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Original article

Does the time of delivery after antenatal corticosteroids matter?

Patrícia Campos[1], Gustavo Rocha[2], Filipa Flor-de-Lima[1,2], Hercília Guimarães[1,2]

[1]Faculty of Medicine of Porto University, Porto, Portugal

[2]Neonatal Intensive Care Unit, Department of Pediatrics, Centro Hospitalar São João, Porto, Portugal

Abstract

Introduction: Preterm delivery is associated with an increased risk of newborn morbidity and mortality. Respiratory distress syndrome (RDS) is the most common comorbidity. It has been proven that this syndrome can be prevented with the administration of antenatal corticosteroids to women at risk of preterm delivery, before 35 weeks of gestational age.

Aim: To evaluate the risk factors, severity, co-morbidities, and mortality of RDS in newborns of less than 35 weeks of gestational age, with specific emphasis on the association between the elapsed time since the administration of the last dose of a full cycle of corticosteroids and the frequency and severity of RDS.

Methods: This descriptive retrospective study includes all newborns of less than 35 weeks of gestational age, who were born at our center between January 1, 2012 and December 31, 2014 and admitted to Neonatal Intensive Care Unit (NICU). Newborns with major malformations, chromosomopathies, hydrops, congenital TORCH infection or outborns were excluded. RDS was diagnosed according to the criteria of the *Update on the European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants* (2013) and classified with a grade of I to III, in accord with radiographic results.

Results: A total of 234 newborns were studied, of which 35.5% had RDS. Antenatal corticosteroids were used for 90.1% of all newborns. When adjusted to the severity of RDS, birth weight, gestational age, and vasopressor support were all predictive factors of newborn mortality. A ROC curve identified a cut-off of at most 10.5 hours between the last dose of a full cycle of corticosteroids and the delivery as higher risk of onset of RDS and another cut-off of at most 6.5 hours as higher risk of onset of moderate to severe RDS (sensitivity of 80.0% and 83.3%, respectively).

Conclusion: The last dose of a full antenatal corticosteroids cycle must be given at least 10.5 hours prior to delivery to prevent the onset of RDS and at least 6.5 hours before to prevent the onset of moderate to severe RDS.

Keywords

Respiratory distress syndrome, antenatal corticosteroids, preterm birth, newborn, neonatal intensive care unit, risk factors.

Corresponding author

Patrícia Campos, Faculty of Medicine of Porto University, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal; email: mimed09113@med.up.pt.

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Introduction

Preterm delivery is associated with an increased risk of newborn morbidity and death. Respiratory distress syndrome (RDS) is the most common consequence and cause of morbidity in preterm newborns [1-3].

The administration of antenatal corticosteroids to women at risk of a preterm delivery before 35 weeks of gestational age has been proved to prevent RDS by increasing the rate of maturation of the fetal lung and other tissues [4, 5]. Additionally, antenatal corticosteroids have been associated to a diminished risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early sepsis, and neonatal death [2, 4].

Major benefits of antenatal corticosteroids are observed in deliveries occurring between 24 hours and 7 days after the beginning of therapy; however, the effect seems to be diminished 14 days after administration [2-4, 6].

Recent studies have shown that multiple courses were not recommended, due to associations with reduced fetal growth, increased risk of adrenal suppression, and a failure to reduce the risk of death [2, 7, 8]. Nevertheless, according to the *Update of the European Consensus Guidelines on the Management of Neonatal RDS in Preterm Infants* (2013), a rescue course can be administered if more than 2 to 3 weeks have passed since the first course for women at risk of preterm delivery and gestational age below 33 weeks [6].

The natural progression of RDS consists of a state of pulmonary inefficiency, caused by the deficiency of surfactant production in fetal lungs with structural immaturity. This is first observed at delivery and increases in severity throughout the first 2 days of the infant's life [2, 6]. If left untreated, the disease can lead to respiratory failure and sometimes to death of a newborn [6].

Risk factors for this pathology are male sex, low birth weight, and low gestational age, multiple gestations, maternal diabetes, pregnancy complications, chorioamnionitis, caesarean section, 5th minute Apgar score lower than 7 [9, 10]. Antenatal corticosteroid therapy and spontaneous preterm rupture of membranes reduce the risk of RDS [10].

