Thieme

Administration of Antenatal Corticosteroids: Optimal Timing

Applikation antenataler Kortikosteroide: optimales Timing

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ABSTRACT

The effectiveness of antenatal corticosteroids (ACS) in significantly reducing respiratory distress syndrome (RDS) depends crucially on the timing. It is successful if delivery takes place between 24 hours and seven days following administration; after this period, the side effects seem to predominate. In addition, an increased rate of mental impairment and behavioral disorders are observed in children born full-term after ACS administration. The optimal timing of ACS administration depends crucially on the given indication; to date, it has been achieved in only 25–40 % of cases. ACS administration is always indicated in PPROM, in severe early pre-eclampsia, in fetal IUGR with zero or reverse flow in the umbilical artery, in placenta previa with bleeding, and in patients experiencing premature labor with a cervical length < 15 mm. The risk of women with asymptomatic cervical insufficiency giving birth within seven days is very low. In this case, ACS should not be administered even if the patient's cervical length is less than 15 mm, provided that the cervix is closed and there are no other risk factors for a premature birth. The development of further diagnostic methods with improved power to predict premature birth is urgently needed in order to optimize the timing of ACS administration in this patient population. Caution when administering ACS is also indicated in women experiencing premature labor who have a cervical length ≥ 15 mm. Further studies using amniocentesis are needed in order to identify the patient population with microbial invasion of the amniotic cavity/intra-amniotic infection (MIAC/IAI), and to define threshold values at which delivery is indicated. ACS administration is not performed as an emergency measure, usually not even before transfer to a perinatal center. Therefore, whenever possible, the indication for ACS administration should be determined by a clinician who is highly experienced in perinatology.

ZUSAMMENFASSUNG

Die Effektivität antenataler Kortikosteroide (ACS), das Respiratory Distress Syndrome (RDS) signifikant zu senken, hängt entscheidend vom Timing ab. Dies gelingt bei einer Entbindung > 24 Stunden bis 7 Tage nach Applikation, nach dieser Zeit scheinen eher die Nebenwirkungen zu überwiegen. Darüber hinaus werden bei Kindern, die nach ACS-Applikation reif geboren werden, vermehrt mentale Beeinträchtigungen und Verhaltensstörungen beobachtet. Das optimale Timing der

ACS-Gabe hängt entscheidend von der jeweiligen Indikation ab und gelingt bisher in lediglich 25–40 % der Fälle. Die ACS-Applikation ist immer indiziert bei PPROM, bei schwerer, früher Präeklampsie, bei fetaler IUGR mit Null- oder Reverse-Flow in der A. umbilicalis, bei einer blutenden Placenta praevia und bei Patientinnen mit vorzeitiger Wehentätigkeit und einer Zervixlänge < 15 mm. Das Risiko von Frauen mit einer asymptomatischen Zervixinsuffizienz, innerhalb von 7 Tagen zu gebären, ist sehr gering. Hier sollte auf die ACS-Gabe auch bei einer Zervixlänge von unter 15 mm verzichtet werden, wenn der Muttermund geschlossen ist und keine weiteren Risikofaktoren für eine Frühgeburt vorliegen. Die Entwicklung weiterer diagnostischer Methoden mit verbesserter Prädiktion für eine Frühgeburt ist dringend notwendig, um das Timing der ACS-Gabe in diesem Patientenkollektiv zu optimieren. Zurückhaltung bei der ACS-Gabe ist ebenso angezeigt bei Frauen mit vorzeitiger Wehentätigkeit und einer Zervixlänge ≥ 15 mm. Hier gilt es, in weiteren Studien mittels Amniozentese das Patientenkollektiv zu identifizieren, bei dem eine intraamniale, mikrobielle Infektion/Inflammation (MIAC/IAI) vorliegt, und Schwellenwerte für die Indikation zur Entbindung zu definieren. Die ACS-Gabe ist keine Notfallmaßnahme, in der Regel auch nicht vor Verlegung in ein Perinatalzentrum. Deshalb sollte, wenn immer möglich, die Indikation zur ACS-Applikation von einem/einer in der Perinatologie sehr erfahrenen Kollegen/Kollegin gestellt werden.

Introduction

The administration of antenatal corticosteroids (ACS) in premature births delivered prior to gestational week (GW) 34 leads to a significant reduction in perinatal morbidity and mortality [1, 2]. Their effectiveness depends crucially on optimal timing [3]. As shown in a meta-analysis from 2006, there is no effect on respiratory distress syndrome (RDS) < 24 hours after the first administration of betamethasone (RR 0.87, 95% CI 0.66–1.15); this effect only becomes apparent at < 48 hours (RR 0.63, 95% CI 0.43–0.92). A significant effect can therefore be expected > 24 hours after the first administration of ACS. After a period of seven days following corticosteroid administration, no further reduction in RDS can be detected (RR 0.82, 95% CI 0.53–1.28) [4]. However, a prospective cohort study by the German Neonatal Network describes positive effects on the rate of intraventricular brain hemorrhage (OR 0.43, 95% CI 0.25–0.72) and on the need for mechanical ventilation (OR 0.43, 95% CI 0.27–0.71) even seven days after administration of ACS [5]. Nevertheless, there is also evidence that extremely premature infants born before GW 28 who are delivered more than 10 days after the first corticosteroid administration have a more than twofold higher rate of brain hemorrhage (17% vs. 7%; aOR 4.16, 95% CI 1.59–10.87)[6], although the retrospective design of this study of course does not allow a causal conclusion to be drawn. In addition, children born full-term after antenatal administration of corticosteroids may have more mental and behavioral impairments compared to children born full-term who did not receive corticosteroids during pregnancy (HR 1.47, 95% CI 1.36–1.69). This effect persisted even after taking socioeconomic influences into account (HR 1.38, 95% CI 1.21–1.58) [7]. The same applies to the psychological and neurosensory development of these children [8]. A further prospective cohort study confirms these results for dexamethasone [9].

