Benefits and Hazards of Postnatal Glucocorticoid Exposure in Preterm Infants

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Disclosures

- Dr. Watterberg has no financial or other conflicts of interest to disclose
- She will be discussing studies of glucocorticoids in preterm infants
Overview of Presentation

- History – how did we get here?
- Where is here? – current information
  - Dexamethasone for BPD
  - Hydrocortisone for BPD
  - Hydrocortisone for early hypotension
- Reasons to worry
  - Immediate side effects
  - Growth and development
  - Very long term outcomes
The dexamethasone story

- Abstracts: early anecdotes
  - (‘78, ‘80, ‘81)
- ‘hastened weaning from ventilator’
  - (Mammel, 6 infants; Lancet, 1983)
- ‘striking short-term improvement’
  - (Avery, 16 infants; Pediatrics, 1985)
- faster weaning from IMV and O₂
  - (Cummings, 36 infants; NEJM 1989)
“The long term effects are not clear . . . Potential complications of glucocorticoid treatment are well known [including] possibly long term neurodevelopmental compromise . . . The treatment cannot be recommended without further study of patient selection, dosage schedules, short and long-term side effects, and the mechanisms of its actions.”

--Mammel, Lancet 1983
And so the therapy was adopted

- High dose – 0.5mg/kg/day
  (Prenatal: 12mg/day to mothers \(\cong 0.15\)mg/kg)

- Long-term – 42 day tapering course
  (Prenatal: 2 days, ± weekly repeat)

- Started earlier and earlier in life, until...
Treatment in the First Week

- Rx works  (Yeh, Pediatrics 100:4E3, 1997)
- Or it doesn’t  (Sinkin, Pediatrics 105:542, 2000)
- Rx works, but dose ↓ for adverse effect  
  (Garland, Pediatrics, 104:91, 1999)
- Study stopped for lack of efficacy and/or safety concerns  
  (Vt-Ox, Pediatrics 108:741, 2001) 
  (NICHD, NEJM 344:95, 2001)
Dex – a few side effects

- Hyperglycemia
- Hypertension, cardiac hypertrophy
- Sepsis
- GI perforation
- Proteolysis, muscle wasting, osteopenia
- Adrenal suppression
- Growth failure
- *Neurodevelopmental impairment*
Dex & neurologic outcome

- Dex is a risk factor for MDI <70 & abnormal neurologic exam
  - Follow up of > 1100 ELBW infants, cohort study

- Dex is associated with ↑CP & neurologic impairment
  - Meta-analysis of >1000 patients in RCTs
  - Barrington KJ, BMC Pediatrics 1:1, 2001

- With that indictment of high-dose dex. . .
The pendulum swung...

Dex is good – the more the better!

All steroids are bad – no babies should get them!
Postnatal Steroids: AAP 2002

- ↓ BPD, ↓ extubation failure, no ↓ mortality
- Many short and long-term complications
- **Routine** use . . . is not recommended
- Outside the context of a randomized trial, use of *corticosteroids* should be limited to exceptional clinical circumstances
- Parents should be fully informed of risks
  - Pediatrics 2002;109:330
Exceptional clinical circumstances?

- Use declined:
  - NICHD 14 → 8%
  - Vt/Ox 18 → 10%
  - Canada 24 → 3%

(Walsh, Pediatr 2006; 118:e1328)

- But (Vt/Ox data)

  ◦ 1000 – 1250g BW 7% 4%
  ◦ 750 – 999g BW 18% 13%
  ◦ 500 – 749g BW 29% 22%
And there’s probably no free lunch

- ↑BPD incidence and/or severity with ↓PNS?
  - Population study, Israel: ↑BPD
    - Shinwell, Arch Dis Child 2007; 92:F30
  - Single center cohort: ↑vent dependence
    - Kobaly – Pediatrics 2008;121:73
  - Pediatrix multicenter data (77,520 babies <32 weeks EGA): ↑ BPD <29 weeks, ↑severe BPD for all
    - Yoder Pediatrics 2009; 124:673
Epoch 1: '97 – '99
Epoch 2: ‘00 – ’03
Epoch 3: ‘04 – ’06
P<0.001, ↓ dex & ↑ BPD

