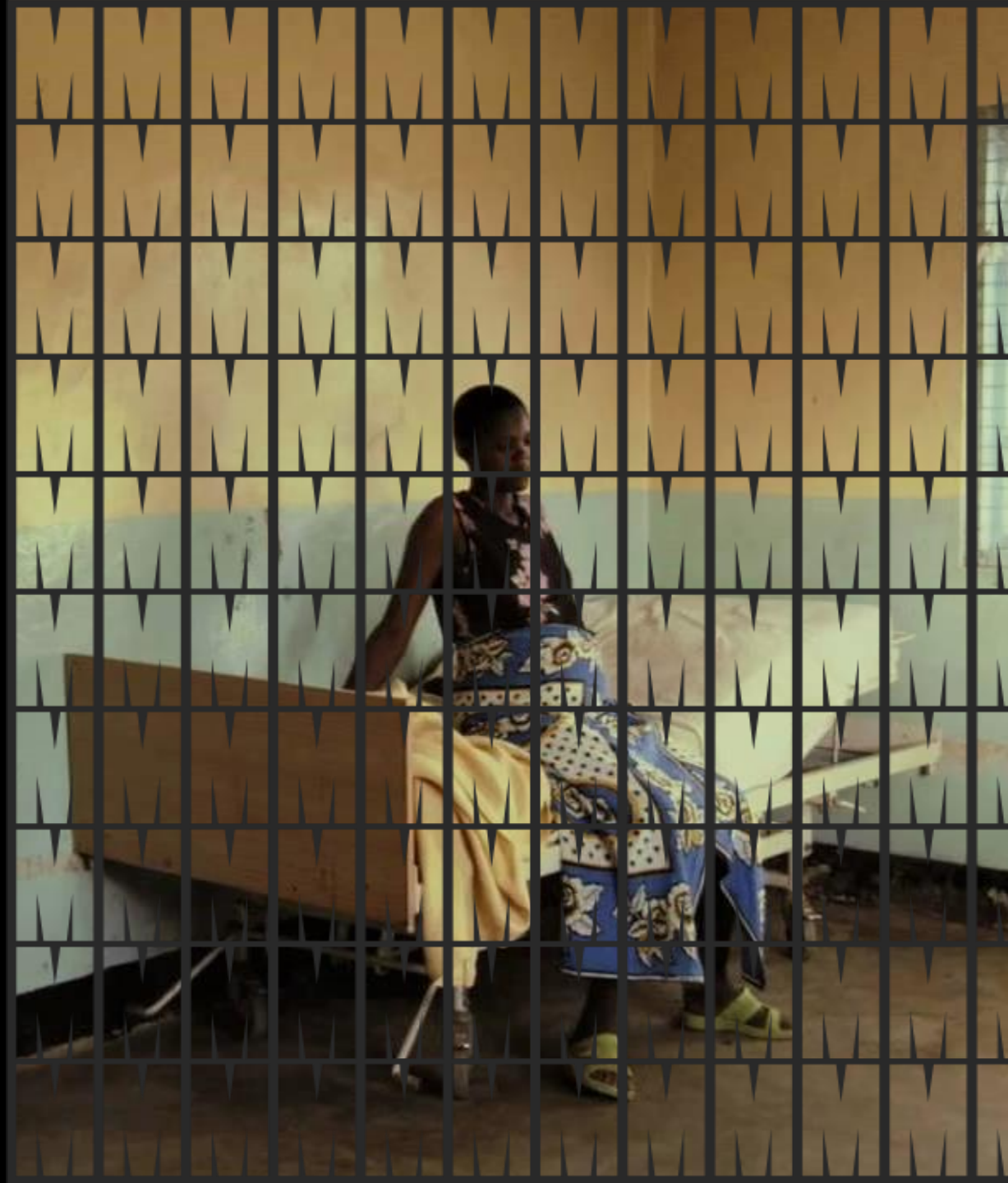


INHALED OXYTOCIN

Adventures in Pharmacokinetics and Bioanalysis
to Save Mothers' Lives

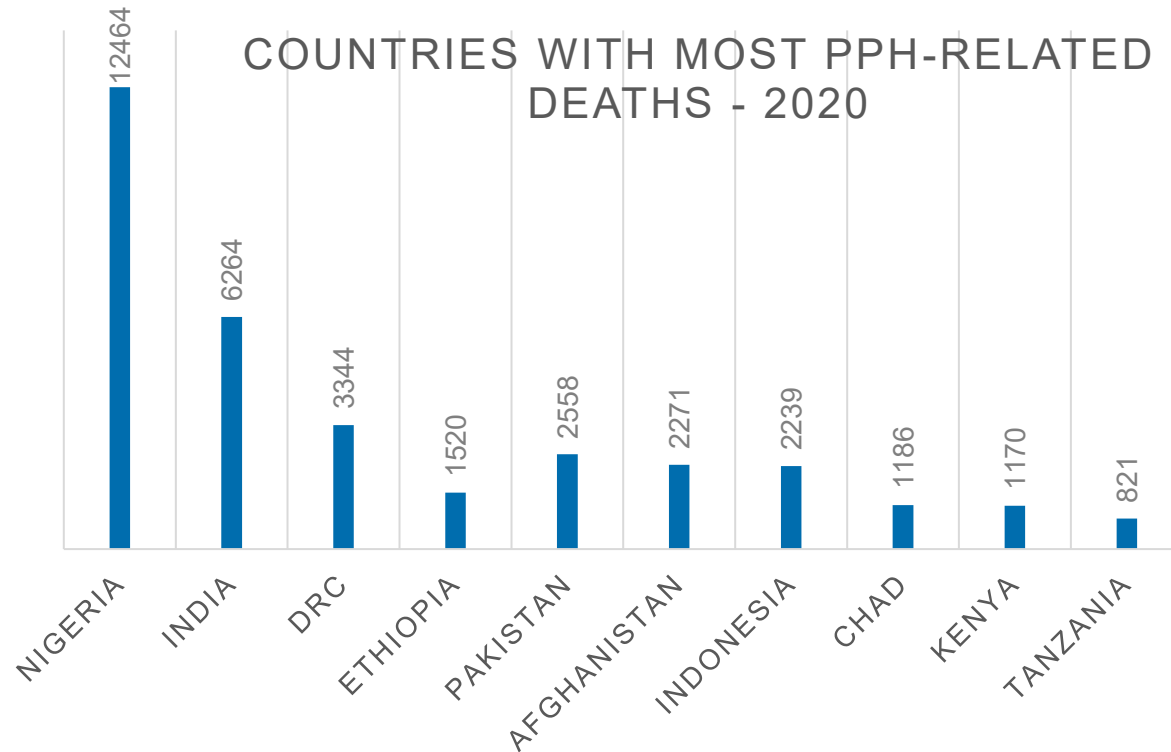
Presentation to DDL 2025

Associate Professor (Practice) Pete Lambert
Monash University
Parkville
Australia



The Issue

- Postpartum haemorrhage (PPH) is the leading cause of global maternal mortality with 14 million women experiencing PPH resulting in an estimated 70,000 maternal deaths globally (WHO)
- PPH occurs in 5-15% of all pregnancies
 - In the UK - 14 women died from obstetric haemorrhage between 2021-2023.
 - In the worlds LMI countries 1 woman dies from PPH every 6 minutes