However, as numerous studies have shown, only 25–40 % of patients are delivered within the optimal timeframe after administration of ACS [10, 11, 12]. The optimal timing depends crucially on the indication for administration of ACS [10]. For example, this treatment is clearly very successful in cases of severe pre-eclampsia or preterm premature rupture of membranes (PPROM), but appears to be less successful in patients with asymptomatic cervical insufficiency (▶ **Fig. 1**) [10]. In this review, we explain the reasons for this and present ways for further optimization.

Literature Search

A selective literature search up to May 2023 was conducted in PubMed for the keywords “corticosteroid”, “timing”, “preterm birth”, “preterm delivery”, “pregnancy prolongation”, and “delivery delay”. Prospective randomized trials, reviews, and meta-analyses relevant to the topic were selected. Cross-references to other important studies have been taken into account.

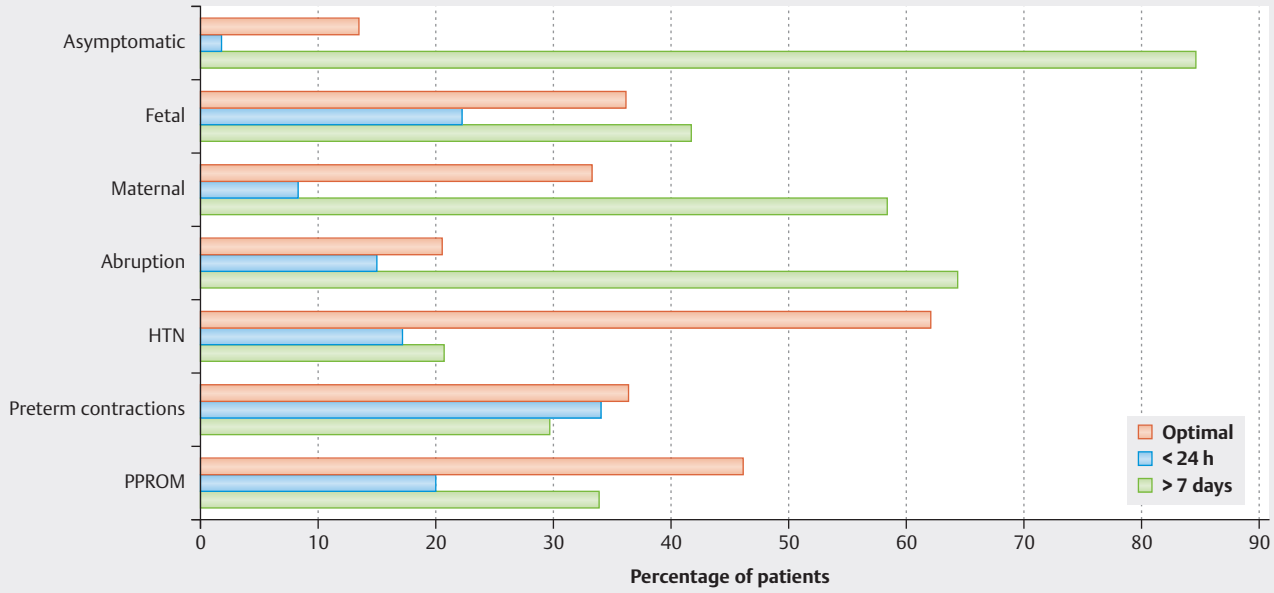
PPROM

More than half of all patients who undergo PPROM deliver within a week. The median duration of pregnancy in a cohort of 239 patients who were negative for B streptococci was 6.1 days. The cumulative delivery rate was 27 % after 48 hours, 56 % after 7 days, 76 % after 14 days, and 86 % after 21 days [13]. The latency period prior to birth is inversely correlated to gestational age at the time of PPROM [14]; the greater the remaining volume of amniotic fluid, the longer the latency [15]. Spontaneous rupture of membranes is very rare, unless it is the result of an amniocentesis [16].

In view of the high probability of delivery within one week of PPROM, the administration of ACS is indicated in these cases. However, the question arises as to what clinical management should look like for the approx. 50 % of women who have not yet given birth seven days after PPROM. The guideline “Prevention and treatment of premature birth” from the Association of Scientific Medical Societies in Germany (AWMF) recommends the following: Women treated more than 7 days previously with steroids for threatened preterm birth before week 29 + 0 of gestation, may receive a further single dose of steroids after re-evaluation if they have an increasing risk of immediately threatened preterm birth [17].

