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The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation

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Abstract

This practice guideline follows the mission of the World Association of Perinatal Medicine (WAPM) in collaboration with the Perinatal Medicine Foundation (PMF), bringing together groups and individuals throughout the world with the goal of improving the use of antenatal corticosteroids (ACS) for fetal maturation. In fact, this document provides further guidance for healthcare practitioners on the appropriate use of ACS with the aim to increase the timely administration and avoid unnecessary or excessive use. Therefore, it is not intended to establish a legal standard of care. This document is based on consensus among perinatal experts throughout the world and also serves as a guideline for use in clinical practice.

Keywords: Corticosteroids, fetal maturation, guideline, pregnancy, preterm delivery.

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Introduction

According to the WHO International Classification of Diseases 10th revision (ICD-10), a preterm birth (PTB) is one that occurs between 22+0 and before 37+0 weeks of gestation (between 154 and 259 days).[1] Approximately two thirds of preterm deliveries are the consequence of preterm uterine contractions with or without preterm rupture of membranes whereas about one third is medically indicated due to maternal, fetal or placental conditions, including preeclampsia, uterine malformations, multiple gestation, fetal growth restriction, fetal anomalies, placenta previa and placenta accreta spectrum disorders.[2] Preterm neonates have complicated medical issues, the earlier a baby is born, the higher the risk of complications.[3] Thus, timely diagnosis and effective management of preterm labor is essential to improve newborn outcomes. The administration of antenatal corticosteroids (ACS) to accelerate fetal lung maturation is considered as one of the most valuable antenatal therapies.[4] Following the landmark study of Liggins and Howie[5] in 1972, the impact of ACS on fetal lung maturation has been extensively studied.

It is obvious that, in elective cases, the clinicians can administer ACS at the time they expect they will be most effective. However, in many cases i.e. PPROM, the situation is less straightforward as some women will be falsely diagnosed with PPROM, some will deliver before a full course is administered and a substantial proportion will remain undelivered for a period of weeks. The situation is even more difficult in cases of spontaneous labor with intact membranes, i.e. women who present reporting contractions, as most of these women will not deliver prematurely. Importantly, there is no consensus on the definition of true preterm labor and this allows for an arbitrary and often unnecessary use of ACS. In fact, this failure to accurately predict imminent PTB became apparent from the first study by Liggins, as less than half of the women delivered within the predicted timeframe of 2 to 7 days; about one in three cases delivered later than 7 days, most commonly later than 21 days after ACS administration.[5] Almost 50 years later, the successful timing of ACS administration has not improved at all.[6]

Mechanism of Action

As glucocorticoid receptors are expressed in almost every human cell, glucocorticoids exert effects throughout the body, including the placental and fetal tissues to result in pleiotropic effects.[7] The binding of glucocorticoids to these receptors induces a modulation of gene expression, transcription and protein synthesis, therefore it is obvious that this sequence takes some time (hours) before exerting effects.[7]

Considering endogenous corticosteroids, the fetus is exposed to low levels of glucocorticoids during early and mid-gestation. Towards the end of pregnancy, a complex process of organ maturation is triggered including a rise of both maternal and fetal glucocorticoids to transition from in to ex-utero.[8] Both betamethasone and dexamethasone's most known effect is at the lung through surfactant production; however, their actions will also affect the growth, heart, brain, hypothalamus, kidneys and thyroid, simulating the endogenous corticoid surge and fetal adaptations that occur late in pregnancy.[8]

Fetal lung development can be divided into five stages: embryonic, pseudoglandular, canalicular, terminal sac and alveolar.[9] From 28 to 35 weeks of gestation, the alveoli increase in number and mature. Lamellar bodies, which store surfactant, appear at 22 to 24 weeks.[9] Surfactant is needed to stabilize alveoli and is a complex mixture of lipids and apoproteins.[10]

