Ir Med J; July-August 2023; Vol 116; No. 7; P801
17th August, 2023

Antenatal Corticosteroids: Setting the Optimal Balance

The administration of antenatal corticosteroids to mothers at risk of preterm birth before 34 weeks gestation is recognised as one of the great therapeutic advances in perinatal medicine. They significantly reduce both neonatal mortality and morbidity in preterm infants. In particular they reduce the incidence of respiratory distress syndrome, pneumothorax, and intraventricular haemorrhage. The evidence for the use of antenatal corticosteroids is robust. At 23 weeks' gestation, death or impairment is reduced from 90.5% to 83.4%, at 24 weeks from 80.3% to 68.4%, and 25 weeks from 67.9% to 52.7%.

More recently, two research papers[1,2] have reported that in 40% of cases where antenatal corticosteroids are administered, birth does not take place until later in the pregnancy at term. This point has previously been somewhat overlooked in clinical practice and most maternity units do not record how frequently this happens among their threatened preterm labour patients. It must be pointed out from the onset that obstetricians, when faced with a mother in preterm labour, have great difficulties in predicting whether preterm birth will take place or whether matters will settle and the pregnancy will continue. The diagnosis of preterm labour is both difficult and uncertain in the presence of a closed cervix and intact membranes. Mild, irregular contractions are a normal finding at all stages of pregnancy. There is no threshold contraction frequency that reliably identifies women who will progress to established labour. Only 5-10% of women who present with preterm contractions will continue to actual labour and delivery. A mother is considered to be in established preterm labour when she has progressive cervical dilatation with regular contractions[3]. The other factor is that the giving of antenatal corticosteroids is time-sensitive. For maximum benefit they should be prescribed at least 12 and optimally 24 hours before the birth.

The second issue being raised in the two papers is that antenatal corticosteroids, like all medications do have some side-effects. These include increased infection susceptibility in infancy, neonatal hypoglycaemia, smaller head circumference, and increased neuro-behavioural problems.

Yao et al[1] looked specifically at the association between antenatal corticosteroids and subsequent serious infection in infants up to age 1 year. The study group was Taiwan pregnant mothers and their infants born between Jan 1, 2008 and December 31, 2019. All mothers who received antenatal steroids were identified. The outcome examined was the infant's admission to hospital during the first 3 months, 6 months, and 12 months of age because of sepsis, pneumonia, gastroenteritis, pyelonephritis, meningitis.
The study cohort was 1,960,545 singleton infants. Of these, 45,232 infants had been exposed to antenatal corticosteroids and 1,915,313 infants had not. Of the 45,232 infants exposed to antenatal corticosteroids, 27,084 (59.9%) were born preterm and 18, 148 (40.1%) were born at term. The hazard ratio was used to determine whether there was an increased risk of

infection in the corticosteroid group. Hazard ratios are commonly in therapeutic trials. The findings were that the hazard ratio for infection was 1.32. This means that the infants in the steroid group had 1.32 times the risk of infection. In per cent terms the overall risk of infection was 0.4% at 3 months, 0.9% by 6 months, and 1.7% by 12 months. There are limitations to the study that need to be considered. Power calculations were not performed. Also the lower 95% confidence intervals were often close to the null hypothesis[2].

Ninan et al[3] conducted a systematic review and meta-analysis to investigate the number of infants exposed to antenatal corticosteroids who subsequently delivered at term, and to determine their short and long term outcomes. The study included 7 RCTs and 10 population based cohort studies. There were 4315 infants enrolled in the RCTs. There were 1,663,450 infants in the population cohort studies. In the former, 45% of infants delivered at term and in the latter 37% delivered at term. Exposure to antenatal corticosteroids was associated with an increased number of adverse outcomes compared with infants who had not been exposed to corticosteroids. The adjusted odds ratio for admission to NICU was 1.49. The unadjusted relative risk for intubation was 2.59. The infants in the corticosteroid group had a reduced adjusted mean head circumference of 0.21 cms. The limitations of the study as pointed out by the authors is that compared with the RCTs, the population based cohort studies were prone to bias and have a lower evidence certainty. The other problem is that the outcomes of the RCTs were not reported specifically for the infants who were born at term or late preterm.

What emerges from this recent data is that 40% of cases receiving antenatal corticosteroids for threatened preterm labour subsequently do not give birth until term or late preterm. It confirms the difficulties in the diagnosis of preterm labour. It appears that in many cases the clinical picture is not sufficiently robust to conclude that a preterm labour will not progress and that antenatal corticosteroids can be safely withheld.

In some of the studies Dexamethasone was used and Betamethasone in others. Crowther et[5] have reported on an RCT of Dexamethasone vs Betamethasone. There were 679 cases in the Dexamethasone group and 667 in the betamethasone group. The incidence of death or neurodisability was similar in both groups - 33% vs 32%. The authors concluded that the outcome with either agent is similar. The factors in deciding which agent is used includes availability and costs.

The first step should be to find out prospectively what proportion of cases administered antenatal corticosteroids for threated preterm labour currently deliver at term or near term. Many of the reports are relatively old, and the accuracy of the diagnosis of preterm labour has improved over time with the centralisation of preterm labour cases.

The second step is to follow-up infants exposed to antenatal corticosteroids antenatally who deliver at term. This is required in order to obtain a more clear picture. The previous studies were not specifically designed to provide this data.

JFA Murphy
Editor

References:

1. Yao TC, Chang SM, Wu CS, Tsai YF, Sheen KH, Hong XH, Chen HY, Wu AC, Tsai HJ. Association between antenatal corticosteroids and risk of serious infection in children: nationwide cohort study. BMJ 2023;382:e075835.
2. Kimpton J, Sammut A, Cox DJ. Antenatal corticosteroids and longer term outcomes. BMJ 2023;382:p 1722.
3. Perinatal management of extreme preterm birth at the threshold of fetal viability. RCPI
4. Ninan K, Gojic A, Wang Y, Asztalos EV, Beltempo M, Murphy KE, McDonald SD. The proportions of term or late preterm births after exposure to early antenatal corticosteroids and outcomes: systematic review and meta-analysis of 1.6 million infants. BMJ 2023;382:e076035
5. Crowther CA, Ashwood P, Anderson CC, Middleton PF, Tram T, Doyle LW et al. Maternal intramuscular dexamethasone vs betamethasone before preterm birth (ASTEROID): a multicentre double-blind randomised controlled trial. Lancet 2019; Sept 12