ACS Booster

Due to the 50 percent likelihood that women who are still pregnant one week after PPROM will give birth in the following week, a



▶ **Fig. 1** Interval between administration of antenatal corticosteroids (ACS) and delivery according to the indication (data from [10]) Patients as % with an interval between ACS administration and delivery of < 24 hours (blue), 24 hours to 7 days (red), and over 7 days (green). Asymptomatic = positive fibronectin test, shortened cervical length, asymptomatic cervical opening; Fetal = intrauterine growth restriction, oligohydramnios; HTN = hypertensive diseases of pregnancy; Maternal = maternal diseases other than pregnancy-induced hypertension; PPROM = preterm premature rupture of membranes.

repeat administration of ACS appears to make perfect sense. However, a recent prospective randomized study shows that this view is controversial [18]. In this study, 192 patients with PPROM occurring between GW 24+0 and GW 31+6 who had already received one dose of ACS and were still pregnant after seven days were randomized to receive either a second dose of ACS (booster) or placebo. The primary study endpoint was combined neonatal morbidity or neonatal death. No significant difference was found between the groups for either the primary or secondary study endpoints. Moreover, this observation was independent of the time interval between ACS booster and delivery, as well as the gestational age at birth (▶ **Table 1**) [18]. Two further studies based on a secondary analysis of a prospective randomized study on neuroprotection with magnesium were also unable to demonstrate any effect of an ACS booster on the RDS rate [19, 20].

It is known that an infection can impair the effectiveness of glucocorticoids. Webster et al. showed that TNF-α, an inflammatory mediator, stimulates synthesis of the glucocorticoid β-receptor and thus induces glucocorticoid resistance [21]. Endotoxins also modulate glucocorticoid receptor expression and the associated signaling mechanism [22]. Ascending inflammatory processes may have impaired the efficacy of the second administration of ACS in the above-mentioned study.

However, the data on the administration of an ACS booster with an intact amniotic sac is also mixed. While Garite et al. were able to observe a reduction in RDS after a second administration [23], this effect has not been demonstrated in other studies [24, 25]. However, RDS was defined differently in these studies. Taking this into account, it is very likely that the administration of an ACS booster only reduces the incidence of mild RDS, whereas it has no effect on the incidence of severe RDS or other parameters of neonatal morbidity [24]. In general, caution is advised when using an ACS booster, as it can lead to a significant increase in small for gestational age (SGA) infants (4.9% vs 10.6%; aOR, 1.63; 95% CI, 1.07–2.47) [24]. This fact is taken into account in the AWMF guideline "Prevention and treatment of premature birth". In this guideline, a booster is only recommended before GW 29 and only if there is a very high risk of a premature birth occurring within seven days [17].

Hypertensive Disorders of Pregnancy

The sFlt/PlGF ratio can be helpful in identifying patients likely to develop pre-eclampsia during the course of their pregnancy [26]. For example, the Pregnancy Outcome Prediction Study showed in a non-selected patient cohort that the positive predictive value (PPV) of an sFlt/PlGF ratio > 38 measured at GW 28 identified 32% of patients who went on to suffer a premature birth due to pre-eclampsia [27]. A value of > 38 between GW 30 and GW 37 detects 79% of all patients who have to be delivered within a week due to pre-eclampsia, with a false-positive rate of 4.5% [28].

The INSPIRE trial showed that an sFlt/PlGF ratio > 85 had a PPV of 71.7% for development of pre-eclampsia within the next four weeks [29]. Similarly, in the Rule Out Pre-Eclampsia Study, an sFlt/PlGF ratio > 85 was found to have a PPV of 74% for the development of severe pre-eclampsia within two weeks in patients prior to GW 34 [30]. Women with an extremely high sFlt/PlGF ratio > 655 have a significantly shorter time interval before delivery

▶**Table 1** ACS booster for preterm premature rupture of membranes. 192 patients with preterm premature rupture of membranes occurring between GW 24 + 0 and GW 31 + 6 who had already received antenatal corticosteroids (ACS) and were still pregnant after seven days were randomized to receive either a second administration of ACS (booster) or placebo. The primary study endpoint was combined neonatal morbidity or neonatal death (data from [18]).

	ACS Booster n = 94 (%)	**Placebo** n = 98 (%)	**P value**
Primary study endpoint: neonatal morbidity and/or mortality	60/94 (64)	63/98 (64)	0.54
Individual components of the primary study endpoint			
Respiratory distress syndrome	57/94 (61)	63/98 (64)	0.44
Bronchopulmonary dysplasia	13/94 (14)	11/98 (11)	0.67
Intraventricular brain hemorrhage, grade 3 and 4	4/94 (4)	3/98 (3)	0.69
Periventricular leukomalacia	0/94 (0)	1/98 (1)	0.31
Sepsis detected by culture	5/94 (5)	3/98 (3)	0.44
Necrotizing enterocolitis	4/94 (4)	3/98 (3)	0.70
Neonatal death	2/94 (2)	4/98 (4)	0.38
Primary study endpoint according to the time interval between ACS booster and delivery			
< 48 hours	7/9 (78)	5/12 (50)	0.47
24 hours to < 7 days	25/35 (71)	15/23 (65)	0.88
48 hours to < 7 days	22/32 (67)	13/18 (72)	0.58
7 to < 14 days	8/14 (57)	20/31 (65)	0.83
≥ 14 days	20/35 (57)	26/35 (74)	0.19
Primary study endpoint according to gestational age at delivery			
Delivery < GW 29	33/36 (92)	23/28 (82)	0.26
Delivery ≥ GW 29	27/58 (47)	42/70 (60)	0.16

[31]. Changes in the sFlt/PlGF ratio over time also appear to be significant. Patients who develop pre-eclampsia have a greater increase in sFlt/PlGF ratio within two weeks than those who do not develop pre-eclampsia (31.22 vs. 1.45) [32].