ACS accelerate the development of type 1 and type 2 pneumocytes, induce pulmonary beta receptors and subsequently are responsible for modifications on alveolar structure, vascularization, surfactant production and airspace fluid clearance.[11,12] The increase of surfactant production will be achieved through both transcription and post-transcriptional mechanisms, enhancing the rate of phosphatidylcholine and fatty acid biosynthesis in the fetal lung.[13] Animal and human studies have shown that ACS also increase lung compliance and volume and increase response to exogenous surfactant treatment.[12,14,15]

The timing of effectiveness of ACS is usually considered to be between 2 and 7 days from administration based on the first paper by Liggins and on a Cochrane review that demonstrated a reduction in RDS in infants treated with ACS in the prior 2 to 7 days.[5,16] However, observational data suggest that neonatal benefits begin as early as within a few hours of ACS administration and can expand beyond a week.[17] There are studies that have found no differences between those delivered 8–14 days after treatment compared to those delivered within 7 days.[18,19] This could be explained as 7 days was an arbitrary cut-off and the decline in the effectiveness of antenatal corticosteroids

over time is gradual. Some authors even postulate that it is likely that this decline is not static across all gestational ages or birthweights.[20,21]

Considerations in Diagnosing Preterm Labor

Clinicians should be cautious, especially in cases of suspected preterm labor, to ensure appropriate and timely administration of ACS.

First, the accurate determination of gestational age is crucial. The WAPM supports the sonographic determination of gestational age in the first trimester using the crown-rump length (up to 84 mm). In later gestations, the head circumference should be used; however, this reduces the accuracy of estimation. In settings where ultrasound is not available and the woman is certain of her dates, the gestational age should be based on the last menstrual period, whereas in unknown dates, the best estimate using the fundal-symphysis height should be applied.[22,23]

In cases of suspected preterm labor, the first step is to diagnose regular contractions, either manually or preferably by cardiotocography. A minimum of 6 contractions per 30 minutes may be used as a reasonable threshold. Moreover, it is expected that in cases of true labor, the uterine contractions are regular, with increasing frequency, duration and strength and cause cervical changes. If such contractions are not observed, it is unlikely that it is a case of true labor.

The next step is to assess the cervix for changes. A speculum examination allows the visualization of the external cervical os; a manual examination may assist in determining dilatation, effacement, consistency and position of the cervix, as included in the Bishop score. Depending on the availability of ultrasound and biomarkers, local protocols should be implemented to provide clear pathways in cases of women presenting with reported uterine contractions before 34+0 weeks of gestation to determine if there is a high-risk of PTB within the next 7 days.[24–27] In cases where a first dose of corticosteroid is administered without any of these criteria met, the clinicians are encouraged to discontinue both tocolysis and the administration of subsequent doses of ACS.

Timing of Administration

22+0–23+6 weeks

A meta-analysis of observational studies including more than 3,500 neonates assessed the effect of ACS administration before 24 weeks of gestation and proved that the rate of mortality to discharge was reduced by 52% in the ACS group compared to the placebo or no treatment group (aOR: 0.48; 95% CI: 0.38–0.61).[28] Moreover, a multicenter study found that neurodevelopmental impairment or death at 18 to 22 months of age was significantly lower in cases that received ACS and were born at 23 weeks (83.4% vs. 90.5%; aOR: 0.58; 95% CI: 0.42–0.80), 24 weeks (68.4% vs. 80.3%; aOR: 0.62; 95% CI: 0.49–0.78) and 25 weeks of gestation (52.7% vs. 67.9%; aOR: 0.61; 95% CI: 0.50–0.74), but not in neonates born at 22 weeks of gestation (90.2% vs. 93.1%; aOR: 0.80; 95% CI: 0.29–2.21).[29] Neonates born at 22-25 weeks of gestation had higher survival rates post ACS exposure in total (72.3% vs. 51.9%); (aRR: 2.11; 95% CI: 1.68–2.65 at 22 weeks), (aRR: 1.54; 95% CI: 1.40–1.70 at 23 weeks), (aRR: 1.18; 95% CI: 1.12–1.25 at 24 weeks), (aRR: 1.11; 95% CI: 1.07–1.14 at 25 weeks).[30] Furthermore, a meta-analysis of neonates born between 22+0 and 22+6 weeks of gestation found that the administration of ACS doubled the rate of survival when compared to those not receiving corticosteroids (39.0% vs. 19.5%; p<0.01).[31] In any case, for fetuses at the periviable period, appropriate consultation should be provided to the parents by the perinatal specialists and the neonatologists.

