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Population pharmacokinetic-pharmacodynamic modelling of follicle-stimulating hormone and inhibin-B to predict ovarian response to follitropin alfa in *in vitro* fertilisation patients

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Introduction

- Women undergoing IVF receive follitropin alfa (**follicle-stimulating hormone; FSH**) to encourage multiple follicles to develop (controlled ovarian hyperstimulation; COH; Fig.1).
- When follicles begin to grow, they release **inhibin-B**.

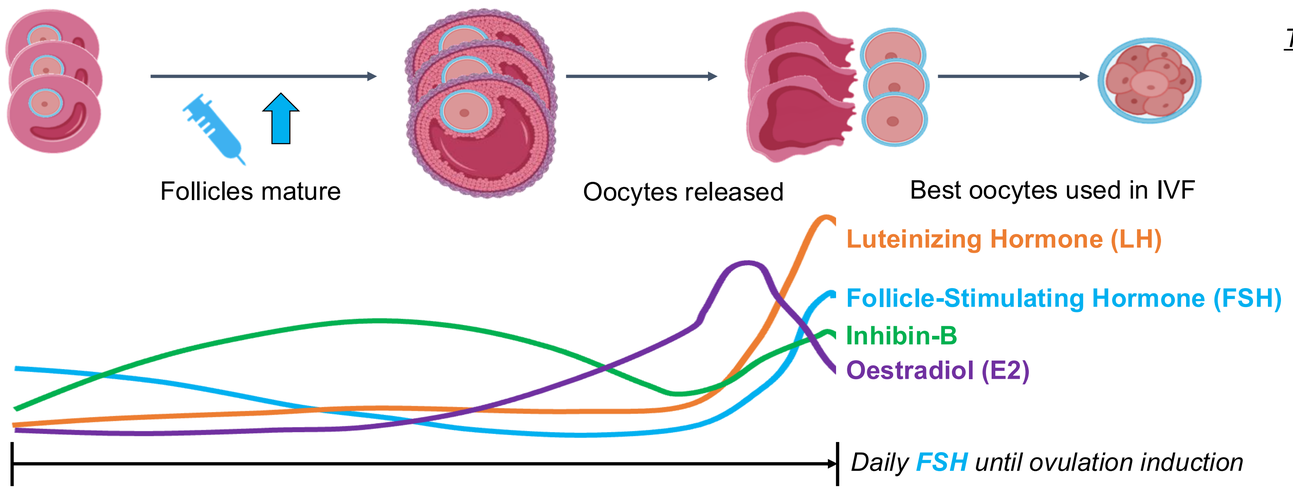

Figure 1. Hormonal fluctuations during folliculogenesis. Adapted from [1].

- Substantial inter-individual variability in FSH pharmacokinetics (PK), meaning optimising the number of oocytes retrieved is difficult [2, 3]. Inhibin-B represents response to COH (pharmacodynamics, PD).
- Population (pop-) PK modelling could enable us to predict response to FSH, with the support of an inhibin-B pop-PD model, thus supporting personalised dosing to optimise oocyte retrieval.

Aims:
- **To update a published popPK/PD model of FSH and inhibin-B [4],**
- **To assess model performance using real-world Australian IVF data to inform individualised FSH dosing practices.**

Methods

Data

- 81 Australian women undergoing IVF prescribed daily FSH.
- FSH concentrations: before first dose (baseline) and ~12h post-dose intermittently (C_{tmid}) (Fig. 2).
- Heterogeneous population characteristics (Tab. 1) and ovarian response (Fig. 3).

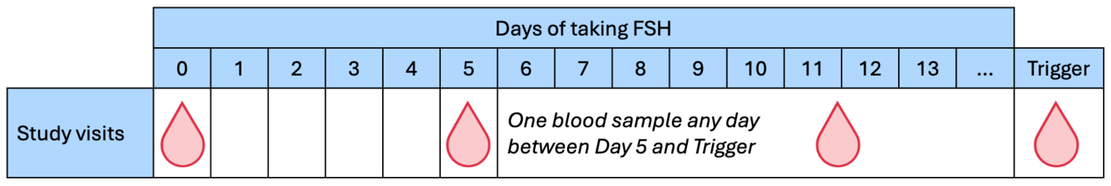

Figure 2. Pathology collection schedule.

A priori model [4]

- PK: one-compartment model with first-order absorption and linear elimination for FSH [4].
- Endogenous FSH: ODE turnover model.
- PD: FSH stimulates inhibin-B in a production stimulation turnover model.

Re-estimation and covariate analysis

- Endogenous FSH converted: µg/L to IU/L.
- *A priori* model evaluated using the data (Monolix, 2024R1). Stepwise re-estimation: PK, endogenous FSH, then PD.
- Covariates: age, weight, COH cycle number, anti-Müllerian Hormone (AMH), E2, LH. Used conditional sampling use for stepwise approach based on correlation tests [5].
- PD parameters have been included at this stage but require further optimisation.

