Tocolytic drugs and corticosteroids

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Finally some progress as to preterm labour

- The old:
  - -Corticosteroids
  - -Antibiotics
  - -Tocolytic drugs
  - -Cerclage

- The new: -Importance of short cervix:
  - -Progesteron
  - -Arabin pessary
  - -MgSO4

But let's now talk about the old and familiar (?)

- The old:
  - -Corticosteroids
  - -Antibiotics?
  - -Tocolytic drugs?
  - -Cerclage?
- The new:
  - -Importance of the short cervix
  - -Progesteron
  - -Arabin pessary
  - -MgSO4

Use of CSs and tocolytic drugs in 29 low to middle income countries

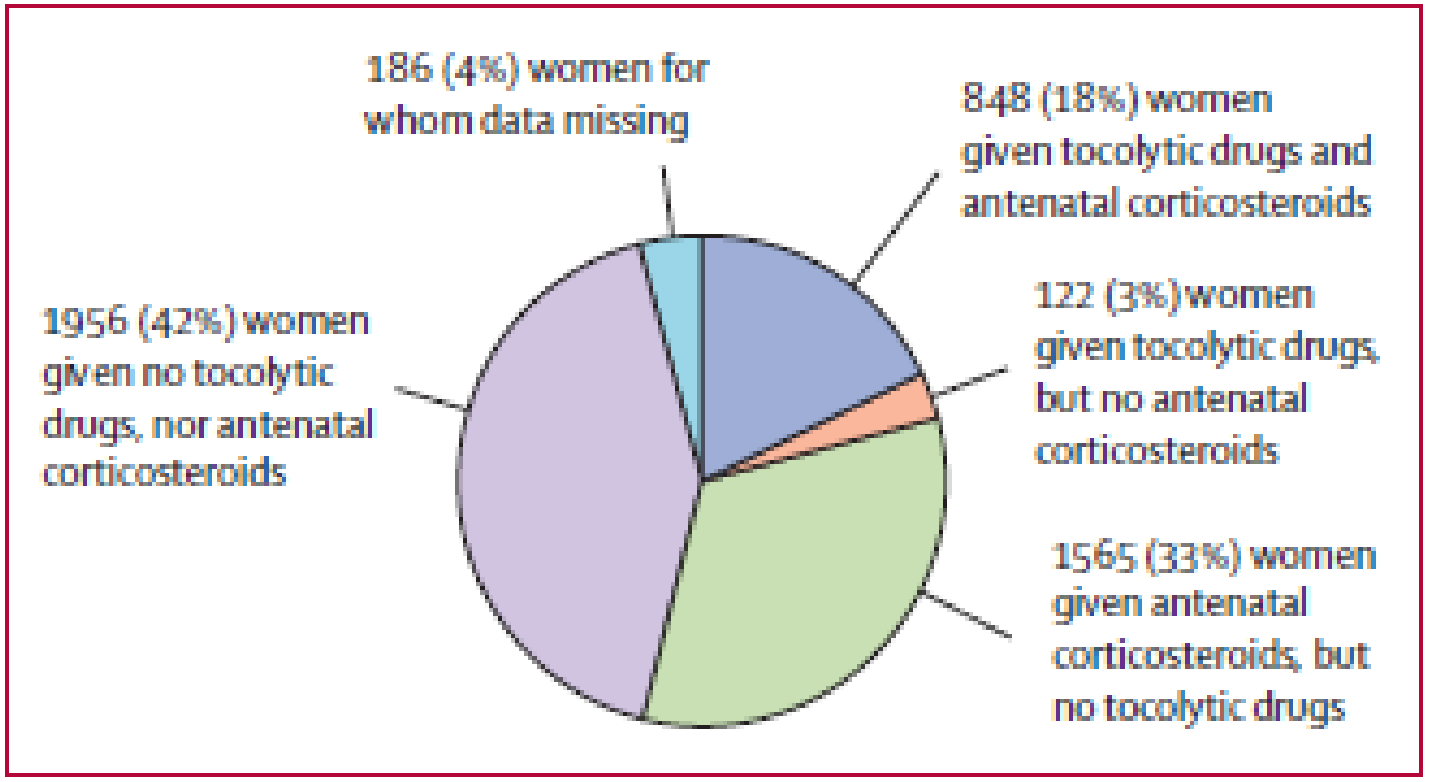

Figure 2: Use of tocolytic drugs, with and without antenatal corticosteroids, in uncomplicated spontaneous preterm births (26–34 weeks' gestation; n=4677)

