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Administration of Antenatal Corticosteroids: Current State of Knowledge

Applikation antenataler Kortikosteroide: aktueller Wissensstand

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Authors
Richard Berger[1], Ioannis Kyvernitakis[2], Holger Maul[2]

Affiliations
1 Marienhaus Klinikum St. Elisabeth, Klinik für Gynäkologie und Geburtshilfe, Neuwied, Germany
2 Asklepios Kliniken Barmbek, Wandsbek und Nord-Heidberg, Frauenkliniken, Hamburg, Germany

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Correspondence
Prof. Dr. med. Richard Berger
Marienhaus Klinikum St. Elisabeth, Akademisches Lehrkrankenhaus der Universitäten Mainz und Maastricht, Klinik für Gynäkologie und Geburtshilfe
Friedrich-Ebert-Straße 59, 56564 Neuwied, Germany
richard.berger@marienhaus.de

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ABSTRACT

The administration of a single course of corticosteroids before week 34 + 0 of gestation in cases with impending preterm birth is now standard procedure in obstetric care and firmly established in the guidelines of different countries. But despite the apparently convincing data, numerous aspects of this intervention have not yet been properly studied. It is still not clear which corticosteroid achieves the best results. There are very few studies on what constitutes an appropriate dose, circadian rhythms, the time frame in which corticosteroids are effective, and the balance between the risks and benefits of repeat administration. As the existing studies have rarely included patients before week 24 + 0 of gestation, we have very little information on the possible benefits of administering corticosteroids before this timepoint. If corticosteroids are administered antenatally after week 34 + 0 of gestation, the short-term benefit may be offset by the long-term adverse effect on psychomotor development. This present study summarizes the current state of knowledge regarding these issues.

ZUSAMMENFASSUNG

Die einmalige Gabe von Kortikosteroiden vor 34 + 0 SSW bei drohender Frühgeburt ist ein Standard in der heutigen Geburtshilfe und in den Leitlinien der verschiedensten Länder fest verankert. Trotz der anscheinend überzeugenden Datenlage sind allerdings zahlreiche Teilaspekte zu dieser Intervention nur wenig geklärt. So war bisher offen, welches Kortikosteroid die optimale Wirkung erzielt. Es gibt kaum Studien zur Dosierung, zur zirkadianen Rhythmik, zum Zeitfenster der Wirksamkeit oder zur Nutzen-Schaden-Bilanz einer wiederholten Gabe. Da in den vorliegenden Studien selten Patientinnen vor 24 + 0 SSW eingeschlossen wurden, haben wir nur wenig Information zum möglichen Nutzen einer Kortikosteroid-Applikation vor diesem Zeitpunkt. Bei einer antenatalen Gabe von Kortikosteroiden nach 34 + 0 SSW stehen dem kurzfristigen Nutzen möglicherweise langfristige Beeinträchtigungen in der psychomotorischen Entwicklung gegenüber. Die vorliegende Arbeit fasst den derzeitigen Wissensstand zu diesen Fragen zusammen.

Introduction

Nowadays, the antenatal administration of corticosteroids is an integral part of the management of pregnant women with impending preterm birth. As Liggins and Howie already showed in 1972, it significantly reduces perinatal morbidity and mortality [1]. Their observations have since been confirmed by numerous prospective randomized studies and were recently summarized in a Cochrane review published in 2020 [2]. The administration of a single course of corticosteroids before week 34 + 0 of gestation in cases with impending preterm birth is part of standard modern obstetric care and firmly established in the guidelines of different countries (▶ **Table 1**) [3 – 6].

But although the available data appears to be convincing, numerous aspects of this intervention have not been resolved. It is still unclear which corticosteroid achieves the best outcome. There are very few studies on doses, circadian rhythms, the time frame in which administration of corticosteroids is effective, and the balance between the risks and benefits of repeat administration. As very few patients have been included in studies before week 24 + 0 of gestation, we have no information on the possible benefits of corticosteroid administration prior to this timepoint. This is a problem, given the fact that perinatal medicine is increasingly offering a chance of survival to even very young children. On the other hand, the short-term benefit of administering corticosteroids in cases of imminent preterm birth after week 34 + 0 of gestation may be offset by a potential long-term impairment to the children's psychomotor development. This overview provides a summary of the current state of knowledge regarding these issues.

