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The impact of quantitative parameters of folliculogenesis in controlled ovarian stimulation on IVF

Abstract

Study question: Are there any advantages to "mild stimulation" protocols before conventional stimulation?

Summary answer: Wide usage of "mild stimulation" in clinical practice seems inappropriate, due to large percentage of women with inadequate (poor and suboptimal) response to stimulation with traditional doses of gonadotropins among patients with IVF programs.

What is known already: Conventional stimulation is a kind of "gold standard" in the modern practice of Assisted Reproductive Technologies (ART). In recent years, many different so-called "mild stimulation" protocols were designed to reduce physical, emotional and financial risks associated with conventional schemes.

Study design, size, and duration: The study included 4445 infertile women from 20 to 43years old.

Participants/materials, setting, and methods: We analyzed results of IVF programs in terms of pregnancy rate in stimulated cycles and embryo transfers (pregnancy rate index per embryo transfer and per cycle). Ovarian stimulation in the IVF cycles was carried out according to the long protocol of down-regulation with the appointment of a GnRH agonist or a short protocol with GnRH antagonist.

Main results and the role of chance: In case of standard stimulation, the highest pregnancy rate indexes per embryo transfer and per cycle were mentioned in patient's groups with 8-22 rather than 4-7oocytes. With hyperergic response in most cases of embryo transfers cancels patients save chances of high enough cumulative pregnancy rate index by using the freeze-all strategy, which provides possibility for subsequent use of obtained embryos in un stimulated cycles.

Limitations, reasons for caution: This study is based on retrospective analysis of data of all patients who were involved in the IVF programs in a specific period of time without considering the factor of patients' infertility.

Wider implications of the findings: Our study shows that proponents of "mild stimulation" do not take into account the fact that quite a significant proportion of women may be resistant to standard (and even high) doses of gonadotropins due to a possible polymorphism of the FSH-receptor, associated with genes mutations encoding them. As a result, the appointment of lower doses of gonadotropins may lead to a deterioration of clinical outcomes of IVF compared to cycles where the conventional scheme is used. In case of hyperergic response, using of freeze-all strategy may be effective in preventing the progression of ovarian hyperstimulation syndrome.

Keywords: infertility, IVF, conventional and mild stimulation, folliculogenesis

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Introduction

In its development the IVF technology has passed through several stages, characterized by the transition from an unstimulated cycle to using inductors of folliculogenesis (clomiphene citrate at first and then gonadotropin). As a result, this led to rationale of the use of gonadotropins on the background of desensitization of the adenohypophysis provided by agonists or antagonists of GnRH.[1] During the evolution of controlled ovarian stimulation many drugs and their usage patterns have been tried. They resulted in two equally successful protocols of ovulation stimulation, which in our opinion can be regarded as a kind of "gold standards" of IVF, because today they are the most universal and suitable in almost all clinical situations:[2]

A. "Long" stimulation protocol with gonadotropins (hMG or rFSH medications from day 2-3 of the cycle) with agonists GnRH from mid luteal phase of previous cycle or on day 2-3 of the menstrual cycle;

B. "Short" protocol simulation with gonadotropins (on day 2-3 of the cycle) with antagonists of GnRH, assigned in the daily form when a leading follicle achieves 14mm diameter or a fixed protocol, in which the antagonists are assigned from the 6th day of stimulation with gonadotropins.

It should be emphasized that these protocols are referred today in literature as "conventional" (i.e. "traditional") and are used as a "control" group in the evaluation of clinical effectiveness of any of

the proposed new schemes of ovarian stimulation. It is interesting to note that the authors of regularly appearing articles in literature offer to assign new protocols of induced folliculogenesis, consistently indicating that their development for clinical and, particularly, economic efficiency, supposedly superior to conventional protocol. However, time passes, and it turns out that these new high-performance designs for some reason are unclaimed by wide clinical practice and, at best, are sporadically used only by the authors of these developments and their few supporters. In contrast, conventional protocols with all their well-known drawbacks (inconvenience of use due to the large number of injections, increased risk of ovarian hyperstimulation syndrome (OHSS), high price) since its "debut" in IVF programs have immediately gained widespread popularity and subsequently have not lost it, i.e. they continue to be assigned by most of the doctors.

