Published in final edited form as:
Pediatr Res. 2009 December ; 66(6): 693–697. doi:10.1203/PDR.0b013e3181bbce86.

The Genetic Susceptibility to Respiratory Distress Syndrome

Orly Levit, **Yuan Jiang**, **Matthew J. Bizzarro**, **Naveed Hussain**, **Catalin S. Buhimschi**, **Jeffrey R. Gruen**, **Heping Zhang**, and **Vineet Bhandari**
Department of Pediatrics [O.L., M.J.B., J.R.G., V.B.], Yale University School of Medicine, New Haven, CT 06520; Department of Epidemiology and Public Health [Y.J., H.Z.], Yale University School of Medicine, New Haven, CT 06510; Division of Neonatology [N.H.], University of Connecticut Health Center, Farmington, CT 06030; Department of Obstetrics and Gynecology [C.S.B.], Yale University School of Medicine, New Haven, CT 06511; Department of Genetics and Investigative Medicine [J.R.G.], Yale Child Health Research Center, New Haven, CT 06519

Abstract

Previous studies to identify a genetic component to respiratory distress syndrome (RDS) have shown conflicting results. Our objectives were to evaluate and quantify the genetic contribution to RDS using data that comprehensively includes known environmental factors in a large sample of premature twins. Data from a retrospective chart review of twins born at ≤32 weeks gestational age were obtained from 2 neonatal units. Mixed effects logistic regression (MELR) analysis was used to assess the influence of several independent covariates on RDS. A zygosity analysis, including the effects of additive genetic and common and residual environmental (ACE) factors, was performed to estimate the genetic contribution. Results reveal that the 332 twin pairs had a mean gestational age of 29.5 weeks and birth weight of 1372 grams. MELR identified significant non-genetic covariates as male gender ($p=0.04$), birth weight ($p<0.001$), 5-minute Apgar score ($p<0.001$) and treating institution ($p=0.001$) as significant predictors for RDS. The ACE model was employed to estimate the genetic susceptibility to RDS by adjusting for the above factors. We found 49.7% ($p=0.04$) of the variance in liability to RDS was the result of genetic factors alone. We conclude that there is a significant genetic susceptibility to RDS in preterm infants.

Respiratory distress syndrome (RDS) is a disease process that results from an absent or diminished amount of surfactant in the newborn lung. Prematurity, therefore, plays a crucial role in the development of RDS. The incidence is inversely proportional to gestational age (GA) and birth weight (BW), with approximately 71% of neonates with BW between 501 and 750 grams affected as compared with 23% of those between 1250 and 1500 grams (1). In addition to prematurity, multiple additional factors have been implicated in the pathogenesis of RDS. These include maternal, intrapartum, and neonatal variables such as advanced maternal age (2), chorioamnionitis (3,[4]), mode of delivery (5), gender(6,[7]), and birth order (8-[11]). Despite major advances, such as increased use of prenatal steroids and postnatal surfactant in perinatal and neonatal care, RDS is a leading cause of morbidity and mortality in preterm infants and incurs an estimated annual economic burden of 2.3 billion dollars (12-[14]).

Corresponding Author: Vineet Bhandari, MD, DM, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, P. O. Box 208064, New Haven, CT 06520-8064, Tel: 203-785-2613, vineet.bhandari@yale.edu.
O.L and Y.J. contributed equally to this work.

Presented as a poster at the Pediatric Academic Societies Meeting at Baltimore, MD, May 2-5, 2009.

In preterm infants of the same GA, the clinical severity of RDS varies widely. We hypothesized therefore that, in addition to environmental effects, unknown genetic factors play a major role in predisposing premature neonates to RDS.

Our major objective was to conduct a heritability study of a large cohort of premature twin pairs, using sophisticated statistical analyses that control for the major known independent risk factors, to identify and quantify the genetic contribution to RDS.

Methods

Subjects

Data on premature twins born at ≤32 weeks of gestation between January 1, 1994, and December 31, 2004, including zygosity information were collected from 2 centers (The University of Connecticut and Yale University). We included only infants who survived beyond a postmenstrual age (PMA) of 36 weeks. The twin database was created to evaluate the genetic contribution to common neonatal disorders (including bronchopulmonary dysplasia). In addition, we wanted to avoid missing the diagnosis of RDS, especially if death occurred early (for example, in the delivery room), and prevented the clinical picture and/or radiographic manifestations to be overtly manifested. Hence, for consistency, we excluded all deaths prior to 36 weeks PMA. The institutional review boards of both centers approved this study and exempted it from obtaining informed consent, as per their guidelines.

