

Prediction of a poor ovarian response in assisted reproductive technology programs in patients after surgical interventions on the ovaries

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ABSTRACT

The aim. To conduct a comparative analysis of clinical and anamnestic data in women of reproductive age after ovarian cyst surgery and with occult premature ovarian insufficiency (POI) to predict a poor ovarian response to stimulation.

Materials and methods. We conducted a retrospective study of medical records of women (aged 18–40 years) with infertility at the Assisted Reproductive Technology Center of Siberian State Medical University from 2017 to 2020. The main group consisted of 84 patients who underwent ovarian cyst surgery. The comparison group consisted of 33 patients with biochemical signs of POI (follicle stimulating hormone (FSH) 10–12 mMU / ml) who did not undergo ovarian cyst surgery. Anti-Mullerian hormone (AMH), FSH, estradiol, the antral follicle count (AFC), and the ovarian response to stimulation were compared.

Results. A correlation was established between AFC and a poor ovarian response both in the main group ($r = -0.7$; $p = 0.004$) and in the comparison group ($r = -0.620$; $p = 0.000$) in women under 35 years of age. A correlation was found between the concentration of estradiol and a poor ovarian response in the comparison group in women over 35 years of age ($r = -0.707$; $p = 0.001$). A moderate negative correlation between AMH and a poor ovarian response was revealed only in the main group of women under the age of 35 years ($r = -0.589$; $p = 0.021$). A moderate negative correlation between AMH and a poor ovarian response was revealed in the comparison group in women under the age of 35 years ($r = -0.648$; $p = 0.000$), a weak negative correlation was found for women at the age of 35 years ($r = -0.500$; $p = 0.004$). In both groups, the level of FSH did not determine the ovarian response to stimulation.

Conclusion. The determination of AFC and AMH is more significant in predicting a poor ovarian response in women after ovarian surgery and in women with occult signs of POI under the age of 35 years, compared with FSH. In the group of women over 35 years with occult signs of POI, the concentration of estradiol may matter in predicting a poor ovarian response, which requires further research.

Keywords: poor ovarian response, ovarian surgery, assisted reproductive technologies, ovaries, ovarian reserve

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of funding. The study was supported by the SSMU Competition Commission (minutes of the meeting of 27.06.2022) in accordance with Regulation No. 51 of 16.05.2022 “On Supporting Research Projects carried out by Young Scientists “SibMed.Scholar”.

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at Siberian State Medical University (Protocol No. 9308 of 15.12.2022).

For citation: Dmitrieva M.L., Petrov I.A., Tikhonovskaya O.A., Logvinov S.V., Duma O.M., Kosimova Z.O., Chernyshova M.A., Yuriev S.Y., Timofeeva O.S., Zhdankina A.A., Gerasimov A.V. Prediction of a poor ovarian

response in assisted reproductive technology programs in patients after surgical interventions on the ovaries. *Bulletin of Siberian Medicine*. 2023;22(4):31–38. <https://doi.org/10.20538/1682-0363-2023-4-31-38>.

Прогнозирование «бедного ответа» в программах вспомогательных репродуктивных технологий после оперативных вмешательств на яичниках

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РЕЗЮМЕ

Цель. Провести сравнительный анализ клинико-анамнестических данных у женщин репродуктивного возраста с оперативными вмешательствами на яичниках и с оккультными признаками преждевременной недостаточности яичников (ПНЯ) для прогнозирования «бедного ответа» на стимуляцию.

Материалы и методы. Проведено ретроспективное исследование медицинских карт женщин (18–40 лет) с бесплодием Центра вспомогательных репродуктивных технологий Сибирского государственного медицинского университета с 2017 по 2020 г. Основная группа – 84 пациентки с оперативными вмешательствами на яичниках. Группа сравнения – 33 пациентки с биохимическими признаками ПНЯ (фолликулостимулирующий гормон (ФСГ) 10–12 мМЕ/мл) без оперативного вмешательства на яичниках. Проводилось сравнение антимюллера гормона (АМГ), ФСГ, эстрадиола, количества антральных фолликулов (КАФ), ответ яичников на стимуляцию овуляции.