Another attempt to "shift conventional-scheme from the pedestal" is now taken by followers of the ideas of the ISMAAR community (The International Society for Mild Approaches in Assisted Reproduction). Supporters of the ISMAAR find it useful to use the so-called "patient friendly" IVF, under which they understand the rejection of typical conventional charts with its relatively aggressive stimulation for its more mild variants ("mild stimulation") with its own benefits.[3,4] Such variants of induced folliculogenesis are aimed to reduce the course doses of gonadotropins by injection them at lower doses, for shorter time (from day 5 of the cycle) and/or by combining with pre-assigned oral inductors of folliculogenesis of indirect action (clomiphene citrate or aromatase inhibitors). Taking into account often voiced by supporters of the ISMAAR provisions of the high efficiency of IVF in cases with controlled ovarian stimulation with less than 8 (ideally 4 to 7) of oocytes, we decided to check out this point of view and its correspondence to reality on the basis of a large number (N=4445) of own observations.

The aim of the study was to clarify the effectiveness of IVF procedure in terms of pregnancy rate index (PR index) per embryo transfer (ET) and per cycle in fresh cycles, using conventional stimulation with an analysis of frequency and causes of embryo transfers cancels in patients groups with different numbers of collected oocytes.

Materials and methods

In accordance with the intended target the results of IVF of 4445 infertile patients at the age of 20 to 43years were analyzed in terms of pregnancy rate in stimulated cycles and embryo transfers (PR index per ET and per cycle). Ovarian stimulation in the IVF cycles in the majority (60%) cases was carried out according to the long protocol of down-regulation with the appointment of a GnRH agonist. In 40% of fresh cycles for controlled stimulation was used a short protocol with GnRH antagonist prescribed when the leading follicle achieved diameter of 14mm.

The selection of the starting dose of FSH (75 to 300 IU/day) in the assigned medications of gonadotropins was performed on the basis of recommendations governing the resolution of this issue taking into account the patient's age and presence/absence of increased likelihood of developing OHSS or poor response.[2] Monitoring of induced folliculogenesis was performed using ultrasound and daily dose of used medication was optionally corrected based on the readings of ultrasound. In all cases, the maximum daily dose of FSH was limited by the level of not more than 450IU.

Upon reaching 18-20mm diameter of the leading follicle 5-10thousands IU of ovulation trigger of human chorionic gonadotropin (hCG) were injected and after 34-36hours transvaginal puncture of all follicles with a diameter greater than 15mm was performed. The allocation, insemination, cultivation of oocytes and transfer of embryos (no more than 2), also as support of the luteal phase with progesterone in posttransfer period was performed in accordance with standard guidelines.[2]

In the analysis of the collected factual material on pre-transform stage, the frequency of cases of cancellation of ET and their causes were specified. In post-transfer period when calculating PR index per ET and per cycle in fresh cycles only clinically confirmed pregnancy were considered (detection using ultrasound of gestational sac in 28days after ET).

The obtained results were processed using methods of variation statistics presented in the Statistic 6.0 program. The differences of frequencies of the analyzed indicators in the paired comparisons were considered reliable at the significance level of $p<0.05$.

Results

The analysis of the patients' age distribution shows that 31-39 years patients dominated in our study with a total share of 61.8% (Table 1). Women aged ≤30years made about ¼ of all the patients (24.5%). The proportion of patients of 40-42years and ≥43years old accounted for 10.7% and 3.1%. From these data, it follows that corresponding material describes the actual patterns revealed in relatively young (under 40years) patients undergoing infertility treatment using IVF.

Table 1 Distribution of patients according to age (n=4445)

	Patient age (years)				
	≤30	31 – 35	36 – 39	40 – 42	≥43
Cycle starts	1087	1590	1155	474	139
% of n	24,5	35,8	26,0	10,7	3,1

The conducted research allows to state (Table 2) that using in the present work conventional-scheme protocols almost in half (50.4%) cases was accompanied by obtaining 8-22 oocytes. In 26% cases managed to get 4-7 oocytes (the perfect number according to the criteria of ISMAAR). Poor and hyperergic response occurred in respectively 15.8% and 6.7% of cycles. The cases of no oocytes collected (absence of ovarian response to gonadotropins) did not exceed 1.1%.

After assessing clinical outcomes of IVF via indicators of the PR index per ET and per cycle it was found that while using conventional-schemes, the best results occurred in case of receiving 8-22, not 4-7oocytes (Table 2). So, in the group of women with 8-22 collected oocytes the PR index per ET and per cycle have reached up to 32.5% and 37.3%, whereas in the group with 4-7 obtained oocytes the same figures amounted to not more than 24.9% and 29.5%, thus the index was about 8% less (with the level of reliability of differences $p<0.001$).

