Bronchopulmonary dysplasia and perinatal glucocorticoids in preterm infants: changing practice based on evidence
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Chapter 5

Open-label glucocorticoids modulate dexamethasone trial results in preterm infants

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Abstract

Context: Open label glucocorticoids (OLG) were often used in the trials investigating postnatal dexamethasone treatment in ventilated preterm infants.

Objective: To determine if OLG use modulates the dexamethasone treatment effect on mortality, bronchopulmonary dysplasia (BPD) and neurodevelopmental outcome.

Data sources: Electronic databases, abstracts from the Pediatric Academic societies and manual reference searches.

Methods of study selection: Two reviewers, independently, identified fifteen randomized controlled trials, including 721 patients, comparing dexamethasone with placebo in ventilated preterm infants older than 7 days and extracted all relevant data. The interaction between dexamethasone treatment effect and OLG use was assessed by meta-regression analysis and subgroup meta-analysis according to the percentage of OLG use in the placebo group. Trials with a moderately early (7-14 d) or delayed (>3 wk) treatment onset were analyzed separately.

Results: Moderately early, but not delayed, dexamethasone treatment significantly reduced mortality in trials with < 30% OLG use in the placebo arm. Meta-regression analysis showed that this reduction was inversely related to OLG use. Increasing OLG use strengthened the positive effect of dexamethasone on BPD in the moderately early trials but attenuated the effect in the delayed treatment trials. In trials with < 30% OLG use, dexamethasone increased the risk for cerebral palsy in the delayed, but not the moderately early, treatment trials.

Conclusions: OLG use in the dexamethasone trials modifies the treatment effect of the reported outcomes. When adjusted for OLG use effect modification, moderately early dexamethasone treatment reduces mortality and the combined outcome mortality and BPD without increasing the risk of adverse neurodevelopmental outcome in ventilated preterm infants.
Introduction

Systematic reviews of placebo controlled trials have shown that the use of systemic dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD), but not mortality in ventilated preterm infants.\(^8,9\) Despite this beneficial effect on BPD, the use of dexamethasone has declined over the recent years because of suspected long-term adverse effects, such as an increased risk of cerebral palsy (CP).\(^10-12\) It is, however, important to recognize that the validity of these results may have been compromised by the fact that the trials included in the reviews differed considerable in the timing of initiating dexamethasone treatment, the cumulative dose and the use of open label glucocorticoids (OLG).\(^{15}\)

In two systematic reviews exploring the effect of timing and cumulative dexamethasone dose on important clinical outcome parameters, such as BPD and neurodevelopmental sequelae we found that initiating treatment between 7 – 14 days of life (moderately early) was superior to late treatment (> 3 weeks) and that higher cumulative doses were more effective than lower doses.\(^{15,16}\) We did not find a significant impact of either timing or cumulative dexamethasone dose on mortality.

The majority of the dexamethasone trials allowed for the use of OLG in both the intervention and the placebo arm, and considerable numbers of patients received OLG in actual fact. As data analyses were done on intention to treat basis the true effect of dexamethasone on mortality, BPD and neurodevelopmental outcome may have been obscured.\(^{17,18}\) To date, two systematic reviews have investigated the impact of OLG use on dexamethasone treatment effects, but showed conflicting results on mortality and neurodevelopmental outcome.\(^{15,20}\) The effect of OLG on BPD was not reported. Furthermore, these reviews did not take into account the timing of initiating dexamethasone treatment, a factor that, based on previous reviews, can be an important modifier of dexamethasone treatment effects.\(^{8,9,15}\)

The aim of the present study was to determine if and how OLG changes the treatment effect of dexamethasone on mortality, BPD and neurodevelopmental outcome taking into account the timing of initiating dexamethasone treatment. To this end, we used both meta-regression and meta-analysis of all randomized controlled trials comparing dexamethasone to placebo in ventilated preterm ventilated infants.