Although the sFlt/PlGF ratio can be helpful in identifying patients with an increased risk of pre-eclampsia, its predictive value is not sufficient to determine the optimal timing for administration of ACS. There is currently no sufficiently reliable way of predicting an imminent delivery within a period of seven days in patients prior to GW 34. The decision on the administration of ACS must therefore be based on the patient's clinical symptoms; however, making an accurate predication and thus determining the correct timing of administration is also difficult in this context. The effect of esomeprazole on a possible prolongation of pregnancy in patients with early, severe pre-eclampsia between GW 26 + 0 and GW 31 + 6 has been investigated in a prospective randomized study. The average systolic blood pressure of the women in the control group at the time of randomization was 168 ± 16.4 mmHg, and the diastolic pressure was 103 ± 11.4 mmHg. The average 24-hour protein urine value was 1.06 (0.57–16.86) g/24 hours (median value and interquartile range). In the control group, a median pregnancy prolongation of 8.3 days (interquartile range: 3.8–19.6 days) was achieved [33]. In other words, administration of ACS following diagnosis would have fallen within the seven-day timeframe in only just on 50% of cases.

Very similar values have also been described by other study groups [34, 35, 36, 37]. In a prospective observational study, Haddad et al. investigated a group of 239 women with severe pre-eclampsia occurring between GW 24 and GW 33. In the context of a watchful waiting approach, they reported a median prolongation of the duration of pregnancy of 6 days before GW 29 (range: 2–35 days), 4 days between GW 29 and GW 32 (range: 2–32 days), and 4 days after GW 32 (range: 2–12 days) [34]. Chammas et al. also described a pregnancy prolongation of 6 days in patients with severe pre-eclampsia occurring before GW 34. If there was also fetal growth restriction, the prolongation was only 3 days [35].

These figures show that in early, severe pre-eclampsia, optimal timing of ACS administration can be achieved with high success in many cases. In the aforementioned study, Levin et al. found that optimal timing (interval from administration to delivery: 24 hours to 7 days) in hypertensive pregnancy was achieved in as many as 62 % of patients [10].

Clinical prediction models for pre-eclampsia are now also available with fullPIERS and PREP to predict the occurrence of maternal and fetal complications within seven days. One example of this is the prospective cohort study by Dadelszen et al. in which 106 out of 2023 women who were hospitalized for pre-eclampsia developed life-threatening complications within 48 hours. The fullPIERS model, which includes gestational age, breast pain, dyspnea, oxy-

gen saturation, platelet count, serum creatinine, and transaminases, showed an AUC of 0.88 (95 % CI 0.84–0.92) for the occurrence of these complications [38]. These models could certainly be developed further in order to predict the optimal timing of ACS administration.

Fetal Growth Restriction

Two prospective randomized studies have investigated the watchful waiting approach to managing intrauterine growth restriction (IUGR) [39, 40]. The GRIT trial recruited 588 patients with IUGR between GW 24 and GW 36. In 77% of cases, there was pathological end-diastolic flow in the umbilical artery. The doctors in charge were unsure whether or not they should deliver these patients immediately. After administration of one cycle of betamethasone, the women were randomized to undergo either immediate delivery or watchful waiting. The primary study endpoint of death or severe disability at two years of age was 19% in the first group and 16% in the second group (OR 1.1, 95% CI 0.7–1.8). However, the rate of disability in children born at ≤ GW 30 was 13% with immediate delivery and only 5% with a watchful waiting approach. The corresponding median interval between randomization and delivery was 0.9 days (interquartile range: 0.4–1.3) and 4.9 days (interquartile range: 2.0–11.0 days); for a gestational age ≤ 30 weeks, the respective values were 0.8 days (0.3–1.1) versus 3.2 days (1.5–8.0) [39].

The TRUFFLE trial recruited 542 patients between GW 26 and GW 32 who had early-onset fetal growth restriction (abdominal circumference < 10 th percentile) and a pathological pulsatility index (PI) in the umbilical artery (> 95 th percentile). The women were randomized into three groups characterized by different strategies used to decide when to deliver. In all groups, the patients were monitored using Oxford CTG and Doppler ultrasound of the umbilical artery; monitoring of the ductus venosus was only planned in two groups. In the first group the decision to deliver was based on the short-term variability of the Oxford CTG (cut-off: 2.6 ms < GW 29 or 3.0 ms at GW 29 to GW 32), in the second group the decision was made based on early changes in the ductus venosus (pulsatility index > 95 th percentile), and in the third group it was based on later changes in the ductus venosus (A-wave absent or negative). Of the children who survived without neurological defects, significantly more belonged to group three than to group one (95 % [95 % CI 90–98] vs. 85 % [95 % CI 78–90]; p = 0.005). The respective median interval from randomization to delivery for the three groups was seven days (interquartile range: 0.5–61), seven days (interquartile range: 0.5–56]), and nine days (interquartile range: 0.5–88) [40].

