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Why do we Modify Ovarian Stimulation Protocols when Repeating a Cycle?" Is it a Scientific Issue, An act of Faith, or a Lack of Trust?

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Abstract

Ovarian Stimulation (OS) is a cornerstone and indispensable step in reproductive medicine. The aim of OS is to induce the growth and maturation of multiple follicles to collect an adequate number of oocytes. The availability of a sufficient number of mature oocytes suitable for in vitro fertilization (IVF) significantly enhances the likelihood of successful fertilization, the development of high-quality euploid embryos, and ultimately, the achievement of a successful pregnancy. Frequently, it becomes necessary to repeat an ovarian stimulation procedure in a patient. In some instances, when faced with a poor ovarian response, the strategy of oocyte accumulation is employed to increase the chances of having a euploid blastocyst available for transfer. Moreover, even among good responders, there are occasions where it becomes necessary to repeat a cycle due to a prior unsuccessful attempt. The present study shows that there is a great variability in ovarian response in successive ovarian stimulation procedures, even administering the same protocol, both in terms of doses and medications. Thus, repeating an ovarian stimulation procedure does not necessarily entail the need to modify the stimulation protocol. There is variability in ovarian response even when the same gonadotropins are administered, as shown in the present study. Hence, in consecutive stimulations, variations in the response are physiological, even though the same protocol and medication are employed. Selecting one protocol over another should prioritize the comfort and convenience of the patient rather than a hypothetical improved response with different medications.

Keywords: Ovarian Stimulation; Gonadotropins; Poor Ovarian Response; Ovarian Reserve

Abbreviations: EIM: European IVF-Monitoring Consortium; ESHRE: The European Society of Human Reproduction and Embryology; OS: Ovarian Stimulation; MAR: Medically Assisted Reproduction; IVF: In Vitro Fertilization; CLBR: The Cumulative Live Birth Rate; ART: Assisted Reproduction Treatments; DHEA: Dehydroepiandrosterone Acetate; BMI: Body Mass Index; rFSH: Recombinant Follicle-Stimulating Hormone.

Introduction

The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) reported that in 2017, 473733 treatment cycles were registered for a total population of approximately 330 million inhabitants. This data allows us to estimate a mean of 1,435 cycles performed per million inhabitants, ranging from 723 to 3,286 [1]. A previous report suggested that more than one in every 50 European children resulted from medically assisted reproduction (MAR) procedures [2,3]. Ovarian Stimulation (OS) is a pivotal and indispensable step in reproductive medicine. The availability of a sufficient number of mature oocytes suitable for in vitro fertilization (IVF) significantly enhances the likelihood of successful fertilization, the development of high-quality euploid embryos, and ultimately, the achievement of a successful pregnancy [4] increasing not only the live birth rate per cycle, but, importantly, also the cumulative live birth rate (CLBR) in assisted reproduction treatments (ART) [5].

Although it is important that treatment should be individualized according to patient characteristics to achieve optimal outcomes [6], women differ greatly in their ovarian response to gonadotrophin stimulation. There is currently no established consensus for determining the optimal gonadotropin formulation and dose, with starting doses often based on patient characteristics, such as age, combined with a physician's clinical experience and judgment. While it is essential to tailor treatments to individual patient characteristics to optimize outcomes, it is worth noting that women exhibit significant variability in their ovarian response to the same gonadotropin stimulation [6]. There has yet to be a universally established consensus for determining the optimal gonadotropin formulation and dosage. Starting doses are often individualized based on patient-specific factors, including age, and rely heavily on the clinical experience and judgment of the treating physician [7].

Frequently, it becomes necessary to repeat an ovarian stimulation procedure in a patient. In some instances, when faced with a poor ovarian response, the strategy of oocyte accumulation is employed to increase the chances of having a euploid blastocyst available for transfer. Moreover, even among good responders, there are occasions where it becomes necessary to repeat a cycle due to a prior unsuccessful attempt. In an attempt to increase the number of retrieved eggs, various protocols involving higher doses of gonadotropins and adjuvant treatments, such as dehydroepiandrosterone acetate (DHEA), androgens, and antioxidants, are frequently proposed to patients following their initial OS procedure [8]. However, there needs to be more evidence for most of the proposed changes. This study aims to assess ovarian stimulation responses and the possible variations that may occur when repeating stimulation procedures using the same protocol.

Materials and Methods

Study design

This was a retrospective, non-interventional study performed between January 2021 and December 2022 at the University-associated Assisted Reproduction RB center. Women scheduled for repeated ovarian stimulation procedures (either for oocyte accumulation or for a previous failed cycle) were included. Patients aged >18 years at recruitment, with at least two conventional stimulation cycles of ART treatment, were included in the study. Repeated OS procedures were performed in a period shorter than six months in each patient.

