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Основные характеристики протоколов ЭКО/ИКСИ у пациенток с субоптимальным ответом на контролируемую овариальную стимуляцию

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Актуальность. По количеству полученных ооцитов в протоколах ЭКО/ИКСИ ответную реакцию яичников на контролируемую овариальную стимуляцию принято разделять на слабый (0–3 ооцита), субоптимальный (4–9 ооцитов), нормальный (10–15 ооцитов) и избыточный (>15 ооцитов) ответ. Однако данные о результативности программ ЭКО/ИКСИ непосредственно у женщин с субоптимальным ответом изучены мало, поскольку эту когорту пациенток нередко рассматривают в одной группе с женщинами, имеющими нормальный ответ.

Цель — определить основные характеристики программ ЭКО/ИКСИ у пациенток с субоптимальным ответом при сравнительном анализе с аналогичными показателями у женщин с нормальным ответом на контролируемую овариальную стимуляцию.

Материалы и методы исследования. В ретроспективное исследование вошли 568 пациенток: 470 женщин с субоптимальным ответом и 98 женщин с нормальным ответом на контролируемую овариальную стимуляцию. Сравнительный анализ включал клинико-анамнестические данные и основные характеристики программ вспомогательных репродуктивных технологий в выделенных клинических группах.

Результаты исследования. В анамнезе у пациенток с субоптимальным ответом на контролируемую овариальную стимуляцию достоверно чаще, чем в контрольной группе, встречались операции на органах малого таза (71,3 % vs 55,1 %; $p < 0,01$) и воспалительные заболевания органов малого таза (70,9 % vs 60,2 %; $p < 0,05$). Значения показателей овариального резерва (концентрация антимюллерова гормона в сыворотке крови и количество антральных фолликулов) у женщин с субоптимальным ответом были достоверно ниже ($p < 0,001$). Кроме того, у женщин с субоптимальным ответом на контролируемую овариальную стимуляцию количество зрелых ооцитов, зигот 2PN, эмбрионов хорошего качества ($p < 0,001$) было достоверно меньше, а частота наступления клинической беременности ниже, чем у пациенток с нормальным ответом (27,2 % vs 41,7 %; $p < 0,01$). Сопутствующая миома матки негативно влияла на эффективность программ ЭКО/ИКСИ у женщин с субоптимальным ответом на контролируемую овариальную стимуляцию (ОШ 0,5; 95 % ДИ 0,3–0,9; $p = 0,03$). При ROC-анализе были выделены предикторы субоптимального ответа яичников на контролируемую овариальную стимуляцию, такие как концентрация антимюллерова гормона в сыворотке крови (AUC = 0,80) с пороговым значением ≤2,57 нг/мл (чувствительность — 74 %, специфичность — 75 %) и количество антральных фолликулов (AUC = 0,90) с пороговым значением ≤10 фолликулов (чувствительность — 80 %, специфичность — 94 %).

Заключение. У женщин с субоптимальным ответом на контролируемую овариальную стимуляцию результативность программ ЭКО/ИКСИ по сравнению с аналогичным показателем у женщин с нормальным ответом на контролируемую овариальную стимуляцию достоверно снижена. Сопутствующая миома матки может дополнительно способствовать снижению эффективности протоколов ЭКО/ИКСИ у пациенток с субоптимальным ответом. К предикторам субоптимального ответа следует отнести уровень концентрации антимюллерова гормона в сыворотке крови и количество антральных фолликулов.

Ключевые слова: субоптимальный ответ; нормальный ответ; ЭКО/ИКСИ; контролируемая овариальная стимуляция; частота наступления клинической беременности.

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Main characteristics of IVF / ICSI protocols in patients with suboptimal response to controlled ovarian stimulation

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HYPOTHESIS/AIMS OF STUDY: According to the number of oocytes retrieved in IVF/ICSI protocols, the ovarian response to controlled ovarian stimulation is divided into: poor (0–3 oocytes), suboptimal (4–9 oocytes), normal (10–15 oocytes) and excessive (>15 oocytes) response. However, the effectiveness of IVF / ICSI programs in women with a suboptimal response is poorly understood, since this cohort of patients is often fallen into the category of women with a normal response. The aim of this study was to determine the main characteristics of IVF / ICSI programs in patients with suboptimal response to be further compared to those in women with normal response to controlled ovarian stimulation.

