Causes of neurological morbidity in the perinate

- Malformations
- Toxins
- Metabolic derangements
- **Trauma**
- Infection- inflammation
- **Hypoxia-ischaemia**
- Coagulation disorders
- Maternal thyroid dysfunction
- **Prematurity**
- RDS
- Multiples

European Association of Perinatal Medicine
"Study Group on "Preterm birth"

Guidelines for the management of spontaneous preterm labour

Chairpersons:

G C Di Renzo (Italy) L Cabero Roura (Spain) F Facchinetti (Italy)

Participants: A. Antsaklis (Greece), C. Sen (Turkey), R. Lamont (UK), G. Breborowicz (Poland), S.C. Robson (UK), M. Robson (Ireland), A. Shennan (UK), F. Stamatian (Romania), A. Mikhailov (Russia), N. Montenegro (Portugal), E. Gratacos (Spain) P. Husslein (Austria),Y. Ville (France)

J Perinat Med 2006 J Mat Fet Neon Med 2011

Tocolytic therapy

- Primary aims
  - to delay delivery for administration of glucocorticoids to reduce idiopathic respiratory distress syndrome and to arrange in-utero transfer to a NICU
- Secondary aim
  - to delay delivery to allow maximum growth and maturity of the fetus and to hopefully reduce perinatal mortality and morbidity

TOCOLYTICS

- LICENSED DRUGS*
  - Atosiban
  - Beta mimetics
    - require constant monitoring
- UNLICENSED DRUGS
  - Prostaglandin synthesis inhibitors
  - Calcium channel blockers
  - Nitric oxide donors
    - incomplete safety profiles
    - some serious maternal adverse events reported
    - use based largely on small investigator-led studies
  - Magnesium sulphate

*Not licensed in North America

Magnesium sulfate tocolysis: time to quit

R Mittendorf
Obstet Gynecol 2007

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The betamimetics' warning

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The permanent shift in the balance of sympathetic-to-parasympathetic tone, as a result of B2AR overstimulation during critical periods of prenatal development, is a biologically plausible mechanism whereby beta 2 adrenergic agonists can induce functional and behavioral teratogenesis

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Currently available data concerning increased risk for autism in the offspring suggest that the duration is likely to be ≥ 2 weeks of continuous high dose exposure

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Antenatal steroids: RCT's over the decades

	1970s	1980s	1990s
RDS	0.55	0.71	0.69
PVH	0.50	0.61	0.53
Neonatal death	0.73	0.98	0.50

So there is a case to give corticosteroids in women at risk of preterm delivery between 24 weeks (23 weeks?, McEnvoy, 08) and 34 weeks

Betamethasone is more effective than dexamethasone

(Roberts and Dalziel, Cochrane, 2006)

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Effects of prophylactic corticosteroid therapy on perinatal and maternal outcomes

OUTCOMES		RR
NEONATAL MORTALITY	- all infants	0.63
	- treated < 1980	0.53
	- treated > 1980	0.86
STILLBIRTH	- all infants	0.84
	- women with hypertension	3.66
INTRAVENTRICULAR HAEMORRHAGE	- all infants	0.55
	- diagnosed after autopsy	0.3
	- diagnosed during ultrasound	0.68
NECROTISING ENTEROCOLITIS		0.6
LONG TERM NEUROLOGICAL ABNORMALITY		0.65
FETAL AND NEONATAL INFECTIONS	- all infants	0.8
	- after PROM	2.16
	- PROM at trial entry	1.21
MATERNAL INFECTIONS	- all infants	1.44
	- after PROM	4.84
	- PROM at trial entry	1.78

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K. Khan, Health Tech Asses, 2009

STEROIDS

30th British Congress of Obstetrics and Gynaecology
7 – 9 July 2004
2004 SECC • Glasgow • UK

	Clyde Auditorium
08.35 - 09.00	**Opening Ceremony**
09.00 - 09.45	**Plenary Lecture 1** The Steroid Story: Iconic Advance or Ticking Bomb? *John Newnham, Australia* **PL1**

Newnham JP, Moss TJ, Nitsos I, Sloboda DM.
Antenatal corticosteroids: the good, the bad and the unknown.
Curr Opin Obstet Gynecol. 2002;**14**:607-12.

