FDA/M-CERSI
Public Workshop on Fetal Pharmacology and Therapeutics
October 2021

Antenatal Steroids to Prevent Respiratory Distress Syndrome in the Preterm Newborn Consideration for Safety and Efficacy

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changing the outcome together

Standard of Care: we have been using the wrong dose and the wrong drug for 39 years

I will cut to the chase; my conclusions are that although ANS have been used clinically since 1972, the conclusion based on clinical literature and our recent studies in monkey and sheep models is that:

- We have been using as Standard of Care drug given to women at risk of preterm delivery using the wrong dose of the wrong drug for 39 years.
  - Without any good PK or PD data
  - With many exposed pregnancies having no benefit and new risk are being reported.
  - ANS should be the poster child for this conference, although it actually is an egregious example of what can transpire if there is no regulation of a treatment.

A brief history of ANS relevant to FDA

- In 1968 a New Zealand Obstetrician (Mont Liggins) was studying labor mechanisms in sheep using maternal and fetal infusions of Corticosteroids – which cause preterm delivery. The very preterm lams breathed.
- He recognized early lung maturation and did an RCT Clinical trial – published in 1972 showing decreased mortality and RDS.
- He used an “off the shelf” corticosteroid Celestone (6 mg Betamethasone-Phosphate + 6 mg x 2 Betamethasone-Acetate second dose after 24 hrs. for a total dose of 24 mg.
- No PK or PD was ever done with this combination drug .
- Accepted worldwide after an NIH Consensus Conference in 1994.
- A second consensus conference in 2000 combined the recommendations and suggested limiting repeated courses of treatment.
- World health Organization picked ANS as the most impactful Rx in LMIC to decrease infant mortality – using 4 doses of maternal IM Dexamethasone for 12 hr (dose 24 mg) – 2015.

A brief history of ANS relevant to FDA

- Ann Zajicek (FDA) and Linda Wright (NICHD) sponsored a reanalysis of published data (about 15 years ago) but data were too incomplete to justify a review by the FDA – to my knowledge NAS have not been evaluated by the FDA.
- ANS are now standard of care worldwide (as recommended by Ob/Gyn Societies).
- We actually do not know how many women are being treated with ANS (use of ANS in US at 24-32 weeks GA for risk of prematurity >90% in US).

Current Status of ANS in Advanced Care Environments

Who Receives ANS?	% of Delivery Population
80-95% of women at risk of PTD at 24-34 weeks	**4%**
Repeated ANS used selectively (no data on % treated)	**---**
ANS for 34-36^{6} week deliveries	**7%**
ANS for previable deliveries (<24 weeks)	**1%**
Elective C-section	**10-60%**
Total potential of pregnant women exposed	**22->70%**

More and more pregnancies are being treated, which changes the benefit to risk ratio.

Treatments Used Worldwide

	Location	Dose	Total dose
Betamethasone-P + Acetate	US Europe Australia New Zealand	2 x 12 mg for 24 hr	24 mg
Betamethasone-P only	UK	2 x 12 mg for 24 hr	24 mg
Dexamethasone-P (WHO dose)	India Africa LMIC	4 x 6 mg for 48 hr	24 mg

Dosing

- **All doses are very high – 24 mg.**
- **Recent meta-analysis included 27 RCT (McGoldrick et al. 2020)**
- **Virtually all trials use the 24 mg dose.**
- **Clearly lost opportunities with all these trials to do PK and PD.**

My colleagues and I realized this deficit about 10 years ago and I requested support from the Bill and Melinda Gates Foundation to do formal PK and PD studies in sheep and Macaque monkeys and nonpregnant reproductive age women.

Person	Institution	Field
Matt Kemp, PhD	University of Western Australia	Fetal Physiologist
John Newnham, MD	University of Western Australia	Obstetrician
Augusto Schmidt, MD, PhD	University of Miami	Neonatology
Mark Milad, PhD	Bill and Melinda Gates Foundation	Pharmacology
Tom Pappard, PhD	Bill and Melinda Gates Foundation	Pharmacology
Bill Jusko, PhD	University of Rochester	Steroid Pharmacology
Lisa Miller	UC Davis National primate Center	Help with Research

Using funding from the Bill and Melinda Gates Foundation, we have asked a number of questions.

- **What is the minimum dose to get lung maturation?**
- **What are the characteristics of exposure?**
  - **Peak vs. Trough exposure**
  - **Duration – continuous or interrupted?**
- **Why only 40% of fetuses respond with lung maturation?**
- **Mechanisms of action?**

Why should we care about the dose?

DOHaD – Developmental Origins of Health and Disease – a major concern internationally.

The major agonist used for most animal models of DOHaD are Corticosteroids.