STUDY DESIGN, MATERIALS AND METHODS: This retrospective study included 568 patients: 470 women with suboptimal response and 98 women with normal response to controlled ovarian stimulation. The comparative analysis comprised clinical and anamnestic data, as well as the main characteristics of assisted reproductive technology programs in the selected clinical groups.

RESULTS: It was found that patients with suboptimal response to controlled ovarian stimulation had significantly more frequent history of pelvic surgery (71.3% vs. 55.1%; $p < 0.01$) and pelvic inflammatory diseases (70.9% vs. 60.2%; $p < 0.05$). Parameters of ovarian reserve (serum anti-Müllerian hormone level and antral follicle count) in women with suboptimal response were significantly lower ($p < 0.001$). In addition, the number of mature oocytes, 2PN zygotes, good quality embryos ($p < 0.001$), as well as the clinical pregnancy rate in women with suboptimal response were found to be significantly lower than in patients with normal response to controlled ovarian stimulation (27.2% vs. 41.7%; $p < 0.01$). It was noted that concomitant uterine fibroids enhanced the negative impact on the effectiveness of IVF / ICSI programs in women with suboptimal response to controlled ovarian stimulation (OR = 0.5; 95% CI: 0.3–0.9; $p = 0.03$). ROC analysis identified predictors of suboptimal response to controlled ovarian stimulation, such as serum anti-Müllerian hormone level (AUC = 0.80) with the cut-off value of ≤2.57 ng / ml (sensitivity 74%, specificity 75%) and antral follicle count (AUC = 0.90) with the cut-off value of ≤10 follicles (sensitivity 80%, specificity 94%).

CONCLUSION: In women with suboptimal response to controlled ovarian stimulation, IVF / ICSI success rates are significantly reduced when compared to those in women with normal response. Concomitant uterine fibroids may further decrease the effectiveness of IVF / ICSI protocols in patients with suboptimal response. Predictors of suboptimal response include the serum anti-Müllerian hormone level and antral follicle count.

Keywords: suboptimal response; normal response; IVF / ICSI; controlled ovarian stimulation; clinical pregnancy rate.

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Progressive development, improved competencies, and extensive practice have allowed reproductive scientists to achieve high levels of qualification, and assisted reproductive technologies have become an important component of modern medicine [1]. The optimal target effect of *in vitro* fertilization and intracytoplasmic sperm injection (IVF/ICSI) depends on it [2]. Among the factors directly affecting the characteristics of the induced reproductive cycle, the gradation of the ovarian response to stimulation in IVF/ICSI protocols is of particular clinical importance. The ovarian response to controlled ovarian stimulation (COS) may be categorized according to the number of oocytes received in the IVF/ICSI protocol as weak (0–3 oocytes), suboptimal (4–9 oocytes), normal (10–15 oocytes), and overstimulated (>15 oocytes) [3, 4]. According to the Human Fertilization and Embryology Authority (UK), the frequency of suboptimal responses to COS is relatively high at 43.3%. Compared with those of patients with a weak or over-response, the characteristics of IVF/ICSI programs in women with a suboptimal response to COS are poorly studied; indeed, the indicators of these women are usually likened to those of women with a normal response. In a retrospective cohort study, Panagiotis Drakopoulos and colleagues (2016) published data showing that the rate of birth of live children in women with a suboptimal response to COS is significantly lower than that in patients with a normal response [5]. In a recent study, Popovic–Todorovic and colleagues (2019) found a correlation between serum concentrations of luteinizing hormone (LH) and the level of ovarian response to stimulation; specifically, the lower the serum concentration of LH, the higher the risk of developing a suboptimal response to COS [6]. Alviggi and colleagues (2011) previously identified a correlation between LH-b variant polymorphisms and a suboptimal response to COS by recombinant follicle-stimulating hormone (rhFSH) [7].

The fragmented nature of data on the features of COS protocols in women with suboptimal ovarian response highlights the need for a consistent comparative analysis of the factors influencing the effectiveness of assisted reproductive technology programs and the detailed markers of a failed outcome.

