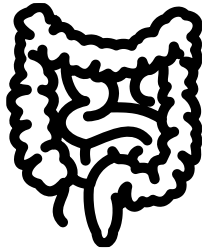


# Dosing regimen optimisation of vedolizumab in pregnancy through physiologically-motivated sequential NLME modelling of albumin trends and vedolizumab PK

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# Pregnant patients: “therapeutic orphans”



Active IBD → adverse pregnancy outcomes<sup>1</sup>

- Vedolizumab blocks T-cells trafficking in gut
- **Dosing intensification** to achieve remission

Safety of mother and foetus



Most mAbs cross placenta (3<sup>rd</sup> trimester)

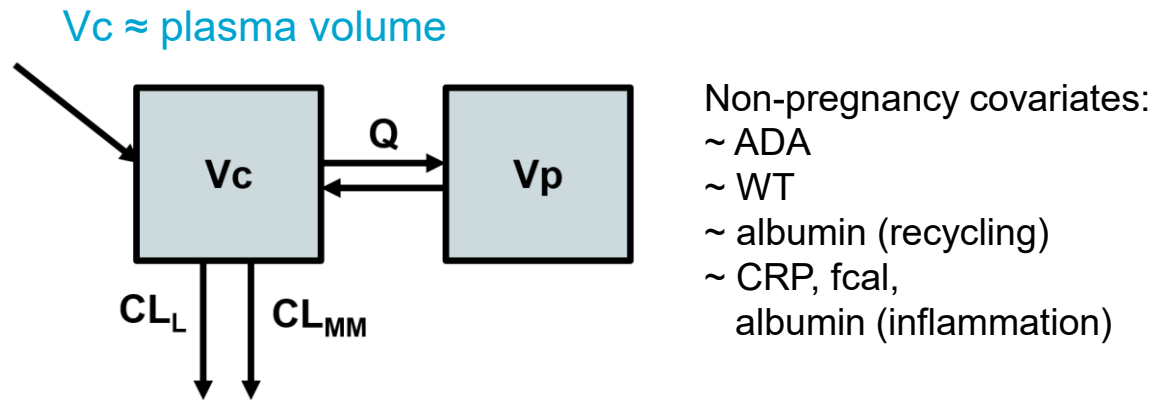
- Vedolizumab: **low risk** for foetus<sup>2</sup>
- **Continuation** of 3<sup>rd</sup> trimester dosing<sup>3</sup>

Limited understanding of mAbs PK in pregnancy<sup>4,5,6</sup>

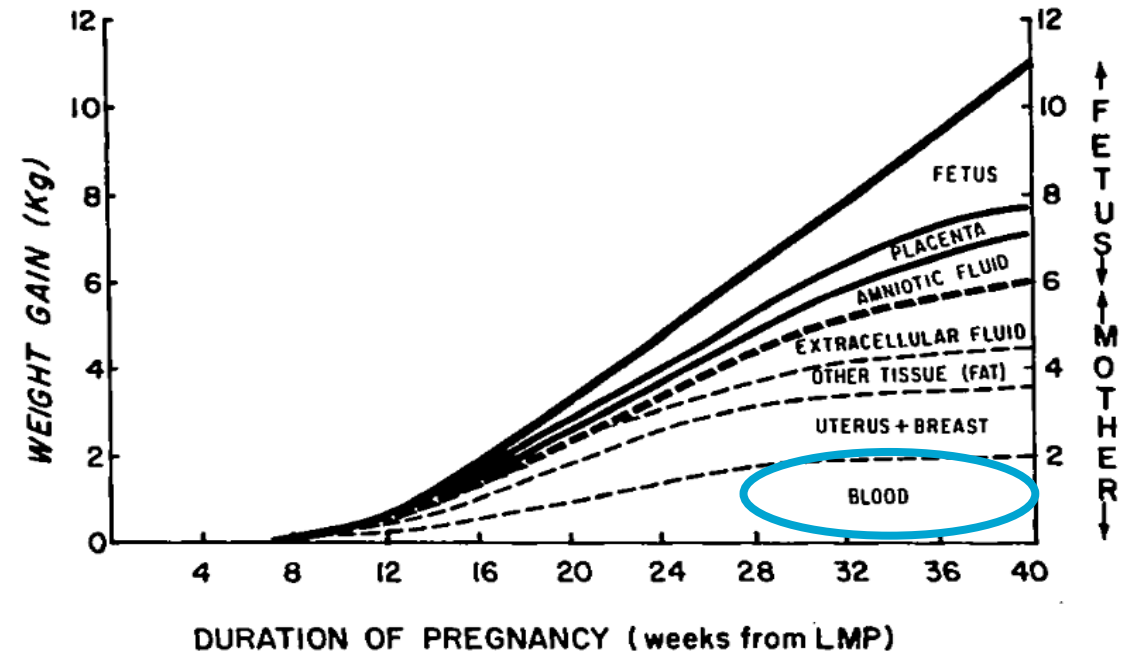
**Impact of pregnancy on vedolizumab PK and its variability?**

**Dosing regimen adjustments throughout pregnancy to maintain pre-pregnancy exposure?**

# PK of mAbs and pregnancy

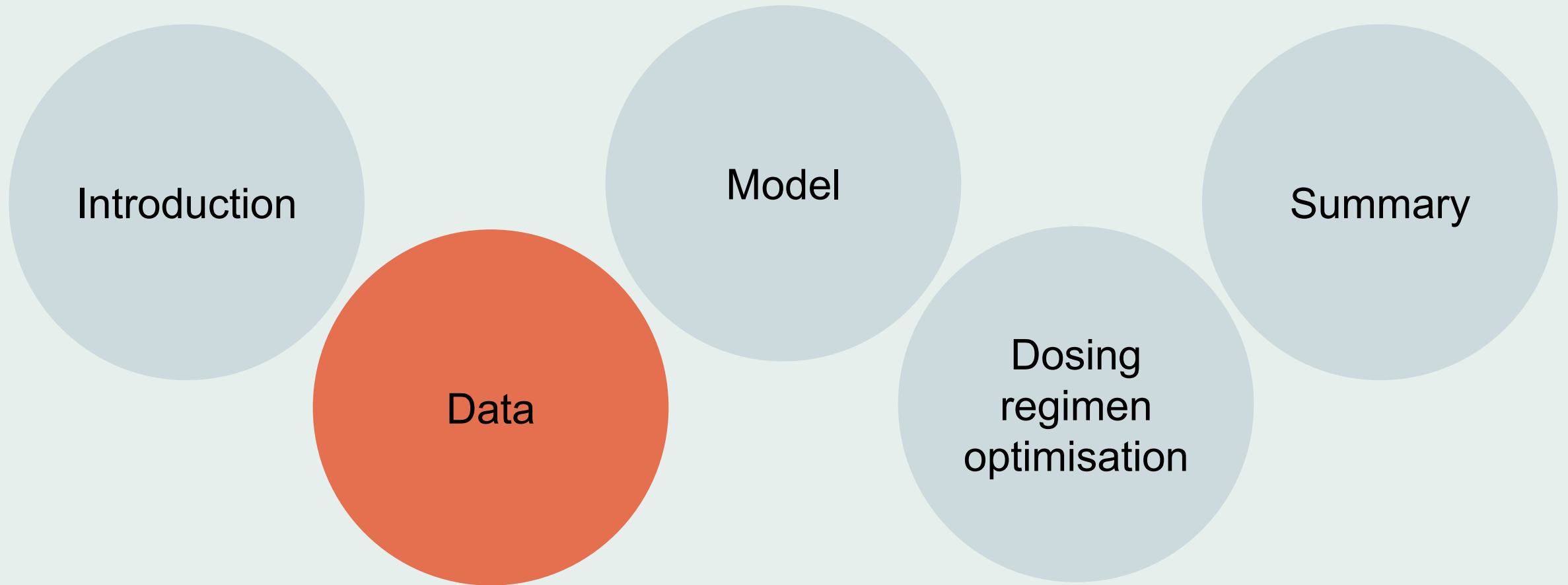


- High IIV in degree of plasma expansion<sup>1</sup>
- Decrease in albumin concentration during pregnancy primarily explained by haemodilution<sup>2</sup>