This study aims to evaluate the risk factors, severity, co-morbidities, and mortality of RDS in newborns of less than 35 weeks of gestational age and to assess if the elapsed time from administration of the last dose of a full cycle of corticosteroids influences the frequency and severity of RDS.

Methods

The authors performed a descriptive retrospective study of all newborn infants of less than 35 weeks of gestational age born between January 1, 2012 and December 31, 2014 at Hospital São João, admitted to the Neonatal Intensive Care Unit (NICU). At our center, all preterm newborns of less than 35 weeks of gestational age are admitted to the NICU, regardless of their respiratory status. Those with major malformations, chromosomopathies, hydrops, congenital TORCH (Toxoplasmosis; Others such as syphilis, varicella-zoster or parvovirus B19; Rubella; Cytomegalovirus; and Herpes) infections, and outborns were excluded.

According to the Protocol of Gynecology and Obstetrics Department at our hospital, the antenatal therapy with corticosteroids is performed in mothers of less than 35 weeks of gestational age, who are at risk of preterm labor. Betamethasone (2 doses of 12 mg separated by 24 hours) was used until February of 2014. Dexamethasone (4 doses of 6 mg every 12 hours) was used since March of 2014. A rescue cycle is used for mothers who maintain criteria for corticosteroids therapy after a medical team decision.

The demographic, antenatal, and placental data, as well as information regarding corticosteroids administration, delivery, admission and evolution in NICU, treatment at discharge, and necropsy results of the newborns that died, were collected from clinical charts and retrospectively analyzed.

RDS was diagnosed by a combination of clinical and radiographic features, according to the criteria of the *Update on the European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants* (2013) [6]. These criteria are: (1) PaO_2 < 50 mmHg or central cyanosis in room air or a need for supplemental oxygen to maintain PaO_2 > 50 mmHg or to maintain oxygen saturation > 85% within the first 24 hours of life; and (2) a chest radiography consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life [6]. For practical purposes, two neonatologists classified RDS with a grade of I to III, according to radiographic results (I – mild, slight reticulogranular appearance; II – moderate, reticulogranular appearance with air bronchograms; III – severe, unclear cardiac borders or white lung) [11].

Gestational age (completed weeks) was determined by menstrual age in women with regular menstrual cycles, by ultrasonography when a discrepancy of two or more weeks between menstrual age and ultrasonographic age occurred or in the absence of a menstrual date, or by the New Ballard Score in the absence of obstetrical indexes [12]. Intrauterine growth restriction was defined as a birth weight below the 3rd centile of Fenton`s growth charts [13]. Histological chorioamnionitis classification was made based on the method proposed by Blanc (stage I: intervilositis, stage II: chorionitis, stage III: chorioamnionitis) [14]. Funisitis was defined as polymorphonuclear leukocytes in the wall of umbilical vessels or in Wharton's jelly [15]. Villitis was diagnosed by the presence of a mononuclear infiltrate in the villous tree [16]. Vasculitis was defined as a polymorphonuclear leukocytes infiltrate in the chorionic or umbilical vessel walls [17].

Bronchopulmonary dysplasia (BPD) was diagnosed when a requirement for supplementary oxygen in the newborn persisted for at least 28 days after delivery associated to characteristic radiographic features. Classification was made according to the National Institutes of Health consensus criteria [18]. Patent ductus arteriosus (PDA) was confirmed by echocardiography with Doppler [19, 20]. NEC was defined by clinical findings (such as a feeding intolerance for longer than 24 hours and abdominal distension, the presence of radiological features such as intramural air, perforation or meconium plug syndrome), or by definitive surgical findings. NEC was classified according to the modified Bell staging criteria [21]. IVH was diagnosed when transfontanellar ultrasound demonstrated intraventricular bleeding confined to the periventricular area (grade 1), without ventricular dilatation (grade 2), with ventricular dilatation (grade 3) or with parenchymal involvement (grade 4) [22]. Periventricular leukomalacia (PVL) was diagnosed when a hypoechoic cyst in the periventricular white matter was observable in the ultrasound [22]. Retinopathy of prematurity (ROP) was diagnosed and graded by ophthalmologists according to the *International Classification of Retinopathy of Prematurity revisited* [23]. Sepsis was suspected in the presence of positive laboratory findings in patients with suggestive clinical features and diagnosed when a blood culture turned out to be positive [22]. Pneumonia was diagnosed by a combination of clinical and laboratory findings, as well as a chest radiography showing patchy infiltrate, granularity, air bronchogram or consolidation [24]. Pneumothorax was suspected by clinical findings and confirmed with a chest radiography showing air in the pleural space [25].