Recommendations

- A course of ACS should be considered between 22+0 and 23+6 weeks of gestation in women at high-risk of PTB within the next 7 days.
- The decision should be based on local standards regarding periviable neonatal support and availability of neonatal facilities, following appropriate consultation to the parents.

24+0–33+6 weeks

A meta-analysis of 27 randomized controlled trials found that in cases of imminent PTB, the administration of ACS was associated with reduced rates of RDS (RR: 0.71; 95% CI: 0.65–0.78), IVH (RR: 0.58; 95% CI: 0.45–0.75), perinatal (RR: 0.85; 95% CI: 0.77–0.93) and neonatal death (RR: 0.78; 95% CI: 0.70–0.87).[32] Importantly, data from the same meta-analysis showed that treatment with ACS did not increase the risk of chorioamnionitis (RR: 0.86; 95% CI: 0.69–1.08) or endometritis (RR: 1.14; 95% CI: 0.82–1.58).[32] It is worthy of note that this meta-analysis included 27 studies and 11,272 women. Of the 20 studies including women

between 24 and 34 weeks of gestation, all but one (WHO 2020, in low-income countries only) were conducted between 1972 and 2002. Overall, 17 studies (all up to 2002) were conducted in high-income countries and 10 in middle- and lower-income countries, 15 of 27 included only singleton pregnancies, whereas the rest included multiples as well, 19 studies used a single course of steroids whereas 8 used either single or repeated doses and 16 used placebo whereas the rest compared ACS with no treatment. It should also be noted that this meta-analysis concluded that more detailed data are needed for certain high-risk groups (including multiple pregnancies, diabetes or hypertension).

In 2015, the ACT study raised some concerns regarding the use of steroids in low-income countries as it found that the administration of ACS probably increased neonatal mortality.[33] However, this study received criticism for certain limitations. The WHO study (2020) was subsequently conducted to resolve this issue and concluded that the use of dexamethasone resulted in significantly lower risks of neonatal death (RR: 0.84; 95% CI: 0.72–0.97) and stillbirth or neonatal death (RR: 0.88; 95% CI: 0.78–0.99) than the use of placebo, without an increase in the incidence of maternal bacterial infection.[34] Therefore, current data supports the use of ACS both in high- and low-income countries.

Recommendation

- A single course of ACS should be administered between 24+0 and 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days.

34+0–36+6 weeks

In the first decade of research on ACS (1972–1981), most studies included cases up to 36+6 weeks. Subsequently, all studies focused on cases up to 34+6 weeks. However, between 2010 and 2018, a series of studies looked again at the possible benefit of steroids in late preterm fetuses.[35]

The Antenatal Late Preterm Steroids (ALPS) study was a multicenter prospective randomized controlled study that assessed the impact of ACS between 34+0 and 36+5 weeks of gestation, using strict criteria for the definition of threatened preterm labor. They found a significant reduction in the primary composite adverse outcome (neonatal respiratory treatment in the first 72 hours, stillbirth or neonatal death within 72 hours of birth) (RR: 0.80; 95% CI: 0.66–0.97), TTN, severe respiratory complications, administration of surfactant and bronchopulmonary dysplasia.[36] No significant differences were identified in the incidence of chorioamnionitis or neonatal sepsis. Interestingly, in subgroup analyses, it was found that only female fetuses had benefit from the administration of ACS regarding the primary outcome (RR: 0.64; 95% CI: 0.47–0.87). Moreover, ACS reduced the rate of the primary adverse outcome in cases of elective cesarean section at the late preterm period (RR: 0.62; 95% CI: 0.43–0.90).[36] On the other hand, neonatal hypoglycemia occurred more frequently in the steroids group (24.0% vs. 15.0%; RR: 1.60; 95% CI: 1.37–1.87).[36] It is worthy of note that hypoglycemia may be associated with subsequent neurodevelopmental morbidity in the future.[37]

Recommendation

- A single course of ACS is not routinely recommended between 34+0 and 36+6 weeks of gestation in women at high-risk of PTB within the next 7 days because of the current uncertainty regarding the benefit to risk ratio.

