Timing of the postpartum curve in pharmacokinetic studies in pregnancy should not be too early

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Radboudumc

panna

- A European clinical pharmacology network to investigate the pharmacokinetics of newly developed antiretroviral agents in HIV-infected pregnant women
- Pregnancy may induce changes in PK of ARVs
- Possibly sub-therapeutic levels in pregnancy as a result

Outline PANNA study protocol

General study protocol, not specified per drug, 17 ARVs

PK curve 3rd trimester

Appr wk 33 gestational age

PK curve postpartum

at least 2 weeks after delivery

How does pregnancy affect pharmacokinetics?

gastric pH
↑

gastric emptying and intestinal motility
↓

Total body water
↑

Plasma volume
↑

Total body fat
↑

Albumin conc.
↓

CYP3A4 activity
↑

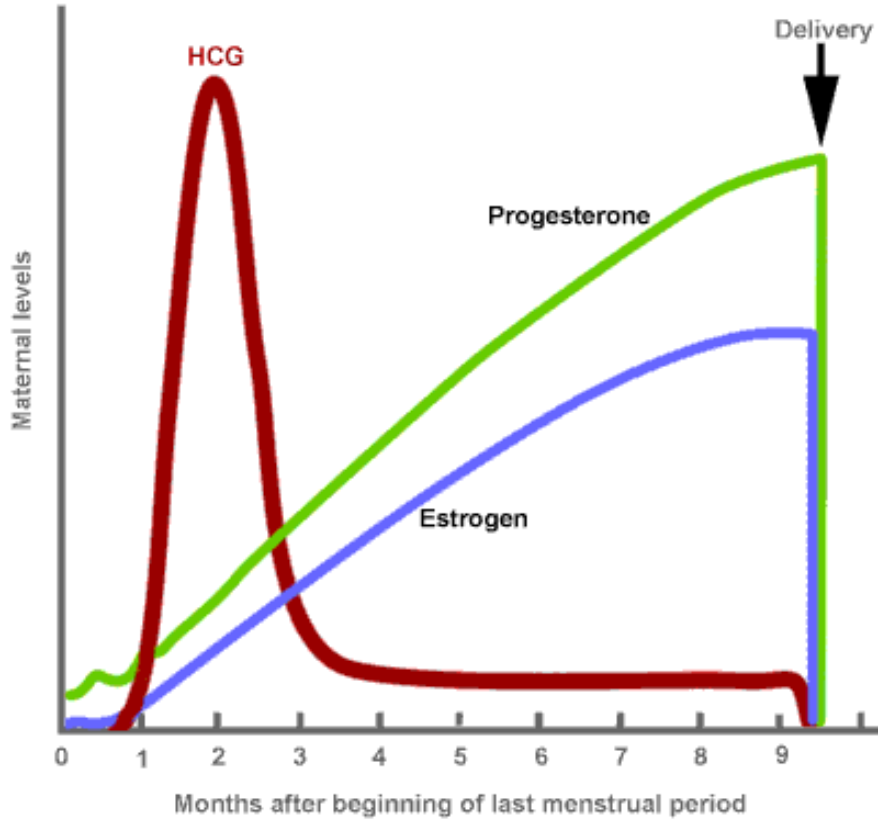
CYP2D6 activity
↑

CYP2C19 activity
↓

GFR
↑

Anderson, Clin Pharmacokinetics, 2005