Use of albumin change as a biomarker of plasma expansion?  
(mixed-effects model of albumin trends)

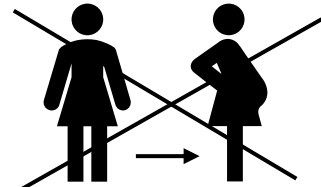
# Outline



# Available PK data



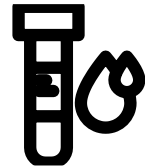
Patients  
N = 39



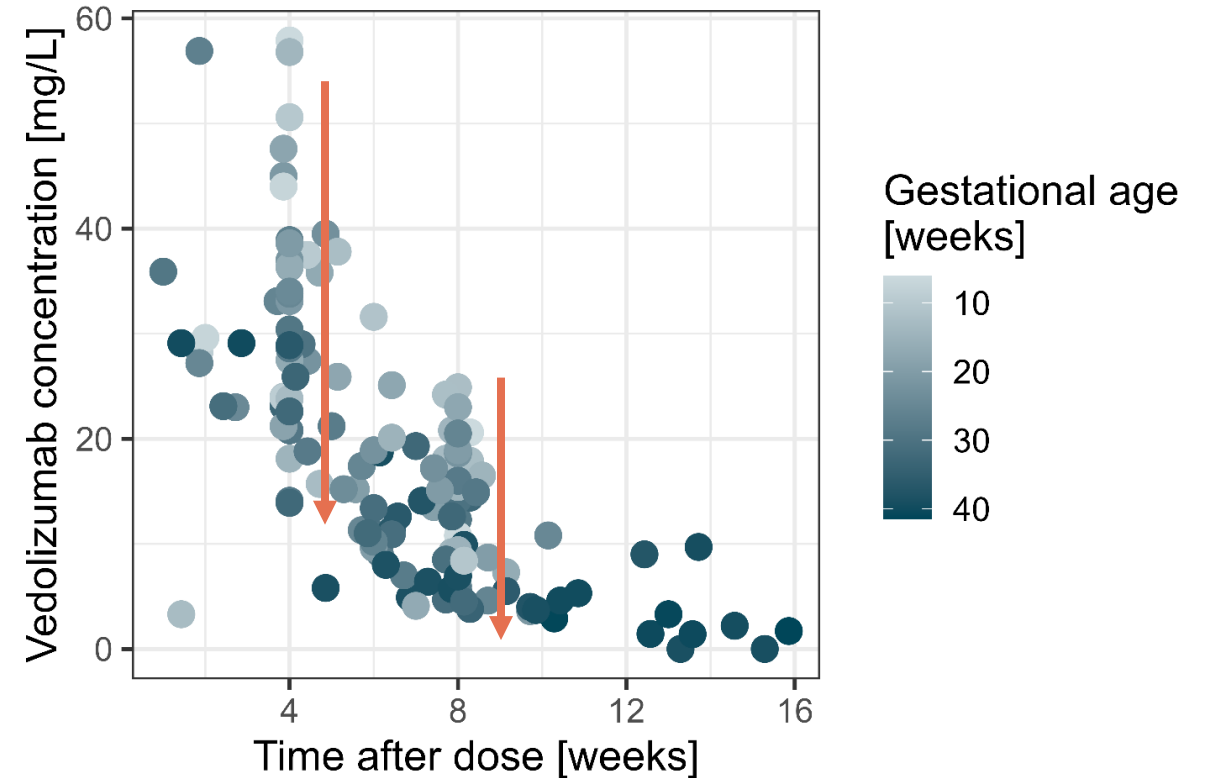
No pre-pregnancy  
vedolizumab data



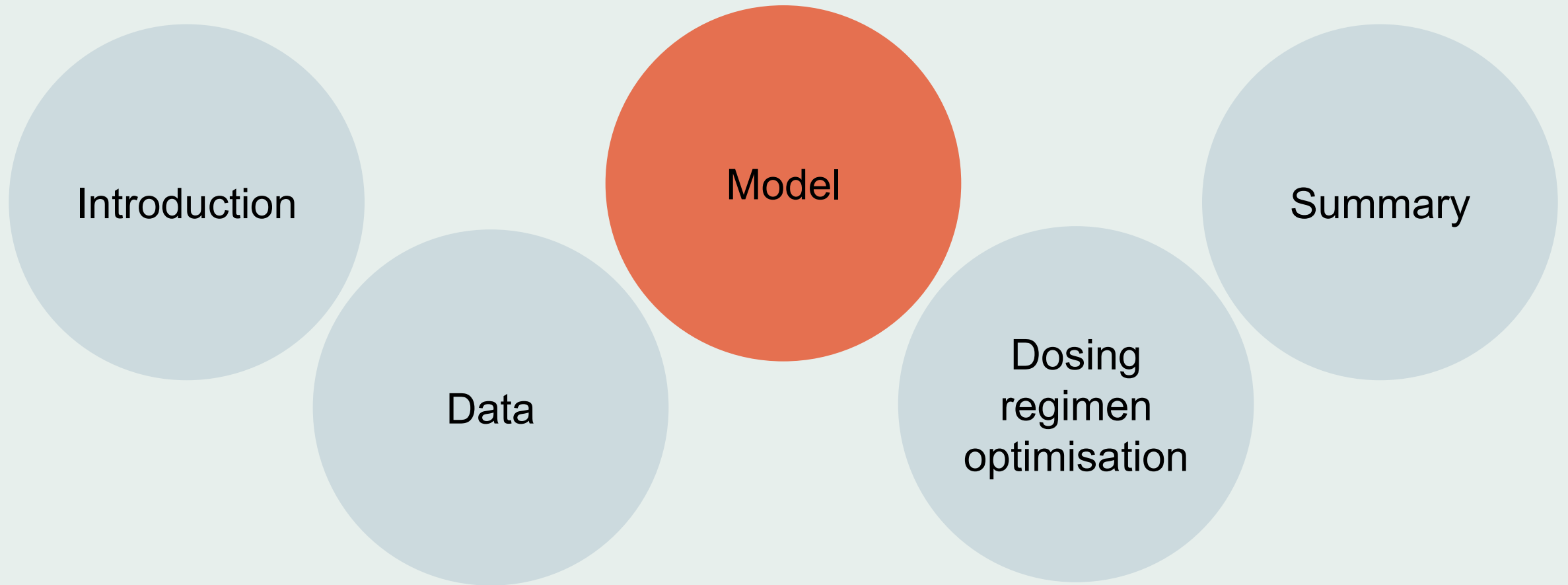
Samples per patient  
median: 3,  
range: 2-5



Samples, N = 138,  
**C<sub>min</sub> only**,  
(same dose, different intervals)

