

## REGULATION OF AN OVULATORY CYCLE

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### INTRODUCTION

Endocrine system is one of the main systems, which determine harmony and coordination of physiological processes of an organism. Endocrinal glands produce biologically active substances, i.e. hormones, through which homeostasis is supported, i.e. the stability of inner medium of an organism independently of changes in external surroundings. That is why the most important problem of endocrinology is to clear out the principles of hormone functioning. Mathematical modelling helps to solve this problem as well. Using mathematical models one may determine new trends in experimental and clinical research, based on new quantitative hypotheses.

In addition to specific function, female reproductive system has an endocrinal feature, i.e. it secretes steroid hormones. We will overview cyclic processes, occurring in gonads and related changeable hormonal function of the ovary. The processes occurring in ovary are called "ovulatory cycle" (Speroff L. et al., 1971). Female ovulatory cycle reflects complicated functional interaction among many anatomically distant structures. Various processes like ovum's maturity and ovulation, changes of activity of tropical structures in brains and pituitary, as well as changes of secondary sexual signs related to reproduction are joined together in the cycle. The above mentioned processes are coordinated and strictly regulated by the speed of hormone production and secretion.

Analysis of interaction of hormones, which regulate ovulatory cycle, helps to understand the reasons of female sterility and, on the other hand, give necessary information for control of birth rate. The birth rate decreases and the number of sterile families increases in Lithuania. That theme is urgent, because 10% of sterile women have disorder in ovulatory cycle (Rimkus E., Matilionis V., 1996).

Physiology of female reproductive system is a very complicated matter. It is difficult to ascertain experimentally such factors as duration of the cycle, the number of hormones, the nature of their relationship, the importance of morphological changes and many other specific features of reproductive functioning. It is difficult to ascertain them mathematically also.

The first attempt to model the menstrual cycle was made in 1940. H.Lamport described the interaction between steroids and gonadotropical hormones by means of linear differential equations. In 1969 A.Thompson has created a mathematical model involving morphological changes of ovaries. Obtained results showed the cyclic behaviour of the system. In 1972 Bogumil, Ferin together with others presented



detailed mathematical model of menstrual cycle. The authors mathematically described morphological and hormonal changes during the cycle. Both hormonal and ovary morphological components of the reproductive system are included into the model. 34 non-linear differential equations describe those components. This work has given a new impact to the modelling of menstrual cycle, but had some shortages: because of big number of equations it is difficult to find the solution.

#### “PITUITARY – GONAD” SYSTEM

Fig. 1 illustrates female hormonal regulation of menstrual cycle. The occurring processes can be described as follows (the numeration is in line with Roman numerals on Fig. 1).

1. While the yellow corpuscle degenerates, the concentration of *estrogen* E and *progesterone* P in blood is reduced.
2. In consequence, FSH (*follicle stimulating hormone*) concentration in blood gradually grows.
3. The increased FSH concentration stimulates the development of a few follicles. In some days one of them begins to mature quickly, while the other follicles degenerate. That occurs in the background of decreased significantly FSH concentration and perhaps increasing LH (*luteinising hormone*) concentration. It can be explained in the following way: “the chosen” follicle allocates estrogen inducing the increase of sensitiveness for gonadotropical stimulation, and decrease of sensitiveness of “the rejected” follicles. The follicles condemned to involution may further produce steroids, but the physiological meaning of that secretional activity is not clear yet. According to some researchers, those follicles are the source of androgens. So they define their importance for endurance libido.
4. The maturing follicle produces more and more estrogen. If we neutralised their growth, then the gonadotropin would not be thrown out in the midcycle. That is why increase of estrogen concentration is direct stimulus of LH and FSH peak, appearing just before the ovulation.
5. The increased LH concentration stimulates the synthesis of progesterone. Progesterone is the component of a signal, which causes LH throw-out according to positive feedback mechanism. Besides that, progesterone participates in the ovulation process, because it is necessary in the production of ferments. Therefore the follicle becomes thin and the ovum is released easier.
6. In the initial phase of the post-ovulation period (then concentration of steroids in blood decreases for short time), the ragged follicle is filled with luteal cells, which are rich of lipids and have a yellow shade. A new net of blood vessels forms. Biochemical purpose of luteal cells is that they produce increasing quantity of progesterone and estrogens. The stimulation of steroidogenesis occurs at the stage, when the catalyse of desmolasa takes place, i.e. in the same way, as for other steroid making cells.
7. The high concentrations of progesterone and estrogens in blood inhibit the secretion of pituitary gonadotropin. This effect come out when centres of hypothalamus are activated.

