Risk factors for neonatal respiratory distress syndrome in severe preeclampsia

Fatores de risco para síndrome do desconforto respiratório do recém-nascido na pré-eclâmpsia grave

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Abstract

Objectives: to identify predictive factors of respiratory distress syndrome (RDS) in severe preeclampsia.

Methods: a cross-sectional study was conducted based on the secondary analysis of a clinical trial about the use of corticosteroids to prevent RDS in severe preeclampsia. Newborn infants with (n=66) and without RDS (n=134) were compared.

Results: only fetal distress and very low birth weight were associated with increased risk of RDS, while corticosteroid therapy was significantly protective after multiple regression analysis.

Conclusions: when deciding whether to interrupt a pregnancy in cases of serious preeclampsia the risk of excessive prematurity has to be weighed up against the patient's exposure to fetal distress, and corticosteroid therapy should always be recommended.

Key words *Respiratory distress syndrome, Preeclampsia, Infant, newborn, Risks factors*

Resumo

Objetivos: identificar fatores preditivos da síndrome do desconforto respiratório (SDR) do recém-nascido em pacientes com pré-eclâmpsia grave.

Métodos: realizou-se um estudo de corte transversal baseado na análise secundária de um ensaio clínico sobre uso de corticosteróides para prevenção de SDR em pacientes com pré-eclâmpsia grave. Compararam-se recém-nascidos com (n=66) e sem SDR (n=134).

Resultados: na análise multivarida, apenas a presença de sofrimento fetal e de muito baixo-peso ao nascer estiveram associados com risco aumentado de SDR, enquanto a terapia corticosteróide apresentou significativo efeito protetor.

Conclusões: na decisão de interrupção da gravidez em casos de pré-eclâmpsia grave deve-se pesar cautelosamente o risco da prematuridade excessiva contra os efeitos deletérios do sofrimento fetal, realizando-se sempre a administração de corticóide para acelerar a maturidade pulmonar fetal.

Palavras-chave *Síndrome do desconforto respiratório, Pré-eclâmpsia, Recém-nascido, Fatores de risco*

Introduction

Premature birth is frequently associated with preeclampsia, either caused by increased uterine contractility in preeclamptic women or, more often, as a result of therapeutic interruption of pregnancy.[1] Pre-term infants account for the majority of all neonatal deaths, which are often related to respiratory distress syndrome (RDS).

The importance of RDS as a cause of neonatal mortality persists despite the progress achieved in preventing or reducing its severity, through prenatal acceleration of fetal lung maturity by corticosteroids and postnatal surfactant therapy.[2] The implementation of strategies for the prevention or early management of RDS requires the identification of predictive factors.

Apart from prematurity several other factors have been associated with higher risk of RDS: male sex, perinatal asphyxia, diabetes, second twin, previously affected newborn infants, cesarean section, maternal hemorrhage and neonatal hypothermia.[3,4] Conversely, conditions that cause chronic stress with reduced placental flow have been described as "protective" factors, promoting acceleration of fetal lung maturity via increased plasmatic cortisol.[5] Preeclampsia, chronic hypertension, vascular diseases, premature rupture of membranes and fetal growth retardation are included in this group.[5]

Nevertheless, the association of RDS with all these factors has not been definitively established and relatively few well-controlled studies have been conducted to evaluate their effect over fetal lung maturation. On the other hand, preeclampsia is one of the most important causes of elective preterm delivery and its "protective" effect over RDS has been questioned by two recent studies whose findings did not confirm the presumed association of preeclampsia with accelerated fetal lung maturation.[6,7] This case-control study was therefore carried out to contribute to determining the association between prenatal and neonatal variables and RDS in pregnancies complicated by severe preeclampsia.

Methods

This is a secondary analysis of data collected for a randomized, double blind trial of corticosteroid use for the prevention of RDS. Two hundred pregnant women with severe preeclampsia and gestational age between 26-34 weeks were enrolled over a 14 month-period (April/97 to June/98). One hundred patients were randomized to receive betamethasone (12 mg IM repeated after 24 hr and then weekly) and 100 served as control (placebo administration). Thirty-five patients received a single dose and 65 multiple doses (2-3). The median of doses was 2. Characteristics of the sample and management of preeclampsia have been published elsewhere.[8]

The overall incidence of RDS was 33%. The newborn infants with respiratory distress syndrome (n=66) were considered as cases and those without respiratory distress syndrome (n=134) as controls.