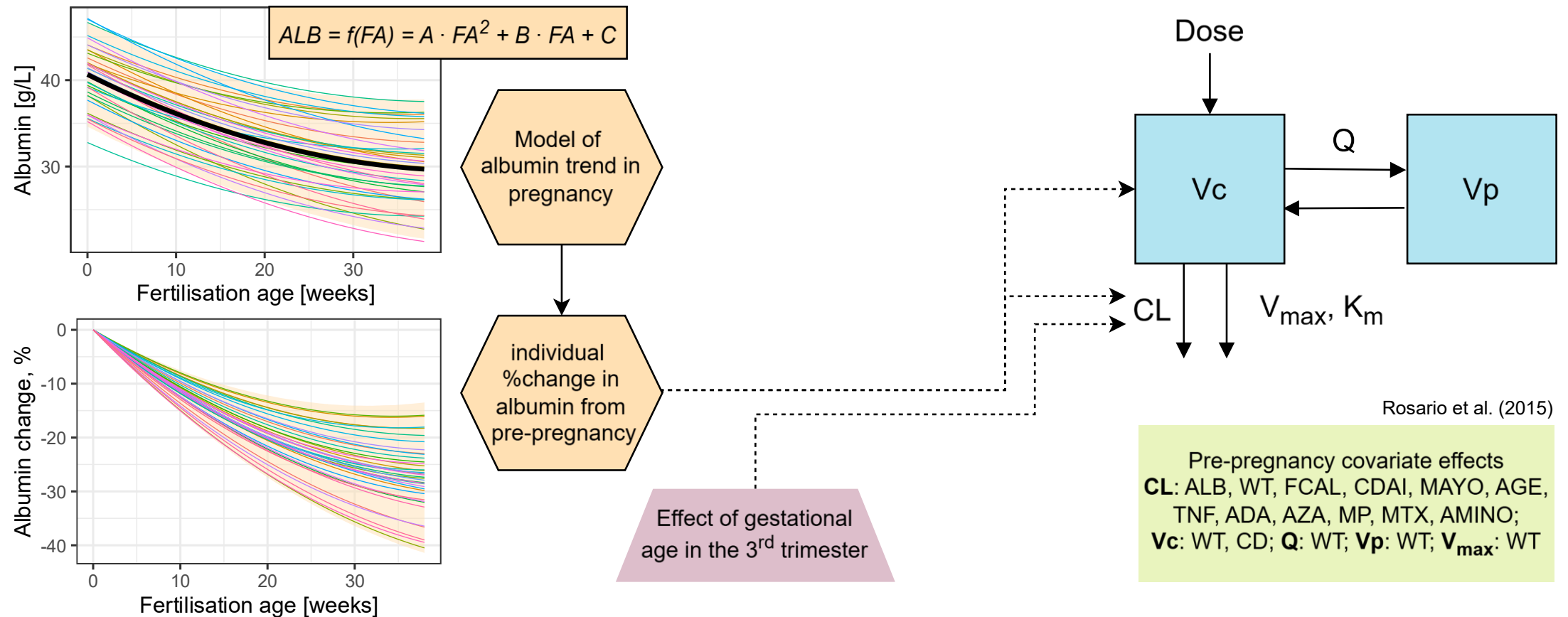


# Outline

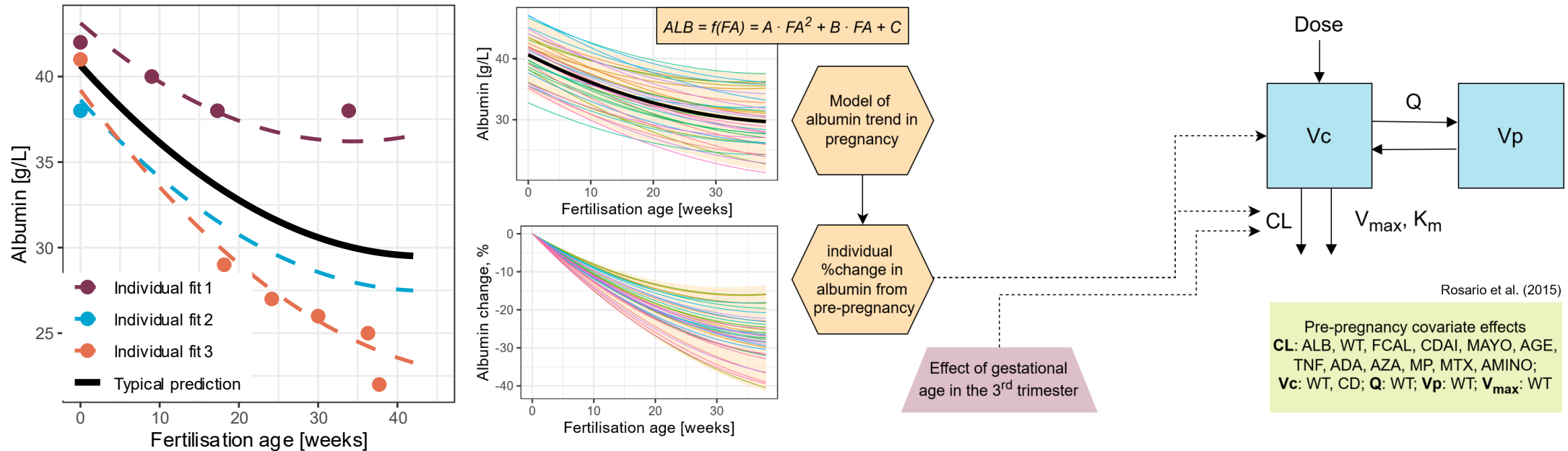


# Albumin trends and vedolizumab PK in pregnancy

## - sequential mixed-effects modelling



# Approach **advantages**



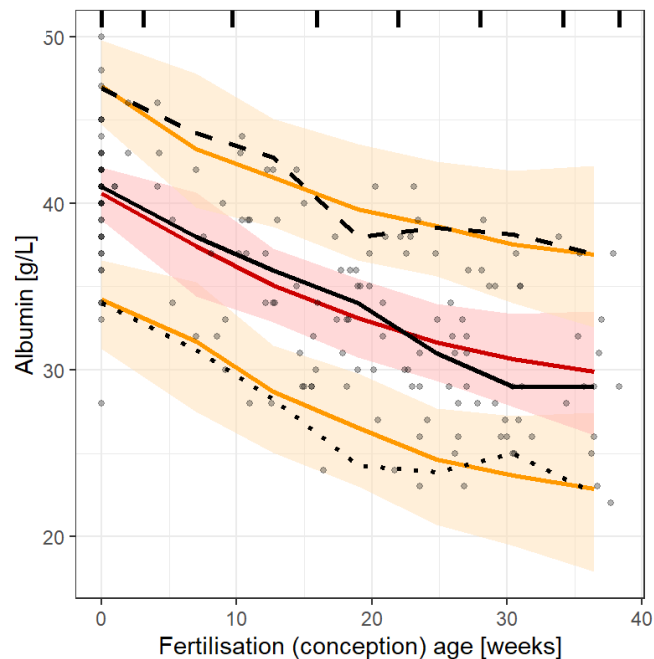
- Albumin measurements not assumed to be error-free, correcting for changes in inflammation status,
- Suitable way of dealing with missing covariate data
- Exploration of covariates

- Size of the pregnancy effect individualised
- Estimation of pre-pregnancy structural parameters possible