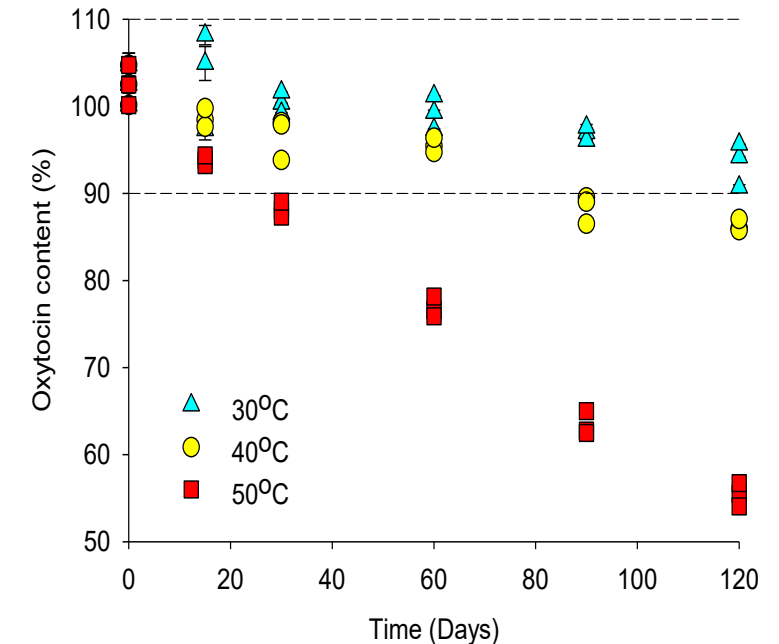


The Issue

- Oxytocin 10IU IM (or IV) is the first line therapy for prevention of PPH
 - Reduces incidence of PPH to <15% and severe PPH to <1.5% (Widmer et al., 2018)
- WHO recommends oxytocin be administered to every woman at every birth

However,...

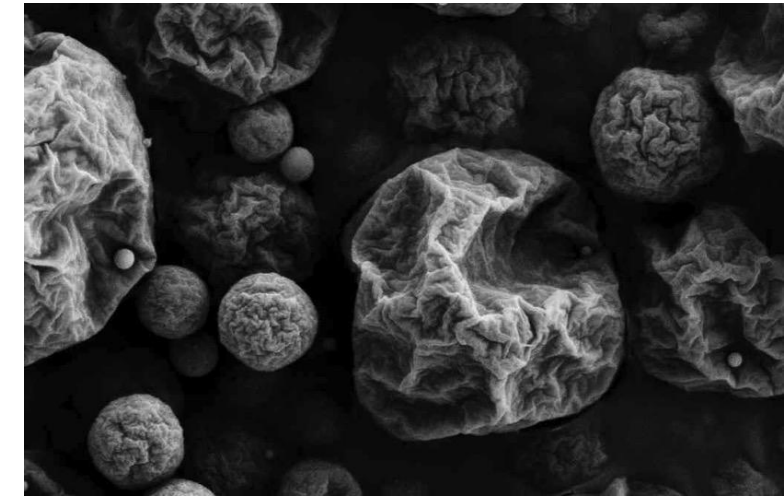
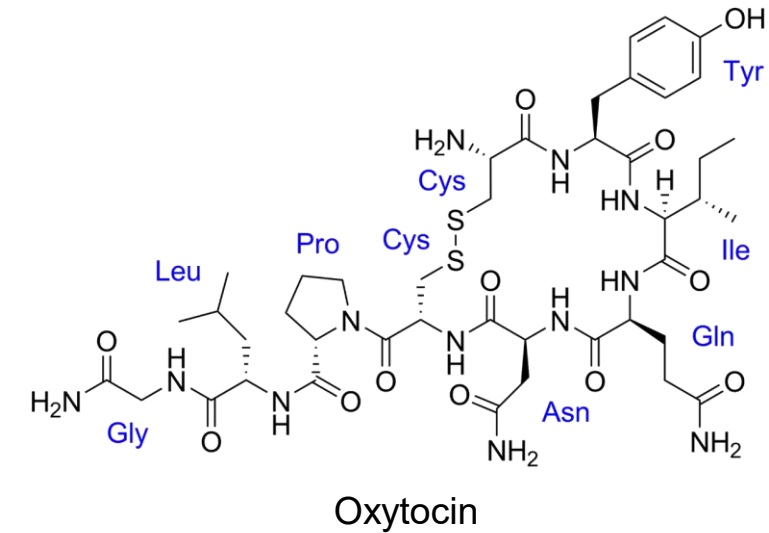
- Oxytocin is currently only available as a solution for injection that requires:
 - Refrigeration to maintain quality (40% of oxytocin in LMICs is poor quality)
 - Skilled healthcare workers for safe and timely administration
 - Additional consumables (syringe, needle etc.)
- **INHALED OXYTOCIN** provides an innovative solution to the limitations of oxytocin injection products in low and middle income countries



Inhaled Oxytocin

Project Status

- Heat stable formulation
 - Trehalose:leucine-based spray-dried (SD) particle
 - Capsule formulation comprising SD particle blended with mannitol and Mg stearate developed to support early clinical studies
 - 36 months stability at 25°C/60% RH
 - 6 months stability at 40°C/75% RH
 - 1 month stability at 50°C ambient
- Preclinical proof of principle in postpartum sheep model demonstrates PK/PD comparability to standard of care (10IU IM oxytocin injection)
- Clinical program initiated using a prototype product (Rotahaler® delivery device)



Regulatory Strategy

Registration strategy utilises the EMA EU-M4All Global Health Process

- Review of medicines to be used outside the EU (countries with limited national regulatory capacity)
- Scientific opinion received from EMA with WHO expert consultation
- Expedited national review in countries outside the EU (typically low- and middle-income countries)