Methods

The clinical studies meeting the inclusion criteria previously described were identified by searching the main electronic databases, references from relevant studies and...
abstracts from the Pediatric Academic Societies (from 1990 onwards). Methodological quality of the trials was assessed by rating the following items using the criteria described in the Cochrane Reviewers' Handbook: risk of bias by insufficient allocation concealment, blinding of intervention, completeness of follow-up and blinding of outcome measurements. The following data were extracted from the original papers: birth weight, gestational age, gender, number of patients randomized, treatment with antenatal glucocorticoids, postnatal surfactant treatment, postnatal age at start and cumulative dose of dexamethasone, percentage of patients treated with OLG in both the intervention and the placebo arm, mortality at 36 weeks postmenstrual age (PMA) and/or at hospital discharge, BPD defined as oxygen dependency at 36 weeks PMA, long term neurodevelopmental sequelae, assessed after at least 1 year corrected gestational age (CGA) and before a CGA of 4 year including cerebral palsy and Bayley's Scales of Infant Development (Mental Development Index MDI). Both quality rating and data extraction were performed independently by two reviewers (WO and ADJ).

The original investigators of the included RCTs were contacted and asked to confirm whether the data extraction was accurate and, where necessary, to provide additional (unpublished) data.

Meta-analysis of the extracted data was performed using the standard methods of the Cochrane Neonatal Review Group. Trial results were analyzed according to the time of initiating therapy, i.e. moderately early (i.e. in the second week of life) and delayed treatment onset (after 3 postnatal weeks). Within each timing group, subgroup analysis was performed based on the percentage of patients receiving OLG in the placebo group, assigning the included studies to one of three subgroups based on the percentage of patients receiving OLG, using arbitrary cut-off points of 30% and 50%. Subgroup analysis based on the percentage of patients receiving OLG in the intervention group was not performed because here OLG use was dichotomous in nature, being either absent or relatively stable across trials at 25-30% (Table 1). Treatment effect estimates were expressed as relative risk (RR) for dichotomous outcomes with a 95% confidence interval. Finally, effect estimates on all outcome parameters were pooled in the predefined subgroups according to the rate of OLG in the placebo group. We explored the relationship of OLG use with the various different DEXA treatment effect sizes. For each clinical outcome parameter, the observed risk difference of the separate trials was plotted against the percentage of patients receiving OLG in the placebo group and a weighted meta-regression with the percentage of patients receiving OLG in the placebo group as the independent covariate was performed.

To identify possible third order effect modifiers, the pairwise Pearson correlation coefficient was calculated using the percentage of OLG use in the placebo group and the following variables as co-variates: birth weight, gestational age, percentage...
of infants treated with antenatal glucocorticoids, cumulative dosage of postnatal dexamethasone treatment, total days of dexamethasone therapy and the percentage of patients receiving postnatal surfactant.

All statistical tests were two-sided and considered significant when \( p < 0.05 \). All data were analyzed using Intercooled Stata 9.2 (Stata Corporation, College Station, Texas, USA). In the absence of statistical heterogeneity \((p > 0.05)\), fixed-effects models were used for the meta-analyses and meta-regression, otherwise random effects models were used.

## Results

### Study characteristics

Based on the search strategy 15 original placebo controlled RCTs, randomizing 721 patients, were included in this review (Figure 1).\(^{15}\) Original investigators of eleven trials provided additional data on their study methods, patients’ characteristics or outcome parameters.

The overall methodological quality of the trials was judged fair to good.\(^{15}\) All trials included preterm infants with a similar gestational age and birth weight (Table 1). Eight trials initiated dexamethasone therapy moderately early (7 – 14 days postnatal) and 7 trials used delayed (> 3 weeks) treatment. The cumulative doses ranged from 0.9 to 7.8 mg/kg. All except 4 trials used a starting dose of 0.5 mg/kg/day and the duration of dexamethasone therapy ranged from 3 to 42 days.