Exclusion criteria were age ≥ 42 years, Body Mass Index (BMI) above 32 or less than 18, and absolute or relative contraindication for a follicular puncture. Women reporting hypersensitivity to Corifollitropin alfa or to any of the excipients of Bemfola® were excluded. The presence of a pituitary or hypothalamic tumor was also an exclusion criterion. Couples involved in other clinical or embryological trials were also excluded.

Ovarian stimulation

All included patients underwent at least, two ovarian stimulations and egg retrieval procedures in a period shorter than six months. No modifications were made to the stimulation protocol (in terms of dosage and the type of administered gonadotropins) in successive cycles. A short GnRH-antagonist protocol was scheduled for ovarian stimulations. A single injection of Corifollitropin alpha (Elonva®, Organon NV, The Netherlands) on day 2 of the menstrual cycle was followed by the administration of recombinant follicle-stimulating hormone (rFSH) (Bemfola, Gedeon Richter Plc. Budapest Hungary) at a starting dose of 225-300 IU depending on the age, body mass index (BMI) and ovarian reserve (OR). A GnRH flexible antagonist protocol prevented premature ovulation (Orgalutran® Ganirelix 250 µg/day, Organon NV, The Netherlands). A GnRH agonist (Decapeptyl 0,2 mg, Ferring Pharmaceuticals) trigger was administered when at least one follicle was above 18 mm. Agonist trigger allows a new ovarian stimulation in a 2-3-day period. Oocytes were retrieved transvaginally 35 hours after triggering.

Definitions and Study Outcomes

Patients and donors with at least two ovarian stimulations performed were assessed. The number of

achieved oocytes in each ovarian stimulation (OS) procedure was compared with the previous OS. *Variability* was defined as either increment (if positive) or decrement (if negative) in the number of achieved oocytes with respect to the previous cycle as a percentage. We defined variability 1 (V1) as the percentage of variability in the number of retrieved oocytes between cycles 1 and 2. The definitions of variability 2 (V2) and 3 (V3) correspond to the percentages between cycles 2 and 3 and between cycles 3 and 4, respectively. The primary outcome was to assess the variability in the ovarian response in a given patient after administering the same medication, both for stimulation and ovulation induction.

Statistics

The mean and median (including quartiles 25 and 75) of the variability were calculated for statistical purposes. However, we also estimated the mode of the variability as it provides, besides a statistical measure of central tendency, the most frequently occurring value in a dataset. Repeated OS were globally assessed and were further divided into three sets of treatments depending on the number of oocytes achieved in the first egg retrieval of a given patient. We included in **Group A** those cycles in which the number of retrieved oocytes in the first attempt was 1 to 5. When 6 to 10 oocytes were recovered in the first OS, cycles were included in **Group B**. Finally, those cycles in which more than 10 oocytes were obtained after first OS, were included in **Group C**.

The Student's t-test was used for comparisons of the number of achieved oocytes in successive ovarian stimulation procedures. Results are presented as mean ± standard error of the mean (SEM) or percentages. Statistical significance was set at a probability (p) value < 0.05. Analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 25.0.0.2, released in 2017, IBM Corp., Armonk, NY, USA).

Ethics

The authors' Institutional Ethical Committee approved this study following ethical principles originating in the Declaration of Helsinki and Ethical Guidelines for Biomedical Research on Human Participants. Each recruited patient has given written and informed consent for the procedure. All data were anonymized.

Results

During the study period 160 women with at least two ovarian stimulation procedures were included as previously described. Among women with a poor ovarian reserve, the policy at our center consists of repeating ovarian stimulations to accumulate oocytes before the IVF procedure is performed. Among patients with a good ovarian response, the procedure is repeated if pregnancy is not achieved in the first attempt, either due to the lack of transferable euploid embryos or after a negative pregnancy test. Finally, some oocyte donors are stimulated up to 3 times. In either case, the stimulation protocol remains unchanged.

Only patients with at least two ovarian stimulations have been included. Results were further divided into three subsets of patients depending on the number of oocytes achieved in the first stimulation. Patients with 1 to 5 oocytes recovered in the first ovarian puncture were included in group A; patients with 6 to 10 oocytes in the first egg retrieval were included in Group B and, finally, patients with more than ten oocytes achieved in the first cycle were included in group C (Figure 1). A total of 551 OS procedures were evaluated.