Literature Search

A selective literature search was carried out up in PubMed until March 2021 using the keywords "corticosteroid", "preterm birth", "preterm delivery". The relevant prospective randomized studies, reviews and meta-analyses were selected. Cross-references to other important works were also considered.

Pharmacology

The external administration of corticosteroids aims to "bring forward" the endogenous physiological increase in corticosteroid levels which occurs in late pregnancy and which promotes the maturation of various fetal organs and prepares the fetus for life postpartum. Nowadays, hospitals use betamethasone or dexamethasone for this. These are fluorinated synthetic corticosteroids which cross the placenta easily as they are not a substrate for 11-β hydroxysteroid dehydrogenase [7].

Betamethasone is administered by intramuscular injection at a dosage of 2 × 12 mg (6 mg betamethasone phosphate and 6 mg betamethasone acetate) at an interval of 24 h. The betamethasone in the phosphate compound is released more quickly and contributes to rapid enrichment whereas the betamethasone in the acetate compound is hydrolyzed more slowly [1]. The maximum betamethasone concentration in maternal serum occurs after 1 h, whereas the peak fetal concentration occurs 1–2 h later. The half-life of betamethasone in the maternal circulation is 6 hours and 12 hours in the fetal circulation. The fetal/maternal concentration ratio is 0.37. No traces of betamethasone are detectable in either the maternal or fetal circulation 48 h after the second injection. Dexamethasone is administered 4 times at 12 h intervals at a dose of 6 mg; this avoids the high peak concentra-

▶ **Table 1** International guidelines on the administration of antenatal corticosteroids to treat impending preterm birth.

Guideline	24 + 0–34 + 0 GW	< 24 + 0 GW	> 34 + 0 GW	Repeat administration
ACOG Committee Opinion No. 713 [4]	Single cycle	Individual approach from GW 23 + 0 to GW 23 + 6	Single cycle between GW 34 + 0 and GW 36 + 6 if no corticosteroids were previously administered	Consider administering repeat cycle depending on the risk of preterm birth At the earliest 7 days after the last administration No more than 2 cycles in total
NICE Guideline Preterm Labour and Birth [3]	Single cycle	Individual approach from GW 23 + 0 to GW 23 + 6	Consider administering single cycle between GW 34 + 0 and GW 35 + 6	Consider administering repeat cycle depending on the risk of preterm birth
No. 364 – Antenatal Corticosteroid Therapy for improving Neonatal Outcomes Canada [5]	Single cycle up to GW 34 + 6	Individual approach from GW 22 + 0 to GW 23 + 6	Consider administering single cycle between 35 + 0 und 36 + 6	Consider administering repeat cycle depending on the risk of preterm birth
Prevention and Therapy of Preterm Birth 015–025 [6] Guideline of the German, Austrian and Swiss Societies of Gynecology and Obstetrics	Single cycle	Individual approach from GW 22 + 0 to GW 23 + 6	No antenatal corticosteroids after GW 34 + 0	Administer a repeat cycle only if there is a very high risk of preterm birth before GW 29 + 0 No more than 2 cycles in total

tions which are observed with the betamethasone regimen but results in higher drug levels over longer periods of time [8].

As the maximum concentration with intramuscular administration already occurs after 1 h, intravenous administration makes little sense. Moreover, experimental data has shown that fetal serum levels must be at least 1 ng/ml for 48 h to induce lung maturation. This can be best achieved if the drug is administered by intramuscular injection. There is very little data available on the oral administration of corticosteroids. An older study, which compared intramuscular injection of dexamethasone with oral administration, found a significantly increased incidence of neonatal sepsis when the corticosteroid was administered orally [9].

Both betamethasone and dexamethasone increase surfactant synthesis, improve pulmonary compliance, increase maximum lung volume, and lead to a better gas exchange and therefore a lower incidence of respiratory distress syndrome (RDS) [8]. The intraventricular hemorrhage rate and the incidence of necrotizing enterocolitis (NEC) are also lower, partly as a result of improved respiration, partly because of the direct effect of corticosteroids on the maturation of various organ systems [8, 10, 11]. More than 300 genes which are regulated by corticosteroids have been identified to date [12].