Definitions

Data was prospectively collected and entered into the databases by trained research personnel at both institutions, as routine practice, using similar definitions. RDS was defined as presence of respiratory distress with an oxygen requirement to maintain oxygen saturations of ≥ 90% in the first 6 hours of life, accompanied by a characteristic chest radiograph. The time frame was selected to allow inclusion of the maximum number of cases of primary/congenital RDS and to avoid cases of acquired RDS. The chest X-ray was used for confirmation of diagnosis by excluding other potential causes of respiratory distress for example, transient tachypnea of the newborn. All radiographs were routinely read by trained pediatric radiologists at both institutions. Zygosity was determined by ultrasound evaluation prior to 20 weeks GA and histopathological examination of the placenta at Yale and the University of Connecticut with an additional confirmation of the gender. Gestational hypertension was defined as any new onset blood pressure >140/90 mm Hg or mean arterial pressure >105 mmHg that occurred after the 20^{th} week of pregnancy. In vitro fertilization (IVF) was defined as any type of assisted reproductive technology that involved extracorporeal fertilization. Premature rupture of membranes (PROM) was defined as rupture that occurred at least 18 hours prior to delivery. Histological chorioamnionitis was defined by pathological examination of the placenta (15).

Statistical Analysis

Demographic data were analyzed using Student's t test, Wilcoxon rank sum test, or chi-square analysis when appropriate. For chi-square analysis of the zygosity data, the observed numbers of twin pairs with both infants affected, with only one infant affected and with neither infant affected were found respectively for monozygotic (MZ) and dizygotic (DZ) groups. These observed numbers formed a 2×3 contingency table. On the other hand, the analog expected numbers of twin pairs were calculated from the corresponding marginal totals. The observed to expected distributions of concordance were compared using chi-square analysis.

Mixed effect logistic regression (MELR) analysis was performed to identify the impact of putative factors on RDS. The covariates utilized in the model included maternal age, IVF, delivery type, birth order, gender, weight, 5-minute Apgar score and treating institution. The

status of the outcomes from twin pairs was treated as a correlated event. A MELR model was fitted to assess the relationship between the covariates listed and the outcome of interest (RDS), and to incorporate the correlation between twin pairs.

The additive genetic, common environmental and residual effects (ACE) model (16) was then used to estimate the variance in liability for RDS. The ACE model is a mixed effects probit model, which included covariate effects, an additive genetic effect, a common environmental effect shared by a twin pair (with no distinction between MZ and DZ twin pairs), and a residual environmental effect. The additive genetic effects, the common environmental effect, and the residual environmental effects were assumed to be independently and normally distributed. The additive genetic effects for MZ twins were assumed to be identical. For DZ twins, the covariance of the additive genetic effects was assumed to be half that of MZ twins (17). The covariates adjusted in the ACE model included all significant covariates utilized in the MELR analysis. The genetic heritability could then be estimated using the ratio of estimated genetic variance and the total variance of the trait.

Statistical analyses were performed using SAS 9.1(PROC NLMIXED). A $p<0.05$ was considered statistically significant.

Results

The cohort consisted of 332 twin pairs with a mean GA of 29.5 weeks and BW of 1372 grams. There were 70 MZ twin pairs and 262 DZ twin pairs. RDS was diagnosed in 465 of 664 (70.0%) infants. Despite a discrepancy in the overall number of twins pairs in each group, no statistically significant differences were observed between MZ and DZ twins with respect to gender, GA, weight, 5-minute Apgar score, maternal race, delivery type, the incidences of gestational hypertension, PROM, maternal diabetes, and chorioamnionitis, and the use of antenatal steroids and antibiotics (Table 1). However, significant differences were found between MZ and DZ twins with respect to maternal age and the proportion of neonates conceived via IVF (Table 1). The distribution of patients with RDS by site and BW are shown in Table 2.

We initially performed an unadjusted concordance analysis to look for a genetic effect for RDS. The analysis revealed a significant difference of concordance distributions between MZ and DZ twin pairs ($p=0.02$), suggesting a significant role for genetic factors in the pathogenesis of RDS (Table 3).