Результаты. Установлена корреляционная связь между КАФ и «бедным ответом» как в основной группе ($r = -0,7$; $p = 0,004$), так и в группе сравнения ($r = -0,620$; $p = 0,000$) у женщин младше 35 лет. Выявлена корреляционная связь между концентрацией эстрадиола и «бедным ответом» в группе сравнения у женщин старше 35 лет ($r = -0,707$; $p = 0,001$). Отрицательная зависимость средней силы между АМГ и «бедным ответом» выявлена только в основной группе в возрасте младше 35 лет ($r = -0,589$; $p = 0,021$). Средняя отрицательная связь между АМГ и «бедным ответом» выявлена в группе сравнения у женщин в возрасте младше 35 лет ($r = -0,648$; $p = 0,000$), слабая отрицательная взаимосвязь – в возрасте старше 35 лет ($r = -0,500$; $p = 0,004$). В обеих группах уровень ФСГ не предопределял ответ яичников на стимуляцию.

Заключение. Определение КАФ и АМГ являются более значимыми при прогнозировании «бедного ответа» у женщин как с оперированными яичниками, так и у женщин с оккультными признаками ПНЯ в возрасте младше 35 лет по сравнению с ФСГ. В группе с оккультными признаками ПНЯ у женщин старше 35 лет при прогнозировании «бедного ответа», вероятно, имеет значение концентрация эстрадиола, что требует дальнейших исследований.

Ключевые слова: «бедный ответ» яичников, операции на яичниках, вспомогательные репродуктивные технологии, яичники, овариальный резерв

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Проект поддержан конкурсной комиссией СибГМУ (протокол заседания от 27.06.2022) в соответствии с положением от 16.05.2022 № 51 «О поддержке научно-исследовательских проектов, выполняемых молодыми учеными “SibMed.Scholar”».

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом СибГМУ (протокол № 9308 от 15.12.2022).

Для цитирования: Дмитриева М.Л., Петров И.А., Тихоновская О.А., Логвинов С.В., Дума О.М., Косимова З.О., Чернышова М.А., Юрьев С.Ю., Тимофеева О.С., Жданкина А.А., Герасимов А.В. Прогнозирование «бедного ответа» в программах вспомогательных репродуктивных технологий после оперативных вмешательств на яичниках. *Бюллетень сибирской медицины*. 2023;22(4):31–38. <https://doi.org/10.20538/1682-0363-2023-4-31-38>.

INTRODUCTION

Predicting the outcomes of assisted reproductive technologies (ART) is relevant not only for fertility specialists, but also for women with infertility themselves. An accurate diagnosis increases the effectiveness of ART and meets patients' expectations. To accomplish this task, using available clinical and laboratory parameters is reasonable, which will not contradict medical examination guidelines.

According to the Bologna criteria adopted in 2011 by the ESHRE, a poor ovarian response (POR) is a failure of woman's ovaries to respond to the selected stimulation protocol. The diagnosis of POR can be established after at least one cycle of ovulation induction and if at least two of the following three features are present: maternal age > 40 years or risk factors for a poor ovarian response; less than three oocytes retrieved with the standard stimulation protocol; an abnormal ovarian reserve test (antral follicle count (AFC) less than 5–7, anti-Müllerian hormone (AMH) less than 0.7–1.1 ng/ml) [1]. Women at risk of POR are those with clinical and anamnestic signs of diminished ovarian reserve: structural chromosome aberrations and gene mutations that can lead to primary ovarian insufficiency, including Turner syndrome and FMR1 premutation [2]; a history of pelvic inflammatory diseases, including chlamydiosis [3, 4]; cyst or endometrioma removal [5, 6]; past chemotherapy [2, 7].

Thus, while POR is already implied in case of a surgical intervention on the ovaries, predicting POR in women with hypergonadotropism is fairly challenging. Women with infertility due to ovarian aging, sometimes referred to as primary ovarian insufficiency, account for a substantial proportion of patients seeking treatment in ART centers. This group of patients is growing, since a large number of women postpone childbearing until 30–40 years of age, and it is impossible to establish a clear cause in more than a half of them [1].

In addition to the 2011 Bologna criteria of POR, fertility specialists also use the POSEIDON stratification proposed in 2016 for low prognosis patients in ovulation induction. The literature data show a need for further clinical research to confirm the effectiveness of the ESHRE and POSEIDON approaches for better ART outcomes [8].

