Antenatal corticosteroids for preterm birth
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EPICE
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EXPRESS
Antenatal corticosteroids (ANS)

- Liggins & Howie 1972
- >8,000 babies included in RCTs
Antenatal corticosteroids (ANS)

- Liggins & Howie 1972
- >8,000 babies randomized

ANS decreases (in high-income settings):
- Neonatal mortality (31%)
- RDS (34%)
- Need for mechanical ventilation (32%)
- IVH (45%)
- NEC (50%)
- Systemic infections <48h (40%)

Roberts D, Brown J, Medley N, Dalziel SR. Cochrane Database of Systematic Reviews 2017;3:CD004454
Outline of talk

- Are they (ANS) used?
- Do they work in extremely preterm infants?
- Timing of ANS revisited
Are ANS used?

Sweden

32 wks

2004-2008
58%
2012-2016
84%

30 wks

2004-2008
70%
2012-2016
89%

Altman M, J Pediatr 2011; Swed Neonatal Quality Registry
Antenatal Steroids - Antenatal Steroids: Ga 24 to 33
Birth Year
Regional variations

Europe 2011-12; GA 24-32 wks

[Bar chart showing regional variations with data for different regions and percentages for ANS and No ANS]
ANS and GA

USA (Pediatrix Medical Group); 2009-13; GA 23-34 wks
Summary part I

- 65-100% of pregnant women delivering at 24-32 weeks of GA receives ANS
- Practice varies:
  - over time
  - between hospitals, regions and countries
  - by gestational age

What should be the target?
Part II: ANS for extremely preterm infants

Only about 100 deliveries <28 wks GA included in the >20 RCTs on ANS

Jobe A, PAS 2017

Previous meta-analysis: no reductions of mortality & morbidity prior to 26 wks

Onland W et al, Am J Perinatol 2011
Part II: ANS for extremely preterm infants

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Previous meta-analysis: no reductions of mortality & morbidity prior to 26 wks

Onland W et al, Am J Perinatol 2011

More recent studies: indicate similar or even more pronounced benefits from
ANS for extremely preterm births

ANS@22-24 wks (review of 8 high quality non-RCTs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Gestational age</th>
<th>Absolute risk</th>
<th>Relative effect OR (95% CI)</th>
<th>Number of participants</th>
<th>Quality of evidence GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>22–24 weeks</td>
<td>Estimated risk in control group: 619 per 1,000</td>
<td>Corresponding risk in intervention group: 433 per 1,000 (388 to 476)</td>
<td>OR 0.47 (0.39 to 0.56)</td>
<td>10109 (7 studies)</td>
</tr>
</tbody>
</table>
**VON 2012-2015, survival rates by GA and ANS**

<table>
<thead>
<tr>
<th>GA</th>
<th>Life support only</th>
<th>Life support and ANS</th>
<th>aRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wks</td>
<td>382 (18.4%)</td>
<td>391 (38.6%)</td>
<td>2.10</td>
</tr>
<tr>
<td>23 wks</td>
<td>946 (35.9%)</td>
<td>3980 (55.2%)</td>
<td>1.54</td>
</tr>
<tr>
<td>24 wks</td>
<td>933 (59.9%)</td>
<td>7467 (71.2%)</td>
<td>1.19</td>
</tr>
<tr>
<td>25 wks</td>
<td>909 (76.1%)</td>
<td>8600 (82.9%)</td>
<td>1.09</td>
</tr>
</tbody>
</table>

_Ehret D, PAS abstract 2017_
Fig 2 | Number needed to treat with antenatal corticosteroids to prevent one death before discharge in infants with gestational age 23 0/7 to 34 6/7
Summary part II

- Observational data indicate that ANS may be effective also for extremely preterm birth
- Confounding by indication may be a problem ->
  effect on survival larger than on morbidity (other way around in meta-analyses of RCTs)

Why should not all extremely preterm births be treated with ANS?
Part III: current concepts about timing

- Maximized benefits -> ANS administered 24-48 hours to 7 days before delivery

Concepts about timing

- Neonatal benefits maximized when ANS are administered 24-48 hours up to 7 days before delivery
  

- Administration-to-birth intervals <24 (-48) hours described and considered as incomplete, suboptimal or partial

Neonatal survival\(^a\) in EXPRESS by ANS administration-to-birth intervals (n=707, GA 22-26 wks, 84% exposed to ANS)

\(^a\) Adjusted for maternal smoking, maternal HT/PE, placenta previa, placental abruption, PPROM, regionalization of care, gestational age, small for gestational age, infant gender and surfactant <2h after birth

Hanna Norberg, BJOG 2016
The problem

Timely prediction of preterm delivery unresolved
  - most women deliver outside the “optimal” interval
  - many deliver before 24 (-48) hours have passed from admin of ANS

*BMJ 2016*
Research question

What is the shortest administration-to-birth interval of antenatal corticosteroids to promote survival in very preterm infants?
EPICE COHORT
Effective Perinatal Intensive Care in Europe

