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Mathematical modelling of follicular growth and ovarian stimulation

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Abstract

The aim of ovarian stimulation in fertility treatment is to increase the number of large follicles and hence the number of eggs that can be retrieved for in vitro fertilisation (IVF). However, large inter- and intra-individual variability in the menstrual cycle and ovarian response to stimulation drugs complicate treatment planning and prediction. Hence, many mathematical models have been developed to support treatment decisions. In this article, we give an overview of mechanistic models that cover different aspects of the processes involved in normal menstrual cycles and ovarian stimulation, including hormonal regulation and follicular maturation. We also review statistical models that have been designed to predict different IVF outcome criteria. Finally, we outline the use of mathematical models for in-silico clinical trials in reproductive endocrinology.

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Keywords

Hypothalamic-pituitary-gonadal (HPG) axis, Hormone dynamics, Follicular competition, Assisted reproductive technology (ART).

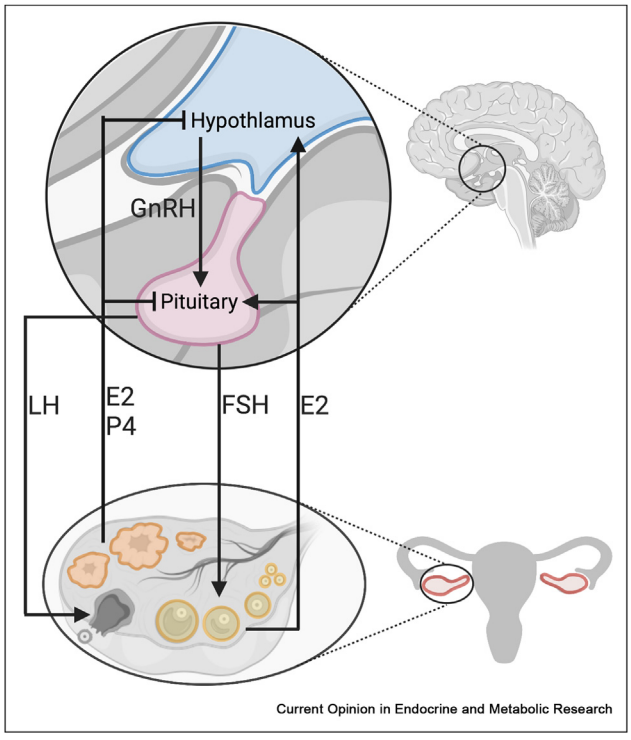
Introduction

Approximately 15% of people of reproductive age are affected by infertility [67], and unwanted childlessness puts a psychological and psycho-social burden on many of them [27,41,14]. This makes infertility and its consequences a global health issue. In 85% of all cases of infertility, the underlying causes are dysfunctions in the female or/and male reproductive system [13]. Female factors, such as ovulatory disorders, endometriosis and tubal abnormalities, are responsible for approximately one-third of all cases [62].

The hypothalamic-pituitary-gonadal (HPG) axis is central to enable reproduction in both sexes. In females, the HPG axis regulates the menstrual cycle, including the maturation and release of oocytes, the periodic release of reproductive hormones, as well as the preparation of the female body for a possible pregnancy. This is enabled through the feedback interactions between ovarian hormones, mainly progesterone (P4) and oestradiol (E2), the pituitary hormones luteinising hormone (LH) and follicle-stimulating hormone (FSH), and the hypothalamic hormone gonadotropin-releasing hormone (GnRH), see Fig. 1. GnRH stimulates the release of FSH and LH. Both regulate follicular maturation [15]. However, the initial recruitment of follicles from the ovarian reservoir is independent of LH and FSH [44]. Within each menstrual cycle cohorts of follicles, called waves, start growing as a result of increasing FSH levels, see Fig. 2 [4–6]. Growing follicles produce E2, which enables a feedback loop back to the hypothalamus. Usually one follicle of the cohort, rarely multiple follicles, ovulates around mid-cycle. During ovulation, the follicle releases its oocyte, and the sac forms the corpus luteum, which produces ovarian hormones in the luteal phase. If the oocyte is not fertilised and pregnancy does not occur, the corpus luteum decays and a new cycle begins [15]. Failure in this endocrine network is one cause of infertility.