Scientific advice received for inhaled oxytocin

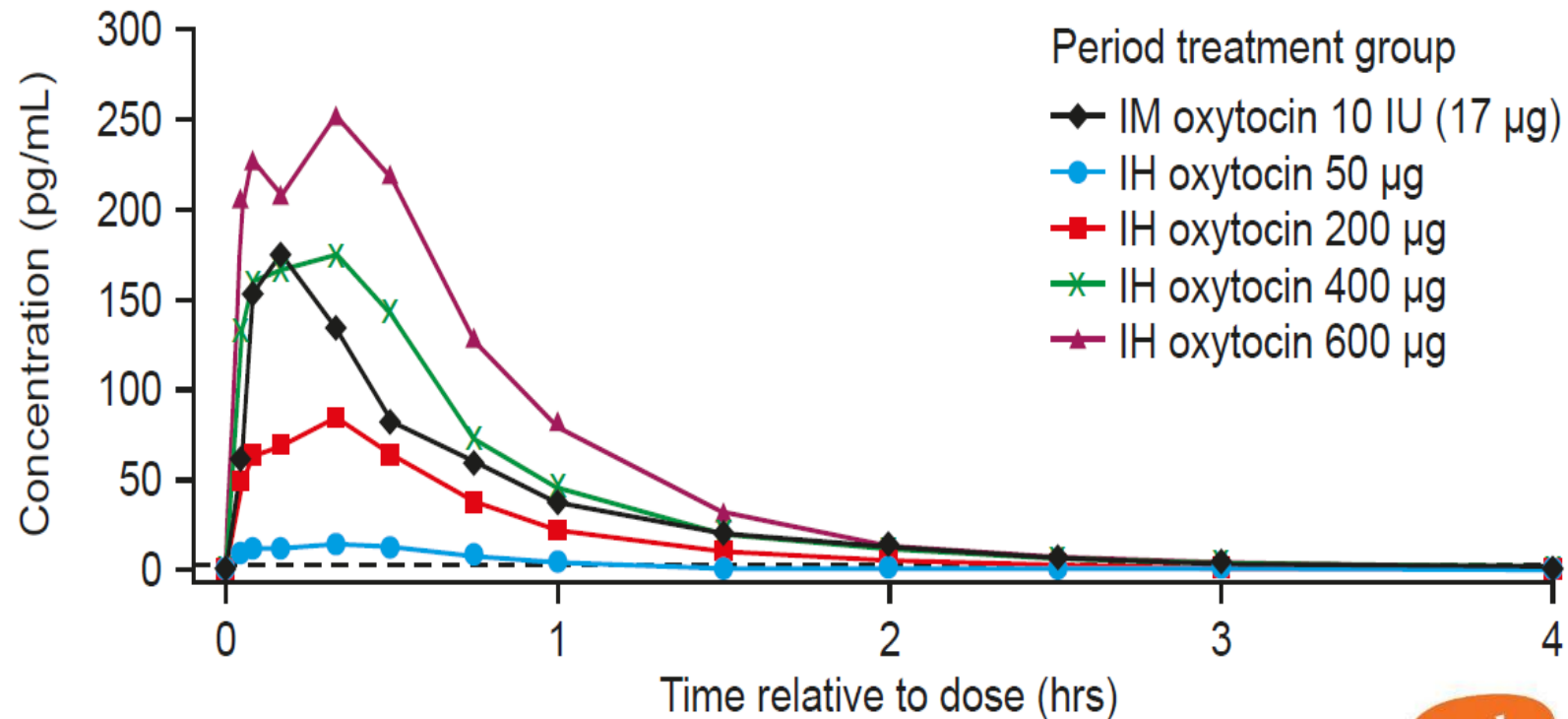
- Registration pathway based on pharmacokinetic similarity to standard of care (IM injection) plus safety and 'utility' data across usage settings
- Efficacy to be extrapolated from IM injection

<https://www.ema.europa.eu/en/partners-networks/international-activities/medicines-assessed-under-eu-m4all-procedure>



Clinical Assessment

- First-in-human phase I study (Fernando et al., 2017)
 - Simple ascending dose, pharmacokinetic and safety study
 - 15 Non-pregnant female volunteers
 - GSK modified inlet Rotahaler® device

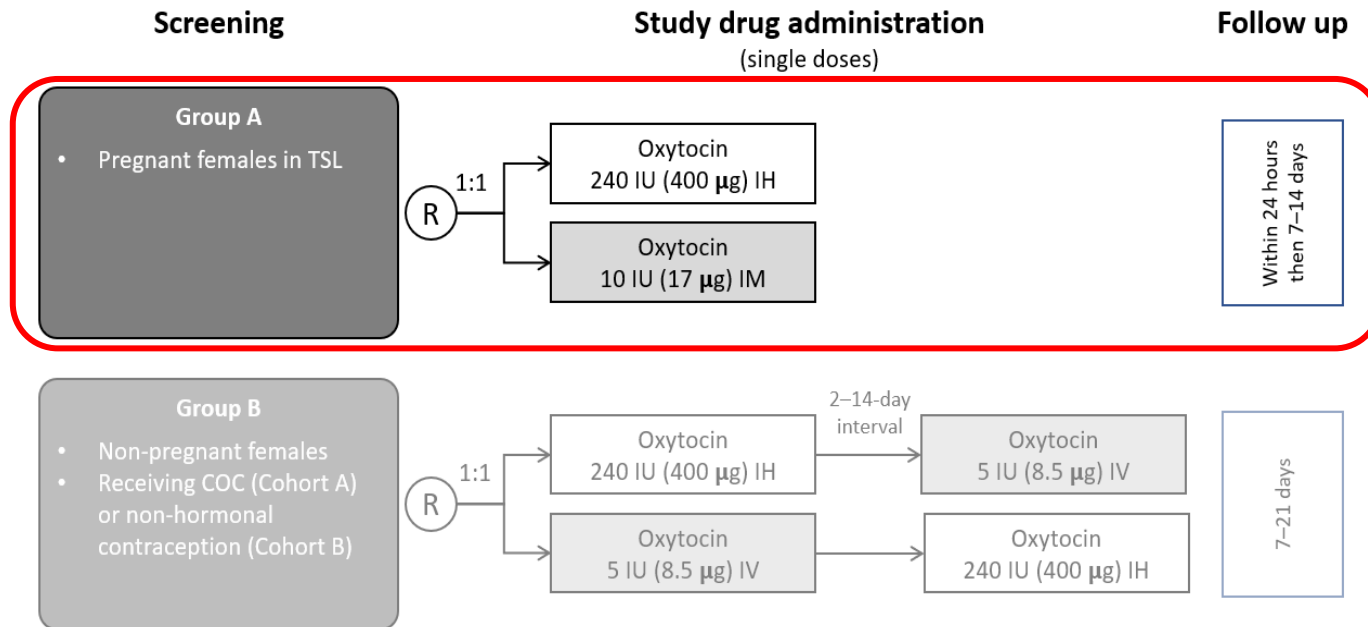


LLQ = 2 pg/mL



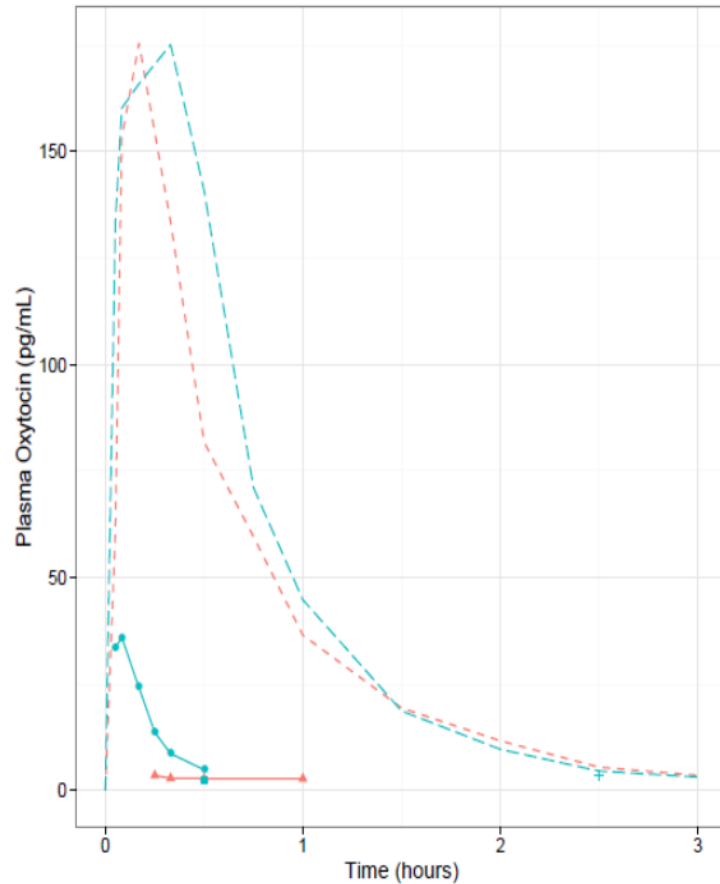
Clinical Assessment

- Phase I/II Study
 - Two cohort, pharmacokinetic and safety study
 - Group A – Women in third stage of labour (TSL) – N=10 per group
 - Interim analysis at N=5 per group
 - Group B – Non-pregnant volunteers – N=5 per group
 - GSK modified inlet Rotahaler[®] device