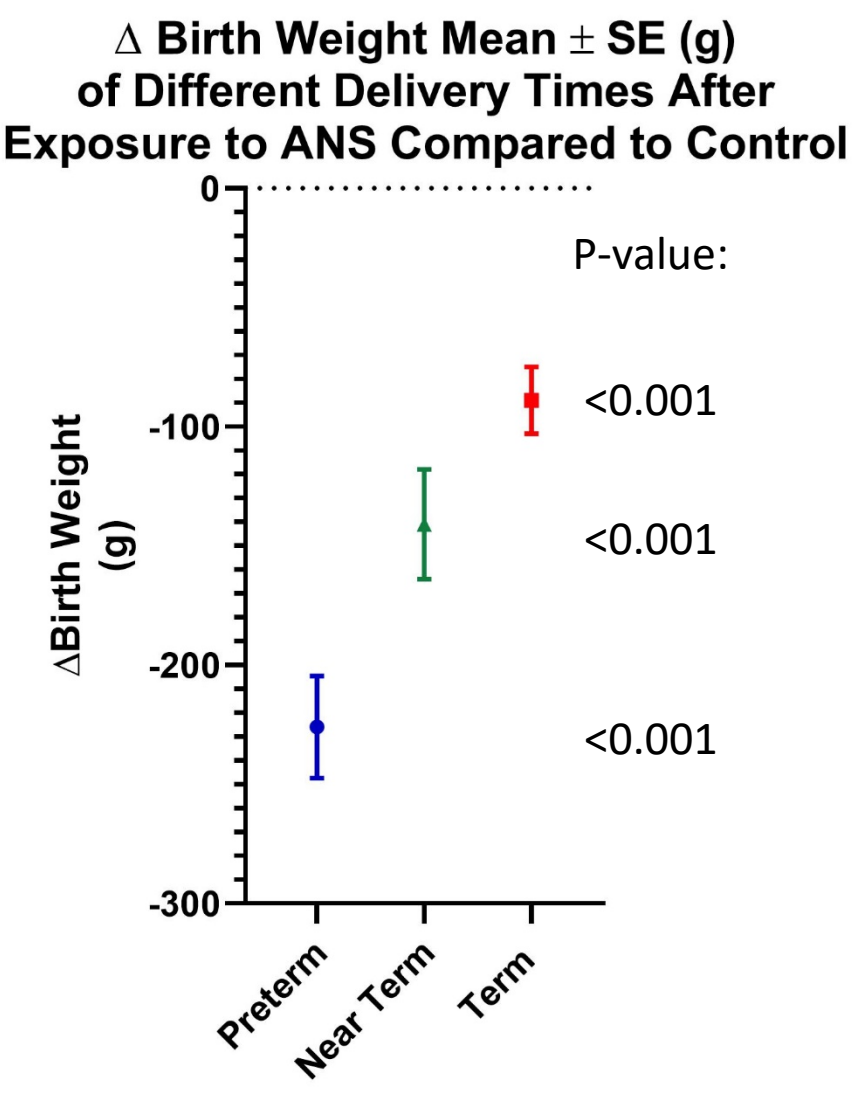
Corticosteroids regulate almost 30% of the transcriptome

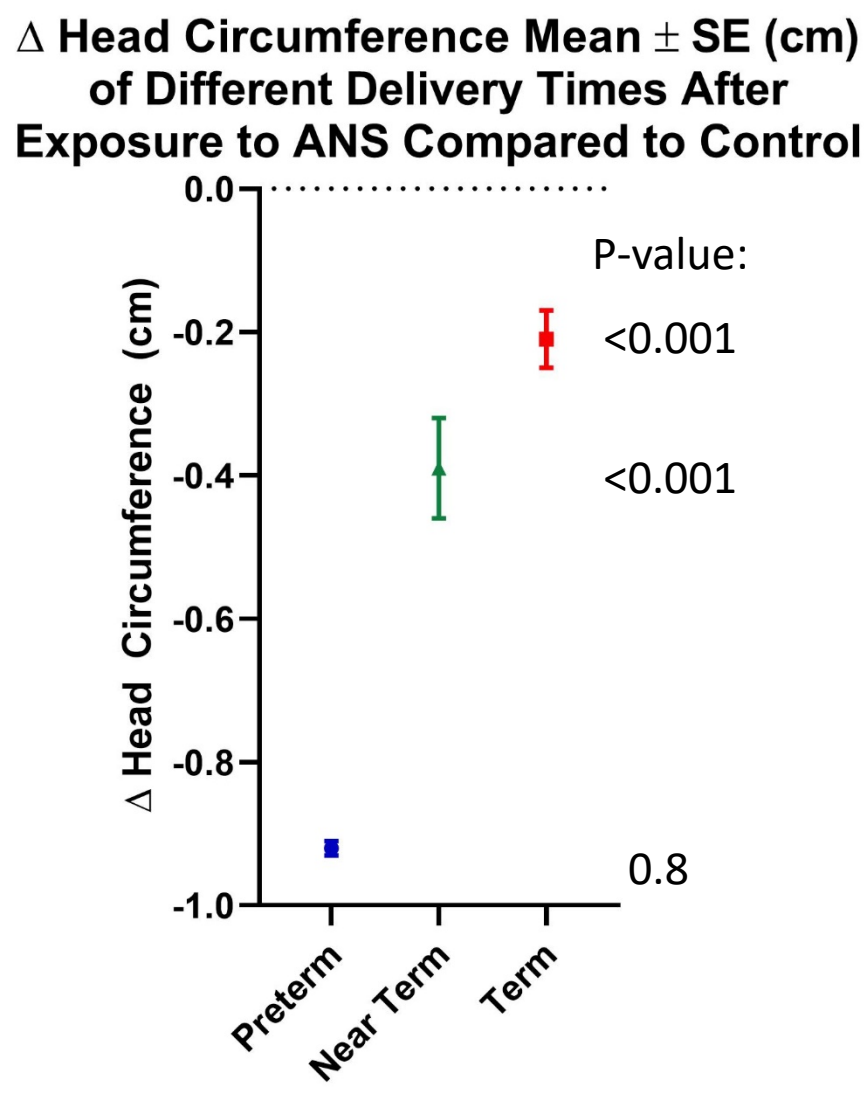
There are risks

Increase mortality of large mature infants in LMIC countries (Althabe, Lancet, 2014)

Increase neonatal hypoglycemia (Gyamfi-Bannerman, NEJM, 2016).

