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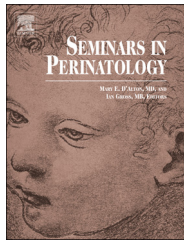

Antenatal corticosteroids for periviable birth

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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 of 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 23–26 weeks of gestation. An advantageous outcome to treatment at 22 weeks is less certain.

There is limited data on the clinical value of antenatal steroids when used in the periviable 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 and 26 weeks of gestation was exceptional. Second, the majority of cohort studies evaluating this have used respiratory distress as the outcome, but at this early gestational age the majority of infants will have respiratory distress syndrome (RDS) secondary to the immature lung anatomy so that evaluation of the benefits of use must include other outcomes. Because of this 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 containing outcomes other than RDS.

Despite the lack of trials, the use of antenatal corticosteroids in the periviable period has become relatively routine. In 1993, less than 20% of pregnancies delivering between 22 and 25 weeks of 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 and 25 weeks were exposed to treatment. At present, corticosteroid treatment is used in 8 of 10 infants delivering between 24 and 25 weeks, in 60% of infants delivering at 23 weeks, but decreases to approximately 10% at 22-week gestations.[1]

1. 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 biochemical effects including accelerated

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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 and 26 weeks of gestation, the fetal lung is in the canalicular stage during which a number of physiologically important changes are occurring. Early in this stage, the conducting airways are formed. As a fetus approaches 22–24 weeks of 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 interface. Biochemically, surfactant begins to appear in both the type 2 alveolar cells and within the airway spaces.[2]

These 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. The results of these studies strongly suggest that the human lung will respond to antenatal corticosteroids in the periviable period.[2]

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 of gestation in steroid-exposed vs. nonsteroid-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 of gestation, but this reduction 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 fetal survival and reduced the frequency of severe intraventricular hemorrhage. There was no improvement in respiratory distress syndrome or chronic lung disease.[4]

There have been 6 cohort studies (Table 2) evaluating antenatal corticosteroid use in the periviable period with surprising consistency. Most studies exhibited an odds ratio for fetal death of approximately 0.6 with steroid treatment, which is the same relative benefit demonstrated for corticosteroid use in later gestation. Overall, 7–9 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 and 25 weeks of gestation continued to demonstrate a reduced death rate (odds ratio 0.55: 95% confidence interval: 0.45–0.66). This suggested a gestational age improvement of approximately 1.14 weeks. In addition, there was a reduction in the rate of death or profound impairment (OR 0.54: 95% CI

Table 1 – Neonatal morbidity and mortality by week of gestation, steroid (STR) vs. no steroid (NoS).[1]

	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[a] (95% CI[b])	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[c] (III/IV) PVL[d]										
%	23.3	19.2	26.9	36.5	20.4	25.5	16.9	26.2	19.2	27.6
OR (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[e]										
%	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)	

[a] Odds ratio.
[b] Confidence interval.
[c] Intraventricular hemorrhage.
[d] Periventricular leukomalacia.
[e] Bronchopulmonary dysplasia.