Clinical Assessment

- Phase I/II Study – Interim Analysis, N=5 per cohort



Solid lines: Current study in TSL subjects
Dotted lines: Historical data in non-pregnant subjects
Green: 400 µg Inhaled
Red: 10 IU (17 µg) IM Injection

Only 4 subjects provided samples with quantifiable timepoints (3 x IH, 1 x IM)

Review of sample handling was conducted, focusing sample tubes

Pharmacokinetics and safety of inhaled oxytocin compared with intramuscular oxytocin in women in the third stage of labour: A randomized open-label study

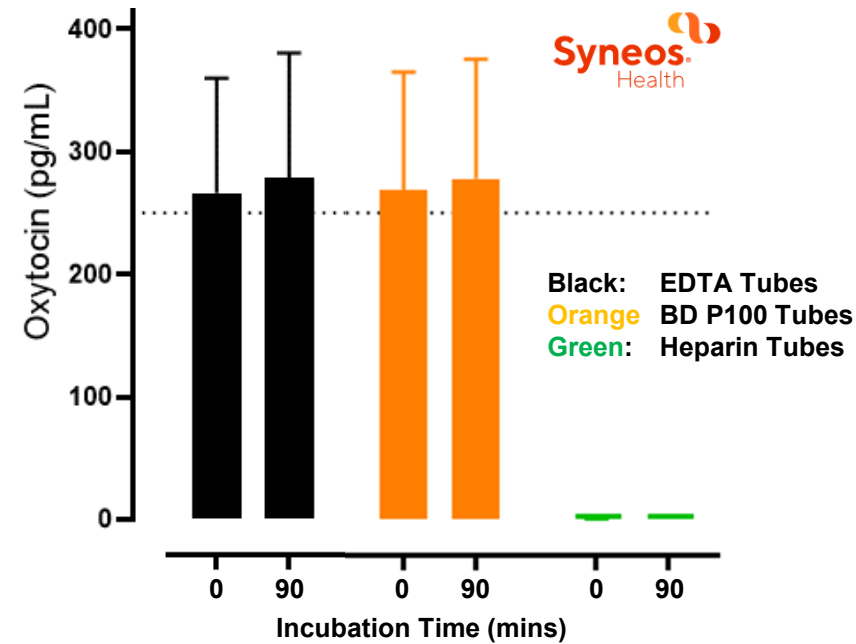
Katarzyna Gajewska-Knapik, Subramanya Kumar, Amy Sutton-Cole, Kirsten R. Palmer, Anthony Cahn, Rachel A. Gibson, Carl Kirkpatrick, Simon Parry, Ian Schneider, Sarah Siederer ... [See all authors](#) ▾



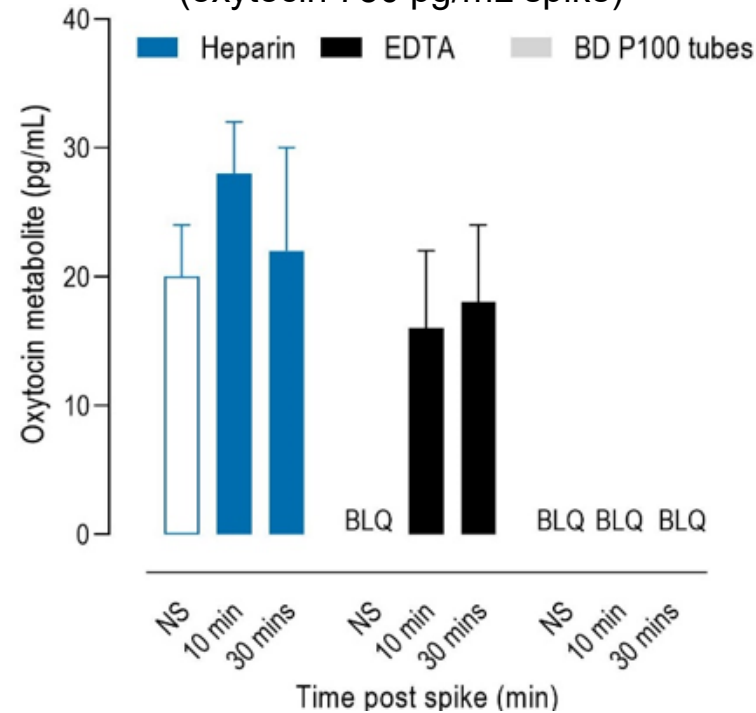
Clinical Assessment

- Review of sample handling – sample tubes and protease inhibition

Stability of oxytocin in whole blood from women >36wks gestation (N=4) in ice (oxytocin 375 pg/mL spike)



Oxytocin metabolite* in whole blood from women >37wks - 4hrs postpartum gestation (N=3) in ice (oxytocin 750 pg/mL spike)



