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The place of antenatal corticosteroids in late preterm and early term births

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ABSTRACT

Infants born in the late preterm period and via non-labour caesarean section in the early term period are at increased risk of respiratory morbidity when compared to their term-born counterparts. The morbidity in these infants is less frequent and severe than in early preterm infants. Antenatal corticosteroids reduce respiratory morbidity in these populations; however, the magnitude of the reduction appears to be small and predominantly in the self-limiting condition of transient tachypnoea of the neonate. The smaller benefit, along with possible harmful effects of corticosteroids, raises a question about the role of antenatal corticosteroids in this population. Special obstetric populations such as twin pregnancies and pregnancies complicated by diabetes and growth restriction are at increased risk of prematurity and more vulnerable to its complications. Nevertheless, there is limited evidence regarding the benefits of corticosteroids in these populations and potential concern regarding adverse effects.

We recommend an individualised approach when administering corticosteroids at later gestations. In these specific obstetric populations, we do not currently recommend administering corticosteroids in the late preterm/ early term periods until more evidence is available.

1. Introduction

Antenatal corticosteroid (ACS) administration to women prior to preterm birth (PTB) has been one of the greatest success stories of modern obstetrics and neonatology. Multiple randomised trials have demonstrated reduction in the rate of neonatal respiratory distress syndrome (RDS) [1,2] with additional benefits, including reduction in the rates of intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC), and reduced hospital stay for infants [3]. Until recently, a single course of ACS was recommended for pregnant women at risk of PTB between 24 and 34 weeks gestation [4]. Recent evidence has found that infants born in the late preterm period (LPT: $34–36^{+6}$ weeks gestation) or via non-labour caesarean section in the early term period suffer from higher rates of morbidity than their counterparts born via either non-labour caesarean section after 39 weeks or planned vaginal delivery after 37 weeks [5,6], and that the rates of these complications can be reduced by administration of ACS [7–12]. These findings have led to a revision of recommendations, with the American College of Obstetricians and Gynaecologists' (ACOG) guidelines now recommending ACS at later gestations [13].Whereas the short-term benefits of ACS have been demonstrated, evidence regarding the long-term implications is lacking, with some studies suggesting both short- and long-term adverse effects [7,14–18].

For early PTB (< 34 weeks) the reduction in RDS and neonatal death has shown that the benefits of ACS vastly outweigh potential risks; however, in the LTP and early term periods this risk:benefit ratio is unclear.

2. Research agenda

In this review article we aim to identify both the beneficial as well as the potentially harmful effects of ACS in these populations and address whether, and when, there is a role for extending the use of ACS to these later gestations.

Attention is given to special obstetric populations who are at increased risk of LPT birth and elective caesarean section in the early term period and in whom the effects of ACS are more poorly understood. These include pregnancies complicated by intrauterine growth restriction (IUGR), maternal diabetes, and multiple gestations.

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3. Mechanism of action of ACS

Corticosteroids, as opposed to other forms of steroids, are readily transported across the placenta [19].

The precise mechanisms underlying the beneficial effects of ACS have not been fully elucidated; however, they are believed to improve respiratory outcomes in several ways:

- maturation of the developing fetal lung [20] through thinning of the alveolar septae, and enhanced alveolar differentiation with induction of type 2 pneumocytes which increases surfactant production, decreasing surface tension within alveoli;
- activation of endothelial nitric oxide synthase [21], effecting pulmonary blood flow, improving pulmonary adaptation at birth;
- increased number of epithelial sodium channels [22], which clear fluid from the alveolar lumen to the interstitium, preventing ventilation/perfusion mismatch [23].

Neonatal respiratory morbidity is a spectrum of conditions [24]. Transient tachypnoea of the neonate (TTN) is caused by delay in fluid absorption from the lungs after birth. It usually presents with grunting and mild signs of respiratory distress which are self-limiting, generally lasting up to 48 h. This contrasts with RDS, which is secondary to surfactant deficiency, resulting in widespread alveolar collapse and is thus more likely to require support with oxygen and mechanical ventilation.

4. Potential adverse effects

Exposure to antenatal corticosteroids is associated with potential harm.

