Bronchopulmonary dysplasia and perinatal glucocorticoids in preterm infants: changing practice based on evidence
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Chapter 1

General introduction
1 Introduction

In the past decades the implementation of antenatal glucocorticoids, postnatal surfactant therapy, new modalities of respiratory support and nutritional intervention in perinatal and neonatal care have led to an increased survival amongst the lowest birth weight infants. However, associated with this improved survival are high rates of short-term morbidities and long term neurodevelopmental sequelae, of which bronchopulmonary dysplasia (BPD) continues to be the most important complication.¹ ²

Since the most important risk factor for BPD is preterm birth, the treatment strategy for preventing BPD starts with avoiding or postponing preterm labour. However, when preterm birth is imminent, the use of antenatal glucocorticoid therapy has gained increasing popularity. In contrast to the view on the benefits of antenatal glucocorticoids, the debate on postnatal use of glucocorticoids to prevent or treat established BPD is still ongoing.

In this general introduction, we will first discuss some basic molecular facts on glucocorticoids and the current insights on the pathophysiology of BPD before addressing the evidence based use of glucocorticoids in three parts: (1) antenatal glucocorticoid therapy aimed at preventing neonatal mortality and morbidity, (2) systemic postnatal glucocorticoid therapy, mainly dexamethasone aimed at preventing BPD or improving clinical outcomes in preterm infants with developing BPD, and (3) alternative strategies of administrating and subtypes of postnatal glucocorticoids. The final chapter of this introduction will outline current knowledge on risk assessment of BPD at an early postnatal age.

Evidence-based medicine or EBM is the integration of best research evidence with clinical expertise and patient values, leading the creation of systematic reviews and concise summaries of the effects of health care, epitomized by the Cochrane Library.³ ⁴ In general, the strongest evidence for therapeutic interventions in medicine is considered to be provided by systematic reviews of randomized, triple-blind, placebo-controlled trials with allocation concealment and complete follow-up involving a homogeneous patient population and medical condition. However, since the systematic reviews on antenatal and postnatal glucocorticoid use include RCTs with tremendous clinical heterogeneity, tailoring these pooled results back to individual patients remains a challenge for the clinician and one of the most often mentioned criticisms of evidence-based medicine.⁵ ⁶ The main outline of this thesis is to investigate the effects of antenatal and postnatal systemic and inhaled glucocorticoids to guide future research and current guidelines in tailoring the
known evidence towards “personalized” evidence based medicine assessing the benefit to risk ratio of these treatments in the individual patient.

2 Glucocorticoids: molecular facts and knowledge

Natural glucocorticoid hormones are produced by the fetal adrenal cortex and regulate intrauterine homeostasis and the maturation of organ systems in order to prepare the fetus for extrauterine life. Synthetic glucocorticoids suppress inflammation in a wide variety of diseases, and therefore are being used in practically every field of medicine, often being the most effective therapy available in diseases such as asthma, immunological and dermatological diseases, cancer etc. Natural and synthetic glucocorticoids contain a basic molecular structure necessary for its function (Figure 1), but the chemical modification of the basic molecule is responsible for the subtypes of glucocorticoids, such as dexamethasone, hydrocortisone etc. (Figure 2). These subtypes of drugs differ in glucocorticoid activity, bioavailability and pharmacokinetics (Table 1).

![Figure 1 Basic molecular structure glucocorticoid](image)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Approximate equivalent dose (mg)</th>
<th>Relative anti-inflammatory activity</th>
<th>Relative mineralocorticoid activity</th>
<th>Duration of actions (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>8-12</td>
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<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>0</td>
<td>36-72</td>
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<tr>
<td>Betamethasone</td>
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<td>30</td>
<td>0</td>
<td>36-72</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.8</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0.5</td>
<td>12-36</td>
</tr>
</tbody>
</table>