The aim of this study was to conduct a comparative analysis of clinical and anamnestic data in women of reproductive age after ovarian cyst surgeries and with

occult primary ovarian insufficiency (POI) to predict a poor ovarian response to stimulation.

MATERIALS AND METHODS

A retrospective study included women who underwent infertility treatment in the ART Center of Siberian State Medical University from 2017 to 2020. The main group encompassed women of reproductive age with infertility and past ovarian surgery ($n = 84$). The main group was divided into two subgroups according to age: subgroup 1 – women under 35 years ($n = 51$), subgroup 2 – women aged 35 years and older ($n = 33$). The comparison group consisted of women of reproductive age with infertility and serum follicle-stimulating hormone (FSH) concentration of 10–12 mIU / ml before ovulation stimulation (which is typical of occult POI) ($n = 33$) [9]. The comparison group was also divided into two subgroups: subgroup 1 – women under 35 years ($n = 15$), subgroup 2 – women aged 35 years and older ($n = 18$). The groups were divided by age according to the current understanding of the hormonal function of the ovaries and the size of ovarian reserve, as well as according to the current POSEIDON stratification assessing diminished ovarian reserve [10].

The inclusion criteria were somatically healthy women of reproductive age (18–40 years) with normoprolactinemia and euthyroidism. The exclusion criteria were failure to meet the inclusion criteria; metabolic and endocrine disorders (diabetes mellitus, all classes of obesity); myoma that requires surgical treatment; endometriosis; premalignant and malignant diseases; extragenital diseases accompanied by immune and endocrine disorders; contraindications to *in vitro* fertilization (IVF) according to the order No. 803n of the Ministry of Health of the Russian Federation of 31.07.2020 “On the Procedure for the Use of Assisted Reproductive Technologies, Contraindications, and Restrictions on their Use”.

The women were examined in accordance with the clinical guidelines “Assisted reproductive technologies and artificial insemination” (letter of the Ministry of Health of the Russian Federation of 5.03.2019 No.15-4/I/2-1908, of 05.03.2019 No.15-4/i/2-1908) and medical examination guidelines. The data analysis included the results of the following tests and procedures: 1) clinical procedures: analysis of medical records, study of past medical history, complaints, and physical exam data; 2) routine clinical laboratory tests; 3) diagnostic imaging and procedures:

pelvic ultrasound (AFC), data of past laparoscopic / laparotomic surgery; 4) measurement of serum FSH, luteinizing hormone (LH), estradiol, and AMH levels; 5) number of follicles before a transvaginal puncture, number of oocytes retrieved. In all the cases, multifollicular ovarian stimulation in the IVF program was performed according to the established protocol using gonadotropin-releasing hormone (GnRH) antagonists from day 6 of stimulation.

The obtained findings were processed using SPSS® 26.0 (© SPSS Inc.). The quantitative data were presented as the median and the interquartile range $Me (Q_1-Q_3)$. The significance of the differences was estimated using the nonparametric Kruskal – Wallis test for independent samples. The correlation between the parameters was studied using the Pearson's correlation coefficient χ^2 and the Spearman's rank correlation coefficient. The differences were considered statistically significant at $p \leq 0.05$.

RESULTS

The clinical and anamnestic parameters of the patients with infertility in the main and comparison groups are presented in Table 1. There were no significant differences between the subgroups in the age, body mass index (BMI), age of menarche, history of IVF (the Kruskal – Wallis test; significant differences between the groups were considered at $p < 0.05$).

Significant differences were found in the duration of infertility in women of subgroup 2 of the main group and subgroup 2 of the comparison group, as well as when comparing subgroups 1 and 2 of the comparison group in the context of hypergonadotropism (Table 1).

The median age of the patients was comparable and was 34 (32–36) years. The duration of infertility ranged from 2 to 15 years and equaled to 6 (4–10) years. It was greater in the comparison group, namely, in the women of subgroup 2 (Table 1).