Surfactant therapy, poractant alfa, was administered to newborns based on the protocol of our unit: in an initial dose of 200 mg/kg and, if needed (RDS with a persistent need of FiO_2 > 0.4), subsequent doses of 100 mg/kg [6].

Postnatal intravenous corticosteroids were administrated according to the DART protocol when indicated [26].

The statistical analysis was performed using SPSS® for Windows®, version 20. Continuous variables were characterized by mean (± standard deviation) or median (medium-maximum) if they had symmetric or asymmetric distribution respectively and categorical variables by absolute and relative frequencies. To compare continuous variables parametric tests (independent t test and One-Way ANOVA) or non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test) were used if they had two or more than two categories, and Chi-squared or Fisher's exact test to compare categorical variables, the latter for expected values lower than 5. A multivariate analysis by logistic regression was performed to evaluate predictive factors of severity and mortality. Receiver operating characteristic (ROC) curve was performed to study the time between last dose of a full cycle of corticosteroids and delivery and the risk of RDS. A p-value lower than 0.05 was considered statistically significant.

This study protocol has been approved by the ethics committee at our hospital.

Results

Two hundred and thirty-four newborns were admitted to the NICU and included in the study. Two hundred and ten (90.1%) of these newborns were treated with antenatal corticosteroids. Eighty-three (35.5%) newborns had RDS while 151 (64.5%) remained without RDS. Seventeen (7.3%) infants died in the NICU.

Tab. 1 describes demographic, antenatal risk factors related to RDS, and administration of corticosteroids.

The mode of delivery, morbidity and mortality related to RDS are represented in **Tab. 2**.

Tab. 3 shows the differences in demographics and clinical characteristics according to severity of RDS. There was no significant association between the severity of RDS and the elapsed time since the administration of the last dose of a full antenatal corticosteroids cycle in the univariate analysis. Severity of RDS was inversely related to gestational age (p = 0.014). Multiple gestation was significantly more frequent in infants with more severe grades of RDS (p = 0.025). Infants with severe RDS completed the cycle of antenatal corticosteroids less frequently (p = 0.013). In more severe stages of RDS, the newborns needed

Table 1. Demographic, antenatal risk factors related to respiratory distress syndrome (RDS), and administration of steroids.

