in vivo *36*: 1777-1784 (2022)
doi:10.21873/invivo.12891

Influence of Timing of Antenatal Corticosteroid Administration on Morbidity of Preterm Neonates

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Abstract. *Background/Aim: We investigated the impact of the timing of antenatal corticosteroid (ACS) administration on the clinical outcome of preterm infants. Patients and Methods: Two hundred and fifty-five preterm infants between 28+0 and 34+0 weeks of gestation were retrospectively assigned to one of two groups: In the first group, ACS was given within 7 days before birth; the second group, did not receive ACS during that period. The primary outcome parameter was respiratory failure (defined by need for continuous positive airway pressure or mechanical ventilation) due to grade 1-4 respiratory distress syndrome (RDS). Secondary outcomes included the rates of intraventricular hemorrhage (IVH), periventricular leukomalacia, and necrotizing enterocolitis. Results: The rate of RDS was significantly higher in the no ACS group (40% vs. 62%, p=0.0009), especially of the more severe grades 2-4 (n=37 vs. n=48, p=0.0121). In addition, IVH (1% vs. 9%, p=0.0041) and neonatal infections (72% vs. 89%, p=0.0025) were significantly increased. Univariable and multivariable regression analyses showed a lower likelihood of RDS in the ACS group [odds ratio (OR)=0.295] in infants born closer to term (OR=0.907) and following preterm onset of labor (OR=0.495). Similarly, we observed a lower probability of IVH in the ACS group (OR=0.098), with a higher probability of occurrence of IVH in pre-eclampsia/HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count) (OR=7.914). Conclusion: ACS treatment within the last 7 days before birth significantly reduced the risk of RDS and IVH in preterm. These data emphasize that the timing of ACS administration determines its success.*

Almost 10% of all newborns are born premature before 37+0 weeks of gestation. This is associated with a high morbidity and mortality despite today's good medical care (1, 2). A major contributory factor is respiratory distress syndrome (RDS), which is primarily due to immaturity of the lungs and the resulting surfactant deficiency. For almost half a decade, the therapeutic pillar has been the induction of lung maturation of the unborn child by antenatal corticosteroid administration (ACS administration) to the mother (3). The more immature the neonate, the higher the therapeutic influence of this prenatal drug administration on the postnatal course of the child. However, ACS treatment in preterm infants below 23+0 weeks of gestation is less effective and is associated with increased morbidity and mortality (4). Possible complications of ACS administration include fetal and placental growth restriction, neurological impairment (5), and an increased risk of infection and hypoglycemia in the first postnatal days (6, 7). Of note, possible side-effects of corticosteroids increase with repetition of an ACS course. The positive effect of ACS administration weakens after a few days (8) and is no longer effective after 1 to 2 weeks. Moreover, the feasibility of multiple, repetitive ACS administrations is limited by the side-effects (9). In this respect, ACS administration in late preterm babies, where severe complications of prematurity

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Key Words: Antenatal corticosteroids, preterm birth, respiratory distress syndrome, RDS, morbidity, mortality.

are no longer expected, is also controversially discussed, and for pregnant women with a low likelihood of delivery before 37 weeks of gestation (GW), it is not recommended (10).

In consideration of the advantages and possible disadvantages, ACS administration from 34+0 GW is no longer generally recommended (11, 12), while currently, the benefits of a single course of ACS administration for women at risk of preterm birth are strongly supported by existing data (13). Therefore, to avoid the need for a repeat use of ACS, the short-term effect of ACS administration should be maximized as much as possible, thus emphasizing the importance of the timing of ACS administration. Based on this consideration, the aim of our study was to investigate the influence of the timing of ACS administration on neonatal outcome in a preterm population between 28 and 34 GW as a function of the time interval from the last administration.

Patients and Methods

In this retrospective cohort study, all pregnant women with delivery between 28+0 and 34+0 GW from birth years 2010 to 2013 at the University Perinatal Center of Franconia (Neonatal Care Level IV) Germany were included. Exclusion criteria were intrauterine fetal death and structural or chromosomal abnormalities. Gestational age was determined by the last menstrual bleeding and corrected, if necessary, by crown–rump length {Rempen, 2016 #26}(14).