Corticosteroids From Week 24 + 0 to Week 34 + 0 of Gestation

The administration of a single cycle of corticosteroids to patients with impending preterm birth before week 34 + 0 of gestation has been included in many different guidelines all over the world [3–6]. The last Cochrane review on this topic was published in 2020. The data of 11 272 women with 11 925 children were evaluated. According to the data, corticosteroids reduce perinatal mortality (RR 0.85, 95% CI: 0.77–0.93) as well as the incidence of RDS (RR 0.71, 95% CI: 0.65–0.78) and intraventricular hemorrhage (IVH) (RR 0.58, 95% CI: 0.45–0.75). They have almost no impact on birth weight (mean difference [MD] − 14.02 g, 95% CI: − 33.79–5.76) [2].

The impact on the long-term development of the children is less well known, as very few follow-up studies have been designed. There is a tendency towards a reduction of developmental delay (RR 0.48, 95% CI: 0.24–1.00) and of cerebral palsy (RR 0.64, 95% CI: 0.35–1.03). However, fewer than 1000 children were available for this analysis [10].

The data on patients with multiple pregnancy is also very limited. The Cochrane meta-analysis of 2017 observed no reduction in RDS (RR 0.90, 95% CI: 0.67–1.22), IVH (RR 0.39, 95% CI: 0.07–2.06) or neonatal mortality (RR 0.79, 95% CI: 0.39–1.61) after antenatal administration of corticosteroids in cases with impending preterm birth before week 34 of gestation. However, only a very small number of patients were included in this meta-analysis, and this aspect has therefore not been followed up here [10].

The Choice of Corticosteroid

A systematic review, published in 2013, which compared the effects of betamethasone and dexamethasone on perinatal morbidity and mortality found no differences between the two substances, with the exception of a slightly lower rate of intraventricular hemorrhage with dexamethasone (RR 0.44, 95% CI: 0.21–0.92) [13]. However, the review did not include information on the long-term development of these infants or data on maternal morbidity.

The ASTEROID trial was launched to compare outcomes for dexamethasone and betamethasone. This prospective, randomized, double-blind multicenter study included 1346 patients with impending preterm birth before week 34 + 0 of gestation. 679 patients received 2 × 12 mg dexamethasone and 667 received 2 × 12 mg betamethasone administered antenatally by intramuscular injection at an interval of 24 h. There was no difference in the primary study endpoint "death or neurosensory disability at the age of 2 years" between the two groups (RR 0.97, 95% CI: 0.83–1.13). No differences were found in perinatal morbidity rates including the rate of intraventricular hemorrhage, and there were likewise no differences in maternal morbidity rates. Only the cesarean section rate was significantly lower in the dexamethasone group, but no medical explanation was proposed for this (RR 0.84, 95% CI: 0.75–0.94) (▶ **Table 2**) [14].

The most recent meta-analysis on this topic, which included data from 45 studies covering 11 227 women and 11 878 children, found no differences with regard to perinatal and maternal morbidity rates between dexamethasone and betamethasone. The meta-analysis did not investigate the incidence of cesarean section [15].

Dosage

The dosage proposed by Liggins consisted of 2 × 12 mg betamethasone administered intramuscularly at an interval of 24 h. This covers around 75% of all fetal glucocorticoid receptors and therefore probably achieves the maximum activation of all downstream genes [16]. In a subsequent study, Howie and Liggins were unable to achieve any further improvement in neonatal morbidity rates by doubling the dose [17]. This has also been confirmed by more recent experimental studies [18]. Moreover, it was found that higher doses of corticosteroids can negatively affect the programming of fetal developmental and metabolic processes [19].

In contrast to the above studies, experimental studies on ovine fetuses suggest that administration of a single 12 mg dose of betamethasone may be as effective for the maturation of fetal lungs as the administration of two doses (2 × 12 mg) at an interval of 24 h [20, 21]. This consideration led to the development of the BETADOSE trial, a prospective randomized, double-blind non-inferiority study. A total of 3244 patients with impending preterm birth before week 32 of gestation were recruited into this study. After receiving an initial dose of 12 mg betamethasone, patients were randomized and 24 h later received either another 12 mg of betamethasone or placebo. The primary study endpoint was the incidence of RDS, defined as the need for surfactant replacement within 48 h after birth. The RDS rate after two administrations of

▶ **Table 2** Comparison of dexamethasone and betamethasone (ASTEROID trial). The impact of 2 × 12 mg dexamethasone was compared with the impact of 2 × 12 mg betamethasone on the mortality/neurosensory development of the children at the age of 2 years and on neonatal and maternal morbidity rates [14].

