Antenatal Dexamethasone and Decreased Severity of Retinopathy of Prematurity

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Objective: To assess risk factors associated with the development of retinopathy of prematurity (ROP) in an urban population.

Design: Observational cohort study.

Setting: Bellevue Hospital Center, a regional perinatal referral center in New York City.

Patients: Surviving inborn infants with birth weight less than 1250 g undergoing an ophthalmologic screening examination.

Main Outcome Measures: Screening examination results for ROP were obtained. Additional data included birth weight, gestational age, maternal factors, and common neonatal diagnoses and exposures.

Results: Sixty-three infants were included in the analysis. Mean ± SD birth weight was 981 ± 179 g and mean gestational age was 27.8 ± 2.4 weeks. Infants whose mothers received antenatal dexamethasone developed significantly less ROP that was stage 2 or higher than infants without a history of antenatal dexamethasone exposure—8.7% (2/23) vs 35% (14/40), respectively (P = .04). Birth weight, gestational age, respiratory distress syndrome, bronchopulmonary dysplasia, and patent ductus arteriosus were also significantly associated with the development of ROP that was stage 2 or higher. After controlling for these confounders by multiple logistic regression analysis, antenatal dexamethasone administration was associated with a significantly decreased risk of development of ROP stage 2 or higher (adjusted odds ratio [OR], 0.14; 95% confidence interval [CI], 0.02-0.93). The association was stronger when the analysis was restricted to the 36 infants who were 24 to 28 weeks of gestational age (adjusted OR, 0.02; 95% CI, 0.00-0.76).

Conclusion: Antenatal dexamethasone administration appears to be associated with a decreased incidence of development of ROP of stage 2 or higher in this urban population.


Retinopathy of prematurity (ROP) is a serious vasoproliferative disorder faced by the smallest infants in the modern neonatal intensive care unit. Improved technologies have led the way toward improving the survival of small infants at earlier gestational ages. Improving the quality of survival and long-term outcome is of utmost importance. Serious visual problems and blindness continue to be included in the long-term neurologic sequelae of these infants. As survival of these small infants improves, the causes and treatment of ROP must be addressed or visual outcome will continue to be a problem.

Major risk factors associated with development of ROP include low birth weight, young gestational age, and degree of illness (respiratory distress syndrome [RDS], patent ductus arteriosus [PDA], intraventricular hemorrhage [IVH], bronchopulmonary dysplasia [BPD], sepsis, and blood transfusions). To date, no preventive or early intervention measures are available to decrease the incidence or severity of this serious condition. Current therapy for ROP, other than preventing prematurity and judicious neonatal management, consists of cryotherapy or laser therapy for severe disease.

Our study was undertaken to track infants at risk for ROP as part of a quality improvement measure, and to identify additional risk factors associated with the incidence of ROP in a New York City urban population.

RESULTS

During the study period, a total of 87 infants born at Bellevue Hospital Center were admitted to the intensive care or special care nurseries with birth weights less than 1250 g. Of these 87 infants, 22...
SUBJECTS AND METHODS

STUDY DESIGN

Bellevue Hospital Center, New York City, is a regional perinatal referral center with a 6-bed intensive care unit and 19-bed special care nursery. Between July 1991 and July 1995, a consecutive sample of infants born at Bellevue Hospital Center with birth weights less than 1250 g were enrolled in the study. Surviving infants were longitudinally followed up as part of a quality assurance indicator and received ophthalmologic screening by 5 to 7 weeks of age in accordance with American Academy of Pediatrics recommendations. Ophthalmologic examinations were performed by 2 staff ophthalmologists. In the event an infant developed prethreshold disease, a second ophthalmologist was consulted to corroborate the examination. Cryotherapy or laser surgery was performed in infants who developed threshold disease.

Prenatal, perinatal, and neonatal data were collected from each patient's medical record using a standardized data collection sheet for the study. Information about birth weight, gestational age (as determined by admitting neonatologist), Apgar scores, IVH, PDA, indomethacin treatment, RDS, methylxanthine treatment, postnatal dexamethasone treatment for lung disease, and surfactant administration was collected from the infants' medical records. The infants were classified by most severe ophthalmology examination findings using the International Classification of ROP method for purposes of data analysis.

Maternal factors, including history of maternal drug use, placental abruption, premature rupture of the membranes, and maternal hypertension, were collected. In addition, the history of any antenatal dexamethasone administration was collected from the infants' medical records (if this was not recorded, the corresponding maternal medical record was reviewed to ensure accuracy). Antenatal dexamethasone was used at the discretion of the obstetrical staff. The protocol was reviewed and approved by the New York University Medical Center's Institutional Board of Research Associates, the Research Review Committee of Bellevue Hospital Center, and the New York City Health and Hospitals Corporation.