Abduljalil, Clin Pharmacokinet., 2012

Physiological explanation



Physiological explanation

Progesterone and estradiol cause

Inhibition of enzymes

Induction of enzymes

Induction of transporters – P-gp

Both AUC and C_{max} can be affected

Research question

Post-partum curve is used as the control curve: normal, non-pregnant situation

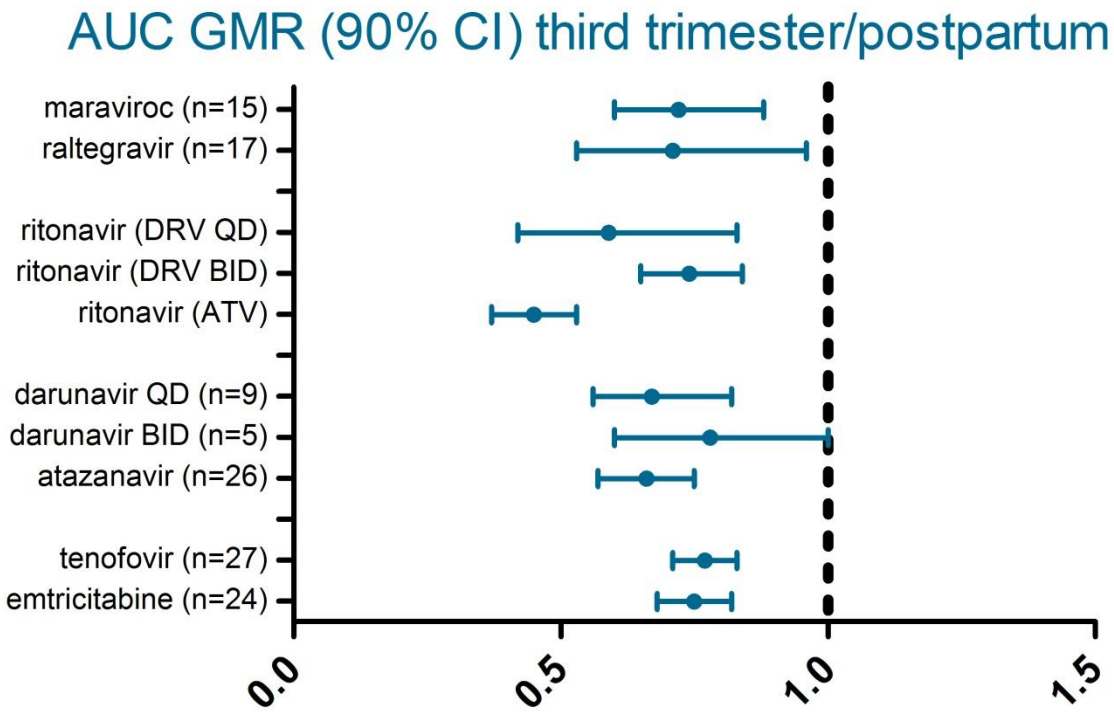
Is this a valid assumption?

When should an increased dose in pregnancy be reduced?

PK curve
at least 2 weeks
after delivery

Methods

Compounds for which lower exposure in pregnancy was observed



Methods

Normalise over different agents

Postpartum AUC and C_{max} values were compared to accepted non-pregnant population AUC and C_{max} for the specific agent

Ratio postpartum / population mean:

$$\frac{\text{Individual postpartum AUC}}{\text{Population AUC for that compound/regimen}}$$

Methods

The time-point of the postpartum curve was grouped per week.

