Supplementary Material

1 EQUATIONS

The equations in this section were used for the simulation of the normal menstrual cycle without drug administration. A list of parameters and short descriptions are provided in section 2 of the supplementary material. Additional explanations and biological motivations for the equations dealing with hormone dynamics (S1-19) can be found in Röblitz et al. (2013).

Hill functions are used to model stimulatory ($H^+$) or inhibitory ($H^-$) effects:

$$H^+(S, T^j_i, n^j_i) = \frac{(S/T^j_i)^{n^j_i}}{1 + (S/T^j_i)^{n^j_i}}, \quad H^-(S, T^j_i, n^j_i) = \frac{1}{1 + (S/T^j_i)^{n^j_i}}.$$  

$S(t) \geq 0$ denotes the influencing substance. The threshold $T > 0$ represents the amount of $S$ at which the Hill function has the value $1/2$, i.e., where $50\%$ of the maximum effect is reached. $n \geq 1$ is called the Hill coefficient and regulates the rate of switching. $i$ denotes the influencing species and $j$ the influenced species.

Equations S1-4 deal with LH dynamics in two compartments. LH synthesis is described by a basal synthesis rate constant $b^{LH}_{syn}$ and is modulated by two Hill equations (stimulation by E2 and inhibition by P4).

$$Syn_{LH}(t) = (b^{LH}_{Syn} + k^{LH}_{E2} \cdot H^+(E2(t), T^{LH}_{E2}; n^{LH}_{E2})) \cdot H^- (P4(t), T^{LH}_{P4}; n^{LH}_{P4}) \quad (S1)$$

LH is released from the pituitary with a basal release rate constant $b^{LH}_{Rel}$, which depends on the amount of LH in the pituitary and which is stimulated by the GnRH-receptor complex.

$$Rel_{LH}(t) = (b^{LH}_{Rel} + k^{LH}_{G-R} \cdot H^+(G-R(t), T^{LH}_{G-R}; n^{LH}_{G-R})) \cdot LH_{pit}(t) \quad (S2)$$

The amount of LH in the pituitary can be described by the difference between the synthesized and the released amount of LH.

$$\frac{d}{dt}LH_{pit}(t) = Syn_{LH}(t) - Rel_{LH}(t), \quad (S3)$$

The released amount of LH is diluted in the blood volume $V_{blood}$. Through the blood stream, LH reaches its receptor and forms complexes. LH is removed from the systems with the clearance rate constant $k^{LH}_{cl}$.

$$\frac{d}{dt}LH_{blood}(t) = \frac{1}{V_{blood}} \cdot Rel_{LH}(t) - k^{LH}_{cl} \cdot LH_{blood}(t). \quad (S4)$$

FSH synthesis is inhibited by progesterone and the frequency of pulsatile GnRH release.
\[ Syn_{FSH}(t) = \frac{k_{FSH}^{P4}}{1 + \left( \frac{P4(t)}{T_{FSH}^{P4}} \right)^{n_{FSH}^{P4}}} \cdot H^-(freq, T_{freq}^{FSH}, n_{freq}^{FSH}) \] (S5)

The fundamentals of the equations S6-8 are analogue to S2-4.

\[ Rel_{FSH}(t) = (b_{FSH}^{Rel} + k_{G-R}^{FSH} \cdot H^+(G-R(t), T_{G-R}^{FSH}, n_{G-R}^{FSH}) \cdot FSH_{P4}(t) \] (S6)

\[ \frac{d}{dt} FSH_{P4}(t) = Syn_{FSH}(t) - Rel_{FSH}(t). \] (S7)

\[ \frac{d}{dt} FSH_{blood}(t) = \frac{1}{V_{blood}} \cdot Rel_{FSH}(t) - (k_{FSH}^{blood} - k_{cl}^{FSH}) \cdot FSH_{blood}(t). \] (S8)

FSH reaches the ovaries through the blood stream and binds to its receptors on the follicular surfaces.

\[ \frac{d}{dt} FSH_{foll}(t) = \frac{V_{blood}}{V_{ovaries}} \cdot k_{FSH}^{FSH} \cdot FSH_{blood}(t) - (k_{on}^{FSH} \cdot R_{FSH}(t) - k_{cl}^{FSH}_{foll}) \cdot FSH_{foll}(t) \] (S9)

The dynamics of the FSH receptors is described in three steps (S10-12). FSH binds to its receptor \( R_{FSH} \), resulting in the formation of an active complex \( FSH-R \). Desensitised receptors \( R_{FSH,des} \) are caused by the dissociation of the complex. Each step has a characteristic reaction rate constant.