DATA ANALYSIS AND STATISTICAL METHODS

Published findings show that most stage 1 ROP resolves without long-term sequelae and that outcome is highly dependent on severity of ROP. Therefore, infants were divided into 2 groups: no ROP or stage 1 ROP (group 1) and stage 2 or higher ROP (group 2).

Statistical analyses were performed using χ² analyses with Yates correction (or the Fisher exact test where appropriate) for categorical data or by 2-tailed t test for continuous data (using the unequal variance approximation where applicable). Hierarchical logistic regression analyses were performed to determine the independent effects of risk factors after controlling for confounding variables. The criterion used to determine statistical significance was P<.05. All data are given as mean ± SD unless otherwise indicated.

Infants were examined at 4 to 7 weeks of chronological age and were followed up sequentially as per examination findings. Among infants with ROP (n=43), the most severe stage was reached at an average of 35.3 ± 2.7 weeks of postconceptual age, with a range of 31 to 41 weeks. The mean postconceptional age of the most severe stage of ROP was not different for varying gestational age. The infants were 8.2 ± 3.3 weeks of chronological age at the most severe stage, with a range of 4 to 16 weeks. The mean chronological age at which point infants reached the most severe stage of ROP for varying gestational age is shown in Figure 1. Of note, the more premature the infant, the longer it took to develop the most severe stage of ROP, as previously described.

For infants with multiple examinations (n=61), 18 regressed or stayed the same while 43 progressed from either (1) immature retina to ROP or (2) less severe to more severe stage of ROP. All of the 18 infants who regressed or stayed the same had stage 1 ROP at the initial examination.

To target the population most at risk for the long-term sequelae of ROP, including myopia, altered visual acuity, strabismus, amblyopia, nystagmus, severe visual impairment, and blindness, the patients were divided into 2 groups: those at low risk for these sequelae of ROP, no ROP, or stage 1 ROP at worst examination (group 1); and those at high risk for sequelae with stage 3+ or 4 ROP, requiring cryosurgery and/or laser surgery.
2 or greater ROP at worst examination (group 2). Infants with ROP of stage 2 or higher were more likely to have smaller birth weight, earlier gestational age, RDS, BPD, PDA, and no antenatal dexamethasone administration (Table). Neither male sex nor intraventricular hemorrhage was associated with differences between the 2 groups. Postnatal dexamethasone treatment for chronic lung disease and surfactant administration (probable markers of severity of illness) showed a trend toward an increased ROP of stage 2 or higher, but did not reach statistical significance at \( P \leq 0.05 \). There were no differences between the 2 groups with respect to maternal hypertension, premature rupture of the membranes, or abruptio placenta. Further analysis showed no differences in antenatal dexamethasone administration and maternal hypertenion (\( P =.26 \)), premature rupture of the membranes (\( P =.69 \)), and abruptio placenta (\( P =.46 \)).

Birth weight and gestational age are known to influence the development of ROP. Patent ductus arteriosus and lung disease have also been correlated with an increased risk of ROP. To assess whether lack of antenatal dexamethasone administration was an independent risk factor for the development of ROP, hierarchical multiple logistic regression analysis was performed to control for confounding factors including birth weight, gestational age, RDS, BPD, and PDA, all of which were significant as given in Table 1. In the first step of the hierarchical multiple logistic regression, the baseline characteristics of birth weight (per gram) and gestational age (per week) were entered. In the second step, predictors of severity of illness (RDS, BPD, and PDA) were entered, controlling for the baseline characteristics. In the third step, antenatal dexamethasone treatment was entered, controlling for baseline characteristics and predictors of severity of illness. Antenatal dexamethasone treatment was highly significant for decreasing the severity of ROP with an adjusted odds ratio of 0.14 and a 95% confidence interval of 0.02 to 0.93. The distribution of antenatal dexamethasone treatment for infants at each stage of ROP is shown in Figure 2.

Although gestational age and birth weight were not statistically different between the 2 groups, newborns who received antenatal corticosteroids had slightly higher values of gestational age (28.3 ± 2.1 weeks) and birth weight (1032 ± 167 g) when compared with those who did not receive antenatal corticosteroids (27.5 ± 2.6 weeks, 952 ± 182 g). The chronological age (7.8 ± 3.0 weeks) and postconceptional age (35.5 ± 2.5 weeks) at which infants who received antenatal dexamethasone developed the most severe stage of ROP were similar (\( P =.74 \) and \( P =.53 \), respectively) to those of infants who did not receive antenatal dexamethasone (8.4 ± 3.6 weeks and 35.2 ± 2.7 weeks). In addition, for infants who developed stage 2 or higher ROP, ages to most severe examination were also similar (\( P =.50 \) and \( P =.87 \)) between infants who received antenatal dexamethasone (8.0 ± 4.2 weeks and 36.5 ± 0.7 weeks) and those who did not receive antenatal dexamethasone treatment (10.9 ± 3.0 weeks and 26.4 ± 2.6 weeks).