The percentage of patients treated with OLG in the placebo group varied from 0 to 65%, with 4, 7 and 4 trials reporting OLG use in, respectively, < 30\%,\(^{22,25}\) 30-50\%,\(^{26-32}\) and >50\%\(^{33-36}\) of the patients. Two trials explicitly prohibited the administration of OLG by protocol.\(^{22,23}\)

Data on pulmonary endpoints and mortality in the study by Kari et al. were obtained from the original investigator and consisted of a single center subgroup.\(^{26}\) The study by Cummings et al. compared a high dexamethasone dose (7.8 mg/kg) to a low dose (3.0 mg/kg) and a placebo, which allowed us to compare both groups to the placebo group.\(^{22}\) The DART trial was analyzed as delayed treatment onset as most infants in this study were included at or after 3 weeks of postnatal age.\(^{29}\) From the Collaborative Dexamethasone Trial Group (CDTG) study, which included both ventilated and non-ventilated infants, we only used the data of ventilated preterm infants.\(^{31}\)
Outcome parameters

Mortality

Meta-regression analysis of the moderately early, but not the delayed trials, showed a significant positive regression coefficient when exploring the OLG use and the risk difference in mortality at 36 weeks PMA and hospital discharge. This suggests that the positive treatment effect of dexamethasone on mortality decreases with increasing OLG use (Table 2, Figure 2A). Subgroup meta-analysis of the moderately
early trials showed similar findings with a significant reduction in the relative risk for mortality at hospital discharge in favor of dexamethasone in the subgroup of trials with OLG <30% (Table 3, Figure 2B).

**BPD**
The moderately early trials meta-regression analysis of OLG use and the risk difference in BPD revealed a negative regression coefficient but this finding failed to

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Moderately early trials</th>
<th>Delayed trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A†</td>
<td>Effect§ (95% CI)</td>
</tr>
<tr>
<td>M36</td>
<td>-22.7</td>
<td>0.44 (0.12, 0.75)*</td>
</tr>
<tr>
<td>MHD</td>
<td>-25.4</td>
<td>0.46 (0.12, 0.80)*</td>
</tr>
<tr>
<td>BPD</td>
<td>0.7</td>
<td>-0.41 (-1.13, 0.30)</td>
</tr>
<tr>
<td>CMBPD</td>
<td>-22.0</td>
<td>-0.02 (-0.73, 0.78)</td>
</tr>
<tr>
<td>CP</td>
<td>-12.0</td>
<td>0.11 (-0.53, 0.76)</td>
</tr>
<tr>
<td>CMCP</td>
<td>-21.7</td>
<td>0.33 (-0.27, 0.92)</td>
</tr>
<tr>
<td>MDI</td>
<td>-30.9</td>
<td>0.44 (-0.20, 1.08)</td>
</tr>
</tbody>
</table>

M36 Mortality at 36 weeks PMA; MHD Mortality at hospital discharge; BPD Bronchopulmonary dysplasia at 36 weeks PMA; CMBPD Combined mortality or BPD at 36 weeks PMA; CP Cerebral palsy; CMCP Combined mortality at hospital discharge and cerebral palsy in survivors assessed; MDI Bayley’s MDI < -2 SD; § Effect percentage change with increasing percentage open label glucocorticoids; † A intercept of risk difference (%); * Statistical significant (p<0.05).
reach statistical significance (Table 2, Figure 3A). In line with this result, subgroup meta-analysis showed an incremental reduction in the relative risk for BPD, in favor of dexamethasone, with increasing OLG use. We found a statistically significant difference in the relative risk for BPD in the subgroup of trials with an OLG use above 50% (Table 3, Figure 3B). This association between BPD risk and OLG use was no longer present when combining BPD with mortality, with all subgroups showing a significant reduction in this outcome parameter in favor of the dexamethasone group (Table 3). The delayed treatment trials showed an opposite association

Figure 2A Moderately early trial meta-regression analysis of the percentage of open label glucocorticoids in the placebo group and the effect on the outcome mortality at hospital discharge. Regression line and 95% confidence intervals for moderately early trials (circles and dotted line) trials. The scale of the symbols represents the calculated weight in the pooled estimate.

