Bronchopulmonary dysplasia and perinatal glucocorticoids in preterm infants: changing practice based on evidence
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Chapter 9

General Discussion
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This thesis investigates the evidence of antenatal and postnatal glucocorticoid treatment in preterm infants at risk for developing BPD by performing subgroup meta-analyses and metaregression. These analyses were done using patients’ characteristics and interventions of the different published RCTs as the independent variables and the various outcome estimates as the dependent variables. Furthermore, the published prediction models on BPD were reviewed and validated for their accuracy in identifying those patients with high risk of developing BPD. It will guide future research and current guidelines in tailoring the known evidence towards “personalized” medicine benefiting the individual patient.

Table: Summarizing the main findings

- Although cohort studies seem to suggest its benefits on neonatal outcomes, the recommended administration of antenatal glucocorticoids by all the web-based practice guidelines to women at risk of preterm birth < 26 weeks gestation is not supported by randomized evidence captured in subgroup meta-analyses of the published RCTs.
- The current practice of lowering the cumulative dose of dexamethasone does not result in a better benefit to risk ratio, as it diminishes the positive effects on the incidence of the combined outcome death or BPD without lowering the risk of adverse neurodevelopmental sequelae.
- Subgroup meta-analyses of the placebo controlled postnatal dexamethasone RCTs confirms that the optimal timing of therapy onset is between 7 and 14 days of postnatal life.
- Open-label use of glucocorticoids in the published RCTs investigating postnatal dexamethasone administration modifies the effects on different outcome estimates, but not on the combined outcome death or BPD.
- Dexamethasone administered in the second week of life (moderately early) significantly reduces mortality at hospital discharge in those trials with a low use of open label glucocorticoids in the placebo group.
- There is no evidence to support or refute the use of the alternative method of glucocorticoid administration (i.e. by inhalation) or the use of alternative drugs, namely hydrocortisone, to prevent the development of BPD in high risk preterm infants.
- Current research is lacking an internationally accepted, validated instrument to critically appraise known prognostic models in literature.
- Current clinical prediction models for BPD are generally not externally validated and not internationally adopted in research and clinical practice. External validation shows that existing clinical prediction rules are moderate predictors for BPD.
Chapter 1 summarizes the basic molecular facts on glucocorticoids, current insights on the pathophysiology and health burden of BPD. We outline that due to improved survival this entity has changed over the last decades, from a disease caused by high pressure ventilation and oxygen toxicity into an entity with a state of developmental arrest, leading to new definitions and new challenges for clinical practice and research.

The current evidence on antenatal and postnatal glucocorticoids is summarized in this chapter. Unlike antenatal glucocorticoids, having an established role in the treatment of women at imminent preterm birth in the international community, the public view on the use of postnatal glucocorticoid therapy drastically changed over the past two decades. The publication of the Cochrane reviews on the matters of using postnatal glucocorticoid therapy changed the public opinion from such therapy being “magic bullets” to “misguided rockets”\(^1,2\). Although the systematic reviews of the Cochrane Library divides the postnatal glucocorticoid trials on timing of therapy onset, within these timeframes the results of the individual postnatal glucocorticoid trials are pooled together and conclusions are drawn with typical risk ratios\(^3-7\). The large differences in trial design, interventions, and patient characteristics lead to one of the main questions in this thesis: does the heterogeneity in the characteristics of the pooled RCTs modify the outcome estimates and what is the evidence concerning alternatives in mode of administration or used drugs to prevent the development of BPD in high risk patients.

