Human Menstrual Cycle Modeling:A review

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***Abstract*—Modeling of such an important and complex system, as human reproductive system is, plays very important role in human medicine. During past years several models of human menstrual cycle systems have been proposed. This paper presents several relevant model systems.**

***Keywords*— Menstrual; Cycle; Hormones; Ovary; Modeling**

I. INTRODUCTION

As reproduction is very important for all species, the nature made responsible the highest centers for its regulation, such as hypothalamus and pituitary gland. The ovaries are executing their instructions. Certainly, hypothalamus is controlled by even higher center, called limbic system, involved in support of functions such as emotion, motivation, long-term memory, behavior and olfaction [1-4].

The female menstrual cycle is responsible for regulation of hormonal balance during follicular growth in the ovaries, in the way that reproduction is enabled after ovulation. Very important role in the female reproductive cycle belongs to the gonadotropin-releasing hormone (GnRH) as GnRH controls the process of follicular growth, ovulation, and corpus luteum development [5]. Simultaneously, it is responsible for the synthesis and release of gonadotropins, like luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both secreted from anterior pituitary into the blood [6]. These processes are known to be controlled by the frequency and size of GnRH pulses [7]. The pulsatile GnRH secretion is necessary for regular reproductive function. Low-frequency pulses cause FSH release, while high frequency pulses lead to LH release [8].

Modeling of dynamical systems is becoming a key topic not only in systems biology that consists of the study of bio-chemical mechanisms happening in real biological context, but also in other disciplines, such as mathematics, and computer science [9, 10]. The real mechanisms of the female menstrual cycle are not completely explored yet. Mathematical modeling is way to explain complex relationships within endocrine system of an individual.The purpose of this paper was to provide an unique source for Menstrual Cycle modeling solutions.

II. MATERIALS AND METHODS

The literature research was done for period between 2000 and 2017, using PubMed and Google Scholar search engines. The key words used for the research were: menstrual cycle, modeling, female, endocrine, hormones. From collected 169 papers 8 of them were included in the study.

Inclusion criteria were:

- Publications from period 2000-2017
- Language of publication was English
- Full text was available
- Include briefly explained model of Menstrual cycle or part of it

III. RESULTS

A. Margolskee&Selgrade (2011) [11]

It is an system of 13 ordinary differential equations and 42 parameters. The model was improved by including a time delay for the effect of inhibin on the synthesis of follicle stimulating hormone. Changes in three parameters were examined with bifurcation diagrams. Changing parameters were:1.the level of estradiol adequate for significant synthesis of luteinizing hormone, 2. parameter that measures mass transfer between the first two stages of ovarian development (indicative of healthy follicular growth), and 3. the time delay.

B. Roblitz et al. (2013) [12]

Aim of this study was, besides menstrual cycle, developing a mathematical model of GnRH analogues administration. Tthere are no delay differential equations in this model. It is based on deterministic modeling of the GnRH pulse pattern. This approach allows faster simulation time and more efficient identification of parameters. This model predicts the changes in the cycle after administration of Nafarelin or Cetrorelix during the cycle. It involves 33 equations and 114 parameters.

C. Margolskee&Selgrade (2013) [13]

Alison Margolskee and James F. Selgrade, developed the system including 16 nonlinear, delay differential equations with 66 parameters for hormonal regulation of the menstrual cycle of a woman in reproductive age. This model predicts changes in follicle numbers and reproductive hormones that occur through everymonthly cycle. This model explains the decline of primordial follicles from age of 20 to menopause and simulates a decrease in antimüllerian hormone (AMH) and inhibin and an increase in FSH with age according to experimental data. Model indicates that administration of exogenous AMH can slow transfer of non-growing primordial follicles to the active state and provide more follicles for development later in life due to delay the onset of menopause. Other effects of AMH agonists and antagonists were investigated in the setting of this model.