Table 1

Comparative characteristics of clinical and anamnestic data of the examined groups, $Me (Q_1-Q_3)$								
Parameter	Main group		*p, subgroups of the main group	Comparison group		*p, subgroups of the comparison group	*p, subgroups 1 of the main group and comparison group	*p, subgroups 2 of the main group and comparison group
	Subgroup 1, $n = 51$	Subgroup 2, $n = 33$		Subgroup 1, $n = 15$	Subgroup 2, $n = 18$			
Age, years	32.0 (29.0–34.0)	36.0 (35.0–37.0)	<0.001*	33.0 (32.0–34.0)	38.0 (36.0–39.0)	<0.001*	0.100	0.060
BMI, kg / m ²	23.4 (20.5–27.5)	25.8 (21.8–31.4)	0.092	23.8 (22.2–25.7)	21.1 (19.8–24.9)	0.190	0.789	0.060
Age of menarche, years	13.0 (12.0–14.0)	13.0 (12.0–14.0)	0.432	13.0 (12.0–14.0)	14.0 (13.0–14.0)	0.325	0.524	0.282
Duration of infertility, years	6.0 (4.0–8.0)	6.0 (2.5–10.0)	0.928	4.0 (2.0–8.0)	10.5 (3.5–15.3)	0.008*	0.105	0.045*
Past IVF	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.742	2.0 (1.0–3.0)	1.5 (1.0–2.0)	0.656	0.462	0.957

Here and in Table 2: * Kruskal – Wallis test; the differences between the groups are significant at $p < 0.05$.

Past surgical interventions on the ovaries in the patients of the main group were performed for the following indications: ovarian apoplexy – 39 cases (46.45%), of which in 13 cases (33.33%), the affected ovarian tissue was sutured, while in 26 cases (66.67%), the ovary was resected; ovarian cystectomy due to a complicated follicular cyst on the ovary (hemorrhage, rupture) – 26 cases (30.95%); ovarian cystectomy due to a complicated corpus luteum cyst (hemorrhage, rupture) – 9 cases (10.71%); ovarian cystectomy due to benign ovarian tumors – 10 cases (11.9%) (serous cystadenoma (4), dermoid cyst (3), fibroma (3)). Four women underwent recurrent surgery: 1 – for ovarian fibroma, 2 – for a complicated follicular cyst, 1 – for ovarian apoplexy. Thus, surgical treatment was predominantly done via laparoscopy using organ-

preserving techniques. A comparative analysis of the indications for ovarian surgery in the subgroups of the main group did not reveal any significant differences.

The data in Table 2 demonstrate that the level of FSH was predictably higher in women aged 35 years and older in both groups; a significant difference was identified in the estradiol levels in women aged 35 years and older compared to the women under 35 years in the main group.

Moreover, there were no significant differences in the AFC ($p > 0.05$). The number of oocytes retrieved showed no significant differences either ($p > 0.05$).

All the patients underwent multifollicular ovarian stimulation in the IVF program according to the established protocol using GnRH antagonists from day 6 of the stimulation.

Table 2

Characteristics of hormonal status and antral follicle count of the examined women with infertility before ovarian stimulation in IVF programs, $Me(Q_1-Q_3)$

Parameter	Main group		p^*	Comparison group		p^*	*p subgroups 1 of the main group and comparison group	*p subgroups 2 of the main group and comparison group
	Subgroup 1, $n = 51$	Subgroup 2, $n = 33$		Subgroup 1, $n = 15$	Subgroup 2, $n = 18$			
FSH, mIU / ml	6.7 (5.8–8.9)	8.5 (6.7–12.2)	0.039*	10.4 (10.1–10.9)	11.1 (10.3–11.6)	0.100	<0.001*	0.004*
LH, mIU / ml	5.1 (3.6–6.9)	4.7 (3.2–6.4)	0.166	5.4 (4.6–8.0)	5.9 (4.7–8.3)	0.708	0.375	0.013*
Estradiol, pmol / l	80.0 (36.7–164.8)	221.0 (105.0–351.0)	<0.001*	108.0 (67.1–179.1)	138.4 (65.9–226.0)	0.911	0.163	0.067
AMH, ng / ml	1.47 (0.66–3.82)	1.34 (0.57–2.22)	0.463	0.69 (0.46–4.73)	1.3 (0.66–1.79)	0.762	0.447	0.754
AFC	9.5 (4.0–14.0)	7.0 (3.5–13.5)	0.637	9.0 (4.8–14.0)	6.0 (5.0–15.0)	0.866	0.851	0.600
Oocytes	5.0 (2.0–9.5)	4.0 (2.0–8.5)	0.761	3.0 (1.0–10.0)	3.0 (2.0–5.0)	0.735	0.708	0.225