Exploring the evidence on benefits for extremely preterm infants who are treated with antenatal glucocorticoids, we show in Chapter 2 that there is no evidence to support or refute the recommendation of administrating antenatal glucocorticoids to women at risk of preterm birth < 26 weeks gestation. This is in contrast with observational cohort studies concluding that administration of antenatal glucocorticoids to infants born at extremely low gestational age is independently associated with reduction of mortality and respiratory distress syndrome\(^8-11\). The limitations of this review are that the included trials are small, are heterogeneous in study design and patient characteristics and do not report all outcome parameters. Unfortunately, only three eligible trials for this review collect data on the number of infants diagnosed with BPD. Moreover, those three studies diagnosed patients with BPD at 28 days postnatal age and not at 36 weeks postmenstrual age according to current international criteria\(^12,13\). Since glucocorticoids are known to cause a decrease in growth and the “new” BPD is characterized by an arrest of development, there is concern that the increasing use of antenatal glucocorticoids at these extremely low gestational age might eventually lead to an increase incidence of BPD\(^14,15\).
Even after 30 years of research, postnatal glucocorticoids remain a subject of hot-tempered and emotional discussions among clinicians and researchers. The current Cochrane reviews of the RCTs exploring the effect of postnatal glucocorticoids clearly show that systemic glucocorticoids, dexamethasone being the main studied glucocorticoid, reduce the incidence of BPD and the combined outcome BPD and death, in preterm infants at risk. This effect is independent of the time of postnatal administration, but there is also a reported association with an increased risk of abnormal neurological development at the early and delayed treatment onset.\textsuperscript{6,7} In response to these reports, the American Academy of Pediatrics, the Canadian Pediatric Society and the European Association of Perinatal Medicine conclude in 2002, that routine use of systemic glucocorticoids can no longer be recommended until further research has established the optimal type, dose and timing of glucocorticoid therapy.\textsuperscript{16,17} This policy is recently reconfirmed, stating that in the absence of RCT results showing improved short- and long term outcomes, therapy with high-dose dexamethasone cannot be recommended.\textsuperscript{18}

Nowadays, the use of prophylactic or early onset of postnatal glucocorticoids therapy (i.e. <96 hrs postnatal age) is no longer used in neonatology. However, the clinician still faces a dilemma taking care of preterm infants who are ventilator dependent after the first week of life. Since the previously mentioned policy statements, overall postnatal glucocorticoid use has fallen, but relatively high use continues among the most immature infants.\textsuperscript{19-22} Alternative to totally discarding the use of postnatal glucocorticoids, but in an attempt to minimize the risk for adverse effects, clinicians have drastically delayed initiating this therapy, only considering starting treatment in those infants that remain ventilator dependent after 3 - 4 weeks PNA, lowered the cumulative doses of glucocorticoids and shorter duration of therapy without any evidence on the benefit to risk ratio.\textsuperscript{19,20,23,24}

To evaluate this benefit to risk ratio Chapter 3 describes the systematic review of the RCTs directly comparing a higher versus a lower dexamethasone regimen after 7 days PNA in ventilated preterm infants. The meta-analyses of 6 studies suggest that a reduction in dexamethasone dose might increase the incidence of BPD without decreasing the risk for adverse neurodevelopmental outcome. However, the validity of this observation is compromised by the small sample of randomized children, heterogeneity of the study populations and designs, the use of late rescue glucocorticoids and lack of long term neurodevelopmental data in some studies.

To further explore the relation between the cumulative dose used in RCTs comparing dexamethasone with placebo in ventilated preterm infants older than 7 days and the different effect estimates, a systematic review is performed using subgroup meta-analyses and meta-regression in Chapter 4. Trials with a moderately
early (7 – 14 days) or delayed (> 3 weeks) postnatal treatment onset are analyzed separately. This review shows that higher dexamethasone doses reduce the relative risk for the combined outcome mortality or BPD, with the largest effect in trials using a cumulative dose above 4 mg/kg. Furthermore, no effect is found of doses on the risk of neurodevelopmental sequelae in the delayed treatment studies. Even more striking is the finding that in the moderately early treatment studies, the risk of neurodevelopmental sequelae is decreased for each incremental mg/kg cumulative dexamethasone dose. Weighing the beneficial pulmonary benefits to the neurodevelopmental sequelae risk ratio leads to the assumption that the optimal timing of administrating postnatal glucocorticoids is in the moderately early timeframe and that a higher cumulative dose favours prevention of BPD.

A recently published large cohort confirms the international decrease in postnatal glucocorticoid use, and underlines the results of this thesis by showing that this decline is associated with increased BPD rates among infants < 29 weeks’ gestation, keeping the urge for future research urgent and alive.