MELR analysis was next performed using RDS as the dependent variable to identify significant non-genetic covariates that may have contributed to the outcome of interest. The analysis determined that male gender (regression coefficient = 0.401; 95% CI: [0.019, 0.783]; $p= 0.04$), BW (regression coefficient = -0.002; 95% CI: [-0.002, -0.001]; $p<0.001$), 5-minute Apgar score (regression coefficient= -0.552; 95% CI: [-0.782, -0.322]; $p<0.001$), and institution (Yale; regression coefficient= 0.688; 95% CI: [0.284,1.091]; $p= 0.001$) were significant covariates for RDS (Table 4). Addition of race as a factor in the logistic regression model did not change our results in a significant manner (data not shown).

After adjusting for all significant covariates identified by the MELR, total genetic effects accounted for 49.7% ($p=0.04$) of the variance in liability to RDS by ACE modeling.

Discussion

In 2 cohort studies of women who delivered two singleton preterm infants, a comparison of the relative risk of RDS in the second infant was done according to the RDS status of the first one (18). There was a significantly increased relative risk of RDS in the second sibling of women whose first preterm infant had RDS versus those whose first preterm infants did not

have RDS. This remained significant even after controlling for confounding variables, suggesting an important genetic (or other familial) contribution to the risk of RDS (18).

Previous twin studies (10,[19-21]) have evaluated the genetic contribution to RDS with contradictory results. The first 2 studies published in 1971 (19) and 2002 (20), showed that RDS had a significant genetic component. Myrianthopoulos et al studied 31 twin pairs and showed a higher concordance rate between MZ compared to DZ pairs (85% concordance in MZ and 44% in DZ). In a retrospective review of all twins born during a 19-year period (1976 to 1995) in Amsterdam, van Sonderen et al found a RDS concordance rate of 67% when the twins were MZ as compared with only 29% when they were DZ (20). The Amsterdam study suggested a strong genetic influence, but only included 80 pairs with a GA of 30-34 weeks (20), a population with a fairly low risk for RDS.

In contrast, Marttila et al (21), evaluated 100 same-gender twin pairs with RDS and found a concordance difference of only 10% [95% CI: -0.1 to +0.3, p=0.32], suggesting an insignificant genetic contribution. The authors' concluded that the small concordance difference did not rule out the possibility of a genetic component of RDS (21). The same group of investigators then conducted a registry-based study that assessed the intrapair differences in susceptibility to RDS in a homogenous population of European ancestry (10). They concluded that environmental factors predominate over genetic factors based on a lack of concordance difference between same-gender twins compared with opposite-gender twins. While this study included a large number of twin pairs, the zygosity was inferred by considering all the gender discordant pairs as DZ and then estimating the number of MZ twin pairs from the gender concordant cohort (10).

A summary of the previous twin studies on the heritability of RDS and a comparison to the present one has been shown in Table 5. Interpretation of the results of previous studies were limited by sample size, variability in the methods for confirmation of zygosity and the exclusion of confounding variables known to contribute to the risk of RDS. Using a large sample size, a standard method for ascertaining zygosity, and including and controlling for virtually all major known non-genetic (i.e. environmental) risk factors for RDS, we were able to establish that a significant genetic contribution to RDS exists. Furthermore, we were able to quantify this contribution.

Despite lacking evidence for a definitive genetic contribution to RDS, investigators have attempted to identify specific genes that may contribute to its risk. The studies of SP-A and SP-B genes associated with RDS have been summarized in Table 6. Logistic regression analysis was used to test whether SP-C alleles coding for 138 Asn or 186 Asn explained the risk of RDS when gender was included in the analysis as a confounding factor. It was found that both alleles were independent risk factors for RDS (22). Recently, a variant of the SP-D gene (rs1923537) was associated with a lower prevalence of RDS (23). Another case-control study has suggested an association of G protein-coupled receptor for asthma susceptibility (GPR154 or GPRA) and neonatal RDS (24).