All cycles				
	OS1	**OS2**	**OS3**	**OS4**
n	160	160	151	80
Mean±SEM(*)	7,96±0,45	9,50±0,45	11,81±0,51	13,76±0,70
	Dif. of means (mean±SEM)		t	p
OS1-OS2	1,54±0,15		10,064	<0,001
OS1-OS3	3,86±0,18		21,359	<0,001
OS1-OS4	5,66±0,35		16,626	<0,001
OS2-OS3	2,31±0,17		13,647	<0,001
OS2-OS4	4,16±0,31		13,280	<0,001
OS3-OS4	1,29±0,25		5,065	<0,001

(*) Mean ±Standard error of mean; OS1: 1st ovarian stimulation; OS2: 2nd ovarian stimulation; OS3: 3rd ovarian stimulation OS4:4th ovarian stimulation

Table 1: Number of achieved oocytes and differences between successive ovarian stimulations.

Table 1 displays the number of oocytes achieved in each ovarian stimulation cycle. It also presents the differences between successive cycles and their statistical significance. Table 2 and Figure 2 show that overall variability was positive in successive OS procedures (44,18%, 31,74%, and 16,49%, respectively, for Variability 1, 2, and 3) even scheduling the same ovarian stimulation protocol. Although the mode (the most repeated value) was 0%, only in 23%, 26%, and 33% of repetitions the number of achieved oocytes was the same as in the previous OS. In other words, in 77%, 74%, and 67% of repetitions, the number of achieved oocytes differed when the procedure was repeated (by administering the same medication). Corresponding results for OS of groups A, B, and C are shown in Table 3. Figure 3 shows graphically as a box diagram, the mean, mode, and quartile values corresponding to Groups A, B, and C.

All cycles			
	Variability 1(*)	**Variability 2(**)**	**Variability 3(***)**
n	160	151	80
Mean	+44,18%	+31,74%	+16,49%
Mode	0%	0%	0%
Q25	0%	0%	0%
Median	20,00%	23,08%	8,01%
Q75	+60,00%	+50,00%	+27,68%
Minimum	-50,00%	-20,00%	-92,00%
Maximum	700%	300%	200%

(*) Variability 1: Difference between 2nd and 1st OS
(**). Variability 2: Difference between 3rd and 2nd OS
(***) Variability 3: Difference between 4th and 3rd OS

Table 2: Variability in the number of achieved oocytes between cycles (all cycles).

	Group A(1)			**Group B (2)**			**Group C(3)**		
	V1(*)	V2(**)	V3(***)	V1(*)	V2(**)	V3(***)	V1(*)	V2(**)	V3(***)
n	84	76	38	46	45	30	30	30	12
Mean	+73,67%	+37,90%	+26,70%	+14,10%	+30,78%	+6,01%	+7,74%	+15,35%	+3,85%
Mode	0%	0%	0%	0%	0%	0%	0%	0%	0%
Minimum	-40,00%	-20,00%	-11,11%	-50,00%	0%	-91,67%	-15,79%	-5,00%	-7,69%
Maximum	700%	300%	200%	+55,56%	125%	+40,00%	+37,50%	+45,00%	+16,67%

(1) 1 to 5 achieved oocytes in the first OS
(2) 6 to achieved oocytes in the first OS
(3) More than 10 achieved oocytes in the first OS
(*) V1: Variability 1: Difference between 2nd and 1st OS
(**). V2: Variability 2: Difference between 3rd and 2nd OS
(***) V3: Variability 3: Difference between 4th and 3rd OS

Table 3: Variability in the number of achieved oocytes between cycles (Groups A, B and C).

Discussion

Although the introduction of ovarian stimulation (OS) improved outcomes of in vitro fertilization (IVF) procedures significantly through the administration of exogenous gonadotropins, IVF does not guarantee success. Between 38% and 49% of the couples have unsuccessful IVF cycles even after undergoing six IVF cycles [9,10]. Therefore, repetition of an IVF procedure is relatively frequent. The aim of OS is to induce the growth and maturation of multiple follicles to collect an adequate number of oocytes. However, even at a younger age, in about 9-24% of the patients, a poor response is encountered, depending on the definition used. Thus, poor ovarian response remains one of the most challenging tasks for an IVF clinician. Despite impressive advances in the field, many women may be included in the "poor or low

responders" setting of patients with higher odds of cycle cancellation, fewer oocytes at retrieval, lower oocyte quality, and reduced number of embryos for transfer [11]. Indeed, the number of oocytes retrieved during an IVF treatment is of utmost importance to overcome two critical problems related to female infertility, namely, oocyte competence and ovarian aging [5].

