Postnatal dexamethasone has been widely used in the treatment of chronic lung disease (CLD) in preterm infants, and several randomised trials have shown that it rapidly reduces requirements for oxygen and ventilation. However, the long-term consequences on mortality and morbidity are less clear, and recent reports have raised concerns that postnatal steroids may cause neurodevelopmental impairment in preterm infants. In animal models, corticosteroids significantly impair cell multiplication in the central nervous system and lung. Murphy et al, using advanced magnetic resonance imaging techniques, documented a reduction in the volume of cortical grey matter in preterm infants exposed to postnatal dexamethasone treatment, and this finding is consistent with clinical trials reporting a reduction in head growth and an increase in the rates of cerebral palsy among children who received steroids as compared with controls. The recent systematic review performed by Barrington, which included eight randomised controlled trials enrolling 679 infants, showed a relative risk for neurodevelopmental impairment among surviving, followed up, treated infants of 1.34 (95% confidence interval (CI) 1.09 to 1.64) and a relative risk for cerebral palsy of 2.02 (95% CI 1.51 to 2.71).

In this study we describe the follow up findings at three years of adjusted age for 30 surviving infants at high risk for CLD who participated in a randomised clinical trial on the moderately early postnatal use of dexamethasone.

MATERIALS AND METHODS

The original randomised clinical trial was carried out in our neonatal intensive care unit over a 16 month period ending June 1997 in order to evaluate the effect of moderately early dexamethasone administration in the treatment of chronic lung disease were routinely followed up. Fifteen babies received a total dose of 4.75 mg/kg over 14 days from the 10th day of life, and 15 babies were untreated. Five infants in each group received open label steroids to facilitate extubation later in their clinical course. Growth and neurodevelopmental outcome are reported.

Results: The mean body weight, height, and head circumference as well as the number of babies with anthropometric measurements within normal range were similar in treated and untreated babies. There was no significant difference between treated and control groups with respect to incidence of cerebral palsy, major sensory impairment, mean intelligence quotient scores, and behavioural abnormalities.

Conclusions: Postnatal dexamethasone treatment with the schedule used in this study did not impair growth and neurodevelopmental outcome in preterm infants. Data from larger trials have raised major concern that postnatal steroid treatment may increase neurodevelopmental impairment. The full extent of the risk will only be known when more trials have reported follow up data.
as the gain in weight, length, and head circumference from birth to discharge. There was no significant difference between the two study groups with respect to the incidence of infants with body weight, height, or head circumference below the 3rd centile at birth and at discharge.

Postconceptional age, weight gain, length gain, and gain in head circumference at discharge were not different between the groups.

All the infants studied (15 treated and 15 controls) were enrolled in, and completed, the follow up performed at 36–42 months of adjusted postnatal age. Follow up controls were performed by the same paediatrician (RL) with periodic visits between 3, 8, 12, 24, 36, and 42 months of adjusted age. At each visit, an interim medical history was associated with a physical examination. Weight, supine crown-heel length, and occipito-frontal head circumference measurements were recorded. On the occasion of visits at 3, 8, and 12 months of corrected age, a cranial ultrasound scan was carried out; the definition of major cranial ultrasound abnormality was based on published criteria. All infants underwent a neurological examination by a paediatric neurologist (GT) to assess motor development. Neuromotor dysfunction was classified as mild, moderate, or severe, based on the mobility of the child: mild if motor dysfunction was not severe enough to interfere with mobility; moderate if the child was independently mobile when provided with a hand to hold, and severe when the child was not independently mobile. Psychometric evaluations were performed at 24 and 36 months of age using the Scale of Intelligence Stanford-Binet (3rd revised version of Terman-Merrill). According to the intelligence quotient (IQ) score, children were subdivided into three groups: (1) IQ < 70; (2) IQ 70–90; (3) IQ > 90. Examiners, both paediatrician and paediatric neurologist, were completely blinded to group assignment.