\[ \frac{d}{dt} R_{FSH}(t) = k_{recy}^{FSH} \cdot R_{FSH,des}(t) - k_{on}^{FSH} \cdot FSH_{foll}(t) \cdot R_{FSH}(t) \] (S10)

\[ \frac{d}{dt} FSH-R(t) = k_{on}^{FSH} \cdot R_{FSH,des}(t) \cdot R_{FSH}(t) - k_{des}^{FSH} \cdot FSH-R(t) \] (S11)

\[ \frac{d}{dt} R_{FSH,des}(t) = k_{des}^{FSH} \cdot FSH-R(t) - k_{recy}^{FSH} \cdot R_{FSH,des}(t), \] (S12)

\( freq \) and \( mass \) characterize the GnRH pulse generator needed to describe the GnRH dynamics in the system. The basal frequency \( f_0 \) is modulated by the stimulatory effect of E2 and the inhibitory effect of P4.

\[ freq(t) = f_0 \cdot H^-(P4(t), T_{P4}^{freq}, n_{P4}^{freq}) \cdot (1 + m_{E2}^{freq} \cdot H^+(E2(t), T_{E2}^{freq}, n_{E2}^{freq})) \] (S13)

The basal released mass \( a_0 \) is regulated by E2 stimulation as well as inhibition depending on the E2 concentration.
The GnRH receptor is present in four states in the model (S16-19). Free active receptors $R_{G,a}$ are available for binding GnRH with a forward rate $k_{on}^G$ and a reverse rate $k_{off}^G$. The receptors and receptor complexes can switch between active and inactive states.

\[
\frac{d}{dt} R_{G,a}(t) = k_{on}^G \cdot G(t) \cdot G-R_a(t) - k_{off}^G \cdot R_{G,a}(t) - k_{inter}^R \cdot R_{G,a}(t) + k_{recy}^R \cdot R_{G,i} 
\]

\[
\frac{d}{dt} R_{G,i}(t) = k_{diss}^G \cdot G-R_i(t) + k_{inter}^G \cdot R_{G,a}(t) - k_{recy}^G \cdot R_{G,i}(t) + k_{syn}^G - k_{degr}^G \cdot R_{G,i}(t) 
\]

\[
\frac{d}{dt} G-R_a(t) = k_{on}^G \cdot G(t) \cdot R_{G,a}(t) - k_{off}^G \cdot G-R_a(t) - k_{inact}^R \cdot G-R_a(t) + k_{act}^R \cdot G-R_i(t) 
\]

\[
\frac{d}{dt} G-R_i(t) = k_{inact}^G \cdot R_{G,i}(t) G-R_a(t) - k_{act}^G \cdot G-R_i(t) - k_{degr}^G \cdot G-R_i(t) - k_{diss}^G \cdot G-R_i(t). 
\]

The concept to simulate follicular maturation is derived from Lange et al. (2018). The Hill term in equation (S20) represents the stimulation of follicular growth and competition as soon as the individual FSH sensitivity threshold $T_{FSH-R}(i)$ is exceeded.

\[
\frac{d}{dt} x_i = H^+(FSH-R, T_{FSH-R}(i), n_{FSH-R}) \cdot (\xi - x_i) x_i (\gamma - \kappa(\sum x'_i - \mu x''_i)) 
\]

The growth rate $\gamma$ is inhibited by P4 and stimulated by the FSH receptor complex,

\[
\gamma = \gamma_0 \cdot H^-(P4, T_{P4}^\gamma, n_{P4}^\gamma) \cdot H^+(FSH-R, T_{FSH-R}^\gamma, n_{FSH-R}^\gamma) 
\]

whereas $\kappa$ is inhibited by the FSH receptor complex,

\[
\kappa = \kappa_0 \cdot H^-(FSH, T_{FSH}^\kappa, n_{FSH}^\kappa). 
\]

The P4 concentration in the model is described by a Gaussian with three parameters $c_1$, $v_{1,2}$ that characterize its height, mean and variance and whose values were determined by fitting the curve to P4
Supplementary Material

data, see Fig. S1. The mean is located with respect to the last time point of ovulation, $T_{ovu}$.

$$P4(t) = c_1 \cdot e^{-v_1(t-(T_{ovu}+v_2))^2}. \quad (S23)$$

We assume that all follicles with a radius larger than $T_{FS}$ contribute to E2 production, and that the amount of E2 produced depends linearly on their surface $FS$.

$$FS = \pi \cdot \sum \frac{(x_i)^{n_{FS}}}{(x_i)^{n_{FS}} + (T_{FS})^{n_{FS}}} \cdot (x_i)^2. \quad (S24)$$

$$\left(E2\right)(t) = \left(p_0^{E2} + c_2 \cdot FS\right) + c_3 \cdot e^{-v_3(t-(T_{ovu}+v_4))^2}. \quad (S25)$$

The second summand represents the amount of E2 produced by the corpus luteum.

