

is better than aspirin alone,^{13,14} whereas long-term aspirin plus clopidogrel is not¹² 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.

- 1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke. The Framingham Study. *Arch Intern Med* 1987; **147**: 1561–64.
- 2 Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. *BMJ* 2002; **325**: 1022–25.
- 3 Verheugt FWA. Can we pull the plug for warfarin in atrial fibrillation? *Lancet* 2003; **362**: 1686–87.
- 4 CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.
- 5 Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**: 2411–20.
- 6 COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366**: 1607–21.
- 7 ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; **367**: 1903–12.
- 8 SPAF Investigators. Adjusted dose warfarin versus low intensity fixed dose warfarin plus aspirin for high risk patients with atrial fibrillation: The Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348**: 633–48.
- 9 SPORTIF-III Investigators. Ximelagatran versus warfarin for stroke prevention in patients with non-valvular atrial fibrillation (SPORTIF-III): randomised controlled trial. *Lancet* 2003; **362**: 1691–98.
- 10 Albers GW, Diener HC, Frison L, et al. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005; **293**: 690–98.
- 11 Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high risk patients (MATCH): a randomised, double-blind placebo-controlled trial. *Lancet* 2004; **364**: 331–37.
- 12 Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354**: 1706–17.
- 13 Van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002; **360**: 109–13.
- 14 Hurlen M, Abdelnoor M, Smith P, Eriksen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; **347**: 969–74.

Neonatal respiratory distress syndrome

See [Articles](#) page 1913

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,² 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 23–28.³ 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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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.

- 1 Crowther CA, Haslam RR, Hiller JE, Doyle LW, Robinson J, for the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Study Group. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. *Lancet* 2006; **367**: 1913–19.
- 2 Crowley P. Prophylactic corticosteroids for preterm birth. *Cochrane Database Syst Rev* 1996; **1**: CD000065.
- 3 Figueras-Aloy J, Serrano MM, Rodriguez JP, et al. Antenatal glucocorticoid treatment decreases mortality and chronic lung disease in survivors among 23- to 28-week gestational age preterm infants. *Am J Perinatol* 2005; **22**: 441–48.
- 4 Rotmensch S, Lev S, Kovo M, et al. Effect of betamethasone administration on fetal heart rate tracing: a blinded longitudinal study. *Fetal Diagn Ther* 2005; **20**: 371–76.
- 5 Lee MJ, Davies J, Sullivan L, et al. Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes. *Obstet Gynecol* 2004; **103**: 274–81.
- 6 Baud O, Foix-L'Hélias L, Kaminski M, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Engl J Med* 1999; **341**: 1190–96.
- 7 Spinillo A, Viazzo F, Colleoni R, Chiara A, Maria Cerbo R, Fazzi E. Two-year infant neurodevelopmental outcome after single or multiple antenatal courses of corticosteroids to prevent complications of prematurity. *Am J Obstet Gynecol* 2004; **191**: 217–24.
- 8 Stonestreet BS, Watkins S, Petersson KH, Sadowska GB. Effects of multiple courses of antenatal corticosteroids on regional brain and somatic tissue water content in ovine fetuses. *J Soc Gynecol Invest* 2004; **11**: 166–74.
- 9 Baud O. Postnatal steroid treatment and brain development. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F96–100.
- 10 Halliday HL. Early postnatal dexamethasone and cerebral palsy. *Pediatrics* 2002; **109**: 1168–69.
- 11 Davis EP, Townsend EL, Gunnar MR, et al. Effects of prenatal betamethasone exposure on regulation of stress physiology in healthy premature infants. *Psychoneuroendocrinology* 2004; **29**: 1028–36.
- 12 Glover V, Miles R, Matta S, Modi N, Stevenson J. Glucocorticoid exposure in preterm babies predicts saliva cortisol response to immunization at 4 months. *Pediatric Res* 2005; **58**: 1233–37.
- 13 Bulet G, Fernet B, Blanchard S, et al. Antenatal glucocorticoids blunt the functioning of the hypothalamic-pituitary-adrenal axis of neonates and disturb some behaviours in juveniles. *Neuroscience* 2005; **133**: 221–30.