Main tocolytic drug: B-mimetics

Vogel et al(WHO) Lancet Nov 22, 2014

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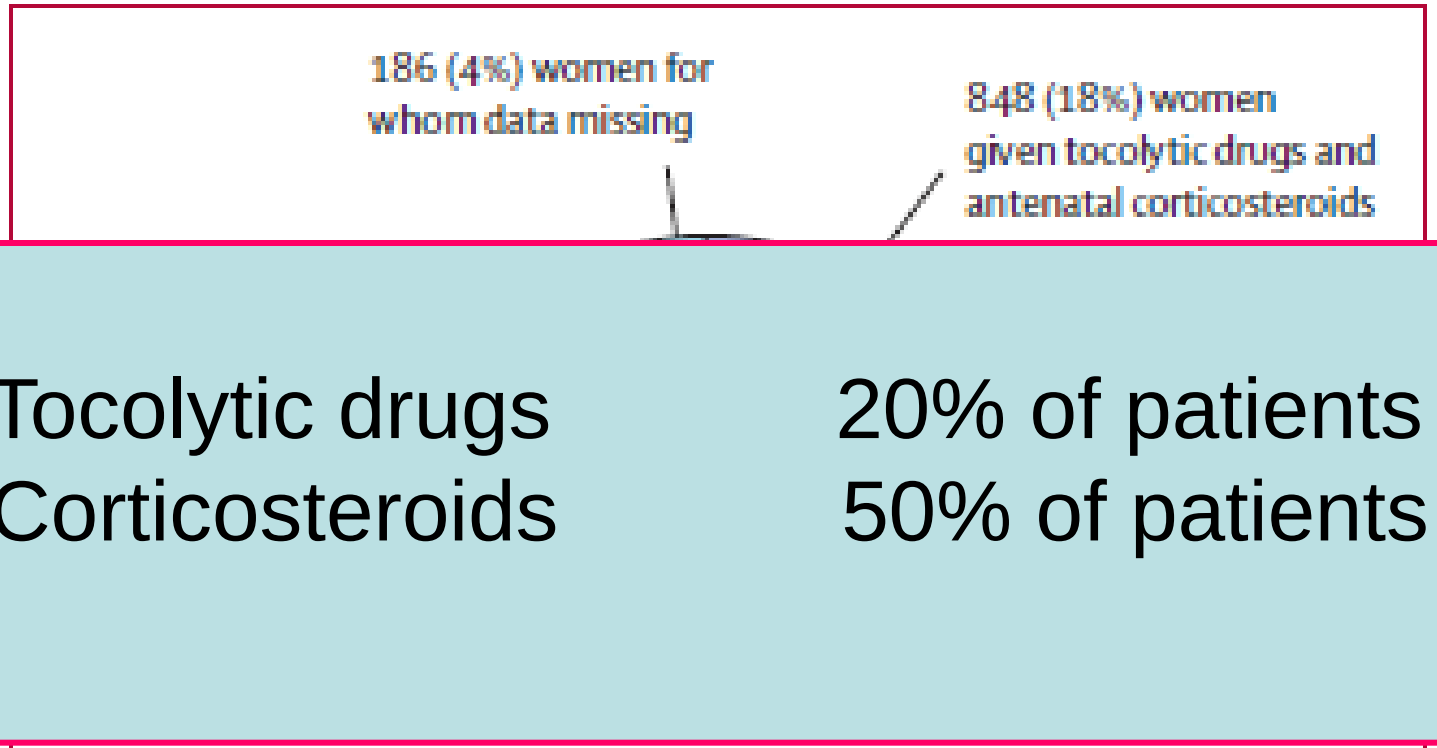

Tocolytic drugs 20% of patients
Corticosteroids 50% of patients

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Should preterm labour be stopped at all?