Model performance

- Assessed using standard diagnostic plots and visual predictive checks (VPC; 90% prediction interval).
- Parameter precision was assessed via relative standard errors.
- Estimated using non-linear mixed-effects modelling through the stochastic approximation expectation-maximization algorithm.

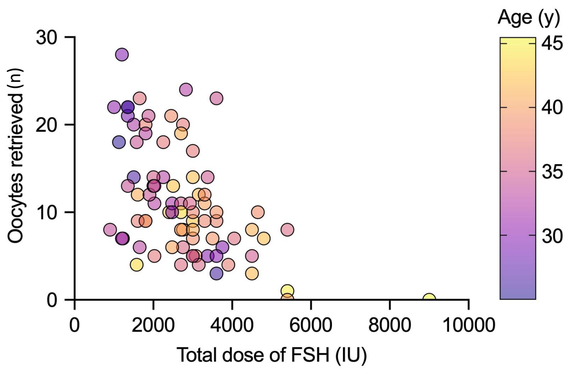

Table 1. Demographic, medication, and cycle characteristics. Reported as median (range), n (%).

Parameter	Population (N = 81)
Demographic characteristics	
Age (year)	37.1 (25.0 – 45.4)
Body weight (kg)	65.0 (44.0 – 100.0)
Height (m)	1.65 (1.48 – 1.75)
Cycle (n)	2 (1 – 10)
COH medication	
Starting dose (IU)	250 (125 – 450)
Dose adjustments (n (%))	
No	72 (88.9%)
Yes - increase	7 (8.6%)
Yes - decrease	2 (2.5%)
Total dose (IU)	2700 (900 – 9000)
COH duration (d)	10 (6 – 20)
Downregulation agent	
GnRH Antagonist	75 (89.3%)
GnRH Agonist/ Analog	3 (3.6%)
P4/ MA	6 (7.1%)
Baseline pathology	
AMH (pmol/L)	10.0 (1.2 – 44.9)
FSH (IU/L)	7.0 (2.4 – 18.1)
LH (IU/L)	5.8 (1.0 – 30.5)
E2 (pmol/L)	150.0 (9.2 – 611.0)
P4 (nmol/L)	1.0 (0.5 – 60.9)
Inhibin-B (ng/L)	
Patients (n (%))	24 (29.6%)
Median (range)	51.5 (10.0 – 106.0)
Oocytes retrieved (n)	10 (0 – 28)

Figure 3. Relationship between total dose of FSH administered and the number of oocytes retrieved per patient. Age represented by colour.

FSH and Inhibin-B in Women Undergoing IVF

- IC50 was omitted from the *a priori* model, as it was not identifiable from the sparse inhibin-B data, introduced model instability and confounded EC50.
- Parameter estimates were re-estimated (Tab. 2).

Table 2. Population parameter re-estimation. The final model includes covariate relationships.

Parameter		Unit	*A priori* model [4]	Final model
Population mean estimate (RSE%)				
PK	K_a (FIX)	h^{-1}	0.14	0.14 [A]
	CL/F	L/h	0.88 (3.5)	0.48 (11.92)
	V/F	L	21.8 (2.28)	6.86 (94.71)
Endogenous FSH	FSH_0	ug/L (IU/L)	0.50 (4.05)	0.44 (8.11)
	K_{endo}	ug/h	0.024 (10.7)	0.024 [A] (FIX)
	Ga (FIX)	-	0.27 (1.67)	0.27 [A]
PD	$Inh\text{-}B_0$	ng/L	41 (7.05)	37.42 (16.51)
	E_{max}	-	86.9 (11)	14.59 (20.25)
	EC_{50}	ug/L (IU/L)	1.21 (3.84)	11.09 (10.10)
	K_{out}	h^{-1}	1.13 (5.4)	1.13 [A] (FIX)
	Gamma (FIX)	-	4.31 (6.12)	4.31 [A]
	IC_{50}	ng/L	333 (57.9)	-
CV (RSE%) [shrinkage]				
PK	BSV CL/F	%	41.7 (17.7) [22.8]	-
	BSV V/F	%	13.26 (18.2) [-14.3]	-
Endogenous FSH	BSV FSH_0	%	17.63 (15.7) [1.17]	15.70 (41.54) [55.75]
	BSV K_{endo}	%	35 (26.4) [-17.4]	-
PD	BSV $Inh\text{-}B_0$	%	34.9 (15.3) [3.04]	93.31 (15.12) [45.11]
	BSV E_{max}	%	35 (26.6) [-0.61]	96.30 (16.15) [43.10]
	BSV EC_{50}	%	13 (21.1) [7.25]	-
	BSV K_{out}	%	25.61 (15.6) [-0.2]	-
	BSV IC_{50}	%	57.9 (35.5) [4.7]	-
Residual error model (RSE%)				
FSH (proportional)		-	0.06 (4.53)	0.36 (FIX)
Inh-B (exponential)		-	0.01 (5.22)	0.22 (12.00)

[A]: *A priori* value. Abbreviations provided at bottom.