Inclusion criteria were singleton live fetus and well-documented gestational age and diagnosis of severe preeclampsia. Exclusion criteria were any other complication of pregnancy (diabetes, premature rupture of the membranes, maternal disease), congenital malformations, and perinatal hemolytic disease.

The dependent variable for this cross sectional study was RDS and the independent variables were: prenatal corticosteroid use, fetal distress, route of delivery, duration of labor, interval from ruptured membranes to delivery, gestational age at delivery, birth weight, fetal sex, Apgar scores and classification of birth weight – small or adequate for gestational age.

Severe preeclampsia was defined according to the criteria proposed by the National High Blood Pressure Working Group.[9] HELLP syndrome was defined according to Sibai.[10] Respiratory distress syndrome was diagnosed using the criteria of the Centro Latino-Americano de Perinatología[11] which include progressive increasing dyspnoea and other signs of respiratory distress, oxygen requirement at 24hr of life and characteristic radiological features (microreticulogranular infiltrates and air bronchiogram).

Gestational age was determined by last menstrual period and ultrasonography. Any difference greater than one week between these two indicators was a reason for exclusion from the study. Fetal distress was defined by one or more altered fetal well-being tests (cardiotocography, Doppler flow velocimetry or fetal biophysical profile). Preterm infants were considered small-for-gestational-age when birth weight was below 10º percentile according to Battaglia and Lubchenco.[12] Birth weight below 1.500g was characterized as very low birth weight.

Statistical analysis was performed using Epi-Info 6.04b and SPSS 6.0 for Windows. Relative risk and its 95% confidence interval ($CI_{0,95}$) of

RDS were calculated for the independent variables. Multiple logistic regression was carried out to evaluate interactions between the independent variables. A forward-conditional logistic model was used and the corresponding coefficients for each variable were adjusted for the effect of other confounding factors. Thus, adjusted relative risk of RDS was determined.[13]

Results

A significantly increased risk of RDS was observed for several prenatal variables: relative risk varied from 1,7 to almost three times greater with gestational age at delivery < 32 weeks, absence of labor, cesarean section, and fetal distress (Table 1). On the other hand, antenatal corticosteroid therapy and longer period with ruptured membranes (≥ 1hr) resulted in a significant reduction of approximately 50% in the risk of RDS (Table 1). There was no association between number of corticosteroid doses and incidence of respiratory distress syndrome (single dose=25,7%; multiple doses=21,5%, p=0,63).

Among the neonatal variables, the relative risk was about twice and significantly increased among newborns with Apgar scores <7 at 1st and 5th minutes. The risk was even greater among small-for-gestational age infants and neonates with birth weight below 1.500g. Although male infants presented a 40% greater risk of RDS, it did not reach statistical significance (Table 2).

In multivariate analysis by logistic regression (Table 3), the variables that persisted strongly associated to RDS were fetal distress, birth weight < 1.500g (increased risk) and corticosteroid use (reduced risk).

Discussion

The association of birth weight and gestational age with higher incidence of RDS had been already found in several other studies.[3,14] Few of them however, had included preeclamptic women.

The association of RDS with fetal growth retardation has been more controversial. The con-

Table 1

Relative risk of respiratory distress syndrome for prenatal variables.

Variable	Cases (n=66)	Controls (n=134)	RR	$CI_{0,95}$
Gestational age < 32 weeks	34	37	1,93	1,31 - 2,84
Corticosteroid use	23	77	0,53	0,35 - 0,82
Fetal distress	23	08	2,92	2,09 - 4,06
Absence of labor	45	67	1,68	1,09 - 2,60
Ruptured membranes (> 1 hr)	19	68	0,53	0,33 - 0,83
Cesarean section	53	80	2,05	1,21 - 3,49

Table 2

Relative risk for respiratory distress syndrome for neonatal variables.

Variable	Cases (n=66)	Controls (n=134)	RR	$CI_{0,95}$
Male sex	39	63	1,39	0,93 - 2,08
Birth weight < 1.500g	45	34	3,28	2,13 - 5,06
Apgar < 7 (1st minute)	26	28	1,76	1,20 - 2,58
Apgar < 7 (5th minute)	14	09	2,07	1,39 - 3,09
Small-for-gestational age infant	28	16	2,61	1,83 - 3,73

Table 3

Adjusted risk for prenatal and neonatal variables (multiple logistic regression analysis).