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Meta analyses on tocolytic drugs

	placebo	tocolytic
• Birth delay > 48 h	53%	75-93%
• Birth delay> 7 days	39%	61-78%

- With no lengthening of gestation beyond one week

Haas et al, Obstet Gynecol 2009;113:585-594

Meta analyses on tocolytic drugs

	placebo	tocolytic
• Birth delay > 48 h	53%	75-93%
• Birth delay> 7 days	39%	61-78%

- And no significant difference in RDS or neonatal survival (in studies in which corticosteroids were given in both arms)

Haas et al, Obstet Gynecol 2009;113:585-594

Meta analyses on tocolytic drugs

	placebo	tocolytic
Birth delay > 48 h	53%	75-93%
Birth delay> 7 days	39%	61-78%

RCOG Greentop Guideline, 2010: no tocolytic drug has been associated with a reduction in prenatal or neonatal morbidity

Haas et al, Obstet Gynecol 2009;113:585-594

Reason for absence of beneficial effects?

- The majority of preterm labours –with or without intact membranes- is associated with infections or inflammation
- And both are related to neurological and respiratory complications, including PVL and CP

- So, delaying delivery may not prevent neurological damage, but may even make it worse (see also Oracle trial: increased incidence of CP after 7 years in intact membranes group; Kenyon et al, Lancet 2008)

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So why don't we only give a (rescue) course of corticosteroids and wait and see

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Or corticosteroids and MgSO4

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- The majority of preterm labours –with or without intact membranes- is associated with infections or inflammation
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Or corticosteroids and MgSO4

Moreover since MgSO4 works < 2 h*

* See also RCOG opinion paper 29, August 2011

Anyhow,

- 2 days should be more than enough
- Also for the achievement of proper action of corticosteroids
- And for in utero transfer to a level 3 hospital

Side effects observed after a single course of a tocolytic drug (n=1.333)

Tocolytic drug	N	Severe	Mild
Nifedipine	543	5 (0.9%)*	8 (1.5%)*
β-agonists	158	3 (1.9%)*	4 (2.5%)*
Atosiban	576	0 (0%)	1 (0.2%)
Indomethacin	35	0 (0%)	0 (0%)

*Significant difference compared with atosiban

If you use a tocolytic drug, use one that is safe for the mother

de Heus R, et al. BMJ 2009

So…

- Do not use β-agonists anymore
- Do not give combined courses
- Consider giving atosiban

So…

- Do not use β-agonists anymore
- Do not give combined courses
- Consider to give atosiban
- Especially in cases of multiple gestation, diabetes and maternal cardiovascular problems
  - i.e. take the maternal condition into account when deciding which drug to use

Reassess the role of prostaglandin inhibitors (but not in MC twins)

And what about maintenance tocolytic therapy?

- Oxytocin antagonists, one trial only
- Oral betamimetics, 13 trials
- Ca channel blockers, 2 trials

No effect on incidence of preterm birth or neonatal morbiditiy

Cochrane databases: Papatsonis et al, 2009; Dodd et al, 2011; Gaunekaret al, 2010; Roos et al, 2013

Conclusions

- There is no convincing evidence that tocolytics improve neonatal outcome
- So, if you want to treat, do it only for a short time (i.e. in utero transfer) and with a drug that is safe for the mother
- But you may also consider to give corticosteroids and $MgSO_4$, instead.
- There is no place for tocolytic maintenance therapy

Antenatal corticosteroids

Poison with some positive side effects

Antenatal CSs in low to middle income countries

(Argentina,Guatemala, India, Kenya, Pakistan, Zambia)

Althabe et al, Lancet Febr 14, 2015

- Implementation program of CSs in case of threatened preterm birth versus standard care (n=98.000)
- Proxi for preterm birth: birthweight< 5th centile (36-37wks)

- Intervention group CS in 45%, in control group 10%

- What will be neonatal outcome in infants weighing < 5th centile?
- What will be the overall perinatal mortality?
- And what about maternal morbidity?