Type and Dose of Corticosteroids

The beneficial effects of ACS on fetal lung maturation necessitate placental transfer from the maternal to the fetal compartment. Placental passage of drugs varies extensively, both between compounds, as well as throughout the different stages of pregnancy. This explains why beta- or dexamethasone are administered for fetal lung maturation; no significant differences have been identified in fetal lung maturation between these two steroids.[38,39] The most commonly offered regimens are a total of 24 mg divided in either two doses of 12 mg IM of betamethasone or 4 doses of 6 mg IM of dexamethasone; up to 80% of corticosteroid receptors are occupied using these doses, leading to the stimulation of corticosteroid receptors response to the fetus.[12,40–42] In addition, using higher doses of betamethasone did not increase its efficacy,[43] while a shortened dosing interval of corticosteroids may be associated with NEC, therefore it should be avoided.[44]

Regarding the differences between the two options, betamethasone has been associated with a lower risk of chorioamnionitis and RDS compared to dexamethasone.[38] On the other hand, in the dexamethasone group, the risk of IVH was lower (RR: 0.44; 95% CI:

0.21–0.92) and the duration of hospitalization in neonatal intensive care unit (NICU) was shorter (mean difference – MD: -0.91 days; 95% CI: -1.77 to -0.05).[39] Based on the available in vitro and in vivo observations, it is reasonable to state that beta- and dexamethasone display similar biological activity and exposure, so that preferences rather relate to availability or costs.[45]

Recommendation

- Either betamethasone (2 doses of 12 mg IM in a 24-h interval) or dexamethasone (4 doses of 6 mg IM at 12-h intervals) may be administered for fetal lung maturation.

Repeated Courses

The ACTORDS study reported that the weekly repeated doses of betamethasone, following an initial course in cases remaining undelivered for more than 7 days, were associated with fewer respiratory complications, including RDS.[46] Accordingly, a Cochrane review found that repeated doses were associated with lower rates of RDS (RR: 0.83; 95% CI: 0.75–0.91) and a reduction in the rates of serious adverse neonatal outcomes (RR: 0.84; 95% CI: 0.75–0.94).[47] However, the policy of repeated dose(s) has been linked to a reduction in the mean birthweight (MD: -75.79g; 95% CI: -117.63 to -33.96).[47] Another meta-analysis confirmed these findings and found lower rates of respiratory support in neonates treated with repeated ACS during pregnancy compared to no treatment (RR: 0.91: 95% CI: 0.85–0.97), but the birthweight was lower in the repeated ACS group (MD: -0.12; 95% CI: -0.18 to -0.06).[48] Furthermore, a trial reported increased rates of SGA for the repeated doses group (≥4 courses) (10th centile: 19.3% vs. 8.4%; 5th centile 10.4% vs. 4.7%).[49] Additionally, repeated corticosteroids doses have been correlated with a reduction in the placental weight.[50] In a pre-planned secondary analysis of data from the ACTORDS study, including neurocognitive function at 6–8 years as primary outcome, it was found that repeated antenatal betamethasone treatment, compared to placebo, was not associated with adverse effects on neurocognitive function at 6 to 8 years of age, even in the presence of FGR.[51] Although there is evidence of a certain short-term respiratory benefit, long-term outcomes remain unclear. It should be noted that the uncertainty on the possible usefulness of repeated ACS doses highlights the continuing failure to accurately predict imminent PTB.