Treatment options for infertility depend on its cause and the patient itself. In vitro fertilisation (IVF) is a form of assisted reproductive technology (ART) that can result in a successful pregnancy for patients suffering from different causes of infertility. IVF can not only be used to overcome female infertility but also assist in cases of male infertility. Intracytoplasmic sperm injection (ICSI), a technique where a sperm cell is injected directly into the egg cell, may be used for patients with low sperm quality or number. IVF treatment proceeds in three steps: (i) egg retrieval through controlled ovarian stimulation (COS), (ii) fertilisation of oocytes in the laboratory and (iii) embryo transfer into the uterus [2]. COS aims to stimulate the growth of multiple ovarian follicles synchronously by the administration of

Figure 1



Schematic representation of the hypothalamic-pituitary-gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH) is synthesised in the hypothalamus and released into the hypophyseal portal circulation system in a pulsatile manner. In the pituitary, GnRH stimulates the synthesis of luteinising hormone (LH) and follicle-stimulating hormone (FSH) and their release into the blood. LH and FSH regulate follicular maturation in the ovaries. FSH stimulates follicular growth, whereas LH triggers the ovulation of a dominant follicle. Growing follicles (yellow) produce oestradiol (E2). After ovulation (dark grey), the corpus luteum (orange) produces both E2 and progesterone (P4). E2 and P4 exhibit feedback mechanisms on the hypothalamus and the pituitary, which closes the loop (created with BioRender.com).

Figure 2

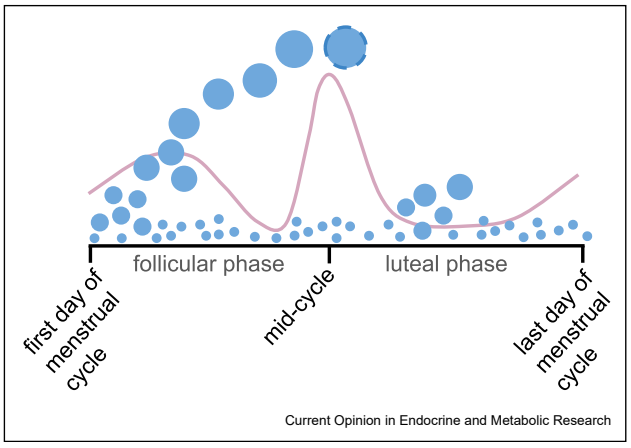


Illustration of the follicular wave theory. Small follicles are available throughout the menstrual cycle. With the beginning of a new menstrual cycle, the follicle-stimulating hormone level (FSH, pink line) starts rising and stimulates the growth of a cohort of follicles. Until mid-cycle, one follicle will be selected for ovulation. During the luteal phase, another cohort of follicles starts growing. However, none of those follicles will ovulate due to the low level of FSH.

gonadotrophins [40]. Several COS protocols are available. The conventional GnRH agonist protocol and the GnRH antagonist protocol are well established [30]. Newer protocols are based on the follicular wave theory [6], which motivates ovarian stimulation at different time points within a menstrual cycle [54]. Protocols which start ovarian stimulation at a random time point are of particular interest in the context of fertility preservation in cancer patients, where time is a determining factor [64,12]. Stimulation treatments that start during the luteal phase have been used to treat patients who did not respond to conventional protocols [50,29] as well as women with normal ovarian response [33]. Double stimulation protocols comprise two consecutive treatment cycles and offer more opportunities for oocyte retrieval in a shorter time interval [32,63]. Overall, it is challenging to find the best therapy for an individual patient in order to achieve the best treatment outcome in terms of pregnancy and live birth rates while simultaneously decreasing treatment-related risks like ovarian hyperstimulation syndrome [53].

Mathematical modelling can improve our understanding of complex regulatory networks involving multiple levels of organisation, such as endocrine systems [73,37]. Computational models can also be helpful to answer scientific questions in cases where appropriate model organisms are not available, and experimental investigations are challenging. Until recently, a menstrual cycle was only observed in primates. Evidence of a menstruating rodent was provided [9]. Since every model is a simplification and based on assumptions, it is important to find a model that is appropriate for the research question [66,65]. Mathematical models can be divided into two main groups: (i) empirical models and (ii) mechanistic models [7,51]. Empirical models are statistical models and therefore data driven. They are tailored towards prediction and are widely used in medical research [26]. An example in the scope of this review is the prediction of menstrual cycle length [47,39]. Mechanistic models are process-based and consider the elements forming a system and their interactions [11]. Their strength lies in generating, testing, and refining hypotheses [20]. An example is the model by Ref. [31] that provides evidence for the follicular wave theory.