Approximately 40 % of patients in the TRUFFLE study had absent or reverse flow in the umbilical artery at the time of randomization [40]. The time interval until manifestation of fetal distress is five or two days respectively, while the probability of delivery within the next seven days is significantly lower in the case of early changes in the PI in the umbilical artery [41]. Absent or reverse flow in the umbilical artery is therefore an indication for the administration of ACS, while restraint should be exercised in the case of early changes in the PI. If ACS is administered immediately in these cases, it usually does not fall within the optimal timeframe.

Taking into account the pathophysiological development of end-diastolic umbilical blood flow on Doppler ultrasound in IUGR fetuses, optimal timing of ACS administration should generally also be possible in this indication, similar to early pre-eclampsia. It should be borne in mind that in IUGR fetuses, an improvement in end-diastolic flow in the umbilical artery is often observed following administration of ACS. However, this is often an expression of an increased cardiac output, rather than reduced placental resistance [42].

There are currently no prospective randomized studies that have investigated the effect of ACS administration on neonatal morbidity in IUGR fetuses. There is concern that glucocorticoids may exacerbate the cardiovascular and endocrinological alterations associated with intrauterine growth restriction. However, in a 2001 prospective cohort study, Schaap et al. showed that IUGR fetuses delivered by caesarean section 24 hours to seven days after administration of ACS had a higher probability of survival without disability at the age of two years (OR 3.2, 95 % CI 1.1–11.2) [43]. A meta-analysis from 2017, which included five retrospective or prospective studies, found no reduction in neonatal morbidity after administration of ACS in IUGR infants; however, it did show a clear trend towards a reduction in the rate of brain hemorrhage. However, it is unclear whether the optimal timeframe of 24 hours to seven days after ACS administration was considered in this analysis [44].

Similarly for fetuses with late-onset intrauterine growth restriction, in another prospective cohort study, no reduction in neonatal morbidity or perinatal mortality was observed following ACS administration between GW 32 + 0 and GW 36 + 6. However, the neonatal morbidity parameters investigated in this study (e.g., pH value in the umbilical artery < 7.00, grade III–IV brain hemorrhage, grade II–III periventricular leukomalacia, respiratory support for more than seven days, mechanical ventilation, etc.) were not suitable for detecting a potentially small benefit from ACS administration [45]. After GW 32, the benefit from administering ACS is hardly demonstrable in any case, as will be explained in the section “Benefit of Antenatal Corticosteroids According to Gestational Age”.

Ex Utero Bleeding

In the event of ex utero bleeding, it is difficult to predict how long the interval will be until delivery becomes necessary. In the case of vasa previa, placental abruption, or placenta previa with heavy bleeding, an emergency caesarean section is indicated. If a watchful waiting approach is possible in the case of placenta previa with moderate bleeding or placental edge bleeding, ACS administration should always be considered. As no information can be found in the literature on the time until delivery in these situations, the decision as to whether ACS administration is indicated must be made based on a subjective assessment in each case. We do not administer ACS if the bleeding is very light, but we recommend it if the bleeding is as severe as during menstruation.

Asymptomatic Cervical Insufficiency

As Levin et al. were able to show in their retrospective study, optimal timing is not adequately achieved in the group of patients with asymptomatic cervical insufficiency. Only 12 % of the women were delivered within the timeframe between 24 hours and seven days after administration of ACS [10]. This phenomenon is due to the inadequate predictive power of the diagnostic methods available to us in this context.

Esplin et al. showed that for cervical length measured by vaginal ultrasound between GW 22 and GW 30 in asymptomatic patients, the AUC (95 % CI) for premature birth before GW 37 was only 0.67 (0.64–0.70) [46]. A further prospective cohort study investigated the significance of cervical length measured by vaginal ultrasound between GW 31 and GW 34 for predicting the occurrence of a premature birth between GW 32 and GW 36. For asymptomatic patients, the AUC (95% CI) was only 0.700 (0.627–0.773) [47].

In addition to ultrasound measurement of cervical length, we have various tests at our disposal that allow us to predict premature birth within seven days by measuring proteins in the cervical secretions (PAMG-1, fibronectin, IGFBP-1). However, as Esplin et al. also showed, with a cervical length > 15 mm, the sensitivity and positive predictive value of an fFN ≥ 50 ng/mL measured between GW 22 and GW 30 for the occurrence of a premature birth before GW 32 were only 32.1 % and 3.1 % respectively. The use of higher or lower threshold values did not improve the test quality either. The fibronectin test did not increase the predictive value of cervical length measured by vaginal ultrasound for the occurrence of premature birth before GW 37 (AUC for cervical length: 0.67; AUC for fibronectin: 0.59; AUC for cervical length + fibronectin: 0.67) [46].