4.1. Short-term risks

4.1.1. Impaired growth

In a large, retrospective cohort study, neonates born in the LPT and term periods exposed to ACS had significantly lower birth weights, with smaller head circumference and body length compared to controls [18]. Differences remained significant when adjusting for major confounding factors. Fetal weight gain decreased in a dose-dependent manner in infants exposed to multiple courses of ACS. This suggests that ACS may impair fetal growth. This short-term complication carries long-term implications, as impaired fetal growth is associated with increased risk of adult disease, and small head circumference has been associated with future learning difficulties [25].

4.1.2. Hypoglycaemia

ACS may result in transient hyperglycaemia in women with diabetes. Increased maternal blood glucose concentrations cross the placenta, leading to fetal hyperglycaemia and subsequent increased fetal insulin production. Immediately postpartum, hyperinsulinaemia places the infant at risk of hypoglycaemia. The Antenatal Late Preterm Steroid (ALPS) study [7], a large multicentre randomised controlled trial investigating the effects of ACS in the LPT period, showed a significant increase in neonatal hypoglycaemia in ACS-exposed infants (relative risk (RR): 1.60; 95% CI: 1.37–1.87; $P < 0.001$). Although hypoglycaemia appears self-limiting, it has been reported to be associated with poor neurological outcomes in preterm infants [26].

4.2. Long-term risks

4.2.1. Poorer school performance

A follow-up study of the UK-based Antenatal Steroids for Term Elective Caesarean Section (ASTECS) study, a large open label randomised controlled trial (RCT) investigating the effects of antenatal betamethasone prior to elective caesarean section [14] showed that children exposed to ACS were twice as likely to be assessed as being in the lower quartile of school performance by their teachers. This study was limited by the numbers lost to follow-up.

4.2.2. Increased vulnerability of stress-related physical and psychiatric disorders

Among term children exposed to ACS, there was an increase in cortisol reactivity to acute psychosocial stress [15], suggesting that ACS have long-lasting effects on the hypothalamic–pituitary–adrenal axis and may increase vulnerability to stress-related physical and psychiatric disorders.

4.2.3. Metabolic illnesses

Follow-up studies of preterm infants showed that those exposed to ACS had higher blood pressures in adolescence [16] and were more likely to have insulin resistance in adulthood [17].

5. ACS for late preterm birth (34–36^{+6} weeks)

This subgroup makes up almost three-quarters of PTB [27]. Though survival rates of infants born in the LPT period are within 1% of those born at term [28], these infants are more likely to require neonatal intensive care (NICU) admission or ventilation and have a higher risk of RDS, TTN, pneumonia and low Apgar scores than their term counterparts [5].

Most recent studies concerning morbidity associated with LPT birth focus on respiratory complications, but the incidence of periventricular leukomalacia (PVL), cerebral palsy, and poorer school performance is still higher in LPT than term born infants [25].

The largest study assessing the efficacy of ACS in the LPT period (the ALPS study) was published by Gyamfi-Bannerman et al., in 2016 [7]. This was a multi-centre RCT of women at risk of spontaneous LPT birth or where LPT delivery was indicated. The results showed ACS to be associated with a significant reduction in the primary outcome, which included stillbirth and neonatal death within 72 h (neither of which occurred) and a composite endpoint of a need for respiratory support in the first three days of life (for the latter RR: 0.67; 95% CI: 0.53–0.84; $P < 0.001$). Notably, secondary analysis demonstrated that this reduction was only significant for TTN and bronchopulmonary dysplasia (which was rare at 0.1% versus 0.6%), but not for other severe or non-respiratory conditions associated with prematurity. The ACS group also had a significantly higher incidence of neonatal hypoglycaemia (RR: 1.60; 95% CI: 1.37–1.87; $P < 0.001$).

Smaller studies investigating the effects of ACS in the LPT period did not show a significant reduction in rates of RDS, TTN or NICU admissions [8–10].

The findings of Gyamfi-Bannerman et al. have led to change in clinical practice, with the ACOG releasing a committee opinion in 2017 [13] recommending treating women at risk of imminent birth in the LPT period, who had not received prior ACS, with a course of ACS, but advising against the use of tocolysis or delay in indicated delivery to allow for completion of treatment. Contraindications to ACS include pre-gestational diabetes and chorioamnionitis.