Recommendations

- Repeated doses of ACS following an initial course of ACS are not recommended.
- A single rescue course of ACS is not routinely recommended. It may be administered up to 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days when a course of ACS has been administered at least 14 days before.

Scheduled Cesarean Delivery at Term

A meta-analysis showed that ACS administration 48 hours before scheduled cesarean section at term was associated with a lower risk of TTN (RR: 0.38; 95% CI: 0.25–0.57), RDS (RR: 0.40; 95% CI: 0.27–0.59) and need for mechanical ventilation (RR: 0.19; 95% CI: 0.08–0.43), and also a shorter stay in NICU (MD: -7.44 days; 95% CI: -7.44 to -7.43) and higher Apgar scores.[52] However, according to the most recent Cochrane review on this issue, which is based on the data from only one trial (Antenatal Steroids for Term Elective Cesarean Section - ASTECS[53]), it is uncertain if ACS reduces the risk of RDS (RR: 0.34; 95% CI: 0.07-1.65) or TTN (RR: 0.52; 95% CI: 0.25-1.11).[54] On the other hand, ACS probably reduces the risk of admission to neonatal special care for respiratory complications (RR: 0.45; 95% CI: 0.22–0.90), while they have no effect on the risk of needing mechanical ventilation (RR: 4.07; 95% CI: 0.46–36.27).[54]

Recommendations

- ACS are not routinely recommended before scheduled cesarean section at term because of the current uncertainty regarding the benefit to risk ratio.
- In the absence of other indications, a scheduled cesarean section should not be performed before 39+0 weeks of gestation.

Special Populations

Multiple gestation

According to data from the EPIPAGE-2 trial, the administration of ACS in twin pregnancies at high-risk of PTB within the next 7 days was significantly associated with a reduced rate of periventricular leukomalacia or IVH grade III/IV (aOR: 0.2; CI 95%: 0.1–0.5) and in-

hospital mortality (aOR: 0.3; 95% CI: 0.1–0.6).[55] Based on a recent Cochrane review, there was no effect of ACS on twin pregnancies regarding the outcomes of fetal death, perinatal death, neonatal death, RDS, and IVH; however, the number of studies and the number of the participants were limited.[32] With regards to the hypothesis that multiple gestations may have higher needs of corticosteroids, it has been proven that cord blood levels of steroids are similar to those observed in singletons.[56,57]

Recommendation

- In multiple pregnancies, ACS should be administered at the same dosage and indications as in singleton pregnancies.

Obesity

Some concerns have been raised whether the doses of ACS should be modified according to body mass index. There is limited data to make relevant recommendations; based on a study of 55 participants, cord blood levels of corticosteroids were comparable between the groups of obese and non-obese pregnant women.[56]

Recommendation

- In obese women, ACS should be administered at the same dosage and indications as in women without obesity.

Preterm prelabor rupture of membranes

There is still no consensus on the criteria to diagnose PPROM and there is very little evidence on the accurate prediction of women with PPROM that are more likely to deliver within 7 days.[58] Moreover, concerns have been raised regarding a possible increase in the incidence of perinatal infection in women with PPROM treated with ACS. A meta-analysis including more than 1,400 women with PPROM found that ACS reduces the risk of RDS (RR: 0.56; 95% CI: 0.46–0.70), IVH (RR: 0.47; 95% CI: 0.31–0.70) and NEC (RR: 0.21; 95% CI: 0.05–0.82) without increasing the risk of maternal infection (RR: 0.86; 95% CI: 0.61–1.20) or neonatal infection (RR: 1.05; 95% CI: 0.66–1.68).[59] Similarly, a subgroup analysis of the latest Cochrane review showed no differences in the effect on perinatal, neonatal and fetal death, RDS, endometritis or chorioamnionitis.[32] A study investigating the effect of a repeat ACS course in cases with PPROM showed that women receiving a repeat course were not at increased risk of chorioamnionitis (aOR: 1.28; 95% CI: 0.69–2.14) or any neonatal morbidity.[60] However, multiple ACS courses may increase the risk of chorioamnionitis.[61]

Recommendation

- A single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.

