Editorial

Antenatal Corticosteroid Administration for Reducing the Risk of Neonatal Morbidities from Prematurity

Corticosteroide antenatal para redução das complicações neonatais da prematuridade

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Prematurity continues to be the most important cause of neonatal complications, with more-severe outcomes with lower gestational age at birth. A recently published multicenter study conducted in the United States analyzed births that occurred between 2000 and 2011 and found that one in every four extreme preterms (< 28 weeks) died before hospital discharge.[1] Deaths that occurred in the first 12h were attributed to generalized immaturity; between 12h and 14 days of life, to respiratory distress syndrome (RDS); and between 15 days and 60 days of life, to necrotizing enterocolitis. This emphasizes the important contribution of prematurity to more-severe outcomes.

Even today, the prevention of prematurity is a major challenge not only because of its multifactorial nature but also because the various causes are not subject to prevention. Thus, when premature delivery is inevitable, the use of antenatal corticosteroids is the only effective intervention for reducing neonatal complications such as RDS, intracranial hemorrhage, necrotizing enterocolitis, and death. However, many misconceptions arise in this area, and hasty conclusions and contradictory information are frequent. These often arise from studies that do not allow to draw the conclusions that are proclaimed.

The first evidence in humans that corticosteroids could be used to accelerate fetal lung maturity came from the study of Liggins and Howie[2] in 1972, in which betamethasone was compared with a placebo. In this study, 6 mg of betamethasone sodium phosphate and 6 mg of betamethasone acetate (total = 12 mg) were administered by intramuscular injection. After 24h, a second identical injection was applied if the first one had no effect. It should be stressed that this is currently the most commonly used scheme. When compared with the placebo group, the treated group displayed a significant reduction in the incidence of RDS and neonatal mortality rate. Further studies with betamethasone or dexamethasone confirmed the initial results and demonstrated not only fetal pulmonary maturation but also improvement in other neonatal results.

A meta-analysis that included 21 controlled and randomized studies (n = 4,269 newborns) revealed a significant reduction in the incidences of RDS (relative risk [RR] = 0.66), intracranial hemorrhage (RR = 0.54), necrotizing enterocolitis (RR = 0.46), and neonatal death (RR = 0.69), without increased incidences of maternal and neonatal infections.[3] In the same study, beneficial results were observed in cases of preterm premature rupture of membranes.

Corticosteroids act by promoting the expressions of proteins that accelerate the functional and structural maturity of pulmonary cells and other organs.[4] The physiological effects on the lungs result from the production of proteins and enzymes involved in the production of phospholipids by type 2 pneumocytes. The physiological effects include improvement of pulmonary expansion, reduction in vascular permeability, improvement of respiratory function, and response to postnatal surfactants.

Betamethasone and dexamethasone are equally effective in promoting the acceleration of lung maturation. Dexamethasone should be administered intramuscularly at 4 doses of 6 mg, with 12-hour intervals between applications. However, in most studies, the use of betamethasone is preferred because long-term follow-up data of fetuses exposed to dexamethasone are still limited.

Briefly, some authors started to suggest weekly courses of corticosteroids between the 24th and 34th weeks of life. After multiple courses of corticosteroids have been applied in clinical practice for several years, several studies questioned

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the practice.[5–7] Besides having no neonatal benefit, administration of multiple courses of corticosteroids to fetuses resulted in impairment of growth with reductions in head circumference, weight, and stature at birth, in addition to behavioral changes in childhood, when compared with the use of a single course. One should emphasize that adverse effects such as impairment of cerebral myelination and other neurological anomalies, alterations of pulmonary tissue growth, and developmental disorders of the hypothalamic-pituitary-adrenal axis have already been observed in animal studies.[8,9] Such findings occur because corticosteroids do not act specifically on the pulmonary tissue but affect other tissues with rapid cell proliferation, such as cerebral tissue, the intestines, the kidneys, and the skin. Taking into account these unfavorable results, along with the risk of premature delivery in the following 7 days, between the 24th and 34th weeks,[10] the consensus of the National Institute of Child Health and Human Development in 2000 reaffirmed what had been decided in the consensus of the same entity in 1994, which is the use of a single course of betamethasone (12 mg per day, intramuscularly, with a 24-hour interval).

In 2015, a new systematic review indicated contradictory results.[11] The use of multiple courses of betamethasone when compared with a single course demonstrated a reduction in the incidence of RDS; nonsignificant reductions in the incidences of severe pulmonary disease, perinatal mortality, chronic pulmonary disease, intracranial hemorrhage, and birth weight. With regard to maternal complications, no significant increase in the incidence of chorioamnionitis or puerperal sepsis was observed. Such results should be analyzed with great care. The main criticism is that this revision did not assess whether the incidence of complications increased as more doses were used (dose dependence), as demonstrated by other studies.[12] Hence, the conclusions should not be considered definitive. The recommendations of the American College of Obstetricians and Gynecologists should be preferred. Moreover, based on the studies cited earlier, as a general rule, only a single course of betamethasone[13] should be administered. However, as an exception, a second course of corticosteroid can be administered when premature delivery is imminent (< 34 weeks) and more than 2 weeks had passed after the initial cycle.

Few studies have assessed the neonatal respiratory benefits of administering corticosteroids to pregnant women in the gestational period of ≥ 34 weeks.[14] Although late preterms (34 to 36 weeks and 6 days) had a significant increase in the prevalence of respiratory complications (RDS, transient tachypnea. and apnea of prematurity) when compared with newborns with gestational ages of > 37 weeks, no sufficient evidence has been found to support the use of corticoid therapy in these cases. The evidence is even more questionable for its use in early preterms (between 37 and 38 weeks and 6 days). In a study conducted in 2005 with 998 pregnant women who were divided between those who received and those who did not receive antenatal corticosteroid 48 hour before the planned cesarean delivery at gestational ages of ≥ 37 weeks, the incidence of respiratory complications was lower in newborns whose mothers received corticosteroids (2.4% *vs* 5.1%; RR = 0.46).[15] In 2010, the Royal College of Obstetricians and Gynecologists (RCOG) started to recommend the administration of corticosteroids for pregnant women with imminent preterm birth up to 34 weeks and 6 days and to all pregnant women with planned elective cesarean section prior to 38 weeks and 6 days.[16] On the other hand, in a randomized study with betamethasone ($n = 163$) in comparison with a placebo ($n = 157$) that was conducted in Brazil with pregnant women between 34 and 36 weeks of gestation who had an imminent risk of premature delivery, no significant difference was observed between the groups regarding the incidence of respiratory disorders of newborns (RDS and transient tachypnea).[17] According to some authors, besides not having benefits, fetal exposure to corticosteroids can cause damage to the newborn babies with gestational ages of ≥ 34 weeks. In a study with 362 fetuses that assessed pulmonary maturity, the use of antenatal corticosteroids showed no benefits regarding respiratory complications for late preterms and early terms. However, the same study found a 2-fold higher prevalence of hypoglycemia and 3-fold higher prevalence of neonatal sepsis when the mothers received the medication.[18] In addition, neurological follow-up data of children submitted to treatment after 34 weeks gestation are still limited. Human and animal studies have demonstrated that at the beginning of pregnancy, antenatal exposure to corticosteroids may delay myelination. On the other hand, close to term, the central nervous system becomes more active mitotically and its exposure to corticosteroids can cause cell death.[19,20] Therefore, in light of the current knowledge, we believe that it is more sensible not to use corticosteroids in late preterm and early-term births.

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