To the extent that some of these candidate-gene studies show significance for various alleles, polymorphisms, and haplotypes, does not address the central question: to what extent is RDS a genetic disease? Knowing this will determine whether further studies are justified to identify the genes that comprise the additive genetic effect in the ACE modeling, to identify genetic modifiers encoded in chromosomes, or to identify epigenetic modifiers, with the ultimate goal of informing rationale drug design. While surfactant-B deficiency is a validated autosomal dominant lethal form of lung disease (25), it is rare and does not significantly contribute to the common forms of RDS encountered by neonatologists daily; nor does it necessarily follow that since surfactant proteins are encoded in chromosomal DNA, that RDS is therefore genetic.

The data reported in the present study are first to quantify the genetic component to RDS. The strengths of our study include a large number of twins from a very heterogeneous population, and data on a large number of known confounding variables, including fertility treatment, prenatal steroids and maternal information related to pregnancy-specific conditions.

There are some limitations to our study. The zygosity was determined using ultrasound, placental histopathology, and gender, instead of DNA confirmation. A monochorionic placenta was regarded as representing MZ twins. Approximately 9% of similar gender dichorionic placentas are MZ (26). The results were not affected when adjustments were made for these worst-case scenarios. We included most of the known potential contributing factors, but there may be other factors that could affect the outcome of RDS. We did attempt to control for these unknown variables in our statistical model.

Twin studies are a powerful non-DNA based approach to determining the amount of the variance contributed by total genetic effects. These analyses are conditioned by the assumption that MZ twins share 100% of their chromosomal DNA and that DZ twins share, on average, 50%. The heritability of ~50% for RDS is significant and comparable to that of other medical conditions, such as bronchopulmonary dysplasia (27,[28]) and retinopathy of prematurity (29). While epigenetics and other modifications to chromosomal DNA may suggest that these assumptions should slightly be adjusted, non-DNA based twin heritability studies remain robust.

We conclude that there is a strong genetic susceptibility to the development of RDS in preterm infants. This should act as a further impetus to spur the identification of the genetic elements of this condition, which, in turn, has the potential to make a significant impact on neonatal outcomes.

Acknowledgments

Financial Support: OL was supported in part by National Institute of Child Health and Human Development Training Grant T32 HD 07094. JRG was supported by National Institute of Neurological Disorders and Stroke R01 NS43530. HZ and YJ were supported in part by National Institute on Drug Abuse K02DA017713 and R01DA016750. VB was supported by National Heart, Lung, and Blood Institute K08 HL 074195.

Abbreviations

ACE	additive genetic, common environmental and residual effects
BW	birth weight
DZ	dizygotic
GA	gestational age
IVF	in vitro fertilization
MELR	mixed effects logistic regression
MZ	monozygotic
RDS	respiratory distress syndrome
SP	surfactant proteins

References

1. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, Bauer CR, Donovan EF, Korones SB, Laptook AR, Lemons JA, Oh W, Papile LA, Shankaran S, Stevenson DK, Tyson JE,

Poole WK. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196:147.e141–e148. [PubMed: 17306659]

