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Antenatal corticosteroids and longer term outcomes

New evidence to consider before prescribing antenatal corticosteroids

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Antenatal corticosteroids are considered one of the most important interventions available to improve outcomes for preterm infants. They are recommended for women at risk of preterm delivery who are <34 weeks pregnant, with most guidance suggesting administration within one week of delivery.[1-3] Administration of antenatal corticosteroids at these gestations reduces the risk of neonatal morbidity and mortality, including respiratory distress syndrome and perinatal and neonatal death.[4] The effects of antenatal corticosteroids on later childhood outcomes are less widely studied, particularly when administration is "mistimed" and infants are born at term. These issues are investigated in the two linked studies by Yao and colleagues (doi:10.1136/bmj-2023-075835) and Ninan and colleagues (doi:10.1136/bmj-2023-076035) and they provide evidence that could influence clinical decision making.[5 6]

Yao and colleagues' cohort study investigated the association between exposure to a single course of antenatal corticosteroids and risk of serious infection in the first 12 months of life.[5] The database they used provides almost complete coverage (99.9%) of the Taiwanese population, including nearly two million mother-infant pairs. After carefully considered analyses (including several subgroup, sensitivity, and sibling matched analyses), they reported that exposure to antenatal corticosteroids versus no exposure increased a child's risk of overall serious infections (adjusted hazard ratio 1.32, 95% confidence interval 1.18 to 1.47), acute gastroenteritis (1.35, 1.10 to 1.65), sepsis (1.74, 1.16 to 2.61), and pneumonia (1.39, 1.17 to 1.65) during the first six months of life, with similar results during the first 12 months of life. Interestingly, subgroup analyses suggested the increase in risk of serious childhood infections was greater for infants born at term than for those born preterm.

There are limitations that should be considered when interpreting the results, such as the possibility of residual confounding and confounding by indication. Also, although the study sample seemed large, the exposed group only represented 2.3% of the total study population (n=45 232 exposed, n=1 915 313 not exposed). Power calculations were not performed, which could be important as several outcome events were rare or non-existent: endocarditis did not occur in the exposed group for example. Outcomes may have been under-ascertained: the authors did not consider attendances at emergency departments and general practices or birth admission data, patients were censored after their first serious illness, only the first diagnosis on the inpatient record was considered, and loss to follow-up was not reported. Finally, the lower 95% confidence intervals were often close to the null.

Ninan and colleagues' systematic review and meta-analysis investigated the proportion of infants born at term or late preterm after exposure to antenatal corticosteroids, and their short term and long term outcomes in childhood. A comprehensive search of eight databases between 2000 and 2023 identified seven randomised controlled trials (n=4315 children) and 10 population based observational studies (n=1 663 450 children) for inclusion. The authors reported that about 40% of infants who were treated with antenatal corticosteroids when at risk of preterm delivery were subsequently born at term, comparable with Yao and colleagues' findings (also 40%) but a greater percentage than was reported by the first randomised trial of antenatal corticosteroids in 1972 (30%).[7]

Drawing firm conclusions from this review about the impact of antenatal corticosteroids on short term and long term outcomes is difficult, as most findings were based on unadjusted analyses from a few population based studies with low or very low certainty evidence: none of the randomised trials reported short term or long term outcomes. Other limitations included the inability to perform some subgroup analyses, such as by type of steroid or sex of the infants, the lack of granularity in some of the data (eg, indication for steroid use), and that most studies were conducted in high income countries, reducing generalisation of the results.

Despite the limitations, some conclusions can still be tentatively drawn from these two studies that may influence clinical practice. Firstly, both studies reported that 40% of mothers given antenatal corticosteroids subsequently delivered an infant at term. This is concerning given the possible short term, medium term, and long term adverse effects.[8-10] Reducing the frequency of mistimed corticosteroid administration should remain a focus for all health professionals working in this area. However, clinicians may be reluctant to withhold antenatal corticosteroids given the difficulty of pre-empting preterm birth and the accepted benefits for infants born preterm. Local clinical leads should consider monitoring and auditing decision making on antenatal corticosteroids, to inform change and help improve clinical care locally.

Secondly, these studies highlight the need for further high quality data investigating longer term outcomes in children who were exposed to mistimed antenatal corticosteroids. Replicating studies such as the one by Yao and colleagues across different health systems could help identify whether there are national or demographic differences in the effects of antenatal corticosteroids on childhood outcomes. National audits, such as the UK's National Neonatal Audit

Programme, could add valuable surveillance of outcomes on a large scale among children who have received antenatal corticosteroids.[11] However, such data collection often misses infants receiving antenatal corticosteroids who were subsequently born at term.

Thirdly, despite the current weak evidence base, it would be prudent to consider reassessing how we counsel parents about antenatal corticosteroids. The tendency is to focus on the short term benefits for preterm neonates rather than the less well understood longer term adverse effects. However, it remains a professional duty to fully counsel parents about the benefits as well as potential harms of any proposed treatment that could affect their children.

These studies highlight the challenge of preventive treatments in fetal and neonatal medicine and should remind clinicians and parents that there is no such thing as a risk-free drug.

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