Increase neuro behavioral disorder in children assessed at age 10 years of age exposed to ANS and that deliver at term. (Population based data - Raikhonen, JAMA, 2020)



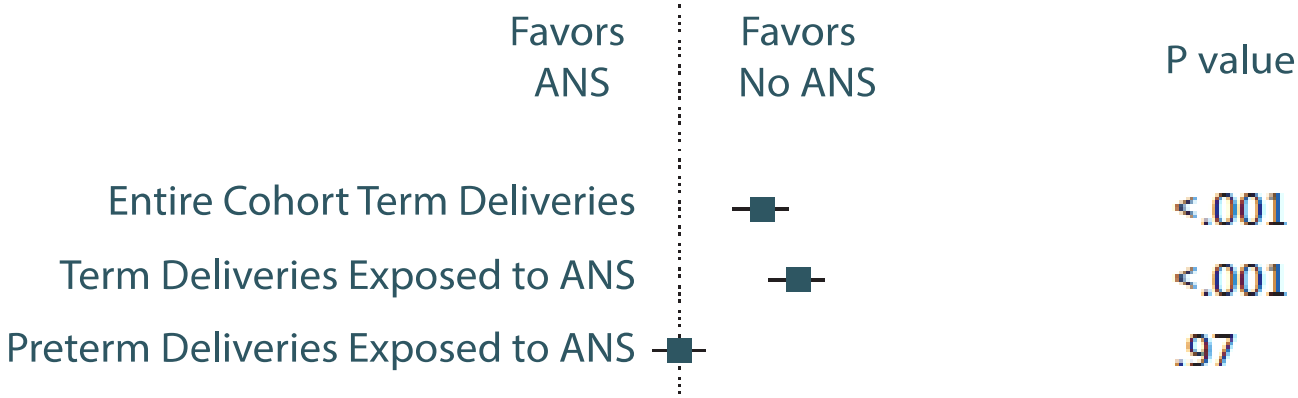


• Preterm Delivery after ANS Exposure ▪ Term Delivery after ANS Exposure

▲ Near Term Delivery after ANS Exposure

Rodriguez et al, PLOS Medicine, 2019

Association between maternal ANS and mental and behavioral disorders in Finnish children 2005 - 2017 (670097 deliveries).

