



RISK FACTORS ASSOCIATED WITH NEONATAL RESPIRATORY DISTRESS SYNDROME: INSIGHTS FROM A CASE-CONTROL STUDY IN PESHAWAR'S TERTIARY CARE HOSPITALS (2024-2025)

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Abstract

Background: Neonatal Respiratory Distress Syndrome (NRDS) is a leading cause of neonatal morbidity and mortality among late preterm infants. Despite ongoing improvements in maternal and neonatal care, NRDS remains a burden in various healthcare settings across Peshawar. Identifying its associated risk factors is essential for guiding future prevention and clinical interventions.

Objective: This study aimed to identify maternal and neonatal factors associated with Neonatal Respiratory Distress Syndrome among neonates in tertiary care hospitals of Peshawar.

Methods: Unmatched case-control study was conducted among 300 neonates (150 cases and 150 controls) admitted to neonatal intensive care units of tertiary hospitals in Peshawar from September 2024 to February 2025. Data was collected through structured questionnaires based on previous research and medical records, focusing on maternal and neonatal factors. Neonates with major congenital anomalies or serious comorbidities were excluded. SPSS version 23 was used for descriptive, comparative, and multivariate analyses. Logistic regression and chi-square tests were applied. Variables with p-value < 0.05 in multivariable analysis were considered significant.

Results: A total of 150 cases and 150 controls were included in this study. Maternal antenatal care visits were associated with NRDS [AOR = 1.139; 95% CI (1.065–1.217)]. Substance exposure during pregnancy showed strong association [AOR = 4.795], while administration of steroids before 30 weeks appeared protective [AOR = 19.872]. Congenital anomalies reduced the likelihood of NRDS [AOR = 0.293]. Neonates requiring immediate respiratory support had higher odds of NRDS, with the strongest association seen in those with ongoing respiratory issues [AOR = 213.2].

Conclusions and recommendations: Substance exposure during pregnancy and lack of antenatal care were identified as maternal risk factors for NRDS. Absence of congenital anomalies, administration of maternal steroids before 30 weeks, and consistent ANC visits were found to reduce the risk. Strengthening prenatal care services and minimizing harmful exposures during

pregnancy are essential for reducing the burden of NRDS.

Keywords: Neonates · Respiratory Distress Syndrome, Maternal Risk Factors, Antenatal Care,

Peshawar, Pakistan

Background

A retrospective case-control study (2006–2015) found that placental abnormalities, particularly placenta previa and antenatal bleeding, significantly increased the risk of Neonatal Respiratory Distress Syndrome (NRDS), even at higher gestational ages [1]. Neonatal Respiratory Distress Syndrome remains a major contributor to neonatal morbidity and mortality in low- and middle-income countries, particularly among preterm infants [2].

Neonatal respiratory distress syndrome (NRDS) has been linked to various maternal and neonatal risk factors. Studies have shown an increased risk of NRDS following elective cesarean section deliveries without the onset of labor [3]. An Indian study reported that 27.8% of neonates delivered via cesarean section developed NRDS [3]. Maternal diabetes is another contributing factor, affecting fetal lung development and birth weight [4, 5, 6]. Additionally, advanced maternal age has been associated with complications such as preterm birth, gestational diabetes, and placental insufficiency, all of which increase the risk of NRDS [7, 8, 9]. While some research suggests maternal age independently influences NRDS risk [10], others attribute the increased prevalence to prematurity [11]. Low birth weight also remains a major concern, with 60.1% of neonates under 1500g diagnosed with NRDS in one study [12]. Male neonates face heightened risk due to hormonal influences on lung maturation, specifically the effects of testosterone on surfactant production [13, 14]. Furthermore, maternal hypertension has been found to double the risk of NRDS, emphasizing the importance of targeted perinatal care in high-risk pregnancies [15].

Studies report NRDS prevalence rates of 60.1% in very low birth weight neonates in China [12], 27.8% among C-section deliveries in India [3], and higher incidence in male neonates due to hormonal influences [13, 14]. Genetic mutations in SP-B and SP-C further contribute to NRDS risk [5, 6]. Identifying key predictors of NRDS is essential for improving neonatal care and reducing mortality.