For analysis of physical growth and developmental performance, the infant’s postnatal age was corrected by the degree of prematurity before term (40 weeks). Anthropometric measurements were plotted on the growth chart for Italian children.

Differences in outcome were analysed using the $\chi^2$ Yates test for categorical variables or the Mann-Whitney U test for continuous variables. $p < 0.05$ was considered significant.

### Results

The mean (SD) corrected postnatal age at the time of follow up was 36.6 (1.7) months for the treatment group and 36.2 (0.6) months for the control group. The incidence of readmission was 40% (6/15) in the dexamethasone group and 67% (10/15) in the control group, the difference was not statistically significant. Two babies in the control group and five treated babies required repeated admissions. The main reason for readmission was the occurrence of bronchiolitis, pneumonia, and asthma. Two babies in each group needed surgical intervention for inguinal hernia.

Table 3 reports growth outcome in the babies studied. There were no significant differences between treated and control groups with regard to mean body weight, height, and head circumference. Data on body weight, height, and head circumference were plotted, based on the corrected age, on the growth chart for Italian children. There was no significant difference between the two study groups with respect to the incidence of infants with body weight, height, or head circumference in the normal range (3rd–97th centile) for corrected age. Three infants in the treated group and four in the control group had head circumference below the 3rd centile. No baby in the dexamethasone treated group and two in the control group had head circumference below the 3rd centile. Two treated and three control infants had head circumference below the third centile.

Table 4 presents data on neurodevelopmental outcome. At 12 months of corrected age, three infants in the treated group (20%) and three in the control group (20%) showed major cranial ultrasound abnormalities, diagnosed as periventricular leucomalacia or persistent ventricular dilation. Cerebral palsy was diagnosed in two treated and three control babies; in all cases this was associated with major cranial ultrasound abnormalities. Major neurosensory impairment was observed.
in four infants (27%) in each group. One infant from each group was blind and two treated babies had poor vision. Visual impairment was always due to severe retinopathy of prematurity, and, in one baby, it was also associated with periventricular leucomalacia and cerebral palsy. Two control infants showed severe deafness; this was secondary to acquired cytomegalovirus infection in the first case and associated with mental retardation and persistent ventricular dilatation in the second case. Moderate hearing loss was observed in one treated infant (apparently without cause) as well as in one control infant (associated with cranial ultrasound abnormality and cerebral palsy). The mean (SD) IQ score was 84.2 (12.4) for the treated group and 83.0 (15.6) for the control group. The proportion of infants with IQ score > 90 was similar in both groups, while IQ score was < 70 for two children in the treatment group and three control infants. Behavioural abnormalities were observed in five treated (33%) and four control (27%) infants.

DISCUSSION

Several studies have reported short term beneficial effects of postnatal steroid treatment in preterm infants at high risk of CLD.\textsuperscript{12–15} Although short term adverse effects such as hyperglycaemia, hypertension, growth impairment, cardiac hypertrophy, gastrointestinal bleeding and perforation, sepsis, and periventricular leucomalacia have been reported,\textsuperscript{16–19} few published trials have been designed to evaluate the long term follow up effects in treated infants. Recent reports have raised concern that postnatal steroids may cause neurodevelopmental impairment in preterm infants.\textsuperscript{3, 4, 17}

We report the three year follow up findings in preterm infants included in a randomised clinical trial of moderately early postnatal dexamethasone treatment. In a previous paper reporting growth data from birth to discharge, we showed that treated infants had a significantly smaller gain in weight and head circumference than controls only during the dexamethasone treatment period. In a previous paper reporting growth data from birth to discharge, we showed that treated infants had a significantly smaller gain in weight and head circumference than controls only during the dexamethasone treatment period. However, published studies are often conditioned by differences in confounding factors between study groups,\textsuperscript{7–9} contamination of randomisation schedules,\textsuperscript{1} or too short a follow up period.\textsuperscript{10–12} Looking at the data from Murphy et al\textsuperscript{13} showing a reduction in cortical grey matter volume in treated infants studied by magnetic resonance imaging techniques, one could argue that preterm infants exposed to dexamethasone were significantly smaller (757 (112) vs 1259 (218) g), more immature (25.4 (2.0) vs 28.8 (1.5) weeks), and affected by more severe respiratory disease than untreated infants.

