Chapter

Artificial Intelligence for Ovarian Stimulation

Jean-Claude Emperaire and J. Charles Eldridge

Abstract

Ovarian stimulation, the basis of treatment strategies for infertility, from anovulation to in vitro fertilization, is a highly efficient therapeutic procedure. The stimulation should ensure a complete development of the follicle(s) along with maturation of the oocyte(s), all without risking hyperstimulation and multiple pregnancies. For these reasons, a stimulation protocol should be personalized, and its evolution must be continually scrutinized using measures of both blood hormone levels and ovarian responses by ultrasound. Essentially all of the stimulation algorithms proposed to date focus only on determination of the starting dose of gonadotropin. But ovarian stimulation should be continually monitored until the final decision is made to trigger or to abort the cycle. This decision can be achieved through use of an experience-based computer software system that monitors menstrual cycles through a beginning pregnancy. This software (*StimXpert*®) should work effectively with a classical stimulation as well as a controlled hyperstimulation for IVF. It may also be modified from experience-based to evidence-based programming through progressive learning.

Keywords: ovarian stimulation, ovulation stimulation, medical software, infertility

1. Introduction

Ovarian stimulation is an essential component of nearly all contemporary approaches for management of a couples' infertility: for mono-follicular stimulation in cases of anovulation, for mono- or bi-follicular stimulation in idiopathic infertility, for assisted procreation to prepare for intra-uterine insemination (IUI), and also for controlled hyperstimulation for in vitro fertilization (IVF).

A successful stimulation requires achievement of both fertilization and then nidation without complications. Each stimulation must be uniquely customized for each patient. A critical factor for success depends on estimation or anticipation of the ovarian response, which in turn relies on the choice of gonadotropin preparation plus an understanding of the patient's own ovarian sensitivity. All of this comes together when deciding on the starting dose, to be administered over 5–7 days. Choices for subsequent stimulation are typically a bit less challenging, as they are likely to be smaller adjustments in light of previous responses. Nonetheless, monitoring of responses may reveal unpleasant surprises, so careful attention is necessary until the process ends with a decision to trigger ovulation or to cancel the cycle.

2. Can computer applications facilitate ovarian stimulation decisions?

Numerous variables must be taken into account when stimulating ovulation. For the starting dose, one must consider patient age, weight, body mass index (BMI), antral follicle count (AFC), plus serum levels of follicle stimulating hormone (FSH) and anti-mullerian hormone (AMH). During stimulation, the ovarian response must be monitored by hormone levels of estradiol (E), luteinizing hormone (LH), progesterone (P), and also by sonographic parameters such as the number and size of growing follicles. Because these parameters, while diverse, are interacting with each other, it becomes conceivable that algorithms might be developed to integrate the entire treatment cycle, for each stimulation protocol.

Curiously, few experience-based proposals have appeared for programs of this sort, despite the fact that ovarian stimulation protocols have been in use for more than 50 years. For this reason alone, a software system should originate with a large clinical practice group having sufficient experience with various stimulation protocols used over a long time. The resulting algorithms should then be validated by peers. Finally, the software needs to be inherently self-evaluating, so that responses can be compared with stored information from previous trials to develop an optimal evidence-based stimulation tool.

The system proposed here represents an initial step derived from the author's personal experience of more than 40,000 ovarian stimulation cycles conducted over 50 years of clinical infertility practice and, in particular, the most recent 1200 stimulation cycles that resulted in a beginning pregnancy [1].

3. Characteristics of the stimXpert system

Ideally, a protocol for ovarian stimulation must compute not only the starting gonadotropin dose, as several existing systems do, but also cover the entire treatment sequence up to the ovulation triggering step, or cycle cancelation, if necessary. It should be designed to optimize the number of mature follicles in concert with the specific stimulation goal and should avoid complications such as the ovarian hyperstimulation syndrome (OHS) or a multiple pregnancies.