Simulating ovarian stimulation with r-FSH, which is structurally identical to FSH, is based on the idea that the administration of a drug which is identical to a species in the system can be modelled as an additional time dependent source term. The following algebraic equation is used to calculate the drug concentration $c(t)$ in the system.

$$c(t) = \frac{D \cdot \beta^2}{(\beta - c_L)^2} \cdot e^{-\beta \cdot t \cdot (c_L \cdot t - \beta \cdot t - 2)} + e^{-c_L \cdot t} \quad (S26)$$

The three parameters $D$, $\beta$ and $c_L$ were calculated uniquely for each administered drug from the corresponding values of three pharmacokinetic parameters given in (Kompendium, 2020). For this work, equation (S25) is used to calculate the concentration of r-FSH, which is then added to the concentration of FSH to form the total FSH concentration in the system.
## 2 LIST OF PARAMETERS

The following table includes all model parameters, their values and short descriptions. Hill terms and coefficients are not described in further detail, since they are represented in a consistent notation which is introduced at the beginning of the first section (1 EQUATIONS) of the supplementary material. Parameters marked with * are either newly introduced or modified compared to Röblitz et al. (2013).

| Symbol               | Value    | Unit  | Explanation                                      |
|----------------------|----------|-------|-------------------------------------------------|
| $b_{LH Syn}^*$       | 1827.48  | IU/d  | LH synthesis rate constant                      |
| $k_{LH E2}$          | 7309.92  | IU/d  | reaction rate constant referring to the stimulatory effect of E2 on the LH synthesis |
| $T_{E2}$             | 192.2    | pg/mL |                                                 |
| $n_{E2}$             | 10       | –     |                                                 |
| $T_{P4}$             | 2.371    | ng/mL |                                                 |
| $n_{P4}$             | 1        | –     |                                                 |
| $b_{LH Rel}$         | 0.00476  | 1/d   | release rate constant of LH into the blood      |
| $k_{LH G-R}$         | 0.1904   | 1/d   | reaction rate constant of the stimulatory effect of GnRH receptor complex on the LH release |
| $T_{LH G-R}^*$       | 0.001    | nmol/L|                                                 |
| $n_{LH G-R}$         | 5        | –     |                                                 |
| $V_{blood}^*$        | 5.5      | L     | blood volume                                    |
| $k_{LH cl}$          | 74.851   | 1/d   | clearance rate constant of LH                   |
| $T_{FSH freq}$       | 12.8     | 1/d   |                                                 |
| $n_{FSH freq}$       | 5        | –     |                                                 |
| $T_{P4}^*$           | 5        | ng/mL |                                                 |
| $n_{P4}^*$           | 2        | –     |                                                 |
| $b_{FSH Rel}$        | 0.057    | 1/d   | FSH release rate constant                       |
| $k_{LH G-R}$         | 0.272    | 1/d   | reaction rate constant of the stimulatory effect of the GnRH-receptor complex on the FSH release |
| $T_{FSH G-R}^*$      | 0.0003   | nmol/L|                                                 |
| $n_{FSH G-R}$        | 2        | –     |                                                 |
| $k_{FSH blood}^*$    | 0.02     | 1/d   | diffusion rate constant of FSH from the blood to the ovaries |
| $k_{FSH on}$         | 3.529    | L/(d-IU) | FSH receptor binding rate constant              |
| $k_{FSH cl}$         | 114.25   | 1/d   | FSH clearance rate constant                     |
| $k_{FSH recy}$       | 61.029   | 1/d   | FSH receptor recycling rate constant            |
| $k_{FSH des}$        | 138.3    | 1/d   | FSH receptor desensitisation rate constant      |
| $k_{FSH Foll}^*$     | 0.1      | 1/d   | FSH clearance rate constant at the follicles    |
### Supplementary Material