The preterm infants were retrospectively analyzed and assigned to two groups: In the first group, ACS administration was given in the last 7 days before birth (+ACS); in the second group, no ACS administration was given in the last 7 days. If the ACS administration was started, but not completed the neonates were included in the ACS group. If no ACS administration had taken place, the neonates were included in the no ACS group (total number 11 out of 99 neonates).

This study was conducted in accordance with the guidelines set forth in the Declaration of Helsinki (World Medical Association) (15) and was deemed ethically sound by the Ethics Committee of the Medical Faculty of the University Hospital Erlangen (no. 20200827 01).

The primary outcome parameter of the analysis was respiratory failure (defined by need for continuous positive airway pressure or mechanical ventilation) due to grade 1-4 respiratory distress syndrome (RDS) (diagnosed by x-ray). Secondary outcome measures were rates of intracerebral hemorrhage (IVH) [diagnosed by cranial ultrasound according to Papile *et al*. (16)], cystic periventricular leukomalacia (diagnosed by cranial ultrasound), grade II or greater of retinopathy of prematurity [diagnosed ophthalmoscopically according to official guidelines (17)], necrotizing enterocolitis stage 2 or greater according to Bell modified by Walsh and Kliegmann (18) (diagnosed by ultrasound or radiographically), persistent ductus arteriosus (diagnosed by echocardiography), bronchopulmonary dysplasia [diagnosed by oxygen or respiratory support need at 36+0 GW (definition by Walsh (19)], and neurological abnormalities at status assessment before discharge in the respective collectives.

All statistical calculations and analyses were performed using the statistical software package SAS, Release 9.4 (SAS Institute Inc., Cary, NC, USA). For nominally scaled characteristics, absolute and relative frequencies were reported; quantitative approximately normally distributed characteristics were described by mean and standard deviation, as well as minimum and maximum. For ordinally scaled and quantitatively discrete characteristics, the median was given in addition to the mean.

To compare two groups with respect to a nominally scaled characteristic, a chi-squared test or (if its conditions were not met) Fisher's exact test was used. The comparison of the means of two groups was carried out with the *t*-test for two unrelated samples. For ordinally scaled characteristics, the Mann and Whitney *U*-test or the Cochran–Armitage trend test was used. All tests were two-sided. A test result was considered significant when the *p*-value was less than 0.05.

Logistic regression analyses were performed to analyze the binary endpoints RDS and IVH and to quantify the strength of influential factors. For each parameter, the odds ratio (OR) was calculated as an approximation for relative risk. In addition, multivariable regression analyses were used to analyze the influence

Table I. *Demographics of the study population.*

Parameter	Value
Age, years	
Mean±SD	31.5±5.8
Maternal height, cm	
Mean±SD	166.9±6.9
Maternal weight, kg	
Mean±SD	78.9±16.3
Body mass index, kg/m^2	
Mean±SD	28.3±5.2
Gravidity	
Median (range)	1 (1-8)
Parity	
Median (range)	0 (0-6)
Gestational age (days)	
Mean±SD	223.7±11.4
Birth weight, g	
Mean±SD	1,702.5±479.6
Sex, n (%)	
Male	109 (54%)
Multiple pregnancy, n (%)	
Yes	58 (28%)
ACS administration, n (%)	
<7 Days before birth	126 (62%)
Mode of birth	
Caesarean	168 (82%)
Antibiotic therapy before birth, n (%)	
Yes	110 (54%)
Amniotic infection syndrome, n (%)	
Yes	10 (5%)
Reason for preterm delivery, n (%)	
Preterm labor	101 (50%)
PPROM	20 (10%)
Pathological CTG	10 (5%)
Pre-eclampsia, HELLP	31 (15%)
FGR, pathological Doppler	21 (10%)
Placental abruption	6 (3%)
Other	15 (7%)

ACS: Antenatal corticosteroids; CTG: cardiotocography; HELLP: hemolysis, elevated liver enzyme levels, low platelet count; PPROM: early premature rupture of membranes; FGR: fetal growth restriction.