StimXpert is a software system designed to initiate and guide all therapeutic decisions for ovarian stimulation using the gonadotropins FSH, LH, and hCG. Because evidence-based algorithms for ovarian stimulation have not existed, this experience-based application was developed to fill the need. The present configuration includes 10 specific protocols: four for mono-follicular anovulatory stimulation (step-up low dose, step-up chronic low dose, step-down and sequential), two for ovulatory patients preparing for intrauterine insemination (mono- or bi-follicular), and four utilized for controlled hyperstimulation (long agonist, short agonist, fixed antagonist, flexible antagonist). For each protocol, the starting dose is dictated by the patient's weight and her level of plasma AMH [1, 2].

Initial Monitoring Control: define the FSH dose and the number of stimulation days. After the first 5–7 days, adjust the dose in accordance with the ovarian response, based on serum hormone levels (LH, estradiol, progesterone) and on sonographic observation (number and diameter of the largest growing follicles).

Additional Monitoring Controls: in patients who continue stimulation after the first control.

Triggering Criteria: computed within the security limits to avoid both hyperstimulation and multiple pregnancies.

Reasons for Aborting the Stimulation Cycle:

- Identified risk for multiple pregnancy in a mono-follicular stimulation
- Need to add LH when sonography and hormonal levels are dissociated
- Abnormal pre-ovulatory increase of plasma progesterone (> 1.5 ng/ml)
- Identified risk for ovarian hyperstimulation, e.g., estradiol rises above 500 pg./ml in a classic stimulation, or above 2500 pg./ml and/or with more than 15 follicles observed during a controlled hyperstimulation for IVF, or when
- Fewer than four follicles are observed during a controlled hyperstimulation for IVF

Of course, all of the signals from the software application may be modified or overruled by the clinician's judgment, in line with his/her own experience and/or knowledge of the situation with each particular patient.

4. Parameters for each protocol

While most of the parameters are basically common to all stimulation protocols, the software needs to include specific aspects of each protocol. To illustrate this importance, two examples are presented here of the application's success:

4.1 Mono-follicular stimulation in a case of anovulation

- ***Stimulation Protocol***: the usual experience with an anovulatory patient producing estrogen favors the low-dose step-up protocol. The rationale is to increase the gonadotropin dose, by 50% of the starting dose, at 7-day intervals until a minimal response of the most sensitive follicle is observed. The same dose is then continued until the follicle attains the pre-ovulatory stage ready for ovulation trigger. The StimXpert application will propose alternative protocols to consider: the standard step-up, chronic low-dose step-up, step-down, or sequential protocols.
- ***Nature of the Gonadotropin:*** with exception of a few rare instances, all commercial FSH preparations are equally efficacious for mono-follicular stimulation. None seems at present to be superior, whether extracted or recombinant, or whether the preparation includes LH. The software includes characteristics of each brand without favoring any. However, one exception of note is that in cases of hypogonadotropic hypogonadism, where LH must be included, recombinant LH is not among the available choices. The software instead offers gonadotropin preparations that already contain FSH and LH, thereby avoiding two separate hormone injections for a better patient's compliance.

- ***Starting Dose:*** mono-follicular cycles do not have a consensus starting dose of gonadotropin, and referencing an AMH level is of little help in making this decision. A very low level is expected in hypogonadotropic hypogonadism [3], while a high level does not establish a need to start with the lowest possible dose [4–6]. StimXpert will suggest two starting levels of 50 and 75 IU to be decided according to the patient's age and BMI.

- ***Monitoring:*** hormonal measures and a sonogram should be done after the starting dose is continued for 7 days. If no significant ovarian response is detected, the software will recommend increasing the dose by 50% for 7 more days, with identical increases initiated each 7 days until a 10 mm follicle appears. At that point, the dosing will be maintained until optimum maturity is reached, a follicle at least 16 mm in diameter with a suitable serum estradiol level. If an adequate response does not appear after three 7-day steps of increased dosing, the program will cancel the stimulation protocol. A new stimulation series should begin with a number of FSH units just over the last used dose in the previous protocol.