It was also found that upon 8-22 oocytes receipt the number of ET in fresh cycles was the highest (87.5%), and it was statistically significant ($p=0.013$) higher than in group of women with 4-7 obtained oocytes (84.4%). But the most noticeable was the difference between these two groups by number of cycles with cryopreservation of embryos – 48% vs 16.9%, ($p<0.001$).

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Table 2 Clinical outcomes of IVF in terms of PR index per cycle and per ET with different number of collected oocytes (n=4445)

Analyzed indicators		The results for different number of collected oocytes				
		Number of collected oocytes				
		0	3/1/2018 (Poor response)	7/4/2018 (Ideal Number of Criteria ISMAAR)	22-Aug	≥23 (Hyperergic response)
The number of patients (fresh cycles)	Cycles	49	703	1155	2241	297
	% of n	1,1	15,8	26,0	50,4	6,7
The number of completed ET in fresh cycles	Number of ET	-	511	975	1961	175
	% of fresh cycles	-	72,6	84,4	87,5*	58,9
Pregnancy (fresh cycles)	Total number	-	115	288	729	52
	PR index per cycle	-	16,3	24,9	32,5*	17,5
	PR index per ET	-	22,5	29,5	37,2*	29,7
The number of cycles with embryo cryopreservation	Cycles	-	26	195	1075	234
	% of fresh cycles	-	3,7	16,9	48,0*	78,8

* - Significant difference from group with 4-7 collected oocytes (p from <0,001 to <0,05)

In group of patients with poor and hyperergic response the PR index per cycle (16.3% and 17.5%) and the PR index per ET (22.5% and 29.5%) in fresh cycles was significantly inferior to the outcomes observed in groups of women with 4-7 collected oocytes, and to an even greater extent with 8-22 oocytes.

Noteworthy that for patients with hyperergic response the number of cycles with cryopreservation of embryos reached 78.8%, which was the highest among all compared groups with different number of collected oocytes. From this observation it follows that the majority of patients with the number of oocytes ≥23 while having unsuccessful attempts of induction of pregnancy in the fresh cycle still remain a very good chance for conception in unstimulated cycle through obtained and cryopreserved genetic material in the form of embryos.

It is interesting to note that in these parameter patients with hyperergic response superior to women:

a. With 8-22 received oocytes in 1.6times (78.8% versus 48%);

b. With 4-7 collected oocytes in 4.7times (78.8% versus 16.9%);

c. With 1-3 oocytes in 21.3times (78.8% versus 3.7%).

When studying the frequency of ET cancels in fresh cycles it was identified (Table 3) that such cases are often observed in groups of patients with hyperergic and poor response, respectively in 41.1% and 27.4% women. The patients with 8-22 obtained oocytes were least likely to have to reject ET – in 12.9% of fresh cycles and it was significantly less ($p<0.001$) than for the patients with 4-7 selected oocytes, for which the figure was 15.6%.

Table 3 Frequency of ET cancels and possibilities for cryopreservation of oocytes/embryos with different number of collected oocytes

Analyzed Indicators	The results for different number of collected oocytes			
	Number of collected oocytes			
	3/1/2018 (Poor Response)	7/4/2018 (ideal number of criteria ISMAAR)	22-Aug	≥23 (hyperergic response)
ET cancels (% of fresh cycles)	27,4	15,6	12,5*	41,1
ET cancels with cryopreservation of embryos (% from total number of ET cancels)	9,1	28,9	51,7*	80,3
(reserve for increasing cumulative PR index by transferring thawed embryos in unstimulated cycles)				
ET cancels for morphological reasons (% from total number of ET cancels)	90,9	71,1	48,3*	19,7

* - significant difference from group with 4-7 collected oocytes (p <0,001)

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It is important to note that among all cases of ET cancels the share of ET cancels with cryopreservation of embryos was highest among patients with hyperergic response (80.3%) and lowest among persons with poor response (9.1%). Conversely, the proportion of cancellations of ET due to morphological reasons (in the absence of fertilization of oocytes, the absence of division or obvious morphological unsuitability of embryos) was highest among patients with a poor response (for 90.9%), whereas in women with hyperergic ovarian response, the number of such cases was the lowest (19.7%). From this observation it follows that among women with hyperergic response the cancel of ET is not of "tragic" character, since most of them remained sufficiently powerful reserve for a cumulative increase of the pregnancy rate due to the high quality of stored cryopreserved embryos and their possible use in future unstimulated cycles. In contrast, the cancel of ET for the vast majority of individuals with a poor response is really "tragic" phenomenon due to non-receipt of cryoembryos because it means the final termination of the initiated treatment cycle and involves repeated IVF with mandatory ovarian stimulation.

