Evaluating the Transplacental Transfer of Apixaban using a Dually Perfused Isolated Human Placental Lobule

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FACULTY OF MEDICINE

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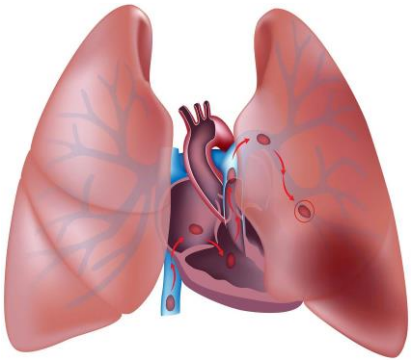
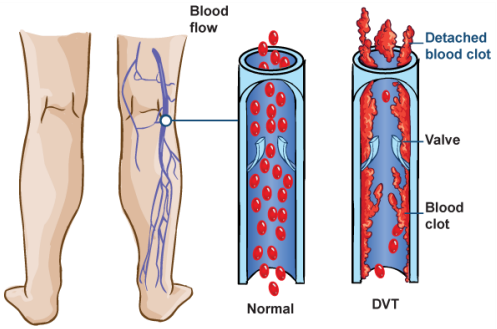
Anticoagulants in Pregnancy

Pregnant women requiring anticoagulation therapy include those with:

- Venous thromboembolism (VTE)
  - Pulmonary embolism
  - Deep vein thrombosis
- Atrial fibrillation
- Mechanical heart valves



Pulmonary embolism



Deep vein thrombosis

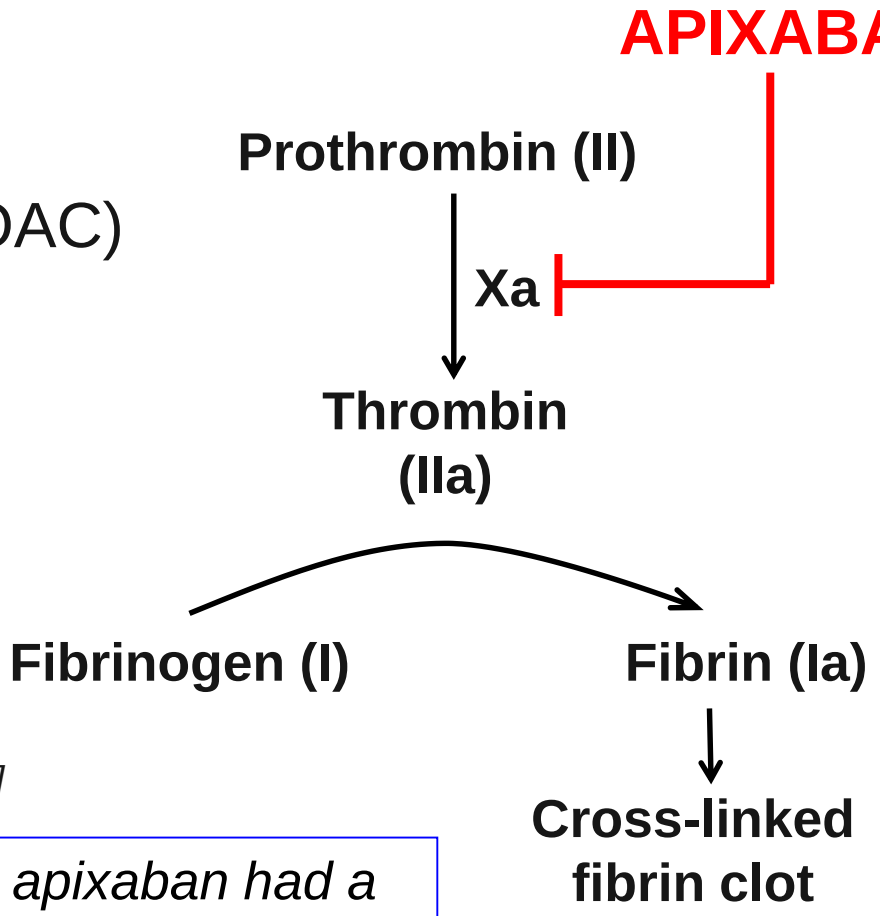
(Bates et al, Chest 2012)

Apixaban

- Novel oral anticoagulant (NOAC)
- Approved in 2012

- Protein binding (87% bound)
  - 66% to albumin
  - 9% to α1 acid glycoprotein
  - 12% unknown

[He et al, Eur J Drug Metab Pharmacokinet 2011]



When compared to other NOACs, apixaban had a relatively low risk of bleeding events and a similar efficacy for acute VTE!

