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Authors' reply

We have several comments regarding the letters about our study.[1] First, Gerard Visser and Gian Carlo DiRenzo state that if corticosteroids are given appropriately they can reduce perinatal morbidity and mortality, whereas inappropriate use is likely to be harmful. However, the evidence showing that corticosteroids reduce neonatal morbidity and mortality are from studies done in hospitals in high-income and middle-income countries with good newborn care. By contrast, our antenatal corticosteroid trial (ACT)[1] was done in low-income and middle-income countries, evidence showed no benefit with use of this drug.[1] Therefore, the setting of where the drug is used matters.

Moreover, Visser and DiCarlo's comment: "if given appropriately", also needs some thought. Even in high-income countries in which many highly trained clinicians and diagnostics—including ultrasound to date gestational age—are available, half or more of the babies whose mothers receive corticosteroids will be delivered after 34 weeks, and many at term.[2,3] Thus, to administer corticosteroids "appropriately" is easier said than done.

In our ACT,[1] to reach most infants who, ultimately, were delivered at the less than the 5th percentile birthweight (proxy for preterm), health-care providers at sites were asked to give corticosteroids to women identified at high risk of preterm birth, and not just to those at risk of imminent delivery. This factor is likely to have resulted in the substantial proportion of women who delivered larger newborns and probably at later gestational-aged infants than the newborns identified as being in the preterm period.[1] Nevertheless, infants born in the less-than-5th-percentile birthweight did not benefit from corticosteroids in these settings. We agree with Visser and DiRenzo that corticosteroids are potentially harmful, as we reported:[1] increased stillbirths and neonatal deaths of fetuses and infants at or above the 25th percentile.[1]

Jeffrey Perlman and colleagues recommend that antenatal corticosteroids, targeted for use in mothers delivering at 26–34 weeks' gestational age, be coupled with implementation of the Helping Babies Breathe (HBB) programme, maintenance of normal infant temperature from birth (36°C), maternal antibiotic administration, and for the premature baby to have Kangaroo Mother Care (KMC) and essential newborn care from birth. Although HBB, KMC, essential newborn care, and maintenance of normal infant temperature from birth have been shown to be beneficial, our study[1] does not support the widespread use of antenatal corticosteroids in low-income settings at any gestational age. Furthermore, we are concerned with indiscriminate antibiotic use, especially for mothers, and believe that randomised controlled trials need to show benefits before implementation of their recommendation.[4]

Finally, we concur with Kathy Burgoine and colleagues in that increased susceptibility to infection caused by corticosteroids, in settings with high exposure to various infectious organisms, might account for our findings[1] and needs further investigation.[5] In fact, we are doing secondary analyses of our trial database[1] to assess the effects of the complex intervention on neonatal infection. Hopefully these results, together with other ongoing analyses to assess the intervention mechanisms of action, will help to inform future research. We recommend research on antenatal corticosteroids to start in low-resource hospital settings.

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Mendelian randomisation study for statin treatment

In their Article (Jan 24, p 351),[1] Daniel Swerdlow and colleagues used a mendelian randomisation analysis to show that low 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) expression is causative of an increased risk of type 2 diabetes. Along with the limitations to this study discussed in the Comment by Timothy Frayling,[2] we have two additional concerns.

First, we wonder if the study population should be limited to the participants that were not given statin treatment to examine the causal relation between HMGCR