Objective

To determine the maternal and neonatal factors associated with Neonatal respiratory distress syndrome in neonates.

Methods

Study design, period, setting, and population

An unmatched case-control study was conducted in the neonatal intensive care units (NICUs) of tertiary care hospitals in Peshawar, Pakistan, from September 2024 to February 2025. The study took place at Hayatabad Medical Complex (1280 beds), Khyber Teaching Hospital (1560 beds), and Lady Reading Hospital (1230 beds), serving a large neonatal population.

Neonates admitted during the study period formed the study population. Cases were diagnosed with NRDS, while controls were those without NRDS. Exclusion criteria included neonates with congenital anomalies or significant comorbidities affecting respiratory function.

Variables

Dependent variable: NRDS status

Independent Variables: Maternal factors including maternal age, gravidity, parity, pregnancy loss, antenatal care (ANC) visits, diabetes, health status, steroid exposure, and mode of delivery were assessed for their association with NRDS. Neonatal factors such as gestational age, birth weight, NICU stay, delivery complications, sex, NICU admission, congenital anomalies, Apgar score, resuscitation care, genetic predisposition, and immediate postnatal care were also considered

potential determinants.

Operational definitions

Case (Neonatal Respiratory Distress Syndrome): Diagnosis was based on the presence of clinical signs including tachypnea (≥ 60 breaths per minute), intercostal or subcostal retractions, nasal flaring, grunting, cyanosis, and poor oxygenation requiring respiratory support. In addition, hematological criteria such as arterial blood gas abnormalities indicating hypoxemia ($\text{PaO}_2 < 50$ mmHg on room air), a chest X-ray showing diffuse ground-glass opacity with air bronchograms, and surfactant deficiency confirmed via clinical assessment or laboratory markers were considered for NRDS classification

Control: Neonates without a diagnosis of Neonatal Respiratory Distress Syndrome (NRDS) admitted to the NICU with their index mother.

Sample size determination and sampling procedure

Sample size was determined using the case-control formula, assuming a two-sided confidence level (95%), power (80%), and a control-to-case ratio of 1:1. Based on these assumptions, the final sample size was 300 neonates (150 cases and 150 controls). Both cases (neonates diagnosed with NRDS) and controls (neonates without NRDS) were selected using a consecutive sampling technique, collecting data from NICU patient mothers and hospital records until the required sample size was reached.

Data collection method and procedure

Data was collected from September 2024 to February 2025 through interviews with mothers and review of hospital records using structured questionnaires. The questionnaire included maternal sociodemographic, obstetric, prenatal, intranatal, and neonatal variables. Data collection was conducted by medical students, ensuring systematic documentation of relevant clinical and maternal factors related to Neonatal Respiratory Distress Syndrome (NRDS).

Data quality control

A pretest was conducted on 5% of the sample size to ensure clarity and reliability of the data collection process. The structured questionnaire was prepared in English, then translated into Urdu (national language) and Pashto (regional language) for better accessibility. Data entry was performed by statistics students, with double-entry cross-checking to ensure accuracy. The supervisor monitored data quality daily, verifying completeness and consistency throughout the study period.

Data processing and analysis

Data was coded and entered SPSS version 23 for analysis. Descriptive, comparative, and multivariate logistic regression analyses were performed on categorical and continuous variables. A p-value of <0.05 was considered statistically significant in identifying determinants of Neonatal Respiratory Distress Syndrome (NRDS).

Ethical Considerations

The study protocol was first presented to the college faculty for initial review, where the research idea, methodology, and references were discussed. An official letter was provided to the tertiary care hospitals in Peshawar for formal permission. Participants (mothers/guardians) were informed about the purpose, procedures, and their right to refuse or withdraw from the study at any time. Both written and verbal consent were obtained before data collection.