In the following, we give an overview of statistical models (Sec. 2) and mechanistic models (Sec. 3) that

have been developed to simulate and predict IVF treatment outcomes, including the number of mature oocytes after ovarian stimulation and pregnancy rates. In addition, we briefly review the use of mathematical models in in-silico clinical trials (ISCT) related to IVF treatment (Sec. 4).

Prediction of IVF outcomes

A review by Ref. [56] summarises the statistical methods and available software tools for scoring embryo quality and predicting pregnancy rates. The review emphasises the role of these models as a clinical decision support tool, and that the final decisions need to be made by the practitioners and laboratory staff. Another publication from the same group [55] gives an overview of statistical models based on patient and/or embryo characteristics for predicting pregnancy and/or live birth rates. The authors suggest that the way forward would be in enriching, improving and strengthening the reproducibility and prognostic value of current models instead of suggesting new ones. However, both the definition of new success criteria as well the advancement of computational methods and tools, particularly in the fields of machine learning (ML) and artificial intelligence (AI), has led to the development of new models over the past years, which we briefly review in the following.

An intermediate marker of successful outcome in IVF/ICSI cycles, which has been introduced by the POSEIDON group,[1] is the ability to retrieve the number of oocytes needed to achieve at least one euploid embryo for transfer, i.e., an embryo that contains a normal number of chromosomes. In Ref. [21], members of the POSEIDON group developed a statistical model to estimate the minimum number of mature oocytes required to obtain at least one euploid blastocyst (based on pretreatment information, including female age and sperm source used for ICSI) and to estimate the individualised probability of blastocyst euploidy per mature retrieved oocyte. External multicentre validation is currently ongoing using suitable ART datasets from different countries.

There are also studies that focus on predicting the total number of oocytes. Ref. [1] demonstrated that results from random forest analysis were consistent with a generalised linear regression model suggesting that follicle sizes of 12–19 mm (but not the total number of follicles) on the day of trigger had the greatest predictive importance for the number of oocytes and number of mature oocytes retrieved. This knowledge enables the accurate determination of trigger efficacy and could potentially also be used to determine the optimal day of trigger administration.

[1] https://www.groupposeidon.com/.

Ref. [60] introduced a logistic regression model based on seven predictors for estimating the assisted fecundity of women before starting the first IVF/ICSI cycle, which translates into the probability of live birth in the first treatment cycle. This kind of prediction complements the approach of estimating cumulative and cycle-specific probabilities of live birth over multiple treatment cycles.

A great challenge for ART is a poor ovarian response, which refers to an unexpected low number of oocytes upon stimulation treatment. Using univariate and multivariate logistic regression analyses, Ref. [69] developed a statistical model based on four predictors (anti-Müllerian hormone, antral follicle counts, basal FSH, and age, in order of their significance) in order to estimate the probability of poor ovarian response and to assess the true ovarian reserve. Similarly, Ref. [38] developed a statistical model that can predict the probability of clinical pregnancy failure in poor ovarian responders before embryo transfer in IVF/ICSI procedure.

ML models allow for including an increased number of features and to untangle their complex relationships. Ref. [8] compared two widely used ML methods (support vector machines with different kernel functions and artificial neural networks) with logistic regression models for the prediction of different IVF outcome criteria. They demonstrated that the ML methods are superior to the standard statistical models. The authors argue that ML algorithms, as opposed to classical statistical models, can take into consideration complex associations between different parameters and can consequently better utilise the synergism between these associated parameters. In the same direction, Ref. [25] used 25 attributes in combination with a feature selection algorithm to assess the prediction ability of IVF pregnancy success for five different ML models. Two features, namely indication of infertility factor and the number of mature eggs, were selected by all classifiers, and antral follicle count (AFC) was selected by four methods. Moreover, age was ranked highest by three of the classifiers, which is consistent with other studies. The authors demonstrated that the prediction performance of all five classifiers improved with the selected features compared to using all features. Their article also includes a summary of studies that applied ML techniques for the classification of IVF outcomes. Those techniques differ in the ML technique used, the attribute/feature selection technique used, the list of selected features, the validation (training/test procedure), and the performance measure reported. These differences make it difficult to compare the methods with each other and also limit their transferability to other clinics due to variations in the amount and quality of data. The publication of codes as well as the availability of benchmark datasets would be preferable in order to increase the reproducibility and reusability of ML methods and results.