	Total (n = 234)	RDS (n = 83)	Without RDS (n = 151)	p
Gender, n (%)				
Male	134 (57.3)	44 (53.0)	90 (59.6)	0.330[a]
Female	100 (42.7)	39 (47.0)	61 (40.4)	0.330[a]
Birth weight (grams), mean (± SD)	1,658 (± 578)	1,225 (± 516)	1,896 (± 462)	< 0.0001[c]
Gestational age (weeks^{+days}), median (min-max)	32 (23-34^{+6})	30 (23-34^{+6})	33 (27-34^{+6})	< 0.0001[d]
Antenatal Steroids, n (%)	210 (90.1)	74 (90.2)	136 (90.1)	0.965[a]
Betametasone	160 (76.2)	52 (70.3)	108 (79.4)	0.137[a]
Dexametasone	50 (23.8)	22 (29.7)	28 (20.6)	0.175[a]
Full first cycle	146 (69.5)	50 (67.6)	96 (70.6)	0.650[a]
Full rescue cycle	8 (3.8)	2 (2.7)	6 (4.4)	0.715[b]
Time between the last dose of a full cycle of steroids and delivery (hours), median (min-max)	75 (1-1,148)	59 (1-1,148)	81.5 (1-1,096)	0.271[d]
Intrauterine growth restriction, n (%)	39 (16.7)	18 (21.7)	21 (13.9)	0.127[a]
Multiple gestation, n (%)	81 (34.6)	24 (28.9)	57 (37.7)	0.174[a]
Maternal diseases, n (%)				
Chronic hypertension	23 (9.8)	12 (14.5)	11 (7.3)	0.078[a]
Human Immunodeficiency Virus infection	1 (0.4)	0	1 (0.7)	0.999[b]
Hepatitis B infection	2 (0.9)	1 (1.2)	1 (0.7)	0.999[b]
Pregnancy complications, n (%)				
Gestational diabetes	21 (9.0)	10 (12.0)	11 (7.3)	0.223[a]
Gestational hypertension	13 (5.6)	3 (3.6)	10 (6.6)	0.390[b]
Pre-eclampsia	46 (19.7)	17 (20.5)	29 (19.2)	0.814[a]
HELLP syndrome	7 (3.0)	4 (4.8)	3 (2.0)	0.249[b]
Clinical chorioamnionitis	13 (5.6)	10 (12.0)	3 (2.0)	0.002[b]
Placental abruption	21 (9.0)	12 (14.5)	9 (6.0)	0.030[a]
Abnormal umbilical flow	34 (14.5)	29 (22.9)	15 (9.9)	0.007[a]
Hydramnios	7(3.0)	3 (3.6)	4 (2.6)	0.701[b]
Oligoamnios	9 (3.8)	5 (6.0)	4 (2.6)	0.286[b]
Premature membrane rupture, n (%)	49 (21.1)	13 (16.0)	36 (23.8)	0.166[a]
Placental histology, n (%)				
Chorioamnionitis	54 (24.3)	25 (30.5)	29 (20.7)	0.101[a]
Funisitis	7 (3.2)	4 (4.9)	3 (2.1)	0.428[b]
Vilitis	14 (6.3)	3 (3.7)	11 (7.9)	0.263[b]
Vasculitis	18 (8.1)	9 (11.1)	9 (6.4)	0.220[a]
Hemorrhage	1 (0.5)	0	1 (0.7)	0.999[b]
Ischemia	97 (43.7)	34 (41.5)	63 (45.0)	0.608[a]

[a]Chi-squared test; [b]Fisher's exact test; [c]Independent t test; [d]Mann-Whitney U test.
HELLP syndrome: Hemolysis, elevated liver enzymes and low platelet count Syndrome.

Table 2. Mode of delivery, and neonatal outcomes in relationship to respiratory distress syndrome (RDS).