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- Neonatal mortality (<28d; <5th c group): RR 0.96 (0.87-1.06)
- Total mortality : RR 1.12 (1.02-1.22)
- Maternal infections : RR 1.45 (1.33-1.58)

Antenatal CSs in low to middle income countries

(Argentina,Guatemala, India, Kenya, Pakistan, Zambia)

Althabe et al, Lancet Febr 14, 2015

- 87% of CS were given to infants weighing> 2000-2500g, where there is no evidence of its usefulness
- With risks of side-effects such as reduced fetal/placental growth, apoptosis in the brain, CP and maternal infection, which may explain the overall poorer outcome
- These data stress the importance of adequate dating of the pregnancy and of identifying women at real risk of preterm birth.

Antenatal corticosteroids

Work !!

But only if given appropriately

Antenatal steroids: RCT's over the decades

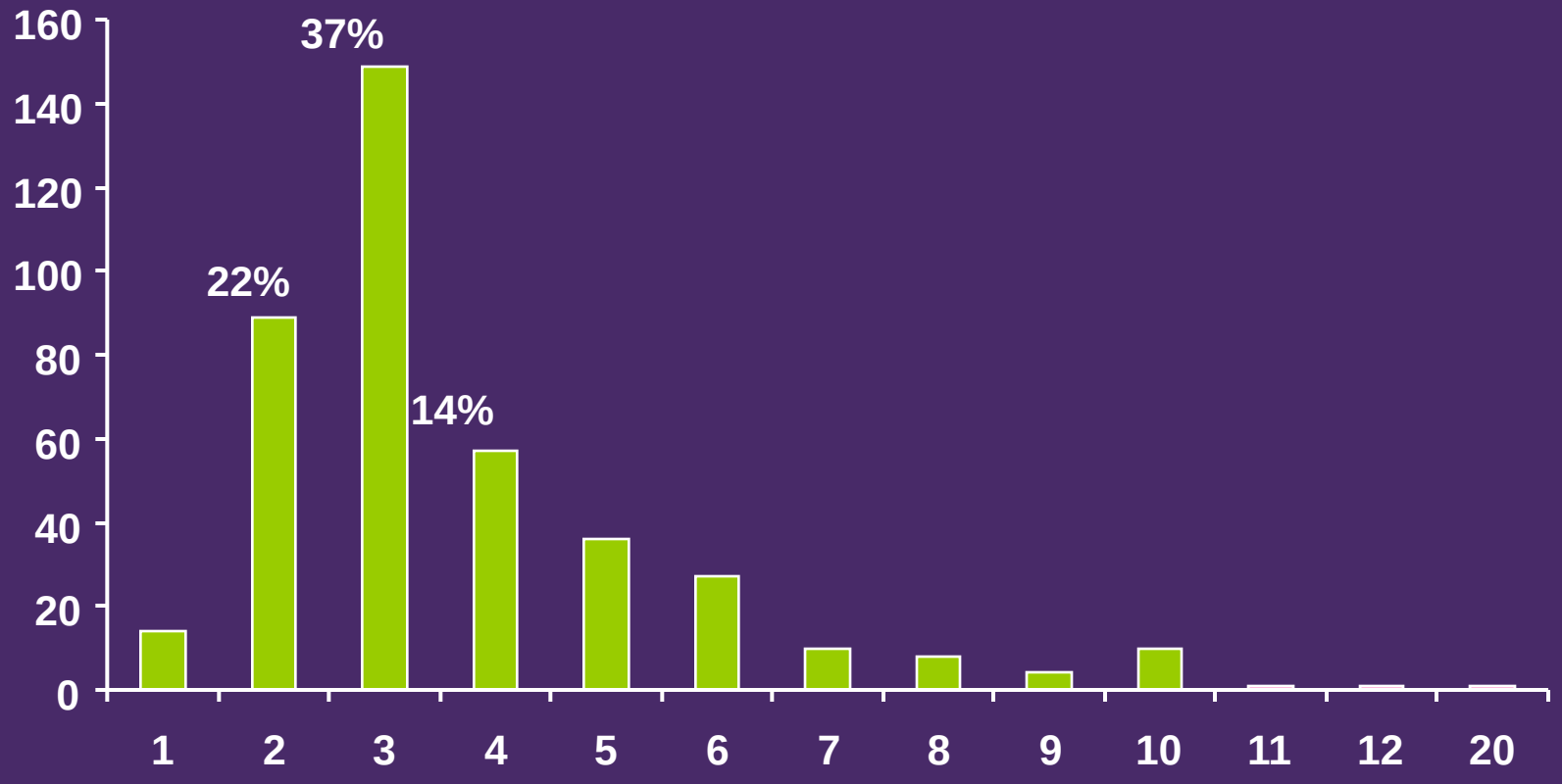
	1970s	1980s	1990s
RDS	0.55	0.71	0.69
PVH	0.50	0.61	0.53
Neonatal death	0.73	0.98	0.50