>8 weeks postpartum pooled

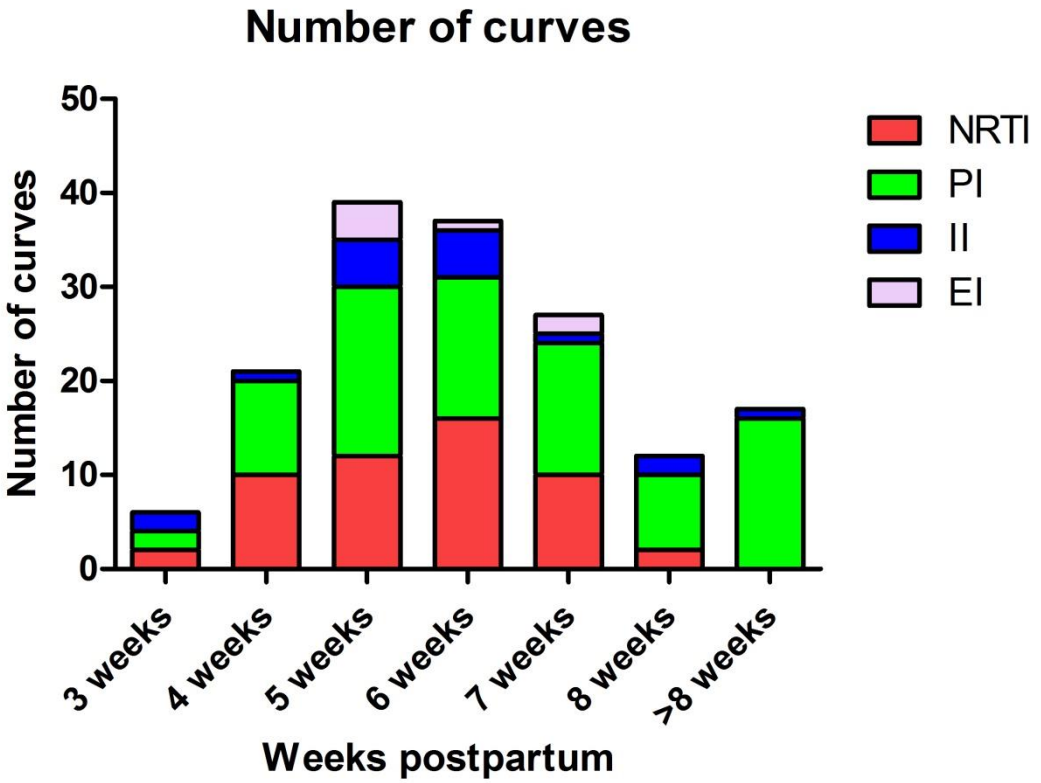
Kruskal Wallis test with weeks postpartum as grouping variable was used for statistical analysis.

Results

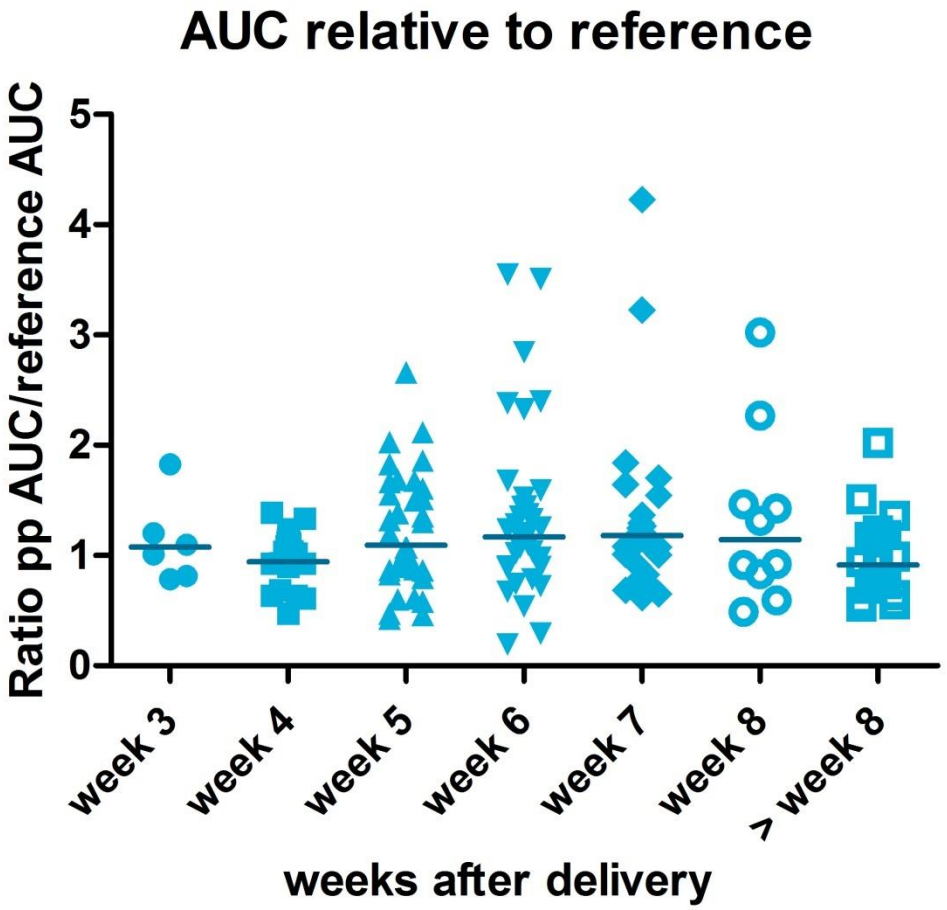
157 postpartum curves, from 67 unique patients