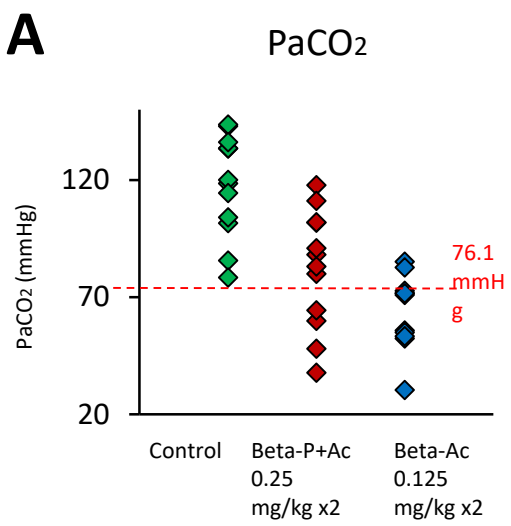


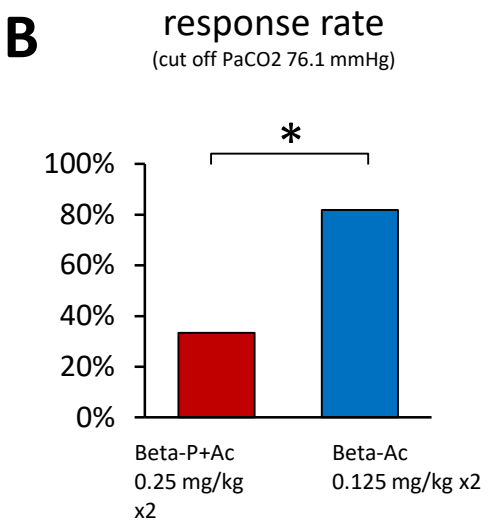
Raikkonen et al JAMA, 2020

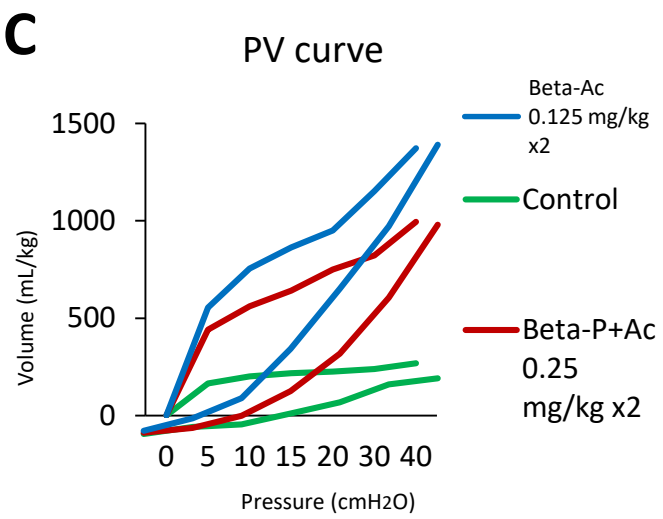
Adverse neurodevelopment with ANS

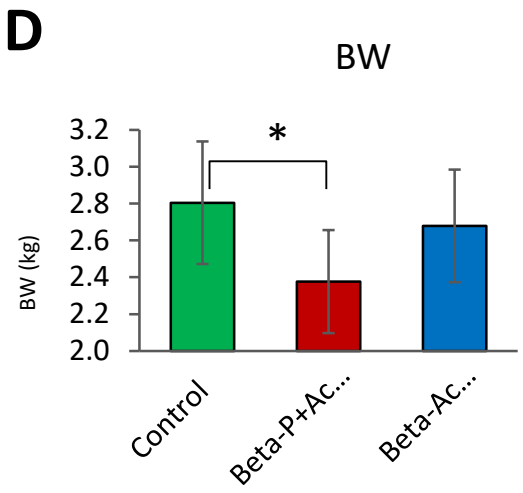
The new striking result is again from the Finnish birth cohort of 670,097 births (2006-2017) a population based analysis, only the Finnish can do this study! This study has a unique subgroup of women who had 2 or more pregnancies – one exposed to ANS and the other not – which controls for genetic/environment effects as variables for the outcomes. For their multiple component neurodevelopmental assessments for the entire cohort, outcomes favor NO ANS. For term deliveries exposed to ANS again more abnormalities with ANS exposure. There was no neurodevelopmental adverse effects of ANS for preterm deliveries, presumably because there will be more abnormalities in a preterm population so ANS are protective. This result is consistent with the multiple follow-up reports on ANS from Crowthers.

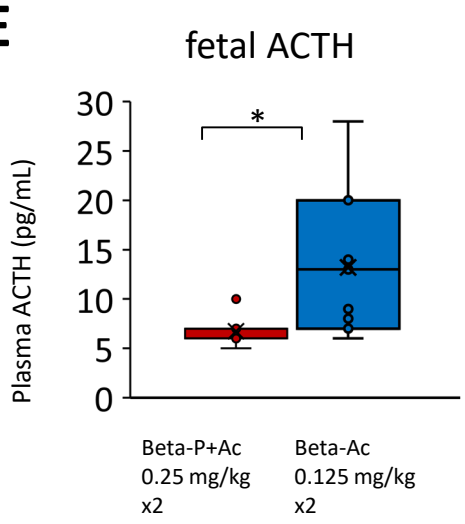
No differences in fetal blood cortisol for responsive vs. nonresponsive at 48 hr after Rx - maternal treatment - sheep.

