ORIGINAL ARTICLES

INFLUENCE OF MATERNAL RISK FACTORS IN PULMONARY MATURITY IN PRETERM NEWBORN

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Abstract

Background: Respiratory distress syndrome (RDS) is one of the most frequent causes for respiratory distress in the preterm newborn. It is one of leading cause of mortality in developing country.

Objective: This study investigated the influence of maternal risk factors and effect of antenatal steroid in pulmonary maturity in preterm newborn.

Material and method: This was a prospective cohort study of 142 preterm babies who were selected randomly and were assessed for development of RDS. Maternal risk factors like pregnancy induced hypertension (PIH), premature rupture of membranes (PROM), anemia, maternal diabetes, twin gestation, high and low socio-economic classes were studied in relation to development of RDS in the preterm newborns. Each group of babies with maternal risk factors was compared with uncomplicated group with respect to the development of RDS. Newborn with antenatal steroid treatment were compared with newborn without antenatal steroid with respect to development of RDS.

Results: Prolonged rupture of membranes, higher socio-economic class, male gender, intrauterine growth restriction were risk factors for RDS, whereas pregnancy induced hypertension, maternal anemia, lower socio-economic class, female gender, appropriate for gestational age (AGA) babies, and antenatal steroid causes accelerated pulmonary surfactant maturity in preterm newborn. RDS incidence decreased with increase in gestational age, and increase in birth weight, but it was not statistically significant. Twin gestation and maternal diabetes does not appear to be a risk factor in development of RDS. Antenatal steroid is unable to demonstrate the beneficial effect in babies with PIH, PROM, male gender and small for gestational age (SGA) babies compared to non- steroid group.

Conclusion: There are several risk factors which influence pulmonary maturity in preterm babies and if identified early with appropriate interventions can prevent RDS.

Introduction

Infants born preterm are at high risk of developing respiratory distress syndrome (RDS) which has its own attendant mortality and morbidity. Therefore, the prevention of RDS in those born preterm makes sound clinical sense. (1) RDS is relatively uncommon in India as compared to the western countries, where RDS is the commonest cause of neonatal morality. Available evidence suggests that the disorder may be less common than the overall 1% incidence reported from developed countries. (2) In developing countries, despite facilities for respiratory care of newborn infants, RDS mortality rate and percentage of complications still remain high in comparison to the developed countries. Survival rates of RDS infants requiring mechanical ventilation ranged from 25% in those newborns with birth weight <1000 grams up to 53% in those with birth weight >2500 grams. (3) There have been limited data about causes of high mortality rate in infants with RDS from developing countries. (3)

There is no general agreement as to the etiology of RDS. However number of maternal and fetal factors influences its occurrence, prematurity is one of these. (4) Certain stressful conditions in the mother for example pre-eclamptic toxemia (PET), anemia, premature rupture of membranes (PROM) may influence the surfactant maturity. (4) In normal pregnancies lecithin?sphingomyelin ratio (L/S ratios) closely correlates with gestational age (and to a lesser extent birth weight). In many high risk pregnancies with maternal disease, however, there is not a good correlation and biochemical maturation of fetal lung may be either accelerated or delayed depending on the maternal disease. (4)

The exact cause of relatively low incidence of RDS in India is unknown but may be partly due to the greater maturity of low birth weight babies due to high incidence of intrauterine growth retardation, chronic placental dysfunction, low neonatal autopsy rate, maternal infections. (5,6) There have been few studies to document the role of maternal risk factors in the development of RDS in preterm babies especially Indian studies. (7,8) The present study was undertaken to study the influence of maternal risk factors like pregnancy induced hypertension (PIH), PROM, anemia, diabetes mellitus, twin gestation and socio-economic status on earlier maturity of surfactant in preterm babies and also the use of antenatal steroids for pulmonary maturity in preterm babies.

Materials and Methods

This prospective study was done to study the incidence of RDS in preterm neonates (born before 36 weeks of gestation) as per gender, gestational age and birth weight. The study analyzed the influence of various maternal risk factors and RDS. The study was carried out in two hospitals offering level II neonatal care at Pune, Maharashtra, India between May 2009 to April 2010. One hundred forty two preterm babies born with vertex presentation delivered vaginally were selected with one or no maternal risk factor and with elimination of exclusive criteria. Mothers with only one risk factor at a time were included in each of the risk groups to exclude the influence of other risk factors on that particular risk factor. All neonates with intrauterine distress, neonates with congenital malformations, mothers with antepartum hemorrhage, Rh incompatibility and neonates with birth asphyxia were excluded. When the fetal heart rate developed either 1) tachycardia above 170 beats per min and alternated with bradycardia and repeated itself in short intervals or 2) bradycardia which persisted or became progressive, the fetus in utero was considered to be in distress.(9)The neonates delivered by caesarean section were also excluded as incidence of RDS is more among neonates delivered by caesarean section.(10)