	Total (n = 234)	RDS (n = 83)	Without RDS (n = 151)	p
Delivery, n (%)				
Vaginal	95 (40.6)	26 (31.3)	69 (45.7)	0.032[a]
C-section	139 (59.4)	57 (68.7)	82 (54.3)	0.032[a]
Apgar score, n (%)				
1st min < 7	74 (31.6)	47 (56.6)	27 (17.9)	< 0.0001[a]
5th min < 7	22 (9.4)	17 (20.5)	5 (3.3)	< 0.0001[a]
Resuscitation, n (%)	96 (41.0)	62 (74.7)	34 (22.5)	< 0.0001[a]
Early nasal CPAP, n (%)	75 (32.1)	28 (33.7)	47 (31.1)	0.682[a]
Early invasive ventilation, n (%)	42 (18.1)	40 (48.8)	0	< 0.0001[b]
Neonatal morbidities, n (%)				
BPD	15 (6.4)	15 (18.1)	0	< 0.0001[b]
PDA	59 (25.2)	42 (50.6)	17 (11.3)	< 0.0001[a]
PDA surgical treatment	6 (10.2)	6 (14.3)	0	0.002[b]
NEC (≥ grade 2A)	0	0	0	-
IVH (≥ grade 3)	9 (3.9)	7 (8.5)	2 (1.3)	0.010[b]
Hydrocephalus	1 (0.4)	1 (1.2)	0	0.355[b]
PVL	5 (2.2)	3 (3.7)	2 (1.3)	0.346[b]
ROP (≥ grade 2)	12 (5.2)	11 (13.4)	1 (0.7)	< 0.0001[b]
Sepsis	27 (11.5)	22 (26.5)	5 (3.3)	< 0.0001[a]
Pneumonia	6 (2.6)	6 (7.2)	0	0.002[b]
Pneumothorax	8 (3.4)	8 (9.6)	0	< 0.0001[b]
Atelectasis	7 (3.0)	7 (8.4)	0	0.001[b]
Seizures	3 (1.3)	3 (3.6)	0	0.044[b]
Acute renal failure	15 (6.4)	14 (16.9)	1 (0.7)	< 0.0001[b]
Thrombocytopenia with platelet transfusion	16 (6.8)	16 (19.3)	0	< 0.0001[b]
Anemia with red blood cells transfusion	58 (24.8)	44 (53.0)	14 (9.3)	< 0.0001[a]
Gastroesophageal reflux	24 (10.3)	17 (20.5)	7 (4.6)	< 0.0001[a]
Vasopressor support, n (%)	15 (6.4)	14 (16.9)	1 (0.7)	< 0.0001[b]
Vasopressor support (days), median (min-max)	2 (1-25)	2.5 (1-25)	1 (1-1)	0.308[c]
Oxygen therapy, n (%)	82 (35.2)	64 (78.0)	18 (11.9)	< 0.0001[b]
Oxygen therapy (days), median (min-max)	4 (1-191)	6 (1-191)	1.5 (1-6)	< 0.0001[c]
Invasive ventilation, n (%)	57 (24.4)	57 (68.7)	0	< 0.0001[b]
Invasive ventilation (days), median (min-max)	5 (1-88)	5 (1-88)	-	-
Parenteral nutrition, n (%)	175 (76.1)	75 (93.8)	100 (66.7)	< 0.0001[a]
Parenteral nutrition (days), median (min-max)	9 (1-90)	14 (1-90)	7 (1-20)	< 0.0001[c]
Surfactant, n (%)	67 (28.6)	67 (80.7)	0	< 0.0001[b]
Doses, median (min-max)	1 (1-5)	1 (1-5)	0	< 0.0001[c]
First dose of surfactant (hours), median (min-max)	1 (0-24)	1 (0-24)	0	0.441[c]
Postnatal iv steroids, n (%)	7 (2.9)	7 (8.4)	0	0.001[b]
Bronchodilators, n (%)	11 (4.7)	11 (13.3)	0	< 0.0001[b]
Inhaled steroids, n (%)	11 (4.7)	11 (13.3)	0	< 0.0001[b]
Stay in NICU (days), median (min-max)	15 (1-191)	33 (1-191)	11 (1-61)	< 0.0001[c]
Transferred to another NICU, n (%)	59 (25.2)	10 (12.0)	49 (32.5)	0.001[a]
Days until transference, median (min-max)	6 (1-25)	9.5 (2-25)	5 (1-22)	0.092[c]
Treatment at discharge, n (%)				
Bronchodilator	8 (3.4)	8 (9.6)	0	< 0.0001[b]
Inhaled steroids	12 (5.1)	12 (14.5)	0	< 0.0001[b]
Oxygen	8 (3.4)	8 (9.6)	0	< 0.0001[b]
Deceased, n (%)	17 (7.3)	17 (20.5)	0	< 0.0001[b]
Causes of death, n (%)				
IVH grade IV	6 (35.3)	6 (35.3)	0	0.647[b]
Multiorgan dysfunction	6 (35.3)	6 (35.3)	0	0.647[b]
Arrhythmia	1 (5.9)	1 (5.9)	0	0.941[b]
Extreme prematurity	1 (5.9)	1 (5.9)	0	0.941[b]
Pulmonary hypoplasia	2 (11.8)	2 (11.8)	0	0.882[b]
Pulmonary hemorrhage	1 (5.9)	1 (5.9)	0	0.941[b]

[a]Chi-squared test; [b]Fisher's exact test; [c]Mann-Whitney U test.
BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; NICU: Neonatal Intensive Care Unit.