2. Dani C, Reali MF, Bertini G, Wiechmann L, Spagnolo A, Tangucci M, Rubaltelli FF. Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Italian Group of Neonatal Pneumology. Eur Respir J 1999;14:155–159. [PubMed: 10489844]
3. Dempsey E, Chen MF, Kokottis T, Vallerand D, Usher R. Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. Am J Perinatol 2005;22:155–159. [PubMed: 15838750]
4. Namavar Jahromi B, Ardekany MS, Poorarian S. Relationship between duration of preterm premature rupture of membranes and pulmonary maturation. Int J Gynaecol Obstet 2000;68:119–122. [PubMed: 10717815]
5. Ziadeh SM, Sunna E, Badria LF. The effect of mode of delivery on neonatal outcome of twins with birthweight under 1500 grams. J Obstet Gynaecol 2000;20:389–391. [PubMed: 15512593]
6. Klein JM, Nielsen HC. Androgen regulation of epidermal growth factor receptor binding activity during fetal rabbit lung development. J Clin Invest 1993;91:425–431. [PubMed: 8432851]
7. Luerti M, Parazzini F, Agarossi A, Bianchi C, Rocchetti M, Bevilacqua G. Risk factors for respiratory distress syndrome in the newborn. A multicenter Italian survey. Study Group for Lung Maturity of the Italian Society of Perinatal Medicine. Acta Obstet Gynecol Scand 1993;72:359–364. [PubMed: 8392266]
8. Hacking D, Watkins A, Fraser S, Wolfe R, Nolan T. Respiratory distress syndrome and birth order in premature twins. Arch Dis Child Fetal Neonatal Ed 2001;84:F117–F121. [PubMed: 11207228]
9. Balchin I, Whittaker JC, Lamont RF, Steer PJ. Timing of planned cesarean delivery by racial group. Obstet Gynecol 2008;111:659–666. [PubMed: 18310369]
10. Marttila R, Kaprio J, Hallman M. Respiratory distress syndrome in twin infants compared with singletons. Am J Obstet Gynecol 2004;191:271–276. [PubMed: 15295378]
11. Shinwell ES, Blickstein I, Lusky A, Reichman B. Effect of birth order on neonatal morbidity and mortality among very low birthweight twins: a population based study. Arch Dis Child Fetal Neonatal Ed 2004;89:F145–F148. [PubMed: 14977899]
12. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2005 period linked birth/infant death data set. Natl Vital Stat Rep 2008;57:1–32. [PubMed: 18972721]
13. Sinha SK, Gupta S, Donn SM. Immediate respiratory management of the preterm infant. Semin Fetal Neonatal Med 2008;13:24–29. [PubMed: 17981103]
14. American Lung Association. Respiratory distress syndrome and bronchopulmonary dysplasia. 2008 [July 23 2009]. Available at: http://www.lungusa.org/site/c.dvLUK9O0E/b.4023541
15. Holzman C, Lin X, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. Am J Epidemiol 2007;166:786–794. [PubMed: 17625222]
16. Feng R, Zhou G, Zhang M, Zhang H. Analysis of Twin Data Using SAS. Biometrics 2008;65:584–589. [PubMed: 18647295]
17. Falconer, DS.; Mackay, TF. Introduction to quantitative genetics. Prentice Hall; Harlow, UK: 1996.
18. Nagourney BA, Kramer MS, Klebanoff MA, Usher RH. Recurrent respiratory distress syndrome in successive preterm pregnancies. J Pediatr 1996;129:591–596. [PubMed: 8859267]
19. Myrianthopoulos NC, Churchill JA, Baszynski AJ. Respiratory distress syndrome in twins. Acta Genet Med Gemellol (Roma) 1971;20:199–204. [PubMed: 5093127]
20. van Sonderen L, Halsema EF, Spiering EJ, Koppe JG. Genetic influences in respiratory distress syndrome: a twin study. Semin Perinatol 2002;26:447–449. [PubMed: 12537317]
21. Marttila R, Haataja R, Ramet M, Lofgren J, Hallman M. Surfactant protein B polymorphism and respiratory distress syndrome in premature twins. Hum Genet 2003;112:18–23. [PubMed: 12483294]
22. Lahti M, Marttila R, Hallman M. Surfactant protein C gene variation in the Finnish population - association with perinatal respiratory disease. Eur J Hum Genet 2004;12:312–320. [PubMed: 14735158]
23. Hilgendorff A, Heidinger K, Bohnert A, Kleinsteiber A, Konig IR, Ziegler A, Lindner U, Frey G, Merz C, Lettgen B, Chakraborty T, Gortner L, Bein G. Association of polymorphisms in the human surfactant protein-D (SFTPD) gene and postnatal pulmonary adaptation in the preterm infant. Acta Paediatr 2009;98:112–117. [PubMed: 18785967]