Details about antenatal profile, treatment history,

complications during pregnancy were recorded. Induction of lung maturity was considered to have been performed in cases in which a full course of betamethasone (two doses of 12 mg 24 hourly) was administered to the mother. All neonates were examined daily and all postnatal records entered in detail. Gestational age was calculated by New Ballard Scoring System. (11) Shake test (12) was done for diagnosis of prematurity as per protocol of the NICU. The following definitions were used for the reference as per standard (13): Pregnancy induced hypertension (PIH)- PIH is a syndrome complex with hypertension of 140/90mm Hg or more, presence of edema or proteinuria or both and induced by pregnancy after the 20th week of gestation. Prolonged Rupture of Membrane (PROM) was defined as spontaneous rupture of membrane any time during pregnancy beyond 20th week but before the onset of labor for more than 24 hours. Anemia was defined as hemoglobin concentration of less than 11gm/dl at term. Socio-economic status was calculated as per updated Kuppuswami?s Scale 2007. Small for gestational age (SGA) included those infants whose birth weight less than two standard deviation below the mean for that particular gestational age. Large for gestational age (LGA) included those infants whose birth weight more than two standard deviation above the mean for that particular gestational age. Silverman-Anderson score (SA Score) was used for assessment of respiratory distress in premature infant. In this score, the lower the total score better the baby. Score of more than 6 indicates respiratory failure.

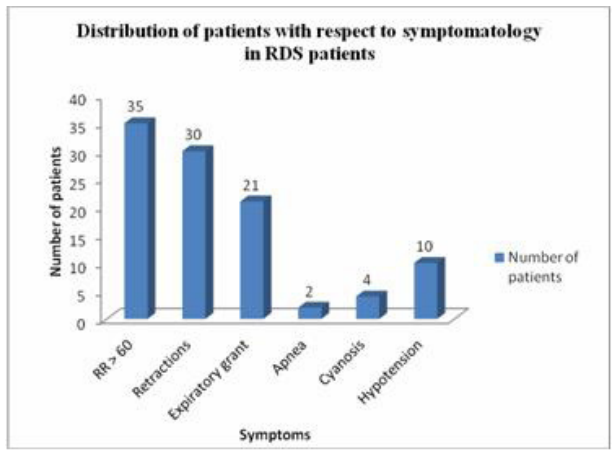
The preterm babies in the study group were divided into three groups. Group I: upto 30 weeks gestation; group II: between 31 and 34 weeks gestation and group III: above 34 weeks gestation. The study was approved by the Ethics committee of hospital and parent?s written consent was taken for the same. Treatment care for preterm babies was taken as per standard protocol. Sample size was calculated by the formula, 4PQ/L2, where P is prevalence of the disease, Q is 1-P and L is experimental error. Each group of babies with maternal risk factors was compared with uncomplicated group with respect to the development of RDS. P-value was derived by using 2 sample proportion tests. 'P' value less than 0.05 was considered significant.

Results

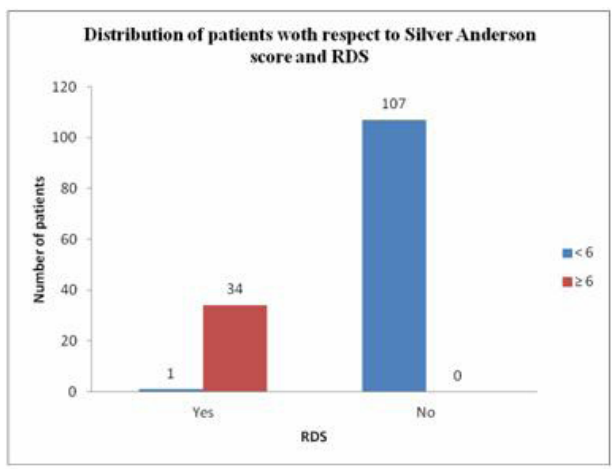
Out of 142 preterm babies, 40 (28.2%) were born to mothers with uncomplicated pregnancies whereas 102 (71.8%) were born to pregnancies with maternal risk factors. Male: female ratio was 62:80. In present study, 63 (44.4%) babies were in Group 1, 54 (38%) were in Group II, whereas 25 (17.6%) were in Group III. Seventy seven (54.2%) babies were appropriate for gestational age (AGA) babies, 62(43.7%) were SGA babies and 3 (2.1%) were LGA babies. Among the mothers, 29 (20.4%) had PIH, 5 (3.5%) had diabetes mellitus, 21 (14.8%) had anemia, 5(3.5%) had twin gestation, 26 (18.3%) had PROM, 6 (4.2%) were from high socio-economic status while 10 (7%) had low socio-economic status. Table 1 shows correlation of various risk factors with respiratory distress syndrome.