- Yoder, Pediatrics 2009; 124: 673
And neurodevelopmental outcomes may not have improved

- Victoria, Australia study of 3 epochs
  - All ELBW or extremely preterm (<28 weeks) infants
  - 1991–2; 1997; 2005

- For 2005 vs. 1997,
  - Steroid use decreased
  - BPD and hospital stay increased
  - “Rates of mortality, CP and major disability, and for death with CP or major disability were similar over time after adjustment for confounding variables.”

  - Cheong, Arch Dis Child Fetal Neonat 2013; 98:F32
BPD is also a risk factor for adverse neurodevelopment

- BPD: ↑ incidence of Bayley MDI & PDI <70, abnormal neurologic exam
  - (NICHD network, 1154 ELBW infants)

- Balancing the risk – RCT “meta-regression”
  - If the baseline risk for BPD in the study population was low (≤35%), dex ↑ risk of death/CP
  - If the risk was >50%, dex ↓ risk of death/CP
    - Doyle, Pediatrics 2005; 115:794

- Decreasing the dex dose might also help
Dexamethasone dosing

- Most earlier studies started with a dose of 0.5mg/kg/day
- Lower doses (0.15mg/kg/day tapered x 10d) not linked to adverse neurodevelopmental outcomes in follow up of 2 small studies
  - Early Rx (n = 144) – Stark, J Pediatr 2014; 164:34
  - Later (n = 58) – Doyle, Pediatrics 2007; 119:717
↑use of Dex based on follow up of

- 76 babies treated early (<24°)
  - NDI 56% vs. 53% placebo (62 babies seen)

- 29 babies treated at ~3 weeks
  - major disability 41% vs. 31% placebo
    (fairly balanced: ↓death (4 vs. 7 babies)
    ↑disability (12 vs. 8 babies))

- But there may be another alternative…
Steroids are not all the same

- Dexamethasone is
  - Synthetic
  - Contains preservative
  - Lacks mineralocorticoid activity
  - Suppresses endogenous cortisol synthesis
  - Has a far longer half life than hydrocortisone
  - Is many times more potent than cortisol
    - May be as much as 150x more powerful d/t amplifying effect of its prolonged half–life
Steroids are not all the same

- Hydrocortisone is
  - Identical to native cortisol
  - Can be obtained without preservative
  - Provides mineralocorticoid activity
  - May suppress HPA axis at high doses, but does not do so at lower doses
But first: at high doses, **all glucocorticoids impair growth**

- Not a side effect – an expected result
- Glucocorticoids promote “maturation”
With too much steroid

- Animal models: fetal/neonatal exposure to high dose steroids:
  - Decreased brain weight
  - Decreased organ weights
  - Decreased total body weight
- And in humans...
School–age outcomes after Dex Rx

- RCT of Dex, 0.5mg/kg/day tapered over 28 d
- 156 children seen at age 8
- Treated children were shorter, and had:
  - Smaller head circumference
  - Lower IQ
  - More clinically significant disabilities
- “substantial adverse effects on neuromotor and cognitive function at school age”

Steroid actions in the brain, or . . .

“why DEX may lead to worse neurologic outcomes while HC may not”

- The brain has 2 types of steroid receptors:
  - mineralocorticoid & glucocorticoid

- Both are in high density in the hippocampus – an area of the brain critical to learning and memory
Cortisol and dex in the brain

- Baby’s own cortisol:
  - Low stress, low [cortisol] – binds 1° to mineralocorticoid receptors
  - High stress, high [cortisol] – also binds to glucocorticoid receptors

- Dexamethasone:
  - Binds ONLY to glucocorticoid receptors
  - And suppresses cortisol production (producing a “chemical adrenalectomy”)
Dex and HC in the brain

- Cortisol deficiency (adrenalectomy) in adult animals leads to neuronal apoptosis (programmed cell death) in the hippocampus.
- Dexamethasone also leads to neuronal apoptosis in both adrenalectomized & control animals.
- Corticosterone (=cortisol in rats) protects animals from DEX-induced apoptosis.
Neuronal apoptosis in hippocampal cell culture, 4–5 day old rat pups

Crochmore, Mol Psychiatry 2005; 10:790
How might this apply to preterm infants?