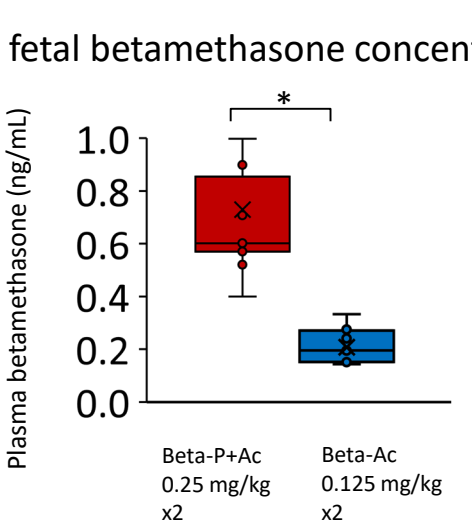




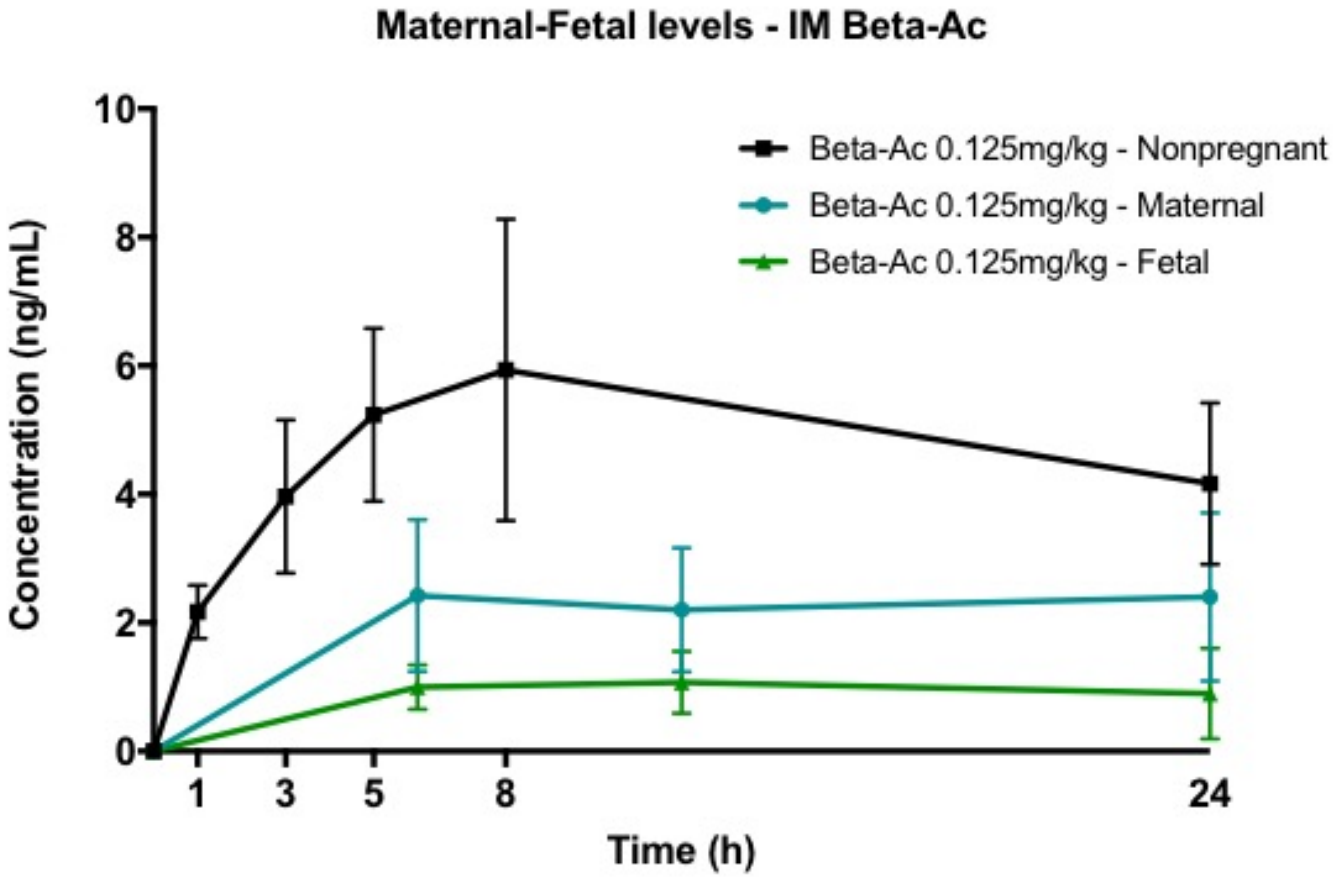








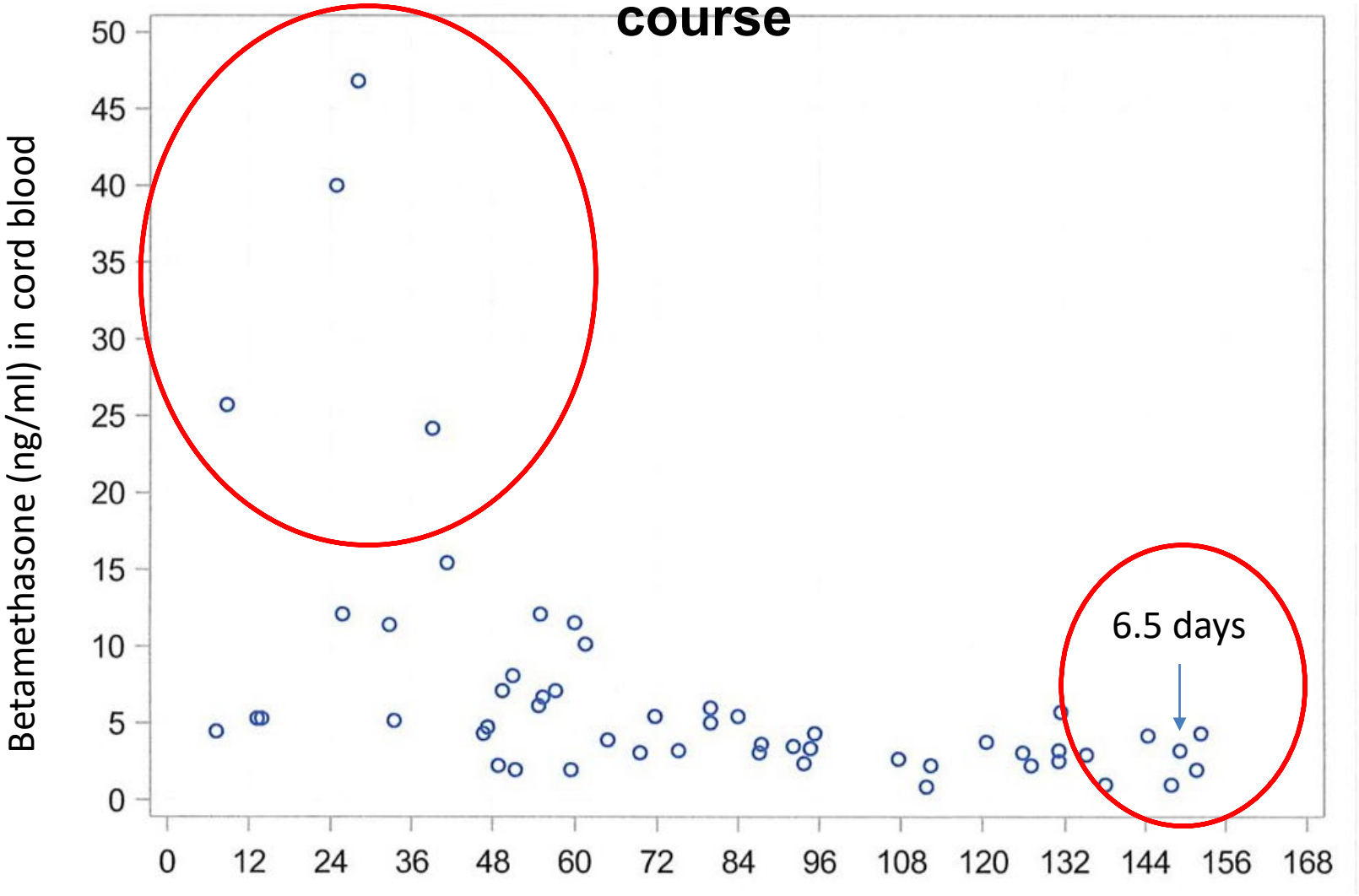
Primate maternal-fetal – IM Beta-Ac



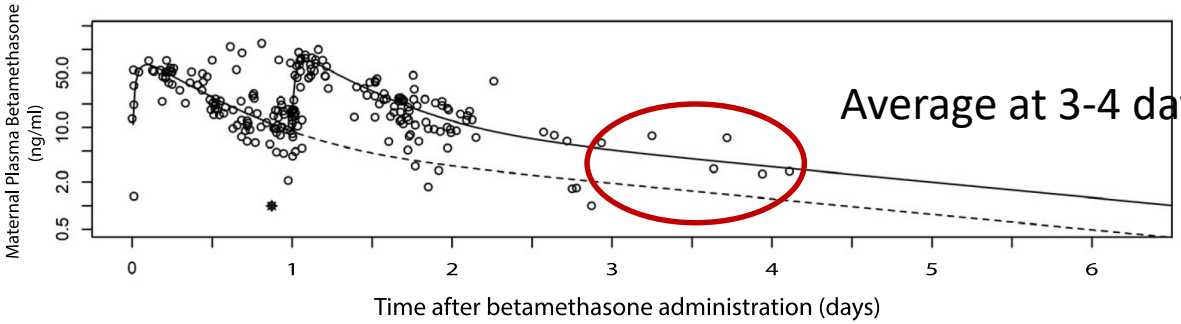
Schmidt et al., submitted

Lower plasma Beta levels in pregnancy?
Fetal Beta – about 1 ng/ml

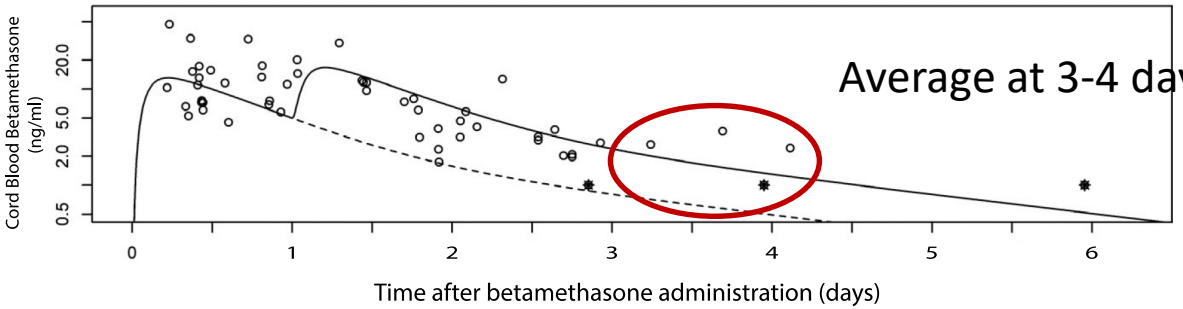