- Covariates were described as follows:

$$V/F = 6.86 * \left(\frac{Weight}{80}\right)^{2.41} L$$

$$FSH_0 = 0.44 * e^{(-0.014 * baseline\ [AMH])} * e^{(0.045 * baseline\ [LH])}\ IU/L$$

- Inclusion of weight and baseline AMH and LH improved model fit (BICc Δ - 30.88; -2LL Δ - 45.35).
- Only 1.94% and 2.27% of the observation-prediction FSH and inhibin-B data, respectively, were outside the 90% prediction interval.
- Visual predictive check (VPC) demonstrated adequate description of PK data (Fig. 4A) despite sparse clinical sampling schedules typical of IVF practice. PD requires further optimisation (Fig. 4B).

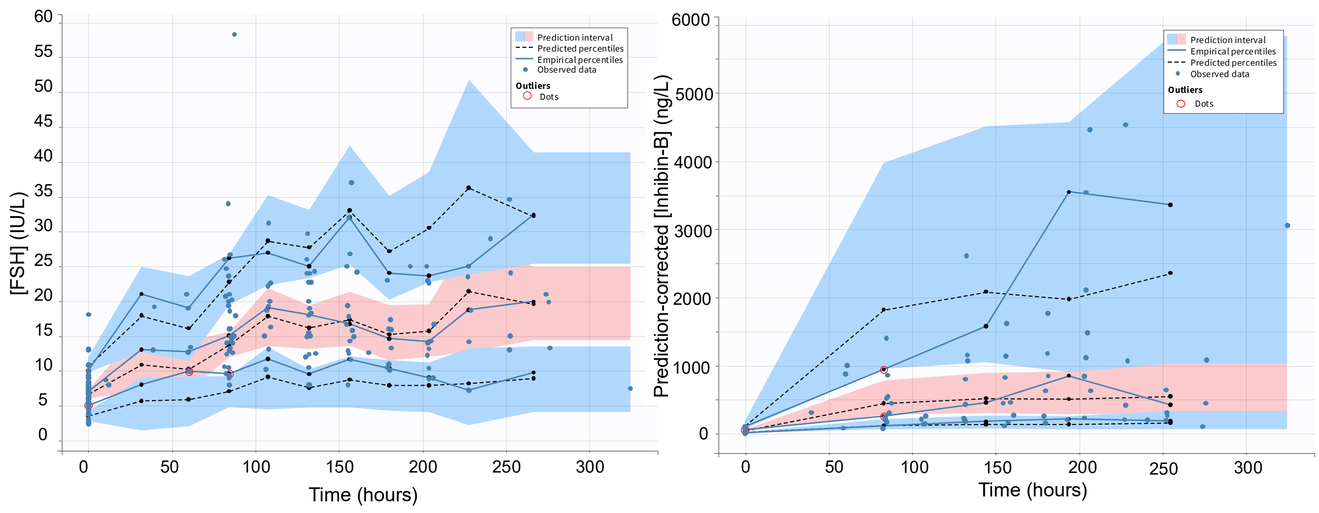

Figure 4. VPC of FSH data (4A), and prediction-corrected VPC of inhibin-B data (4B).

Discussion

- FSH is a large and hydrophilic glycoprotein [6], so weight only slightly alters volume of distribution.
- AMH and LH indirectly influence FSH concentrations through endocrine feedback loops [7].
- The model characterised patient trajectories, demonstrating feasibility for clinical application.
- Estimates consistent with another pop-PK model of FSH that used a GnRH agonist [8].

Future directions

- Optimise the inhibin-B pop-PD model.
- Explore the effect of time-varying covariates (e.g., in-cycle biomarkers LH and E2).

Significance

- The updated model supports the development of model-informed precision dosing tools for FSH to optimise follicular stimulation, enabling target oocyte retrieval for more IVF patients.
- Planned *in silico* simulations of FSH dosing regimens will help to achieve optimal number of oocytes.

Acronyms. AMH: anti-Müllerian hormone; BICc: corrected Bayesian information criteria; BSV: between subject variability; CL/F: clearance; COH: controlled ovarian hyperstimulation; C_{tmid}: concentration in the middle of a dosing interval; E2: oestradiol; FSH: follicle-stimulating hormone; FSH_0: baseline FSH; GnRH: gonadotropin-releasing hormone; Inh-B: inhibin-B; IU: international units; IVF: *in vitro* fertilisation; K_a: absorption rate constant; LH: luteinizing hormone; MA: medroxyprogesterone acetate; ODE: ordinary differential equation; PD: pharmacodynamics; PK: pharmacokinetics; P4: progesterone; RSE: residual standard error; SCM: stepwise covariate modelling; V/F: volume of distribution; VPC: visual predictive check; -2LL: -2 log-likelihood.

Acknowledgements. The authors would like to thank Dr. Mahmoud Ibrahim for sharing the structural *a priori* model, and A/Prof. Daniel Wright and Dr. Ranita Kirubakaran for their feedback. T.M.'s research is supported by an Australian Government Research Training Program Scholarship and a PhD Top-Up Scholarship (Medical Research Future Fund). T.M.'s conference attendance is supported by Virtus Health Pty Ltd.

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Images: BioRender, Canva. Graphs: RStudio, Monolix.