So there is a case to give corticosteroids in women at risk of preterm delivery between 24 weeks and 34 weeks

Betamethasone is more effective than dexamethasone; but be aware of its effects on FHR variation and movements

(Roberts and Dalziel, Cochrane, 2006)

Number of courses, Europe 2000



In 40% of 420 European Centres >3 courses will be given
(Empana et al, Eurail, 2001)

Should steroids be repeated?

Author	N	Reduction severe/comp morbidity	
		Total group	Early
Guinn 01	502	No	Yes <27 weeks
Wapner 06	495	No	Yes <32 weeks
Crowther 06	982	Yes	<32 weeks
MACS trial 08	2304	No	No < 32 weeks

Direct side effects

Decreased birth weight and head circumference

	Antenatal corticosteroids	Placebo	Mean difference (95% CI)	p value
Total number of infants	1164	1140		
Birthweight (g)	2216 (28·3)	2330 (28·7)	-113·1 (37·3) (-187·0 to -41·17)	0·0026
Length at birth (cm)	44·5 (0·2)	45·4 (0·2)	-0·9 (0·25) (-1·34 to -0·37)	<0·001
Mean head circumference (cm)	31·1 (0·1)	31·7 (0·1)	-0·6 (0·15) (-0·90 to -0·32)	<0·001

MACS, Lancet December 2008

2-year follow up (Wapner et al, NEJM, 2007)

	Placebo	Repeat
N	236	248
Weight/HC/Bayley	–	–
CP	1 (0.5%)	6 (2.9%)*

* 5 of 6 cases >3 courses, 5 >32 weeks of gestation

Early neonatal treatment with corticosteroids

For every 100 babies treated…

- **14 more extubated by 7 days**
- **11 less have CLD**
- **7 less will die**
- **14 avoid late CS treatment**
- **6 more have GI bleeding**
- **4 more have GI perforation**
- **12 have cerebral palsy**
- **14 have abnormal neurological development at follow-up**

(data from 19 RCT; Halliday, 2001)