- ***Triggering ovulation:*** this should be done when a single 16-mm follicle is reached, and with no other follicles of 12-mm diameter or larger being detected, so that multiple ovulations and pregnancies will be avoided. Serum estradiol should not exceed 500 pg./ml. Note that numerous responsive small follicles may contribute to the estradiol pool, but the risk for ovarian hyperstimulation (OHS) must also be taken into account: the program will cancel the process if maximum limits of follicular size or hormone levels are exceeded. Alternatively, the program may allow for triggering to proceed by using a GnRH agonist, which decreases but does not obviate risk for multiple pregnancies or OHS.

- ***At each step of the StimXpert protocol, the clinician can still decide to override the software decisions.*** **Figure 1** illustrates an example algorithm for mono-follicular stimulation.

4.2 Multi-follicular stimulation for in vitro fertilization (IVF)

This type of stimulation aims to recruit 8–15 follicles to full maturation. Large numbers may actually be less necessary at present, with so-called "friendly stimulations" being recommended. To be sure, high numbers are inadvisable when risks of OHS are present, even when embryo freezing for later transfer is considered.

- ***Stimulation Protocol***: StimXpert offers a choice of the two main types of controlled follicular hyperstimulation, using GnRH analogs. There appears to be no recognized difference among analog products; the choice of the GnRH preparation or its mode of administration (daily or long-acting) does not influence the program algorithm.

- ***Agonist Stimulation Protocols***: the "long protocol," where ovarian stimulation is preceded by agonist-driven ovarian desensitization, continues to be the gold standard approach. The "short protocol," where GnRH agonist and gonadotropin are administered together, yields somewhat poorer results, and thus is relegated to special situations, such as the case of a low responder.

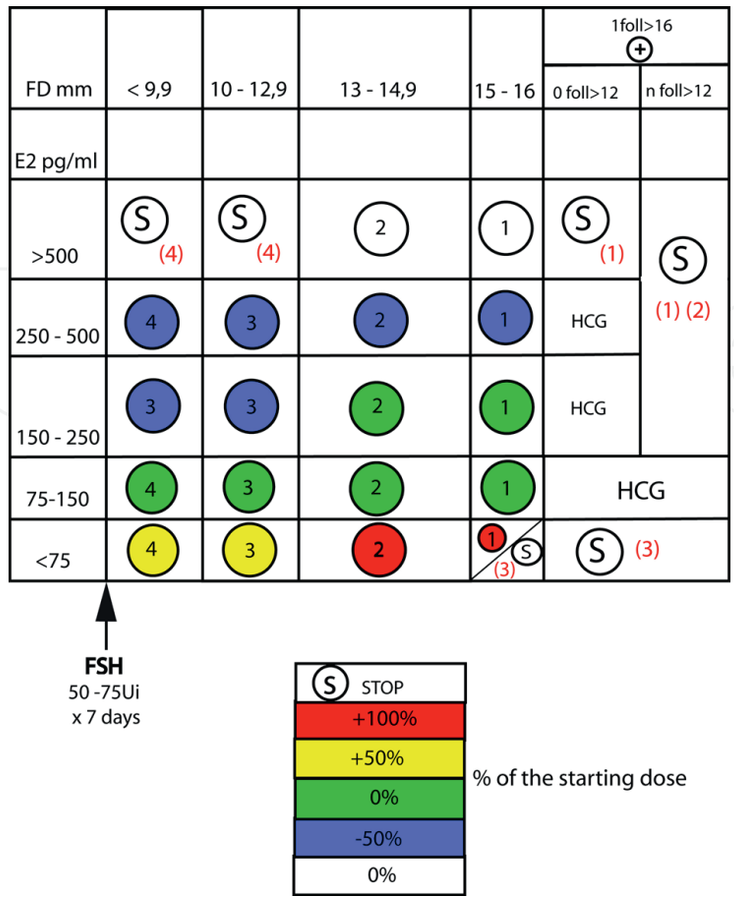

Figure 1.
Standard step-up protocol for a mono-follicular stimulation: example of an algorithm showing the possible scenarios after the administration of 50–75 UI FSH for 5 days (StimXpert).