Adapted from: Schimmer BP, Parker KL: Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones; Chapter 59 Pharmacological basis of therapeutics: 11th ed Brunton LL et al. (eds.) 2006 McGraw Hill, New York, NY.
Very low birth weight infants are described to have transient adrenocortical insufficiency and those who have a low or suboptimal serum cortisol, the natural form of glucocorticoid might have a higher risk of developing BPD.\textsuperscript{11} Another important natural pathophysiological mechanism to keep in mind when judging known literature on the use of glucocorticoids in newborns is the presence (or absence) of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2). Studies in animals show that this enzyme is in large amounts present in the placenta and causes lower fetal than maternal glucocorticoid levels.\textsuperscript{12} It has been shown that this enzyme has a high expression in the fetal and neonatal brain, gut and kidney tissue and none in lung tissue.\textsuperscript{13} Even more important is the fact that only glucocorticoids such as (methyl)-prednisolone and hydrocortisone are substrates for inactivation by this enzyme, whereas dexamethasone and betamethasone are not inhibited.\textsuperscript{14}
3 Bronchopulmonary dysplasia as a health burden

The first description of BPD by Northway et al. in 1967 was one of severe lung injury in relatively mature preterm infants, who were ventilated with high pressures and high concentrations of oxygen, before the advent of surfactant therapy.\textsuperscript{15} This so called “classical” BPD is characterized by profound lung parenchymal inflammation, fibrosis and muscle hypertrophy and diffuse airway damage.\textsuperscript{16}

Both the etiology and clinical picture of BPD have changed over the last decades. After the introduction of prenatal steroids and postnatal surfactant, the “classical” form of BPD is infrequently seen in infants exceeding a birth weight of more than 1200 grams and 30 weeks of gestational age.\textsuperscript{17,18} Despite these advances in neonatal care the prevalence of BPD has changed little over the last decades due to the improved survival rate of ever more very preterm infants. Treatment of the very young has led to a new pattern of lung injury.\textsuperscript{1} This so called “new” BPD is mainly seen in very preterm infants with gestational ages less than 30 weeks. It is characterized by an arrest in lung development with fewer and larger alveoli, and less striking fibrosis and inflammation.\textsuperscript{19,20} Due to the recognition of this new entity, the international criteria for BPD have been changed from 28 days postnatal age to 36 weeks postmenstrual age.\textsuperscript{21} Cohort studies showed that the latter timing of diagnosis determined the long term pulmonary and neurological outcome superior to the old definition.\textsuperscript{22}

BPD is characterized by extended respiratory support, a compromised lung function during a prolonged primary hospitalization for several months and recurrent respiratory infections during the first years of life, as well as long-term pulmonary morbidity into adolescence.\textsuperscript{23-26} Furthermore, patients with established BPD are at high risk of cerebral palsy and developmental delay as BPD has repeatedly been shown to be an independent risk factor for adverse neurodevelopmental outcome.\textsuperscript{22,27-29}

BPD is considered a multifactorial disease, where besides genetic susceptibility, intrauterine growth restriction, nutritional deficits, direct mechanical injury caused by artificial ventilation, oxygen toxicity and pulmonary inflammation has been identified as an important cause in the development of BPD, explaining the rationale of using antenatal and postnatal glucocorticoids (Figure 3).\textsuperscript{17,18,30,31}
4 Evidence on antenatal glucocorticoid therapy

In an attempt to postpone preterm birth, Liggins et al. by accident demonstrated that antenatal glucocorticoid therapy reduced the incidence of respiratory distress syndrome (RDS) and mortality in their offspring when administered to women at risk for preterm delivery.\(^{32,33}\) Since that landmark publication, numerous placebo controlled RCTs summarized in the Cochrane review by Roberts et al. confirmed these findings, including lower requirements for surfactant therapy, lower concentrations of supplemental oxygen, decreased need for prolonged mechanical ventilation, a lower incidence of intraventricular hemorrhage and necrotizing enterocolitis.\(^{34}\) However, the Cochrane review does not provide answers at what gestational age these effects start to appear.