After the beneficial effects of dexamethasone became apparent in the 1990s, all dexamethasone trials allowed the use of open label glucocorticoids (OLG) in both the intervention and the placebo arm, and a considerable number of patients received OLG in actual fact. This can be an important effect modifier of dexamethasone treatment effects. This is confirmed by the systematic review described in Chapter 5. We show that 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.

In Chapter 6 the effect of an alternative mode of glucocorticoids administration at moderately early onset is explored, namely by inhalation. This method of administration might give a better balance of beneficial versus adverse effects, because, ideally and in theory, inhaled glucocorticoids demonstrate a high pulmonary deposition resulting in less pulmonary inflammation, with in addition less adverse effects due to a low systemic bioavailability and rapid systemic clearance.

Although we have identified 8 RCTs initiating therapy ≥ 7th day of life, randomising 232 preterm infants, there is a paucity of data on short and long term adverse effects. Furthermore, the included trials differ considerably in patient characteristics, inhalation therapy and outcome definitions. The sparse meta-analyses that can be performed showed that inhaled glucocorticoids do not reduce the separate or

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combined outcomes death or BPD, or have beneficial effects on short term respiratory outcomes such as failure to extubate, total duration of mechanical ventilation or oxygen dependency, although there is a trend to a reduced use of systemic glucocorticoids in favour of inhalation corticosteroids. Based on these results the use of inhalation glucocorticoids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time.

Given the uncertainties of the timing of onset, the cumulative dose used and which endpoint to prevent surrounding postnatal glucocorticoid use, the research community seeks new trials to be carried out. Chapter 7 outlines the study protocol of a multicenter RCT investigating an alternative glucocorticoid drug after the first week of life, namely hydrocortisone (the SToP-BPD trial). So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants. Eight RCTs including 880 infants investigated a low hydrocortisone dose started within < 72 hours after birth (early treatment). Meta-analysis of these trials failed to show a clear reduction in the incidence of BPD or harmful effects. Several historical cohort studies and only one of the previous mentioned early treatment trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.

The proposed trial, funded by the Dutch MRC (ZonMW), will start recruiting patients in September 2011. It is a randomised double blind placebo controlled study in preterm infants, who are ventilator dependent at a postnatal age of 7 – 14 days and suspected with a diagnosis of developing BPD. Compared to the early RCTs using a low dosage regimen, the investigated regimen of hydrocortisone has a cumulative dose 72.5 mg/kg and will be administered during a 22 day tapering schedule. The expected inclusion of 400 patients (200 per group) in an inclusion period of three years has a power of 80% to detect an absolute risk reduction of 15% for the primary outcome death or BPD in the treated group, which is considered clinically relevant. At the end of 2014 this trial will determine the role of postnatal hydrocortisone administration at a moderately early onset in ventilator dependent preterm infants.

Many interventions for BPD have been tested in randomized controlled trials, but only a few have resulted in significant treatment effects. One of the possible explanation for these disappointing results may be the general poor ability to predict which infant will experience this morbidity at an early stage in life and therefore failing to identify patients who will benefit most from interventions that reduce the risk of BPD.

Doyle et al. published a systematic review in 2005 showing that the adverse effects of postnatal glucocorticoids on long term neurodevelopmental outcome might be
modified by the a priori BPD risk. Using metaregression they showed that every 10% increase in BPD risk reduced the risk difference of death or cerebral palsy by 9.1%, meaning that in infants with a high risk of BPD, the use of glucocorticoids reduces the risk of long term neurodevelopmental sequelae. This emphasizes the importance of identifying those infants with the highest risk of developing BPD at an early stage using a clinical prediction model.

The aim of the systematic review described in Chapter 8 was to identify all existing clinical prediction models for BPD in international literature, and subsequently validate these models using a large external cohort of preterm infants in order to determine which model has the highest accuracy in predicting BPD in very low birth weight infants. External validation showed that existing clinical prediction rules are moderate predictors for BPD and that the best models used low birth weight, low Apgar scores, and respiratory distress as important independent predictors. Although Chapter 8 presents a systematic review in line with the previous chapters, the aim of this particular study exceeds the dilemmas concerning the use of glucocorticoids in perinatology, since a well validated and implemented prediction model could be applied to all known and new therapy strategies for the prevention of BPD in high risk preterm infants.