# Model described the data well

Albumin-trends model



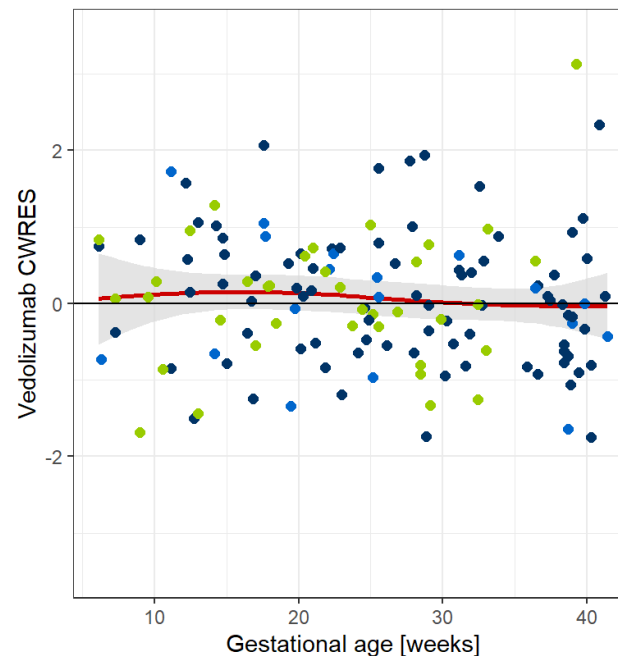
Observed Percentiles (black lines)

- 5%
- 50%
- 95%

Simulated Percentiles Median (lines) 95% CI (areas)

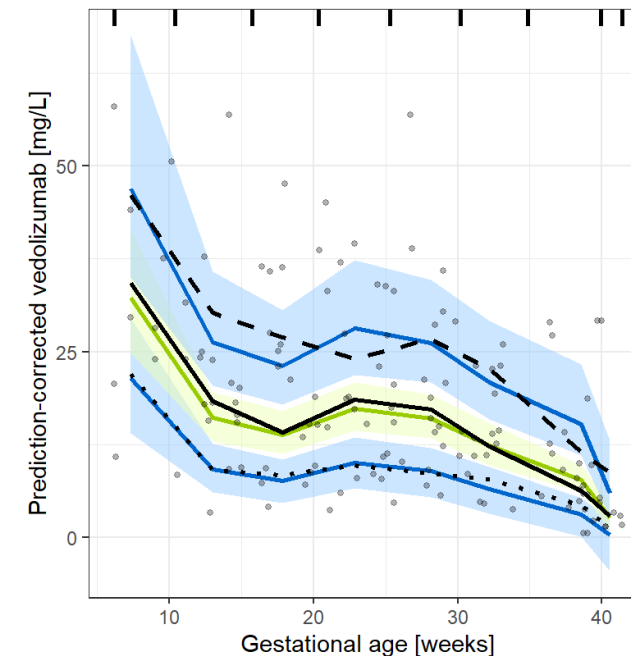
- 5%
- 50%
- 95%

PK model of vedolizumab in pregnancy



Dosing interval [weeks]

- 4
- 6
- 8



Observed percentiles (black lines)

- 5%
- 50%
- 95%

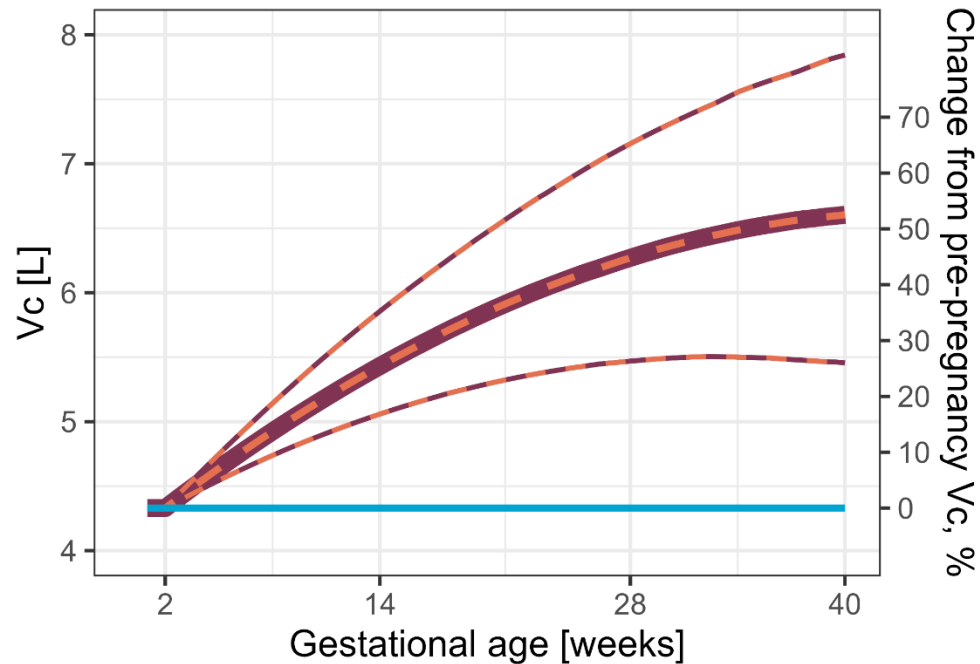
Simulated percentiles Median (lines) 95% CI (areas)

- 5%
- 50%
- 95%

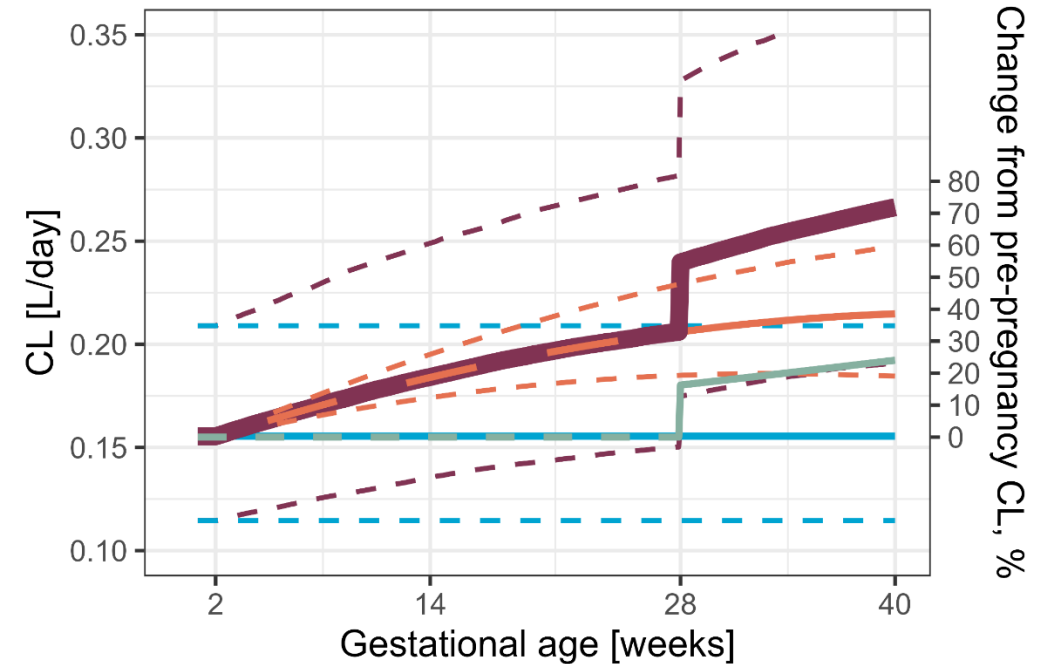
All parameters were estimated with good precision

(fixed effects <25%, random effects <45, covariate effects <35%)

# Impact of pregnancy on structural parameters



- $V_c$  estimate reasonable for vedolizumab
- Estimated %increase in  $V_c$  (52%) aligns with reported extent of plasma expansion (50%)<sup>1</sup>