The aim of the present study is to conduct a comparative assessment of the main characteristics of IVF/ICSI programs between women with suboptimal and normal ovarian responses to COS.

MATERIALS AND METHODS

This retrospective study recruited 568 patients, including 470 women with a suboptimal response (Group 1) and 98 women with a normal response (Group 2) to COS, who underwent examination and treatment at the Department of Assisted Reproductive Technologies of the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Peterburg, Russia.

Inclusion criteria:
- suboptimal ovarian response to COS in IVF/ICSI protocols (4–9 oocytes received);
- normal ovarian response to COS in IVF/ICSI protocols (10–15 oocytes received).

Exclusion criteria:
- age over 42 years;
- FSH level > 15 IU/L;
- IVF/ICSI cycle using donor eggs.

Serum concentrations of FSH, LH, estradiol, and anti-Müllerian hormone (AMH) were determined on days 3–5 of the menstrual cycle; serum concentrations of progesterone and prolactin were determined on days 19–22 of the menstrual cycle; and serum concentrations of TTH and free T_4 were determined free of the menstrual cycle. Transvaginal ultrasound was employed to assess the number of antral follicles (NAF) on the day of entry into the COS protocol, and the thickness of the endometrium was measured on the day of embryo transfer. The COS protocol involved the use of antagonists gonadotropin-releasing hormone or agonists gonadotropin-releasing hormone (GnRH). Stimulation of the ovaries with FSH (rhFSH, hMG) alone or in combination with LH was initiated on the second or third day of the menstrual cycle. When three follicles had grown to >17 mm in diameter, the patient was injected with the trigger, i.e., human chorionic gonadotropin (HCG), or the GnRH agonist. The follicles were punctured 36 hours after the trigger was administered. The number of embryos of good quality at the cultivation stages was determined by assessing the degree of fragmentation and compaction of blastomers. The onset of clinical pregnancy in women with a positive test for HCG was confirmed by ultrasound diagnosis 3–4 weeks after the transfer of embryos into the uterine cavity and the presence of the fetal heartbeat.

Intergroup analysis was conducted by comparing the clinical-anamnestic data and hormonal status and ovarian reserve indicators of women with suboptimal and normal responses to COS. The embryological data and the effectiveness of IVF/ICSI programs, including taking into account the impact of the initial gynecological status of the women surveyed, were evaluated in the parameters of the protocols of COS. Correlations between age, ovarian reserve, and IVF/ICSI cycle parameters were identified for each of the selected clinical groups. Predictors of the level of ovarian response to controlled stimulation were established by receiver operating characteristic (ROC) analysis.

We used Stata version 14 software (StataCorp LLC, College Station, TX, USA) for MacOS for statistical analysis. The average arithmetic mean, standard deviation, lower and upper quartiles, chi-squared (χ^2) statistic, Mann–Whitney *U* criterion, Kolmogorov–Smirnov criterion, logistic

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regression, ROC curve, odds ratio, 95% confidence interval (95% CI), *p*-value, and Spearman correlation were calculated. A *p*-value of <0.05 was considered to indicate statistical significance.

RESULTS

The clinical-anamnestic data of the surveyed women are presented in Table 1. No reliable differences in age, body mass index, and age of menarche were observed between the groups of women surveyed. The incidence of patients with a history of birth and spontaneous abortions was comparable between groups, but women with a suboptimal response to COS had a higher rate of induced abortions. The number of unsuccessful ECO attempts was roughly equal between the two clinical groups, but the duration of infertility in the first group of women with a suboptimal response to COS was reliably longer. Patients with a history of suboptimal response to stimulation reliably demonstrated more indications of pelvic organ and pelvic inflammatory diseases than those with a normal response. No significant difference in the frequency of concomitant genital endometriosis and uterine fibroids was observed between the two groups of women. Uterine fibroids were mainly represented by fibroids, most of which were intramural in nature. Women with comparable frequencies of suboptimal and normal responses to COS (30% vs. 41%, respectively; $p = 0.34$) received surgical intervention for uterine fibroids in the form of myomectomy.