Betamethasone (given as 12 mg as 6mg Beta P and 6 mg Beta Ac) Level in Cord Blood – Time from last course



Wapner et al, 2020



Average at 3-4 days = ~4ng/ml Beta



Average at 3-4 days = ~4ng/ml Beta

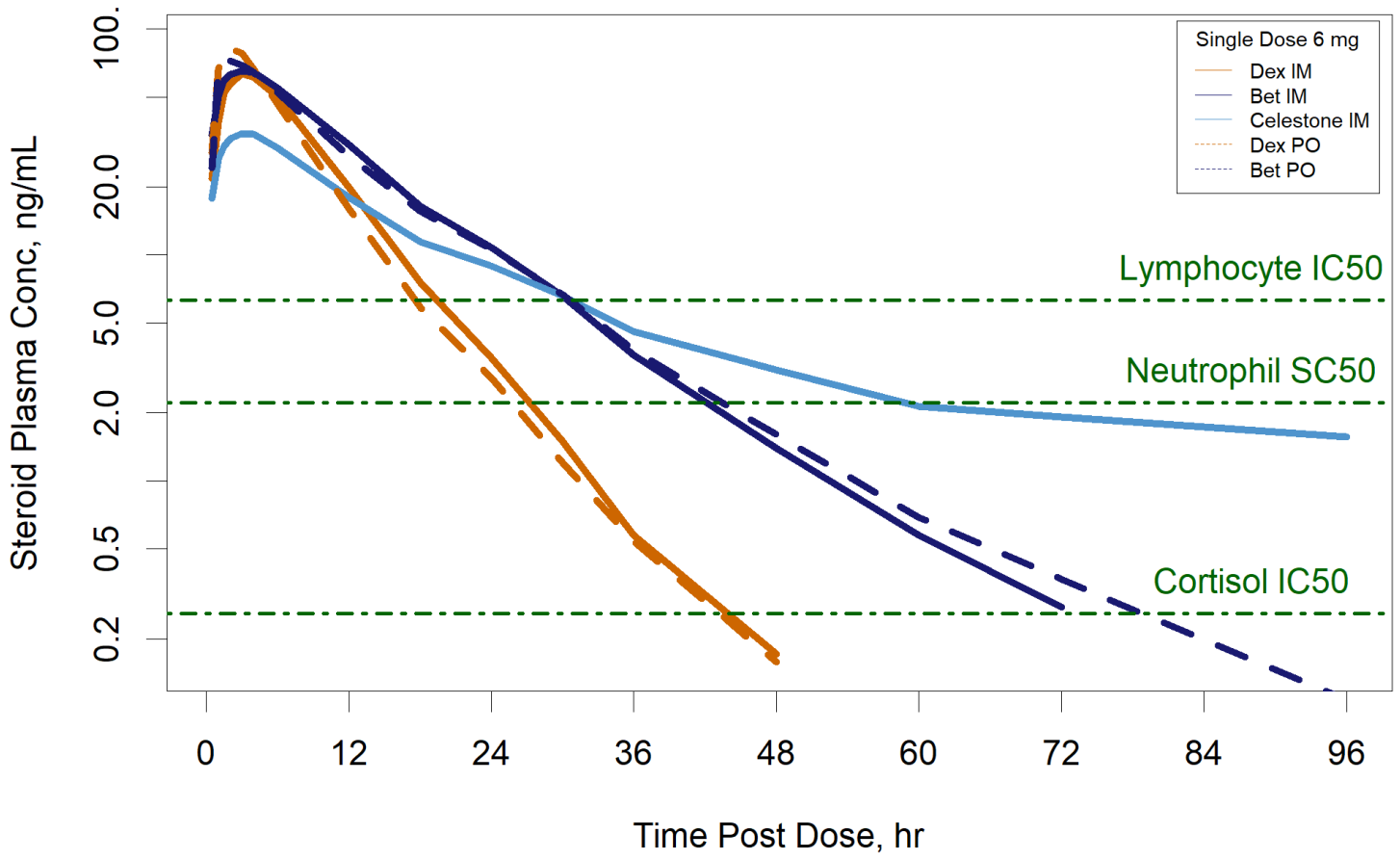
Betamethasone Concentrations – after 1 or 2 doses of 12 mg Beta-P + Beta Ac.

