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Antenatal Corticosteroids for Periviable Birth

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Abstract

Antenatal Corticosteroids have been proven to accelerate fetal lung development and reduce neonatal morbidity and mortality when given between 28 and 34 weeks gestation. However, there is only limited research to guide their use in the periviable period (22–26 weeks). Laboratory studies suggest that it is biologically plausible for antenatal steroids to be effective in this gestational period. In addition, cohort studies have demonstrated the efficacy of antenatal corticosteroids in reducing neonatal mortality and IVH. Follow-up studies performed between 18 and 22 months of age also suggest a long term benefit to antenatal use in this period. Based on this information antenatal corticosteroids should be used in appropriate patients at high risk for preterm birth at 23 to 26 weeks gestation. An advantage to treatment at 22 weeks is less certain.

There is limited data on the clinical value of antenatal steroids when used in the perinatal period. Two reasons account for this. First, the majority of the trials comparing antenatal corticosteroid use to placebo were performed over 20 years ago; a time when survival of fetuses between 23–26 weeks gestation was exceptional. Second, the majority of cohort studies evaluating this have only been sized respiratory distress as an outcome. However, even if steroid use is beneficial in this early gestational age, the majority of infants will still have Respiratory Distress Syndrome (RDS) so that evaluation of the benefits of use in this gestational period must include other outcomes. Because of this, there will be effective limited data; decisions on steroid use must be based on the biologic plausibility that corticosteroids will be effective in this gestational age period, combined with information gleamed from large cohort studies.

Despite the lack of trials, the use of antenatal corticosteroids has become relatively routine. In 1993, less than 20% of pregnancies delivering between 22–25 weeks gestation were treated. Following the NICHD special emphasis report in the early 1990s, numbers of treated pregnancies increased dramatically, so that by 1996, approximately 80% of infants delivering between 24–25 weeks were exposed. At present, corticosteroid treatment is used in 8 out of 10 infants delivering between 24–25 weeks, in 60% of infants delivering at 23 weeks, but steroid treatment decreases to approximately 10% 22-week gestations.[1]

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Biologic Plausibility for efficacy of antenatal corticosteroids in the Periviable Period

Antenatal corticosteroids work through multiple mechanisms to prepare the fetal lung for air breathing. The most well-known of these mechanisms is the induction of proteins and enzymes, including increased tissue and alveolar surfactant production. However, there are a number of other important effects including accelerated antioxidant production and induction of beta-receptor expression in the alveolar cells.[2, 3] An equally important effect of antenatal corticosteroids is the acceleration of parenchymal changes, which means that corticosteroid exposed lungs are structurally more mature than unexposed lungs at the same gestational age.[3] This results in increased compliance and lung volume, and decreased vascular permeability.

Between 22–26 weeks gestation the fetal lung is in the canalicular stage. During this stage a number of physiologically important changes are occurring. Early in this stage, the conducting airways are formed. As a fetus approaches 22–24 weeks gestation, epithelial differentiation occurs in which the cells lining the subsequent alveoli become thinner and more epithelial in appearance. At approximately the same time, the capillaries move closer to the epithelial lining of the airways, which results in the beginning of the subsequent air-blood barrier. Biochemically, surfactant begins to appear in both the type 2 alveolar cells and within the airway spaces.[2]

These structural changes are all known to be accelerated by corticosteroid exposure. In vitro studies of lung tissue cultures from fetuses less than 24 weeks gestation demonstrate a response to antenatal corticosteroids with an increase in both epithelial cell lining maturation and the appearance of lamellar bodies. Studies in fetal monkeys at a similar early gestational age also demonstrate steroid induced lung parenchymal maturation. This results of this study strongly suggesting that the human lung will respond to antenatal corticosteroids in the periviable period.[2]

Cohort Studies of Antenatal Corticosteroids in the Periviable Period

Table 1 demonstrates the experience of the NICHD Neonatal Network evaluating neonatal morbidity and mortality at 22–25 weeks gestation in steroid exposed versus non-steroid treated infants.[1] The study demonstrated a significant reduction in mortality in exposed neonates born in weeks 23, 24, and 25. Neonates delivered at 22 weeks showed a reduced mortality rate, which did not meet statistical significance. Overall, an odds ratio of 0.5 (95% CI: 0.52–0.65) was demonstrated for neonates born in the periviable period. Similarly, the frequency of Grade 3 and 4 intraventricular hemorrhages was significantly reduced from 23 through 25 weeks gestation, but it was not clearly demonstrated at 22 weeks gestation. However, the study failed to demonstrate any reduction in chronic lung disease or bronchopulmonary dysplasia. Subgroup analysis demonstrated that the effect was significant in all subgroups except small for gestational age infants and mothers with hypertension and preeclampsia.

A similar large cohort study has been reported from the Neonatal Network of Japan. Of 11,607 preterm births from 87 tertiary care centers, those delivering in the periviable period were reviewed. Antenatal corticosteroids improved fetus survival and reduced the frequency of severe intraventricular hemorrhage. There was also no improvement in respiratory distress syndrome or chronic lung disease.[4]

There have been six cohort studies (Table 2) evaluating antenatal corticosteroid use in the periviable period with surprising consistency. Most studies exhibited an odds ratio of

approximately 0.6 with steroid treatment. This is the same relative benefit demonstrated by corticosteroid use in later gestation. Overall, 7 to 9 infants need to be treated to prevent 1 death. All studies in which intraventricular hemorrhaging was evaluated have demonstrated improvement in this outcome as well.