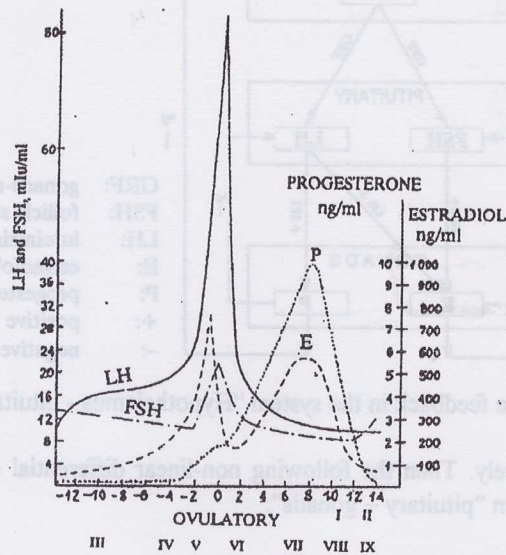


Fig. 1. Hormonic regulation of female ovulatory cycle

8. After some time a yellow corpuscle degenerates.
9. While the yellow corpuscle degenerates, the concentration of estrogens and progesterone in blood instantly decrease. Then FSH concentration grows, therefore the new follicles begin to develop and menstrual cycle repeats again.

The block-diagram of the menstrual cycle regulation is shown on the Fig. 2.

#### MATHEMATICAL MODEL OF THE SYSTEM

Based upon the circuit of Fig. 2, the mathematical model of hormone interaction during the menstrual cycle was created. The menstrual cycle consists of two phases: preovulatory and postovulatory, which are different in both hormone production and regulative mechanism. The biochemical properties of steroid production also change, i.e. in preovulatory phase estrogens are synthesised from androgens during the fragrant reaction and in postovulatory phase they are produced from cholesterol with the help of ferments. That is why estradiol  $E$  which is secreted by gonads, consists of two components: estradiol  $E_-(t)$  in preovulatory phase and estradiol  $E_+(t)$  in postovulatory phase. Referring to the general scheme of hormone interaction (Fig. 2), we may interpret those relations of the analysed system in terms of an ecological problem "a predator - prey". Let us say that  $L(t)$ ,  $F(t)$ ,  $P(t)$  are the concentrations of LH, FSH, and progesterone  $P$  in blood at the moment  $t$ , respectively,  $E_-(t)$ ,  $E_+(t)$  are concentrations of estradiol  $E$  in blood at the moment  $t$  in pre- and postovulatory



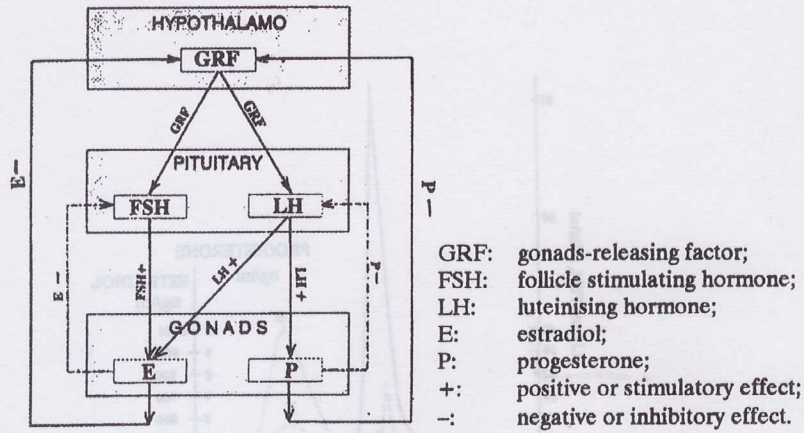


Fig. 2. The feedback in the system "Hypothalamus - pituitary - gonads"

phases, respectively. Then the following non-linear differential equations with delay describe the system "pituitary - gonads":

$$\dot{F}(t) = r_F \left[ 1 + a \left( 1 - \frac{E_-(t-1)}{K_{E_-}} \right) - \frac{F(t)}{K_F} \right] F(t), \quad (1)$$