In the group of patients with 8-22 obtained oocytes among all cancellations of ET the proportion of cases involving cryopreservation of embryos reached 51.7%, which is significantly ($p<0.001$) higher than the same among patients with 4-7 collected oocytes, in which it was 1.8times lower (28.9 percent). It is obvious that the reason was the high frequency of cancellations of ET due to morphological reasons among patients with 4-7 selected oocytes compared to women with 8-22 obtained oocytes – 71.1% vs. 48.3 ($p<0.001$).

Discussion

Despite the fact that the need for induction of multiple folliculogenesis in the implementation of IVF is not disputed today, a debate still remains in the question of what should ideally be a degree of stimulating effect on the ovaries of the used protocol of induced folliculogenesis, which is usually estimated by the number of collected oocytes. Today the most common conventional schema of ovarian stimulation is not universally recognized as optimal. Alternatively, proponents of ISMAAR actively promote "soft" schemes of stimulation, aimed at reducing the amount of FSH.[3,4] It is assumed that "soft" stimulation, followed by a reduction of the number of retrieved oocytes (ideally up to 4-7oocytes), somehow increases their quality, and supposedly provides relatively higher performance of the PR index, which does not inferior or even superior to the results observed when using conventional schemes.

Our study, however, casts doubt on the usefulness of the idea of "soft stimulation", because the recommendations of ISMAAR do not explicitly take into account the fact that quite a significant proportion of women may be resistant to standard (and even high) doses of gonadotropins due to a possible polymorphism of the FSH-receptor (FSH-R), associated with genes mutations encoding them.[5] For example, it is known that mutation N680S (replacement of serine for asparagine at codon 680 of the gene FSH-R) entails the buildup of resistance to stimulatory effect of FSH.[6,7] To compensate the attenuation of receptor sensitivity to FSH can only be done by increasing the applied dose of gonadotropins. However, in this case among the part of patients (women with a higher percentage of the modified FSH-R), the ovarian response will remain weakened (poor), or even not manifest at all.[6] This is what our observations confirmed, according to which the part of the patients failed to overcome the weakened reaction of the ovaries to gonadotropins, even with the increase in their daily dose. So, when performing this work it was found that in the context of use of rather aggressive conventional schemes, supposing to increase the daily dose from the start of FSH of 150IU (2-3 day of the cycle) up to a maximum of 450IU, the frequency of poor response in non-selective population reached in stimulated cycles of 15.8%, while the frequency of cancellations due to lack of follicle growth was 1.1%. Taking into account these results and assuming that "soft" stimulation (implying a reduction in the pressure of exogenous FSH) will be conducted "blind", i.e. be appointed in accordance with the recommendations of ISMAAR to everyone (including women with insufficiently sensitive receptors to FSH), it is foreseeable that this will inevitably lead to a deterioration of clinical outcomes of IVF compared to cycles where the conventional schema is used. It is logical to assume that the decrease in the efficiency of IVF in such cases will be associated as with the effects of increasing cases of poor response (preventing the use of the therapeutic potential of cryotechnologies), as with the increase in interruption frequency of fresh stimulated cycles due to the lack of follicle growth.

The obtained results allowed to establish that in obtaining 4-7oocytes (i.e., the ideal criteria according to ISMAAR numbers), the results of treatment on indicators of the PR index per cycle and per ET were significantly 8% worse than it was in case of 8-22oocytes. In our opinion, the fact of receiving in a traditional stimulation of one or the other of the patient 4-7oocytes instead of the expected 8-22 is evidence of presence of a sensitivity reduction of a growing follicles cohort to FSH due to the potential polymorphism of their FSH-R for this woman. In turn, the consequence of the weakening receptor-effects of exogenous FSH, providing multifollicular response, is the possible deterioration in the quality of oocytes and reduced implantation potential of derived embryos. This conclusion was indirectly confirmed by the fact that we accurately registered fall rate of the PR index per ET when generating 4-7 (instead 8-22) oocytes.