* = below detection

= Values 3-4 days after treatment

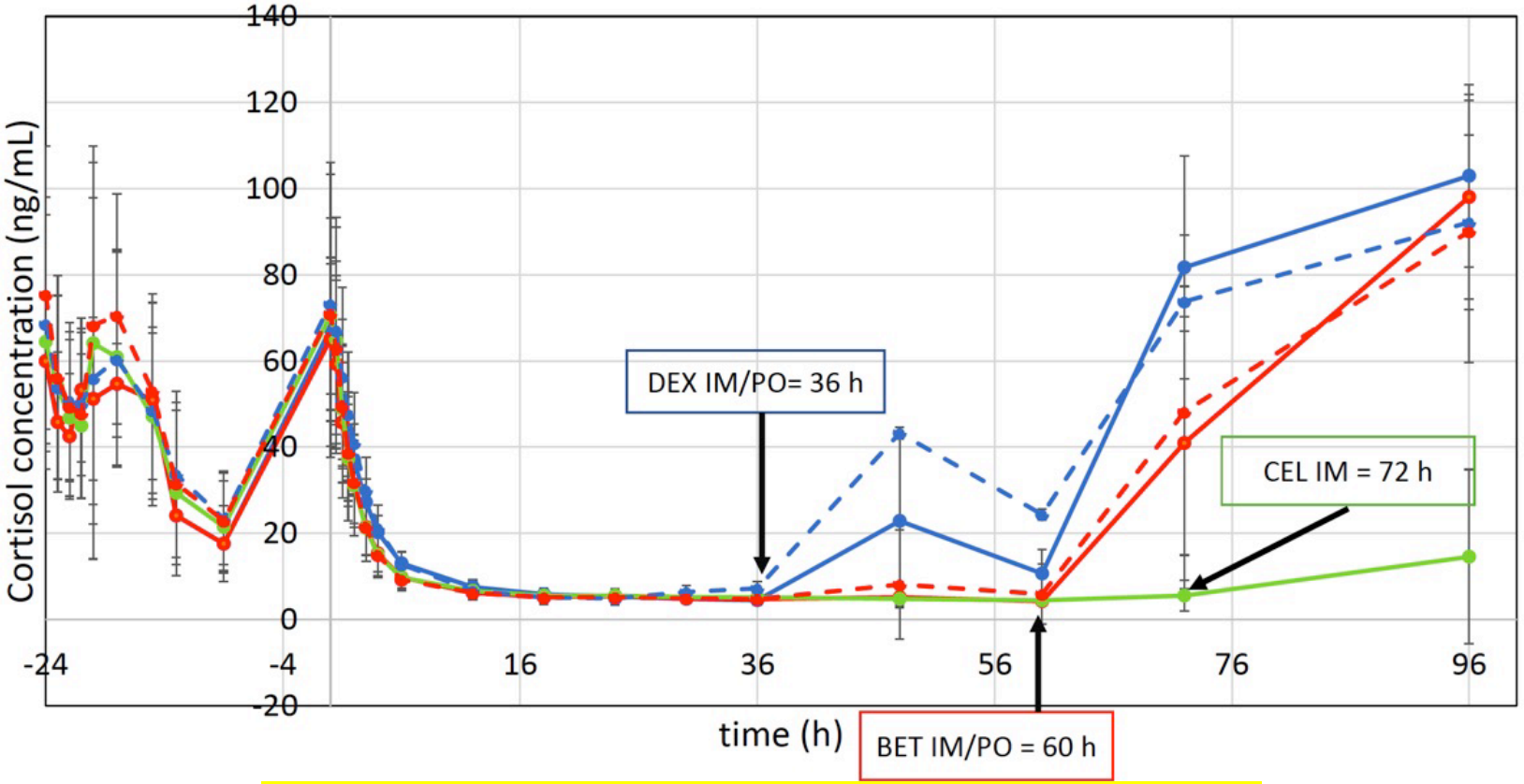
Foissai et al, Clinical Pharm Therapeutics (2020)