The American College of Obstetricians and Gynaecologists (ACOG), Royal College of Medicine, and other major organizations have recommended antenatal
glucocorticoid treatment for women at risk for preterm delivery prior to 34 weeks of gestation, regardless of gestational age.\textsuperscript{35-38} Although the positive effects of antenatal glucocorticoids administered to women at imminent birth is internationally and unanimously embraced, there is growing evidence that repeated courses of antenatal glucocorticoids might have adverse long-term sequelae in terms of growth and neurodevelopmental outcome of the preterm infant.\textsuperscript{37,39} Therefore, it is of the utmost importance to confirm the efficacy of antenatal glucocorticoids in the subgroup of patients born at extremely preterm gestational age, because these infants have the highest chance of receiving multiple courses when the delivery is postponed.

5 Evidence on postnatal glucocorticoid therapy

Pulmonary inflammation plays a central, modulating role in the pathogenesis of BPD and glucocorticoids have a strong anti-inflammatory effect, making them an ideal candidate to attenuate the inflammatory response associated with BPD: the rationale of glucocorticoids seems justified. However, after 40 years of research, glucocorticoids for the prevention and treatment of BPD in preterm infants still is one of the most controversial and ongoing hot topics in neonatology. In the mid 1990s randomized controlled trials (RCTs) clearly showed that systemic glucocorticoids, mainly dexamethasone, significantly reduced the incidence of BPD and the combined outcome BPD and death, in preterm infants at risk, independent of the time of postnatal administration.\textsuperscript{40,41} This led to the belief that glucocorticoids could be the “magic bullet” in the treatment of preterm infants at high risk of BPD. As a consequence, 25-50% of all extreme preterm infants were treated with this medication at the end of the 1990s.\textsuperscript{42,43}

However, after the first reports on long-term neurodevelopmental outcome were published the view of glucocorticoids changed into a stigma of “misguided rockets” for these trials showed an association with increased risk of abnormal neurological development.\textsuperscript{44-47}

RCTs investigating postnatal glucocorticoids, mainly dexamethasone were summarized in several reviews. These reviews divided the therapy according to the timing of administration, being early (<96 hr), moderately early (7-14 days) or late (>3 weeks) onset.\textsuperscript{48-52} All these reviews showed a significant reduction in the combined outcome mortality and BPD at 28 days postnatal age and 36 weeks PMA in the group of patients receiving systemic glucocorticoids compared to placebo, regardless of the timing of administration. Furthermore, the treated infants could be extubated earlier,
however at the costs of short-term transient adverse effects, such hyperglycemia, gastrointestinal bleeding, perforation and hypertension. The meta-analysis of trials investigating glucocorticoid therapy at an early onset showed a significant increase in adverse long term neurological development, such as cerebral palsy, neurological exams and developmental delay.\textsuperscript{52} However, the reviews on moderately early and late administration (> 7th day of life) did not show any difference between the treated patients and the placebo group.\textsuperscript{49-51}

In response to these reports, the American Academy of Pediatrics, the Canadian Pediatric Society and the European Association of Perinatal Medicine concluded that routine use of systemic dexamethasone in the treatment of BPD could no longer be recommended until further research has established the optimal type, dose and timing of glucocorticoid therapy.\textsuperscript{55,56}

The international neonatal community has discarded the use of early postnatal glucocorticoids completely for the above reasons and therefore was not a subject for this thesis. Regarding the use of moderately early or late postnatal systemic glucocorticoids, the clinicians face a dilemma in those patients at high risk of BPD, since BPD is associated with an increased risk of adverse neurological outcome itself. A systematic review using meta-regression showed that the adverse effects of moderately early or late administrated postnatal glucocorticoids on long term neurodevelopmental outcome might be modified by the BPD risk.\textsuperscript{57} In line with the current opinion of postnatal glucocorticoids being “misguided rockets”, clinicians postpone its administration until the 3-4th week of postnatal life and lowering the dosage schedule without knowing the effect of this policy change on the benefit to risk ratio.