Fetal versus neonatal dose

0.05–0.20 mg/day for 2 days

0.5 mg/kg/day for many days

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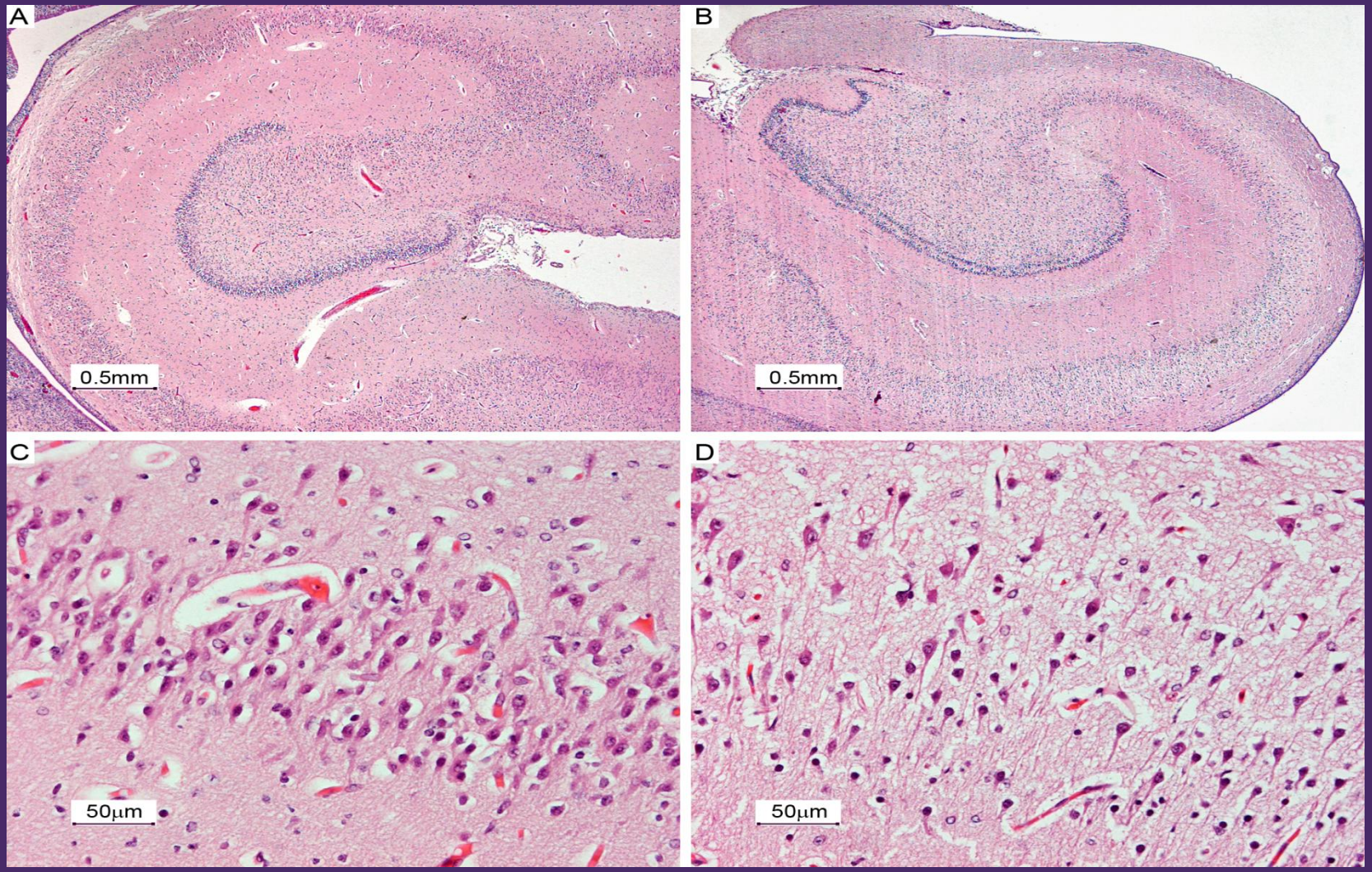
Potent drugs may have potent side effects

Follow-up after one course of corticosteroids is reassuring

- no impairment at the age of 6 (maybe some impaired visual memory)
- normal behaviour and motor function at 7-10 years
- normal physical and psychological development at the age of 12 and 20 years
- normal cardiovascular and psychological development at the age of 30 years (apart from increased insulin resistance)

(McArthur et al, 1990; Smolders – de Haas et al, 1990; Schmand et al 1990; Dessens et al, 2000; Dalziel et al, 2005 (2x),Karemaker 2006)