Modelling follicular maturation on a systems level

Both classical statistical models as well as ML models are based on predefined input and output variables. They do not explicitly include time as a variable and can therefore not be used to predict system behaviour over time, e.g., the growth of ovarian follicles. For this purpose, process-based models have been developed, which will be summarised in the following.

Moment models that describe the response of follicles in IVF

Ref. [72] developed a mathematical model that describes how the discrete follicle size distribution evolves over time, whereby it is assumed that the number of follicles activated during an IVF cycle is constant, i.e., that no new follicles start growing during stimulation. The kinetics of follicle growth is modelled as a function of injected FSH, and the follicle properties are represented in terms of the moments of the (unknown) statistical size distribution. Initial data from two treatment days (follicle sizes and prescribed FSH dose on days 2 and 5) of an individual patient are used to obtain patient-specific model parameters and predict the follicle size distribution for the remaining treatment days, whereby the dose is not adjusted but constant throughout treatment. The authors demonstrate that the follicle size distribution predicted by the moment model is in good agreement with the actual size distribution seen in the IVF cycle data for five patients.

In [71], the authors extended their model by an optimal control approach in order to predict the optimum FSH dosage for the desired treatment outcome, which is to have as many follicles as possible in the largest size class. A proof of concept based on data from five patients was presented in Ref. [71], before the model was tested in a double-blinded trial involving 10 patients [45]. Even though the cohort size was small, the results from Ref. [45] demonstrate that model-based treatment planning can lead to lower doses and fewer tests and monitoring requirements along with higher numbers of mature follicles and a similar percentage of good quality eggs compared to standard treatment routines.

Since the model does not include hormone dynamics and does not consider outcomes other than follicle number and sizes, the risk of ovarian hyperstimulation syndrome still needs to be checked by the physician, which might overrule the model-based treatment suggestions in many cases.

Cellular population models

Ovarian follicles carry two types of hormone-sensitive cells: (i) LH-responsive theca cells and FSH-responsive granulosa cells. Both cell types are crucial for the development of ovarian follicles and ovarian hormone production. Proliferation and cellular signalling processes of these cells have been investigated experimentally and by mathematical modelling [16]. Recently, Ref. [18] introduced a continuous-time Markov chain model for cell population dynamics to identify events in follicle maturation. Modelling follicular maturation on different levels of organisation, for example, by incorporating cell dynamics in follicle population dynamic models, can be valuable to characterise the pool of follicles over the lifetime of individuals [17,10].

Models based on follicular maturation stages and masses

A number of models have been developed [24,48,49,46] in which discrete stages of follicular maturation are defined as a state variables to describe follicular growth dynamics. Thereby, each maturation stage encodes a specific capability to produce ovarian hormones, but the variables do not refer to the size or number of follicles in that stage of maturation. However, this heuristic approach is useful to study different aspects of the female menstrual cycle. For example, Refs. [49,68] used this approach to model drug administrations, while Ref. [46] investigated follicular wave dynamics. Ref. [23] used the model to investigate the effect of testosterone on normal menstrual cycles and ovulatory function. The model provides a framework to investigate polycystic ovary syndrome and ovulatory dysfunctions.