| Symbol         | Value  | Unit | Explanation                                      |
|----------------|--------|------|--------------------------------------------------|
| $V_{ovaries}$  | 0.011  | L    | ovarian volume                                   |
| $f_0$          | 16     | 1/d  | basal GnRH pulse frequency                      |
| $T_{freq}^{P_4}$ | 1.2    | ng/mL|                                                  |
| $n_{freq}^{P_4}$ | 2      |       |                                                  |
| $m_{freq}^{E_2}$ | 1      |      | GnRH pulse amplitude                             |
| $T_{freq}^{E_2}$ | 220    | pg/mL|                                                  |
| $n_{freq}^{E_2}$ | 10     |      |                                                  |
| $a_0$          | 5.593e-3 | nmol | basal GnRH pulse amplitude                      |
| $T_{mass,1}^{E_2}$ | 220   | pg/mL|                                                  |
| $n_{mass,1}^{E_2}$ | 2      |      |                                                  |
| $T_{mass,2}^{E_2}$ | 9.6    | pg/mL|                                                  |
| $n_{mass,2}^{E_2}$ | 1      |      |                                                  |
| $k_G^{degr}$   | 0.447  | 1/d  | GnRH receptor degradation rate constant          |
| $k_G^{on}$     | 322.18 | L/d nmol | GnRH receptor binding rate constant               |
| $k_G^{off}$    | 644.35 | 1/d  | GnRH-receptor complex reverse-rate constant      |
| $k_{G-degr}^{R}$ | 32.218 | 1/d  | inactive GnRH-receptor complex degradation rate constant |
| $k_{G-diss}^{R}$ | 3.222  | 1/d  | inactive GnRH-receptor complex dissociation rate constant |
| $k_{RG}^{inter}$ | 32.218 | 1/d  | GnRH receptor inactivation rate constant         |
| $k_{RG}^{recy}$ | 32.218 | 1/d  | GnRH receptor recycling rate constant            |
| $k_{G-R-degr}^{R}$ | 0.0895 | 1/d  | GnRH-receptor complex degradation rate constant  |
| $k_{G-R-inact}^{R}$ | 32.218 | 1/d  | inactive GnRH-receptor complex inactivation rate constant |
| $k_{R-G-degr}^{R}$ | 3.222  | 1/d  | inactive GnRH receptor degradation rate constant  |
| $k_{RG-syn}$   | 8.949e-5 | nmol L/d | GnRH receptor synthesis rate constant            |
| $\xi$          | 25     | mm   | maximal follicle size                            |
| $\kappa_0$     | 0.000048 |      | competition strength                            |
| $T_{FSH-R}^*$  | 0.85   | nmol/mL |                                                 |
| $n_{FSH-R}^*$  | 25     |      |                                                  |
| $\nu$          | 2      |      | fractal dimension                                |
| $\mu$          | 1      |      | self-harm                                       |
| $\gamma_0$     | 0.03   | mm/d | basal growth rate                                |
| $T_{PA}^*$     | 0.33   | ng/mL|                                                  |
| $n_{PA}^*$     | 5      |      |                                                  |
| $T_{FSH-R}^*$  | 0.45   | nmol/L|                                                  |
| $n_{FSH-R}^*$  | 10     |      |                                                  |
| Symbol | Value | Unit | Explanation |
|--------|-------|------|-------------|
| $T_{FSH-R}$ | 0.85 | nmol/L | |
| $n_{FSH-R}$ | 25 | – | |
| $c_1$ | 13 | – | scaling factor for P4 production |
| $c_2$ | 0.02 | pg/mL | scaling factor for follicular surface effect in E2 production |
| $c_3$ | 150 | – | scaling factor for E2 production |
| $v_1$ | 0.06 | – | |
| $v_2$ | 7 | d | |
| $v_3$ | 1 | – | |
| $v_4$ | 0.02 | d | |
| $T_F$ | 15 | mm | follicular size threshold for E2 production |
| $n_F$ | 5 | – | |
| $P_0^{E2}$ | 1 | pg/mL | |
| $D_{FSH}$ | 5.0201 | IU/d | Menopur administartion 225 IU |
| $\beta_{FSH}$ | 9.87 | 1/d | Menopur administartion 225 IU |
| $c_{L}^{FSH}$ | 0.42 | 1/d | Menopur administartion 225 IU |
| $D_{LH}$ | 2.14 | IU/d | Menopur administartion 225 IU |
| $\beta_{LH}$ | 6.04 | 1/d | Menopur administartion 225 IU |
| $c_{L}^{LH}$ | 3.199 | 1/d | Menopur administartion 225 IU |
3 PROGESTERONE CURVE

Figure S1. Fit of Gaussian curve to P4 serum concentration measurement in woman provided by Pfizer Ltd. The measurement points are represented in purple. The black line presents the progesterone curve as it is implemented in the model.
Figure S2. Representation of the cycle length of 42 simulated menstrual cycles.