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RISKS OF ANTENATAL STEROIDS (1)

- In animal studies, steroids delay myelination in the fetal brain and reduces the growth of all fetal brain areas particularly the hippocampus
- In humans, decreased neonatal head circumference and decreased birthweight
- an increase in behavioural disorders at 3 years of age

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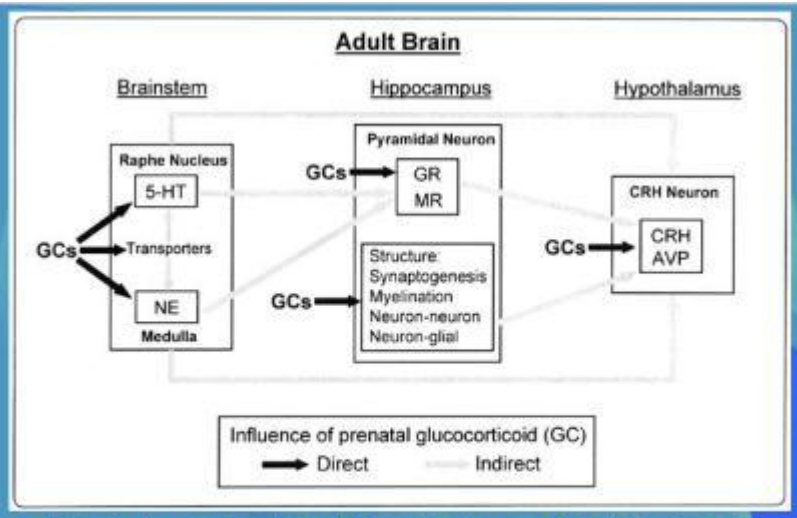

Diagram illustrating the potential routes by which prenatal GC exposure leads to alterations in behavior and HPA activity in adulthood. During development, fetal exposure to GCs directly affects 1) development and subsequent function of neurotransmitter systems (and their transporter mechanisms) in the brainstem, *2)* development of corticosteroid receptor expression and structural components in the hippocampus, and *3)* development and subsequent function of parvocellular neurons (CRH/AVP).

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RISKS OF ANTENATAL STEROIDS (2)

- No changes in umbilical and uterine blood flows either in normal or IUGR fetuses
- Vasodilatatory effects on placental bed in presence of high vascular resistance
- Infants exposed to repeated courses have a significantly lower cortisol response to stressors than infants exposed to single course up to 7 days after birth

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RISKS OF ANTENATAL STEROIDS (3)

- long-term effects on the setting of the hypothalamo-pituitary axis and glucose homeostasis
- higher systolic and diastolic blood pressures in adolescence, and possible clinical hypertension in survivors well beyond birth

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Again, that was just to remind you, that…

- Corticosteroids are very potent drugs, and…
- Potent drugs may have serious side effects

Key guidelines

- Administration of one single-course of antenatal glucocorticoids is the most important treatment to prevent brain injury and increase survival that can be provided by the obstetrician to patients at risk of preterm delivery at 24—34 weeks of gestation
- Based on observational clinical and animal studies, betamethasone is preferable to dexamethasone

Even after a prolonged interval (10-14 days) from initial antenatal corticosteroid treatment, an empiric rescue course of steroids is not justified (except < 32 wks)

- Multiple courses of corticosteroids should be avoided
- Antibiotic treatment following PPROM is recommended

ASSOCIATED THERAPIES

Prevention of neonatal severe neurological morbidity by a new antenatal combined pharmacological approach

G C DI RENZO ET AL.
Centre of Perinatal Medicine and Reproductive Medicine,
University of Perugia,
Perugia, Italy

Am J Ob/Gyn 2005

Combined antenatal treatment

- **Betamethasone** (12mg twice/ 24 hr apart)
- **Aminophylline** (480mg/die min 48 hrs)
- **Magnesium sulphate** (8 gr/ die min 48 hrs)

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Perinatal characteristics of study population

	Group A (No 78)	Group B (No 68)	Significance
Maternal characteristics			
Multiple pregnancy (twin – triplets)	13	12	
PIH-Preeclampsia-HELLP	11	10	NS
Severe IUGR (<3 centile)	10	9	
PPROM	44	37	
Route of delivery			
Vaginal delivery	27 (34,6%)	21 (35,3%)	NS
Cesarean section	51 (65,4%)	44 (64,7%)	
Mean Apgar			
1 min. (range)	1-9	1-9	NS
5 min. (range)	6-10	5-10	
Birth weight (g)			
range	565-1220	600-1260	NS
mean ±SD	757±215	821±275	