- Preemies have ↓ hippocampal volume on MRI
  - Isaacs Pediatr Res 2001; 47:713

- Preemies Rx’d with dex have ↓ hippocampal volume vs. controls (small cohort studies)
  - Murphy, Pediatr 2001; 107:217
  - Parikh, Pediatr 2007; 119:265

- Preemis Rx’d with HC have no ↓ volume or ↑ lesions vs. untreated controls (large cohort study & small RCT)
  - Rademaker, J Pediatr 2007; 150:351
  - Parikh, J Pediatr 2013; 162:685
Steroids and the cerebellum

- Cohort study: 57 pts at UCSF; 115 at UBC
- Mean EGA 28 weeks
- Volumetric MRI when stable
  - 1\textsuperscript{st} at about 4 weeks postnatal age
  - 2\textsuperscript{nd} at 36 (UCSF) – 40 weeks (UBC)
- About 28 babies were treated with HC
- Unclear how many got HC but not dex
  - 11 at UCSF; perhaps 2 at UBC

  - Tam, Science Transl Med 2011; 3:105ra105
Tan study: Multivariable analysis
HC & the cerebellum: RCTs

- Parikh: HC at 3/kg/day tapered over 10 days
  - 23 HC, 21 placebo
  - Cerebellar volumes similar, p= 0.86
    - Parikh et al, J Pediatrics, 2013

- PROPHET study (early low-dose HC for BPD)
  - Babies on open-label HC at study start had significantly higher mortality (37% vs. 13%)
  - Babies randomized to HC did not
    - Watterberg et al, Pediatrics, 2004

- Beware of cohort studies of therapeutic interventions
Meta-analysis, 8 early HC studies

- “Postnatal hydrocortisone in the doses and regimens used in the reported trials has few beneficial or harmful effects and cannot be recommended for prevention of BPD.”
  - Doyle, Neonatology 2010; 98:111

- One study was from 1972
- Two were for early hypotension
- One investigated T3 to improve fluid reabsorption
- Only 4 treated for >7 days
- Only 4 aimed to treat/prevent BPD
HC: 4 RCTs of early Rx for BPD

- Intubated infants, <48° of age
- HC 1–2mg/kg/day tapered over 12–15d
  - Watterberg (n=40): ↑ survival w/o BPD
  - Watterberg (n=360): no significant benefit
  - Peltoniemi (n=51): 64% vs. 46% – NS
  - Bonsante (n=50): ↑ survival w/o BPD
Meta-analysis, adjusted odds ratio

- Peltoniemi
- Watterberg pilot
- Bonsante
- Watterberg multicenter
But...enrollment stopped in 3 trials

- Increased spontaneous GI perforations
  - Peltoniemi, Watterberg (2nd study)

- Likely an interaction with indomethacin in infants with higher cortisol concentrations
  - (median 50 vs. 15 μg/dl)
Outcomes at 18 – 22 months

- Meta-analysis (3 studies): no adverse effects
  - Peltoniemi, Neonatology 2009;95:240

- Multicenter trial (n=252):
  - No adverse effects on growth or development
  - Possible benefits:
    - Fewer babies had MDI <70 on Bayley II scales
    - More babies had achieved object permanence, an early measure of pre-frontal cortex development
  - Watterberg, Pediatrics 2007; 120: 40
After a gap of ~10 years: PREMILOC multicenter RCT