The serum concentrations of FSH and prolactin were reliably higher and the serum concentrations of LH and

Table 1. Clinical characteristics of the included patients

Parameters	Group 1	Group 2	*p*
Age, years	34.0 ± 4.5	33.7 ± 4.3	0.47[a]
Body mass index, kg/m^2	23.3 ± 3.9	22.9 ± 4.2	0.17[a]
Age of menarche, years	13.2 ± 1.2	13.2 ± 1.3	0.9[a]
Patients with a history of childbirth, *n* (%)	72 (15.3%)	13 (13.3%)	0.6[b]
Patients with a history of spontaneous abortion, *n* (%)	69 (14.7%)	17 (17.3%)	0.5[b]
Patients with a history of induced abortion, *n* (%)	103 (21.9%)	6 (0.6%)	**<0.001**[b]
Number of failed attempts of *in vitro* fertilization in history	0.91 ± 1.4	0.84 ± 1.6	0.27[a]
Duration of infertility, years	6.1 ± 3.9	5.0 ± 3.2	**0.003**[a]
Patients with uterine fibroids, *n* (%)	108 (23.0%)	17 (17.3%)	0.22[b]
Patients with genital endometriosis, *n* (%)	147 (31.3%)	32 (32.7%)	0.79[b]
Patients with surgery of the uterus and appendages (%)	335 (71.3%)	54 (55.1%)	**0.002**[b]
Patients with inflammatory diseases of the uterus and appendages (%)	333 (70.9%)	59 (60.2%)	**0.038**[b]

Note. [a] Mann–Whitney *U* criterion; [b] chi-squared (χ^2) statistic. Bold-faced fonts highlight statistically significant results.

Table 2. Characteristics of the hormonal status and ovarian reserves of the included patients

Parameters	Group 1			Group 2			*p*
	Me ± SD	LQ	UQ	Me ± SD	LQ	UQ	
FSH, IU/l	7.45 ± 2.58	5.63	9	6.75 ± 2.24	5.48	7.81	**0.035**[a]
LH, IU/l	5.22 ± 2.57	3.5	6.53	5.73 ± 2.57	3.8	7.14	**0.041**[a]
E_2, pg/ml	156.8 ± 149.6	54.05	208	127.8 ± 100.9	45.7	194	0.33[a]
TTH, IU/l	1.75 ± 0.87	1.1	2.2	1.83 ±0.87	1.15	2.34	0.34[a]
free T_4, pmol/l	19.14 ± 19.62	12.31	15.9	14.13 ± 10.49	11.58	15.15	0.05[a]
Prolactin, mkIU/ml	359.0 ± 207.1	213.1	453.3	255.0 ± 159.4	167.7	337.5	**<0.0001**[a]
Progesterone, nmol/l	31.14 ± 28.26	6.14	49.28	24.16 ± 25.07	5.16	32	0.1[a]
AMH, ng/ml	1.94 ± 1.03	1.17	2.64	3.92 ± 2.54	2.38	4.99	**<0.0001**[a]
NAF, *n*	7.6 ± 2.4	6	9	12.3 ± 2.9	10	14	**<0.0001**[a]

Note. [a] Mann–Whitney *U* criterion; Me ± SD, average ± standard deviation; LQ, lower quartile; UQ, upper quartile; FSH, follicle-stimulating hormone; LH, luteinizing hormone; free T_4, free thyroxine; E_2, estradiol; TTH, thyroid hormone; AMH, anti-Müllerian hormone; NAF, number of antral follicles. Bold-faced fonts highlight statistically significant results.