Various factors have been identified that may be associated with ovarian response to OS, including patient age, body mass index (BMI), estradiol, basal FSH, inhibin-B, anti-Müllerian hormone, ovarian stromal blood flow, and antral follicle count (AFC) [7,12]. However, ovarian stimulation can only support the growth of the follicles available during each ovarian cycle, but it cannot generate follicles ex-novo [13,14]. Multiple interventions have been proposed to improve reproductive outcomes in women with a poor ovarian response (POR). However, the randomized intervention studies and meta-analyses of these studies reveal conflicting results [15]. In those patients, the question arises whether changing the type or dose of gonadotropins is meaningful to increase the oocyte yield and improve prognosis. Different studies have demonstrated that it is worthless to increase the dose of gonadotrophins beyond a maximal threshold, which has been set as 300–375 IU/day of FSH plus 75–150 IU/day of LH [16,17].

One common strategy to improve the pregnancy rate among poor responder patients is to cryopreserve and cumulate oocytes, thus increasing the chances of developing transferable euploid embryos. The CLBR per cycle markedly increases as the number of oocytes retrieved increases [18]. Although the ovarian response from a quantitative point of view may not reflect oocyte quality and, thus, ongoing pregnancy rates, it is evident that increasing the number of achieved oocytes increases the chances of pregnancy. Furthermore, the number of oocytes needed to obtain at least one live birth increases exponentially with age [19]. In this line, Drakopoulos, et al. [20] reported that the odds ratio (OR) for CLBR significantly increases with the number of oocytes. When comparing the group of patients who had 0-3 oocytes retrieved, patients with 4-9 oocytes had an OR of 2.4 (95% confidence interval [CI] 1.3-4.4), 10-15 oocytes an OR of 3.5 (95% CI 1.9-6.7), and >15 oocytes an OR of 5.6 (95% CI 3.1-11.6). The group of patients with 4-9 oocytes, previously classified as normal, was renamed as suboptimal responders, as the CLBR per initiated cycle was poorer than patients with ten or more oocytes.

The results of the present study confirm the convenience of an oocyte accumulation policy to enhance the probability of developing blastocysts that are suitable for genetic screening and subsequent embryo transfer. The administration of the ovulatory trigger using GnRH agonists allows for a new stimulation within a short timeframe, enabling the completion of 2 or 3 stimulations in a relatively brief period. This approach helps alleviate patient discomfort. Moreover, the number of oocytes may increase even when administering the same protocol and doses. In other words, changing the ovarian stimulation protocol is not worthy it, and there is no evidence that such a change may increase the oocyte yield.

For ovarian stimulation (OS) procedures, various protocols and the use of several forms of gonadotrophins have been proposed and evaluated [21]. Indeed, gonadotropin therapy in various forms has been applied to stimulate multiple follicle development. Currently, available gonadotropins for OS include both, recombinant technology based and human urinary derived products [6]. However, given the extensive range of options available, it seems advisable to recommend recombinant products [22]. Selection of the most appropriate regimen among recombinant preparations remains challenging, with the currently available literature reporting no significant differences in the number of oocytes retrieved or pregnancy rates among the available types of gonadotropins and stimulation schedules.

Although many randomized trials (RCT) have been published comparing the different available options, they have reported conflicting results. Furthermore, RCT includes very specific types of patients, which may not reflect patients in real clinical practice. Consequently, real-world studies that include a broader spectrum of patients may reflect better the populations seen in actual clinical practice [3]. In the present study, two different gonadotropins were administered. Bemfola® was the first recombinant follicle-stimulating hormone (rFSH) biosimilar introduced in Europe in 2014, following approval in the EU based on Phase III clinical trials that demonstrated non-inferiority to the reference product GONAL-f® in terms of the number of retrieved oocytes and comparable safety [23]. Corifollitropin alfa (Elonva®) represents a novel hybrid molecule with sustained, long-acting follicle-stimulating activity designed to address the need for daily injections of traditional FSH preparations to maintain steady-state FSH levels above the threshold during ovarian stimulation [4].

Repeating an ovarian stimulation procedure does not necessarily entail the need to modify the stimulation protocol. There is variability in ovarian response even when the same gonadotropins are administered, as shown in the present study. Hence, in consecutive stimulations, variations in the response are physiological, even though the same protocol and medication are employed. Selecting one protocol over another should prioritize the comfort and convenience of the patient rather than a hypothetical improved response with different medications.

Conclusion

In cases in which a repeated OS procedure is indicated, changes in stimulation protocols do not guarantee an increased oocyte yield. Furthermore, such changes are not based on scientific evidence. Although the safety and comfort of our patients should be our objective, often (too often), the OS protocols are modified to make our patients believe that a change is needed (faith) instead of reassuring patients that such modifications are generally not necessary (science).

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