24. Pulkkinen V, Haataja R, Hannelius U, Helve O, Pitkanen OM, Karikoski R, Rehn M, Marttila R, Lindgren CM, Hastbacka J, Andersson S, Kere J, Hallman M, Laitinen T. G protein-coupled receptor for asthma susceptibility associates with respiratory distress syndrome. Ann Med 2006;38:357–366. [PubMed: 16938805]
25. Nogee LM, Garnier G, Dietz HC, Singer L, Murphy AM, deMello DE, Colten HR. A mutation in the surfactant protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. J Clin Invest 1994;93:1860–1863. [PubMed: 8163685]
26. Bhandari V, Zhou G, Bizzarro MJ, Buhimschi C, Hussain N, Gruen JR, Zhang H. Genetic contribution to patent ductus arteriosus in the premature newborn. Pediatrics 2009;123:669–673. [PubMed: 19171636]
27. Bhandari V, Bizzarro MJ, Shetty A, Zhong X, Page GP, Zhang H, Ment LR, Gruen JR. Familial and genetic susceptibility to major neonatal morbidities in preterm twins. Pediatrics 2006;117:1901–1906. [PubMed: 16740829]
28. Lavoie PM, Pham C, Jang KL. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the national institutes of health. Pediatrics 2008;122:479–485. [PubMed: 18762515]
29. Bizzarro MJ, Hussain N, Jonsson B, Feng R, Ment LR, Gruen JR, Zhang H, Bhandari V. Genetic susceptibility to retinopathy of prematurity. Pediatrics 2006;118:1858–1863. [PubMed: 17079555]
30. Kala P, Ten Have T, Nielsen H, Dunn M, Floros J. Association of pulmonary surfactant protein A (SP-A) gene and respiratory distress syndrome: interaction with SP-B. Pediatr Res 1998;43:169–177. [PubMed: 9475280]
31. Ramet M, Haataja R, Marttila R, Floros J, Hallman M. Association between the surfactant protein A (SP-A) gene locus and respiratory-distress syndrome in the Finnish population. Am J Hum Genet 2000;66:1569–1579. [PubMed: 10762543]
32. Haataja R, Ramet M, Marttila R, Hallman M. Surfactant proteins A and B as interactive genetic determinants of neonatal respiratory distress syndrome. Hum Mol Genet 2000;9:2751–2760. [PubMed: 11063734]
33. Floros J, Fan R, Diangelo S, Guo X, Wert J, Luo J. Surfactant protein (SP) B associations and interactions with SP-A in white and black subjects with respiratory distress syndrome. Pediatr Int 2001;43:567–576. [PubMed: 11737731]
34. Haataja R, Marttila R, Uimari P, Lofgren J, Ramet M, Hallman M. Respiratory distress syndrome: evaluation of genetic susceptibility and protection by transmission disequilibrium test. Hum Genet 2001;109:351–355. [PubMed: 11702216]
35. Makri V, Hospes B, Stoll-Becker S, Borkhardt A, Gortner L. Polymorphisms of surfactant protein B encoding gene: modifiers of the course of neonatal respiratory distress syndrome? Eur J Pediatr 2002;161:604–608. [PubMed: 12424586]
36. Marttila R, Haataja R, Guttentag S, Hallman M. Surfactant protein A and B genetic variants in respiratory distress syndrome in singletons and twins. Am J Respir Crit Care Med 2003;168:1216–1222. [PubMed: 12947025]
37. Thomas NJ, Fan R, Diangelo S, Hess JC, Floros J. Haplotypes of the surfactant protein genes A and D as susceptibility factors for the development of respiratory distress syndrome. Acta Paediatr 2007;96:985–989. [PubMed: 17524024]

Table 1

Comparison of demographic data for monozygous (MZ) and dizygous (DZ) twins.

	MZ (n=140)	DZ (n=524)	p value
Maternal age* (years)	29.01 ± 6.11	31.30 ± 6.36	0.007
Maternal Race (n, %)			0.750
Caucasian	50 (71.4)	188 (71.8)	
African-American	13 (18.6)	53 (20.2)	
Hispanic	1 (1.4)	7 (2.7)	
Asian	1 (1.4)	1 (0.4)	
Others	5 (7.1)	13 (5.0)	
Gestational hypertension (n, %)	15 (10.7)	80 (15.3)	0.218
PROM (n, %)	17 (12.1)	73 (13.9)	0.682
Chorioamnionitis (n, %)	9 (6.4)	37 (7.1)	0.941
Diabetes Mellitus (n, %)	6 (4.3)	43 (8.2)	0.163
Antenatal Steroids (n, %)	85 (60.7)	279 (53.2)	0.138
Antibiotics (n, %)	40 (28.6)	182 (34.7)	0.203
IVF (n, %)	4 (2.9)	95 (18.2)	<0.001
Delivery type vaginal (n, %)	37 (26.6)	156 (29.8)	0.534
Male gender (n, %)	72 (51.4)	283 (54.0)	0.654
GA* (weeks)	29.7 ± 2.2	29.5 ± 2.5	0.252
BW* (grams)	1338 ± 410	1382 ± 466	0.284
Apgar <7 at 5 minutes (n, %)	15 (10.7)	49 (9.4)	0.756
RDS (n, %)	100 (71.4)	365 (69.7)	0.762

* Mean + SD.