Table II. *Outcome parameters in the no antenatal corticosteroids (ACS) group and the ACS group of preterm neonates.*

Parameter		ACS (n=156)	No ACS (n=99)	*p*-Value
Birth mode, n (%)	Vaginal	19 (15%))	17 (21%)	0.2783
	Caesarean	105 (85%	63 (79%)	
Arterial cord blood pH value	Mean±SD	7.34±0.08	7.34±0.08	0.9584
	pH<7.10, n (%)	2 (1%)	2 (2%)	0.6368
Arterial cord blood BE value	Mean±SD	−2.81±3.36	−2.63±2.80	0.6450
Umbilical cord blood arterial BE value, n (%)	<−12	2 (1%)	1 (1%)	>0.999
Apgar value after 5 min	Median (range)	8 (4-10)	8 (2-10)	0.8706
	<7, n (%)	11 (9%)	10 (13%)	0.3086
Neonatal death, n (%)	Yes	2 (1%)	2 (2%)	0.6429
Respiratory distress syndrome, n (%)	Yes	63 (40%)	60 (62%)	**0.0009**
Stage	1	18 (33%)	6 (11%)	**0.0121**
	2	17 (31%)	20 (37%)	
	3	17 (31%)	21 (39%)	
	4	3 (5%)	7 (13%)	
Intraventricular hemorrhage, n (%)	Yes	2 (1%)	9 (9%)	**0.0041**
Stage	1	2 (100%)	3 (33%)	0.3455
	2	0	4 (44%)	
	3	0	2 (22%)	
Periventricular leukomalacia, n (%)	Yes	0	1 (1%)	0.3898
Retinopathy of prematurity, n (%)	Yes	1 (0.6%)	1 (1%)	>0.999
Necrotizing enterocolitis, n (%)	Yes	3 (2%)	2 (2%)	>0.999
Surgery required	Yes	1 (33%)	0	>0.999
Neonatal infection, n (%)	Yes	113 (72%)	85 (89%)	**0.0025**
Sepsis, n (%)	Yes	6 (4%)	5 (5%)	0.7535
Persistent ductus arteriosus, n (%)	Yes	30 (19%)	27 (29%)	0.1112
Ibuprofen required	Yes	18 (62%)	17 (63%)	0.9449
Surgery required	Yes	2 (7%)	3 (11%)	0.6642
Bronchopulmonary dysplasia, n (%)	Yes	3 (2%)	1 (1%)	>0.999
Stage	Mild	2	0	0.3333
	Moderate	0	1	
	Abnormal	19 (12%)	15 (15%)	0.4886

BE: Base excess. Statistically significant *p*-values are shown in bold.

of several parameters simultaneously. The backward selection method was applied at a significance level of 0.05.

Results

In the studied period from 2010 to 2013, taking into account the inclusion and exclusion criteria, 255 pregnancies were included in the study. Table I shows the demographic parameters. The sample predominantly included first-time mothers, with a mean gestational age at birth of their child of 224 days. Almost one in four pregnancies was a multiple pregnancy (28%). The most common causes of preterm delivery were preterm labor (49%), pre-eclampsia/HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count (15%), fetal growth restriction/placental insufficiency (10%), and premature rupture of membranes (10%). Most pregnancies were terminated by cesarean section (82%), and 62% of pregnancies had ACS administration within 7 days before delivery.

Table II shows the neonatal outcome in the two studied groups with and without ACS administration in the last 7 days before birth. The rate of RDS was significantly higher in the no ACS group (40% *vs*. 62%, $p=0.0009$). In particular, more severe RDS (grade 2, 3 and 4) made the difference here (n=37 *vs*. n=48, $p=0.0121$). The RDS grade could not be clarified in all cases retrospectively. This resulted in deviation of the total number of RDS cases in contrast to the sum of those for RDS grades. Furthermore, the rate of IVH was significantly higher in the no ACS group (1% *vs*. 9%, $p=0.0041$). In addition, there were significantly more neonatal infections in the no ACS group (72% *vs*. 89%, $p=0.0025$).