- Most of variability is pre-pregnancy variability
- CL is estimated to increase less than  $V_c$  (due to albumin change)
- 3<sup>rd</sup> trimester effect aligns with the drop in endogenous IgG levels<sup>2</sup>

--- 5<sup>th</sup>-95<sup>th</sup> percentile

— Median

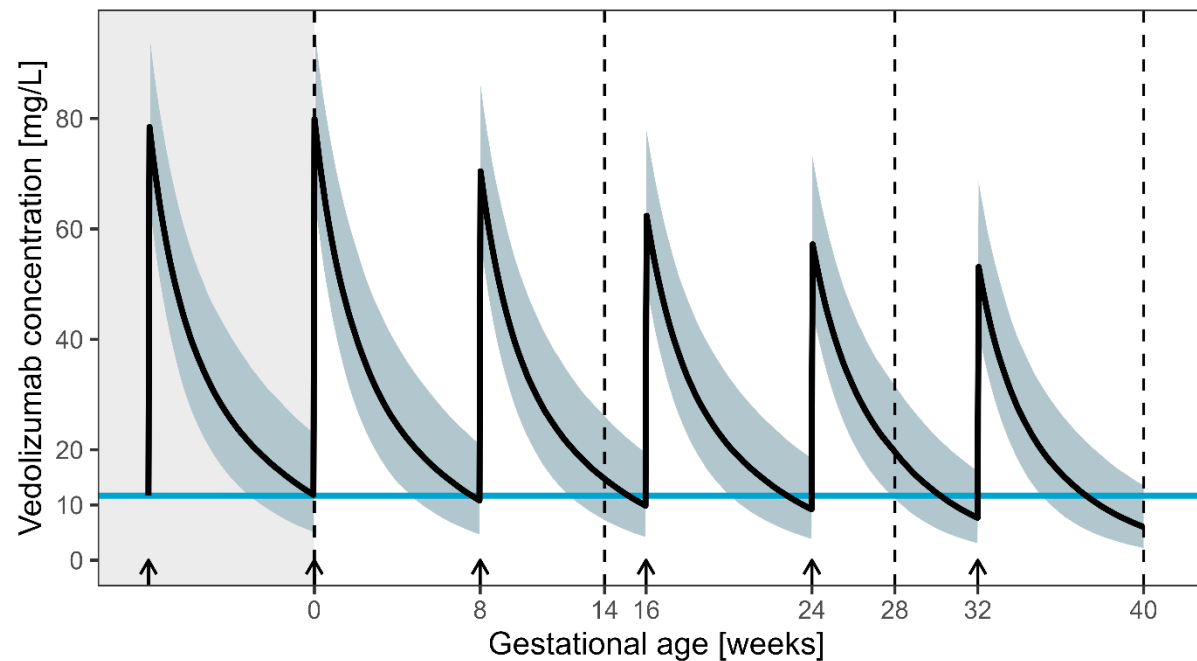
— Pre-pregnancy

— Albumin change contribution

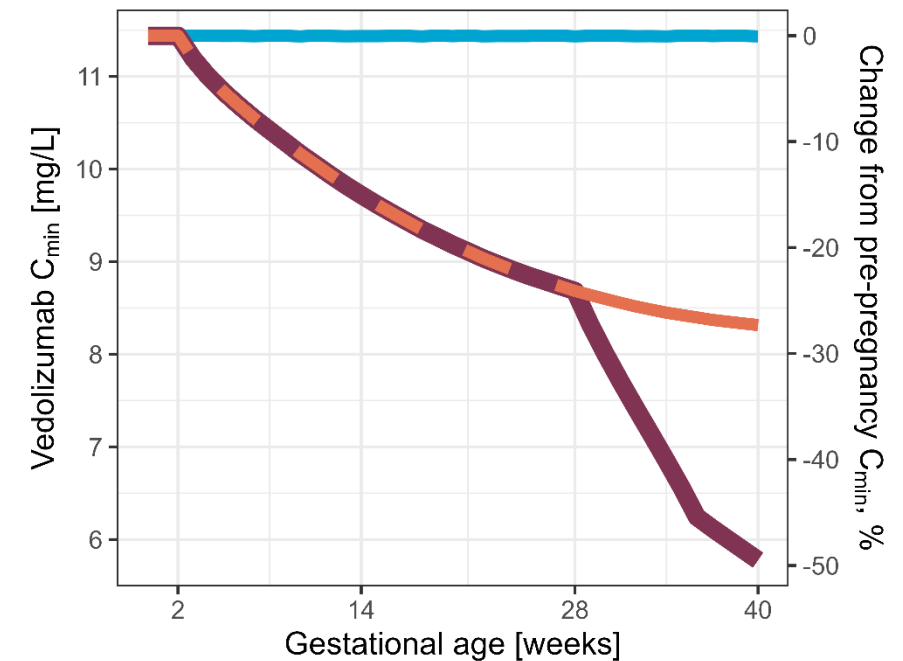
— Effect of gestational age in the third trimester contribution

— Parameter throughout pregnancy (with all pregnancy effects)

# Impact of pregnancy on PK profile



5<sup>th</sup> to 95<sup>th</sup> simulated percentiles    Median    Pre-pregnancy  $C_{min}$



albumin-change effect only    full pregnancy model

Exposure gradually decreased: >20% until end of the 2<sup>nd</sup> trimester and 50% at the end of pregnancy

→ Need for dosing regimen optimisation?