Further analysis was performed in infants from 24 to 28 weeks of gestational age. Infants younger than 24 weeks of gestational age (n=3) were excluded from this analysis based on the National Institutes of Health consensus statement that recommends antenatal steroid treatment for mothers at risk for delivery at gestational ages of 24 to 34 weeks to reduce mortality and morbidities, including RDS and IVH. Because these recommendations exclude the infant younger than 24 weeks of estimated gestational age, mothers who have preterm labor at 22 to 23 weeks of estimated gestational age may not have received antenatal steroids. These cases were considered to be of borderline viability and the recommendation for steroids did not apply. Three infants were younger than 24 weeks of gestational age; none of these infants received antenatal dexamethasone, and all

### Table 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1 (No ROP or Stage 1)</th>
<th>Group 2 (ROP Stage 2 or Higher)</th>
<th>( P )</th>
<th>Crude Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) birth weight, g</td>
<td>1030 ± 161</td>
<td>838 ± 155</td>
<td>&lt;.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean (± SD) gestational age, wk</td>
<td>28.6 ± 2.0</td>
<td>25.6 ± 2.1</td>
<td>&lt;.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Premature rupture of the membranes</td>
<td>17 (36)</td>
<td>6 (38)</td>
<td>.64</td>
<td>0.30-2.90</td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>2 (4)</td>
<td>1 (6)</td>
<td>.72</td>
<td>0.07-4.66</td>
<td></td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>11 (23)</td>
<td>2 (13)</td>
<td>.57</td>
<td>2.14</td>
<td>0.41-8.16</td>
</tr>
<tr>
<td>I illicit drug use</td>
<td>10 (21)</td>
<td>1 (6)</td>
<td>.26</td>
<td>0.03-2.10</td>
<td></td>
</tr>
<tr>
<td>Antenatal dexamethasone</td>
<td>21 (45)</td>
<td>2 (13)</td>
<td>.04</td>
<td>0.04-0.87</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (49)</td>
<td>7 (44)</td>
<td>.71</td>
<td>0.26-2.54</td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>32 (68)</td>
<td>15 (94)</td>
<td>.05</td>
<td>0.85-58.29</td>
<td></td>
</tr>
<tr>
<td>Surfactant administration</td>
<td>27 (57)</td>
<td>14 (88)</td>
<td>.06</td>
<td>5.18</td>
<td>1.01-18.43</td>
</tr>
<tr>
<td>PDA</td>
<td>17 (36)</td>
<td>13 (81)</td>
<td>.005</td>
<td>7.65</td>
<td>1.91-30.68</td>
</tr>
<tr>
<td>BPD</td>
<td>17 (36)</td>
<td>14 (88)</td>
<td>.001</td>
<td>12.35</td>
<td>2.50-60.98</td>
</tr>
<tr>
<td>IVH</td>
<td>10 (21)</td>
<td>5 (31)</td>
<td>.50</td>
<td>1.68</td>
<td>0.47-5.97</td>
</tr>
<tr>
<td>Postnatal dexamethasone</td>
<td>4 (9)</td>
<td>1 (25)</td>
<td>.10</td>
<td>3.58</td>
<td>0.78-16.49</td>
</tr>
</tbody>
</table>

*Student t tests were used to compare sample means; \( \chi^2 \) analyses were used to compare sample proportions. Crude odds ratios and 95% confidence intervals are shown for nonparametric data. Birth weight and gestational age were statistically significant between the 2 groups, as were antenatal dexamethasone administration, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). Results are expressed as number (percentage) unless otherwise indicated. Crude odds ratios are the ratio of the odds of developing retinopathy of prematurity (ROP) with reference to the presence or absence of a given variable. IVH indicates intraventricular hemorrhage.
of them developed ROP (stage 2, 3, and 4, respectively). Infants older than 28 weeks of gestational age (n=24) were excluded from this subset, as most of these infants do not go on to develop serious sequelae of ROP. However, these infants still benefit from antenatal glucocorticoid treatment by reductions in pulmonary and central nervous system morbidity and reductions in mortality.