Table 3. IVF/ICSI cycle parameters in the included patients

Parameters	Group 1	Group 2	*p*
Duration of stimulation, days	8.8 ± 1.6	8.9 ± 1.4	0.31[a]
Total dose of FSH drugs, IU	1939.5 ± 803.5	1980.3 ± 992.9	0.87[a]
Average dose of FSH drugs, IU	218.2 ± 70.5	216.9 ±77.6	0.45[a]
Effective dose of FSH drugs, IU	329.6 ± 179.3	167.5 ± 90.9	**<0.001**[a]
Number of points	7.6 ± 2.4	14.0 ± 2.5	**<0.001**[a]
Number of received oocytes	6.4 ± 1.7	12.1 ±1.7	**<0.001**[a]
Number of mature oocytes	5.7 ± 1.9	10.6 ± 2.4	**<0.001**[a]
Number of double-nuclear zygotes	3.8 ± 1.9	6.8 ± 2.9	**<0.001**[a]
Number of good quality embryos on day 3	2.1 ± 1.9	4.4 ± 2.6	**<0.001**[a]
Number of good quality embryos on day 4	1.4 ± 1.6	3.1 ± 2.3	**<0.001**[a]
Number of good quality embryos on day 5	1.3 ±1.3	2.8 ± 2.1	**<0.001**[a]
Number (%) of embryos transfer cycles	423 (90.0%)	84 (85.7%)	0.21[b]
Number of transferred embryos	1.8 ± 0.5	1.6 ± 0.5	**<0.001**[a]
Endometrium thickness on the day of transport, mm	9.9 ± 1.6	10.1 ± 1.7	0.59[a]
Number (%) cycles with cryopreservation of embryos	179 (38.1%)	79 (80.6%)	**<0.001**[b]
Number of embryos per cryopreservation	2.7 ± 1.4	4.2 ± 1.9	**<0.001**[a]

Note. [a] Mann–Whitney *U* criterion; [b] chi-squared (χ^2) statistic. FSH, follicle-stimulating hormone. Bold-faced fonts highlight statistically significant results.

parameters of ovarian reserve (i.e., serum AMH concentration and NAF) were much lower in women with a suboptimal response to COS compared those in women with a normal response. No reliable difference in the serum concentrations of estradiol, progesterone, FSH, and free T_4 were observed between the two groups (Table 2).

Comparative analysis of the main characteristics of the IVF/ICSI protocols and embryological data indicated that the numbers of received and mature oocytes, double-nuclear zygotes, and embryos of good quality at the stages of cultivation and cryopreservation are significantly fewer in women with a suboptimal response than in women with a normal response to COS. No significant difference in the duration of stimulation and the total and average doses of FSH drugs was found between groups. Moreover, the frequency of cycles with embryo transfer and the thickness of the endometrium on the day of embryo transfer in women with a suboptimal response to COS were comparable with those in patients with a normal response (Table 3). The frequency of implantation and the onset of biochemical pregnancy did not show statistically significant differences between groups. However, the incidence of clinical pregnancy in women with a suboptimal response to COS was significantly lower than that in patients with a normal response (27.2% vs. 41.7%, $p < 0.01$; Figure 1).

Uterine fibroids, regardless of localization, had a negative impact on the effectiveness of IVF/ICSI programs in women with a suboptimal response to COS. Patients with a normal response to COS did not exhibit this negative effect of uterine fibroids on the frequency of clinical pregnancy (Table 4). The need for FSH drugs during COS reliably and comparably correlated with the indicators of ovarian reserve (i.e., serum AMH concentration and NAF) and age of patients. A reliable and comparable intragroup correlation between the number of oocytes received and ovarian reserve rates (i.e., serum AMH concentration and NAF) in the women surveyed was also found (Table 5). ROC analysis (Figure 2) identified predictors of suboptimal ovarian responses to COS,

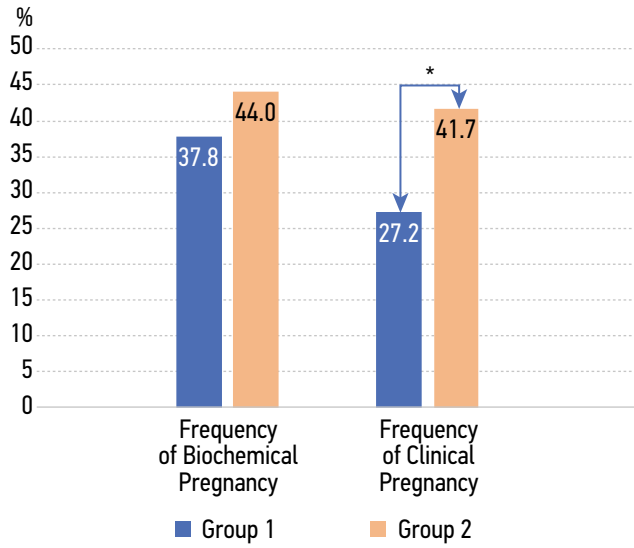

Fig. 1. Results of IVF/ICSI. *$p < 0.01$

Table 4. Effect of gynecological status indicators on the effectiveness of IVF/ICSI programs in women with suboptimal and normal responses to COS