- Multicenter RCT in France
- 523 infants 24° – 27° weeks GA; enrolled <24°
- 10 day course: HC 0.5mg/kg q12° x 7d, then q day x 3 d
- Survival w/o BPD 60% vs. 51% of placebo
  - OR 1.48 (95% CI: 1.02 – 2.16; p=0.04)

- Baud et al, Lancet 2016; 387:1827
Meta-analysis, adjusted odds ratio

Peltoniemi

Watterberg pilot

Bonsante

Watterberg multicenter

Baud, 2016
Other significant outcomes

- ↑ % extubated by day 10 (60% vs. 44%)
- ↓ PDA ligation (15% vs. 21%)
- ↓ mortality in 26 – 27 week GA (8% vs. 15%)
- ↑ late-onset sepsis in 24 – 25 week GA (40% vs. 23%)
- **No** difference in spontaneous GI perforation
Early HC Rx: now what?

- PREMILOC 2 year outcomes: no evidence of harm (JAMA 2017;317:1329)

- Is it time to treat these babies?

- In process – individual patient data meta-analysis of early Rx trials
  - Including only studies that treated past the end of the first postnatal week

- Discuss it at your journal clubs?
Later HC Rx for BPD: cohort studies

- 5mg/kg/d tapered over 22 days
  - Acute: efficacy = DEX; ↓ adverse (25HC, 23dex)
    - Lodygensky Acta Paediatr 2003; 92:827
  - At 8 – 10 yrs: HC Rx (n=62) vs. more mature, untreated group (n=164): similar functional & structural outcomes
    - Rademaker J Pediatr 2007; 150:351
  - At 14 – 17 yrs, vs untreated group: Dex (n=63) adverse effects on neuropsychological, motor & school fx; HC (n=67) – no difference vs. non-treated group
    - Ter Wolbeek Psychoneuroendocrinology 2013; 38:975
Later HC for BPD: Pilot RCT

- Infants enrolled at 10 – 21 postnatal days
  - Intubated, mechanically ventilated
  - Respiratory index score (MAP \times \text{FiO}_2) >2
- HC: 3mg/kg/day tapered over 7 days
- No mandatory extubation specified
- Survival w/o severe BPD: 3/31(10\%) vs 5/33(16\%)

- Parikh, J Pediatr 2013; 162:685
Later HC for BPD: multicenter RCT

- NICHD Neonatal Research Network
- Currently enrolling
- Ventilated infants, 14 – 28 postnatal days
- HC: 4mg/kg/day tapered over 10 days
- Extubation criteria specified
- Outcome to include neurodevelopment (safety) as well as BPD (efficacy)
Summary: Early (<7d) therapy for BPD

- “the benefits...especially dex, may not outweigh the risks”
  - Facilitates extubation, ↓ BPD, but adverse effects
    - GI perforation
    - Hyperglycemia, hypertension
    - Hypertrophic cardiomyopathy
    - Growth failure
    - Increased cerebral palsy, abnormal neurologic exam
- “a compelling need for long term follow up”
- HC – few positive or negative effects
  - Halliday/Ehrenkranz/Doyle, Cochrane review 2014
High dose DEX (0.5mg/kg/day) associated with numerous adverse effects.

There is no basis for postulating that such high doses confer additional benefit over lower dose therapy.

This therapy cannot be recommended.
Summary: later Dex for BPD

- Lower dose DEX (<0.2mg/kg/day) may facilitate extubation
- Limited data suggest ↓ short- and long-term adverse effects vs. higher dose
- Additional RCTs with long-term assessment of neurodevelopmental outcomes are warranted
- Pending additional data, Rx cannot be clearly recommended
Caveats

- Most trial results are contaminated by open-label steroid use.
- The global outcome of BPD yes/no may be too broad – does the Rx reduce severity?
  - Parikh trial – almost all babies dx’d with BPD.
- The appropriate outcome should be both BPD reduction and neurodevelopmental outcome.
Implications for practice

• Pending further studies, clinicians must balance
  ◦ the known adverse effects of BPD with
  ◦ the potential adverse effects of treatments

• “it appears prudent to reserve the use of late corticosteroids for infants who cannot be weaned from mechanical ventilation and to minimise the dose and duration of any course of treatment”

  • Doyle/Ehrenkranz/Halliday, Cochrane Database 2014
The pendulum swings again?