Table 3. Demographic and clinical characteristics according to severity of respiratory distress syndrome (RDS).

	Mild RDS (n = 35)	Moderate RDS (n = 32)	Severe RDS (n = 16)	p
Gestational age (weeks^{+days}), median (min-max)	33 (27-34^{+6})	31 (24-34^{+6})	29 (23-34^{+6})	0.014[c]
Multiple gestation, n (%)	7 (20.0)	8 (25.0)	9 (56.2)	0.025[a]
Antenatal Steroids, n (%)	33 (94.3)	25 (80.6)	16 (100)	0.082[b]
Full first cycle	26 (78.8)	18 (72.0)	6 (37.5)	0.013[a]
Time from last dose of steroids and delivery (hours), median (min-max)	66.5 (1-1,148)	57 (5-559)	8 (1-120)	0.102[c]
Early invasive ventilation, n (%)	11 (31.4)	17 (53.1)	12 (75.0)	0.010[b]
Neonatal morbidities, n (%)				
PDA with surgical treatment	3 (8.6)	0	3 (18.8)	0.044[b]
PVL	0	1 (3.2)	2 (12.5)	0.043[b]
Thrombocytopenia with platelet transfusion	5 (14.3)	4 (12.5)	7 (43.8)	0.035[b]
Vasopressor support, n (%)	1 (2.9)	7 (21.9)	6 (37.5)	0.003[b]
Oxygen therapy, n (%)	24 (68.6)	24 (75.0)	16 (100)	0.032[b]
Invasive ventilation, n (%)	18 (51.4)	25 (78.1)	14 (87.5)	0.016[c]
Surfactant, n (%)	22 (62.9)	29 (90.6)	16 (100)	0.001[b]
Doses, median (min-max)	1 (1-2)	1 (1-5)	2 (1-4)	0.044[c]

[a]Chi-squared test; [b]Fisher's exact test; [c]Kruskal-Wallis test.
PDA: patent ductus arteriosus; PVL: periventricular leukomalacia.

early invasive ventilation more frequently (p = 0.010). PDA with surgical treatment, PVL and thrombocytopenia with platelet transfusion were more frequent in more severe stages of RDS. The need for vasopressor support, oxygen therapy and invasive ventilation were significantly higher (p = 0.003, p = 0.032 and p = 0.016, respectively) in infants with higher grades of RDS. The surfactant was given according to the severity of RDS (p = 0.001).

Higher request for invasive ventilation and higher median number of surfactant doses were predictive factors of severity of RDS, when adjusted to birth weight and gestational age (OR = 3.0, 95% CI [1.04-8.67] and OR = 3.2, 95% CI [1.46-6.97]).

Birth weight, gestational age and need for vasopressor support, when adjusted to RDS severity, were predictive factors of mortality (OR = 0.990, 95% CI [0.98-0.99], OR = 0.459, 95% CI [0.31-0.68] and OR = 14.4, 95% CI [3.2-63.6]).

The ROC curve identified a cut-off of at most 10.5 hours between the last dose of a full cycle of corticosteroids and the delivery as a higher risk of onset of RDS. The sensitivity value of this cut-off was 80.0%.

Another ROC curve also determined a cut-off of at most 6.5 elapsed hours between the last dose of a full cycle of corticosteroids and the delivery as a higher risk of onset of moderate to severe RDS. The sensitivity value of this cut-off was 83.3%.

Discussion

Our study showed that the administration of a full cycle of antenatal corticosteroids was associated with less severe forms of the RDS. It also showed that: 1) the prevalence of RDS in newborns of less than 35 weeks of gestational age was 35.5%; lower gestational age, lower birth weight, clinical chorioamnionitis, placental abruption, abnormal umbilical flow, caesarean section, and 1st and 5th minutes Apgar score lower than 7 were more frequent in those infants; 2) co-morbidities were more frequent in preterm infants with RDS; 3) a higher request for invasive ventilation and number of surfactant doses were associated with a significantly higher severity of RDS; 4) lower gestational age and lower birth weight, as well as higher need for vasopressor support, were associated with an increased risk of mortality; 5) an elapsed time between the last dose of a full cycle of antenatal corticosteroids and the delivery of at most 10.5 hours was associated with a higher risk of onset of RDS, with a sensitivity of 80%, and of at most 6.5 hours was associated with a higher risk of onset of moderate to severe RDS, with a sensitivity of 83.3%.