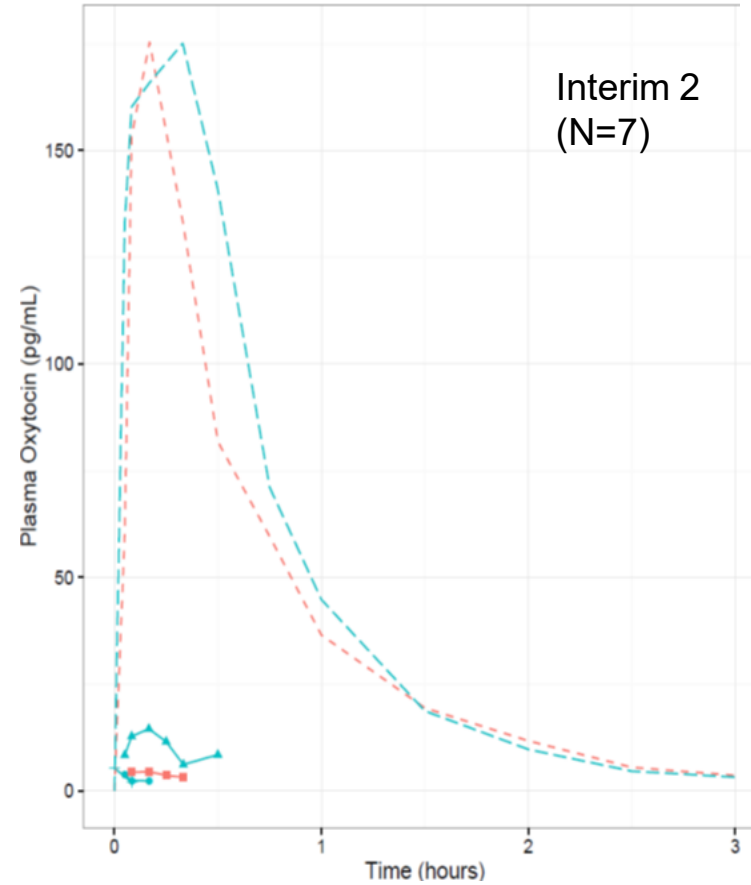
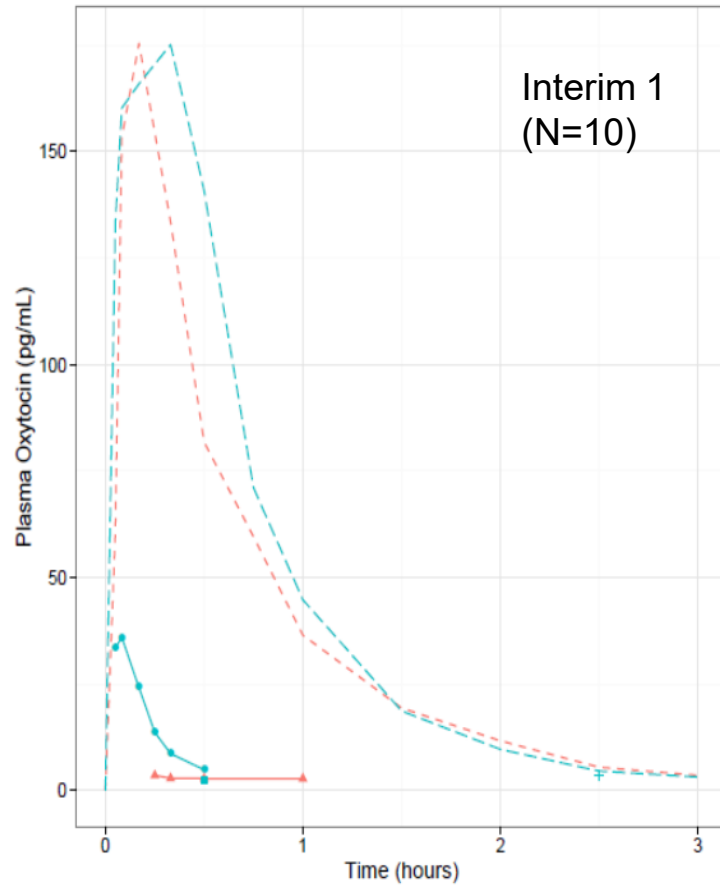
Study restarted using improved procedures and P100 sampling tubes containing increased protease inhibition

* 7-amino acid peptide (Glu-Asp-Cys-(Cys)-Pro-Leu-Glyc-NH2)



Clinical Assessment

- Phase I/II Study



Pharmacokinetics and safety of inhaled oxytocin compared with intramuscular oxytocin in women in the third stage of labour: A randomized open-label study

Katarzyna Gajewska-Knapik, Subramanya Kumar, Amy Sutton-Cole, Kirsten R. Palmer, Anthony Cahn, Rachel A. Gibson, Carl Kirkpatrick, Simon Parry, Ian Schneider, Sarah Siederer ... [See all authors](#) ▾

➤ Plasma concentrations remained largely below the LoQ

Study terminated at N=17 after a 2nd interim analysis



Clinical Assessment

- Oxytocinase Assay Development

L-leucine-7-amido-4-methylcoumarin hydrochloride (Leu-MCA)
+ Oxytocinase



Hydrolysis

7-amino-4-methyl coumarin (AMC)

Fluorescence detected using Ensign plate reader
(Excitation, 340nm; emission 480nm)

Under these experimental conditions AMC formation rate is linear.

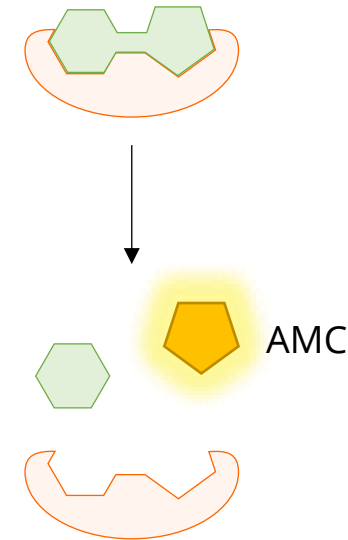
AMC formation (nM/min) is measured over 50 minutes as a measure of enzyme activity

ORIGINAL ARTICLE



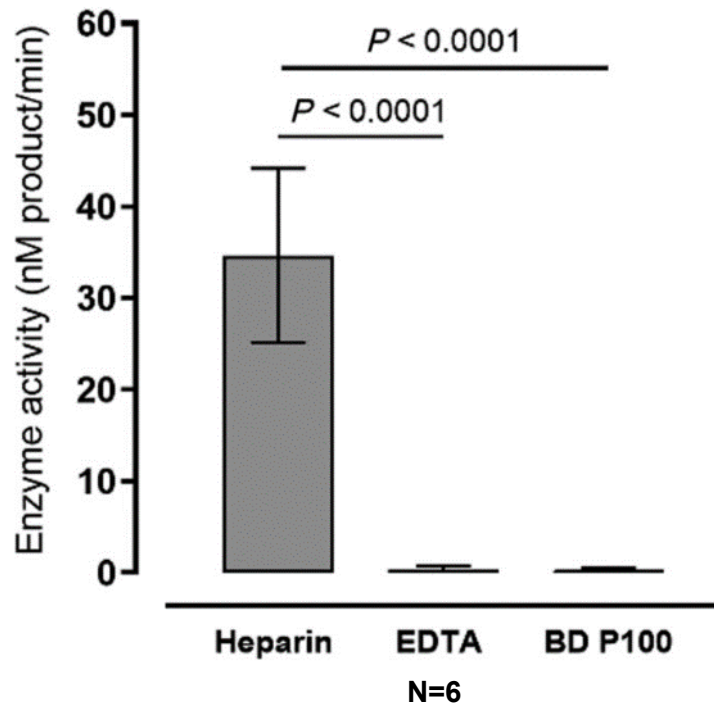
Exploring the role of ex vivo metabolism on blood and plasma measurements of oxytocin among women in the third stage of labour: A *post hoc* study

Victoria L. Oliver¹ | Sarah Siederer² | Anthony Cahn² |
Katarzyna Gajewska-Knapik³ | Rachel A. Gibson² | Cleo Goodall¹ |
Carl Kirkpatrick¹ | Jack Murray¹ | Tri-Hung Nguyen¹ | Ian Schneider⁴ |
Pete Lambert¹ | Michelle P. McIntosh¹ | Simon Parry⁵



Clinical Assessment

- Oxytocinase Assay – Further Assessment of Sampling Tubes
 - Late-stage pregnancy/postpartum blood