These changes in recommendations have raised concerns, with several publications advising caution with administration of ACS in the LPT period until further evidence regarding the long-term effects is available [26,27]. This is due to the reduced benefit incurred by ACS in the LPT when compared to early pre-term period, combined with the concern regarding the increased risk of hypoglycaemia as well as potential long-term complications which are still not well understood.

There is also difficulty in anticipating spontaneous preterm birth. In the study published by Gyamfi-Bannerman et al., 32% of patients who received ACS delivered at term. Expanding the recommendations of ACS to the LPT period would expose many infants to the potential harms of ACS without receiving any benefits.

Consistent with current New Zealand and Australian Guidelines

[29], we recommend administration of antenatal corticosteroids for those at risk of preterm birth prior to 34^{+6} weeks. We recommend against routine administration of ACS after 34^{+6} weeks in the LPT period, but rather administration only to those women who are most likely to deliver preterm and benefit from the reduction in respiratory morbidity.

Practice points.

- LPT birth makes up 75% of the preterm population and is associated with higher rates of morbidity and mortality than infants born at term. ACS are associated with a reduction in mild and self-limiting respiratory conditions such as TTN but with minimal impact on RDS in the LPT population.
- ACS may be associated with short-term harms including neonatal hypoglycaemia.
- There are no studies that adequately address the long-term benefits or harms of ACS in the LPT period.
- We recommend administration of ACS to women at risk of PTB at up to 34^{+6} weeks gestation.
- Routine administration of ACS after 34^{+6} weeks is not recommended, but rather individualised consideration of each patient and administration only to those most likely to deliver preterm and benefit from ACS.

6. ACS prior to elective caesarean section at early term

Infants born in the early term period are more likely to suffer respiratory morbidity, particularly if born via caesarean section prior to the onset of labour [6].

For this reason, the timing of elective caesarean section is generally recommended at 39 weeks gestation. There are many instances where delivery is indicated prior to this, raising the question of the place of ACS in such situations. Furthermore, delaying an elective caesarean section to 39 weeks carries a risk that the woman may commence labour spontaneously prior to the scheduled date and thus require an emergency caesarean section, which carries greater risks of maternal morbidity as well as the associated staffing disruptions related to an unplanned caesarean delivery.

The pathophysiology behind respiratory complications following elective caesarean section appears different to preterm infants born vaginally. Lack of a catecholamine surge and fluid retention in the lungs are the most likely causes, rather than underdevelopment of alveoli [30,31].

ACS increase the number and function of sodium channels responsible for fluid drainage from the lung and the responsiveness to catecholamines [32], providing a rationale for their potential benefit in cases of early term caesarean section.

In 2005, the large Antenatal Steroids for Term Caesarian Section (ASTECS) trial, a non-blinded RCT of ACS prior to elective caesarean section after 37 weeks, reported that infants exposed to ACS had lower rates of NICU or special care admission and were less likely to require resuscitation/ventilation at birth. The number needed to treat (NNT) to prevent one admission to NICU/special care unit was 37 and the rates of both RDS or TTN appeared to be reduced to an equivalent extent [11].

A smaller study from Israel [12] also showed lower rates of respiratory morbidity in infants exposed to ACS at term prior to caesarean section but the difference was significant only for TTN. There was a reduction in NICU admission and RDS, but this was not statistically significant (the authors attributed this to small numbers as the rate of RDS in these patients are already low).

A follow-up to the ASTECS study – the only long-term follow-up study published to date – showed that ACS prior to elective caesarean section was associated with a reduction in school performance [14].

Due to the marginal short-term benefits and concern regarding possible long-term harm, we do not currently recommend administration of ACS in this population until further evidence regarding its safety is available.

Practice points.

- Infants born via pre-labour caesarean section have higher rates of respiratory morbidity than those born vaginally or via caesarean section in labour.
- ACS administration prior to pre-labour caesarean section in the early term period reduces admissions to NICU/special care and the need for resuscitation/ventilation at birth.
- ACS exposure does not reduce rates of RDS, with inconsistent evidence regarding reduction in TTN.
- ACS may be associated with short- and long-term harms and we therefore do not recommend administration in this population until further evidence regarding safety of ACS is available.

7. Special obstetric populations

7.1. Twin pregnancies

The incidence of twin pregnancies has increased over the past four decades [33]. Twin pregnancies are more likely to deliver in the LPT period and via elective caesarean section than singletons – comprising up to one-third of LPT deliveries in some institutions [34].

