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Antenatal corticosteroids: Sharpening our aim

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Since the original study by Liggins and Howie in 1972 that demonstrated that antenatal corticosteroids improved survival in preterm births, obstetricians and neonatologists worldwide progressively adopted this practice.[1] This happened much faster in South America, Europe, New Zealand, and Australia than in North America. It took more than 20 years for the American College of Obstetricians and Gynecologists to issue a formal recommendation on their use.[2]

The impact of antenatal corticosteroids in accelerating lung maturation was so positive that, observing their immediate effects (a decrease in the frequency and severity of respiratory distress syndrome among preterm infants), their use was extended even to late preterm pregnancies and scheduled C-sections at term. Randomized clinical trials showed marginal benefits in the latter 2 populations.[3,4] However, in these cases, their use continued to be quite frequent. Why?

Obstetricians and neonatologists "love" antenatal corticosteroids: a vast scientific information and long experience demonstrate that betamethasone or dexamethasone, given to pregnant women with threatened preterm labor, markedly decrease the incidence and severity of respiratory distress syndrome and morbidity and mortality among preterm infants, especially those younger than 32 weeks of gestation. Most of us would say that antenatal corticosteroids are the most cost-effective drug in perinatology. Unfortunately, there is no drug that causes benefits in all populations in which it is used without incurring some risks. Already in 2014, Althabe et al. developed a large cluster-randomized clinical trial in 6 countries, in regions with suboptimal perinatal care, with the objective of scaling up the use of antenatal corticosteroids to most early preterm births. That study demonstrated that the use of a multifaceted intervention that included training in the identification of women at risk for preterm delivery increased corticosteroid use to 45% of preterm infants. However, that intervention also substantially increased corticosteroid use in women who had been identified as being at high risk for preterm delivery, but whom ultimately gave birth at term. The unfortunate and unexpected consequence was that neonatal mortality increased by 12% in the general population.[5] As a consequence of the results of that study, the World Health Organization (WHO) recommends antenatal corticosteroid management for women at high risk for preterm delivery (between 24 and 34 weeks of gestation) when certain conditions are met, including an accurate assessment of gestational age and a high probability of preterm delivery in the next 7 days.[6]

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Subsequently, in 2020, the WHO ACTION-I trial, designed to administer antenatal corticosteroids following the aforementioned recommendation and conditions, ratified their benefit and safety in low-resource settings.[7] In that trial, only 10% of newborn infants who received antenatal corticosteroids were born at term. In practical terms, the administration of antenatal corticosteroids is recommended for pregnancies of less than 34 weeks of gestation, when there is a very high probability (90%) that birth will occur in the next 7 days. If such probability is uncertain, it may be better to refrain from their use.

In addition to the issues mentioned above, there are other concerns for those of us who participate in decisions on the management of pregnancies at risk for preterm birth: a population-based study conducted in Finland showed that the administration of antenatal corticosteroids is associated with a higher frequency of mental and behavioral disorders in children.[8] Another study carried out in Canada reached similar conclusions.[9] A meta-analysis that included randomized and cohort studies with long-term neurodevelopmental follow-up concluded that the use of a cycle of antenatal corticosteroids was associated with improved neurodevelopment in cases of extremely preterm birth, but also with a significantly increased risk of neurocognitive and psychological disorders in the case of late preterm and term births (which occurred in 50% of cases who had received corticosteroids).[10] Similarly, other studies show that the administration in late preterm pregnancies increases the risk of hypoglycemia by 3–6 times.[11]

More recently, Yao et al. alerted to the increased risk of serious infections during the entire first year of life in infants whose mothers had received antenatal corticosteroids.[12] That study was an analysis of a large cohort from Taiwan, with almost 2 million births, of which 45 000 had received antenatal corticosteroids. That study showed a 32% relative increase in serious infections during the first 6 months of life in exposed versus unexposed infants, with a 95% confidence interval between 18% and 47%. Importantly, such increase was observed not only in infants born preterm, but also in those born at term. The increase in the risk of infections was greater in infants born at term. Other call for attention is that 40% of the pregnancies that received corticosteroids reached term gestation.

Is it perhaps that the betamethasone (or dexamethasone) dose is excessive? Although we are not certain, a multicenter randomized clinical trial conducted in France in 3200 pregnancies failed to demonstrate that administering half the usual dose of betamethasone is equivalent to the dose that has been used for years.[13]

What should we do? First of all, we must not fail to recognize the enormous value of antenatal corticosteroids in situations of appropriate perinatal care. Second of all, we should take into account that antenatal corticosteroids are not harmless and we should strive to perfect our aim: they should be used when the chances of very preterm birth are really high, since the benefits clearly outweigh the risks in that group. In addition, it would seem reasonable to avoid them after 34 weeks of gestation and even more so in scheduled C-sections in term newborns, until new evidence clarifies the picture.

Finally, let us not waste the lessons of this long history. It is clear that the very favorable impact of antenatal corticosteroids in the short term is appealing, but an important lesson learned from the publications cited in this editorial for those of us who develop clinical studies is the importance of long-term follow-up of the populations subjected to a study intervention. ■

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