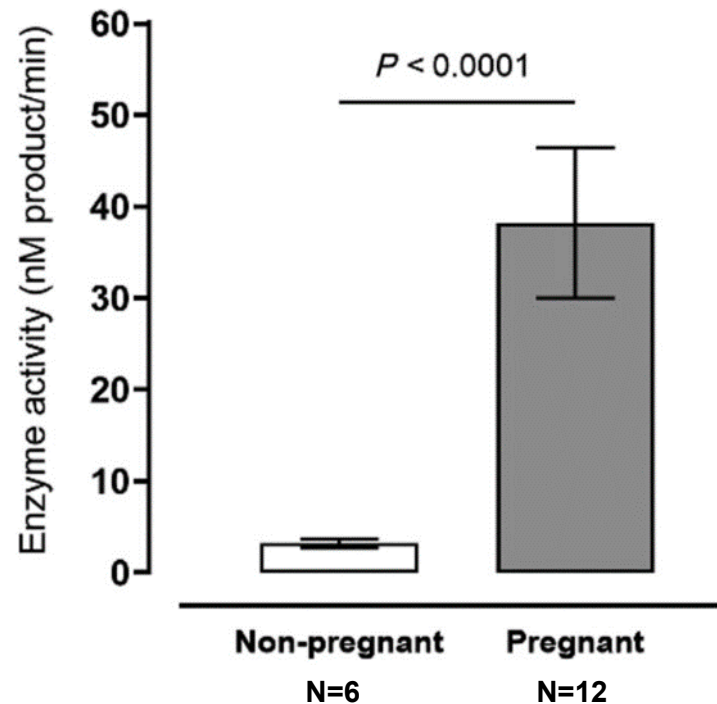
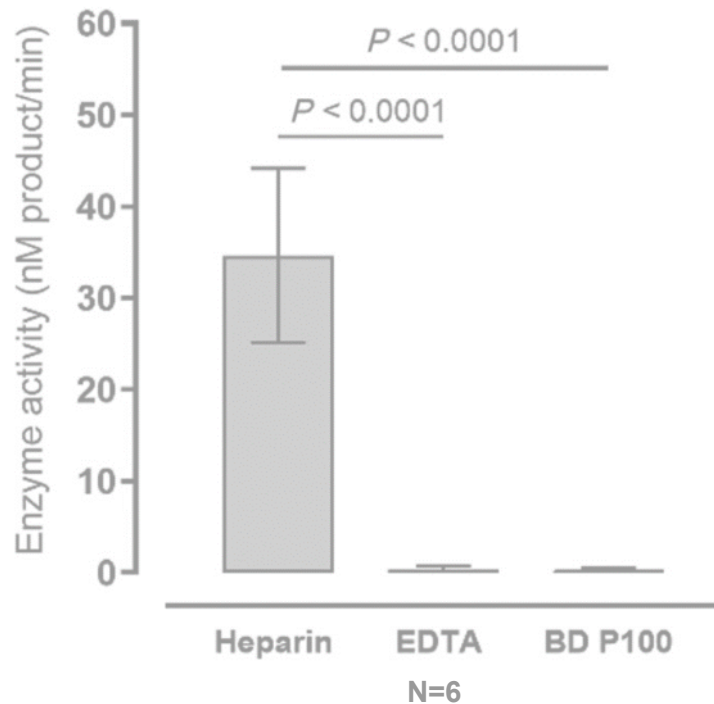
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Clinical Assessment

- Oxytocinase Assay – Non-Pregnant vs Late-Stage Pregnancy/Postpartum Blood



Exploring the role of ex vivo metabolism on blood and plasma measurements of oxytocin among women in the third stage of labour: A *post hoc* study

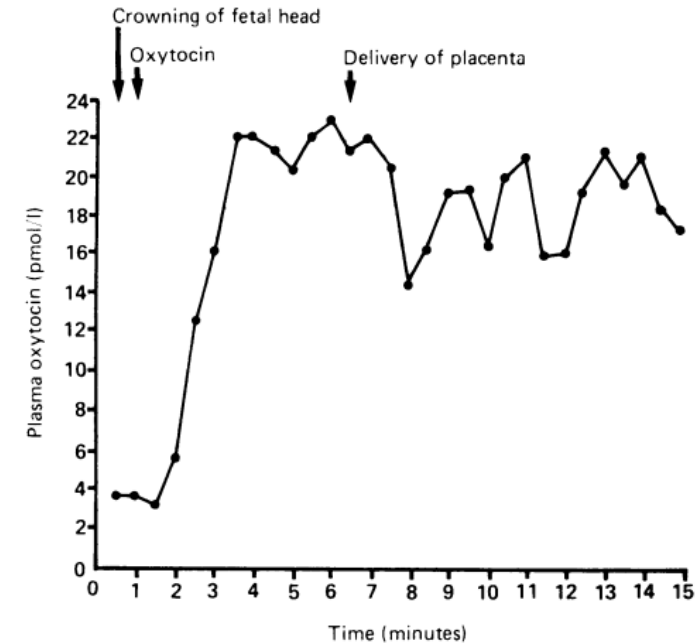
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Indicate that oxytocinase activity is
~11-fold higher in late-stage
pregnancy/postpartum blood



Clinical Assessment

- Why was our data different to the literature?
- Bioanalytical Method – LCMS vs Ligand Binding Assays
- Most studies conducted pre-1990's
- Used ligand binding assays
- Emerging evidence that ligand binding assays are unreliable due to cross-reactivity and sensitivities to sample preparation



Thornton et al., BMJ, 1988

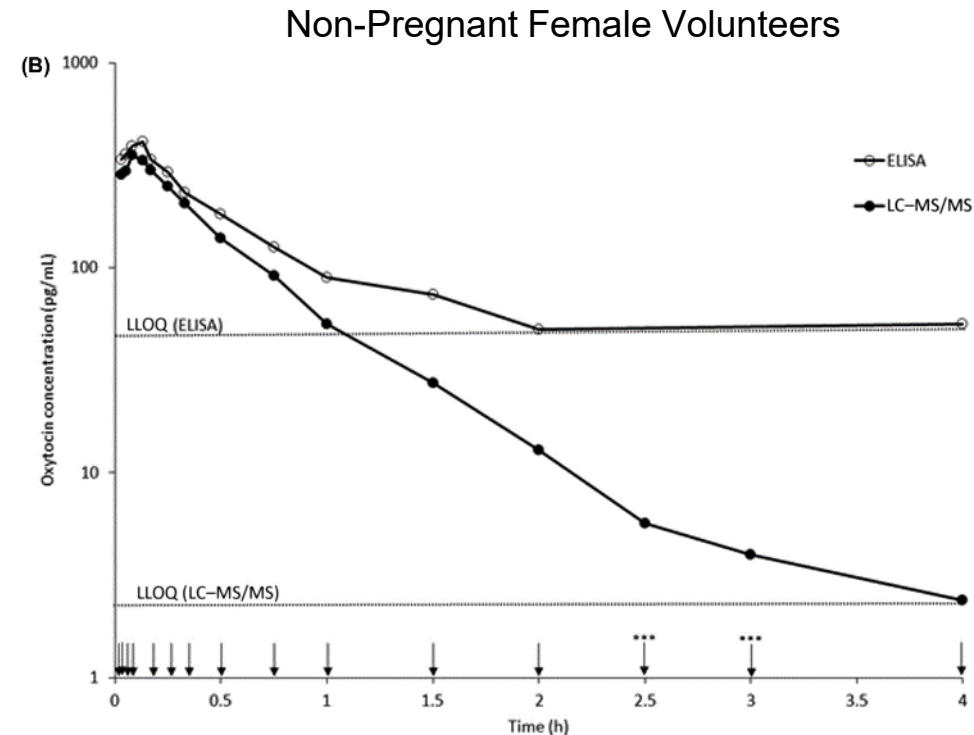


Clinical Assessment

- Bioanalytical Method – LCMS vs Ligand Binding Assays

Exploring the role of ex vivo metabolism on blood and plasma measurements of oxytocin among women in the third stage of labour: A *post hoc* study