- Mantha et al, J Thromb Thrombolysis 2015

Apixaban and Pregnancy

Clinical Practice Guidelines (2012): “There are no published reports describing the use of new oral direct thrombin inhibitors or anti-Xa inhibitors (**apixaban**) in pregnancy… The human reproductive risks of these medications are unknown.”

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

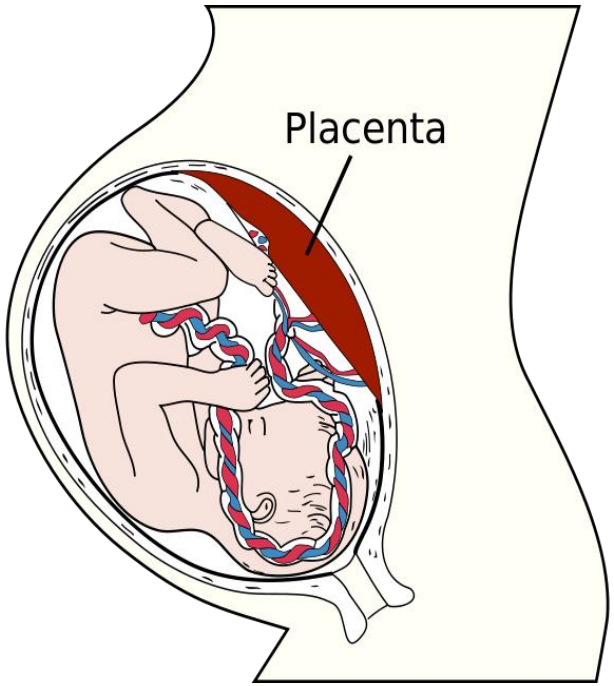
Shannon M. Bates, MDCM; Ian A. Greer, MD, FCCP; Saskia Middeldorp, MD, PhD; David L. Veenstra, PharmD, PhD; Anne-Marie Prabulos, MD; and Per Olav Vandvik, MD, PhD

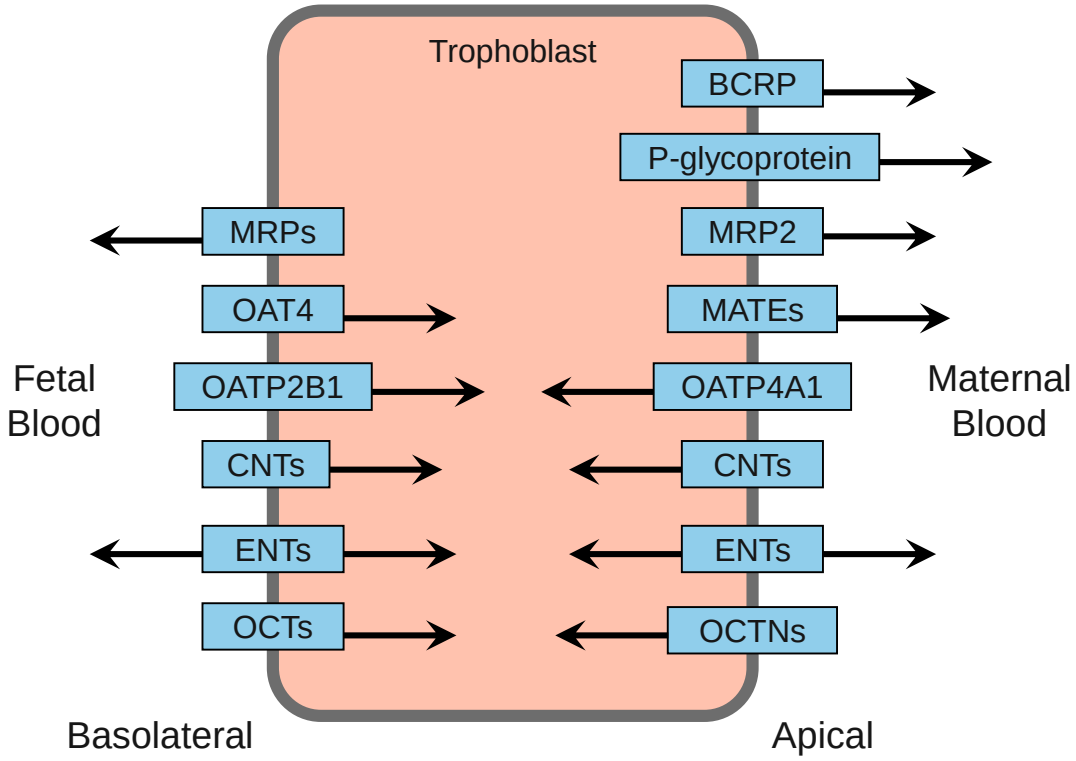
Chest 2012; 141: e691S-736S.