In general, the risk of women with asymptomatic cervical insufficiency giving birth within seven days is very low. For example, in a retrospective study that included 126 asymptomatic patients with a cervical length ≤ 25 mm between GW 23 and GW 28, no patients were delivered within seven days, and only one patient was delivered within 14 days. The length of this patient's cervix was less than 10 mm [48]. These data are supported by a further retrospective study of 367 largely asymptomatic women – vaginal spotting and pressure or pulling in the lower abdomen were not considered exclusion criteria – with a cervical length of less than 25 mm between GW 24 and GW 34. Only two of these patients gave birth within seven days [49].

A retrospective analysis investigated the negative predictive value of the fibronectin test in asymptomatic patients between GW 22 and GW 32 whose cervical length was less than 10 mm. This value was 100 % for a birth within seven or 14 days [50]. Another retrospective study shows almost identical results [51].

Based on these results, the following recommendation was made in the AWMF guideline: If asymptomatic patients with a cervical length of 5–15 mm who have tested negative for fibronectin, phIGFBP-1 or PAMG-1 have no additional risk factors for preterm birth, they should not be administered antenatal steroids because of the very low probability (< 1 %) that they will give birth within 7 days. Nevertheless, the patient should continue to be monitored closely with regards to her risk of preterm birth [17].

In order to determine when ACS is indicated in this patient group, we need diagnostic methods that have a better positive predictive value. However, despite numerous innovative approaches, there are currently no viable solutions on the horizon [52, 53].

Premature Labor

Premature labor alone has a < 50 % predictive value for the occurrence of a premature birth; e.g., premature labor stops spontaneously in 30 % of cases, 50–70 % of pregnant women treated with placebo give birth close to term [54], and only 12–17% give birth within one week [55]. The fibronectin test and ultrasound measurement of cervical length can help to enable better assessment of the risk of these patients giving birth within seven days. In a prospective cohort study of 655 patients experiencing preterm labor, van Baaren et al. observed the rate of delivery within seven days to be 12% [56]. If the cervical length was < 15 mm, the delivery rate was 47% regardless of the fibronectin test. If the cervical length was between 15 and 30 mm, 2.7% (4/149) of children were born within seven days if the fibronectin test was negative, and 14.1% (21/148) if the test was positive. With a cervical length > 30 mm, only 0.7% of women gave birth within seven days, regardless of the fibronectin test.

Within the group of women experiencing preterm labor, in addition to those with a cervical length < 15 mm, there is another group of patients who are highly likely to undergo a premature birth within seven days. These are women with an intra-amniotic infection/microbial invasion of the amniotic cavity (IAI/MIAC) [57, 58, 59]. In a cohort of 358 women experiencing preterm labor, Cobo et al. found the condition known as MIAC to be present in 68 patients, diagnosed by means of amniocentesis. In these women, the gestational age at delivery was significantly lower (GW 26.9 [25.2–31.1] vs. GW 35.0 [29.7–38.3]; p = 0.001) (median value and interquartile range). The time until delivery was also significantly shorter (1 day [0–3] vs. 31 days [6–62]; p = 0.001) [60]. This observation is supported by other studies [57, 58]. Studies are currently planned to investigate the extent to which the neonatal outcome can be improved by the administration of antibiotics in cases of proven intra-amniotic infection [61].

There is an urgent need for research to optimize the identification of patients with intra-amniotic infection. It is precisely in this small patient group, representing approx. 10 % of all women who experience premature labor [62], that the administration of ACS is indicated. Strict restraint should be exercised in the remaining cohort, as evidenced by the long median latency period of 31 days observed in the study by Cobo et al. [60]. Since an intra-amniotic infection can only be diagnosed through amniocentesis, better identification of affected patients can only be achieved through increased use of this method in the clinical setting. From a technical perspective, amniocentesis should be easy to perform in this situation for the vast majority of patients.

Combined Indications

Of course, in everyday clinical practice there can often be a number of obstetric clinical pictures that do not individually constitute an indication for ACS administration, but may do so in combination. As there is a general absence of information in the literature on the interval between administration and delivery in situations of this kind, it is up to the team providing care to estimate the remaining time until birth on a case-by-case basis.

Timing of the Indication

ACS administration is not performed as an emergency measure, usually not even before transfer to a perinatal center. Therefore, whenever possible, the indication for ACS administration should be determined by a clinician who is highly experienced in perinatology. In particular, patients who experience preterm labor or have asymptomatic cervical insufficiency with a closed cervix have a low probability of giving birth within the next seven days. The same applies to IUGR fetuses with an incipient reduction in end-diastolic flow in the umbilical artery. The timing of ACS administration can probably be further optimized through appropriate organizational management.

Quality Assurance

Unfortunately, the previous quality parameter from IQTIG QI 330, defined as "Antenatal corticosteroid therapy in premature births with a prepartum inpatient stay of at least two calendar days", led to a strong disincentive. With a required cut-off > 95 %, the optimal timeframe of 24 hours to seven days was largely disregarded when administering ACS. This has now been corrected following evaluation of the 2021 cohort. That quality parameter has been removed. Instead, the number of mothers who had a premature birth before GW 34 and for whom the administration of ACS did not occur within the optimal timeframe of 24–168 hours is now stated (72.9 %; n = 11 873/16 278), as is the number of women who received ACS and then did not give birth until after GW 34 (41.2 %; n = 6715/16 278) [63].

