is better than aspirin alone.13,14 whereas long-term aspirin plus clopidogrel is not15 and seems to have quite similar bleeding complications to oral anticoagulants.

Thus warfarin remains the standard of antithrombotic care for all eligible patients with atrial fibrillation. New developments are to be expected from innovative oral direct-thrombin blockers or oral factor-Xa inhibitors, rather than from available antiplatelet agents.

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I have received departmental research funding and consultancy fees from Sanofi-Aventis and speakers’ honoraria from AstraZeneca.


Neonatal respiratory distress syndrome

In today’s Lancet, Caroline Crowther and colleagues1 report beneficial effects on neonatal outcome of repeat compared with single courses of antenatal corticosteroids in women at risk of preterm birth. The single course has been in use for more than 30 years and reduces respiratory distress syndrome (RDS), neonatal mortality, and intraventricular haemorrhage in newborn babies. Whether the single course reduced RDS in infants born before 28 weeks’ gestation, chronic lung disease, or necrotising enterocolitis was not clear,1 but a systematic review last year lent support to its use by showing decreased rates of neonatal mortality and chronic lung disease in 1537 infants in gestational weeks 23–28.1 The optimum time for delivery is 24 h or more after the administration and up to 7 days, although a substantial reduction of RDS is seen in babies born more than 7 days after the first dose,2 and hence the importance of Crowther and colleagues’ study.

Betamethasone can cause profound, but transient suppression of fetal heart-rate patterns, which might mimic fetal distress.4 Betamethasone single versus weekly courses was associated with an increased risk of chorioamnionitis in women with preterm rupture of membranes.5 There are worrying reports of association between multiple doses of dexamethasone and cystic periventricular leucomalacia6 and neurodevelopmental abnormalities at 2 years of age.7 Multiple but not single courses of antenatal dexamethasone in pregnant ewes

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1 www.thelancet.com Vol 367 June 10, 2006
results in reduced water content in the brain, kidney, muscle, and skin in the offspring. In the liver, the same effects were seen after a single course.\(^8\)

The issue about adverse neurological development and possible increase in the frequency of cerebral palsy with early neonatal administration of steroids has been of great concern to neonatal paediatricians for decades.\(^9,10\) Concern has also been raised about growth of grey matter resulting in a smaller brain size in the offspring.

Furthermore, giving corticosteroids to pregnant women suppresses the hypothalamic-pituitary-adrenocortical response in the infant, a stress typically encountered in a neonatal intensive care situation.\(^11\) The babies can have an exaggerated response as shown by salivary cortisol measurement at time of immunisation.\(^12\) A response which might occur because of the glucocorticoid effect of cortisol on the functional maturity of the developing brain. Abnormal neurological behaviours for the first week of life in the juvenile period after dexamethasone exposure in utero in rats has also been reported.\(^13\)

In Crowther and colleagues’ study, repeatedly giving doses of corticosteroid antenatally compared with a single dose reduced RDS and morbidity from severe lung disease. Although the study tries to reassure that the effect on the brain might be transient, on the basis of the catch-up growth of the head circumference, long-term follow-up studies are essential to address this point.

Other areas that could be explored are the reasons why more babies born after repeated doses of corticosteroids to the mother were delivered by caesarean section. Is the increased rate of caesarean section because of the influence of multiple courses of corticosteroids on our present methods of fetal surveillance, such as fetal heart rate monitoring, fetal ultrasound biometry or Doppler ultrasound evaluation of fetal haemodynamics? Confounding factors, such as use of tocolytics, antibiotics, and other drugs might also affect perinatal outcome in women at risk of preterm birth.

If a preterm baby is not delivered within a week of the mother having steroids, one is not sure when the baby is going to be born. In Crowther and colleagues’ series, the delay was several weeks. Nearly 35% of infants in the two groups were delivered after 34 weeks. In these cases, outcome would be favourable even after one dose although ten doses might have been given if corticosteroids were started at 24 weeks. We wonder whether weekly courses of steroids are warranted in such cases. An alternative strategy is to give the next course of steroids when confronted with the need for delivery, and meanwhile inhibiting uterine activity for 24–48 h in the absence of contraindications. Cases with immediate threat to the mother or fetus and those who have gone beyond 34 weeks’ gestation could probably be delivered without additional steroids. We think that routine use of multiple courses of antenatal corticosteroids should be considered with caution until results from long-term follow-up studies are known. Crowther and colleagues have planned a follow-up of infants at 2 years of corrected age.

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We declare that we have no conflict of interest.