Fetal growth restriction

There are no randomized studies on the effect of ACS in FGR. It has been proposed that these fetuses may not benefit as much from this therapy as their lung maturation might be physiologically enhanced (given chronic stress and 11-B-HSD II breakdown) or may even be detrimental as shown by some animal studies. Furthermore, some reports have described that ACS can reduce mean birthweight at the expense of the reduction of the cranial perimeter. However, more recent studies have shown that the detrimental effect on weight may only be a consequence of repeat courses and that some poor outcomes associated to these fetuses may have been influenced by maternal comorbidity. Furthermore, a secondary analysis from the ACTORDS trial found that, in 139 FGR fetuses, repeated antenatal betamethasone treatment compared with placebo was not associated with adverse effects on neurocognitive function at 6 to 8 years of age, even in the presence of FGR.[51]

A 2009 review that included 5 studies with 664 fetuses found no differences in terms of morbidity, mortality, respiratory distress syndrome, IVH or NEC.[62] These results, however, may have been underpowered to detect differences among outcomes. A more recent meta-analysis conducted in 2020, including 13 studies with 6,387 FGR and small for gestational age infants, found that neonatal mortality was significantly lower among infants who received ACS (12.8% vs. 15.1%; OR: 0.63; 95% CI: 0.46–0.86), with significant heterogeneity between studies (I^2=55.1%; p=0.011).[63] There was no significant difference in respiratory distress syndrome, NEC, IVH and periventricular leukomalacia, bronchopulmonary dysplasia or chronic lung disease of prematurity, or neonatal sepsis.

Finally, a small sub-analysis from the TRUFFLE 2 feasibility study found no benefit from ACS administration beyond 32 weeks of gestation.[64] However, in

this matched case-control study, the sample size was too small to enable evaluation of all outcomes.

Therefore, most recent data indicate that ACS reduces neonatal mortality in FGR cases delivered preterm (specially <32+0 weeks of gestational age), with no apparent effect on neonatal morbidity short or long term.

Recommendation

- In cases complicated with FGR, ACS should be administered at the same dosage and indications as in appropriate for gestational age fetuses.

Diabetes mellitus

Pregnant women with diabetes are usually excluded from studies due to the adverse effects of corticosteroids on glycemic control.[65] Accordingly, a systematic review could not retrieve any comparative studies of ACS in cases of either pregestational or gestational diabetes.[65] An increase in glucose levels is usually identified after ACS administration for up to seven days after the first dose in pregnant women with or without diabetes.[66,67]

Recommendations

- In diabetic women, ACS should be administered at the same dosage and indications as in women without diabetes.
- Close monitoring of the maternal blood glucose levels is recommended for women with diabetes in the following days after the administration of ACS.
- After the administration of ACS, screening with glucose tolerance test should be delayed for at least one week.

Short- and Long-Term Outcomes of Corticosteroids in the Offspring

As the primary stress hormone is cortisol, ACS given to women with a singleton or multiple pregnancy prior to PTB interfere with endogenous stress hormone action and thus may have short- and long-term implications.[68] Whereas a single course of ACS is associated with immediate adverse effects such as postnatal hypoglycemia,[36,69] long-term adverse effects including reduced fetal growth[48,70,71] or poor academic performance were only unequivocally documented when ACS have been administered repeatedly.[72,73] Moreover, according to data from a population-based study in Finland, exposure to ACS was significantly associated with mental and behavioral disorders in children.[74]

The latest Cochrane meta-analysis found that a single course of ACS given to women with a singleton or multiple pregnancy prior to anticipated PTB (elective, or following rupture of membranes or spontaneous labor) leads to a reduction in the incidence of developmental delay in childhood (RR: 0.51; 95% CI: 0.27–0.97).[32] The same meta-analysis found no increase on intellectual impairment, visual impairment, or hearing impairment, neither in childhood nor in adulthood. It is worthy of note that, in this meta-analysis, a large proportion of deliveries occurred at >37 weeks of gestation. Another meta-analysis that included only children born before 34 weeks of gestation and focused specifically on neurodevelopmental outcome after a single course of ACS found an improvement in most neurodevelopmental outcomes in the offspring.[75]

