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Multicentric networks and the quality of neonatal care

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One of the major public health problems today concerns the increase in preterm births on a worldwide basis and their growing importance as a cause of infant mortality. The studies that demonstrate an increase in prevalence of preterms in the United States and Canada^{1,2} show that their most frequent causes are increase in obstetric interventions, increase in the number of multiple births, and improvements in the quality of gestational age determination, due to the replacement of date of last menstrual period by estimations made by fetal ultrasound early in pregnancy

In Brazil, there seems to be an increase in preterm births too, as shown by several studies, including one conducted in Ribeirão Preto, state of São Paulo, and another one in Pelotas, state of Rio Grande do Sul. In Ribeirão Preto³ there was a significant rise in the prevalence of preterm births from 7.6% in 1978-1979 to 13.6% in 1994. The authors suggest that the larger number of cesarean sections may have contributed to this increase, although it is quite hard to rule out problems with reverse causality in this case.

In Pelotas, the prevalence of preterm births increased from 5.6% to 7.5% between 1982 and 1993.⁴ Currently, we are conducting a new perinatal study in this city, and the results for the first four months of 2004 indicate an important

increase in preterm births, to around 18%. This increment apparently occurs in large newborns with 35 and 36 weeks of gestation – and is observed both in vaginal and cesarean deliveries. This finding suggests that we should regard all forms of interventions (not only C-sections, but also induced labor) as possible causes for this problem (Barros et al.; unpublished data).

Since preterm newborns are responsible for a significant proportion of neonatal and infant morbidity and mortality in any population, the topic discussed by the Brazilian Neonatal Research Network (BNRN) in the current issue of *Jornal de Pediatria* – the antenatal use of corticosteroids in preterm labor – is of extreme importance today.⁵ Corticosteroid therapy is considered to be highly effective as a preventive measure, but is often underused. Recent meta-analyses have shown that the use of corticosteroids in preterm labor or prior to the elective termination of preterm pregnancy, may substantially reduce neonatal mortality and severe morbidities such as hyaline membrane disease and intraventricular hemorrhage. Therefore, it is worrying that the recent and acclaimed series on Infant Survival, published by The Lancet, has estimated the use of this intervention – to be only 5% on a worldwide basis.⁶

In Latin America, the prevalence of antenatal corticosteroid therapy in preterm labor is not well known, since there is a paucity of population-based studies that allow its determination. A study conducted in Montevideo, Uruguay, and published in *Jornal de Pediatria*, showed that the use of corticosteroids in very low birth weight newborns amounted to 59.7%, 65.6% in public hospitals and 53.5% in private ones.⁷

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In Brazil, a methodologically well-designed study carried out in public hospitals of Rio de Janeiro, including data from the early 1990s, showed that corticosteroids were used in only 4.3% of preterm labors between 28 and 34 incomplete weeks of gestation.⁸ More recently, between 1998 and 1999, the BNRN has published information on antenatal corticosteroid therapy for very low birth weight newborns, revealing a mean prevalence of 29%, with a range from 10 to 39%.⁹

In the current issue of *Jornal de Pediatria*, the authors of the BNRN describe the characteristics and outcome of a group of preterm newborns and their mothers, who were split into two categories: those who received antenatal corticosteroid therapy and those who did not.⁵ The BNRN consists of eight neonatal care units located in teaching hospitals in southeastern and southern Brazil, and the current study is a -multicenter observational investigation.

The first positive finding of the BNRN study was that the use of antenatal corticosteroid therapy in preterm labor at less than 34 weeks reached 61%. As far as we know, this figure is much higher than in any other Latin American study. The authors describe maternal and newborn characteristics in detail, including morbidity and mortality. This serves a dual purpose: to identify possible maternal risk factors for nonuse of corticosteroids and to evaluate the possible effect of corticosteroids on the health of preterm newborns. With regard to the latter purpose, it should be noted that the group who received corticosteroids did not have a decrease in the incidence of hyaline membrane disease, but had an increase in necrotizing enterocolitis, which is inconsistent with the results reported in the literature. The inclusion criteria may have contributed to this fact. Interestingly enough, the prevalence of maternal infection and/or prolonged rupture of membranes, diabetes, and hypertension was higher in the group that received corticosteroids.

The comparison of preterm newborns who received corticosteroids with those who did not may yield results that are difficult to interpret, since these groups are different in other aspects than the use or not of corticosteroids. Mothers who did not receive corticosteroids might have been those who were already in labor at admission and therefore too late to receive preventive management (use of tocolytics in less than 2%) or those who did not meet the inclusion criteria.