Variable	Coefficient	S.E.Coefficient*	P	RR	$CI_{0,95}$
Fetal distress	1,151	0,513	0,025	3,16	1,16 - 8,66
Corticosteroid use	-0,973	0,353	0,006	0,38	0,19 - 0,75
Birth weight < 1.500gr	1,515	0,380	0,001	4,55	2,14 - 9,66
Constant	- 1,149	0,275	0,000		

cept that chronic placental dysfunction could contribute to accelerate fetal lung maturation acting as a stress factors is being reviewed.[7,15] In our study the relative risk of having RDS was 2,6 times greater among small for gestational age newborns than in infants of adequate weight.

This is in line with the increased risk of RDS after fetal distress shown in this study, as well as in several previous publications.[5]

It is interesting that the known association of RDS with gestational age disappeared in the multiple regression analysis, while birth weight below 1.500g remained significantly associated with higher risk of RDS. There are three possible explanations for this statistical result. First, the sample included only premature infants, thus reducing the chances of finding a difference by gestational age; second, it is obvious that infants with a lower gestational age had a lower birth weight, and third, small-for-gestational age babies also will weigh less than those with adequate weight. As the relative risk of RDS was between twice and 2,6 times greater in cases with gestational age < 32 weeks and small for date in the bi-variate analysis, the conjunction of these two factors may have led to the highly significant association of birth weight < 1.500g with RDS, with adjusted relative risk of –5,8 while the other two factors were excluded.

The belief that there is an accelerated fetal lung maturation in pregnancies complicated by hypertension is common among obstetricians and this "protective" effect was only recently (in 90's) questioned.[16] In a previous study, we found no significant difference in incidence of RDS between the newborn of hypertensive and normotensive mothers.[6] Similar results were published in 1993 by Schiff *et al.*[7] Consequently, obstetrical management of hypertensive pregnancies should consider the risk of respiratory distress syndrome as a possible consequence of prematurity.

The logical conclusion would be to corroborate the role of conservative management of preeclampsia diagnosed early in pregnancy, although the only definitive treatment for preeclampsia is the delivery. Sibai[10] demonstrated a significant improvement in neonatal outcome in severe preeclampsia before 34 weeks and this approach has been recommended by other authors in several situations when there is no life-threatening risk for the pregnant women or her baby.[1,17]

Nevertheless, conservative management has potential deleterious risks, such as higher incidence of maternal complications[18] and stillbirth or fetal distress.[10,19] The latter is a common problem in preeclampsia, since intrauterine hypoxia can develop as consequence of reduced uteroplacental perfusion.[12,20,21] The strong association between fetal distress and RDS found in this study, may be explained by the depletion of surfactant store caused by intrauterine hypoxia.

This finding carries several implications for obstetrical practice in deciding premature therapeutic interruption of pregnancy. Obstetricians have to weigh the risks of an extremely premature or very low birth weight infant, versus the risk of delivering a baby in later gestational age compromised by hypoxia. Intensive fetal surveillance by Doppler flow velocimetry, cardiotocography and fetal biophysical profile should be recommended when preeclamptic patients are being followed conservatively.

Although several other variables presented an elevated risk of RDS in bi-variate analysis, as cesarean section and absence of labor, this risk did not persist when logistic regression analysis was carried out, probably because they are strongly associated with very low birth weight and fetal distress.

The incidence of respiratory morbidity was reported by other authors to be significantly higher for newborn babies delivered by cesarean section, especially if carried out before the onset of labor,[22,23] but the circumstances that indicated abdominal delivery were not considered and its confounding role was not controlled.

On the other hand, corticosteroid therapy was associated with a strong and significant reduction in the incidence of RDS, an association that persisted after controlling for confounding factors in multiple regression analysis. The efficacy of corticosteroid therapy for prevention of RDS has been accepted for the last decades,[24-26] and its effectiveness and safety in preeclamptic women has been recently confirmed.[8] Therefore, the administration of corticoids should be mandatory wherever conservative management is indicated, particularly because some risk factors for RDS, such as fetal distress, are not always easy to detect or to predict with certainty.

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