	Dexamethasone	Betamethasone	RR	95% CI
	n (%)	n (%)		
Primary study endpoint				
Death or neurosensory disability at the age of 2 years	198/603 (33%)	192/591 (32%)	0.97	0.83–1.13
Neonatal				
Intraventricular hemorrhage	34/752 (5%)	32/737 (4%)	1.09	0.67–1.78
Periventricular leukomalacia	2/752 (< 1%)	2/737 (< 1%)	NA	NA
Respiratory distress syndrome	183/752 (24%)	174/737 (24%)	1.03	0.87–1.13
Maternal				
Infections	125/679 (18%)	132/667 (20%)	0.95	0.77–1.18
Cesarean section	295/679 (43%)	346/667 (52%)	0.84	0.75–0.93
Postpartum hemorrhage	128/679 (19%)	141/667 (21%)	0.87	0.71–1.08

RR: relative risk; 95% CI: 95% confidence interval

▶ **Table 3** Comparison of a single dose of 12 mg betamethasone and two doses administered at an interval of 24 hours (BETADOSE trial). The trial compared the effect of administering a single dose of 12 mg betamethasone with the effect of two doses administered at an interval of 24 hours on neonatal mortality and morbidity [22].

	1 × 12 mg betamethasone	2 × 12 mg betamethasone	Risk difference (95% CI)	p-value for superiority
	n (%)	n (%)		
Primary study endpoint				
Respiratory distress syndrome	304/1508 (20.2%)	268/1484 (18.1%)	2.2 (− 0.7–4.9)	
Secondary study endpoints				
Neonatal mortality	54 (3.4%)	50 (3.2%)		0.68
Intraventricular hemorrhage grade III–IV	17 (1.1%)	27 (1.7%)		0.13
Periventricular leukomalacia	20 (1.3%)	25 (1.6%)		0.46
Necrotizing enterocolitis grade ≥ II	31 (2.0%)	20 (1.3%)		0.12
Bronchopulmonary dysplasia	66 (4.3%)	73 (4.7%)		0.55
Neonatal survival without severe morbidity	1230 (78.6%)	1270 (80.9%)		0.11

95% CI: 95% confidence interval

betamethasone was 18.1% and therefore significantly lower than in the study group (20.1%). However, there were no other differences in perinatal morbidity or mortality between the two groups (▶ **Table 3**) [22].

Timing of Administration

The release of maternal cortisol follows a circadian rhythm. If this rhythm is disturbed, for example by stress, sleep deprivation, or a shift in the time zone, then experimental and epidemiological data have shown that the risk of affected children developing psychological disorders in later life increases [23]. But this type of impairment can also arise from the administration of a corticosteroid during pregnancy, which does not take account of maternal endogenous circadian rhythms. Mice whose dams were injected with glucocorticoids out of phase with their endogenous rhythms showed significantly stronger behavioral anxiety and were less able to deal with stress situations. It appears that the dyssynchronous administration of corticosteroids increases the concentrations of glucocorticoid receptors in the hypothalamus. REVERBα, a "clock protein" plays an important role in this. Out-of-phase administration resulted in dysregulation of the hypothalamic-pituitary-adrenal axis, which led to the described behavioral disorders in the animals [24]. A retrospective observational study of five-year-old children also found significant impairments in dealing with stress situations. There was also a trend to a higher incidence

▶ **Table 4** Incidence of respiratory distress syndrome depending on the interval between corticosteroid administration and delivery [25].

	Betamethasone		Control		RR	95 % CI
	n	RDS (%)	n	RDS (%)		
Interval to delivery						
< 24 h	260	26.1	257	28.7	0.87	0.66–1.15
< 48 h	171	22.2	203	33.5	0.63	0.43–0.92
1–7 days	563	10.1	547	23.0	0.46	0.35–0.60
> 7 days	498	6.4	490	7.6	0.82	0.53–1.28

RR: relative risk; 95 % CI: 95 % confidence interval

of hyperactivity, anxiety and a lack of self-confidence [24]. Wherever possible, circadian rhythms should therefore be considered when administering corticosteroids. Cortisol serum levels are highest between 6 and 8 o'clock in the morning, after which they decline during the day and drop to their minimum level between 0 and 6 o'clock at night. However, despite the importance of circadian rhythms, the administration of antenatal corticosteroids must not be delayed if corticosteroids are urgently required.