There is conflicting evidence regarding morbidity and mortality rates associated with twin pregnancies when compared to singletons born in the LPT period [35,36] and the benefit incurred by ACS in this population [37,38]. Twin pregnancies are often excluded from studies and clinical trials, further reducing available evidence.

A large retrospective, observational Dutch cohort study from 2007 showed a seven-fold increase in morbidity and mortality rates in twin pregnancies compared to singletons [35]. By contrast, a smaller but more recent study showed similar rates of respiratory complications in twin pregnancies born in the LPT period compared to gestation-matched LPT singletons [36].

The benefit of ACS in twin pregnancies is also uncertain. A prospective cohort study of preterm twins showed that ACS reduced NICU admissions and need for mechanical ventilation but had no effect on the rates RDS, BPD, pneumonia, sepsis, NEC, IVH, PVL and neonatal death [37]. Another retrospective study showed no significant effect of ACS on Apgar scores, umbilical cord gases, infections, or respiratory morbidity [39]. The same study showed that preterm twins exposed to ACS had lower birth weights, smaller head circumferences, and shorter body lengths than controls.

Both studies did not focus specifically on twins born in the LPT period, but these findings raise concern that ACS may not benefit twins to the same extent as they do singletons, while still exposing them to the risks.

A suggested explanation for the limited benefit is that the standard ACS dosing regimen, designed for singletons, is sub-therapeutic in twins [37]. Betamethasone has been shown to have a shorter half-life in mothers of twin pregnancies [38].

Further evidence regarding the benefit of ACS and efficacy of different dose regimens in LPT twins is needed prior to implementation of ACS administration in this population.

Practice points.

- Twin pregnancies make up one-third of LPT deliveries.
- There is currently no evidence regarding the efficacy of ACS in reducing respiratory morbidity in LPT twins.
- In early preterm twins, ACS did not show the same reduction in prematurity-related conditions seen in singletons.
- Standard ACS dosing may be sub-therapeutic in twin pregnancies.
- ACS exposure has been associated with signs of growth restriction in twins.
- More evidence is needed prior to recommending administration of ACS in LPT twins.

7.2. Gestational/pre-gestational diabetes mellitus

Women with diabetes have higher rates of obstetric complications such as stillbirth and pre-eclampsia and are therefore more likely to be electively delivered earlier than women without diabetes [40] and thus more likely to be exposed to ACS.

Babies born in the LPT period to women with diabetes have higher rates of respiratory morbidity than those born to women without diabetes [41,42]. Several mechanisms have been suggested, including cardiac hypertrophy with subsequent left ventricular outflow obstruction and a delay in surfactant production [43], both caused by hyperglycaemia and hyperinsulinemia.

Despite higher rates of respiratory morbidity in this population, women with diabetes have largely been excluded from studies investigating the efficacy of ACS. Only eight of 26 studies considering the benefit of ACS in early preterm period, and one study on ACS prior to caesarean section, included a small number of women with diabetes [29].

The New Zealand and Australian Clinical Practice Guideline on antenatal corticosteroids recommends administration of ACS in women with diabetes at risk of early PTB despite the fact that fewer than 50 women with diabetes have been included in studies investigating the role of ACS in this population. However, there is an absence of evidence regarding the efficacy and risk of ACS in the LPT or term population [29].

Women with diabetes require close monitoring of blood glucose levels and are more likely to require treatment with insulin following ACS administration [29], thus adding to the burden of disease on both the patient and the health care system.

Infants of women with diabetes have a 10-fold increase in neonatal hypoglycaemia [44]. The effects of ACS could potentially increase this risk further. The study by Gyamfi-Bannerman et al. investigating the role of ACS in the LPT period included women with gestational diabetes who did not require pharmacological treatment. Women with pre-gestational diabetes or gestational diabetes requiring treatment with insulin were specifically excluded. While this study showed a reduction in respiratory complications, it also showed a significant increase in the rates of neonatal hypoglycaemia in response to ACS (RR: 1.60; 95% CI: 1.37–1.87; $P < 0.001$) [7]. Another RCT demonstrated significant increases in maternal blood glucose levels following ACS administration [45].