Dex is good – the more the better!

Equipoise???

Setting the stage for new trials

All steroids are bad – no babies should get them!
Hydrocortisone for hypotension

- HC increases blood pressure reliably in individuals with relative adrenal insufficiency
- Term infants have a longer T½ than adults
- Preterm infants have a much prolonged T½
- Doses for other populations (‘stress doses’) result in very high serum concentrations
- Guidelines for approaching the newborn with cardiovascular insufficiency

  - Watterberg, J Pediatr 2016; 174:23
Decision made to treat with hydrocortisone

Give a test dose of 1 mg/kg

- No rise in blood pressure after 2 – 4 hours:
  - No further dosing

- Rise in blood pressure within 2 – 4 hours:
  - <34 weeks:
    - Dose at 0.5mg/kg every 12 hours*
  - ≥34 weeks:
    - Dose at 0.5mg/kg every 6 – 8 hours*

  - Monitor cardiovascular status and modify as needed*

* Cortisol metabolism is highly variable between individuals. If an individual infant responds to the test dose, but hypotension recurs using a dosing interval as short as 6 hours, the dose can be increased to 1mg/kg, with the interval guided by cardiovascular status.
What about REALLY long term outcomes?

"Fetal origins of adult disease"
Perinatal origins of adult disease

- “The Barker hypothesis”
- Many developmental events occur during a specific window of opportunity
- Changing the environment in that window may permanently change outcomes
- Low birth weight in term infants has been linked to a variety of adult diseases
Adult diseases linked to altered perinatal ‘programming’

- Cardiovascular – hypertension, MI, stroke
- Metabolic syndrome, Type II diabetes
- Polycystic ovary syndrome
- End–stage renal disease
- Depression
What’s the link between IUGR and these adverse outcomes?

- The ‘thrifty gene’ hypothesis:
  - malnutrition *in utero* → changes in gene expression to adapt to relative starvation
  - adaptive *in utero*, maladaptive when food is plentiful
  - may be analogous to exposure of subsistence cultures to modern abundance of food

- Linked with ↑ fetal exposure to cortisol
Glucocorticoids and fetal development

Glucocorticoids promote “maturation”

- Cell growth & division
- Differentiation

Glucocorticoids promote and inhibit cell growth, division, and differentiation.
What about the effects of *endogenous* cortisol in the preterm infant?

“The ex-utero fetus”
Premature infants and cortisol

- They have no choice – increased cortisol is necessary to survive under stress
- And cortisol is necessary to control inflammation.
- But . . . could increased exposure to cortisol contribute to some of their long-term adverse outcomes?
ELBW infants

Fetal cortisol values

Cortisol nmol/L

3.6mcg/dl

Gestational age

Critically ill adults and children

ELBW infants

Fetal cortisol 10-90%ile range

Preemies – caught between a rock and a hard place

Cortisol µg/dl

Gestational age
Possibly related outcomes?

- Short stature, ↓ head circumference
- ↓ brain volume, ↑ neurodevelopmental difficulties
- ↑ blood pressure, insulin resistance, adiposity

Other adverse outcomes in adulthood?
- Increasing data of concern
In summary...

- Exogenous glucocorticoid:
  - Strong medicine
  - Powerful side effects
  - Randomized trials with long term follow-up are essential to assess risk/benefit

- Endogenous glucocorticoid:
  - Preterm infants have ↑ exposure vs. fetus
  - May affect long term outcomes
  - Could decreasing stress in the nursery improve outcomes?
Thanks for listening!

Questions?
Beware of cohort studies of therapeutic interventions

- Always an unknown variable . . . or many!

**Diagram:**

- Sicker baby → Dexamethasone → Worse outcomes

- Sicker baby → Dexamethasone
  - Dexamethasone
  - Worse outcomes