Figure 2B Subgroup meta-analysis of the outcome mortality at hospital discharge in the moderately early studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLG ≤ 30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cummings (a)</td>
<td>0.46 (0.15, 1.40)</td>
<td>3/12</td>
<td>6/11</td>
<td>20.82</td>
</tr>
<tr>
<td>Cummings (b)</td>
<td>0.56 (0.21, 1.50)</td>
<td>4/13</td>
<td>6/11</td>
<td>21.61</td>
</tr>
<tr>
<td>Scott</td>
<td>0.11 (0.01, 1.92)</td>
<td>0/10</td>
<td>2/5</td>
<td>10.76</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.503)</td>
<td>0.43 (0.21, 0.87)</td>
<td>7/15</td>
<td>14/27</td>
<td>53.18</td>
</tr>
<tr>
<td>OLG ≥ 30% and ≤ 50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vento</td>
<td>0.55 (0.06, 5.21)</td>
<td>1/11</td>
<td>2/12</td>
<td>6.36</td>
</tr>
<tr>
<td>Romagnoli</td>
<td>1.00 (0.07, 13.87)</td>
<td>1/10</td>
<td>1/10</td>
<td>3.32</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.722)</td>
<td>0.70 (0.13, 3.82)</td>
<td>2/36</td>
<td>3/37</td>
<td>9.69</td>
</tr>
<tr>
<td>OLG &gt;50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durand</td>
<td>0.43 (0.09, 2.13)</td>
<td>2/23</td>
<td>4/20</td>
<td>14.23</td>
</tr>
<tr>
<td>Kovacs</td>
<td>1.60 (0.59, 4.33)</td>
<td>8/30</td>
<td>5/30</td>
<td>16.62</td>
</tr>
<tr>
<td>Walther</td>
<td>1.12 (0.18, 7.09)</td>
<td>2/17</td>
<td>2/19</td>
<td>6.28</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.394)</td>
<td>1.07 (0.51, 2.25)</td>
<td>1/120</td>
<td>11/89</td>
<td>37.13</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.574)</td>
<td>0.70 (0.43, 1.12)</td>
<td>21/141</td>
<td>28/133</td>
<td>100.00</td>
</tr>
</tbody>
</table>
between OLG use and the risk for BPD, reporting the largest dexamethasone treatment effect on BPD in trials with a low OLG use (Table 4). Combining BPD with mortality showed an even stronger association, as indicated by the significant regression coefficient (Table 2).

**Neurodevelopmental outcome**

Both meta-regression analysis and subgroup meta-analysis of the moderately early trials showed no clear association between adverse neurodevelopmental outcome in terms of CP or the rate of a MDI below -2SD and the use of OLG in the placebo arm (Table 2-3, Figure 4). Although meta-regression and subgroup meta-analysis suggested an increased risk of the combined outcome mortality or CP with increasing use of OLG in the placebo arm, this finding was not statistically significant. The analysis of the delayed trials showed the opposite effect of OLG use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OLG&lt;sub&gt;plcb&lt;/sub&gt; &lt; 30% RR (95% CI)</th>
<th>30% ≤ OLG&lt;sub&gt;plcb&lt;/sub&gt; ≤ 50% RR (95% CI)</th>
<th>OLG&lt;sub&gt;plcb&lt;/sub&gt; &gt; 50% RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M36</td>
<td>0.51 (0.25, 1.07)</td>
<td>0.70 (0.13, 3.82)</td>
<td>1.19 (0.55, 2.54)</td>
</tr>
<tr>
<td>MHD</td>
<td>0.43 (0.21, 0.87)*</td>
<td>0.70 (0.13, 3.82)</td>
<td>1.07 (0.51, 2.25)</td>
</tr>
<tr>
<td>BPD</td>
<td>1.06 (0.58, 1.96)</td>
<td>0.63 (0.38, 1.02)</td>
<td>0.53 (0.32, 0.88)*</td>
</tr>
<tr>
<td>CMBPD</td>
<td>0.78 (0.61, 0.98)*</td>
<td>0.63 (0.41, 0.97)*</td>
<td>0.70 (0.57, 0.86)*</td>
</tr>
<tr>
<td>CP</td>
<td>0.69 (0.25, 1.92)</td>
<td>0.67 (0.22, 2.05)</td>
<td>0.65 (0.20, 2.17)</td>
</tr>
<tr>
<td>CMCP</td>
<td>0.67 (0.41, 1.07)</td>
<td>0.71 (0.27, 1.91)</td>
<td>0.93 (0.51, 1.69)</td>
</tr>
<tr>
<td>MDI</td>
<td>0.39 (0.15, 1.02)</td>
<td>0.75 (0.19, 2.99)</td>
<td>0.71 (0.33, 1.54)</td>
</tr>
</tbody>
</table>