Characteristics	Median (range)
Age at delivery (years)	32 (19-45)
Race	
Black	60%
White	39%
Other	1%
Weight at postpartum (kg)	71 (43-126)
Weight at 3rd trimester (kg)	76 (48-139)

Results

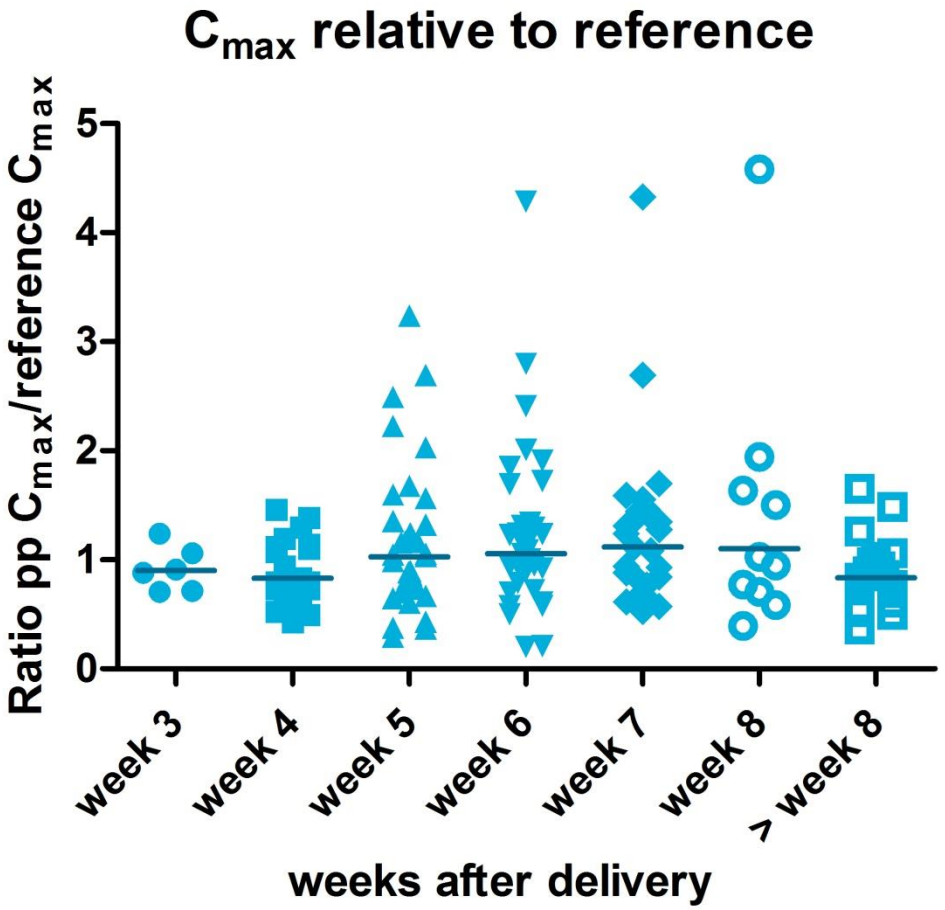

Number of curves
Number of curves
50
40
30
20
10
0
3 weeks
4 weeks
5 weeks
6 weeks
7 weeks
8 weeks
>8 weeks
Weeks postpartum
NRTI
PI
II
EI

Results



Kruskall Wallis
p = 0.337

Results



Kruskall Wallis
p = 0.227

Conclusion

- No time effect was observed for postpartum curves taken at least 3 weeks post delivery
- Postpartum curves from at least 3 weeks post delivery were comparable to non-pregnant population means
- Dose reductions (after dose increase in pregnancy) should be considered from > 2 weeks post delivery onwards

THANKS TO

Participants in PANNA study

Investigators of the PANNA study

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Website: panna

www.pannastudy.com