor and delivery. Race/ethnicity of the infant was based on maternal self-report. We created a combined race/ethnicity designation by first classifying subjects' ethnicity as Hispanic or non-Hispanic. We further subdivided non-Hispanic subjects according to race into White, Black, Asian and American Indian/Eskimo. Parents could designate race as other if they did not identify with any of these discrete designations. If race/ethnicity was not recorded, the infant's race/ethnicity was assigned as unknown. We assigned maternal diagnoses of diabetes (including gestational) (250 to 250.9; 648.0 to 638.04; 775), pre-eclampsia/eclampsia (642.4 to 642.63), chorioamnionitis (658.4 to 658.43; 762.7), and prolonged rupture of membranes (658.2 to 658.23) based on The International Classification of Diseases-9th revision diagnosis codes. We extracted the use of surfactant and mechanical ventilation from each infant's medical record.

We compared demographic characteristics of infants with and without RDS using χ^2 -tests and the Mann-Whitney test, when appropriate. We created a multivariate logistic regression model with RDS as the dependent variable, and sex, race/ethnicity, GA, size for GA, mode of delivery, multiplicity of gestation,

Table 1 Infant demographics

Predictor	No. RDS (N = 286,559)	RDS (N = 895)	P Value
Male	145,973 (51.1%)	588 (65.7%)	<0.001
<i>Race and ethnicity</i>			
White	116,712 (40.73%)	471 (47.48%)	<0.001
Hispanic	72,061 (25.15%)	222 (22.38%)	
Black	19,879 (6.94%)	74 (7.46%)	
Asian	56,992 (19.89%)	163 (16.43%)	
American Indian	902 (0.31%)	6 (0.60%)	
Other	13,500 (4.71%)	36 (3.63%)	
Unknown	6,473 (2.26%)	20 (2.02%)	
Gestational age (weeks)	39.0 ± 1.5	36.2 ± 2.2	<0.001
Birth weight (g)	3421 ± 520	2880 ± 729	<0.001
<i>Size for gestational age</i>			
SGA	17,507 (6.1%)	64 (7.2%)	<0.001
LGA	20,908 (7.32%)	102 (11.4%)	
Cesarean delivery	68,636 (24.0%)	512 (57.2%)	<0.001
Multiple gestation	8,130 (2.9%)	158 (17.7%)	<0.001
Mechanical ventilation	452 (0.2%)	401 (44.8%)	<0.001

Abbreviations: LGA, large for gestational age; RDS, respiratory distress syndrome; SGA, small for gestational age.

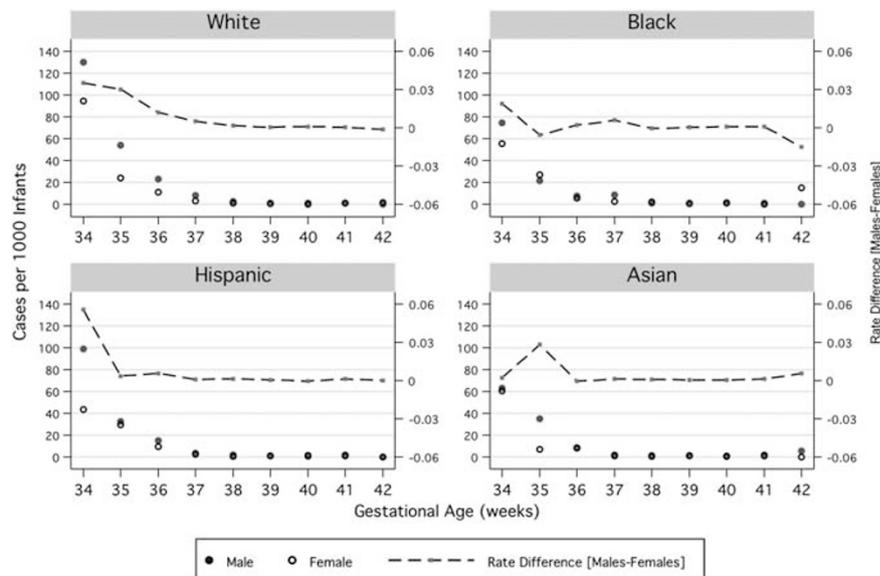


Figure 1 Race- and sex-specific risk of RDS by GA (circles, left Y axis) and absolute difference in risk between sexes (dashed line, right Y axis).

