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Invited Editorial

Prophylactic antenatal corticosteroids for fetal lung maturity: Known unknowns and unknown unknowns

The use of prophylactic antenatal corticosteroids (ACS) was arguably one of the most important advances in obstetric care to be made during the second half of the 20th century, with clear benefits for babies born before 34 + 6 weeks of gestation [1]. The 21st century has seen progressive expansion of the criteria for ACS use to include women at risk of late pre-term (35 to 36 + 6 weeks of gestation) birth [2] and women having early term(37 to 38 + 6 weeks of gestation) elective caesarean sections [3], although this is not universal. Women having a planned induction of labour at 35 to 38 + 6 weeks of gestation are, however, not generally considered for ACS. Questions remain about the balance between the risks and benefits of ACS after 34 + 6 weeks of gestation as there are no data on long-term outcomes. There are also increasing concerns about the long-term outcomes for babies exposed to ACS before 34 + 6 weeks of gestation but subsequently delivered at term [4,5]. This more recent evidence reveals new unknowns about ACS, only some of which are currently being actively investigated.

The benefits of ACS in babies born before 34 + 6 weeks of gestation are profound and include a reduction in rates of perinatal and neonatal mortality, respiratory distress syndrome (RDS), intraventricular haemorrhage, necrotizing enterocolitis and systemic infections in the first 48 h of life [1]. However, the majority of women given ACS do not deliver within the optimal window of between 24 h and 7 days of administration [6], and a large proportion deliver at term, where no benefits are anticipated. Combined with the current low threshold for ACS administration, this means that a large number of babies exposed to ACS before 34 + 6 weeks of gestation may not actually benefit from the intervention. There is increasing concern about the potential for harm in such babies [4,5]. A Finnish observational register-based study found that ACS exposure was associated with a reduction in birth weight, birth length and head circumference in babies subsequently born at pre-term, early-term and term gestations [4]. These findings on in-utero growth are consistent with reports from animal studies. In a Canadian population-based study, Melamed et al. [5] found an association between exposure to ACS during pregnancy and healthcare utilisation during childhood related to suspected neurocognitive and neurosensory disorders in babies born at term. While these data are concerning, they should not deter clinicians from offering ACS to women at increased risk of giving birth before 34 + 6 weeks of gestation. However, there is an urgent need for risk-assessment strategies to enable better targeting of ACS. Avenues to explore include digital tools supported by machine learning or artificial intelligence.

The use of ACS after 34 + 6 weeks of gestation is not universal. There is high-quality evidence that ACS between 34 + 0 and 36 + 6 weeks of gestation result in a reduced incidence of RDS, transient tachypnoea of the newborn (TTN) and surfactant use [2]. However, the risk of neonatal hypoglycaemia is also increased [2], for which the long-term consequences are unknown. In women having a planned early term caesarean section (at 37 + 0 to 38 + 6 weeks of gestation), ACS reduce the risk of RDS, TTN and admissions to neonatal units, and also reduce the length of stay on neonatal units. However, there are no data on long-term outcomes following the administration of ACS after 34 + 6 weeks of gestation. Based on data on animal studies and recent observational data from population studies [4,5], there is some concern for neurodevelopmental, cardiovascular and metabolic outcomes. Given the large number of babies born at late pre-term gestations (35 to 36 + 6 weeks) and by early (37 + 0 to 38 + 6 weeks) caesarean section, any long-term consequences of ACS are likely to impact a large number of individuals and families, with implications for health, educational and social services and the wider economy. Research is needed to identify any long-term benefits and risks. Currently, clinicians and parents have to balance the known short-term benefits and risks with unknown but potential long-term risks and benefits. It is therefore not surprising that there are marked variations in care within maternity units, across maternity units, and across nations with respect to ACS use after 34 + 6 weeks of gestation. There are no data on the short- and long-term benefits of ACS prior to induction of labour at 35 to 38 + 6 weeks of gestation, again resulting in variations in clinical care. This is of particular importance as the rate of induction of labour at these gestational ages has risen sharply over the last decade.

ACS are a highly effective intervention in women at increased risk of giving birth before 34 + 6 weeks of gestation and their use should be encouraged. However, tools should be developed to facilitate better targeting. Maternity care providers should monitor and report ACS use, including number of babies born before 34 + 6 weeks of gestation without ACS exposure, the number of exposed babies that are born between 24 h and 7 days of administration, after 7 days and after 37 + 0 weeks of gestation. Monitoring should continue until it is clear that there are no long-term adverse effects in babies born after 37 + 0 weeks of gestation. With respect to the use of ACS after 34 + 6 weeks of gestation, parents should be given individualized information on the neonatal risks associated with early birth, the known benefits and risks of ACS, informed that there are no data on long-term risks and benefits and supported to make an informed choice. Given the known short-term risks and benefits of ACS in women at increased risk of giving birth at 35 to 36 + 6 weeks of gestation and those having early caesarean section, including such women in clinical trials in order to obtain long-term outcomes may not be justifiable. However, there are no data on the use of ACS prior to induction of labour after 34 + 6 weeks of

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gestation. This is an ideal population for a clinical trial of ACS with a focus on both short- and long-term outcomes.

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