Repeated courses of ACS (a second or weekly doses after an initial ACS course) decreased fetal growth as an indicator of a global effect on the fetus.[48,70,71] At 5 years of age, children exposed to repeated ACS that were delivered after 37 weeks of gestation showed a significant increase in neurosensory disability but were otherwise intact.[73] There was also a directional trend for more cerebral palsy at 2–3 years of age following repeat ACS in a National Institute of Child Health and Development trial, but no other abnormalities were identified.[72] In a complex study approach to judge gestational age-specific risks vs. benefits of multicourse ACS for preterm labor, it was found that below 29 weeks of gestation a repeat course in case of anticipated PTB is beneficial whereas after 29 weeks the long-term side effects, including growth retardation and neurodevelopmental delay predominate.[76]

Conclusion

Despite the usefulness of ACS in improving neonatal outcomes, there are still certain unresolved issues. The main setback remains the failure to accurately identify which of the women that present with preterm contractions or PPROM are most likely to deliver within the next 7 days. In view of the uncertainty regarding the long-term effects of ACS and neonatal hypoglycemia, especially in late preterm neonates, the WAPM recommends that the use of ACS should adhere to strict guidelines. Thus, until more data are available from prospective studies, the clinicians are advised to administer a single course of ACS in cases that are at high-risk of PTB within the next 7 days and the gestational age is between 22+0 and 33+6 weeks. To achieve that, they should be

supported by comprehensive protocols that describe the diagnosis of preterm labor based on the availability of resources and expertise in their settings.

Implications for future research

- Accurate diagnosis of preterm labor with intact membranes
- Accurate prognosis of PTB within the next 7 days in cases with PPROM
- Effectiveness of strict criteria of preterm labor on the timely use of ACS
- Effect of ACS on multiple pregnancies
- Value of administration of ACS in women already on steroids for other indications
- Exact timing of ACS administration in elective cases to maximize their effectiveness
- Cardiovascular long-term outcomes of the offspring following the administration of ACS
- Long-term outcomes in the offspring of women that received ACS but subsequently not delivered preterm

Summary of recommendations

- A course of ACS should be considered between 22+0 and 23+6 weeks of gestation in women at high-risk of PTB within the next 7 days. The decision should be based on local standards regarding periviable neonatal support and availability of neonatal facilities, following appropriate consultation to the parents.
- A single course of ACS should be administered between 24+0 and 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days.
- A single course of ACS is not routinely recommended between 34+0 and 36+6 weeks of gestation in women at high-risk of PTB within the next 7 days because of the current uncertainty regarding the benefit to risk ratio.
- Either betamethasone (2 doses of 12 mg IM in a 24-h interval) or dexamethasone (4 doses of 6 mg IM at 12-h intervals) may be administered for fetal lung maturation.
- Repeated doses of ACS following an initial course of ACS are not recommended. A single rescue course of ACS is not routinely recommended. It may be administered up to 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days when a course of ACS has been administered at least 14 days before.
- ACS is not routinely recommended before scheduled cesarean section at term because of the current uncertainty regarding the benefit to risk ratio. In the absence of other indications, a scheduled cesarean section should not be performed before 39+0 weeks of gestation.
- In multiple pregnancies, ACS should be administered at the same dosage and indications as in singleton pregnancies.
- In obese women, ACS should be administered at the same dosage and indications as in women without obesity.
- A single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.
- In cases complicated with FGR, ACS should be administered at the same dosage and indications as in appropriate for gestational age fetuses.
- In diabetic women, ACS should be administered at the same dosage and indications as in women without diabetes. Close monitoring of the maternal blood glucose levels is recommended for women with diabetes in the following days after the administration of ACS.
- After the administration of ACS, screening with glucose tolerance test should be delayed for at least one week.

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