pre-eclampsia/eclampsia, maternal diabetes, chorioamnionitis and prolonged rupture of membranes as predictor variables. We chose variables on the basis of prior studies of risk factors for RDS in lower GA populations.^{25–28} Data from a subgroup of infants admitted to a level III Neonatal Intensive Care Unit (6.43% of the cohort) included antenatal glucocorticoid administration and permitted analysis of differential administration by race/ethnicity and sex. We calculated odds ratios for each predictor variable along with 95% confidence intervals and tested hypotheses using a two-sided $\alpha = 0.05$. To explore effects of interactions of race or GA with sex on the risk for RDS, we calculated race- and GA-specific odds ratios, adjusting for size for GA, mode of delivery, multiplicity of gestation pre-eclampsia/eclampsia and maternal diabetes. We conducted all analyses using STATA v.9.2 (StataCorp LP, College Station, TX, USA). The NC-KPMCP Institutional Review Board approved this project.

Results and discussion

The overall incidence of RDS in this cohort was 0.31% ($n = 895$), with incidence in late preterm infants of 3.22% and in term infants of 0.12%. Infants with RDS were more likely to be male, White, of lower GA and delivered by cesarean section. Our data analysis showed RDS infants to be either SGA or LGA. Among infants with RDS, 44.8% required mechanical ventilation and 38.9% received surfactant (Table 1).

To characterize the relationships among GA, sex, and race/ethnicity and the absolute risk of RDS, we plotted the crude incidence of RDS by GA for each race and sex category (Figure 1). At 34 weeks of GA, White males had the highest risk of RDS (13.0%), whereas Hispanic females had the lowest risk of RDS (4.3%). In each race/ethnicity and sex category, risk for RDS decreased with increasing GA until 37 weeks of gestation. Regardless of race/ethnicity, females had a lower incidence of RDS than males. In Whites, the absolute risk difference between males and females persisted until approximately 38 weeks of GA. However, the difference decreased with advancing GA. In the other race/ethnicity categories, we observed no consistent differences between males and females after 34 weeks GA, except for an unexplained large difference between Asian males and females at 35 weeks (0.7% in females and 3.5% in males).

In the multivariate logistic regression model, GA was the strongest predictor of RDS (Table 2). Compared with infants born at 40 weeks GA, those born at 34 weeks GA had an adjusted odds ratio (aOR) for RDS of 114.12 (95% confidence interval 84.71 to 153.74). Even infants born at 38 weeks gestation had a greater risk of RDS (aOR 1.67; 95% confidence interval 1.16 to 2.41). After adjusting for other covariables, males still had a greater risk of RDS than females (aOR 1.68; 95% confidence interval 1.45 to 1.93). Consistent with previously reported racial/ethnic risk