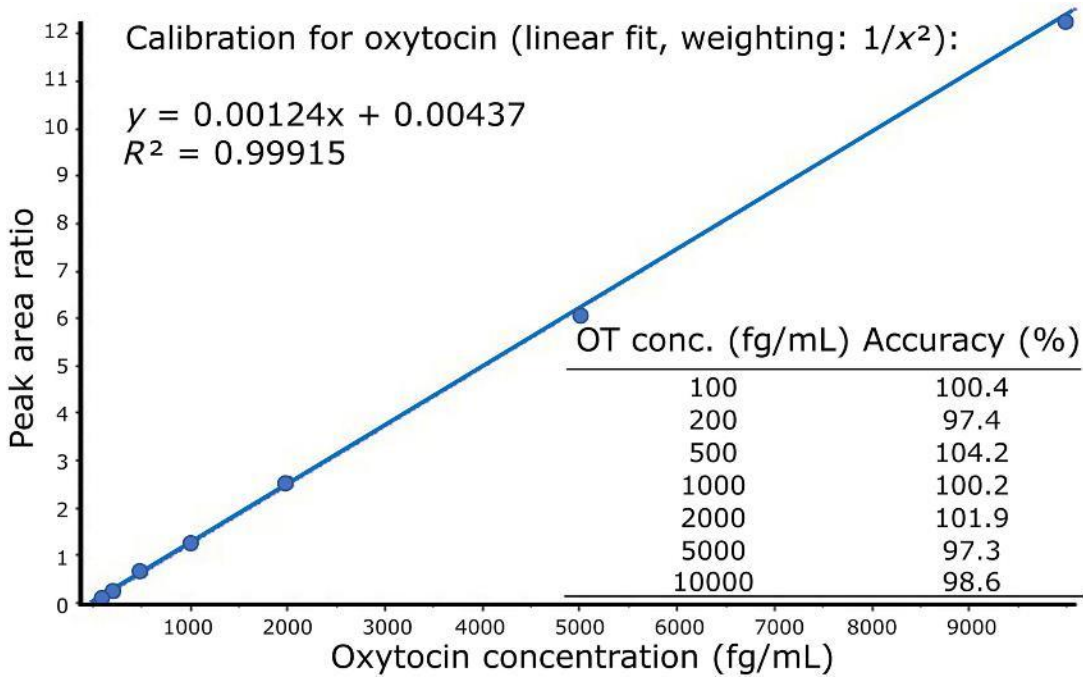
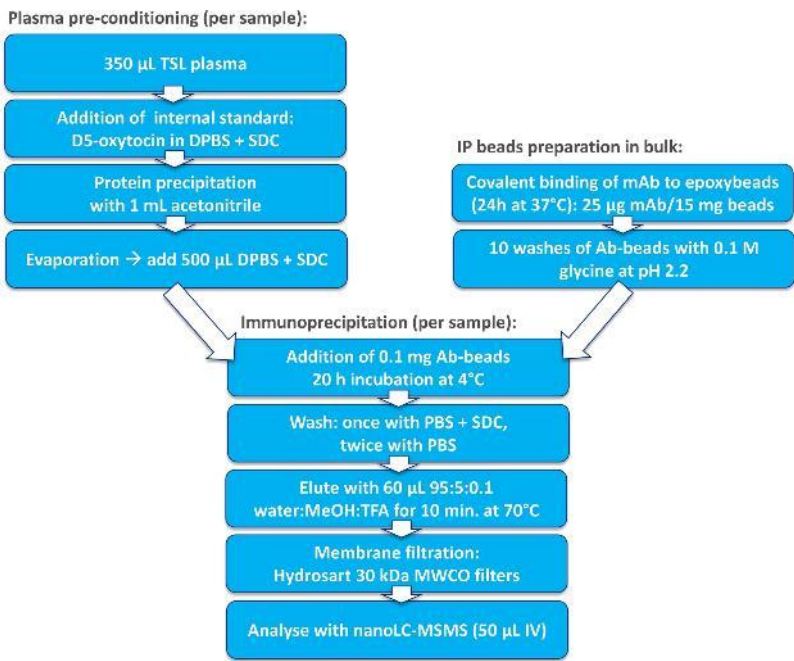
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Carl Kirkpatrick¹ | Jack Murray¹ | Tri-Hung Nguyen¹ | Ian Schneider⁴ |
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Clinical Assessment

- Bioanalytical Method Optimisation
- Method improvement using the orthogonal selectivity of immunoassays and nano-LCMS/MS

gaff



Clinical Assessment

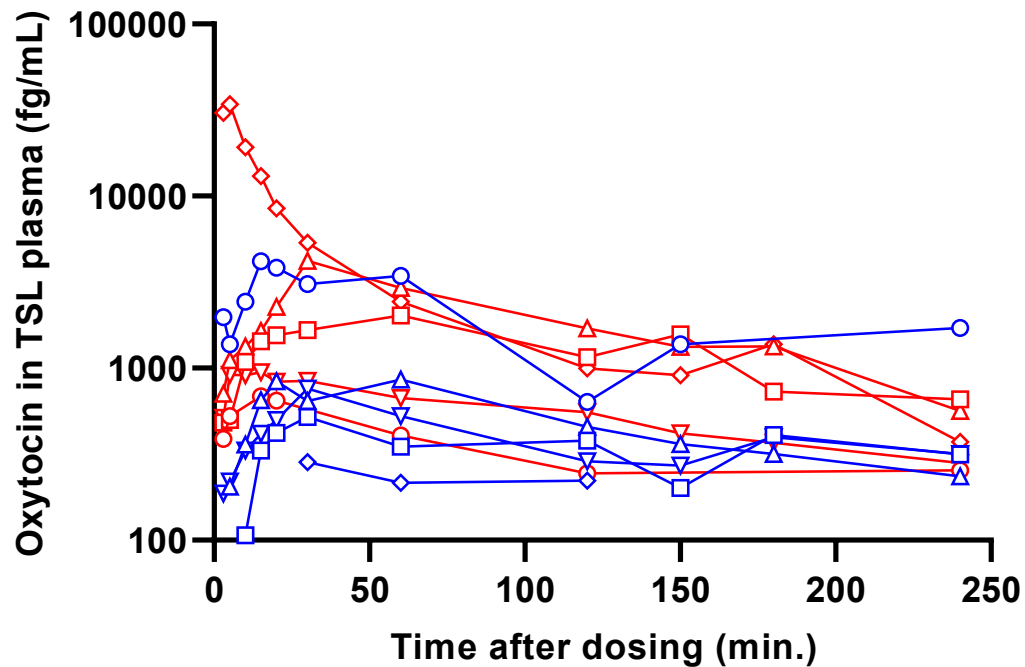
- Re-analysis of clinical samples (N=5 per route of administration)
- While variable, shows similarity between inhaled and IM dosing