The Society for Maternal Fetal Medicine is thinking along very similar lines and has defined two quality parameters. The first is a ratio which has as its denominator the total number of mothers with premature infants born between GW 24 + 0 and GW 33 + 6, excluding stillbirths, and as its numerator the total number of mothers who received a complete or partial ACS administration or a first ACS booster 6–168 hours before giving birth. The second quality parameter is a ratio consisting of the total number of women who gave birth at full term over the total number of women who received one or more doses of ACS [64].

Quality parameters of this kind can help to objectively assess the management of ACS timing, providing an impetus for internal evaluation processes that ideally lead to an improvement in neonatal morbidity and mortality.

Benefit of Antenatal Corticosteroids According to Gestational Age

As numerous prospective randomized studies have shown, ACS undoubtedly contribute to a reduction in perinatal morbidity and mortality. However, almost all of these studies were carried out more than 20 years ago and in no way represent the current standard in perinatology. This can be seen from the fact that only around 100 children born before GW 28 are included in these studies; moreover, this group of children probably did not receive any surfactant treatment or neuroprotection with magnesium [1, 4]. Since randomized studies on ACS administration prior to GW 34 are now considered unethical, no further information on this topic will be available in the foreseeable future.

As an alternative, large prospective cohort studies have been conducted in an attempt to obtain information on the effect of ACS on perinatal mortality and morbidity in relation to gestational age. Carlo et al. studied a prospective cohort of 10 541 children born between GW 22 and GW 25. The primary study endpoint of death or neurological impairment was significantly reduced following ACS administration between GW 23 and GW 25 (GW 23: aOR, 0.58 [95 % CI, 0.42–0.80]; GW 24: aOR, 0.62 [95 % CI, 0.49–0.78]; GW 25: aOR, 0.61 [95 % CI, 0.50–0.74]), but not at GW 22 (aOR, 0.80 [95 % CI, 0.29–2.21]). The results for severe grade 3/4 brain hemorrhage were almost identical (GW 22: aOR, 0.94 [95 % CI, 0.20–4.49]; GW 23: aOR, 0.59 [95 % CI, 0.40–0.87]; GW 24: aOR, 0.81 [95 % CI, 0.61–1.08]; GW 25: aOR, 0.56 [95 % CI, 0.44–0.72]) [65]. In a prospective cohort study of almost 118000 women, Travers et al. were able to show that in children born between GW 23 and GW 34, mortality before discharge following ACS administration was significantly lower for almost every gestational age within this range (aOR 0.47–0.32). However, the number needed to treat at GW 23 was 6, while at GW 34 it was 798. ACS was observed to have a significant impact on the rate of severe cerebral hemorrhage up to GW 30, and on survival without severe disability up to GW 27 (▶ **Table 2**) [66]. The EPICE cohort study of children born between GW 24 and GW 31 also showed a 50% reduction in perinatal mortality after administration of ACS [67].

However, when considering these cohort studies it must always be borne in mind that nowadays approx. 90 % of children born before GW 34 + 0 have received ACS. The mothers who were not given ACS before delivery exhibit differing patient characteristics; these can only be taken into account to a limited extent, even using multiple regression analysis. This is also evident, for example, from the EPICE cohort study. Of the group of patients who had received ACS, only 18 % were delivered on the day of admission, compared to 67 % of women who did not receive ACS [67]. It is very likely that ACS administration is a significant indicator of orderly and structured patient care, while the lack of ACS administration indicates emergency situations. Due to the increased risk profile of patients who do not receive ACS, the benefit of corticosteroids for neonatal morbidity and mortality is likely to be overestimated in this study design.

Nevertheless, the benefit of administering ACS before GW 30 is obvious. Beyond GW 32, the number needed to treat in order to reduce mortality before discharge is extremely high. An influence

▶**Table 2** Benefit of ACS in children born between GW 23 and GW 34. Adjusted odds ratio (aOR) and 95% confidence interval (CI); antenatal corticosteroids (ACS) (data from [66]).