Antenatal corticosteroids reduce the risk of RDS [6]. We demonstrated that a full cycle of antenatal corticosteroid was associated with less severe forms of the condition. These results exhibit the importance of using complete corticosteroid cycles in the prevention of more severe grades of RDS.

The prevalence of RDS in newborns of less than 35 weeks of gestational age was 35.5% in our samples, which is similar to the results of previous studies [2]. Lower gestational age, lower birth weight, clinical chorioamnionitis, placental abruption, abnormal umbilical flow, caesarean section, and 1st and 5th minutes Apgar score lower than 7 were more frequent in infants with RDS, which is consistent with existing literature [9, 10, 27, 28].

Lower gestational age and multiple gestations were significantly more frequent in more severe grades of RDS, as has been shown in other studies [29].

According to the literature, the use of early invasive ventilation is more frequent in the more severe grades of RDS [6]. The newborns with RDS had a significantly higher need for resuscitation and early invasive ventilation. The use of early invasive ventilation was more frequent in the more severe grades of RDS.

BPD, a complication associated with the premature lung injury, usually occurring after RDS and more frequently in more immature infants [30], also occurred in our study in newborns with RDS with an incidence of 18.1%.

PDA was the most common neonatal morbidity in the data, affecting 25.2% of all newborns and 50.6% of those with RDS, according to current literature [31]. Surgical treatment for PDA was only needed in 6 infants with RDS, because most of PDAs closes spontaneously or after the use of pharmacological treatment.

Pneumonia was observed only in newborns who had RDS (7.2%). Chorioamnionitis and invasive ventilation increased the likelihood of pneumonia [24]. Pneumothorax was observed in infants with RDS (9.6%), probably due to the higher incidence of clinical chorioamnionitis, resuscitation attempts, and mechanical ventilation [25].

IVH (≥ grade 3) and sepsis had a significantly higher incidence in infants with RDS. This could be related to the varied administration of a full cycle of antenatal corticosteroids in different grades of RDS, as corticosteroids reduce the incidence of IVH and sepsis [2, 4].

Sepsis occurred in 11.5% of all preterm newborns of less than 35 weeks of gestational age, and in 26.5% of the preterm infants with RDS, which is a known risk population for bacterial infections [32].

ROP is mainly characterized by the presence of risk factors for newborns such as prematurity, low birth weight and oxygen therapy [6]. In our study we found that RDS was associated with a significantly higher incidence of ROP (≥ grade 2).

Other observed morbidities, such as atelectasis, seizures, acute renal failure, thrombocytopenia with platelet transfusion, anemia with red blood cells transfusion, and gastroesophageal reflux, were significantly more frequent in infants with RDS, which justifies the necessity for RDS prevention.

Vasopressor support was used more frequently for newborns with RDS, especially in more severe forms. These results were in accord with our predictions since the newborns with RDS were observed to have higher morbidity, especially those who had more severe forms of RDS.

In addition, oxygen therapy was used for a significantly higher median number of days. Invasive ventilation only was needed for infants with RDS and the difference in need for invasive ventilation in the newborns was significant: when comparing the different grades of RDS, invasive ventilation was used more often for infants with more severe grades. According to literature, preterm infants with RDS who are unsuccessful with CPAP may require invasive ventilation, although this is more injurious to the lungs [6].

Parenteral nutrition was used significantly more for infants with RDS and for a higher median number of days. This result was expected because infants with RDS had lower gestational age and birth weight, and thus required longer parenteral nutrition [6].