Gynecological status	Clinical pregnancy			
	Group 1		Group 2	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Uterine fibroids	0.5 (0.3–0.9)	0.03*	0.8 (0.3–2.5)	0.71
Inflammation of the uterus and appendages	0.9 (0.5–1.4)	0.52	0.6 (0.3–1.5)	0.31
Genital endometriosis	1.4 (0.9–2.2)	0.12	1.3 (0.5–3.3)	0.53
Ovary surgery	1.4 (0.8–2.3)	0.19	1.0 (0.4–2.5)	0.94

Note. OR, odds ratio; 95% CI, 95% confidence interval. Statistically significant result. * Statically significant result.

Table 5. Characteristics of the relationship between age, ovarian reserve, and IVF/ICSI cycles of the women surveyed

Parameters	Group 1 Spearman's correlation (*r*)			Group 2 Spearman's correlation (*r*)		
	Age, years	AMH, ng/ml	NAF	Age, years	AMH, ng/ml	NAF
AMH, ng/ml	–0.27*			–0.09		
NAF (*n*)	–0.31*	0.49*		–0.14	0.51*	
Number of received oocytes	–0.17*	0.29*	0.42*	–0.15	0.32**	0.44*
Number of mature oocytes	–0.08	0.25*	0.32*	–0.12	0.30**	0.37*
Number of double-nuclear zygotes	–0.08	0.17**	0.23*	–0.02	0.21***	0.26**
Total dose of FSH drugs, IU	0.42*	–0.30*	–0.27*	0.41*	–0.31**	–0.32**
Average dose of FSH drugs, IU	0.49*	–0.36*	–0.35*	0.45*	–0.38*	–0.39*
Effective dose of FSH drugs, IU	0.41*	–0.41*	–0.45*	0.44*	–0.41*	–0.44*

Note. * $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$. FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone; NAF, number of antral follicles.

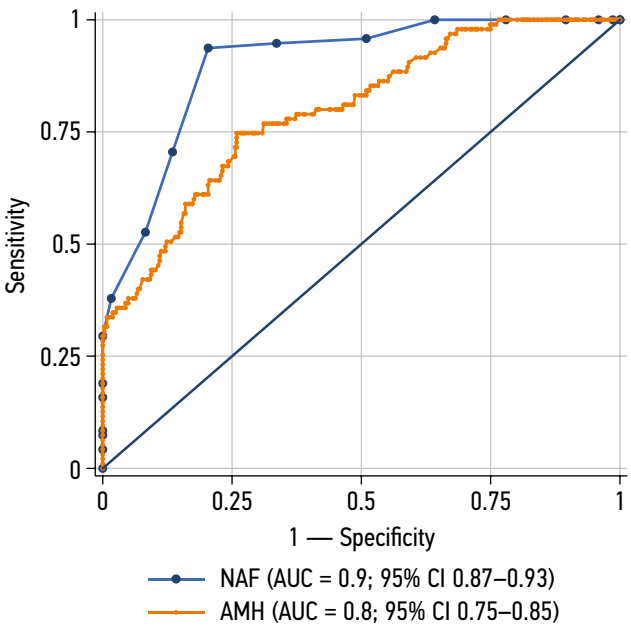

Fig. 2. ROC curve of the dependence of the ovarian response to controlled ovarian stimulation on variations in serum AMH concentration and NAF. AMH, anti-Müllerian hormone; NAF, number of antral follicles

including serum AMH concentration (AUC = 0.80; 95% CI 0.75–0.85), with a threshold of ≤2.57 ng/ml (sensitivity, 74%; specificity, 75%), and NAF (AUC = 0.90; 95% CI 0.87–0.93), with a threshold of ≤10 follicles (sensitivity, 80%; specificity, 94%).