Duration of effect is a result of conc-time profile and IC50/SC50



Jobe et al, Clinical Pharm Therapeutics, 2020

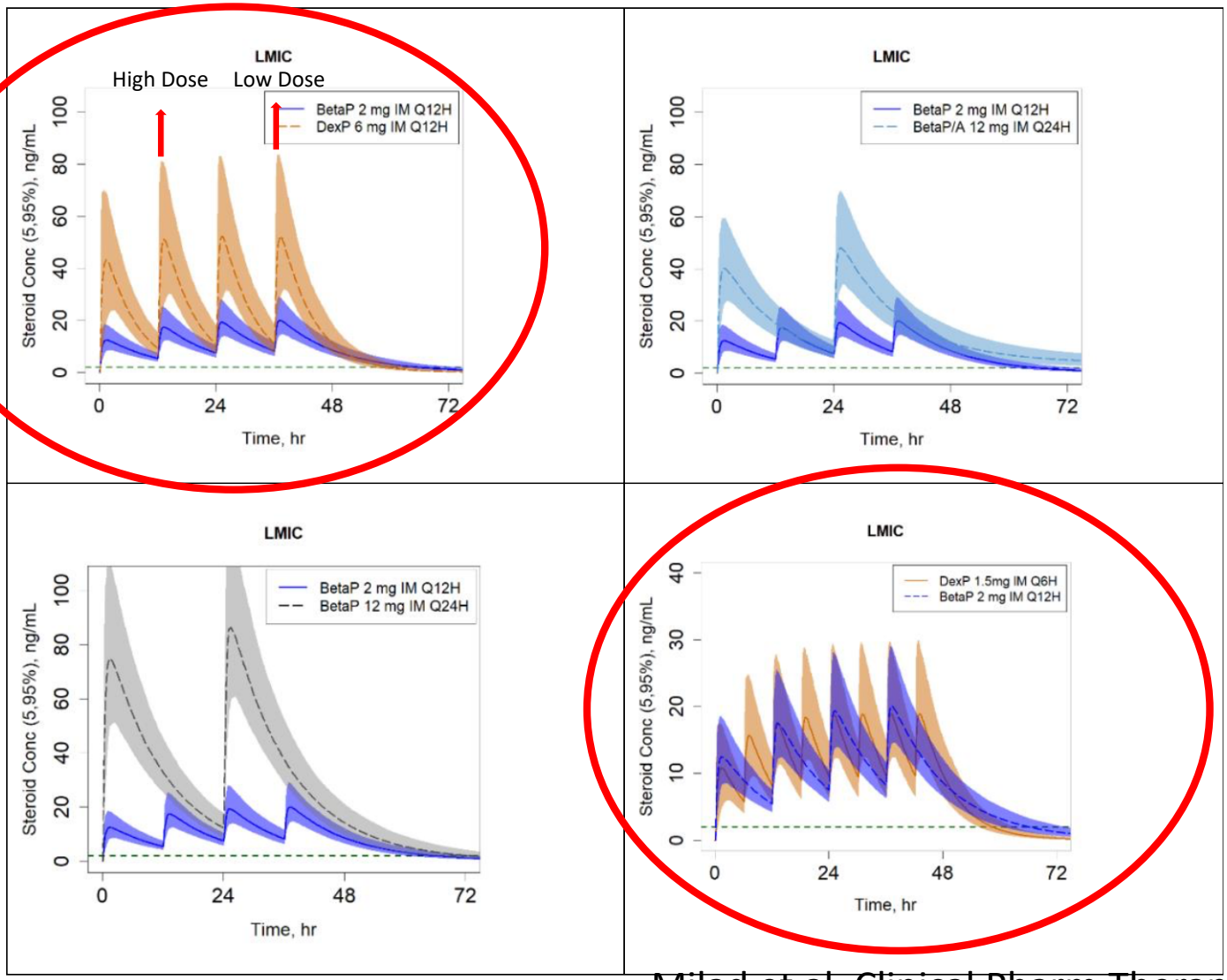
Cortisol concentration in non-pregnant Indian women before and after treatment with 6mg Dex-P or Beta-P IM and with the suppression time in the order of CEL>>BET>DEX



Profound cortisol suppression with all treatments

Jobe et al, Clinical Pharm Therapeutics 2020

Simulated plasma concentration profiles from the PopPK model following a low dose regimen compared to the three standards of care, and a low dose regimen for BetaP and DexP.



Milad et al, Clinical Pharm Therapeutics, 2020

Summary

- ANS have very different PK but similar PD depending on drug
- Effective PD for fetal lung maturation in sheep ~2 ng/ml
- monkey ~1 ng/ml (perhaps less in human)
- Fetal exposure should be >48 hrs. for a durable 7d effect.
- Very low dose probably does not cause FGR or as much adrenal suppression.
- Newer follow up data indicates substantial risk for injury in many newborns.
- Many pregnancies do not benefit from ANS.
- A low-dose RCT is needed.