The known reviews stacked information from trials with tremendous clinical heterogeneity in their inclusion criteria, number of patients included, dose and duration of therapy, route of administration, and timing of therapy onset. Furthermore, these reviews are flawed due to missing patient characteristics and outcome parameters and are possibly biased due to the unrestrained allowance of late ‘rescue’ glucocorticoid therapy in the placebo group. Using this clinical heterogeneity by dividing the different RCTs into subgroups according to the used cumulative dexamethasone dose and percentage of open label glucocorticoids prescribed in the placebo group, the effect modification of these variables can be determined.
6 Evidence on alternative administration glucocorticoid therapy

The Cochrane review pooling the results of 5 studies investigating early postnatal administration of inhaled glucocorticoids in ventilated preterm infants showed that it did not prevent BPD at 36 weeks PMA or mortality. More patients who had received placebo eventually received systemic glucocorticoids compared to treated infants, although this difference did not reach significance. The meta-analysis in the Cochrane review found that inhaled glucocorticoids have no advantages over systemic administration in mortality, duration of oxygen therapy, or the incidences of BPD. Meta-analyses of the systematic review performed in 2000 provide little evidence of long term benefit of inhaled glucocorticoids for infants with established BPD. The four included RCTs randomized preterm infants who were dependent upon mechanical ventilation after 14 days of life. They showed that patients who received inhaled glucocorticoids were more likely to be successfully extubated than the controls. Data were insufficient to reach any conclusion on the effectiveness of inhaled glucocorticoid therapy on the incidence and severity of BPD. Since the last update of this review was performed in 2000 renewal was necessary to establish the most current evidence on this topic.

7 Evidence on alternative glucocorticoids

Based on the above described concern on the long term neurodevelopmental outcomes administering dexamethasone, the use of alternative anti-inflammatory glucocorticoids, such as hydrocortisone have been suggested. Animal studies have suggested that, in contrast to dexamethasone, hydrocortisone has no detrimental effect on the brain. Retrospective cohort studies have suggested that hydrocortisone treatment is equally effective in reducing death or BPD compared with dexamethasone treated infants without causing an increased risk of adverse neurological outcome. To date, eight RCTs investigated a low hydrocortisone dose started within < 72 hours after birth (early treatment onset). Meta-analysis of these trials failed to show a clear reduction in the incidence of death or BPD. Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae. No placebo controlled randomized trials have investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.
8 Risk assessment of BPD at an early postnatal age

Taking into account the results of the aforementioned systematic review showing that the adverse effects of moderately early or late administrated postnatal glucocorticoids on long term neurodevelopmental outcome might be modified by the BPD risk, underlines the importance of predicting BPD at an early age.\textsuperscript{57} Extending the scope of BPD prevention outside the glucocorticoid debate, many interventions possibly contributing to the prevention of BPD have been investigated in RCTs, yet with disappointing results.\textsuperscript{66,67} One of the possible explanations for these disappointing trial results may be our current poor ability to predict which infant will experience this morbidity at an early stage in life. Clinicians and researchers fail to identify those patients who will benefit most from interventions aimed at reducing the risk of BPD and even more important, fail to prevent exposure to unnecessary potential harmful therapies, for example early glucocorticoid use. Although recently several models have been developed to predict BPD, appropriate quantitative validation of these models has not been conducted and none of these models has been implemented in clinical care or in recently performed randomized controlled trials preventing or treating BPD.

At present, the clinician is left with uncertainty and bias: which of his preterm patients will develop BPD and what is the true effectiveness-harm ratio of an early intervention with steroids?

9 Aim of this thesis

The aim of this thesis is to answer the following questions:
1. Is the established overall effect of antenatal glucocorticoids on neonatal mortality and morbidity as effective in the subgroup of extremely preterm born infants (i.e. born with a gestational age < 26 weeks)?
2. Will lowering the dose of postnatal glucocorticoids change the risk to benefit ratio known from randomized trials in reducing the risk of late neurodevelopmental sequelae without reducing the beneficial effects on pulmonary outcomes?
3. Does the use of open label glucocorticoids outside the study protocol change the observed effects on short-term and long-term pulmonary effects, short term adverse effects, and subsequent neurodevelopmental sequelae?
4. What is the evidence regarding the use of inhalation glucocorticoids as an alternative therapy for systemic glucocorticoids administered at a moderately early onset?
5. What is the accuracy of the recently published clinical prediction models for BPD?
10 Outline of this thesis