$$\dot{E}_-(t) = r_{E_-} \left[ 1 + b \left( 1 - \frac{F(t)}{K_F} \right) - \frac{E_-(t-h_{E_-})}{K_{E_-}} \right] E_-(t), \quad (2)$$

$$\dot{L}(t) = r_L \left[ 1 + c \left( \frac{E_-(t-1)}{K_{E_-}} - \frac{P(t)}{K_P} \right) - \frac{L(t)}{K_L} \right] L(t), \quad (3)$$

$$\dot{P}(t) = r_P \left[ \alpha \frac{L(t-h_{E_-})}{K_L} + (1-\alpha) \frac{E_+(t-h_{E_+})}{K_{E_+}} - \frac{P(t)}{K_P} \right] P(t), \quad (4)$$

$$\dot{E}_+(t) = r_{E_+} \left[ \frac{E_-(t)}{K_{E_-}} - \frac{E_+(t-h_{E_+})}{K_{E_+}} \right] E_+(t), \quad (5)$$

$$E(t) = E_-(t) + E_+(t-h_{E_-}). \quad (6)$$

Here  $K_{E_-}$ ,  $K_{E_+}$ ,  $K_P$ ,  $K_L$ ,  $K_F$  are average concentrations of estradiol E (in pre- and postovulative phases), progesterone P, LH, FSH in blood, respectively. The parameters  $r_{E_-}$ ,  $r_{E_+}$ ,  $r_P$ ,  $r_L$ ,  $r_F > 0$  characterise the growth rate of hormone

concentration. The term  $a \left( 1 - \frac{E_-(t-1)}{K_{E_-}} \right)$ , ( $a < 0$ ) in equation (1) reflects the fact that

estradiol  $E_-$ , circulating in blood, affects FSH secretion. For example, at the moment when  $E_-(t) < K_{E_-}$ , the growth rate of  $F(t)$  increases, i.e. the FSH secretion intensifies in pituitary and when  $E_-(t) > K_{E_-}$ , the FSH concentration in blood decreases, because

the inhibitive influences of  $E_-$  reveal. In equation (3),  $E_-$  stimulates the secretion of LH hormone, but LH "doesn't respond" at once to this signal, because for its secretion a particular time interval is required. That's why we introduce the delay of 24 hours into the model. Similarly, in equation (1) for FSH secretion time delay is needed, as well. Progesterone P stifles LH secretion. That regulation, which is governed by the parameters  $a, b, c$  in the equations (1), (2), (3), occurs through the feedback mechanism. At increase of parameters  $a, b, c$  production and secretion of hormones FSH, LH, and  $E_-$  becomes more intensive, as well. Production of  $E_-$  plays the main role in the system. Some period of time is needed for the follicle to mature and to begin producing estradiol. We put it into the equations (2) and (5) as the delays  $h_{E_-}$  and  $h_{E_+}$ . Therefore, the changes of estradiol  $E_-$  concentration at the moment  $t$  depend on that hormone concentration at a time moment  $t - h_{E_-}$ , i.e. depend on the level of follicle's maturity. The more sensible follicle is, the less estrogens it produce, and vice versa. It is possible to interpret the delay  $h_{E_+}$  in the postovulative phase similarly. Referring to the experimental data from [2], we assume, that  $h_{E_-} > h_{E_+}$ , because the typical structure of cells, i.e. steroid producers, forms in the cells of the yellow corpuscle. Therefore the estradiol biosynthesis in postovulative phase is shorter, that is  $h_{E_-} = 7$  days,  $h_{E_+} = 2$  days. The pituitary hormone FSH is a stimulating hormone, therefore the member  $b \left( 1 - \frac{F(t)}{K_F} \right)$ ,  $b < 0$ , represents that feature in the equation (2).