M36 Mortality at 36 weeks PMA; MHD Mortality at hospital discharge; BPD Bronchopulmonary dysplasia at 36 weeks PMA; CMBPD Combined mortality or BPD at 36 weeks PMA; CP Cerebral palsy; CMCP Combined mortality at hospital discharge and cerebral palsy in survivors assessed; MDI Bayley’s MDI < -2 SD; OLG<sub>plcb</sub> Open label glucocorticoids in the placebo group; * Statistical significant (p<0.05).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OLG&lt;sub&gt;plcb&lt;/sub&gt; &lt; 30% RR (95% CI)</th>
<th>30% ≤ OLG&lt;sub&gt;plcb&lt;/sub&gt; ≤ 50% RR (95% CI)</th>
<th>OLG&lt;sub&gt;plcb&lt;/sub&gt; &gt; 50% RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M36</td>
<td>0.54 (0.14, 2.04)</td>
<td>0.96 (0.60, 1.53)</td>
<td>1.50 (0.34, 6.70)</td>
</tr>
<tr>
<td>MHD</td>
<td>0.90 (0.42, 1.94)</td>
<td>0.97 (0.62, 1.51)</td>
<td>1.50 (0.34, 6.70)</td>
</tr>
<tr>
<td>BPD</td>
<td>0.76 (0.58, 1.00)</td>
<td>0.99 (0.85, 1.15)</td>
<td>1.50 (0.34, 6.70)</td>
</tr>
<tr>
<td>CMBPD</td>
<td>0.73 (0.58, 0.93)*</td>
<td>0.98 (0.90, 1.08)</td>
<td>1.24 (0.74, 2.08)</td>
</tr>
<tr>
<td>CP</td>
<td>3.75 (1.13, 12.43)*</td>
<td>1.24 (0.74, 2.08)</td>
<td>1.24 (0.74, 2.08)</td>
</tr>
<tr>
<td>CMCP</td>
<td>1.56 (0.85, 2.87)</td>
<td>1.05 (0.77, 1.42)</td>
<td>1.24 (0.74, 2.08)</td>
</tr>
<tr>
<td>MDI</td>
<td>1.09 (0.40, 3.01)</td>
<td>0.83 (0.50, 1.37)</td>
<td>1.24 (0.74, 2.08)</td>
</tr>
</tbody>
</table>

M36 Mortality at 36 weeks PMA; MHD Mortality at hospital discharge; BPD Bronchopulmonary dysplasia at 36 weeks PMA; CMBPD Combined mortality or BPD at 36 weeks PMA; CP Cerebral palsy; CMCP Combined mortality at hospital discharge and cerebral palsy in survivors assessed; MDI Bayley’s MDI < -2 SD; OLG<sub>plcb</sub> Open label glucocorticoids in the placebo group; * Statistical significant (p<0.05).
on neurodevelopmental outcome with an increased risk of CP in the subgroup of trials using less than 30% OLG (Table 4). 