Conclusions

From this thesis, several conclusions can be drawn. First, although cohort studies confirm its benefits on neonatal outcomes, the recommended administration of antenatal glucocorticoids by all the web-based practice guidelines to women at risk of preterm birth < 26 weeks gestation is not supported by evidence based medicine using subgroup meta-analyses of the published RCTs.

Second, the systematic reviews on postnatal systemic glucocorticoids show that the current practice of lowering the cumulative dose of dexamethasone does not result in a better benefit to risk ratio, but diminishes the positive effects on the incidence of the combined outcome death or BPD without lowering the adverse neurodevelopmental sequelae. Furthermore, it confirms that the optimal timing of therapy onset is between 7 and 14 days of postnatal life and that open-label use of glucocorticoids modifies the effects on different outcome estimates, but not on the combined outcome death or BPD.

Third, we show that there is no evidence to support or refute the use of the alternative method of administration (i.e. inhalation glucocorticoids) or alternative
drugs, namely hydrocortisone to prevent the development of BPD in high risk preterm infants.

Finally and probably most important for future research, we demonstrate that the clinical prediction models for BPD are generally not externally validated and not internationally adopted in research and clinical practice. The current clinical prediction models for BPD appeared to be moderate predictors for BPD after external validation and can, therefore, not be used yet for identifying those infants with the highest risk of developing BPD at an early age.

Implications for clinical practice

Although the conclusions of Chapter 2 regarding the use of antenatal glucocorticoids given prior to 26 weeks gestation do not support the recommendations of the available practice guidelines, the use of antenatal glucocorticoids in daily practice at this extremely low gestational age should not be discarded, taking the evidence based on observational cohort studies into account.

The conclusions of Chapter 3 and 4 have two important implications for daily practice. First, clinicians should not delay initiation of glucocorticoid treatment to infants who remain ventilator dependent until 3 - 4 weeks of PNA, but consider therapy in high risk patients at an earlier stage, namely between 7 and 14 days, since the available evidence showed that this onset of therapy has a better benefit to risk ratio. Second, although we show that a reduction in cumulative dexamethasone dose might increase the incidence of BPD without decreasing the risk for adverse neurodevelopmental outcome, this suggestion should be confirmed by a large multicenter trial before a definitive conclusion can be drawn and implemented.

Alternative modes of administration (e.g. inhalation) as well alternative glucocorticoid drug such as hydrocortisone should not be used outside the realm of a well designed clinical trial, as discussed in Chapter 6 and 7.

Implications for research

The numbers of implications for future research directly follows the numbers of conclusions drawn in this thesis. First, regarding the lack of evidence for administrating antenatal glucocorticoids to women at imminent birth before 26 weeks of gestation, the results of this review should be reanalyzed in an “individual patient data” (IPD) meta-analysis, allowing for more appropriate and flexible
analyses of both subgroups and outcomes. If the uncertainty still exists after such an IPD analysis, the international obstetric and neonatal community will have to decide whether a large placebo controlled RCT of this specific subgroup of patients is needed to confirm or refute its findings.

Second, a large multicenter study, comparing a higher cumulative dexamethasone dose ($\geq 4 \text{ mg/kg}$) with a lower dose ($\leq 2 \text{ mg/kg}$) using a comparable duration of treatment at moderately early onset, is urgently needed. The clinical community should decide if there is still room for a placebo arm in such a trial, or that hydrocortisone be used as comparator. Such a trial should be adequately powered to detect small but clinically relevant treatment effects and outcome measurements should be collected in an uniform, internationally recognized matter, being BPD at 36 weeks PMA with degree of severity and the oxygen reduction test as described by Walsh et al., mortality at 36 weeks PMA and at discharge, and a complete assessment of major neurosensory impairment using predefined definitions, diagnostic tests and time points. Short term benefits (i.e. time of extubation, duration of ventilation) and adverse effects (i.e. hypertension, infection, and hyperglycemia) should be reported as secondary outcomes. Dilution of treatment effect due to the use of glucocorticoids outside the study protocol, or crossing over between trial arms should be avoided as much as possible. Data should be analyzed on an intention-to-treat basis, per-protocol, and in an adherers-only analysis in order to accurately estimate the true effect of dexamethasone treatment on the clinical outcome parameters, as described in Chapter 5.

