

The impact of prenatal and postnatal steroids and surfactant replacement therapy on the outcome of preterm infants

Eric S. Shinwell

Department of Neonatology, Kaplan Medical Center, Rehovot and Hebrew University, Jerusalem, Israel

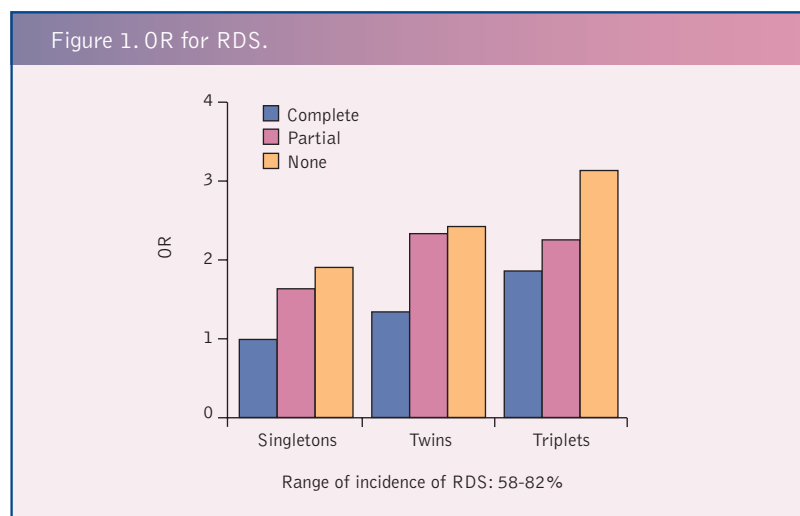
The concept that surfactant deficiency plays a role in RDS was first discovered in the late 1950s. Since the 1980s, surfactant replacement therapy in preterm infants has been shown to dramatically reduce disease severity, pneumothorax ($\approx 60\%$) and mortality ($\approx 40\%$). However, while the surfactant revolution has meant that mortality due to RDS is very low, a significant number of infants are still affected by BPD. It is likely that surfactant reduces the severity of BPD to an extent but it has not reduced the incidence of this disease.

Antenatal steroid therapy is beneficial in multiple pregnancies

A single course of antenatal corticosteroids has been shown to accelerate fetal lung development and prevent RDS and brain haemorrhage. However, the final conclusions from a Cochrane Collaboration review indicate that further information is required concerning the optimal dose to delivery interval, optimal corticosteroid use, effects in multiple pregnancies and to confirm the long-term effects into adulthood.^[1]

Between 1995 and 2001 the Israel Very Low Birth Weight (VLBW) infant network evaluated the effect of antenatal corticosteroids on the incidence of RDS in single and multiple births (n=8120 infants) weighing <1500 g and aged 24 to 32 weeks.^[2] Confounding variables such as gestational age, resuscitation in delivery, mode of delivery, maternal hypertension, gender and MV, which all potentially independently influence short- and long-term outcome were taken into account. For single and multiple births whose mothers received no steroid therapy, the incidence of RDS ranged from 58 to 82% (Figure 1). Despite a complete course of steroid therapy (a single course consists of two 12 mg doses of betamethasone given intramuscularly 24 hours apart or four 6 mg doses of dexamethasone given orally 12 hours apart) multiple births were at increased risk of RDS relative to single births. In addition, single births were at an increased risk with only partial or no steroid therapy. These results indicate that the effect of steroids decreases with increasing plurality, and irrespective of plurality a full course of steroids reduces the risk of RDS. However, partial treatment is similar to no treatment in multiple births.

An enlarged sample from the Israel VLBW network was examined to determine the incidence of IVH.^[3] Singleton birth with a full course of antenatal steroids was associated with a 6.85% risk of IVH compared with a 29.3% risk for triplet births with no steroid therapy. A complete course of steroids was effective in single, multiple and triplet births. There was also a significant difference in the risk of IVH between partial and no treatment for single, multiple and triplet births, suggesting that even partial treatment makes a difference.



Antenatal steroids may adversely affect the fetal brain

The relationship between steroid therapy and the fetal brain has been widely studied in a variety of species, with different types of steroids, doses and timing. These studies indicate that steroid therapy changes the developmental pattern, affecting neurotransmitters (e.g. norepinephrine and dopamine) and glucocorticoid and mineralocorticoid receptors, particularly in the hippocampus. Brain growth is also reduced: animal studies demonstrate that steroid therapy reduces brain weight and induces hippocampus degeneration.^[4,5] A recent large randomised controlled trial in premature infants showed that multiple steroid courses were associated with a reduced incidence of RDS and BPD at the expense of smaller head circumference and lower birth weight.^[6]

Studies with up to 22 years follow-up, primarily including larger more mature infants, suggest that a single course of steroid therapy was not associated with adverse outcomes in terms of physical, intellectual and emotional development. A non-randomised, cohort study (n=541) in infants of 20 to 32 weeks gestation demonstrated that multiple steroid courses were associated with a reduced incidence of cerebral palsy (OR 0.31-0.35; 95% CI 0.16-0.75). However, while there were no effects on intelligence, in this cohort there were more behavioural problems.