Application of immunocapture and nanoflow LC–MS/MS to overcome the barriers to the quantitation of oxytocin in plasma of women in third stage labour

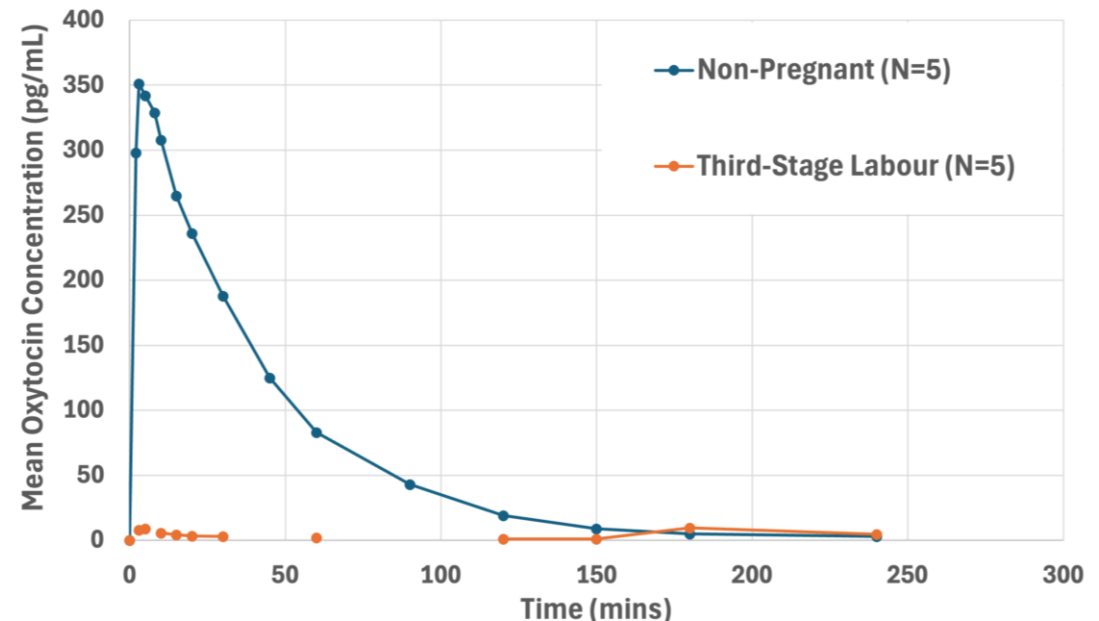
Sebastiaan Bijttebier, Tri-Hung Nguyen, Michelle P. McIntosh, Carl Kirkpatrick, Bart Remmerie, Lieve Dillen, Pete Lambert 

First published: 18 June 2024 | <https://doi.org/10.1111/bcp.16135> | Citations: 2

Oxytocin profiles in TSL plasma after IM and IH



Inhaled Oxytocin 400µg



Inhaler Device Transition

Iconovo ICOone Inhaler

- Single dose, disposable dry powder inhaler
- Single molded plastic component
- Foil sealed, powder cavity
- Simple to use

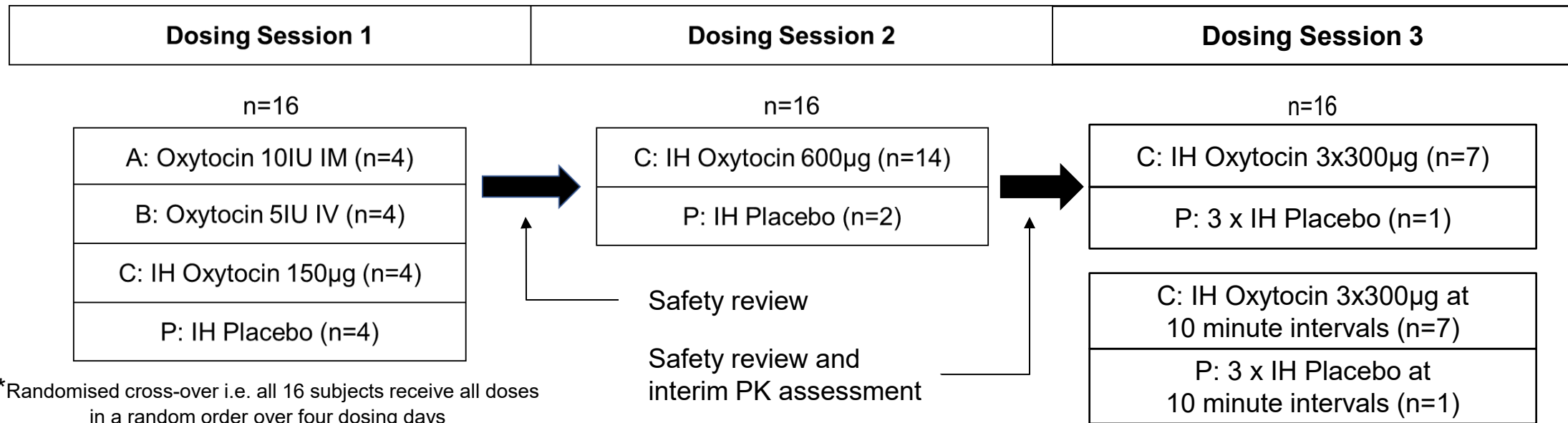


Key Requirements:

- ✓ Ultra-low cost
- ✓ Single use disposable device
- ✓ Simple to use
- ✓ Self-contained with no ancillary components needs
- ✓ Passive device to avoid co-ordination issue
- ✓ Performance at least at Rotahaler benchmark

Phase 1 Clinical Study – Study Design

- Optimised ICOone product
- 16 healthy, non-pregnant female subjects
- Study site – Nucleus Network, Melbourne, Australia
- Safety reviews conducted prior to each IHO dose increase
- 10IU IM is used as the reference for efficacy (i.e. the objective is a IHO profile similar to 10 IU IM)
- 5IU IV is used as a reference for safety (i.e. no IHO dose should exceed the maximum blood concentrations observed for IV as this is known to cause adverse effects)



*Randomised cross-over i.e. all 16 subjects receive all doses in a random order over four dosing days



Future Development

Opportunities

- Inhaled oxytocin has been independently assessed as the only innovation in development for PPH with the potential for **high impact** (McDougall et al., 2022)
 - Estimated with **potential to save 146,000 lives** in 8-years post launch (IC2030, 2015)
- Potential **streamlined regulatory pathway** to market based on PK and safety only, based on EMA scientific advice

Challenges

- Funding required to support development of **commercial manufacturing and late-stage clinical trials**
- **Industry partner required** for development and commercialisation
- Low market potential in high income (for-profit) markets, provides **barrier to investment**

Aim

Bring together a coalition of public, philanthropic, and private sector funders with an industry partner **to save the lives of mothers in greatest need**





With thanks to our pharma partners:

- Johnson & Johnson
- GSK

Funding partners:

- Bill & Melinda Gates Foundation
- Saving Lives at Birth
- McCall MacBain Foundation
- Planet Wheeler Foundation
- Grand Challenges Canada