# Outline

Introduction

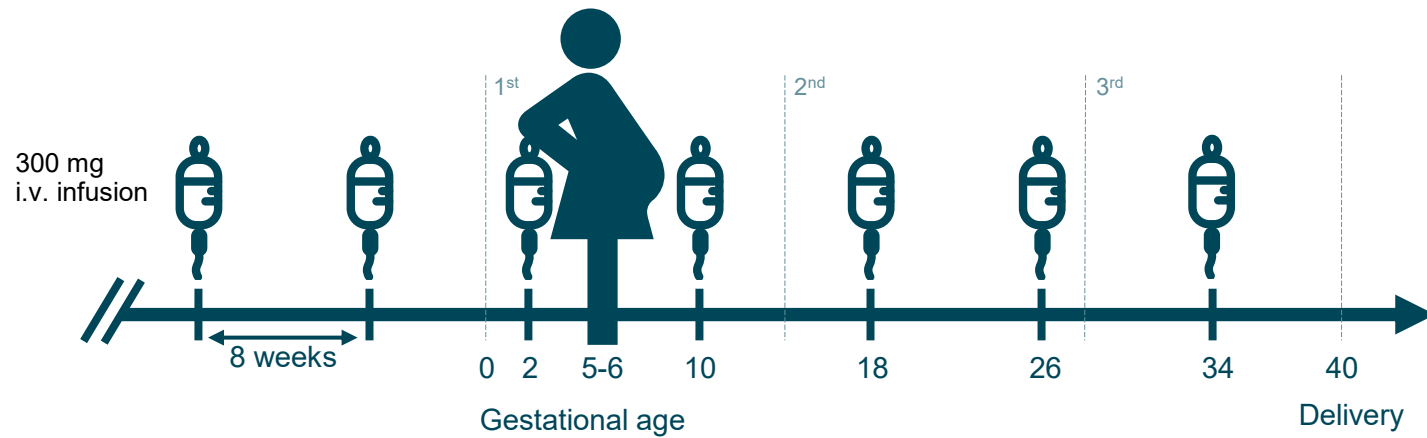
Data

Model

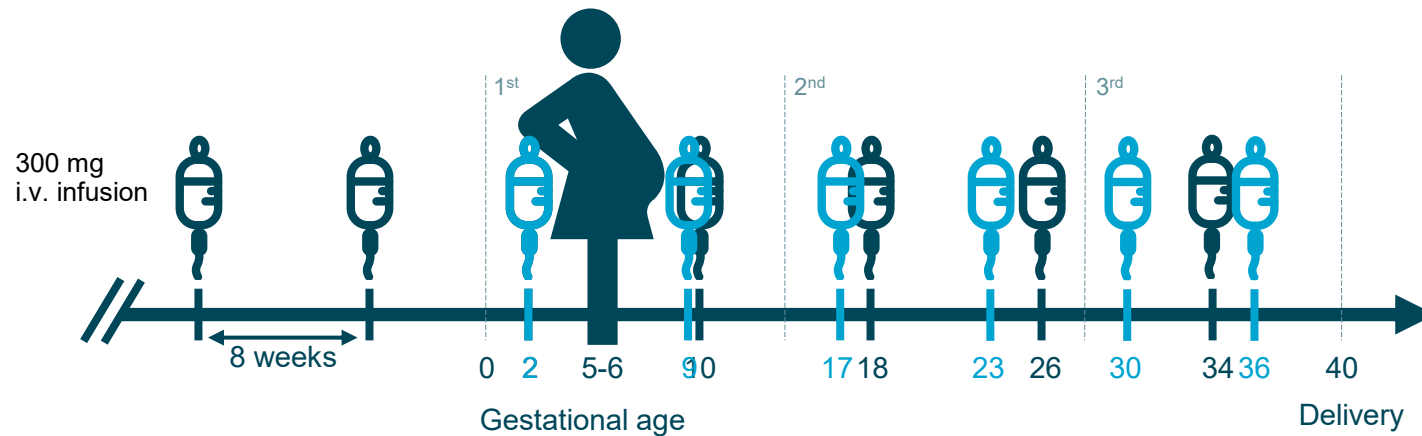
Dosing  
regimen  
optimisation

Summary

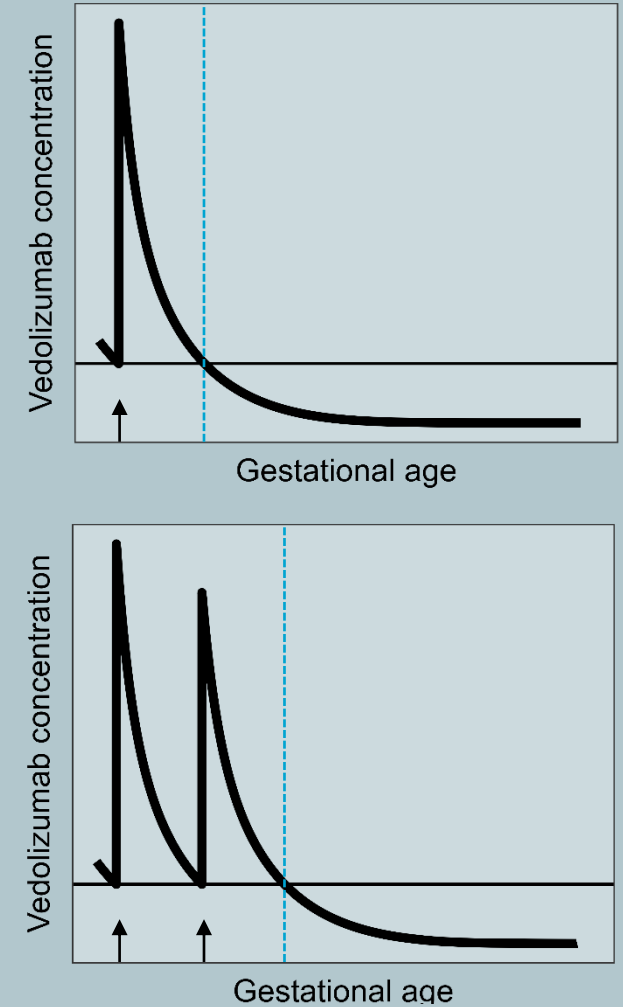