Table III summarizes the results of the univariable and multivariable regression analyses regarding the primary outcome parameter RDS. According to the final model, RDS was reduced in the ACS group (OR=0.295), with higher gestational age (OR=0.907) and with preterm labor (OR=0.495).

Table III. *Univariable and multivariable logistic regression analysis of the primary outcome parameter respiratory distress syndrome. The outcome parameters of the total collective of of neonates delivered at 28-34 weeks of gestational age are shown.*

		Univariable analysis		Multivariable analysis	
Factor		Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
ACS administration	<7 Days before birth *vs.* none	0.418 (0.248-0.702)	**0.0010**	0.295 (0.159-0.547)	**0.0001**
Body mass index, kg/m^2	Per unit increase	0.993 (0.944-1.045)	0.7945		
Gestational age, days	Per unit increase	0.915 (0.890-0.940)	**<0.0001**	0.907 (0.879-0.935)	**<0.0001**
Birth weight	100 g increase	0.877 (0.827-0.930)	**<0.0001**		
Sex	Male *vs.* female	1.242 (0.757-2.039)	0.3916		
Multiple pregnancy	Yes *vs.* no	0.968 (0.588-1.593)	0.8976		
Amniotic infection syndrome	Yes *vs.* no	1.615 (0.445-5.868)	0.4662		
Reason for premature birth					
Preterm labor	Yes *vs.* no	0.427 (0.258-0.707)	**0.0009**	0.495 (0.278-0.882)	**0.0170**
PPROM	Yes *vs.* no	1.867 (0.785-4.440)	0.1517		
Pathological CTG	Yes *vs.* no	1.247 (0.407-3.819)	0.6992		
Pre-eclampsia, HELLP	Yes *vs.* no	1.867 (0.785-4.440)	0.1517		
FGR, pathological Doppler	Yes *vs.* no	1.247 (0.407-3.819)	0.6992		
Placental abruption	Yes *vs.* no	1.818 (0.918-3.599)	0.0865		
Other	Yes *vs.* no	1.063 (0.458-2.465)	0.8866		
Mode of birth	Caesarean *vs.* vaginal	2.710 (0.516-14.232)	0.2388		

ACS: Antenatal corticosteroids; CTG: cardiotocography; HELLP: hemolysis, elevated liver enzymes levels, low platelets; PPROM: early premature rupture of membranes; FGR: fetal growth restriction. Statistically significant *p*-values are shown in bold.

When analzing the ACS group for the effects of glucocorticoid administration before the observational period of 7 days prior to birth, the following observations were made (data not shown in Tables): Most women (n=88, 89%) had received glucocorticoids before the observation period of our study (>7 days before delivery). The RDS rate was significantly lower in these neonates than in children whose mothers had never received glucocorticoids (p=0.0059), but significantly higher (p=0.0132) compared to the ACS group. All 11 neonates whose mothers had not received ACS administration throughout pregnancy showed RDS; four of them developed IVH during the postnatal course, which was significantly higher than the IVH rate of pregnancies with glucocorticoid therapy outside the prepartum observation period (>7 days) (p=0.0081). This result is congruent with previous evidence (8).

The results of the univariable and multivariable regression analyses regarding the primary outcome IVH are listed in Table IV. The risk of IVH was significantly lower in the ACS group (OR=0.098) than in the no ACS group. However, the rate of IVH was significantly higher when pre-eclampsia/HELLP syndrome was the indication for termination of pregnancy (OR=7.914).

The sex of the child had no influence on the rate of RDS and IVH. Mode of delivery (caesarean section *vs.* vaginal delivery) had only a marginal influence on RDS and IVH (univariable analysis, p=0.0871 and p=0.0611, respectively). Infant birth weight had a significant negative effect on the occurrence of RDS (univariable analysis, p<0.0001). However, this variable was not included in the final model because it was closely correlated with gestational age. In contrast, no association of birth weight with IVH was detected in our collective (p=0.6610).