	GW 23 n (%)	GW 24 n (%)	GW 25 n (%)	GW 26 n (%)	GW 27 n (%)	GW 28 n (%)	GW 29 n (%)	GW 30 n (%)	GW 31 n (%)	GW 32 n (%)	GW 33 n (%)	GW 34 n (%)
Death before discharge												
With ACS	439/754 (58.2)	642/1781 (36.0)	432/2161 (20.0)	302/2602 (11.6)	213/3315 (6.4)	141/4237 (3.3)	90/5019 (1.8)	75/6466 (1.2)	45/8556 (0.5)	44/13203 (0.3)	22/16810 (0.1)	9/16928 (0.1)
Without ACS	331/447 (74.0)	182/352 (51.7)	114/381 (29.9)	77/444 (17.3)	51/468 (109)	46/685 (6.7)	30/813 (3.7)	22/1172 (1.9)	21/1591 (1.3)	18/3070 (0.6)	18/5954 (03)	37/20732 (0.2)
aOR (95% CI)	0.47 (0.36–0.62)	0.51 (0.40–0.64)	0.52 (0.41–0.67)	0.55 (0.42–0.74)	0.50 (0.36–0.71)	0.48 (0.34–0.69)	0.44 (0.29–0.68)	0.66 (0.41–1.12)	0.42 (0.25–0.74)	0.61 (0.36–1.08)	0.43 (0.23–0.80)	0.32 (0.14–0.63)
Survival without severe disability												
With ACS	51/754 (6.8)	270/1781 (15.2)	594/2161 (27.5)	1127/2602 (43.3)	1988/3315 (60.0)	3068/4237 (72.4)	4125/5019 (82.2)	5676/6466 (87.8)	7817/8556 (91.4)	12409/13203 (94.0)	16177/16810 (96.2)	16507/16928 (97.5)
Without ACS	8/447 (1.8)	38/352 (10.8)	96/381 (25.2)	175/444 (39.4)	265/468 (56.6)	494/685 (72.1)	653/813 (80.3)	1008/1172 (86.0)	1443/1591 (90.7)	2876/3070 (93.7)	5728/5954 (9.2)	20220/20732 (9.5)
aOR (95% CI)	4.2 (2.1–9.7)	1.64 (1.15–2.41)	1.26 (0.98–1.64)	1.27 (1.03–1.58)	1.23 (1.00–1.50)	1.09 (0.90–1.31)	1.19 (0.98–1.44)	1.18 (0.98–1.42)	1.08 (0.89–1.30)	1.08 (0.91–1.27)	1.04 (0.88–1.21)	0.99 (0.87–1.13)
Severe brain hemorrhage												
With ACS	186/745 (24.7)	314/1781 (17.6)	267/2161 (12.4)	204/2602 (7.8)	146/3315 (4.4)	126/4237 (3.0)	76/5019 (1.5)	63/6466 (1.0)	50/8556 (0.6)	34/13203 (0.3)	25/16810 (0.1)	12/16928 (0.1)
Without ACS	133/447 (29.8)	92/352 (26.1)	71/381 (18.6)	78/444 (17.6)	47/468 (10.0)	36/685 (5.3)	25/813 (3.1)	26/1172 (2.2)	15/1591 (0.9)	12/3070 (0.4)	10/5954 (0.2)	13/20732 (0.1)
aOR (95% CI)	0.75 (0.57–0.98)	0.61 (0.46–0.80)	0.60 (0.45–0.81)	0.40 (0.30–0.54)	0.40 (0.29–0.58)	0.56 (0.38–0.83)	0.50 (0.32–0.81)	0.44 (0.28–0.71)	0.61 (0.15–1.12)	0.65 (0.35–1.32)	0.87 (0.43–1.90)	1.08 (0.48–2.40)

on the rate of brain hemorrhage is hardly to be expected at this point, as this is now only in the per-thousands range [66]. Surfactant is now available for the treatment of RDS. In light of this, serious questions may be asked as to whether it still makes sense to administer ACS at GW ≥ 32. Unfortunately, we have no data from prospective randomized studies that would enable a precise assessment.

Conclusion

ACS should ideally be administered 24 hours to seven days prior to delivery, as corticosteroids only reduce the rate of RDS within this timeframe. Their impact on neonatal morbidity and mortality is much higher in extremely premature births than it is after GW 32. In addition, children born full-term after ACS administration are significantly more likely to have mental and psychological development disorders. However, delivery within the optimal timeframe only occurs in approx. 25–40% of cases. This means that the indication for ACS administration needs to be much stricter than it has previously been. ACS is always indicated in PPROM, severe early pre-eclampsia, fetal IUGR with absent or reverse flow in the umbilical artery, placenta previa with bleeding, and patients experiencing preterm labor with a cervical length < 15 mm. The risk of women with asymptomatic cervical insufficiency giving birth within seven days is very low. In such cases, ACS should not be administered even in patients with a cervical length less than 15 mm, provided that the cervix is closed and there are no other risk factors for premature birth (▶ **Table 3**). In order to optimize the assessment of when ACS administration is indicated in this patient population, we need diagnostic methods that have a better positive predictive value. Caution is also indicated for women experiencing premature labor who have a cervical length ≥ 15 mm. Further studies using amniocentesis are needed in order to identify the patient population with MIAC/IAI and to define threshold values for determining when delivery is indicated. Whenever possible, the indication for ACS administration should be determined

▶**Table 3** Indication for the administration of antenatal corticosteroids (ACS).

Indication for the administration of antenatal corticosteroids	Indicated	Not indicated
Early premature rupture of membranes	+	
Severe early pre-eclampsia	+	
Fetal intrauterine growth restriction with absent or reverse flow in the umbilical artery	+	
Placenta previa with bleeding or premature placental abruption, if a watchful waiting approach is possible	+	
Asymptomatic cervical insufficiency with a cervical length < 15 mm, with a closed cervix and no other risk factors for premature birth		+
Premature labor with cervical length < 15 mm	+	

by a clinician who is highly experienced in perinatology. Emergency administration of ACS prior to transfer to a perinatal center should be avoided if possible, except in clear cases (see above). In addition, quality parameters can help to objectively assess how the timing of ACS administration is managed, providing impetus for internal evaluation processes that will ideally lead to an improvement in neonatal morbidity and mortality.

Conflict of Interest

The authors declare that they have no conflict of interest.

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