Although it is generally accepted that antenatal corticosteroids reduce neonatal complications after preterm labor, it is unclear at what gestational age this effect starts to occur. Chapter 2 describes a systematic review and consequently meta-analysis determining the short- and medium long-term effects of antenatal glucocorticoids on fetal and neonatal mortality and pulmonary and neurodevelopmental sequelae using information from the available RCTs of women at risk of preterm birth prior to 26 weeks treated with antenatal glucocorticoids for accelerating fetal lung maturation.

Systemic postnatal dexamethasone treatment given after the first week of life reduces the risk of BPD in preterm infants but also may be associated with increased risk of neurodevelopmental impairment. Because it is not known whether these effects are modulated by the cumulative dexamethasone dose, we systematically reviewed the available randomized evidence on the effects of lower versus higher cumulative dexamethasone doses, in terms of death, pulmonary morbidity, and neurodevelopmental outcomes, in preterm infants. In Chapter 3 the results of the systematic review of the trials comparing higher- versus lower-dosage dexamethasone regimens head to head in ventilated preterm infants are summarized.

Chapter 4 shows the RCTs comparing dexamethasone with placebo in ventilated preterm infants after 7 days, analyzed by using subgroup meta-analysis and meta-regression. Subgroups were created by assigning each included study to 1 of 3 subgroups on the basis of the cumulative dexamethasone dose used in the intervention arm. Weighted meta-regression analysis was performed to explore a dosage/effect size relation by plotting the individual risk difference of the separate trials against the respective cumulative dose and duration of therapy of that study as the independent variable for each outcome parameter.

Open label glucocorticoids (OLG) outside the protocol are often used in the trials investigating postnatal dexamethasone treatment in ventilated preterm infants making interpretation of these results difficult. To determine if OLG use modulates the dexamethasone treatment effect on mortality, BPD and neurodevelopmental outcome, Chapter 5 outlines the results of meta-regression analysis and subgroup meta-analysis of the RCTs comparing dexamethasone with placebo in ventilated preterm infants older than 7 days according to the percentage of OLG use in the placebo group.
In Chapter 6 a systematic review of placebo controlled RCTs is presented comparing the effectiveness of inhaled glucocorticoids versus placebo administered after the first week of life in preterm infants on the incidence of death or BPD at 36 weeks PMA and adverse effect during hospitalization and long-term follow-up. The balance between beneficial and adverse effects of glucocorticoids may be more favorable when using the inhalation route, because, ideally, inhaled glucocorticoids should demonstrate high pulmonary deposition, in addition to a low systemic bioavailability and rapid systemic clearance.

Taking the controversy of postnatal dexamethasone into account, hydrocortisone has been suggested as an alternative glucocorticoid therapy. However, so far no randomized controlled trial has investigated its safety and efficacy when administered after the first week of life. In Chapter 7 we describe the study protocol of a multicenter randomized placebo controlled trial, currently recruiting participants in the Netherlands and Belgium. The trial (the SToP-BPD trial) will evaluate the safety and efficacy of postnatal hydrocortisone administration at a moderately early onset, i.e. after 7 postnatal days.

Identifying risk factors and development of clinical prediction models for BPD could possibly provide prognostic information, identifying infants likely to benefit from preventive strategies, and stratifying infants for clinical trial enrollment. Although several models have recently been developed to predict the risk of BPD in individual patients, no quantitative external validation of these models has been conducted. In Chapter 8 a systematic review is presented identifying all currently existing clinical prediction models for BPD in the international literature, subsequently validating these models in a large external cohort of preterm infants to determine which model has the highest accuracy in predicting BPD in very low birth weight infants.

The thesis continues with a general discussion in Chapter 9 findings are put in context, and implications for practice and results are formulated. Finally, this thesis concludes with a summary in English and in Dutch.
11 References


General introduction and outline


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