The human hippocampus

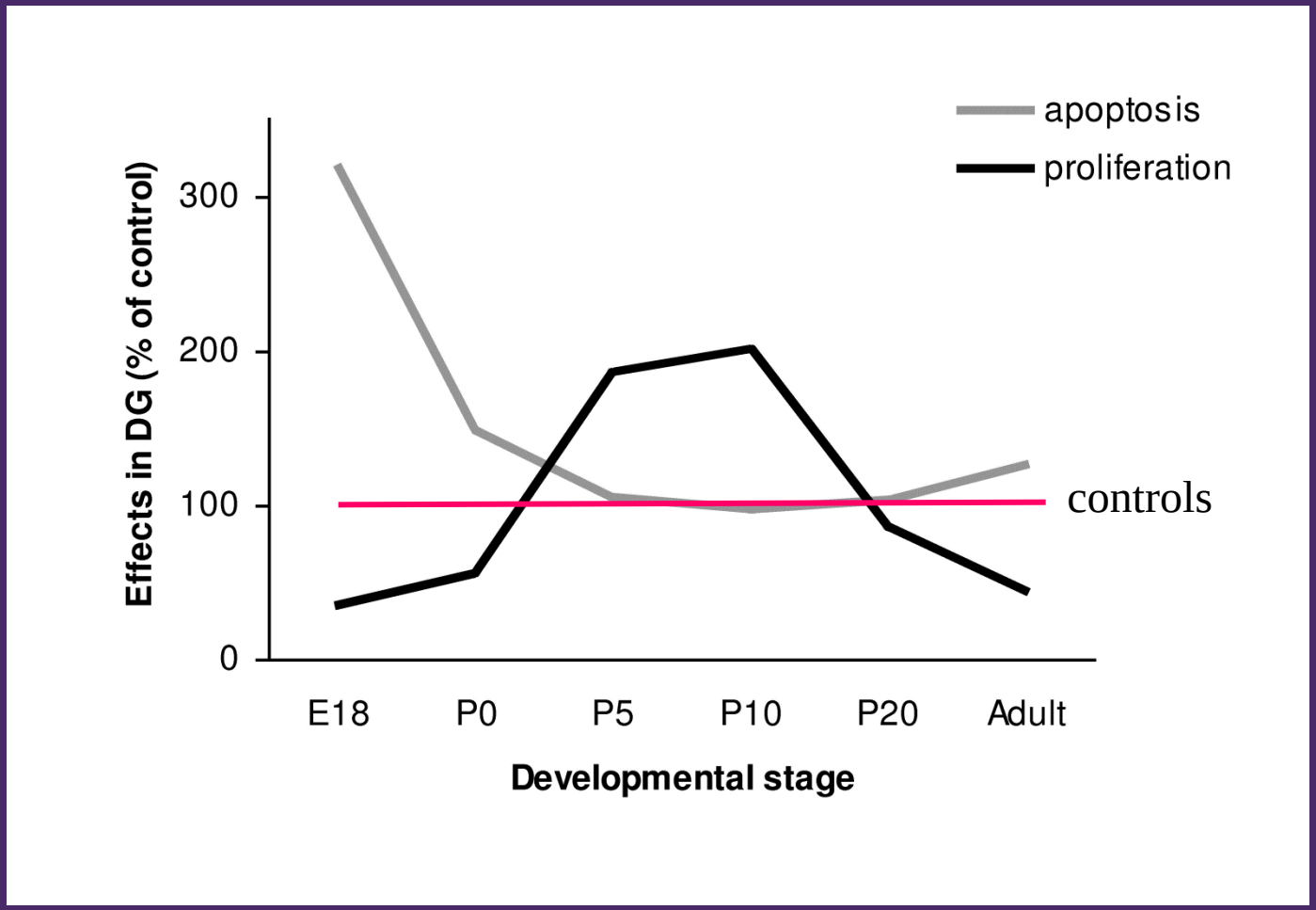


Impact of corticosteroids on the density of large neurons in the human hippocampus