Objective

Therefore, the objective of our study was to examine the disposition of apixaban across the term human placenta *ex vivo*, in order to estimate fetal drug exposure.

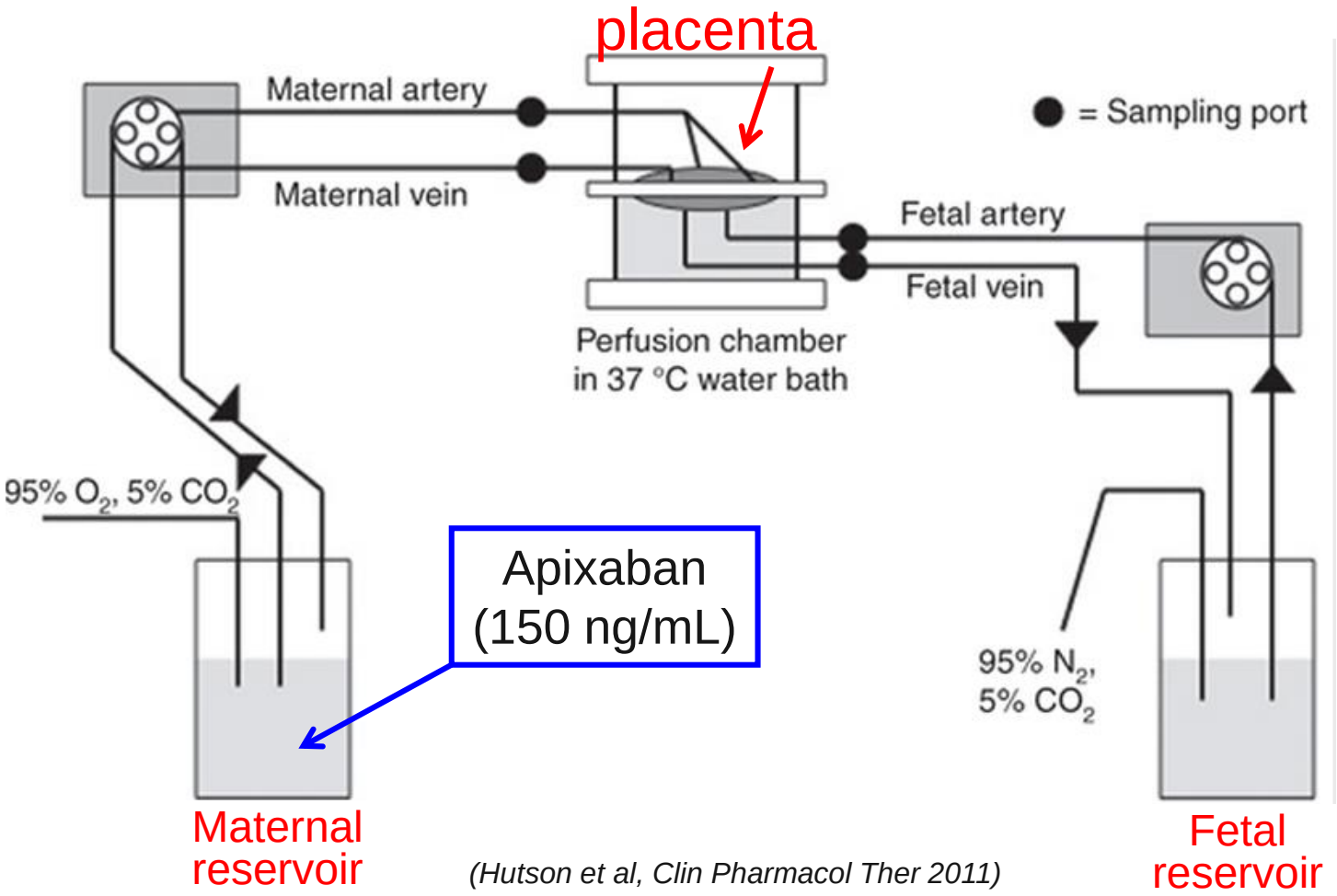
Human Placenta





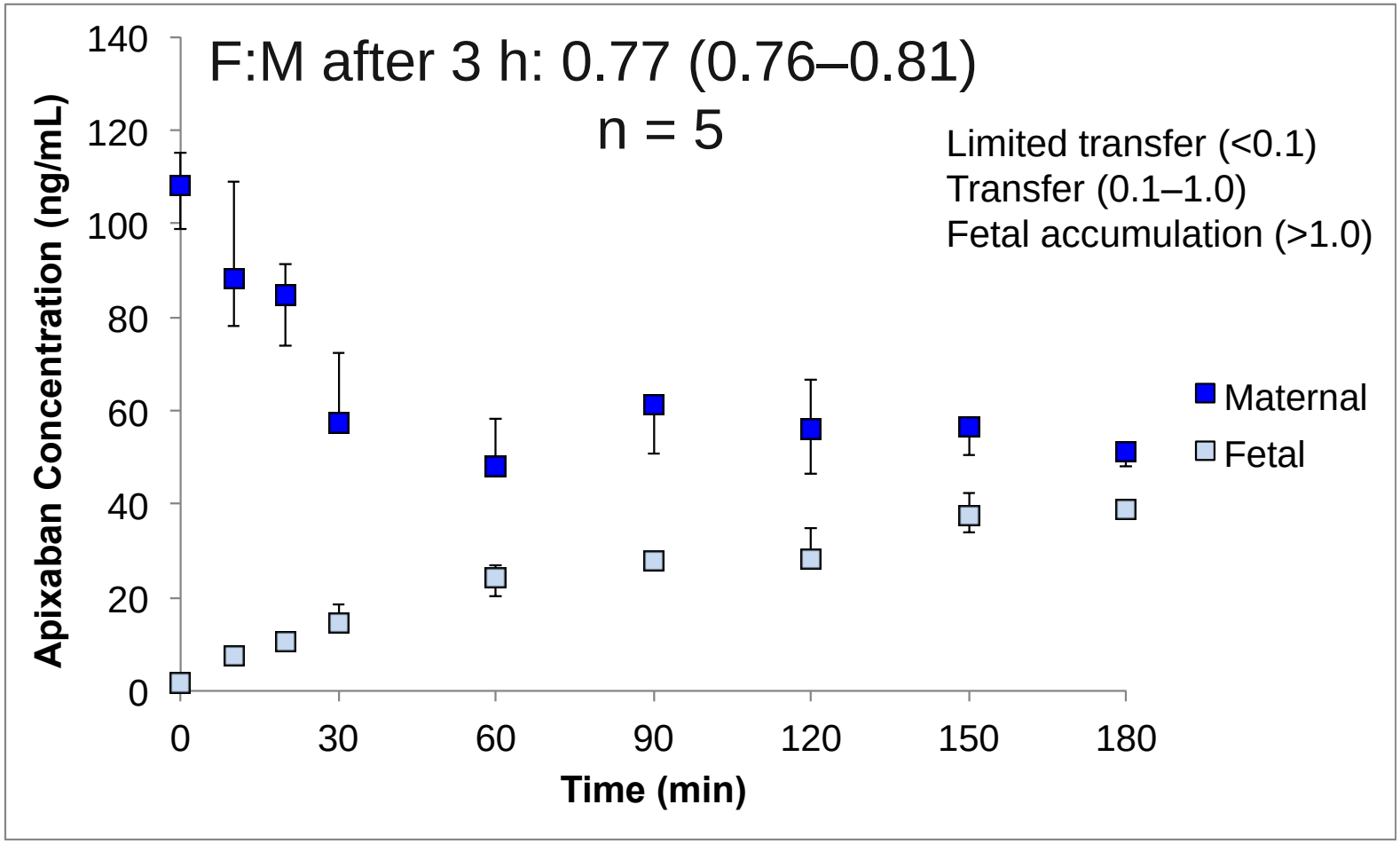
Modified from Staud et al, Expert Opin Drug Metab Toxicol 2015