We would like to emphasize that the prevention of BPD, although desirable looking at the long-term pulmonary outcomes and consequently health burden, it is not the ultimate endpoint of interest in perinatal care of preterm infants. Taking into account that the diagnosis of BPD is independently associated with adverse neurodevelopmental sequelae, the debate is still ongoing on BPD being a direct cause of adverse long term neurological outcome or an indirect sign of increased inflammatory status leading to that adverse outcome. Therefore, intervention trials should especially be focused on collecting and preferably be powered to detect the differences on these long term outcomes.

Third, future research should focus on the optimal aerosol delivery system for administration of inhaled glucocorticoids in ventilated and non-ventilated infants, which is quite a challenge since preterm infants have low tidal volumes and functional residual capacity, high respiratory rates, a shortened particle residence time and in general smaller airway diameters. A large RCT administrating inhaled glucocorticoids at an early onset is currently recruiting patients, whereas
the SToP-BPD trial will provide data on the use of hydrocortisone at a moderately early onset in the near future.\(^{30}\)

Finally, and most urgently needed is a clinical prediction model with accurate discriminating and calibration performances for the outcome death or BPD to allow the clinician and researcher to predict high risk patients with the diagnosis “new BPD” at an early age of life. International collaboration, Delphi-methodology and consensus processes are keys in the decision on what the model should contain, and to reach a prediction model that is to be used in research and practice for the years to come.

**Summary**

Although RCTs investigating antenatal and postnatal use of glucocorticoids are generally considered homogeneous and pooled in systematic reviews, there are in fact tremendous differences in trial design, investigated intervention and patient characteristics between these trials. By analyzing these trials in subdividing the trials according to these differences in subgroups and meta-regression, we explored the effect modification caused by this clinical heterogeneity.

First, we explored in **Chapter 2** whether the beneficial effects of antenatal glucocorticoids are dependent on the gestational age at which they are given and found that those RCTs including infants with lower gestational age showed no effect on neonatal outcomes, whereas those trials including larger infants had a definite beneficial effect on both pulmonary and other short outcomes.

The next question was what the effect of lowering the used postnatal glucocorticoid therapy in dose and duration, would be as shown by the evidence from RCTs. We found that lowering the cumulative dose or duration of postnatal glucocorticoid therapy on pulmonary effects might lead to regression to the mean, diminishing the beneficial effects on the outcome BPD, without decreasing the possible negative adverse effects on neurodevelopmental outcome. These results were shown in **Chapter 3** including RCTs directly comparing a higher versus a lower dosage regimen, as well as in **Chapter 4** comparing glucocorticoid therapy analyzed by subgroup analyses and meta-regression.

Since these previous findings might be flawed due to the high rate of open label glucocorticoid therapy in the placebo group, we explored and found in **Chapter 5** that this trial characteristic indeed modified the outcome estimates in the known systematic reviews. However, when adjusted for open label 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.

Next, we explored the evidence on inhalation glucocorticoids in Chapter 6 as an alternative therapy for systematic administration of postnatal glucocorticoids after the 7th day of life. Due to paucity of outcome data no conclusion could be drawn in the efficacy of this therapy.

For another alternative type of glucocorticoid drug, hydrocortisone, we present a study protocol in Chapter 7 in order to establish the role of this choice of drug for the prevention of BPD in a moderately early timeframe.

In order to predict which infant has the highest probability of developing BPD and therefore possible candidates for high risk intervention trials such as future glucocorticoid trials, we finally sought all available clinical prediction models known in literature in Chapter 8 and determined their accuracy in predicting BPD by validation using a large external cohort. Of the 24 published models, we could determine the accuracy for 19 of them, showing that the current known models are moderate prediction for developing BPD and therefore we need to improve, validate and implement a new clinical prediction model.
References

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