# Dosing regimen



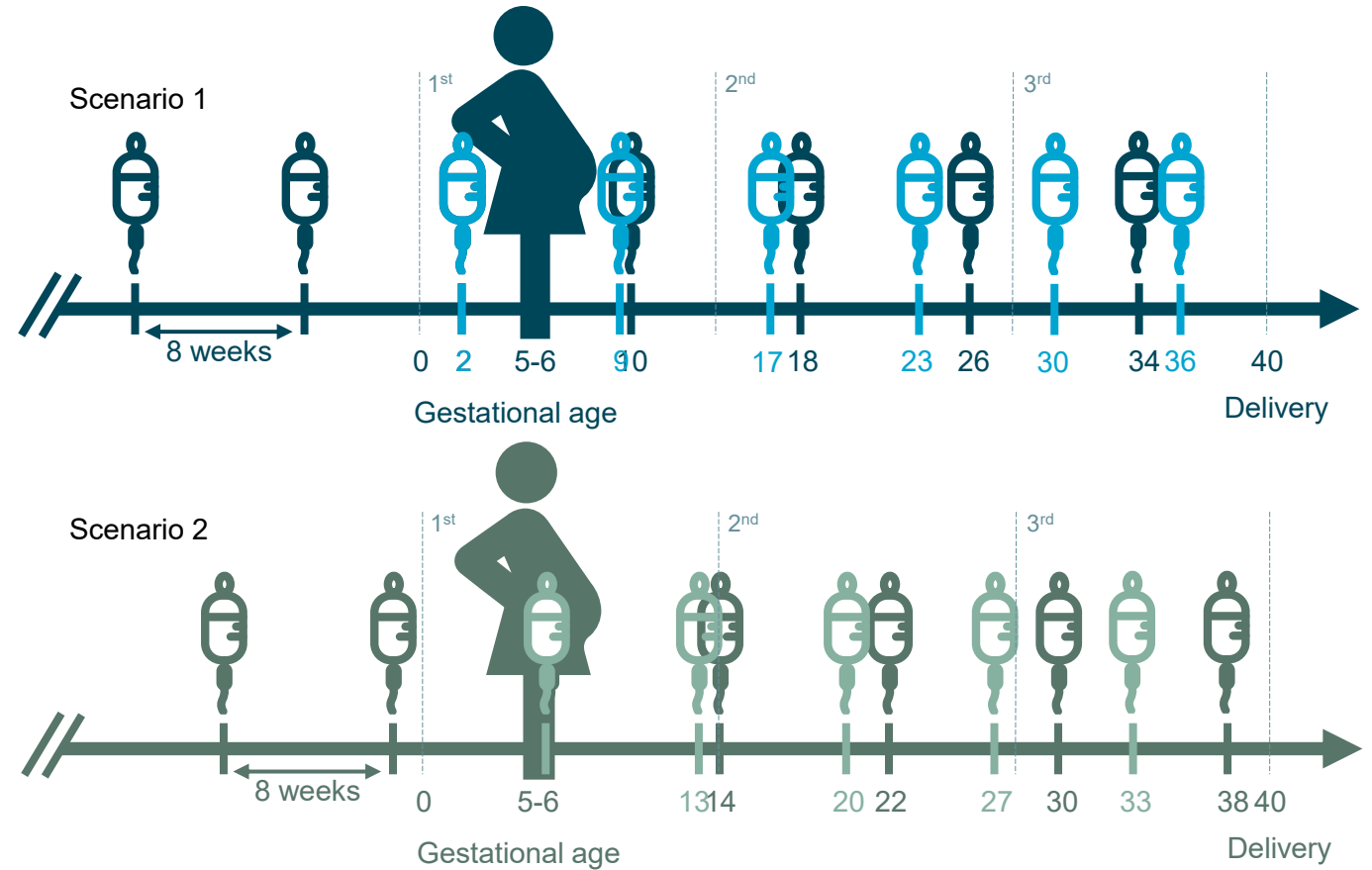
# Dosing regimen optimisation



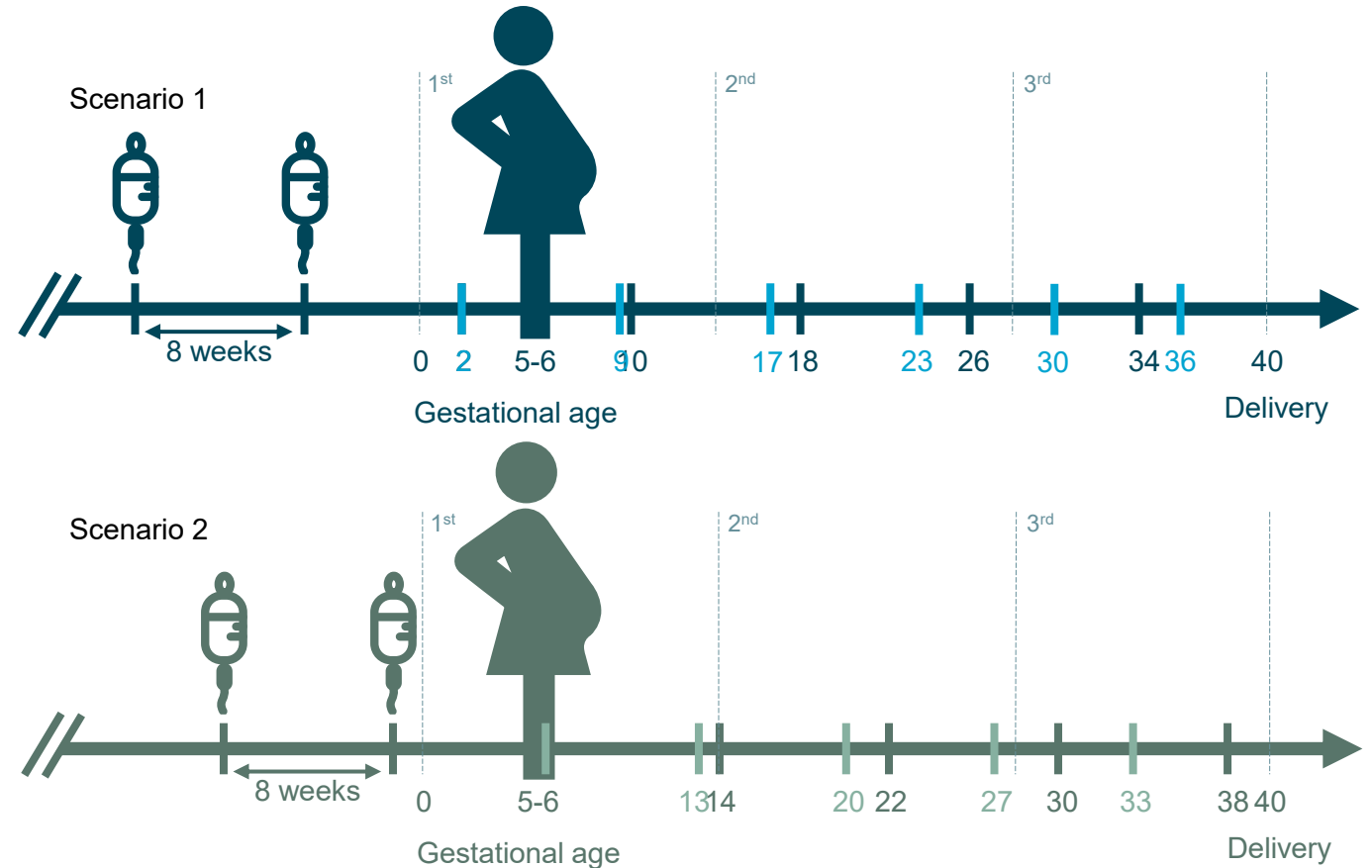
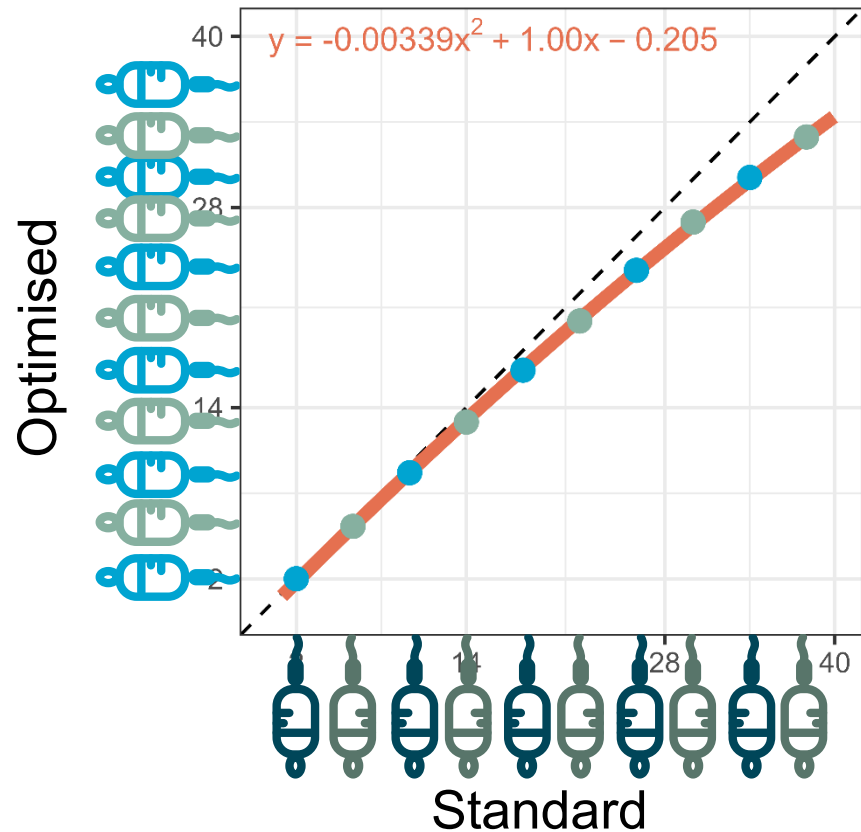
To maintain pre-pregnancy  $C_{min}$   
dosing interval was gradually shortened