Table 2 Multivariate logistic regression

Variable	OR	95% Confidence interval		P value
		(Lower limit)	(Upper limit)	
Male	1.68	1.45	1.93	<0.001
<i>Gestational age (weeks)</i>				
34	114.12	84.71	153.74	<0.001
35	41.03	30.13	55.87	<0.001
36	15.43	11.22	21.21	<0.001
37	4.80	3.40	6.79	<0.001
38	1.67	1.16	2.41	0.005
39	1.16	0.82	1.62	0.4
40	Reference			
41	1.29	0.86	1.95	0.22
42	1.08	0.34	3.45	0.90
<i>Size for gestational age</i>				
AGA	Reference			
SGA	0.87	0.67	1.14	0.31
LGA	0.95	0.76	1.19	0.66
Cesarean delivery	2.64	2.29	3.05	<0.001
Multiple gestation	0.80	0.66	0.97	0.024
<i>Race and ethnicity</i>				
White	Reference			
American Indian/eskimo	1.64	0.70	3.84	0.248
Asian	0.57	0.47	0.70	<0.001
Black	0.66	0.50	0.87	0.003
Hispanic	0.76	0.64	0.90	0.002
Unknown	0.74	0.47	1.17	0.20
Other	0.76	0.54	1.08	0.13
Maternal pre-eclampsia	0.72	0.57	0.91	0.006
Infant of a diabetic mother	2.31	1.81	2.94	<0.001
Chorioamnionitis	1.95	1.51	2.52	<0.001
Prolonged rupture of membranes	0.71	0.51	1.00	0.049

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; RDS, respiratory distress syndrome; SGA, small for gestational age.

differences for RDS among infants born at <32 weeks gestation, we found Blacks had a lower risk of RDS than Whites.^{29–32} As our cohort had a large proportion of Hispanics (25%) and Asians (20%), we were able to evaluate their risk of RDS compared with non-Hispanic Whites, and found both Asians and Hispanics to be at lower risk for RDS (Table 2). Additional significant independent predictors of RDS in the multivariate regression were Cesarean delivery, maternal diabetes and chorioamnionitis. Multiple gestation, maternal pre-eclampsia and prolonged rupture of membranes were significant protective factors.

We also developed GA- and race/ethnicity-specific regression models (Figure 2). For GAs <39 weeks, males had a higher risk

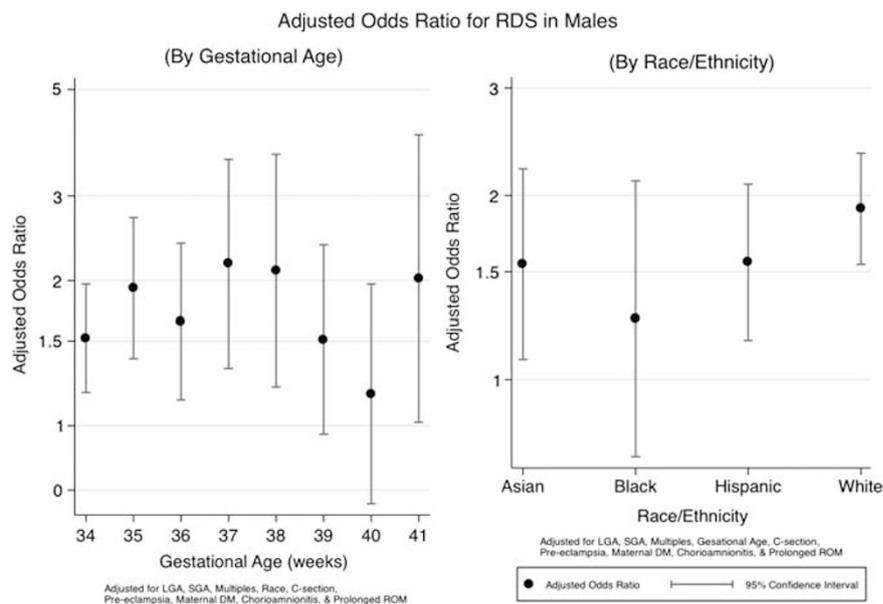


Figure 2 aOR for RDS in males by GA (left panel) and by race (right panel).

of RDS compared with females (point estimates for the aOR of 1.2 to 2.2). After 39 weeks, the point estimates still showed males at increased risk but were not statistically significant. For race/ethnicity, males were at a statistically increased risk for RDS compared with females in Whites, Asians and Hispanics.