Timing und Interval

As a meta-analysis published in 2006 showed, no impact on RDS has been observed before 24 h after the initial administration of betamethasone (RR 0.87, 95 % CI: 0.66–1.15); the effect only occurs < 48 h (RR 0.63, 95 % CI: 0.43–0.92) (▶ **Table 4**) [25]. Given this context, it made sense to attempt to investigate whether it would be possible to shorten the administration interval for betamethasone to achieve faster lung maturation. In 2012, Khandelwal and colleagues published a prospective, randomized study to test this hypothesis. Their study compared the administration of two doses of betamethasone, given at an interval of 24 h between doses, with a 12 h interval. A total of 228 patients were recruited into the study. Patients were randomized 2 : 1. The shorter administration interval had no impact on the RDS rate (36.5 vs. 37.3 %) or the perinatal mortality (11.9 vs. 12.8 %) of treated infants. The rate of necrotizing enterocolitis was even significantly higher (0.0 vs. 6.2 %, p = 0.03) (Khandelwal et al., 2012) [26]. Irrespective of this, an evaluation of the EPICE cohort suggests that in-hospital mortality may already begin to decrease from 3 h after the first administration of betamethasone [27].

In addition, no further reduction of RDS could be detected > 7 days after corticosteroid administration (RR 0.82, 95 % CI: 0.53–1.28) (▶ **Table 4**) [25]. In contrast, Liebowitz and Clyman found in a retrospective analysis that extremely preterm babies born before week 28 of gestation who were delivered > 10 days after the first administration of a corticosteroid had a more than two times higher rate of intraventricular hemorrhage (17 % vs. 7 %; AOR 4.16, 95 % CI: 1.59–10.87). However, if the mother had received a second cycle for lung maturation, this rate was only 8 % and did not differ from that of infants born < 10 days after the first administration [28]. These studies confirm how important the correct timing of administration for lung maturation is.

▶ **Table 5** Interval between corticosteroid administration and delivery depending on the indication, based on [29].

	Interval: from corticosteroid administration to delivery	
	> 24 h – 7 days	< 24 h or > 7 days
	n (%)	n (%)
Indication		
Preterm rupture of membranes	60 (46.2)	70 (53.8)
Preterm labor	49 (36.3)	86 (63.7)
Pregnancy-induced hypertension	90 (62.1)	55 (37.9)
Asymptomatic cervical shortening	6 (11.8)	45 (88.2)
Fetal growth restriction, oligohydramnios	13 (36.1)	23 (63.9)
Vaginal bleeding, placental separation	15 (20.6)	58 (79.5)

In a retrospective analysis, Levin and colleagues investigated the timing of lung maturation in the context of different indications for preterm delivery between week 24 and week 34 of gestation [29]. Data from 630 patients were included in this study. Irrespective of the respective indication, only 40 % of cases could be delivered within the optimal time frame after administration (24 h – 7 days). As expected, the optimal timing of delivery was easiest to achieve in women with hypertension (62.1 %); patients who were not in labor but had cervical shortening, cervical opening, or a positive fibronectin test came off worst (11.8 %) (▶ **Table 5**) [29]. This can be ascribed to the poor positive predictive value of cervical length measurement and of different biochemical tests to evaluate the risk of preterm birth [30]. This observation is supported by further studies. In a retrospective examination, Adams and colleagues showed that it was far more difficult to achieve optimal timing of lung maturation (24 h – 7 days) in an infant born < 37 weeks of gestation who had to be delivered because of fetal indications than in cases when delivery was necessary because of a maternal indication (fetal-optimal vs. non-optimal: 24 vs. 76 %; maternal-optimal vs. non-optimal: 60 vs. 40 %) [31]. Makhija et al. reported similar findings [32].

▶ **Table 6** Development of children at the age of 5 years after multiple administrations of corticosteroids compared to administration of a single cycle (MACS trial). Children who were born at term after receiving multiple administrations of corticosteroids (≥ 37 + 0 weeks of gestation) had significantly more neurosensory developmental disorders compared to infants born preterm (< 37 + 0 weeks of gestation) [37].