Results

Table1: Descriptive and Comparative Analysis of Continuous Clinical and Obstetric Variables Among Cases and Controls in Neonatal Intensive Care Unit (NICU) in Peshawar, 2024–2025

Variables	Cases (Mean ± SD)	Controls (Mean ± SD)	t-value	p-value	95% CI
Maternal age	28.6 ± 6.67	27.8 ± 6.60	1.070	0.286	-2.328, 0.687
Maternal Gravidity	3.53 ± 2.15	3.06 ± 1.80	2.035	0.043	-0.918, -0.158
Maternal parity	2.87 ± 1.74	2.50 ± 1.70	1.809	0.071	-0.752, 0.316
Maternal Pregnancy Loss	0.81 ± 1.53	0.47 ± 0.79	2.374	0.018	-0.610, -0.056
Maternal ANC Visits	7.07 ± 5.48	5.27 ± 3.23	3.473	0.001	-2.831, -0.782
Neonate GA	36.04 ± 2.86	33.39 ± 5.99	5.439	p < 0.001	-2.7817, -1.3030
Neonate BW	2711.8 ± 612.5	2530.0 ± 829.9	2.159	0.032	-347.67, -16.059
Neonate NICU stay	4.007 ± 6.062	7.946 ± 8.45	2.561	0.011	0.59062, 4.5282

Clinical and Obstetric characteristics of the mothers and neonates

A total of 150 cases (neonates with NRDS) and 150 controls (neonates without NRDS) were included. The mean maternal age was 28.6 ± 6.67 years in cases and 27.8 ± 6.80 years in controls ($p = 0.286$). Mean gravidity (3.35 ± 2.15 vs. 3.06 ± 1.80 , $p = 0.043$) and pregnancy loss (0.81 ± 1.53 vs. 0.47 ± 0.79 , $p = 0.018$) were significantly higher in cases. ANC visits were also higher in cases (7.07 ± 5.48 vs. 5.27 ± 3.33 , $p = 0.001$). The mean gestational age was lower in cases (33.39 ± 5.99 vs. 36.04 ± 2.86 weeks, $p < 0.001$), as was birth weight (2530.0 ± 829.9 g vs. 2711.87 ± 612.5 g, $p = 0.032$). NICU stay was significantly longer in cases (7.946 ± 8.45 vs. 4.007 ± 6.062 days, $p = 0.001$). Lower gestational age, birth weight, and prolonged NICU stay were significantly associated with NRDS (Table 1).

Table 2: Multivariable logistic regression analysis result of cases and controls attending Neonatal intensive care unit in Peshawar, 2024–2025

Variables	AOR (95% CI)	p-value
Maternal age	1.014(0.991-1.093)	0.106
Maternal gravidity	1.051(0.683-1.618)	0.820
Maternal parity	0.984(0.640-1.512)	0.940
Maternal pregnancy loss	1.078(0.686-1.694)	0.746
Maternal ANC Visits	1.139(1.065-1.217)	p < 0.001
Neonate GA	1.23(1.12-1.34)	p < 0.001
Neonate BW	1.00(0.99-1.00)	0.041
Neonate NICU stay	0.91(0.86-0.96)	p < 0.001

Determinants of Neonatal Respiratory Distress Syndrome

In multivariable logistic regression analysis, gestational age was significantly associated with NRDS (OR = 1.23, $p < 0.001$), indicating that for each additional week of gestation, the odds of developing NRDS increased by 23%. Birth weight was also significantly associated (OR = 1.000, $p = 0.041$), though the effect size was minimal. NICU stay was inversely associated with NRDS (OR = 0.91, $p < 0.001$), suggesting that each additional day in the NICU decreased the odds of NRDS by 9%. Among maternal factors, antenatal care (ANC) visits showed a significant association with NRDS (OR = 1.139, $p < 0.001$), while maternal age, gravidity, parity, and pregnancy loss did not show statistically significant associations ($p > 0.05$) (Table 2).