Discussion

ACS administration represents a major milestone for the care and survival of premature infants (20). In recent years, the timing of ACS administration has emerged as a critical factor in the therapeutic success of this therapy. Recent studies show that an ACS administration interval to time of birth of longer than 7 days has a significantly reduced impact on the prevention of RDS (21-23). In addition, it is important to use ACS administration in a reflective manner: Recent data from a large collective showed potential neurological impairment in mature infants, following antenatal ACS administration (5). In our retrospective cohort study, we investigated the effect of timing of ACS administration between 28+0 GW and 34+0 GW. We showed that ACS administration in the last 7 days before birth was associated with a significant reduction of RDS, both in univariable and multivariable regression analysis.

Notably, the prevalence of higher grade RDS (grades 2-4) was significantly lower in the ACS group compared with neonates in the no ACS group. Higher grade RDS in particular is associated with respiratory failure. The occurrence of RDS with increasing prematurity or decreasing

Table IV. *Univariable and multivariable logistic regression analysis of the primary outcome measure intraventricular hemorrhage. The outcome parameters of the total collective of neonates delivered at 28-34 weeks of gestational age are shown.*

		Univariable analysis		Multivariable analysis	
Factor		Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
ACS administration	<7 Days before birth *vs*. none	0.131 (0.028-0.618)	**0.0103**	0.098 (0.028-0.572)	**0.0328**
Body mass index, kg/m^2	Per unit increase	1.153 (1.021-1.302)	**0.0221**		
Gestational age, days	Per unit increase	0.996 (0.920-1.013)	0.1551		
Birth weight	100 g increase	0.971 (0.853-1.106)	0.6610		
Sex	Male *vs*. female	1.496 (0.427-5.242)	0.5290		
Multiple pregnancy	Yes *vs*. no	0.764 (0.218-2.678)	0.6737		
Amniotic infection syndrome	Yes *vs*. no	n.c.	0.9753		
Reason for premature birth					
Preterm labor	Yes *vs*. no	1.250 (0.372-4.207)	0.7181		
PPROM	Yes *vs*. no	n.c.	0.9626		
Pathological CTG	Yes *vs*. no	n.c.	0.9731		
Pre-eclampsia, HELLP	Yes *vs*. no	4.792 (1.389-16.533)	**0.0131**	7.914 (1.748-35.830)	**0.0073**
IUGR, pathological Doppler	Yes *vs*. no	n.c.	0.9626		
Placental abruption	Yes *vs*. no	n.c.	0.9803		
Other	Yes *vs*. no	n.c.	0.9683		
Mode of birth	Caesarean *vs*. vaginal	0.294 (0.082-1.059)	0.0611		

ACS: Antenatal corticosteroids; CTG: cardiotocography; HELLP: hemolysis, elevated liver enzyme levels, low platelet count; PPROM: early premature rupture of membranes; FGR: fetal growth restriction. Statistically significant *p*-values are shown in bold.

gestational age can be explained by lung immaturity and the increasing lack of endogenous surfactant production. Interestingly, an association was found between preterm labor and a lower rate of RDS. This might be due to endogenous cortisol production in the fetus triggered by intrauterine stress during labor. In turn, endogenous cortisol can contribute secondarily to lung maturation. Furthermore, maternal labor induces amniotic fluid reabsorption in the fetus and thus improves lung function after birth (24). Clinically, it is important to note that ACS can still be administered during preterm labor, which seems to have a favorable effect on postnatal outcome (25, 26).

Prepartum ACS administration can often avoid intubation (27). Even if intubation is necessary, the infant can often be managed with gentler ventilation parameters when ACS was administered, thus reducing the risk of baro- and oxidative trauma. In our collective, these factors contributed to the fact that neonates in the ACS group also had relevantly fewer IVHs. The results of the univariable and multivariable regression analyses regarding the primary outcome IVH showed significantly lower incidence in the ACS group (OR=0.098).