Table 2 summaries comparison of patients with positive risk factor with respect to RDS and antenatal steroid. Graph 1 summaries distribution of patients with respect to symptomatology in RDS patients. Comparison of patients with respect to Silverman Anderson (SA) score and RDS is shown in graph 2.

Graph 1: Distribution of patients with respect to symptomatology in RDS patients.



Graph 2: Comparison of patients with respect to Silverman Anderson (SA) score and RDS.



Discussion

In this study, there was a statistically significant decrease in incidence of RDS in female babies. Antenatal steroids may have contributed for decrease in the incidence of RDS in females as 60% females had received antenatal steroids while in males it was 54%. Maternal risk factors also contributed for this. None of the female babies with PIH risk factor developed RDS. Powers et al (14) observed RDS in 35% males while only 12% females were affected. Similarly male predominance in RDS has been depicted in other studies. Slower lung maturation among male fetuses is a major contributing factor to the sex differential in neonatal mortality. (14-15)

Total RDS incidence in this study was 24.6%.

Table 1: Correlation of various risk factors with respiratory distress syndrome

Variables		Respiratory Distress Syndrome		p-value
		Present	Absent	
Gender	Male	22 (35.5%)	40 (64.5%)	0.009
	Female	13(16.2%)	67(83.8%)	
Gestational Age	<30 weeks	18(28.6%)	45(71.4%)	0.4634
	30-34 weeks	13(24.1%)	41(75.9%)	
	>34 weeks	4 (16%)	21 (84%)	
Weight in kg	<1	8 (33.3%)	16 (66.7%)	0.176
	1-1.5	21 (27.3%)	56(77.7%)	
	>1.5	6(14.6%)	35(85.4%)	
Gestational Weight	AGA	11(14.3%)	66(85.7%)	0.0076
	SGA	23(37.1%)	39(62.9%)	
	LGA	1(33.3%)	2(66.7%)	
Pregnancy induced hypertension		2 (6.9%)	27(93.1%)	0.029
Maternal Diabetes Mellitus		2 (40%)	3 (60%)	0.107
PROM		13 (50%)	13 (50%)	0.037
Duration Of PROM	>48 hours	4(30.8%)	9(69.2%)	0.024
	24-48 hours	11(73.3%)	4(26.7%)	
Twin	Present	2 (40%)	3 (60%)	0.513
Socioeconomic Status	High	4(66.7%)	2 (33.3%)	0.018
	Low	1 (10%)	9 (90%)	
Maternal anemia		1 (4.8%)	20 (95.2%)	0.017
Antenatal steroid		15(18.3%)	67(81.7%)	0.04

Note: AGA: Appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, PROM: Premature rupture of membranes.

Table 2: Comparison of patients with positive risk factor with respect to RDS and antenatal steroid

Positive risk factor	Antenatal steroid	RDS		Total	p- value	Relative risk
		Present	Absent			
PIH	Given	0	13(100%)	13	0.127	0
	Not given	2 (12.5%)	14 (87.5%)	16		
PROM	Given	8 (44.4%)	10(55.6%)	18	0.384	0.711
	Not given	5 (62.5%)	3 (37.5%)	8		
Male	Given	11(32.4%)	23(67.6%)	34	0.571	0.82
	Not given	11(39.3%)	17(60.7%)	28		
Female	Given	4 (8.3%)	44(91.7%)	48	0.026	0.212
	Not given	9 (28.1%)	23(71.9%)	32		
AGA	Given	3 (6.9%)	40(93.1%)	43	0.025	-
	Not given	8 (23.5%)	26(76.5%)	34		
SGA	Given	11(28.9%)	27(71.1%)	38	0.094	-

Note: PIH- pregnancy induced hypertension, AGA: Appropriate for gestational age, SGA: small for gestational age, PROM: Premature rupture of membranes

However, there was no statistical association between gestational age and RDS, though incidence decreased with increase in gestational age. This may be related to small sample size. Similarly, McElrathet al (16) observed RDS in 26.3% babies <32 weeks, 15% babies born at 33-34 weeks and 6.9% at 35-37 weeks of gestation. Heljic found no statistical difference in gestational age and RDS. (17)

Though incidence of RDS decreased as birth weight increased, it was not statistically significant in our study. Similar findings have been reported by Bhutta et al. (18) In our study, there was statistically significant increase in RDS in SGA as compared to AGA babies. Similarly Procianoy et al (19) observed 74% RDS in SGA while 5% in AGA babies. Similarly, increased incidence of RDS among SGA babies has been found in other studies. (20,21) Probable reason for lower incidence of RDS in AGA babies may be due to the fact that AGA may be prone to earlier pulmonary maturity due to delayed maturation.