It is worth noting that, according to some experts, obtaining under standard stimulation 4-7 oocytes should be treated as "suboptimal" response, inhibiting more complete disclosure of the therapeutic potential of IVF.[8] In the application to patients with a suboptimal response, the share of which according to our data reaches 26% on the background of assigned conventional schemes, the prospect of using "soft" stimulation obviously does not bode anything well from the point of view of consequences for the clinical outcome of IVF. This is because reducing the applied dose of FSH at the lack of sensitivity of FSH-R can translate suboptimal responders to the category of patients with a poor response or even in a group of patients who had to interrupt the cycle due to the lack of follicle growth.

Thus, the assumption of the supporters of ISMAAR about the expected improvements in IVF results in "mild" stimulation clearly does not hold water, if taking into account the % of patients with normal stimulation who can get not only poor, but also suboptimal response. In our study, the proportion of such patients in the general population of surveyed (which was dominated by women <40years) were, respectively, 15.8% and 26%, from which we can conclude that very many patients with "soft" stimulation, in principle, may not benefit.

In our opinion, the "soft" stimulation will be justified only when specialists in reproduction will learn to predict the adequacy of response to gonadotropins accurately, including on the basis of

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an assessment of the sensitivity of the FSH-R. While this has yet not happened, it seems appropriate to use the standard stimulation within the traditional schemes. It is obvious that such an approach provides the maximum possibility to prevent situations of lack of ovarian response due to possible conformational changes of FSH-R, accompanied in one way or another with expressed lack of sensitivity of the ovaries to the stimulation of FSH-containing preparations.

It should also be emphasized that, despite the apparently high cost conventional-schemes in comparison with "soft" protocols, in fact for the majority of women receiving a standard stimulation will be an economic benefit, since they have less risk of cancellation of fresh stimulated cycle, forcing patients to incur additional costs for the continuation of repeated IVF attempts.

As for the advantages of "soft" schemes over the standard stimulation on the criterion of reducing the risk of OHSS (which is constantly repeated the supporters of ISMAAR), its real value, in our opinion, is not so great. The fact is that the process of progression of OHSS in pre-ET stage today can be quite easily stopped by using the "freeze-all" strategy.[9] The essence of this strategy is to puncture all follicles that are actively growing and cryopreserve all obtained embryos with a prospective to their subsequent use for the same patient in the further unstimulated cycles. The fact that the implementation of the "freeze-all" strategy due to the threat of OHSS leads to necessary cancel of the transfer of fresh embryos does not affect the final frequency of induced pregnancy because the ability to have implantation of cryopreserved embryos according to the latest RAHR (Russian Association of Human Reproduction) observations[10] is not worse than that of fresh embryos. Besides, one should not forget that to reduce the risk of OHSS (among women with predictors of the hyperergic response) in the "traditional" stimulation, it is customary to assign the minimal starting dose of FSH and to use the "short" protocol with GnRH antagonist instead of a "long" scheme with a GnRH agonist.[2] These measures are usually enough to prevent OHSS. If OHSS still starts to progress, the solution to this situation is the use of the strategy of "freeze-all",[9] which can be supplemented by the appointment of selective stimulants of dopamine D_2-receptors.[11] This approach not only helps to eliminate clinical manifestations of OHSS, but also provides cumulative effectiveness of IVF on the same level as among comparable in age patients with an adequate response in fresh cycles.

From the above it can be concluded that in IVF programs the "soft" stimulation, in spite of all arguments of the supporters of ISMAAR, cannot be considered as a serious alternative to traditional protocols that are considered "gold standards". When using the standard stimulation the best results in fresh IVF cycles for the indicators of the PR index per cycle and per ET are observed in groups of patients with 8 to 22 collected oocytes, not 4-7. In case of hyperergic response, despite the frequent cancellation of ET in fresh cycles, patients still have a chance for quite high cumulative pregnancy rate due to the use of the freeze-all strategy, which is also exceptionally effective in preventing the progression of OHSS.

Authors' roles

K.V., T.A. and V.M. developed and wrote the first draft of the manuscript. O.A. and T.V. were involved in data analysis and interpretation, and manuscript preparation. V.M. did the statistical analysis. All authors approved the submitted final version of the manuscript.

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Conflict of interest

Author declares that there is no conflict of interest.

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