DISCUSSION

Increases in age are a well-known negative factor influencing the ovarian reserve; other factors affecting this reserve include surgical interventions on the uterus and appendages of the uterus of various forms, such as minimally invasive procedures performed with the use of modern technologies (e.g., cystectomy, ovarian resection, excision and coagulation of pockets of endometriosis, ovariectomy, adnexectomy, salpingectomy, myomectomy). Vascularization of the ovarian tissue with the outcome of sclerosis and fibrosis disrupts the ovarian reserve and reduces functional activity [8, 9]. In this study, decreased NAF, low serum AMH concentrations, and high serum FSH concentrations contributed to an inadequate response of the ovaries to COS.

The results of this study indicated that the gradation of the ovarian response (i.e., the number of oocytes

received) to COS is correlated with the ovarian reserve (i.e., serum concentrations of AMH and NAF), consistent with the findings of other authors [10, 11]. Thus, ovarian reserve indicators prior to stimulation in IVF/ICSI can be considered possible personalized predictors of the number of oocytes received. ROC analysis found that serum AMH concentration (AUC = 0.80), with a threshold of ≤2.57 ng/ml (sensitivity, 74%; specificity, 75%), and NAF (AUC = 0.90), with a threshold of ≤10 follicles (sensitivity, 80%; specificity, 94%), may be predictors of the development of a suboptimal response to COS. Some reports have illustrated the predictive roles of AMH and NAF; however, unlike the results of the present study, previous authors generally focused on the projected risk of developing a weak response or hyperstimulation [11–13]. According to the data obtained in this work, the dose (effective, medium, and total) of rhFSH/hMG drugs for COS is reliably correlated with the ovarian reserve (i.e., serum AMH concentration and NAF) and age of patients. A low ovarian reserve in patients with a suboptimal response to COS could also predict a credible increase in the need for FSH drugs to obtain one oocyte. Clinicians may consider focusing on the age and ovarian reserve indicators of patients and offer a personalized choice of the optimal dose of rhFSH/hMG drugs to obtain a sufficient number of oocytes. Besides a decrease in ovarian reserve, a significant decrease in serum basal pulmonary concentration was found in patients with a suboptimal response to COS. This finding is consistent with previous reports of a negative correlation between serum LH concentration and the projected high risk of a suboptimal ovarian response to COS [6].

While patients with a suboptimal response to COS are able to transfer significantly more embryos, the effectiveness of IVF/ICSI programs in this group was reliably lower than that in women with a normal response. Thus, the incidence of clinical pregnancy was 27.2% versus 41.7%, respectively ($p < 0.01$). These indicators with suboptimal response to COS should be explained due to the inadequate number of obtained and mature oocytes, the presence of bipronuclei zygotes (2PN) and the presence of future developed embryos of good quality. However, chronic inflammatory diseases of the uterus and its appendages, including the effects of artificial and spontaneous abortion, which are more common in women with a suboptimal response than in those with a normal response, may also have a negative impact on the effectiveness of IVF/ICSI programs. Long-term chronic inflammatory processes alter the prescription and implantation activity of the endometrium. Moreover, inflammatory mediators and cytokines may have a direct negative effect on embryos during implantation, which could certainly cause a decrease in the incidence of pregnancy in women with a suboptimal response and a limited number of embryos of good quality [14, 15].

High basal concentrations of serum prolactin and duration of infertility should be considered among the negative factors influencing the effectiveness of IVF/ICSI programs in women with a suboptimal response. Assessment of the role of concomitant organic pelvic diseases reveals that uterine fibroids are an additional factor leading to a decrease in the incidence of clinical pregnancy among women with a suboptimal response to COS. Some researchers believe that women with a limited number of good quality embryos prior to the transfer of uterine fibroids, regardless of the type of localization of the myomatous node, can have a negative impact on the implantation and prolongation of pregnancy due to various associated factors, including deformities of the myometrium and uterine cavity, changes in the structure of the endometrium and myometrium, and changes in the ratio between progesterone and estrogen receptors in the myoma zone and adjacent endometrium [16-18].

CONCLUSION

The effectiveness of IVF/ICSI programs is reliably reduced in women with a suboptimal response to COS compared with women with a normal response. Predictors that could determine the personal risk of a suboptimal response include serum AMH concentration and NAF. Uterine fibroids in patients with a suboptimal response may contribute to a decrease in the effectiveness of IVF/ICSI protocols.

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