This hypothesis is consistent with the results of the studies by Klebermass-Schrehof *et al*. (28) and Kribs *et al*. (29) who showed with the less invasive surfactant application concept that less ventilation correlated with a reduction in IVH .

In particular, our cohort showed hardly any serious IVH (grade 2 and 3). This finding matches other studies that found mainly increased IVH when no prepartum ACS administration had occurred. However, the result varied depending on the study. Chawla *et al*. showed a clear reduction of RDS and IVH in their preterm neonatal collective of 5,886 neonates born between 29+0 and 33+6 GW, when ACS administration was started. They also showed that ACS administration already started but not completed led to a reduction of RDS and IVH compared to the group without ACS administration (30). Boghossian *et al*. analyzed even more immature preterm infants between 22+0 to 28+0 GW. In the 5,775 neonates evaluated, ACS administration correlated with less IVH and mortality but the analyzed neurological outcome at 18-22 months did not significantly differ (31). Roberts *et al*. again looked at all neonates whose mothers had received ACS administration for threatened preterm birth, regardless of GW. They included 8,158 infants from 30 studies in their analysis and, because of the large number of cases, were able to demonstrate a reduction for all preterm co-morbidities when ACS administration had been given to the mother (32). The results of our cohort study correlate with these data.

Multivariable regression analysis showed a significant association of increased IVH prevalence with the presence of pre-eclampsia/HELLP syndrome (OR=7.914, p=0.0073). In other collectives, pre-eclampsia/HELLP syndrome also correlated with an increased likelihood of RDS, IVH, sepsis, or prolonged ventilation time in the neonate (33, 34). The occurrence of IVH seemed unrelated to the gestational age

and birth weight in our collective. In general, the incidence of IVH is negatively associated with gestational age, especially affecting extremely preterm infants (24+0 to 28+0 GW) and neonates with adjustment disorder in the first postnatal hours (35, 36).

The mode of delivery had no influence on the incidence of RDS and only a weakly significant influence on the occurrence of IVH. The advantages and disadvantages for mother and child of caesarean section versus spontaneous delivery in preterm birth have been widely discussed for years (37-39). The majority of large cohort studies showed no difference in outcome of preterm infants regarding the mode of delivery (40, 41).

Overall, our study shows a clear association between recent ACS administration and lower postnatal morbidity (severe RDS and IVH) in a clearly circumscribed collective. Limitations of the study are its retrospective study design and the monocentric approach. Thus, the outcomes and the results of the analyses remain influenced by center-specific procedures and therapeutic approaches.

Conclusion

Our retrospective cohort study showed the most detrimental neonatal outcome when no ACS administration at all had occurred during pregnancy, thus emphasizing the importance of ACS administration in preventing morbidity and mortality in preterm infants. But we also showed that the timing of the ACS administration plays an important role. In preterm infants born between 28 GW and 34 GW, ACS administration <7 days before birth can significantly reduce the risk of RDS and IVH. Therefore, ACS should be administered only with impending preterm birth to ensure its effectiveness. This recommendation is also found in the latest German Association of the Scientific Medical Societies guideline 015-025 "Prevention and Therapy of Preterm Birth" (25, 26) and the “European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update“ (27) from 2019.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors’ Contributions

P.M. and S.K. conceived the study, investigated patients, curated and interpreted data, and wrote the first draft of the article. C.W. performed the statistical analysis. J.G., C.W., F.S., U.D., Fl.F., and Fa.F. collected and evaluated clinical data. P.M., M.B. and S.K. supervised the project. P.M., S.K. and Fa.F. critically revised the article. All authors read and approved the final version of the article. Data acquisition and interpretation were performed by Janis Gärtner in partial fulfillment of the requirements for obtaining the degree "Dr. med." at the Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Pediatrics and Adolescent Medicine, Germany.

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Received March 8, 2022
Revised April 4, 2022
Accepted April 8, 2022