- ***Antagonist Stimulation Protocols***: a progressive shift to this approach has occurred, with the need for more "friendly stimulations." It results in pregnancy rates comparable to the long agonist protocol and appears to include a lower risk for ovarian hyperstimulation. GnRH antagonist may be introduced along with gonadotropins, on a fixed stimulation day (fixed antagonist), or at a later time when ovarian response meets specified sonographic and/or hormonal levels (flexible antagonist). *All four protocols (long/short agonist, fixed/flexible antagonist) are available with StimXpert*

- ***Nature of the Gonadotropin***: All FSH gonadotropins are suitable for multi-follicular stimulations. Although the isoforms of each hormone differ from each other, research has never established one to be superior. Thus, StimXPert offers a choice from among all products, and clinicians may choose their favorite without affecting the algorithm.

- **Starting Dose:** Most controversies appear in choices at this step, and multiple algorithms have emerged in relation to the patient characteristics: age, weight, BMI, antral follicular count (AFC), and blood levels of FSH or AMH [7, 8]. This program offers a starting dose based on only two of these parameters, namely weight and AMH level. There is no concrete evidence that BMI has a significant predictive effect over weight, while age, FSH, and AFC appear to be consistently

related to AMH level. Note that the recommended starting dose for follitropin delta is based on these same two variables [9].

- ***Monitoring:*** Initial monitoring should occur after 5 days of FSH injections (or 4 days for the short agonist protocol). The StimXpert software will, as usual, adapt the continued dosing and monitoring schedules according to ovarian responses. One exception, when using follitropin alpha: the starting dose level continues unchanged during the entire stimulation period [9]. In case of a poor ovarian response, e.g., when fewer than five developing follicles are detected, the program will recommend cancelation of the cycle. This decision may be overcome by the physician, who remains free to override any programmed recommendations. The software remains ready to recalculate after modifications by the clinician.

- ***Ovulation Triggering***: Ovulation is triggered using hCG when 5–15 follicles are present, and estradiol level is less than 2500 pg./ml. StimXpert will recommend cancelation at higher sonographic and hormonal levels, in order to avoid risk of OHS. If the antagonist protocol is being used, the program will propose to trigger using a GnRH agonist, even though the risk of OHS is not completely absent.