	Children born preterm (n = 1257)		Children born at term (n = 462)		p-value of preterm vs. at-term infants
	OR (95% CI)	p-value	OR (95% CI)	p-value	
Primary study endpoint					
Death or neurological disability at the age of 5 years	0.87 (0.67–1.14)	0.32	1.69 (1.04–2.77)	0.04	0.02
Secondary study endpoint					
Death	0.91 (0.58–1.44)	0.66	0.58 (0.52–6.47)	0.65	0.72
Neuromotor disability	No convergence		No convergence		
Neurosensory disability	0.84 (0.55–1.29)	0.43	3.70 (1.57–8.75)	0.004	0.005
Neurocognitive disability	0.89 (0.62–1.28)	0.53	1.31 (0.75–2.29)	0.35	0.31

OR: odds ratio; 95% CI: 95% confidence interval

It follows, therefore, that the decision to administer antenatal corticosteroids should only be made if there is a high risk of preterm birth within the next 7 days. A twin pregnancy alone or fetal growth restriction is insufficient.

Repeat Administration for Lung Maturation

A possible solution for this problem could be the administration of a so-called rescue cycle. Crowther and colleagues summarized the results of 11 prospective randomized studies on repeated antenatal administration of corticosteroids in a meta-analysis of individual patients' data [33]. The data of 4857 women and 5915 children were included in their evaluation. The age of gestation at recruitment ranged from week 27.4 to week 30.2 of gestation. There were no differences in serious outcomes (RR 0.92, 95% CI: 0.82–1.04), which was defined as death, severe RDS, IVH ≥ grade 3, chronic pulmonary disease, necrotizing enterocolitis, retinopathy ≥ grade 3 or periventricular leukomalacia (PVL). The rate of infants who required respiratory support was significantly lower after repeat administration of corticosteroids (RR 0.91, 95% CI: 0.85–0.97). The number needed to treat was 21 (95% CI: 14–41). However, the z-score of the birth weights of infants who received repeated administrations of corticosteroids was also significantly lower (−0.12, 95% CI: −0.18 – −0.06). The difference was even higher following more lung maturation cycles [33]. Although the meta-analysis by Crowther et al. found no difference for the combined variable "death or neurosensory impairment", nevertheless there are some concerns that the repeated administration of corticosteroids can impair the development of affected children.

There are a number of retrospective studies and results from animal experiments which show that a repeated administration of glucocorticoids can lead to growth restriction and neuronal damage of the fetus. Behavioral disorders at a later stage of development have also been reported [34–36]. Data from the MACS trial, the largest prospective, randomized study which investigated the impact of a repeated induction of lung maturation on the development of children compared to the administration of a single cycle of corticosteroids, point to the same conclusion. The primary study endpoints after 5 years were death or impairment of neurological development in one of the following areas: neuromotor skills, neurosensory skills, neurocognition. No significant differences with regard to these variables were found between the groups. What was interesting, however, was a subgroup analysis of infants who had received multiple administrations for lung maturation. The primary study endpoint for infants born at term was significantly poorer compared to children born preterm (OR 1.69, 95% CI: 1.04–2.77). On closer observation, these differences were found to manifest particularly with regard to neurosensory characteristics (blindness, deafness, need for visual or hearing aids) (OR 3.70, 95% CI: 1.57–8.75) (▶ **Table 6**) [37]. The NICHD study also reported an increased rate of children with cerebral palsy after repeated doses of corticosteroids (2.9 vs. 0.5%; RR 5.7, 95% CI: 0.7–46.7). Even though this difference was not significant, it is nevertheless not possible to exclude the possibility of corticosteroids impairing neurological development. It is also worth mentioning that five of the six affected children in the group which received repeated corticosteroid administrations were born after week 34 of gestation and that all six children had received at least four cycles [38].