The secretion mechanism of the estradiol E is essentially different in the postovulative phase, therefore the equations (2) and (5), describing the dynamics of  $E_-$  and  $E_+$  are different.  $E_-$  produced by follicle when the ovulation is over, doesn't vanish and joins  $E_+$ , which is produced by a yellow corpuscle. The term  $\frac{E_-(t)}{K_{E_-}}$  in the equation (5) governs that process. It is obvious, that the amount of  $E_+$ , which is secreted in the postovulative phase, will depend on the concentration of  $E_-$  produced in the preovulative phase. It means, that if  $E_-$  secretion before ovulation occurs normally, then  $E_+$  secretion after ovulation will not be deranged. On the contrary, if the follicles produce not enough  $E_-$ , then the secretion of the hormones of the yellow corpuscle in the postovulative phase will be deranged. Clinical data confirm such dependency, which is appreciable during unovulative cycles [4]. The characteristic feature of unovulative cycles is as follows: follicles secrete less E in the preovulative phase than normally, therefore the LH, as well as FSH peaks are not called when the positive feedback is deranged. After that the follicles does not tear and the ovum does not release. The yellow corpuscle can not develop normally and can not secrete neither  $E_+$  or P.

Progesterone P is secreted actively only after the ovulation is finished. LH and  $E_+$  stimulate the secretion of that hormone. The terms  $\alpha \frac{L(t)}{K_L}$  and  $(1 - \alpha) \frac{E_+(t)}{K_{E_+}}$  in the equation (4) corresponds that. When concentrations of LH and  $E_+$  in blood increase, concentration of P increases also. Similarly to the system of "a predator-prey", as the number of preys increases, the number of predators grows also because of good



nourishment conditions until the system regulation mechanism begins to work. In our case parameter  $\alpha$  defines the extent of influence of LH and  $E_+$  to secretion of P.

The last equation (6) expresses aggregative dynamics of estradiol E. As already was noticed, E is produced in different ways before and after the ovulation. The equation (6) is required to reflect final E concentration, which is measured actually during experiment.

## THE RESULTS

Using PC and Euler's numerical method, we find the solutions of system (1)-(6) for the values of parameters as follows: the time step is equal 0.1;  $a = -0.23$ ;  $b = -0.1$ ;  $c = 0.15$ ;  $\alpha = 0.1$ ;  $r_L = 5.5$ ;  $r_{E_-} = 0.33$ ;  $r_{E_+} = 0.15$ ;  $r_P = 0.49$ . The received results are shown on Fig. 3. Let's analyse the received dynamics of the estrogenic hormones. In our case, the period of menstrual cycle is 28 days. In the beginning of the menstrual cycle, FSH stimulates the early growth of follicles, but "young" follicles can produce a very small amount of estradiol E. Therefore E concentration almost doesn't increase during the first four days of the cycle. While maturing, the follicles produce more and more estradiol, then E concentration begins to grow exponentially. The increased E concentration stimulates LH production through the positive feedback. Then LH stimulates the maturity of the chosen preovulative period and also stimulates E secretion. The rest follicles are atrophied. The preovulative follicle produces E (E concentration reaches 600 pg/ml on the 13th day of the cycle) so intensely, that through the positive feedback it induces a sudden LH throw into blood. Some time is necessary for pituitary to react to such an effect, therefore we see the LH and FSH peak after one day, i.e. on the 14th day of the cycle. The FSH peak is unlogical, because according to all general regularities, the FSH concentration should decrease as E increases. But the physiology of pituitary explains such misunderstanding. LH and FSH both are localised in the same cell, therefore that cell secretes not only LH, but FSH, as well. The high concentration (55  $\mu\text{I/ml}$ ) causes the changes of follicle's biochemical and structural characteristics. Consequently, the follicle tears, the ovum becomes free and the menstrual cycle occurs. In the postovulative phase, the torn follicle is filled up by the luteal cells, the production of estradiol ceases, therefore on either the 16th or 17th day concentration of E is again reduced to 180 pg/ml. But after some days the yellow corpuscle begins to produce E and P with all its capacity. Therefore on the 20th, 21st day the estradiol concentration reaches the second peak, but already it is less (500 pg/ml) than the peak before ovulation. The P concentration also increases exponentially, until it reaches 8.9 ng/ml. The high E and P concentrations stifle LH secretion (LH concentration reaches only 15  $\mu\text{I/ml}$ ). Through some time (approximately on the 23rd, 24th day of the cycle), the yellow corpuscle degenerates. Then the E and P concentrations suddenly decrease. In result, FSH activity becomes more active again, the new follicles grow and new menstrual cycle begins.

