

BETAMETHASONE (Comment)**Repeated antenatal corticosteroid use**

The American College of Obstetrics and Gynecology (ACOG) came out with an update of the Opinion Paper it had original issued in May 2002 in March 2008¹ and this reaffirmed their view that there was still no good evidence that women at risk of preterm delivery should be offered more than one course of betamethasone except as part of a formal randomised controlled trial. The review article by Belteki and Smith² which came out in *Archives of Disease in Childhood* nine months later came to a more nuanced conclusion, but it appeared, by chance, just as the outcome of two more trials became known. The Canadian MACS trial,³ the largest trial to date, which recruited 1858 women into a study of further corticosteroid treatment once every 14 days for women still undelivered 14–21 days after a first course of treatment in order to minimise neonatal respiratory problems, found no evidence that such a strategy offered any benefit and concluded that, because repeat treatment lowered birth weight, repeat treatment is not appropriate. That, certainly, was the conclusion reached in the linked editorial,⁴ as replicated by subsequent reporting in other journals⁵ and reiterated in recent review articles.⁶

However, although it is clear that repeat treatment once every two weeks delivered no benefit in the MACS trial, this does nothing to discredit the evidence from other trials, as summarised by the recent Cochrane review,⁷ that repeat treatment once a week can deliver benefit (even if it did not do so in the subset delivered within a week of further treatment in the MACS trial). In fact the Cochrane review's conclusions have now received support from yet another study, by members of the Pediatrix Medical Group, which was published in abstract in December⁸ and in full four months later.⁹ Although undelivered mothers in this trial were not given further *regular* treatment, they did receive one more course of treatment if delivery again seemed imminent, and the treated babies in this trial derived clear benefit. Belteki and Smith were not, of course, in a position to mention the outcome of either of these trials, in their review.

That treatment did not benefit even the 321 babies in the MACS trial who delivered within a week of treatment and before 32 weeks gestation is difficult to explain – the fact that the babies were older when recruited than they were in the large Australasian ACTORDS trial may be one partial reason. The outcome of the MACS trial has, however, been widely interpreted as showing that repeat treatment is not just ineffective but also potentially harmful^{4,5} because the treated babies in this trial weighed, on average, 113 grams less at birth, and had a matching difference in length and head circumference. What the trial report did not stress was that the treated babies were also, by chance, delivered three days earlier than the control babies on average and that this, in itself, could be enough to account for virtually all the observed difference in weight, length and head circumference. (One can assume that earlier delivery was a chance event because no such difference has yet been seen in any other trial.)

Some very minor difference in weight did persist in the MACS trial when allowance is made for this, but readers have not yet been told whether the difference in the number weighing less than the 10th centile at birth (17% v. 14%) is statistically significant. Even if it is, one may still doubt whether it is clinically significant, because a similar difference had been seen at delivery in earlier trials, but was no longer detectable either at discharge or at follow up two years later.⁷ Continuing concern that repeated treatment might affect later behaviour⁴ even if it has no lasting impact on growth is also reassuringly, and very directly addressed by a report from those involved in the earlier Finnish trial also published earlier this year.¹⁰

The trial by the Pediatrix Medical Group did not include women with premature pre-labour rupture of membranes, and the ACOG has been particularly cautious over recommending repeat treatment to these women because of the findings from a couple of observational non-randomised studies.^{11,12} The analysis of the data from the one trial where this information was available by Crowther and Harding found that repeated steroid use increased the risk of chorioamnionitis (RR 1.56 [95% CI 1.05 to 2.31]) but not the risk of puerperal sepsis (RR 0.65 [95% CI 0.19 to 2.22]).¹³ It will be instructive to see whether these conclusions change when the results for the many women who had had pre-labour rupture of membranes before entry into the ACTORDS and MACS trials (33% and 15%) become known.

In summary recent reports do nothing to change the conclusions reached by current overviews,^{2,7} despite media reports to the contrary – women *should* be offered more than one antenatal course of steroids, but only if there is clear evidence that the baby is likely to derive substantial short term benefit (which is probably true if delivery seems likely before 32 weeks and certainly true if seems likely before 30 weeks gestation). And, if it is given, it is increasingly clear that it only offers measurable benefit if the baby does then end up being delivered within the next seven days, and probable that (as this *Formulary's* updated monograph now recommends) a single 12 mg booster is as effective as a full 24 mg repeat course. However we will only begin to know whether the good done to the minority who do derive short term benefit of treatment outweighs the long term harm that we might be doing not only to these children but also to the many who never eventually derived even any short term benefit. This will start to become clearer when we know, in two years, how the children in the Australasian trial are doing when they are five.

Just how long it takes for two 12 mg IM doses of betamethasone given 24 hours apart to have an effect on lung surfactant production and how long this effect persists after treatment is over has long been a matter for debate. Liggins and Howie reached a tentative conclusion, at the end of their first landmark trial in 1972, that an effect could be detected within 12–24 hours of treatment being started and that it only persisted for about a week.¹⁴ Similar conclusions were suggested by the way in which lecithin production continued to be stimulated for a further five days after short term exposure to cortisol in tissue culture experiments,¹⁵ but, as Gates and Brocklehurst argued very convincingly in 2007¹⁶, it was far from clear how long benefit really persisted when betamethasone is put to use in human pregnancy. With the publication of the outcome of the MACS and ACS trials we can now see that Liggins and Howie were almost certainly right in the conclusions that they reached almost forty years ago.

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