Given this data, the question is, under which circumstances should corticosteroid administration for lung maturation be repeated if there is still a high risk of preterm birth after a single course of corticosteroids. On the one hand, the repeated administration of corticosteroids reduces the short-term need for respiratory support in preterm children; on the other hand, repeated administrations may lead to growth restriction and long-term impairment of neurological development. Zephyrin and colleagues carried out an interesting analysis which focused on this issue [39]. Using a Markov model, they contrasted the improved neonatal outcomes after repeated glucocorticoid administrations with the risk of fetal growth restriction. Their calculations were based on the results of a study by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network [40]. After week 29 + 0 of gestation, repeated courses of corticosteroids to induce fetal lung maturation

were associated with increased disadvantages for the children [39]. Administering a repeat course to induce lung maturation should therefore be limited to patients with a very low gestational age (≤ 29 + 0 weeks of gestation) [6]. The majority of international guidelines also only recommend a single repeat course for lung maturation [3 – 6]. As gender is an important variable, particularly in extremely preterm birth, and has a significant impact on neonatal morbidity and mortality [41], it is worth considering whether, in future, the limit of 29 + 0 weeks of gestation for a repeat administration of corticosteroids also needs to be discussed with respect to the infant's gender.

Corticosteroids and Late Preterm Birth (> 34 Weeks of Gestation)

Even if the respiratory morbidity of preterm infants decreases significantly after 34 weeks of gestation, it is still much higher than that of children born at term [42]. The logical step was therefore to investigate whether an administration of corticosteroids even after 34 weeks of gestation would result in a further decrease in infant morbidity.

The ALPS trial was designed to clarify this point [43]. A total of 2827 women who were about to give birth between week 34 + 0 and week 36 + 5 of gestation were included in this prospective randomized study. Inclusion criteria were a cervix dilated by at least 3 cm and preterm labor, premature rupture of membranes or a medical requirement for the baby to be delivered very soon (e.g., pre-eclampsia, placental insufficiency, etc.). The women in the study group received 2 × 12 mg betamethasone injected intramuscularly at an interval of 24 hours, while the women in the control group received placebo. Primary study endpoints were need for respiratory therapy or stillbirth or neonatal mortality.

Only around 60 % of the women received two betamethasone injections; around 85 % were delivered before week 37 + 0 of gestation. This underlines how important it is to weigh up the indications before administering medication for lung maturation. The primary study endpoint was significantly lower in the betamethasone group (RR 0.80, 95 % CI. 0.66–0.97) as was the need for surfactant replacement (RR 0.59, 95 % CI: 0.37–0.96) and the rate of bronchopulmonary dysplasia (RR 0.22, 95 % CI: 0.02–0.92). However, the number needed to treat for bronchopulmonary dysplasia was 200. Because of the administration of betamethasone, the rate of neonatal hypoglycemia in the study group was significantly increased, although this was expected (RR 1.60, 95 % CI: 1.37–1.87) [43]. This was also confirmed in subsequent meta-analyses (RR 1.61, 95 % CI: 1.38–1.87) [44, 45].

Although the results of the ALPS trial have been welcomed enthusiastically by the American College of Obstetricians and Gynecologists [4], caution is still advised, as no long-term examinations of these children have been carried out yet and the impact of the administered corticosteroids on their further neurological development is still unclear.

In this context, it is also important to discuss the ASTECS trial, in which mothers undergoing elective cesarean section at term were given 2 × 12 mg betamethasone antenatally. This intervention significantly reduced the rate of children admitted to a pediatric unit and monitored for RDS (RR 0.46, 95 % CI: 0.23–0.93) [46]. About 50 % of mothers were questioned more than ten years later about the subsequent psychosocial development and health of their children. No significant differences were observed between the groups. However, when schools carried out their assessments, significantly more children in the treatment group were classified into the lower performance quartile by their teachers (17.7 vs. 8.5 %, p = 0.03) and fewer children were classified into the top performance quartile [47]. These data also show how long children whose mothers were given corticosteroids should be followed up to obtain a clear picture of the long-term consequences of this intervention.

It is even possible that mental impairment and behavioral disorders occur more frequently in children who were born at term after the administration of a single cycle of corticosteroids compared to children born at term who did not receive corticosteroids during pregnancy. This is certainly what has been suggested by a Finnish registry study (HR 1.47, 95 % CI: 1.36–1.69). To take account of the potential bias created by socioeconomic effects, the comparison was also calculated for siblings and the difference remained significant (HR 1.38, 95 % CI: 1.21–1.58) [48].