Third order effect modification
Analysis did not reveal a significant correlation between OLG use and the prespecified variables, making third order effect modification unlikely (data not shown).
Figure 4 Subgroup meta-analysis based on the percentage open label glucocorticoids in the placebo group and the effect on the combined outcome mortality or cerebral palsy for moderately early studies.

### Discussion

Up to now, systematic reviews of randomized controlled trials comparing postnatal systemic dexamethasone to placebo in ventilated preterm infants at risk for BPD have shown that dexamethasone has no effect on mortality, reduces the incidence of BPD, and may increase the risk for adverse neurodevelopmental outcome.\(^9,37\) However, in the majority of the available RCTs infants in the placebo group received OLG as a rescue treatment. This may have confounded the results as all RCTs analyzed the data on an intention to treat basis.\(^38\)

The first and most important finding of this review is that dexamethasone administered in the second week of life (moderately early) significantly reduces mortality at hospital discharge in those trials with a low OLG use (< 30%) in the placebo group. In addition, subgroup meta-analysis and meta-regression analysis showed a clear association between the percentage of OLG use in the placebo group and the dexamethasone treatment effect on mortality. These two findings suggest that moderately early dexamethasone treatment does indeed reduce mortality, but that this effect has so far not been recognized because of the OLG use in most of the trials. In the delayed treatment onset trials (> 3 weeks) OLG did not modulate mortality risk, indicating that delayed dexamethasone treatment probably has no effect on mortality in chronically (> 3 weeks) ventilated preterm infants.

OLG use also influenced the dexamethasone treatment effect on BPD. In the moderately early trials, increasing use of OLG resulted in a decreasing relative risk for BPD, reaching statistical significance in the trials with more than 50% OLG use in the placebo arm.
Two important factors need to be taken into consideration when trying to explain these findings. First, OLG use in the placebo arm might, similar to dexamethasone in the intervention arm, reduce the risk of BPD, diluting the contrast. Second, as shown by this review, OLG use in the placebo arm will also impact mortality. In trials with a low percentage of OLG use, mortality in the placebo group was higher, with an obvious selection of surviving patients at a lower risk of BPD. In the other trials a high percentage of OLG use might lead to improved chances of survival of the sickest infants, resulting in a higher risk for BPD in the placebo group. The different selection of patients in the a priori risk of BPD in the placebo group will also impact the treatment effect of dexamethasone on BPD. The results from the subgroup analysis and the meta-regression analysis on BPD seem to suggest that the indirect effect of survival on BPD in the moderately early trials is more important than the direct effect of OLG. This is also supported by the fact that the combined outcome mortality or BPD at 36 weeks did not show a clear correlation with OLG use.

In the delayed treatment onset trials, the opposite effect of OLG use was found on BPD, i.e. a lower relative risk for BPD in trials with a low OLG use in the placebo arm. As OLG use does not seem to affect mortality risk in these delayed trials, this finding is probably best explained by the direct effect of OLG use on BPD in the placebo arm, thus attenuating the true treatment effect of dexamethasone.

Despite the beneficial effect of dexamethasone on BPD, there have been growing concerns on the possible adverse effects on neurodevelopmental outcome. Up to now, these concerns have only been substantiated in trials starting dexamethasone in the first days after birth. The effect on neurodevelopmental outcome is much less clear when starting dexamethasone treatment moderately early or delayed. Some have argued that the latter is caused by the fact that infants assigned to the placebo arm were often treated with OLG, which may have attenuated the negative effects of dexamethasone on neurodevelopmental outcome. As far as the moderately early trials are concerned, the present review does not support this line of reasoning, showing no clear association between OLG use and adverse neurodevelopmental outcome variables. Analysis of the delayed trials showed that low OLG use in the placebo group strengthened the previously reported negative effect of dexamethasone on neurodevelopmental outcome.