Hypoglycaemia has short-term implications, including need for treatment in a special care unit with subsequent separation from the mother and prolonged admission. There is also a well-established association between neonatal hypoglycaemia and seizures [46] and brain injuries [47]. Reports have suggested that mild hypoglycaemia which responds to treatment is still associated with poor neurocognitive and developmental outcomes [47].

Whereas there appears to be sufficient evidence regarding the benefit of ACS in the early preterm period in pregnancies complicated by diabetes, more evidence is required regarding their effect in the LPT and early term periods in this population, especially given the adverse implications that ACS can have on these patients and their babies.

Practice points.

- Infants born to women with diabetes have higher rates of respiratory complications and are at increased risk of LPT birth.
- Despite under-representation in clinical trials, ACS are recommended in pregnancies complicated by diabetes in the early preterm period.
- There is currently no evidence regarding the safety or efficacy of ACS in the LPT period in women with diabetes.
- ACS may impair glycaemic control, thus adding to the burden of disease to the mother and to the risk of hypoglycaemia and its sequelae to the infant.
- More evidence is needed prior to the recommendation of administration of ACS to women with diabetes in the LPT or term period.

7.3. Intrauterine growth restriction (IUGR)

IUGR is a risk factor for PTB, especially clinician-indicated PTB, due to concern about demise of a growth-restricted fetus, making growth-restricted infants more likely to be exposed to ACS [29].

Similar to maternal diabetes, studies investigating the efficacy of ACS often exclude pregnancies complicated by IUGR [29]. Available evidence is inconsistent and focuses on infants born in the early preterm period.

One meta-analysis [48] revealed no reduction in the incidence of RDS or neurological impairment in growth-restricted or small for gestational age (SGA) early preterm infants exposed to ACS. It did, however, show a reduction in handicap at two years of age among ACS exposed early preterm infants.

Another systematic review from 2015 [29] included three studies which included pregnancies complicated by IUGR in the early preterm period. These showed a non-significant reduction in the rates of RDS in IUGR infants exposed to ACS. Perinatal mortality was higher among IUGR infants exposed to ACS, although once again this was not statistically significant.

Although these findings cannot definitively be applied to the LPT and early term period, they raise questions about the lack of benefit and possible harm of ACS in IUGR infants.

It has been suggested that chronic intrauterine stress caused by placental insufficiency may stimulate the fetal adrenal gland to produce cortisol. Endogenous steroids enhance fetal lung maturation, thus reducing added benefit of ACS administration [49,50].

Growth-restricted fetuses may be exposed to higher levels of cortisol following ACS treatment, due to both the production of endogenous steroids and the breakdown of 11β-hydroxysteroid dehydrogenase, the enzyme responsible for preventing maternal cortisol from crossing the placenta [50].

Growth-restricted infants have been suggested to be at increased risk of harm from ACS compared to their normally grown counterparts, including an increased risk of further growth impairment following ACS treatment due to the higher levels of endogenous steroids. This may also be linked with long-term impaired growth, as one study showed that ACS-exposed IUGR infants, born in the early preterm period, were more likely to exhibit growth below the 10th percentile in childhood [51].

Administration of ACS in pregnancies complicated by IUGR has shown a divergent effect on altered fetoplacental blood flow [52–54]. ACS improves some but not all cases of absent end-diastolic flow in the umbilical arteries, with some fetuses exhibiting a worsening in Doppler flow studies. In growth-restricted animal models, ACS alters cerebral blood flow, impairs brain growth, and is associated with brain damage [55].

A limitation in reviewing the evidence is the lack of distinction between studies focusing on IUGR versus SGA fetuses. The distinction is challenging and in clinical practice is often difficult to make definitively [56]. SGA fetuses are a heterogeneous group consisting of both constitutionally small fetuses and those that are small secondary to placental insufficiency. Constitutionally small infants would not be subject to the same chronic intrauterine stress seen in IUGR and would not exhibit the same response to ACS. The inclusion of constitutionally small fetuses may contribute to the heterogeneity of the findings.

There is insufficient evidence regarding the benefits or harms of ACS therapy in women with IUGR infants, especially in the late preterm period, where the evidence regarding the benefit in well grown infants is already limited. ACS should therefore only be used in growth-restricted LPT pregnancies in the context of RCTs, as there is increased vigilance regarding potential detrimental effects.