Multivariate logistic regression analysis was used to determine which of the variables were associated with outcomes such as mechanical ventilation, positive blood culture and survival. The aim was to check whether the protective effect of the use of corticosteroids against mortality and the use of mechanical ventilation, and its possible effect of facilitating infections were still the same after adjusting for differences between mothers and infants who received and did not receive corticosteroids, including important variables such as birth weight, gestational age and perinatal conditions in the delivery room. In this study, the analysis confirmed that the effect is maintained, which is in agreement with the literature.

However, these results should be taken with caution, due to the methodological problems inherent to this process. Some difficulties lay in some of the variables included in the model, which clearly were intermediate variables of the analyzed outcomes. This group includes the use of oxygen at 36 weeks, SNAPPE II and mechanical ventilation (for the other two outcomes). Moreover, other variables included in the model have a very particular relationship with the use or not of corticosteroids, not being fully investigated as they should have been. These variables encompass the use of tocolytics, maternal hypertension and type of delivery. On top of that, in multivariate analyses there is always the possibility of not including in the model important variables that could have changed the association between exposure and outcome. This residual confounding is a problem in observational studies and may be minimized by repeated observations and careful measurements. Therefore, the results of the multivariate analyses should take into account these limitations and should be regarded as interesting findings to be explored in the future using a more appropriate methodology.

Multicenter studies have been very much in vogue and can be found in the most renowned medical publications all around the world. They often are randomized clinical trials (RCTs) recruiting a large number of patients in a short period of time for studies that require large samples. Also, because these studies are conducted in several places, they can increase the external validity, allowing the results to be generalized to a larger group of patients.

But another great advantage of multicenter studies is the use of standardized variables and case-notes, which allow the effectiveness of preventive or therapeutic measures previously tested in RCTs to be assessed through observational studies, providing results on the local populations. This is the design of the current study and there are many other examples of neonatal networks, as the US-based Vermont-Oxford Network and the Neonatal Network of the National Institute of Child Health and Human Development (NICHD). It is our hope that the BNRN can be expanded by including new centers from other Brazilian regions, and actively contribute to the promotion of more appropriate practices and to the improvement of the quality of neonatal care in Brazil.

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When should we start phototherapy in preterm newborn infants?

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Unconjugated hyperbilirubinemia is commonly observed in all preterm infants, especially in very low birthweight newborns. Studies show that the large amount of short-lived red blood cells, and the increase in enterohepatic circulation of bilirubin and the deficient hepatic conjugation of bilirubin are the most important physiological conditions that cause hyperbilirubinemia. In addition, the delayed implementation of enteral nutrition, which is common in critically ill preterm newborns, may restrict intestinal blood flow and enhance the enterohepatic reuptake of bilirubin. Therefore, due to erythrocyte, hepatic and gastrointestinal immaturity, "physiological" jaundice is more intense than that observed in full-term newborns. The total bilirubin concentration ranges between 10 and 12 mg/dl on the fifth day of life and may not reach normal values until the end of the first month.¹

One of the most frequent specific causes concerns blood extravasation caused either by extensive hematomas in upper and lower limbs due to birth trauma or by intraventricular hemorrhage, especially in those infants aged less than 34 weeks. However, despite the proper investigation into unconjugated hyperbilirubinemia based on the history and outcome of preterm newborns, most cases do not have a clear etiology. On top of that, patients submitted to intensive care may show association of predisposing factors for penetration of bilirubin into the brain, such as hypoxemia, acidosis, hypothermia, hypoalbuminemia, hypercapnia, among others.²

Although unconjugated hyperbilirubinemia is almost universally found in preterm newborns, several studies published in the 1990s do not show a causal relationship between hyperbilirubinemia within controlled limits (total bilirubin that is on average lower than 15 mg/dl) and neurological, hearing, visual, speech and developmental disorders.³⁻⁴

Nevertheless, in 2001, Sugama et al.⁵ questioned the rare occurrence of bilirubin encephalopathy in preterm newborns after they detected kernicterus in two patients at 31 and 34 weeks of gestational age, respectively, with bilirubin levels between 13.1 and 14.7 mg/dl; none of the patients had symptoms that could suggest the disease in the neonatal period. The first case revealed athetoid cerebral palsy at the age of three years, and the second patient could not hold his head up and had hypotonia. Magnetic resonance revealed findings compatible with bilirubin encephalopathy, resulting in the hypothesis that low bilirubin levels may cause brain injury in preterm newborns and that the risk for kernicterus is difficult to be determined in the neonatal period.

Thus, the risks of brain injury associated with hyperbilirubinemia in preterm newborns and the quantification of this risk have been widely discussed. One of the greatest challenges is concerned with the determination of tolerable levels of unconjugated bilirubin for the prevention of bilirubin encephalopathy in this group of patients. Although most of these patients, especially those weighing less than 1,500 g, are submitted to phototherapy, several questions need to be answered: When should it be initiated? What bilirubin levels determine the use of phototherapy? What is the maximum bilirubin

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