Tyson et al[5] have looked at the follow-up of periviable infants exposed to antenatal corticosteroids compared to those not treated with steroids. They demonstrated that when evaluated at 18–22 months, the infants that delivered between 22–25 weeks gestation continued to demonstrate a reduced death rate (odds ratio 0.55: 95% confidence interval: 0.45–0.66). This suggested a gestational age acceleration of approximately 1.14 weeks. In addition, there was a reduction in the rate of death or profound impairment (OR 054: 95%CI 0.44–0.64 0.54:0.44–0.66) representing a gestational age equivalent effect of 1.23 weeks. When death or any impairment was evaluated, a similar reduction was demonstrated.

The Neonatal Network recently published an expanded follow-up. In this report of almost 5,000 infants delivering between 22–25 weeks gestation, there was a significant reduction in death or neuro-developmental impairment in the steroid exposed cohort. This resulted in a significant increase in infants that were alive and intact. Also, moderate or severe cerebral palsy was decreased by periviable antenatal steroid treatment. When Bayley scores <70 were evaluated at 18–22 months, there was a non-significant improvement with an odds ratio of 0.63 (0.34–1.17).[1]

Choice of Antenatal Steroid in the Periviable Period

Cohort studies have compared dexamethasone and betamethasone for periviable steroid treatment. A study from the Neonatal Network of infants weighing between 400–1,500 grams demonstrated a mild benefit of betamethasone.[6] The 18–22 month follow-up of these infants (birth weight 400–1,000 gram) evaluating neurodevelopmental outcomes, showed reductions in most neurodevelopmental outcomes with betamethasone compared to dexamethasone.[7] This difference was found to only be statistically significant for deafness. This work suggests that if both drug options are available, that betamethasone should be used. However, if betamethasone is not available dexamethasone also appears to be effective.

Conclusions

While further study would be beneficial, the information that we presently have strongly suggests that antenatal corticosteroids have value when given in the periviable period and should be offered when clinically appropriate. This benefit is clear from 23 weeks on. It is less certain whether they should be utilized at 22 weeks or less. Because of the uncertainty in gestational age prediction, it is suggested that they should also be used at this gestational age if preterm birth appears to be imminent.

However, one must remain cautious when making decisions based on cohort studies, which have the potential for unintended bias. For example, the use of steroids may be more frequently offered to patients in whom the obstetrician is willing to intercede with a C-section and to perform fetal heart rate monitoring. Conversely, in situations in which a decision of non-intervention is made, steroids as well as aggressive delivery management may be withheld. Alternatively, if steroids are given antenatally this may bias neonatal treatment including the willingness to resuscitate in the delivery room.

Finally, it must be recognized that the safety of corticosteroids administered in the periviable period has not been confirmed. There is clear animal data suggesting that antenatal corticosteroid exposure has an effect on fetal growth including brain growth.[7] However,

long-term (age 5–7) follow-up of humans exposed to a single course of corticosteroids have been reassuring, but the number treated at very early gestational ages is limited. Another concern is that follow-up studies have only been performed in neonates delivering between 22–26 weeks gestation, not those treated who remain in-utero. In many of these cases one or many additional courses of antenatal corticosteroids have been given. While less than three repeat courses of antenatal steroids appears to be safe, most studies have occurred at later gestational ages.[8, 9]

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Table 1

Neonatal Morbidity and Mortality by Week of Gestation Steroid (STR) vs. No Steroid (NoS)

		22 weeks		23 weeks		24 weeks		25 weeks		Total (10,541)	
		STR	**NoS**	**STR**	**NoS**	**STR**	**NoS**	**STR**	**NoS**	**STR**	**NoS**
	N	119	283	1147	831	2979	814	3563	805	7808	2733
Mortality	%	73.2	82.4	59.1	73.5	41.2	52.3	25.0	36.2	35.3	56.0
	OR[I] (95% CI[II])	0.61 (0.34–1.07)		0.49 (0.39–0.61)		0.64 (0.54–0.76)		0.57 (0.47–0.69)		0.58 (0.52–0.65)	
IVH[III] (III/IV) PVL[IV]	%	23.3	19.2	26.9	36.5	20.4	25.5	16.9	26.2	19.2	27.6
	O% (95% CI)	0.94 (0.2–4.49)		0.59 (0.37–0.59)		0.81 (0.61–1.08)		0.56 (0.44–0.72)		0.67 (0.57–0.79)	
BPH[V]	%	64.5	57.8	65.7	70.1	66.4	53.8	55.2	47.1	60.3	54.0
	OR (95% CI)	1.33 (0.51–3.45)		0.83 (0.57–1.21)		1.69 (1.30–2.20)		1.33 (1.06–1.67)		1.43 (1.23–1.67)	

Table from Carlo et all: JAMA 2011[1]

[I] Odds Ratio

[II] Confidence Interval

[III] Intraventricular Hemorrhage

[IV] Periventricular Leukomalacia

[V] Bronchopulmonary Dysplasia

Table 2

Summary of Cohort of Periviable Birth Studies Reporting Neonatal Outcomes of Steroid Treated vs. Non-Treated Pregnancies

Study PI[I]	Year Published	Country of Origin	Time of Delivery	OR[II] Deaths	OR IVH[III]
Costelo[11]	2000	U.K	<26 weeks	0.6	0.39
Tyson[5]	2008.	U.S.	<26 weeks	0.6	-
Hayes[12]	2008.	U.S.	<23 weeks	0.3	-
Mori[4]	2011	Japan	<26 weeks	0.7	0.65
Bader[13]	2010	Israel	<26 weeks	0.6	-
Carlo[1]	2011	U.S.	<26 weeks	0.6	0.7

I Principal Investigator

II Odds Ratio

III Intraventricular Hemorrhage

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