Thirteen (36%) of 36 infants 24 to 28 weeks of gestational age were treated with antenatal dexamethasone. Of these, 1 (7.7%) developed stage 2 or higher ROP while 12 (92%) had no ROP or stage 1 ROP. Sixty-four percent of infants 24 to 28 weeks of gestational age did not receive antenatal dexamethasone and 43% went on to develop stage 2 or greater ROP. When the hierarchical multiple logistic regression was restricted to this selected subset of the population (n=36), the protective effect of antenatal dexamethasone was stronger (adjusted odds ratio, 0.02; 95% confidence interval, 0.00-0.76). The subset of infants from 24 to 28 weeks of gestational age had similar birth weight and gestational age characteristics when divided into those who received antenatal corticosteroids (927 ± 171 g, 26.6 ± 1.0 weeks) and those who did not receive antenatal corticosteroids (915 ± 133 g, 26.3 ± 1.3 weeks).

The regression analysis was performed on infants older than 28 weeks (n=24) and no relation was seen with antenatal dexamethasone treatment and severity of ROP. In this group, 10 (42%) infants received antenatal dexamethasone, and 2 (20%) developed stage 2 ROP (no higher stages). Fourteen infants (48%) did not receive antenatal dexamethasone and 1 (7%) of these developed stage 2 ROP.

Antenatal dexamethasone administration in this urban population is associated with a decrease in severity of ROP. In this study, the incidence of ROP was 68%, which is similar to an inner-city population that demonstrated a 72% incidence of ROP in infants weighing less than

1200 g at birth. The incidence is also similar to the rate of 65.8% described in the Cryotherapy for Retinopathy of Prematurity study.

The National Institutes of Health consensus statement for antenatal corticosteroid therapy will undoubtedly lead to increased use of antenatal corticosteroid therapy. Corticosteroid therapy has been shown to reduce neonatal mortality, decrease the incidence of respiratory distress syndrome, and to reduce the incidence and severity of IVH. The beneficial role of antenatal corticosteroids with ROP has not been previously described. Moise et al found no difference in the development of ROP necessitating cryotherapy between infants exposed to antenatal corticosteroid therapy (59 of 240) and no antenatal treatment from 1986 to 1991. In contrast, our study included infants born in a consecutive sample from 1991 to 1995. Although our study did not include a sufficient number of severely affected infants to be able to critically evaluate ROP requiring surgical intervention (n=5), we did find an independent association of antenatal dexamethasone administration with the development of stage 2 or greater ROP. In addition, the Vermont-Oxford Trials Network found no difference for any ROP and severe ROP in infants weighing less than 1500 g exposed to antenatal corticosteroids when compared with those not exposed to corticosteroids. However, as discussed by the authors, ROP data were missing on 3485 of 8749 infants in the study, which limited the interpretability of their findings. In contrast, our study looked at a different grouping of ROP, ie, no ROP or stage 1 and stage 2 or higher ROP. This method of categorizing infants by stage of ROP may be more relevant to long-term outcome, as stage 1 ROP usually does not lead to long-term sequelae. Dividing groups into no ROP or stage 1 ROP and stage 2 or higher ROP was not explored in other studies. In addition, it is not known if betamethasone or dexamethasone have different antenatal protective effects.

Although the study design was not experimental or randomized, there was also no systematic bias in the approach to steroid use. Antenatal corticosteroids were given at the discretion of the obstetrical staff. The regression analysis was done because of the possibility that differences might have existed in a nonrandomized study and the results were significant for a protective effect of antenatal corticosteroids and ROP. Thus, while our results are not those of a prospective, double-blind, placebo-controlled randomized clinical trial, we believe that they suggest an association between antenatal steroid use and decreased severity of ROP. It is possible that antenatal steroids may decrease the severity of ROP in our study population by mechanisms that are as yet undescribed. Steroids have been shown to inhibit preretinal neovascularization in a pig model and subretinal neovascularization in a primate model. Corticosteroids may “accelerate maturation” of the retinal vasculature, thus placing the infant at lower risk of developing serious ROP. Furthermore, steroids have been postulated to “stabilize” capillaries, which could be another mechanism of action whereby the developing fragile retinal blood vessels have a decreased susceptibility to injury. Finally, steroids may decrease the response to injury of the devel-
oping retinal blood vessels, thus protecting them from the injurious elements of the premature postnatal environment such as oxygen.

The results of this study may have important implications for decreasing the severity of ROP, a long-term complication of prematurity. The results of this study support a reduction in the severity of ROP, suggesting an additional benefit of antenatal corticosteroid treatment. Decreasing the severity of ROP is extremely important. Further clinical and laboratory studies are needed to reproduce these findings in a larger population and to elucidate the exact mechanism of this observation.

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REFERENCES


A look at the past . . .

D e Wecker reports the case of a new-born infant whose left orbit was emptied by the finger of the obstetrician, who thought that his finger was in the infant’s mouth. A more frequent accident is muscular paralysis caused by the forceps. The condition is not noticed until the infant is older, when a convergent squint is observed which, as most infants are hyperopic, is taken to be a convergent squint due to hyperopia.