# Controversies in obstetrics

## Are multiple doses of antenatal corticosteroids safe and effective?

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Changes in the management and care of neonate resemble the swings of the pendulum. Just as the force of gravity keeps the pendulum from swinging too far, continuing medical research keeps the management from becoming too extreme. One classical example of this is the administration of antenatal corticosteroids to a patient with threatened preterm labour. Research on the evaluation of the risks and benefits of this treatment has refined the risk-benefit ratio and thus altering the protocol clinical care.

Liggins and Hinie[1] (1969) were the first to describe the beneficial effects of antenatal corticosteroids in lung maturity of preterm neonates. Use of antenatal corticosteroids has been associated with a decrease in the respiratory distress syndrome related morbidity and mortality in infants less than 34 weeks of gestation. The NIH consensus statement of 1995 endorsed the use of antenatal corticosteroids and since then, this has become the gold standard in the management of preterm labour. A Cochrane systemic review[2] indicates that even a single dose of antenatal corticosteroids reduces significantly the risk of intraventricular haemorrhage and neonatal mortality in premature babies in addition to respiratory distress syndrome.

The beneficial therapeutic effects of antenatal corticosteroids to enhance lung maturity seem to decrease after seven days and this has prompted clinicians to use multiple courses to maintain the effect. The NIH consensus statement of 1995 did not resolve the issue of multiple courses and suggested repeated doses may be used after seven to ten days of the last dose. Two basic questions need to be answered regarding multiple courses of antenatal corticosteroids. Firstly, are they effective in enhancing lung maturity? Since 1995, various retrospective studies have documented that mortality and morbidity related to respiratory distress syndrome continues to improve with multiple doses of corticosteroids. Therefore, it seems that the effect on lung maturity can be sustained effectively by repeated courses of corticosteroids. The second issue is the potential side effect of steroids on the fetal hypothalamic-pituitary-adrenal axis and future growth and development. Hence the effect of multiple doses of antenatal corticosteroids on fetal growth and development is of some concern[3].

A recent survey of obstetric units in the UK showed that 98% of these units are prescribing repeated courses. This trend is worrying because there is no good evidence to support advantages of multiple courses over single course, whereas there is an increasing body of evidence suggesting that fetal exposure to repeated doses of antenatal corticosteroids may have long term adverse consequences for childhood and adult development[4].

In a recent study of 447 preterm singleton infants in Western Australia, multiple courses of antenatal corticosteroids seemed to reduce foetal growth rates and head circumference corrected for sex and gestational age and no additional survival benefit was found[5]. There was also a significantly increased risk of lower birth weight, neonatal death, and early neonatal suppression among those exposed to multiple courses[6].

Corticosteroids are important initiators of programmed cell death, so prenatal exposure to these compounds may influence organ growth. Late second or early third trimester is a time for rapid fetal body and brain growth. Neurons and glia in the brain are potentially susceptible to any adverse pertubulation[7]. Cells with gluccocorticoid or mineralcorticoid receptors such as the pyramidal neurons in the hippocampus and the dentate gyrus are probably at higher risk of steroid induced modifucation[8]. Repeated prenatal exposure to corticosteroids causes short and long term modification of neuroendocrine function and behavior[9]. A study by French, et al [10] found long term behavioral problems in neonates who had received multiple antenatal corticosteroid courses. These deleterious effects are proportional to the number of repeated corticosteroid treatments, measurable effects being observed with three or more courses.

Thus, does the proven positive effect on the incidence

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of respiratory distress syndrome outweigh the hypothetical negative developmental effect of multiple doses? On one hand, a reasonable compromise may be that only one or two repeat doses of corticosteroid are administered to women at higher risk of delivery of extremely low birth weight infants. On the other hand use of multiple antenatal corticosteroid courses outside clinical trials represent uncontrolled experimentation and the patients for whom such therapy is considered should be so informed by the prescribing physicians.

The prospective randomized trial reported by Guinn et al[11] demonstrates no difference in composite morbidity for neonates whose mothers have received a single versus multiple courses of antenatal corticosteroids. This study contributes to the concern that multiple courses of antenatal corticosteroids, particularly when administered weekly for three or more times may have negative effects on neurodevelopmental outcomes. The pendulum on this issue should not swing back so far that ongoing studies evaluating long term outcomes are stopped. These data reinforce the need to test multiple course therapy in the context of clinical trials and not routinely use multiple course therapy in clinical practice.

Decisions to use multiple dose steroid therapy should be made individually, based on an assessment of the likelihood of delivery and the risk of respiratory distress syndrome at a given gestational age.

In conclusion the benefits and risks must be carefully weighed before repeated doses of corticosteroids are given antenatally . However, this should in no way deter us from offering the benefit of the first course of antenatal corticosteroids to every preterm delivery less than 34 weeks of gestation.

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