Two previous reviews also explored the possible impact of OLG use on the treatment effect of dexamethasone on mortality and neurodevelopmental outcome. Barrington reported that dexamethasone increased the risk for adverse neurodevelopmental outcome and that this risk was highest in the RCTs with less than 30% OLG use. Dexamethasone did not reduce mortality and this finding...
Effects of open-label glucocorticoids in trials

was not modulated by OLG use. Comparing these results to the present review is difficult because the review of Barrington included only 8 RCTs, half of which started dexamethasone administration in the first days of life (early). Including these early trials may have influenced the dexamethasone treatment effect on both mortality and neurodevelopmental outcome, because the *a priori* mortality risk is probably lower in infants mechanically ventilated in the first days of life compared with chronically ventilated infants put on steroids after the first week of life, and because the association between dexamethasone treatment and adverse neurodevelopmental outcome is almost exclusively reported in early treatment trials.\(^8\) The review by Doyle and colleagues, including early (n=8), moderately early (n=4) and delayed (n=5) treatment trials, showed a significant reduction in mortality and an increased risk for CP in the dexamethasone treatment arm, but only in the subgroup of trials that did not allow OLG use. The present review adds new and important information to this finding. First, meta-regression analysis shows a significant association between OLG use and the effect of dexamethasone on mortality. Second, the present review shows that dexamethasone will only reduce mortality if administered between 7 – 14 days of life (moderately early). Third, the adverse effect of dexamethasone on neurodevelopmental outcome in RCTs using less than 30% OLG is only seen after delayed (> 3 weeks) treatment and not after moderately early treatment in the second week of life. Finally, this study includes 6 additional trials\(^{24,28,29,34,36,45}\) and obtained non-published information from the original trialists on the reported outcome parameters from 11 of the 15 trials, thereby increasing the robustness of the results.

**Limitations**

This review has several limitations that need to be discussed. First, most trials did not provide detailed information on OLG use in terms of clinical indication, cumulative dose, duration, and timing. It is unknown if and how these factors affect the findings of this review. Second, the included RCTs differed considerably in study design including differences in the dexamethasone starting dose, the duration of therapy and cumulative dose. Although we pooled the data as if they were from clinical homogeneous studies, this apparent clinical diversity compromises the validity of the results of our meta-analysis. We therefore used, when appropriate, the more conservative random effect models to avoid overestimation of spurious effects. In addition we looked for possible third order effect modifiers, but were unable to show a significant correlation between the use of OLG and several prespecified variables. Finally, the above described associations should be interpreted with caution because of the small sample size of the trials and the large variance in treatment effect across trials. The consequence of using meta-regression and subgroup meta-analysis is that the already small sample size may have resulted
in inadequate power to detect small, but clinically relevant differences in some of the important outcome parameters.

**Implications for practice and research**

This review has important implications for clinical practice, because it shows that, in addition to the previously reported beneficial effect on BPD, dexamethasone when administered moderately early may also reduce mortality. However, this effect is not seen after delayed treatment. Furthermore, this review shows that moderately early use is not accompanied by an increased risk for adverse neurodevelopmental outcome, even in the subgroup with low OLG use. These results once again show that the optimal time to start dexamethasone treatment in ventilated preterm infants at risk for BPD is in the second week of life. Yet, given the limitations discussed above, including the small sample sizes of most trials, we feel that the results of this review should be confirmed or refuted in a large randomized controlled trial of moderately early administered dexamethasone versus placebo. In such a trial OLG use should be limited as much as possible. Data should be analyzed on an intention-to-treat basis, per-protocol, and in a adherers-only analysis in order to accurately estimate the true effect of dexamethasone treatment on the clinical outcome parameters.44

**Conclusion**

Dexamethasone treatment started 7 – 14 d after birth (moderately early) reduces mortality and BPD without increasing the risk of adverse neurodevelopmental outcome in ventilated preterm infants at risk for BPD. OLG use in the placebo arm can modify these treatment effects and should therefore be taken into account when analyzing future trials.

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