Two studies reporting a higher incidence of neuroromotor dysfunction and an increased risk of cerebral palsy\textsuperscript{14} included babies treated with high doses of dexamethasone for a very long time (28 days from the first day of life and 42 days from the 3rd week after birth). More recently, Shinwell et al\textsuperscript{15} reported follow up data obtained for 159 of 190 infants included in a randomised, double blind, placebo controlled study, and concluded that a three day course of dexamethasone (total dose 1.5 mg/kg) administered shortly after birth in preterm infants with respiratory distress syndrome is associated with a significantly increased incidence of cerebral palsy and developmental delay. In our study, infants were treated with a total dexamethasone dose of 4.75 mg/kg over 14 days from the 10th day of life. The two study groups of our trial were well matched with respect to all clinical data except for incidence of CLD, and results were not influenced by contamination of randomisation schedules because five infants of each group received two doses of 0.5 mg/kg dexamethasone to facilitate weaning from mechanical ventilation after the first month of life. Although our results do not show any severely negative effect due to dexamethasone treatment on long term growth and neurodevelopmental outcome, some possible limitations of our study should be outlined. Firstly, the sample size was calculated on the basis of the incidence of CLD in our high risk population to detect the reduction of CLD in treated infants and was thus probably insufficiently powered to detect small but significant differences in rare adverse outcome. Secondly, it is difficult to compare our results with those reported by authors who used different schedules for steroid treatment, and it is possible that doses higher than ours could be more dangerous for preterm infants, even if this hypothesis is not in agreement with the results obtained by Shinwell et al\textsuperscript{15} in a larger trial. In conclusion, the alarm raised about the potential detrimental effect of postnatal steroids on brain growth and developmental outcome should not be ignored and such treatment should be restricted to preterm infants with the highest risk of severe CLD on the basis of a risk/benefit ratio. The full extent of the risk will only be known when more trials have reported follow up data.

\begin{table}
\caption{Neurodevelopmental outcome in preterm babies treated or not with dexamethasone}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Treatment} & \textbf{Control} \\
\textbf{group (n=15)} & \textbf{group (n=15)} \\
\hline
Major cranial ultrasound abnormalities at 12 months of corrected age & 3 (20) & 3 (20) \\
Periventricular leucomalacia & 1 (6.7) & 0 \\
Persistent ventricular dilatation & 2 (13.3) & 3 (20) \\
Cerebral palsy & 2 (13.3) & 3 (20) \\
Spastic quadriplegia & 1 (6.7) & 2 (13.3) \\
Spastic hemiplegia & 1 (6.7) & 0 \\
Ataxia & 0 & 1 (6.7) \\
Major neurosensory impairment & 4 (26.7) & 4 (26.7) \\
Blind & 1 (6.7) & 1 (6.7) \\
Poor sight & 2 (13.3) & 0 \\
Severe deafness & 0 & 2 (13.3) \\
Moderate hearing loss & 1 (6.7) & 1 (6.7) \\
Mean IQ Score (SD) & 84.2 (12.4) & 83.0 (15.6) \\
> 90 & 5 (33.3) & 8 (53.3) \\
70 – 90 & 8 (53.3) & 4 (26.7) \\
< 70 & 2 (13.3) & 3 (20) \\
Behavioural abnormalities & 5 (33.3) & 4 (26.7) \\
\hline
\end{tabular}
\end{table}

Values are expressed as number (%) or mean (SD).
REFERENCES