NS= non significant

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Neonatal mortality and morbidity according to different antenatal treatments

	Group A	Group B	Significance
RDS*	28 (35,9%)	26 (38,2%)	NS
IVH and PVL (total)	4 (5,1%)	14 (20,6%)	p<0.001
IVH (3-4-degree)	1(1.3%)	7 (10.3%)	p <0.001
PDA	7 (9,0%)	5 (7,5%)	NS
ROP	2 (2,6%)	4 (5,9%)	NS
Neonatal death**	8 (10,2%)	7 (10,3%)	NS

Severe degree needing surfactant replacement and HPPV

** within 28 days from delivery

Di Renzo et al, Am JOG 2005

Studies that have examined the use of $MgSO_4$ for neuro prophylaxis and prevention of cerebral palsy

- MagNET (2002)
- ACTOMgSO4 (2003)
- MAGPIE (2007)
- PREMAG (2008)
- BEAM (2008)

It appears that we should consider using $MgSO_4$ to prevent neurologic complications of pregnancy in the neonate.

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Meta-Analysis of Mortality, Celebral Palsy, Substantial Gross Motor Dysfunction and Combined Outcomes

OUTCOME AND SUBCATEGORY	RR
Mortality Neuroprotective intent	0.94
Cerebral palsy Neuroprotective intent	0.71
Mortality or cerebral palsy Neuroprotective intent	0.85
Substantial gross motor dysfunction Neuroprotective intent	0.60
Mortality or Substantial gross motor dysfunction Neuroprotective intent	0.84

Doyle, Ob Gyn, 2009

Perinatal and maternal effects of magnesium sulphate

OUTCOME	RR
Fetal, neonatal and postnatal deaths	0.82
Substantial gross motor dysfunction	**0.53**
Neurosensory disability	1.00
Bayley PDI (WMD)	-1.30
Bayley MDI (WMD)	-1.40
Delayed development	1.00
Blindness	0.96
Deafness	1.10
Chronic lung disease	1.07
Necrotising enterocolitis	0.96
Mechanical ventilation	1.02
Maternal infusion stopped due to adverse effects	2.74
Any maternal adverse effects	2.36

K. Khan, Health Tech Asses, 2009

Effect of magnesium sulfate on cerebral palsy and pediatric mortality

OUTCOME	RELATIVE RISK (95% CI)
Cerebral palsy	**0.69 (0.55-0.88)**
Moderate/severe cerebral palsy	**0.64 (0.44-0.92)**
Mild cerebral palsy	**0.74 (0.52-1.04)**
Total pediatric mortality	1.01 (0.89-1.14)
Fetal mortality	0.78 (0.42-1.46)
Under 2 y of corrected age mortality	1.00 (0.84-1.19)
Death or cerebral palsy	0.92 (0.83-1.02)

Conde-Agudelo, Am J Ob Gyn, 2009

$MgSO_4$ offers us the opportunity to improve the neurodevelopmental future of fetuses destinated to deliver at early gestational ages. In the United States, 2% of women deliver prior to 32 weeks' gestation. If $MgSO_4$ were uniformly administered to the 75% who deliver spontaneously and it were as effective as in NINDS/NICHD MFMU Network trial, then more than 1000 fewer children a year would suffer from handicapping cerebral palsy. For their sakes, we should avail ourselves of this opportunity.

Dwight, Am J Ob Gyn, 2009

There is little doubt that antenatal magnesium sulfate therapy given to women at risk of preterm birth is a neuroprotective agent against motor disorders for the preterm fetus.

It reduced the rates of celebral palsy and substantial gross motor dysfunction in early childhood, both overall and in the neuroprotective subgroup, and also the rates of the combined outcomes of death or cerebral palsy and death or substantial gross motor dysfunction in the neuroprotective subgroup.

Doyle, Ob Gyn, 2009

CONCLUSIONS

PREVENTION OF PERINATAL NEUROLOGICAL MORBIDITY

- Prevention of lung immaturity
- Prevention of intrauterine infection
- Stabilization of cerebral and systemic circulations
- Prevention of intrapartum asphyxia
- Prevention of extreme prematurity

MAIN METHODS

- Appropriate use of corticosteroids
- Combination of more drugs
- Antibiotics-antiinflammatory agents
- Consider to use magnesium sulphate
- Safe tocolysis
- Complementary methods of monitoring
- Neonatal resucitation
- Place of birth (and transport in utero)


GRAZIE!
THANKS!