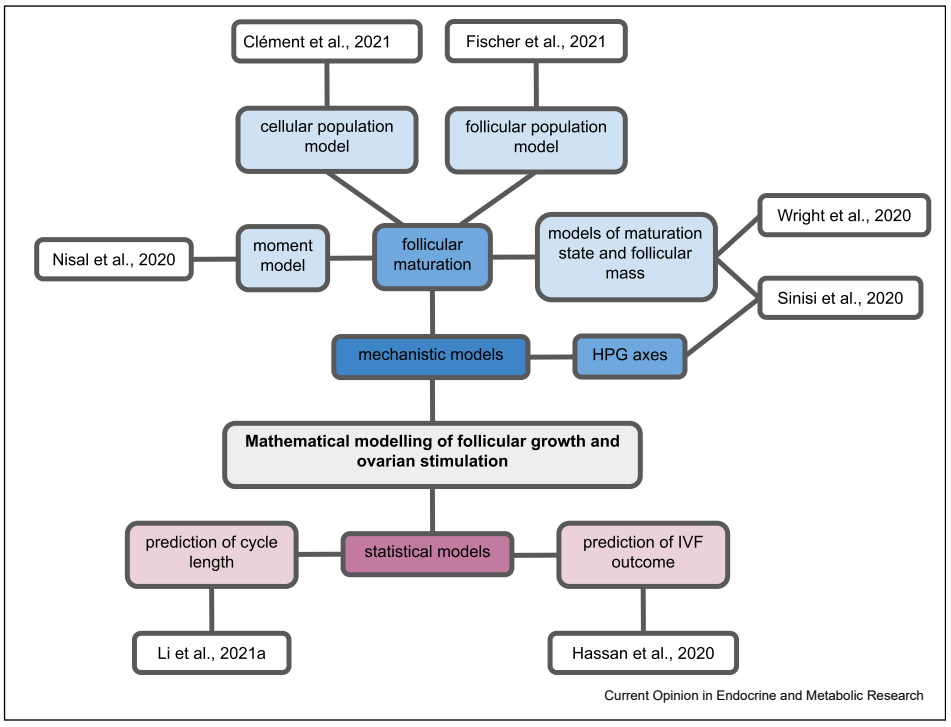
Follicle population models

A mathematical formulation for ovarian follicle maturation dynamics in terms of number and sizes of follicles was first introduced to the literature by Refs. [34,35]. Ref. [52] used this model to predict ovarian response in stimulation treatments. Ref. [59] modified the Lacker's model in order to simulate higher ovulations rates, i.e., double and multiple ovulations, in sheep and cattle. Based on these previous modelling attempts for follicular maturation on the level on individual follicles, Ref. [36] introduced a follicular growth equation that includes competition between follicles, with the follicular size as state variable. All these models, however, can only be used to simulate one follicular wave. Ref. [22] coupled the Lange model with the hormone dynamics along the HGP axes. The coupled model allows us to study the interplay between hormone dynamics and follicular maturation throughout consecutive menstrual cycles and can be used to simulate ovarian stimulation protocols with random start times.

Treatment computations and in-silico clinical trials

Mechanistic models can be used as a safe and efficient tool to predict patient-specific treatment outcomes as part of ISCT. Those approaches promise to decrease experimental efforts, including animal and human

Figure 3



This review gives an overview of different mathematical modelling approaches focusing on ovarian follicle maturation and female health. There are two main model types, namely statistical models and mechanistic models, both branching into sub-classes depending on the application. Each sub-class links to one of its most recent references, which are also cited in this review.

testing, and optimise the individual treatment outcome. The group of E. Tronci developed methods and software based on intelligent search strategies, and statistical model checking to find sets of model parameters that result in physiologically meaningful model behaviours [61,43]. In Ref. [57], they applied these methods to compute huge populations of virtual patients (VPs) for a non-identifiable quantitative virtual physiological human (VPH) model of the human menstrual cycle, including drug treatments [49]. Using the same VPH model, Refs. [42,58] showcased how VPs can be used to support precision medicine. Their work demonstrates how to compute a personalised down-regulation treatment protocol (a protocol used for assisted reproduction) that maximises the aimed outcome while simultaneously minimising the risk for severe side effects.

These methods and software tools have reached a high level of technological readiness, and the indispensable next step would be to test their performance in clinical trials. In particular, ethical and legal issues need to be considered carefully before such tools can become part of clinical practice [19].

Conclusion

This review summarises different mathematical approaches to model follicular maturation and ovarian stimulation in humans, see Fig. 3. It demonstrates how medical research in the context of female health already has or might in the future benefit from computational work, such as statistical and mechanistic modelling. Statistical models are a powerful tool to predict different outcome criteria of IVF treatment based on both patient and embryo characteristics. In particular, ML models help determine which phenotype and cycle factors are the most useful in making predictions.

Mechanistic modelling, with its way of thinking about complex dynamical systems in biology, can provide valuable insights on its own [20]. In particular, mechanistic models can be used to test the hypothesis about the underlying processes and identify parameters on which measurement efforts should be focused on. Moreover, they can be combined with pharmacokinetic models to study drug administration schemes, which is not possible with statistical models. Recent publications have demonstrated how mechanistic and ML models can be combined to infer hidden dynamics in biological networks and enable robust predictions, e.g., Ref. [70]. This is certainly a promising avenue for future research.

The review here focuses on follicular dynamics, and there are several ongoing modelling efforts in closely related areas, for example, on the endometrial cycle

[3]. Also, we did not discuss modelling approaches based on images, as this would be out of the scope for this review. The reader interested in the application of ML methods to predict embryo ploidy from images is referred to Ref. [28] and references therein. It is likely that in future, different models and model types will be combined in order to achieve an even more holistic picture of the processes that are involved in female fertility.

Declaration of competing interest

Nothing declared

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