An RCT is warranted to clarify whether treatment brings any added benefit in this population and to address the possible harms.

Practice points.

- Pregnancies complicated by IUGR are at increased risk of PTB due to concern regarding fetal demise.
- This population is often excluded from clinical trials, leading to limited and inconsistent evidence.
- Evidence from early preterm IUGR infants did not demonstrate the same benefit from ACS seen in normally grown babies.
- It is suggested that IUGR fetuses are exposed to endogenous steroids secondary to chronic intrauterine stress – reducing added benefit gained from ACS.
- Increased endogenous steroid production may also exacerbate the potential harm from ACS exposure –contributing to further growth impairment.
- Routine use of ACS in the LPT or term period in this population is not recommenced until further evidence regarding the effects of ACS in cases of IUGR during this period is available.

8. Discussion

Despite recent advances in neonatal care, prematurity remains a major obstetric and neonatal challenge, associated with increased mortality, respiratory conditions, and other complications. ACS administration has been shown substantially to reduce the burden of these adverse events in the early preterm period. The incidence and severity of conditions associated with prematurity decrease in the LPT and early term periods; however, infants born at $34–36^{+6}$ weeks or via non-labour caesarean section prior to 39 weeks are still at increased risk when compared to their late-term born counterparts. Importantly, LPT birth accounts for the majority of PTBs.

This has led to recent research into the benefits of ACS in the LPT and early term period. Whereas a reduction in (mainly respiratory) morbidity has been demonstrated, this reduction was predominantly in mild and self-limiting conditions (TTN and need for respiratory support).

Despite the benefits of ACS, adverse effects have been documented, including impaired growth, neonatal hypoglycaemia, and long-term effects such as poor school performance, increased vulnerability to stress related conditions, and predisposition to metabolic illnesses.

In the early preterm period, the benefits of ACS are so pronounced that they outweigh the risks; however, in the LPT and early term period the added benefit is small and of questionable clinical value. Moreover, due to the difficulty in predicting PTB and the majority of PTBs being in the LPT period, implementing guidelines recommending routine administration of ACS after 34^{+6} weeks gestation would greatly increase the number of infants exposed to, and therefore to the risk of, the adverse sequelae of ACS without enjoying its benefits.

We therefore do not recommend routine administration of ACS in such cases but rather administration only to women at greatest risk of PTB and whose infants are likely to benefit most from ACS. With regard to caesarean section in the early term period, we do not recommend ACS administration until further evidence is available regarding the long-term effects of ACS.

Examples of scenarios in which ACS in the LPT period may be appropriate include the following:

- Clinician-initiated delivery is indicated in the LPT period for conditions such as pre-eclampsia or obstetric cholestasis, where ACS have not been previously administered. Delivery should not be delayed, however, for completion of treatment.
- A woman who has not previously received ACS in this pregnancy presents with regular, palpable and painful contractions in the LPT period with features suggesting that birth in the next 48 h is likely (e.g. cervical dilatation, positive fetal fibronectin), especially if there is a history of PTB in a previous pregnancy, but delivery is not imminent.

Even when the above (or similar) scenarios are met, there are special obstetric populations to consider including twin pregnancies, maternal diabetes, and pregnancies complicated by IUGR. These are more likely to deliver in the LPT period and via non-labour caesarean section; they are also at increased risk of complications associated with prematurity.

Despite this, these three important subgroups are often excluded from studies investigating the effects of ACS and are under-represented in the literature. Evidence regarding the effect of ACS in these groups in the LPT and early term periods is lacking, making it difficult to be certain whether ACS would be of benefit, especially given the limited benefit gained by ACS in uncomplicated pregnancies.

The available evidence suggests that these subgroups would benefit less from ACS than the general population and that they are at increased risk of harm from ACS. In twin pregnancies and pregnancies complicated by IUGR, ACS have been associated with further impaired growth; whereas, in pregnancies complicated by diabetes, ACS would increase the already increased risk of neonatal hypoglycaemia and its sequelae.

More evidence is needed regarding both the risks and the benefits of ACS in the LPT and early term periods, especially in these obstetrics subgroups. We would recommend against administration of ACS in these populations until such evidence is available.

Conflicts of interest

None declared.

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