Table 2

The incidence of RDS by birth weight and site

Birth Weight (grams)	UCONN (n= 333)	Yale (n= 330)	p value
<1000	81/86 (94.2) *	70/72 (97.2) *	0.592
1000 -1249	40/53 (75.5) *	53/69 (76.8) *	1.000
1250-1999	86/171 (50.3) *	111/163 (68.1) *	0.001
≥ 2000	9/23 (39.1) *	15/26 (57.7) *	0.312

* n, (%)

Table 3

Zygosity analysis.

Twin pairs	Both have RDS	One has RDS	Neither has RDS	Total	p value
MZ	44 (38.4)*	12 (21.3)	14 (10.3)	70	
DZ	138 (144)	89 (79.7)	35 (38.7)	262	0.02
Total	182	101	49	332	

* Observed number of twin pairs (expected number of twin pairs). Expected number 38.4 calculated as 182×70/332.

Table 4

Mixed effects logistic regression analysis for RDS

	Coefficient	95% CI	p value
Birth Order (B)	0.180	[-0.198, 0.558]	0.350
Male Gender	0.401	[0.019, 0.783]	0.040
BW	-0.002	[-0.002, -0.001]	<0.001
Apgar	-0.552	[-0.782, -0.322]	<0.001
Institution (Yale)	0.688	[0.284, 1.091]	0.001
Mother's Age	-0.013	[-0.045, 0.018]	0.409
Delivery Type (Vaginal)	-0.291	[-0.718, 0.137]	0.182
IVF	-0.309	[-0.831, 0.214]	0.246

Abbreviations as in the text.

Table 5

Comparison of twin studies evaluating the genetic contribution to RDS.

Number of twin pairs in study	Determination of zygosity	Genetic effect	Remarks	References
31	Based on gender, blood group, placental exam	Yes	Comparison of concordance MZ-DZ	19
80	Placental exam gender discordance	Yes	Comparison of concordance MZ-DZ	20
100	Multiple gene markers	No	Comparison of concordance MZ-DZ	21
638	MZ calculation	No	Comparison of concordance MZ-DZ	10
332	Placental exam, gender	Yes	Comparison of concordance MZ-DZ MELR and ACE model	Present study

Table 6

Surfactant protein gene allelic variants associated with risk for RDS.

Total number of infants in study	SP-A	SP-B	Population	Effect on RDS	References
241	SP-A2 $1A^0/1A^0$	SP-B intron 4 polymorphism	White population>28 weeks	Increased risk	30
241	SP-A2 $1A^1/1\ A^1$	SP-B intron 4 polymorphism	White population>28 weeks	Decreased risk	30
176	SP-A1 allele $6A^2$		Finnish population	Increased risk	31
176	SP-A allele $6A^3$		Finnish population	Decreased risk	31
684		SP-B Ile131 Thr	Finnish population twins	Determines the SP-A allele effect on RDS	32
White 511; Black 73	SP-A1 ($6A^2/6A^2$) SP-A2 (1A°/1A° or 1A°/*	SP-B (9306 A/G or del/*	White population	Increased risk	33
White 511; Black 73	SP-A1 ($6A^3/6A^3$ or $6A^3$/*)	SP-B (1580 T/T)	Black population	Reduced risk	33
White 511; Black n= 73		SP-B intron 4 del variant			33
White 511; Black 73		SP-B intron 4 ins variant	Black females	Increased risk	33
Parent-offspring trios 107	SP-A1-A2 haplotype $6A^2$-1A°		Caucasian Finnish population	Increased risk	34
Parent-offspring trios 107	SP-A1 $6A^3$-$1A^1$ 6A4-1A5		Caucasian Finish population	Decreased risk	34
198		SP-B intron 4 polymorphism	Caucasian German population	Increased risk	35
Singletons 441; Twins or multiples 480)	SP-A1 $6A^2/6A^2$	SP-B exon 4 genotype Thr/Thr	Caucasian Finnish population	Increased risk	36
Singletons 441; Twins or multiples 480	SP-A $6A^2$	SP-B Ile/Thr	Caucasian Finnish population	Decreased risk	36
132 families	SP-D/SP-A2 haplotype DA160-A/SP-A2 $1A^1$ Also DA11-T present in SP-A containing haplotypes		Mixed population	Reduced risk	37