- Overall aim: to study implementation of evidence based practices in perinatal and neonatal medicine
- 19 regions from 11 European countries
- GA<32 weeks
- All deliveries in 2011-2012
All very preterm births (<32 gestational weeks) 
n= 10 329

- Terminations of pregnancy and stillbirths (n=2 429)
- Severe malformations (n=126)
- Births <24 weeks of gestation (n=300)
- Multiples (n=2 336)
- Unknown timing of antenatal corticosteroids (n=362)
- Repeat courses of antenatal corticosteroids (n=182)

4 594 infants included
Design

Exposure: ANS administration-to-birth interval in hours

Outcomes:

1) In-hospital mortality
2) Mortality or severe neonatal morbidity (IVH ≥3, cPVL, NEC or ROP stage ≥3)
3) Severe neonatal brain injury ((IVH ≥3 or cPVL)

Co-variates:

- maternal age
- parity
- pregnancy complications
- GA
- small for gestational age
- infant sex
- delivery on day of admission
- mode of delivery
- delivery in level III unit
Results

<table>
<thead>
<tr>
<th>Categories</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;14 days</td>
<td>10.2%</td>
</tr>
<tr>
<td>8 days - 14 days</td>
<td>8.0%</td>
</tr>
<tr>
<td>5 days - 7 days</td>
<td>7.0%</td>
</tr>
<tr>
<td>2 days - 4 days</td>
<td>22.8%</td>
</tr>
<tr>
<td>25 hours - 48 hours</td>
<td>9.4%</td>
</tr>
<tr>
<td>13 hours - 24 hours</td>
<td>8.4%</td>
</tr>
<tr>
<td>6 hours - 12 hours</td>
<td>5.2%</td>
</tr>
<tr>
<td>3 hours - 5 hours</td>
<td>4.3%</td>
</tr>
<tr>
<td>&lt;3 hours</td>
<td>9.4%</td>
</tr>
<tr>
<td>No ANS</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

4 categories

>7 days
24 hours - 7 days
<24 hours
No ANS

10 categories

>7 days
8 days - 14 days
5 days - 7 days
2 days - 4 days
25 hours - 48 hours
13 hours - 24 hours
6 hours - 12 hours
3 hours - 5 hours
<3 hours
No ANS
Main finding

Infant mortality by ANS administration-to-birth intervals

RR adjusted for **patient case-mix** (maternal age; parity; pregnancy complications including preeclampsia, eclampsia and HELLP-syndrome and PPROM; GA; small for gestational age and infant sex) and factors related to **management** (delivery on day of admission, mode of delivery, delivery in hospital with level III neonatal unit)

Norman M et al, JAMA Peds 2017
Summary III

77% of women did not receive ANS or received ANS outside of the desired administration-to-birth interval, i.e., 2 to 4 days

ANS associated with immediate and rapid decline in mortality

Under the assumption of a causal relationship, a simulation of ANS given 3 hours before delivery to infants who did not receive ANS -> their estimated decline in mortality would be 26%

Infants with an ANS administration-to-birth interval >7 days (19% of all infants in our study) exhibited 40% higher mortality than those with ANS given 1-7 days before birth
Conclusion

ANS may be effective even if given only hours before delivery

meaning

Infants of pregnant women at risk of imminent/immediate very preterm delivery may benefit from its use
Topic for future research?

Given the suggestion of very rapid actions, immediate postnatal corticosteroid rescue for very preterm infants unexposed to ANS may be interesting to test

*Compare PREMILOC-trial by Baud O et al, Lancet 2016*
BELGIUM: Flanders (E Martens, G Martens, P Van Reempts); DENMARK: Eastern Region (K Boerch, A Hasselager, L Huusom, O Pryds, T Weber); ESTONIA (L Toome, H Varendi); FRANCE: Burgundy, Ile-de France and Northern Region (PY Ancel, B Blondel, A Burguet, PH Jarreau, P Truffert); GERMANY: Hesse (RF Maier, B Misselwitz, S Schmidt), Saarland (L Gortner); ITALY: Emilia Romagna (D Baronciani, G Gargano), Lazio (R Agostino, D DiLallo, F Franco), Marche (V Carnielli), M Cuttini; ; NETHERLANDS: Eastern & Central (C Koopman-Esseboom, A van Heijst, J Nijman); POLAND: Wielkopolska (J Gadzinowski, J Mazela); PORTUGAL: Lisbon and Tagus Valley (LM Graça, MC Machado), Northern region (Carina Rodrigues, T Rodrigues), H Barros; SWEDEN: Stockholm (AK Bonamy, M Norman, E Wilson); UK: East Midlands and Yorkshire and Humber (E Boyle, ES Draper, BN Manktelow), Northern Region (AC Fenton, DWA Milligan); INSERM, Paris (Jennifer Zeitlin, M Bonet, A Piedvache).
Thank you for your attention

Questions?