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Editorial

Corticosteroids for preterm deliveries: missing evidence

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Preterm birth is a major cause of death and morbidity in babies worldwide.[1] The majority of preterm deliveries and deaths occur in Africa and Asia. Antenatal corticosteroid administration to pregnant women at high risk of preterm delivery is a proven hospital-based intervention to reduce adverse effects associated with preterm birth.[2] This intervention has significantly contributed to reductions in adverse neonatal outcomes in high-income countries.

The efficacy of antenatal corticosteroids to promote fetal lung maturation in women at risk of preterm birth was first demonstrated in a randomized trial by Liggins and Howie over four decades ago.[3] Several randomized and observational studies have since then confirmed this important effect.

The recent Cochrane Review update considers data from 30 randomized trials and includes outcomes for 7774 women and 8158 babies.[4] The quality of evidence, assessed using GRADE, was moderate. Key findings were that antenatal corticosteroid administration is associated with reductions in relative risks for perinatal death (28%), neonatal death (31%), respiratory distress syndrome (34%), intraventricular haemorrhage (45%), necrotising enterocolitis (50%), need for mechanical ventilation (32%), and systemic infections in the first 48 hours of life (40%). Corticosteroids did not increase the risk of chorioamnionitis, endometritis, or maternal death. These findings are consistent with the previous version of the Cochrane Review,[5] and they support the World Health Organization (WHO) recommendation of antenatal corticosteroids for women at risk of preterm birth worldwide.[6]

Most of the studies included in the Cochrane Review were undertaken in high-resource country hospital settings with access to intensive care and other essential supportive treatments for preterm births. In these settings, the safety and effectiveness of corticosteroid therapy for reducing preterm-associated adverse effects is unequivocal, and the priority is scale-up to address remaining gaps in coverage. However, whether similar benefits are replicable in low-resource settings (where the burden of preterm births is higher, and access to neonatal intensive care is limited) remains to be demonstrated.

Findings from the ACT trial, a large multi-country cluster-randomized trial of a multifaceted intervention to increase the use of antenatal corticosteroids for preterm birth at all levels of care (community, health centre, district hospitals) in low- and middle-income countries found that the intervention increased the risk of neonatal deaths (risk ratio 1.12, 95% confidence interval 1.02 to 1.22).[7] For every 1000 women exposed to the multifaceted intervention, an excess of 3.5 neonatal deaths occurred. The risk of maternal

infection was similarly increased (odds ratio 1.67; 95% confidence interval 1.33 to 2.09). These findings are in sharp contrast to the positive results from trials in high-income countries. This trial was excluded from the Cochrane Review update because it was an evaluation of a strategy to scale-up steroid treatment, rather than a test of the safety and efficacy of steroids: the multifaceted implementation strategy comprised training to improve identification of women at risk of preterm birth and measures to facilitate appropriate use of steroids.

Post-hoc exploratory analysis of the ACT trial data suggested that the excess mortality could have arisen from the use of steroids in babies who were not preterm (i.e. more than 34 weeks' gestation), possibly owing to misclassification of gestational age.[8] The lack of facilities to manage preterm newborns and associated complications may also have contributed to the excess mortality, masking any potential benefit from steroids. The important finding of increased maternal sepsis associated with corticosteroid administration may reflect the very different burden of infections in low-resource settings relative to the 'evidence for no harm' that was again confirmed for the well-resourced clinical context of the trials included in the Cochrane Review update.

There is equipoise regarding the impact of antenatal corticosteroids in low-resource settings. Evidence from primary research in such settings is critically needed before we can be certain of the balance of the risks versus benefits of this intervention. A WHO multi-country randomized trial is ongoing and is expected to provide missing evidence with regard to the place of corticosteroid administration at later gestational ages.[9,10] As illustrated by the questions raised from the ACT trial, studies need to be able reliably to establish gestational age so as to be fully informative, rather than relying on proxy measures such as low birthweight. It is likely that appropriate targeting of this intervention is only feasible where gestational age can be confirmed by ultrasonography, and where an appropriate range of other supportive elements of preterm care can be provided. Finally, we also need to bear in mind our continued limited understanding of the pathophysiology of preterm birth: rather than a single disease entity it represents the outcome of several different underlying processes.[11] Better understanding of these basic mechanisms will allow more specific targeting of interventions.

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Declarations of interest

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