Surfactant (prophylactic or as rescue therapy) is used as management of RDS and reduces the risk of pneumothorax and neonatal death in infants with RDS or who are at risk of developing it [6]. In our study surfactant administration was needed in 67 (80.7%) of the newborns with RDS, with a median of one dose. Surfactant administration was significantly greater for infants with more severe grades of RDS. This result was consistent with our expectations because the management of ongoing RDS includes rescue therapy with two or more doses of surfactant [6].

Postnatal intravenous corticosteroids were used in 7 (8.4%) newborns with RDS, since this facilitated the extubation procedure [6].

Bronchodilators and inhaled steroids were used in an early period of BPD in 11 (13.3%) of the newborns with RDS during the hospitalization in NICU [30].

Infants with RDS stayed for a significantly longer period in NICU. Infants without RDS

were significantly more likely to be transferred to another NICU in order to continue the treatment, due to their lower morbidity.

The mortality rate was significantly higher in newborns with RDS, as was expected. Of the 17 deceased infants, 7 (41.2%) had severe RDS, 6 (35.3%) had moderate RDS and 4 (23.5%) had mild RDS. Six infants with RDS died following grade IV IVH and 6 died following multiorgan dysfunction. These patients were given antenatal corticosteroids that did not have an appropriated therapeutic effect due to several causes, including suboptimal administration timing or incomplete cycles [6]. Arrhythmia, extreme prematurity, pulmonary hypoplasia and pulmonary hemorrhage are associated with immaturity, low birth weight, and low gestational age. This explains the deaths of an additional 5 infants with RDS [33].

Newborns with a significantly higher severity of RDS had a higher request for invasive ventilation and surfactant doses, when values were adjusted to birth weight and gestational age [6].

A higher birth weight and gestational age were associated with a lower risk of death in the infants, when results were adjusted to account for the severity of RDS. These results are in accord with existing literature, which states that gestational age is the most important predictor of survival [34]. The opposite results were observed for vasopressor support, which instead was significantly associated with an increased mortality.

In our study, a time between the last dose of a full cycle of antenatal corticosteroids and the delivery of less than 10.5 hours was associated with a higher risk of onset of RDS, with a sensitivity of 80%. An elapsed time of less than 6.5 hours between the last dose of a full cycle of antenatal corticosteroids and the delivery was associated with a higher risk of onset of moderate to severe RDS, with a sensitivity of 83.3%. It has been reported that the optimal interval between the start of corticosteroid treatment and the delivery is comprised between 24 hours and 7 days [6]. Nevertheless, our results demonstrate that the benefits of antenatal corticosteroids were observed when the delivery occurred 10.5 hours after the last dose of a full cycle.

Some limitations of our study are that it may include biases, such as a misclassification bias, due to the nature of a descriptive retrospective study. An additional limitation is that a cohort was used without a control population. Lastly, antenatal corticosteroid administration regimens have changed since March 2014, so it could be a confounding factor. Nevertheless, the aim of the study was not to compare the effect of both drugs used in prevention of RDS, which have shown a similar effect.

Conclusion

In our study, the prevalence of RDS in newborns of less than 35 weeks of gestational age was 35.5% and the identified risk factors were lower gestational age, lower birth weight, clinical chorioamnionitis, placental abruption, abnormal umbilical artery flow, caesarean section, and 1st and 5th minutes Apgar score lower than 7. Co-morbidities were more frequent in RDS preterm infants. A higher frequency of requests for invasive ventilation and number of surfactant doses were associated with a significantly higher severity of RDS. Lower gestational age and lower birth weight, as well as higher need for vasopressor support, were associated with an increased risk of mortality.

It was reported that the optimal interval between the start of corticosteroid treatment and delivery is more than 24 hours and less than 7 days.

We showed that the administration of a full cycle of antenatal corticosteroids was associated with less severe forms of the RDS and there were benefits to the administration of antenatal corticosteroids, when the delivery occurred 10.5 hours after the last dose of a full cycle of steroids. A birth time of less than 6.5 hours after the last dose of a full steroid cycle was associated with a higher risk of the onset of moderate to severe RDS.

Prospective studies could be useful for the identification of an accurate timing in the birth of preterm newborns.

Declaration of interest

The Authors declare that there is no conflict of interest.

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