We evaluated a potentially confounding association between maternal antenatal corticosteroid administration and either race/ethnicity or sex by comparing a subgroup of male and female infants admitted to a level III neonatal intensive care unit for whom data on maternal antenatal corticosteroid administration were available ($n = 1015$). In this subgroup, 5.35% of males and 5.72% of females were born to mothers who received antenatal corticosteroids (χ^2 P value = 0.28). In addition, using pairwise comparisons, we found that the only significant difference occurred between Asians (4.62%) and Blacks (6.25%) (χ^2 P value = 0.009) who had similar rates of RDS. Differential administration of antenatal corticosteroids by sex or race/ethnicity does not appear to have confounded the overall analysis.

Our findings confirm and extend a recent, large population-based European cohort study of RDS risk factors,² and are consistent with prior studies that found increased risk of RDS by week through 39 weeks of gestation.^{16,33–36} These findings illustrate the importance of each week of gestation for RDS risk reduction through 39 weeks gestation. We also found that the increased risk of RDS associated with male sex and White race/ethnicity observed in preterm infants persists in late preterm and term infants. Differences in hormonal regulation of lung development provide candidate mechanisms to account for an increased risk of RDS associated with male sex.^{37–42} The racial disparity in risk of RDS between Whites and Blacks previously

observed in infants <32 weeks GA also persists in late preterm and term infants.^{29,30} The composition of our cohort permitted demonstration of increased RDS risk in White infants versus both Asian and Hispanic infants. The mechanisms that account for these differences require further investigation and replication in other cohorts. These findings contrast with those of studies that have not shown lower rates of RDS among Asian infants, and may reflect admixture in the California Asian population.⁹ Hispanics in Northern California are also an ethnically heterogeneous group associated with admixture with European, African, and Indigenous American populations.⁴³ On the basis of the low frequency of Medi-Cal insurance in our cohort (<5% compared with 47% in the general population in California),⁴⁴ race/ethnicity likely had a minimal influence on access to care.

Although the size of our cohort provides adequate statistical power to observe the difference in RDS risk in male versus female infants and between infants of different races/ethnicities, our study has several limitations. First, although maternal and neonatal data were collected prospectively, our analysis was retrospective and therefore, we did not have complete data for the entire cohort on antenatal steroids. However, subgroup analysis suggested that differential antenatal corticosteroid administration did not account for sex and race/ethnicity differences in RDS risk. Second, our case definition may include infants with transient tachypnea of the newborn. To reduce misclassification, we repeated our multivariate analysis using a more restrictive definition of RDS (only infants who received surfactant). Males remained at a greater risk of RDS than females (aOR 1.75; 95% confidence interval 1.39 to 2.20). Asians were still at a lower risk of RDS than Whites (aOR 0.54; 95% confidence interval 0.39 to 0.74). Although not statistically

significant, there was trend for Hispanics (aOR 0.83; 95% confidence interval 0.63 to 1.08) and Blacks (aOR 0.70; 95% confidence interval 0.46 to 1.06) to have a decreased risk of RDS compared with Whites. The reduced number of cases with the more restrictive definition of RDS diminished our ability to find statistical differences. Third, although it is unlikely that changes in frequency of use of inhaled nitric oxide that occurred during the 9-year interval of cohort accumulation impacted RDS risk,⁴⁵ other unrecognized practice changes may have confounded our analysis. Despite these limitations, our study suggests that decisions concerning timing of delivery should acknowledge RDS risk associated with male sex and White race/ethnicity in late preterm and term infants. For example, because cesarean delivery on maternal request prompts 4 to 18% of the ~1 000 000 cesarean sections annually in the United States,^{46,47} counseling for women to avoid elective delivery before 39 completed weeks of gestation should also include acknowledgement of RDS risk associated with male sex and White race/ethnicity.⁴⁸

In conclusion, our study shows that male sex and White race/ethnicity are independent risk factors for RDS in late preterm and term infants. Future studies to elucidate mechanisms that account for this differential risk^{38,39,49} will inform obstetrical counseling and decision-making.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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