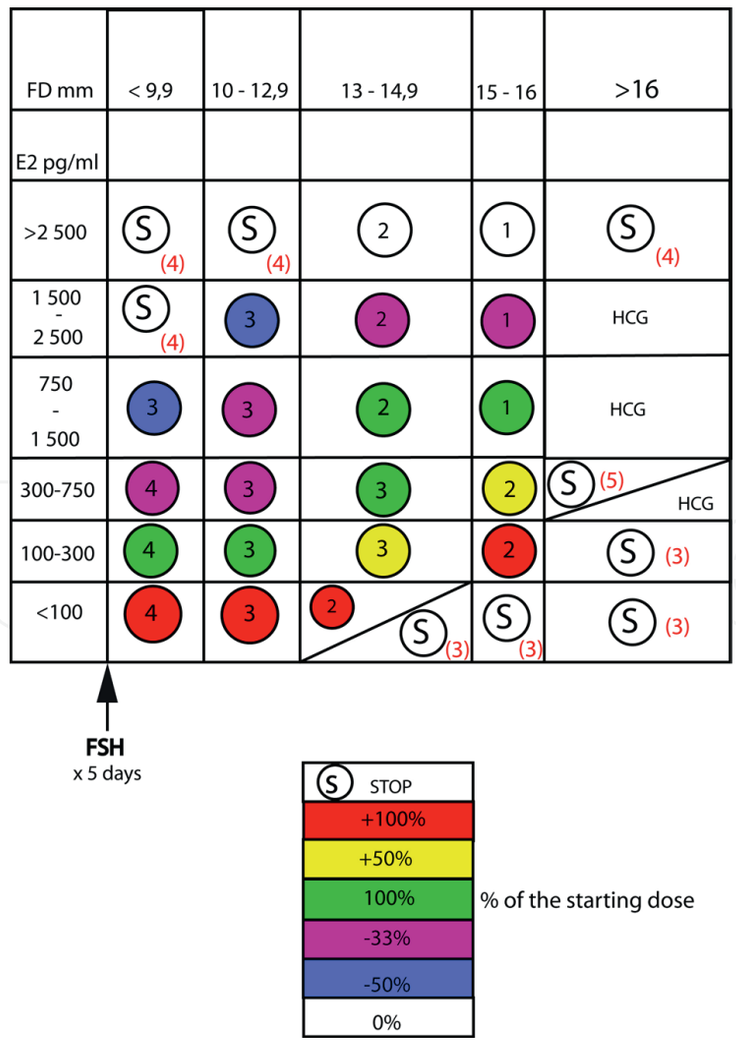

Figure 2.
Long agonist multifollicular stimulation protocol with a target of 6–14 follicles: example of an algorithm showing the possible scenarios after 5 days of FSH (StimXpert).

Again, the clinician can override these recommendations and trigger with hCG, to enable freezing of embryos for later transfer as well as to avoid a secondary OHS. The software also will recommend cancelation of the cycle in a case of poor ovarian response, for example, with fewer than five mature follicles, and this too may be overridden.

Figure 2 illustrates an example of the algorithm used by the software for the agonist long protocol.

5. Software for whom?

The StimXpert program does not pretend to cover the whole field of ovarian stimulation possibilities, as different decisions might attain similar results otherwise. It does, however, establish how using programmed recommendations can enable a stimulation cycle to result in a successful beginning pregnancy without numerous complications. This system is not intended for clinicians with established experience in ovarian stimulations, although its utilization within a team of clinicians may help to harmonize varied practices of each member. In particular, it should limit the more predictable complications associated with human factors, working toward creation of a "hyperstimulation-free" clinic.

More directly, StimXpert is recommended for:

- Medical students and trainees learning the principles of ovarian stimulation.
- Gynecologist and endocrinologist practitioners assuming direct care of their infertility patients, but who have had apprehensions about the undertaking.
- Any practitioner who feels inexperienced in ovarian stimulation protocols, thus seeking some assistance in the decision-making process.
- Clinicians in developing countries where infertility therapy remains scarce.

6. What about other algorithm-based systems?

Only one computer decision support system encompasses the whole stimulation cycle with day-to-day decisions, but exclusively for IVF controlled hyperstimulation [10]. The few other algorithm-based treatments ever published take into account only one of two specific steps of the stimulation cycle and quite exclusively for IVF purposes: the starting dose [7–11] or the criteria for ovulation triggering [12, 13]. To date, StimXpert represents the only stimulation software available assuming both 1 – the entire treatment cycle, and 2 – all validated protocols, from mono-follicular classic stimulation to multi-follicular controlled hyperstimulation.

7. Conclusion

The StimXpert software aims to facilitate the acquisition of technical principles of ovarian stimulation and to optimize the chances of pregnancy together with

diminishing risks for complications such as multiple pregnancies and OHS. As designed, the program may be modified, completed, and turned into an evidence-based stimulation software protocol, or it can alternatively be converted into a self-learning system by integrating increasing numbers of cycles leading to safe beginning pregnancies.

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