PIH was associated with statistically significant decrease in incidence of RDS suggesting acceleration of pulmonary maturity. In these babies, female sex (55%), antenatal steroid (51%) and gestational age more than 30 weeks (66%) also contributed for earlier pulmonary maturity. Similar observations in other studies had also found acceleration of pulmonary maturity with PIH. (22-23). Pregnancies complicated by PIH were associated with raised maternal ACTH levels and reduced plasma cortisol levels. The maternal adrenal gland in PIH may be relatively unresponsive to ACTH stimulation so that excess ACTH crosses the placenta and induces maturity of surfactant by causing release of glucocorticoids in fetus. (24)

There was no significant association between maternal diabetes and incidence of RDS. Antenatal steroid was not given in all babies who developed RDS. Both babies who developed RDS were SGA who were prone for late pulmonary maturity. In this study, glucose control was not considered. Though diabetes mellitus in mother is associated with increased incidence of RDS in some studies (25), opposite results have been seen in other studies. (26) Hubbett et al could not demonstrate any role of maternal diabetes as an independent variable in RDS. (27)

PROM was associated with significant increase in incidence of RDS. Increased incidence of RDS in babies with PROM may be due to high number of babies (46%) with less gestational age (<30 weeks) in this study. Again different results have been obtained in various studies about effect of PROM and RDS with Mercer et al (28) reporting increased incidence of RDS in PROM whereas Jone et al found there was no association between PROM and RDS. (29)

There was no significant association between twin delivery and RDS. In twin babies who did not develop RDS, female sex (66%), and antenatal steroid (60%) contributed for earlier pulmonary maturity. Zygosity of twins and comparison of RDS in first and second born twin was not considered in this study. Similar findings have been reported in other studies. (30-31)

In this study, incidence of RDS was higher in high socio-economic class. In low socio-economic status, poor nutrition and recurrent infection may have produced stressful environment to the fetus and accelerated the fetal lung maturity. Maternal anemia was a risk factor for RDS in the baby. Maternal anemia may have produced stressful environment to the fetus which accelerated the pulmonary maturity. Naeye et al showed that poorly nourished mother had more mature lungs as compared to well-nourished mothers. (32)

There was statistically significant decrease in RDS after antenatal steroid therapy. Multiple antenatal steroid doses and other benefits of antenatal steroid were not considered in this study. Steroids increase phosphatidylcholine synthesis and morphologic remodelling of alveolar structure, including the thinning of interstitial components of fetal lung and enhance maturity. Similar findings of antenatal steroids were seen in other studies. (33-34)

There was no significant decrease in RDS when antenatal steroid was given in PIH mothers as seen in other studies. The exact etiology for these finding is not known and same findings were seen in other studies. (35-36) Similarly, steroids had no effect on incidence of RDS in mothers having PROM as seen in other studies. (37-38) However, RDS was less in patients having longer duration of PROM as prolonged rupture of membranes causes induction of glucocorticoids due to fetal infection and causes earlier surfactant maturity. (39) Antenatal steroids causes significant decrease in RDS in AGA babies, but not in SGA babies. Similar effects have been seen in other studies by Elimian et al (36) and Van Stralenc. (40)

Silverman-Anderson score 6 or more correlates with presence of RDS (41) as was also seen in our study. Thus, this score is useful in to predict RDS.

Conclusion

Prolonged rupture of membranes, higher socio-economic class, male gender, intrauterine growth restriction were risk factors for RDS, whereas pregnancy induced hypertension, maternal anemia, lower socio-economic class, female gender, AGA babies, and antenatal steroid causes accelerated pulmonary surfactant maturity in preterm newborn. Twin gestation and maternal diabetes does not appear to be a risk factor in development of RDS. Antenatal steroid is unable to demonstrate the beneficial effect in babies born to mothers with PIH, PROM, male gender and SGA babies compared to non- steroid group. These risk factors which influence pulmonary maturity in preterm babies, if identified early and appropriate interventions done at time, incidence of RDS can be decreased.

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