D. Chen&Ward (2013) [14]

This model is a very simple system of 3 nonlinear differential-delay equations and 37 parameters that be used as a basic model that describe hormonal interactions in hypothalamus, pituitary and ovaries. The model can be extended in order to in order to investigate any abnormality of menstrual cycle. In this study GnRH extension was designed and added to basic model in order to to describe the desensitisation of the pituitary when GnRH is continuously stimulating it, or when hormonal therapy is given.

E. Brueggemann et al. (2013) [15]

In this study, presented model is made of 4 ordinary differential equations, two algebraic equations and 33 parameters. Firstly unknown, parameters were identified as a solutions of nonlinear least squares problem, using Gauss-Newton method and NLSCON code implementation with a linearly-implicit Euler extrapolation (Limex). Since very simple, the model designed to simulate complex system cannot give results with high accuracy. But can serve as a very good basis for development of more complex models.

F. Hendrix et al. (2013)[16]

The model is based on hypothalamus–pituitary–ovarian axis, and involves 16 delay differential equations and 5 auxiliary equations, with 71 parameters. It is expected to predict levels of LH, FSH, E2, P4, InhA, InhB, and T in the serum of PCOSpatients. This model could lead to development of individualized therapeutic interventions.

G. Harris et al. (2014) [17]

This study presents a mathematical model describing blood levels of hormones that regulate the human menstrual cycle. The system of 13 nonlinear, delay, differential equations with 44 parameters predicts the serum concentrations of ovarian and pituitary hormones for normally cycling women. The model may describe a biologically abnormal condition (polycystic ovarian syndrome).

H. Isabel Reinecke et al. (2009) [18]

GynCycle is a mathematical model of 50 differential equations and 208 parameters for the female menstrual cycle and describes it with hormones, enzymes, receptors follicular masses, and the GnRH pulse generator. According to author the simplest and the most economical way for female menstrual cycle modeling is to use delay differential equations.

TABLE I. HUMAN MENSTRUAL CYCLE MODELS.

No	Equations	Parameters	References
1.	13	42	[11]
2.	33	114	[12]
3.	16	66	[13]
4.	3	37	[14]
5.	6	33	[15]
6.	21	71	[16]
7.	13	44	[17]
8.	50	208	[18]

IV. DISCUSSION AND CONCLUSIONS

The menstrual cycle has so far received little attention in the field of mathematical modeling. There are very few publications available based on feedback mechanisms in the female menstrual cycle. A differential equation model that contains the regulation of LH and FSH synthesis, release, and clearance by E2, P4, and inhibin was firstly introduced by Schlosser and Selgrade [19]. This model was later extended by Selgrade and Harris 20] and later by Pasteur [21] to describe the roles of LH and FSH during the development of ovarian follicles and the production of the ovarian hormones E2, P4, inhibin A (IhA), and inhibin B (IhB). Reinecke and Deuflhard [22] also added, among other things, like a stochastic GnRH pulse generator and GnRH receptor binding mechanisms. Later on, Röblitz [23] noticed that this model was insufficient for our purpose and needed modifications. On the other hand, there are some new, pharmacokinetic/pharmacodynamic (PK/PD) models for GnRH analogues. These models describe the influence on LH and/or FSH but do not include the GnRH receptor binding mechanisms.

This modeling approach was deterministic and completely different to the stochastic GnRH pulse generator that was used by Reinecke. Stochastic modeling, when implemented, had required extremely small-time steps. Those conditions would be totally impractical for the simulation of some cycles, mostly related to parameter identification. Also, in the model a constant GnRH pulse frequency was noticed to have no effect on the course of the menstrual cycle, which contradicts scientific findings. Authors who were not interested in the stochastic pulse pattern but in the mean frequency and the amount of GnRH in the pituitary, the deterministic modeling was sufficient.

Menstrual cycle modeling is significantly important for reproductive medicine. By changing the parameters, it is possible to do many predictions with designed model. Controlling reproduction, adjusting therapy treatments to the individual patient or the adequate prediction of fertile phases are only a few of the numerous features and possible applications of such a model. Also, all parameters of the menstrual cycle model can be analyzed using artificial intelligence such as artificial neural network, since similar activities have been conducted in healthcare for diagnosis of various diseases [24-29].

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