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Letter to Editor

Antenatal Dexamethasone For Women at Risk af Preterm Birth and Intraventricular Haemorrhage: What is the Truth?

Raffaella Mormile

[a]Division of Pediatrics and Neonatology, Moscati Hospital, Aversa-Italy. [b]Division of Pediatrics and Neonatology, Moscati Hospital,Via A. Gramsci, 3- 81031 Aversa-Italy.

Abstract

Administration of antenatal corticosteroids to pregnant women with imminent delivery of a newborn at 24 to 34 weeks of gestation represents one of the most important advances in perinatal medicine in the past 25 years (1, 2). A single course of antenatal steroid has been associated with a decrease in acute neonatal systemic morbidity and mortality after preterm birth reducing the risk of respiratory distress syndrome and intraventricular haemorrhage (IVH) (2, 3). Currently, the only corticosteroids that are used for such prophylactic therapy are betamethasone administered intramuscularly as two doses of 12 mg each 24 h apart or four doses of 6 mg of dexamethasone given intramuscularly 12 h apart (1, 2). Both readily cross the placenta in their active form with nearly identical biological impact[1]. Both are devoid of mineralcorticoid activity and have relatively weak immunosuppressive actions with short term use in comparison to other forms of steroids (1, 2 and 4). However, there is conflicting evidence on efficacy and safety of these agents to prevent adverse outcomes in preterm babies for what concerns IVH in particular (1-3). To date, considerable disparity exists between physician beliefs and actual practice habits in worldwide Obstetrics Units lacking sufficient data to recommend one steroid regimen over the other (1-3). IVH is the most common neurological complication of prematurity (6). It has emerged as a global health problem in relation to the increasing incidence of preterm birth (6). No therapy of IVH is currently available and the use of prenatal corticosteroids in women in preterm labor represents the only widely practiced preventive strategy (1, 2 and 6). IVH typically initiates in the germinal matrix (5). It has been suggested that prenatal corticosteroids reduce the propensity of germinal matrix to hemorrhage through its vasculature stabilization (5). Dexamethasone treatment has been shown to reduce the rate of IVH more than betamethasone (1, 3). In contrast, others found that dexamethasone may be neurologically detrimental when compared with betamethasone (2-4). It has been observed that there is abundance of apoptotic neuronal cells and neuronal degeneration after exposure to prenatal glucocorticoids with marked discrepancy among the human, rabbits and sheep fetuses (5). Betamethasone has been found to be safer and more protective for the immature brain than dexamethasone (6). On the contrary, dexamethasone has been related to a higher risk of persistent brain parenchymal hyperechogenicity in comparison to betamethasone (7). It has been demonstrated that dexamethasone down-regulate survivin expression (8, 9). Survivin is the smallest member of the inhibitors of apoptosis gene family that plays an essential role in vascular cell responses to ischemia in brain (10-14). It has been highlighted that survivin mediates the

* Corresponding author:
E-mail: raffaellamormile@alice.it

antiapoptic effects of ischemic preconditioning via phosphatidylinositol 3'–kinase/AKT(PI3K/AKT) pathways (15). Concordantly, dexamethasone causes a significant down-regulation of PI3K/AKT signaling pathway resulting in increases in indices of cell apoptosis in brain (11, 15). The signaling interaction between survivin and PI3K/AKT has also been described to be essential for endothelial progenitor cells (EPCs) proliferation that are the major source of cells in endothelial repair after vascular injury (15, 16). A variety of studies not only has proposed a role for survivin in the extent of vascularization of the infarct but also has suggested the notion for treatment of brain injury by up-regulation of surviving (10-12). Dexamethasone has also been linked to over-expression of MAPK phosphatase-1 (MKP-1) which antagonizes the activity of mitogen-activated protein-kinases (MAPKs) (13). Intriguingly, the activity of MAPKs has been described as a signal transduction pathway upstream of surviving (14). With respect to the above, we advance the hypothesis that prenatal dexamethasone exposure may not protect preterm infants against IVH down-regulating the expression of survivin that plays a key role in the protection of brain cells against insult-induced apoptosis**.** Research studies are needed to better define whether antenatal betamethasone may be the best alternative therapy for antenatal prevention of IVH and whether dexamethasone may sensitize immature brain to IVH involving dose timing and treatment regimen.

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