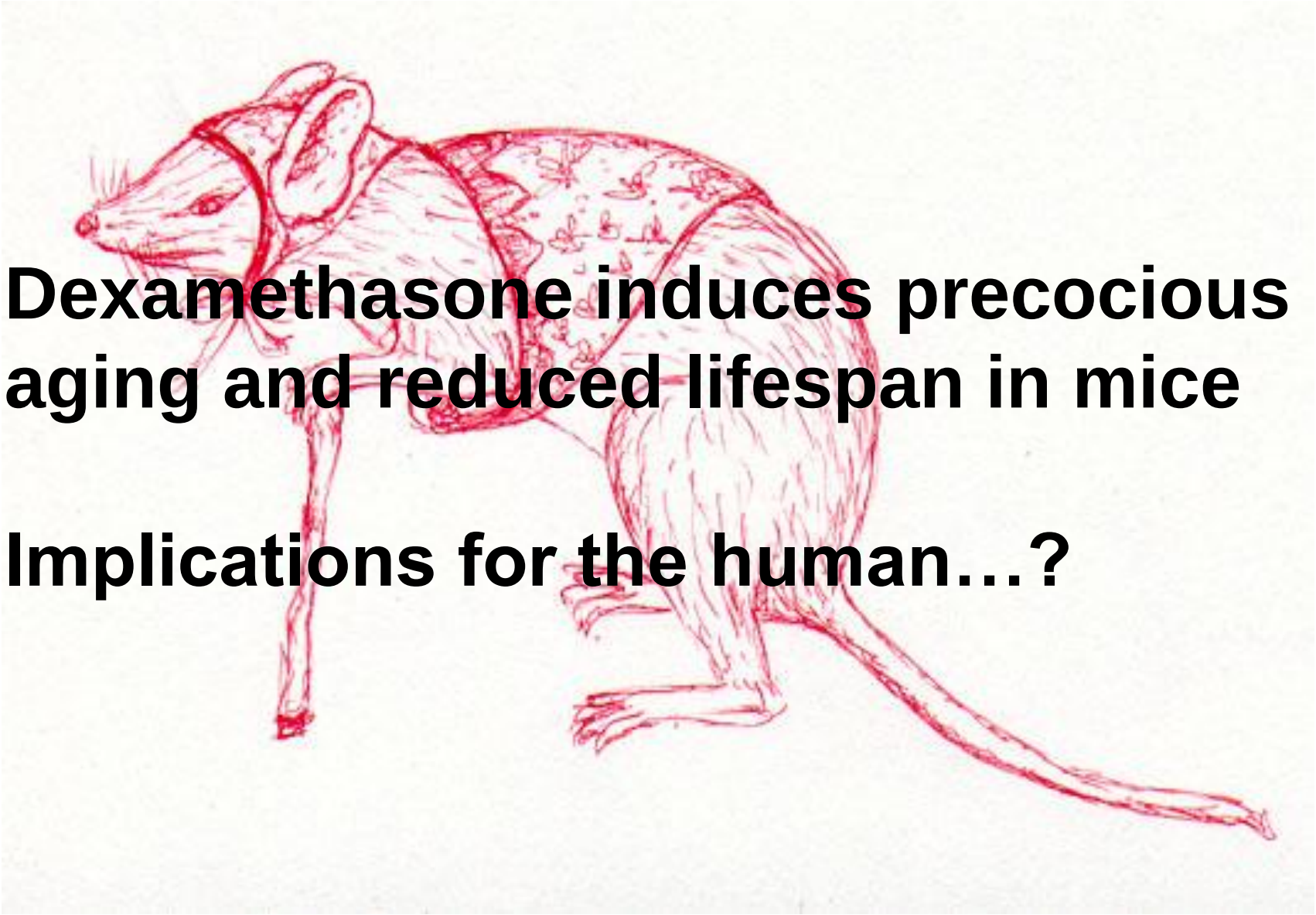
Density of neurons	Antenatal CS	No antenatal CS
High (4)	1	6
Moderate (3)	4	3
Moderate/low (2)	6	2
Low (1)	0	0
Total n of neonates	11	11 ($p<0.02$)

(22 infants, 25–32 weeks, who died <4 days after delivery; Thijsseling et al, PLoSOne 2013)

Apoptosis versus cell proliferation



Noorlander et al, 2013; similar findings pren/neon exposure: Zuloaga et al, 2011; Chun-I Sze et al, 2013



Dexamethasone induces precocious aging and reduced lifespan in mice

Implications for the human…?

Should steroids be repeated?

- Multiple courses of antenatal steroids do not increase or decrease the risk of death or developmental difficulties by 5 y of age.
- Because there is no clear benefit, this approach is not recommended for routine use
- Future research may be warranted for a more specified use of repeated courses

MACS-5; Asztalos et al, AJOG 2013 (abstract)

Most importantly

- Use of corticosteroids may well be reduced by a better identification of women who really are at increased risk of preterm delivery (CL measurement, fibronectin); Van Baaren et al O&G 2014

- And by determining fetal lung maturation by amniocentesis before a planned preterm delivery (CS). Note: almost 50% of IUGR infants at 32 wks will have sufficient lung maturation and do not need CSs

- Question: How many of your patients who received corticosteroids actually delivered preterm? Utrecht area: 34% delivered < 1 wk; Boesveld et al AJOG, 2014)

Thank you