Table 3: Maternal factors of cases and controls attending Neonatal intensive care unit in Peshawar, 2024–2025

Maternal Factors	Categories	Cases (n, %)	Controls (n, %)	(χ^2)	p-value	AOR [95%CI]	p-value
Maternal Diabetes	No Diabetes	131(87.3)	129(86.0)	1.312	0.519	0.964(0.199-4.662)	0.963
	Gestational Diabetes	14(9.3)	12(8.0)			0.773(0.134-4.460)	0.773
	Gestational, Type1 and Type2 Diabetes	5(3.3)	9(6.0)			1	
Maternal Health Status	No Condition	104(69.3)	117(78.0)	6.139	0.105	1.211(0.244-5.997)	0.815
	Hypertensive Disorder	23(15.3)	22(14.7)			0.557(0.103-3.010)	0.497
	Other Health Conditions	17(11.3)	6(4.0)			0.213(0.031-1.481)	0.118
	Other Health Conditions and Hypertensive Disorder	6(4.0)	5(3.3)			1	
Maternal Steroid Exposure	No Steroids	145(96.7)	129(86.0)	12.571	0.002	1.859(0.206-16.782)	0.581
	Early (Before 30 Weeks)	3(2.0)	19(12.7)			19.872(1.349-292.930)	0.029
	Late (>30 weeks or Later)	2(1.3)	2(1.3)			1	
Maternal Delivery Type	Vaginal	77(51.3)	74(49.3)	1.832	0.400	0.525(0.248-1.110)	0.091
	Elective C-Section	48(32.0)	42(28.0)			0.533(0.231-1.231)	0.140
	Emergency C-Section	25(16.7)	34(22.7)			1	

Maternal-related variables

Gestational diabetes was slightly more common in cases (9.3%) than controls (6.0%), but the association was not significant. Most mothers had no health conditions, with a higher proportion in controls (78.0%) than cases (69.3%). Hypertensive disorders were reported in 15.3% of cases and 14.7% of controls, while other health conditions were more frequent in cases (11.3%) than controls (4.0%), though the association was not significant. Antenatal steroids before 30 weeks were associated with higher odds of NRDS, while no steroids showed no significant difference. Vaginal delivery was slightly more frequent in cases (51.3%) than controls (49.3%), while elective C-sections were slightly higher in cases (32.0%) than controls (28.0%). Emergency C-sections were less frequent in cases (16.7%) than controls (22.7%), but delivery type was not significantly associated with NRDS.

Table 4: Neonatal factors of cases and controls attending Neonatal intensive care unit in Peshawar,

2024–2025					
Neonatal Factors	Categories	Cases (n, %)	Controls (n,%)	(χ^2)	p-value
Neonate Del Comp	No complications	111(74.0)	99(66.0)	9.47	0.024
	PPROM	15(10.0)	21(14.0)		
	Rapid labor	8(5.3)	21(14.0)		
	Other delivery complications.	16(10.0)	9(6.0)		
Neonate Sex	Male	85(56.7)	96(64.0)	1.68	0.194
	Female	65(43.3)	54(36.0)		
Neonate Cong Anom	No congenital anomalies	134(89.35)	145(96.7)	221.8	P<0.001
	Congenital anomalies	16(10.66)	5(3.33)		
Neonate Apgar	0-3	7(4.7)	25(16.7)	12.24	0.002
	4-6	36(24.0)	38(25.3)		
	7-10	107(71.3)	87(58.0)		
Neonate Resus Care	No intervention needed.	39(26.0)	48(32.0)	4.32	0.038
	Resuscitation immediate care	111(74.0)	102(68.0)		
Neonate Genetics	No known genetic condition	137(91.3)	131(87.3)	1.67	0.43
	Family history of NRDS	6(4.3)	11(7.3)		
	Other hereditary conditions	7(4.7)	8(5.3)		
Neonate Immediate care	No respiratory support.	45(30.0)	87(58.0)	15.41	p < 0.001
	Respiratory support	105(70)	63(42.0)		
Neonate NICU	No NICU admission and no respiratory issues.	2(1.3)	81(54.0)	59.85	P<0.001
	Admitted to NICU, respiratory issue, readmitted.	148(98.6)	69(46.0)		