A single course of steroids is associated with a reduced incidence of IVH and appears to have little effect on long-term outcome despite the questionable data on brain growth. Multiple courses of steroids require further study; the preclinical data is a cause for concern and there is mixed data on long-term outcomes.

Postnatal steroids are associated with adverse outcomes

When administered postnatally the anti-inflammatory effects of corticosteroids can prevent or treat BPD.

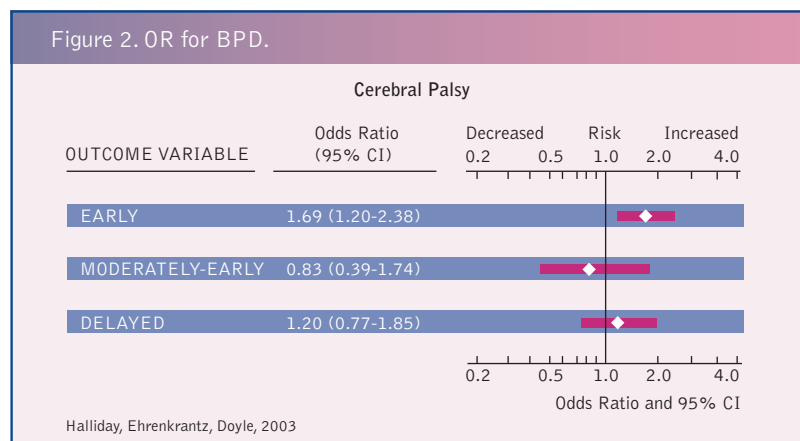
However, the adverse neurologic effects of dexamethasone became known at the end of the 1990s,^[7-9] resulting in changes to the American, Canadian and European paediatric guidelines. In 2006, clinicians are coping with less postnatal steroid use. Steroid therapy, primarily dexamethasone, has been shown to reduce the incidence of BPD with early, moderate-early and delayed administration (*Figure 2*).^[10] Although, there appears to be no effect on mortality with early (OR 1.02; 95% CI 0.9-1.17) or delayed administration (OR 1.03; 95% CI 0.71-1.50).

Moderate-early administration, within 1 to 2 weeks, was associated with a significant reduction in mortality prior to discharge but no significant reduction in overall mortality (OR 0.66; 95% CI 0.4-1.05). Early administration of postnatal steroids appears to be associated with an increased risk of cerebral palsy (OR 1.69; 95% CI 1.2-2.16).

Scientific basis for steroid neurotoxicity

A systematic review conducted by Plint et al.^[11] evaluated 98 animal models and controlled trials on the effect of steroids, and many different findings were reported. However, across all trials general somatic and brain growth restriction was a universal finding. While the neurological results were highly variable they were mostly adverse and the effects were often prolonged. In preterm infants, relative to full-term controls, dexamethasone has been associated with a 35% reduction in cortical grey matter,^[12] abnormal frontal microstructure and a lower MDI at age 2 years.^[13] However, in preterm infants low-dose hydrocortisone had no effect on white or grey matter or hippocampal size at 8 years, although there was a reduction in grey and white matter volume.^[14] In 10 extremely preterm infants (mean age 34 days) with severe BPD, betamethasone reduced flow velocity and increased resistance in the cerebral arteries leading to vasoconstriction. The lenticulostriate arteries were less affected.

In 2006, the NICHD Network determined that in extremely low birth weight infants 1 mg/kg of dexamethasone



reduced the MDI by 2 points and increased the risk of cerebral palsy by up to 40%. These adverse effects were apparent at all ages, not just following early administration, indicating that there is no 'safe window' for the postnatal administration of this agent.

Reduced steroid use evident in clinical practice

Given the relationship between dexamethasone use and adverse neurological and developmental outcomes, changes have been implemented in clinical practice guidelines aimed at reducing postnatal steroid use. The Israel VLBW network has compared steroid use across four eras; the unadjusted data before correction for confounding variables indicate that from 1997/1998 to 2003/2004 there was a small reduction in mortality, a dramatic reduction in steroid use and an increase in oxygen at 28 days and 36 weeks.^[15] On closer inspection this increased oxygen use at 28 days translates into a mean difference of 4 days. Logistic regression analysis accounting for confounding variables (i.e. GA, RDS, antenatal steroid use) determined that between 1997/1998 and 2003/2004 there was an increased risk of requiring oxygen at 28 days (OR 1.75; 95% CI 1.47-2.09) and 36 weeks (OR 1.41; 95% CI 1.15-1.73). These findings confirm that clinicians are using steroids less frequently but there is a greater requirement for oxygen at 28 days and 36 weeks as well as a modest increase in the overall duration of oxygen. If the adverse events reported with postnatal steroids hold true, their use would be definitely dangerous and therapy should be avoided.

Antenatal versus postnatal steroids: why the difference?

When administered antenatally to the mother, the fetus receives a physiological dose of steroids in contrast to the pharmacologic dose received postnatally by the preterm infant. To a large extent the fetus is protected by the mother and is in a stable environment within the amniotic fluid. In addition, the placental effects are not completely known. The neonate, however, has a different pathophysiology and may be exposed to respiratory distress, fluctuating blood pressure and other therapeutic interventions. What is clear is that the effects of steroid treatment on the fetus and newborn are very time-dependent.

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