Methods: Placenta Perfusion



(Hutson et al, Clin Pharmacol Ther 2011)

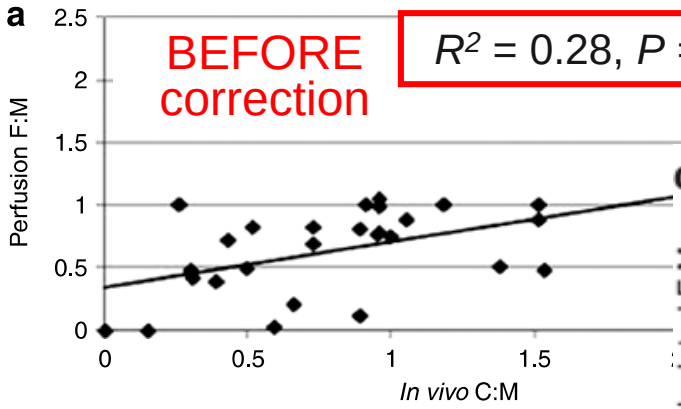
Results: Apixaban

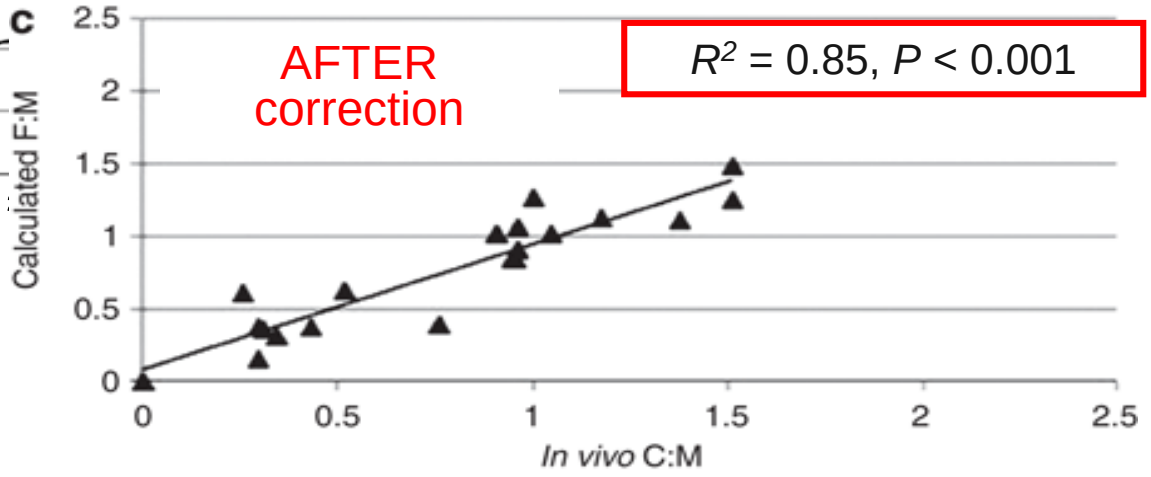


Prediction of *in vivo* F:M ratio

Adapted from Garland, Obstet Gynecol Clin North Am 1998

$$\mathrm{F{:}M} = \frac{\%\ \mathrm{unbound}_{\mathrm{M}}}{\%\ \mathrm{unbound}_{\mathrm{F}}} \times \frac{1 + 10^{\mathrm{pK_a} - \mathrm{pH_F}}}{1 + 10^{\mathrm{pK_a} - \mathrm{pH_M}}} \times \frac{\mathrm{CL_{MF}}}{\mathrm{CL_{FM}}}$$





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- *In vitro* protein binding (87% bound)
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[He et al, Eur J Drug Metab Pharmacokinet 2011]

Drug literature
maternal pH = 7.4
fetal pH = 7.35

Perfusion F:M ratio

Predicted apixaban F:M *in vivo:* 0.74–0.81

Conclusions

- Fetal levels of apixaban *in vivo* are predicted to be 70-80% of the corresponding maternal levels
  - Raises the possibility for neonatal complications due to their hypocoagulability status

- Future studies will need to explore safety before clinicians can consider the use of apixaban in pregnant women.

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