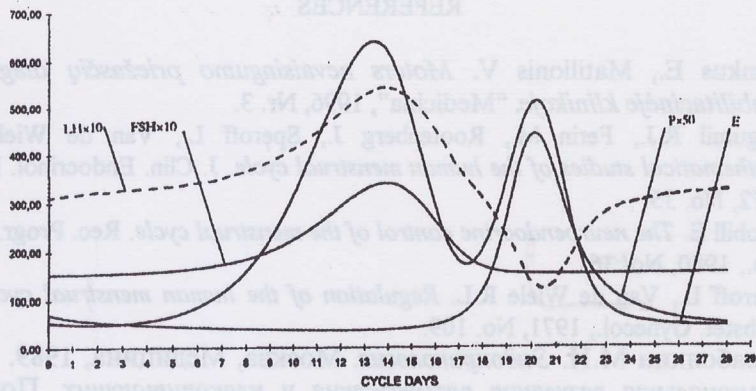


Fig. 3. The dynamics of estrogenic hormones

If we compare the obtained results with the experimental data and considering that blood of each woman have different LH, FSH, E and P concentrations, we can assert, that the obtained results conform well available experimental data (Fig. 4, 5). Thus the offered mathematical model (1)–(6) describes well the dynamics of estrogenic hormones.

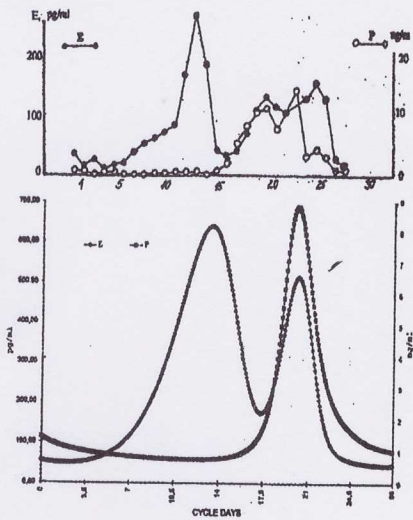


Fig. 4. E and P blood concentration during the ovulatory cycle

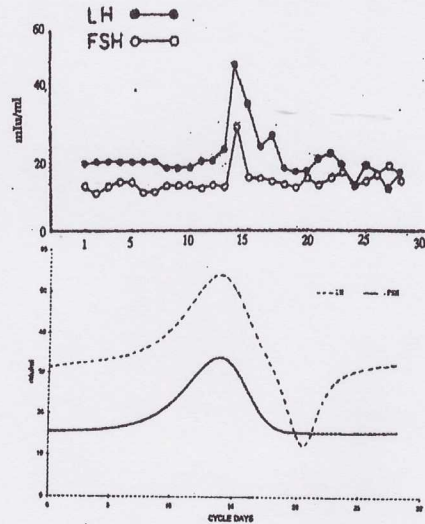


Fig. 5. LH and FSH blood concentration during the ovulatory cycle



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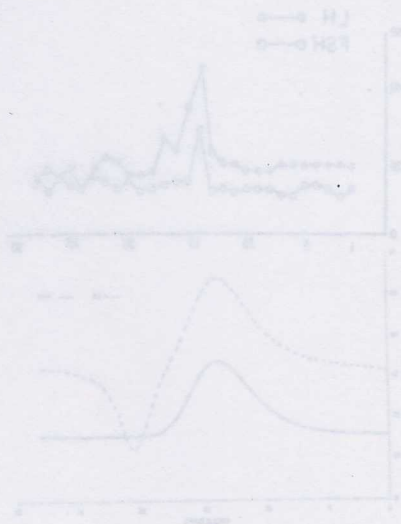


Fig. 2. LH and FSH blood concentration during the ovulatory cycle.

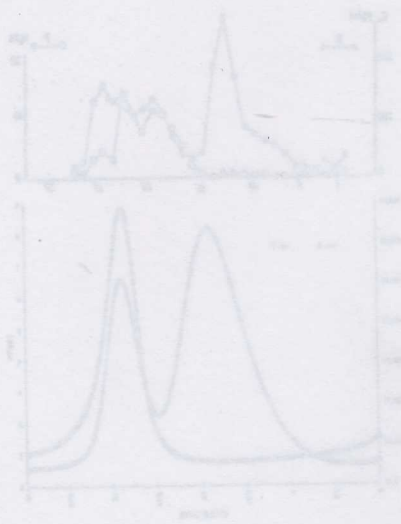


Fig. 4. E and P blood concentration during the ovulatory cycle.