Corticosteroids and Extreme Preterm Birth (Week 22 + 0 to 23 + 6 of Gestation)

Between week 22 and week 26 of gestation, the fetal lung is in its canalicular phase of development. After the bronchioles have developed, the alveolar epithelium begins to differentiate and gradually becomes thinner, facilitating gas exchange with the capillaries. Surfactant can already be detected in type 2 alveolar cells and is secreted in the alveolar space. These developmental steps can be accelerated by corticosteroids, as has been shown in experimental studies (Schnittny and Burri et al., 2008) [49].

The rapid advances in perinatal medicine mean that we are now increasingly moving into areas which, up until a short time ago, were unimaginable. For a long time, week 24 + 0 of gestation was considered the limit of viability for the delivery of a live born infant, but now many perinatal centers carry out interventions already in the 23rd or even the 22nd week of gestation. This requires an intensive discussion between the affected parents and the respective perinatology team, which is discussed in more detail in the German-language guideline "Preterm Infants on the Edge of Viability" [50].

The obvious question in this context is, when is the right time to start with the administration of corticosteroids to induce fetal lung maturation. Prospective randomized studies cannot answer this question. They were designed at a time when children of this gestational age had almost no chance of survival and were therefore not considered when designing the study. Since then, however, a number of cohort studies have been published on this topic [51 – 61].

The most comprehensive of these studies analyzed the data of children with birth weights from 401 to 1000 grams, who were born between 1993 and 2009 in one of the 23 perinatal centers of the National Institute of Child Health and Human Development Neonatal Research Network [61]. A total of 10 451 children were

registered in this period. Their gestational ages ranged from week 22 to week 25 of gestation. 86.5% of the surviving children (n = 4924) were re-examined after 18–22 months. Death or impaired neurological development was significantly lower after the administration of corticosteroids in children born in the 23rd week (AOR 0.58, 95% CI: 0.42–0.80), the 24th week (AOR 0.62, 95% CI: 0.49–0.78) and the 25th week of gestation (AOR 0.61, 95% CI: 0.50–0.74). For infants born in the 22nd week of gestation, a benefit was only found with respect to the combined outcome "death or NEC" (AOR 0.54, 95% CI: 0.30–0.97) [61]. A more recent Norwegian cohort study also confirmed the benefit of antenatal corticosteroid administration in these very immature infants (OR 3.5, 95% CI: 1.4–8.8) [54]. A meta-analysis published in 2017, which reported a reduction of neonatal mortality and a lower incidence of IVH and PVL after the administration of antenatal corticosteroids in infants below the age of 25 weeks of gestation, came to the same conclusion [62].

In the event of a preterm birth at the edge of viability, most international guidelines recommend that affected parents be offered open-ended, interdisciplinary and interprofessional counselling to ensure shared participatory decision-making [3–5]. If the parents opt for a maximum intervention with an extreme preterm birth in week 22 + 0 to 23 + 6 of gestation, then corticosteroids should be administered antenatally [6].

Summary

A single cycle of corticosteroids administered before week 34 + 0 of gestation to treat impending preterm birth is now considered a standard obstetric procedure and is firmly established in the guidelines of a number of different countries. According to the current state of knowledge, betamethasone and dexamethasone are equally effective. A single dose of betamethasone results in a slightly higher incidence of RDS compared to the administration of two doses at an interval of 24 h, but there were no differences with regard to other parameters of neonatal morbidity. Corticosteroids should, if possible, be administered in the morning before midday. There are some indications that a dyssynchronous administration of corticosteroids which are not attuned to the mother's endogenous rhythm can have a negative impact on the capacity of affected infants to deal with stressful events in later life. Neonatal morbidity only decreases significantly if delivery occurs within the optimal period (> 24 h – 7 days) after administration of the corticosteroid. Some data have also shown that infants who are born at term, i.e., from week 37 + 0 of gestation onward, after antenatal administration of corticosteroids may suffer mental impairment and behavioral disorders. This means that the decision to administer corticosteroids antenatally must be considered very carefully. A theoretical calculation weighing up the benefits against the disadvantages suggests that a repeat administration of corticosteroids is only useful in cases of imminent preterm birth before week 29 + 0 of gestation. No corticosteroids should be administered in cases of impending preterm birth after week 34 of gestation as long as there is no data on the long-term development of affected children. If a maximum intervention is planned in a case of impending preterm birth before week 24 of gestation, then the administration of corticosteroids will improve neonatal morbidity and mortality.

Conflict of Interest

The authors declare that they have no conflict of interest.

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