Neonatal-related variables

Comparative analysis showed that congenital anomalies, low APGAR scores, need for resuscitation, immediate postnatal care, and NICU stay were significantly associated with NRDS ($p < 0.05$, chi-square test). A higher proportion of cases had APGAR scores compared to controls. In multivariate analysis, congenital anomalies (AOR = 0.293), APGAR 0–3 (AOR = 0.111), lack of immediate care (AOR = 39.3), and need for supplemental oxygen (AOR = 3.38) remained significant predictors of NRDS. These findings highlight the importance of early neonatal interventions in reducing NRDS risk.

Table 5: Multivariable logistic regression analysis result of cases and controls attending Neonatal

intensive care unit in Peshawar, 2024–2025

Variables	Categories	OR (95% CI)	p-value
Neonate Del Comp	No complications	1.47(0.83-2.591)	0.187
	Complications	1	
Neonate Sex	Male	0.67(0.390-1.121)	0.125
	Female	1	
Neonate Cong Anom	No congenital anomalies	0.293(0.088-0.974)	0.045
	Congenital anomalies	1	
Neonate Apgar	0-3	0.111(0.039-0.315)	p < 0.001
	4-6	0.592(0.314-1.114)	
	7-10	1	
Neonate Resus Care	No intervention needed	1.526(0.367-6.352)	0.561
	Resuscitation required	0.719(0.189-2.714)	
	Resuscitation care	1	
Neonate Genetics	No known genetic condition	0.70(0.228-2.156)	0.535
	Family history of NRDS	0.47(0.102-2.160)	
	Genetic and hereditary conditions	1	
Neonate Immediate care	No respiratory support	39.3(15.3-100.8)	p < 0.001
	Supplemental oxygen	3.38(1.48-7.74)	
	Mechanical ventilation	0.44(0.05-3.85)	
	Respiratory issues	1	

Discussion

The findings of this study showed that both maternal and neonatal-related factors had a significant effect on the risk of Neonatal Respiratory Distress Syndrome (NRDS). Prematurity (were identified as key predictors of NRDS. These results highlight the complex interplay of biological and healthcare-related factors contributing to NRDS incidence in tertiary care hospitals of Peshawar (2024–2025).

This study identified prematurity (as significant risk factors for Neonatal Respiratory Distress Syndrome (NRDS). Prematurity was the strongest independent predictor, aligning with studies that confirm immature lungs and surfactant deficiency as key contributors (16). The Cesarean section, particularly elective procedures, was significantly associated with NRDS, consistent with findings that lack of labor-induced catecholamine release impairs lung fluid clearance (17). Low birth weight was an independent predictor, like studies that found LBW (<1.5kg) significantly increased neonatal mortality (18). Male neonates were more likely to develop NRDS, supporting research on testosterone delaying surfactant production (19). Maternal diabetes was significantly associated with NRDS, reinforcing evidence that fetal hyperinsulinemia inhibits surfactant production (20). Antenatal corticosteroid underuse was highlighted, highlighting implementation gaps in preventive therapy, despite strong recommendations for antenatal steroids in preterm labor (21). Seasonal trends showed higher NRDS incidence in winter, possibly linked to maternal infections, hypothermia, and vitamin D deficiency, contributing novel data on climatic influences (22).

Limitation Of the Study

This study did not assess mortality or treatment outcomes, and seasonal analysis may be confounded by infections and air pollution. Findings may also lack generalizability as the study was conducted on hospital-admitted neonates.

Conclusion

NRDS is strongly associated with modifiable maternal and neonatal factors, including prematurity, low birth weight, cesarean delivery, and maternal diabetes. Preventive strategies such as timely antenatal steroid administration and improved maternal care can significantly reduce NRDS risk. In neonates, factors like low gestational age and birth weight serve as key indicators for clinicians. This study highlights the need for enhanced prenatal care, targeted neonatal monitoring, and region-specific research to improve NRDS management in resource- constrained settings like Peshawar.

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