# Dosing regimen optimisation

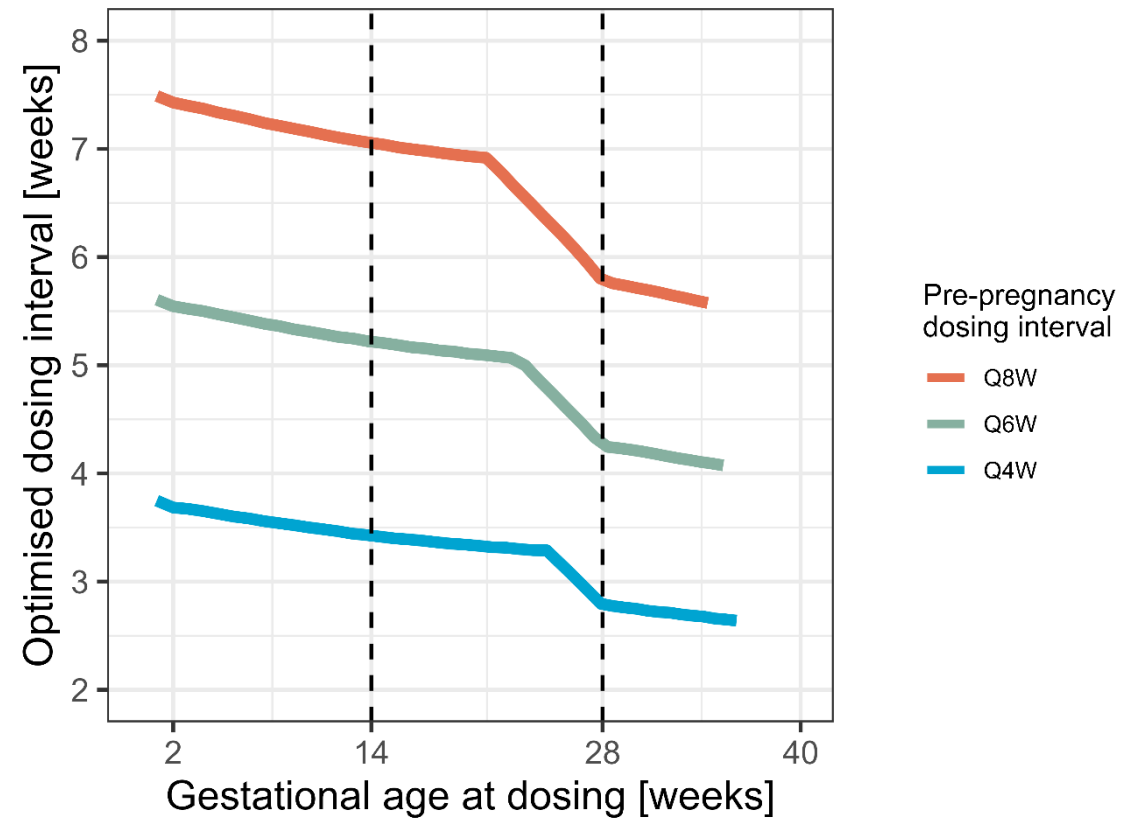
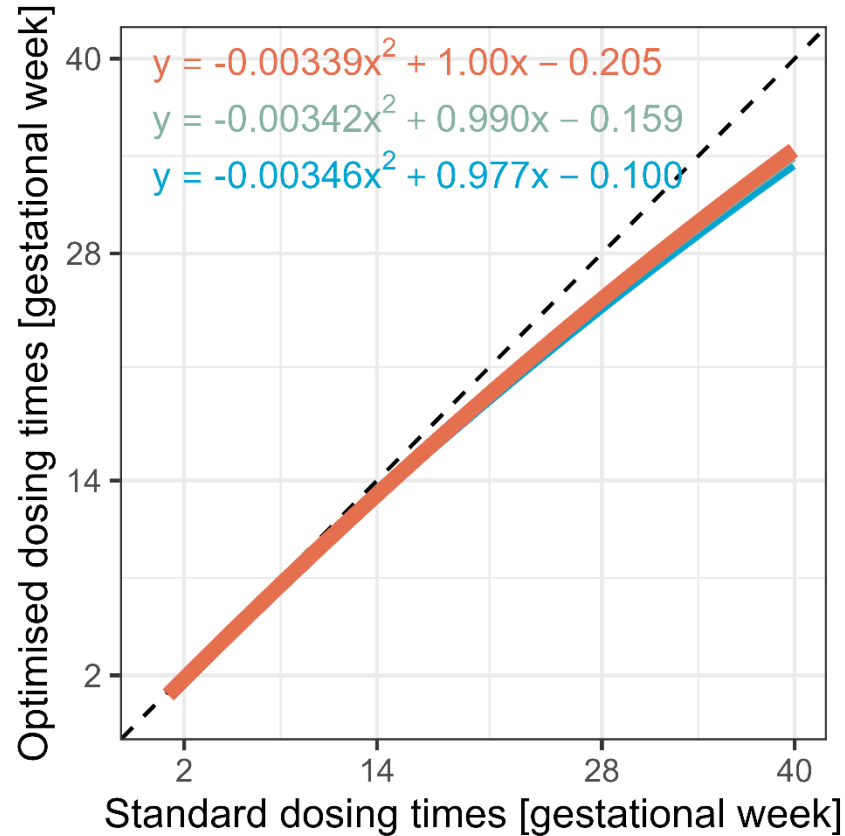


# Dosing regimen optimisation





# Optimised dosing regimen **generalisation**



# Outline

Introduction

Data

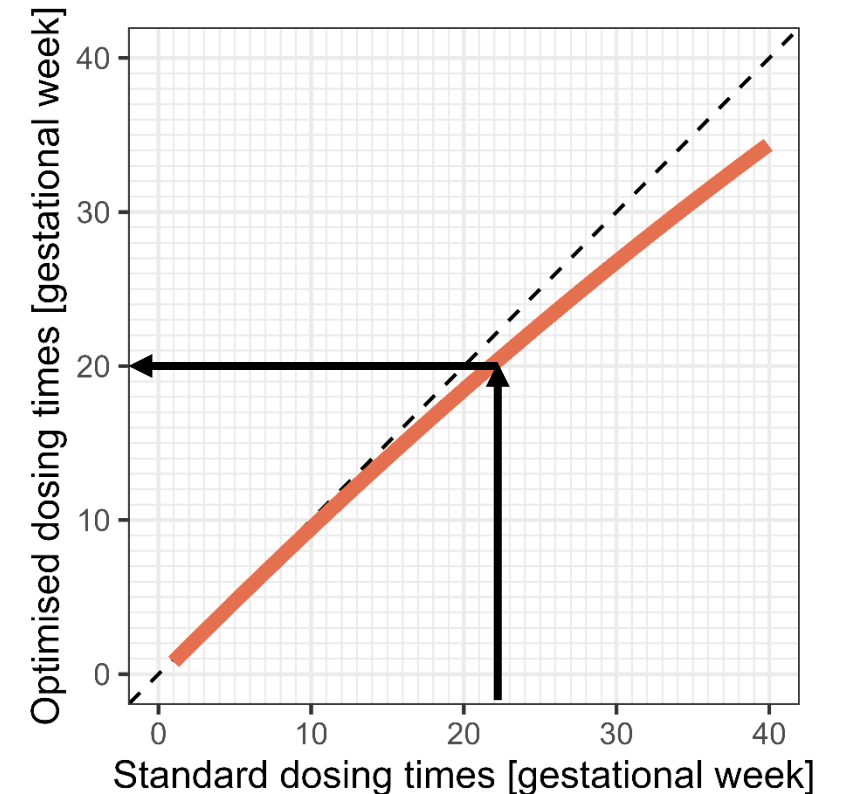
Model

Dosing  
regimen  
optimisation

Summary

# Physiologically-motivated model

- **Albumin change (%)** from pre-pregnancy - **biomarker of plasma expansion**
  - **model of albumin trends** in pregnancy – dealing with missing data, covariates exploration, effect isolation
  - $V_c$  estimated to typically increase 52% – same as reported extent of plasma expansion
- **Residual effect** of gestational age on **CL** – found to **start in the 3<sup>rd</sup> trimester**
  - coinciding with the drop in endogenous IgG (transplacental transfer)
- **$C_{min}$  typically dropped:**
  - >20% by the end of the 2<sup>nd</sup> trimester
  - 50% by the end of pregnancy**
- Nomogram-like plot for deriving optimised times to **keep pre-pregnancy vedolizumab concentrations**
  - covering all timings of pregnancy onset



- Perspective: clinical relevance, Shiny app

# Acknowledgements

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