In the main group, a poor ovarian response accounted for 39.3% of cases and was distributed in the following way: 40.8% in subgroup 1 and 39.4% in subgroup 2 ($p = 0.465$, $\chi^2 = 0.533$). In the comparison group, a poor ovarian response occurred in 57.6 % of cases. In patients under 35 years, a poor ovarian response to stimulation was recorded in 53.3% of cases; in women over 35 years, it was detected in 58.8% of cases ($p = 0.782$, $\chi^2 = 0.077$). In subgroup 2 of the main group, a poor ovarian response to stimulation occurred less often than in subgroup 2 of the comparison group ($p = 0.000$, $\chi^2 = 0.486$).

A subsequent correlation analysis revealed a phenomenon that had not previously been described by other researchers: a moderate negative correlation between AFC and a poor ovarian response in women under 35 years in the main group ($r = -0.7$, $p = 0.004$) and in the comparison group ($r = -0.620$, $p = 0.001$). Such correlation was not established in the main group of women older than 35 years ($r = -0.034$, $p = 0.894$). Only a weak negative linear relationship was found in the comparison group in women over 35 years ($r = -0.372$, $p = 0.033$). This fact suggests that it is possible to estimate the expected response to stimulation based on AFC only in the age group under 35 years.

No correlation was detected between the FSH concentration and a poor ovarian response in the subgroups of the main group ($r = 0.295$, $p = 0.042$; $r = 0.072$, $p = 0.692$) and in the subgroups of the comparison group ($r = 0.124$, $p = 0.659$; $r = 0.363$; $p = 0.139$).

The investigation of the relationship between a poor ovarian response to stimulation and the AMH concentration revealed a moderate negative correlation

($r = -0.648$, $p = 0.000$) in women younger than 35 years and a weak negative correlation ($r = -0.500$, $p = 0.004$) in women older than 35 years in the main group. In the comparison group, there was a weak negative correlation between a poor ovarian response to stimulation and the AMH concentration in women younger than 35 years ($r = -0.589$, $p = 0.021$) and no correlation in women over 35 years ($r = 0.154$, $p = 0.542$).

Interestingly, a positive correlation was established between the concentration of estradiol and a poor ovarian response in the comparison group in women over 35 years of age ($r = -0.707$, $p = 0.001$). However, such correlation was not found in the other subgroups ($p > 0.05$).

DISCUSSION

The review by Q.H.Y. Wong and R.A. Anderson (2018) presents studies estimating changes in the ovarian reserve marker, AMH, before and after gonadotoxic treatment [11]. Ovarian reserve was reported to decrease after cystectomy, which resulted in lower concentrations of AMH [12, 13]. The main mechanism through which ovaries are damaged during a surgical intervention (thus, the ovarian reserve is diminished) is believed to be excision of contact ovarian tissue by employing surgical energy devices [14]. Two systematic reviews and a meta-analysis demonstrated that the use of bipolar electrocoagulation is associated with a considerable decrease in the AMH level compared to non-thermal hemostasis techniques, including sutures or application of a hemostatic sealant [15, 16].

It is worth noting that most studies did not find a correlation between a reduced AMH concentration

and the size of retention cysts [17–20]. However, patients with follicular and endometrial cysts exhibited a significant decrease in the AMH level within 6 months after surgical treatment. It was also established that surgical removal of dermoid cysts and true ovarian neoplasms (including serous tumors) did not significantly change the AMH concentration [21].

According to the data of the conducted retrospective study, a poor ovarian response accounted for 39.3% in the main group and 57.6% in the comparison group. Yet, when dividing the groups according to the Bologna criteria and the POSEIDON stratification, no statistical significance was revealed. In this research, when the groups were stratified according to the POSEIDON classification, the risk of a poor ovarian response was higher in women under 35 years who underwent ovarian surgery than in women over 35 years, which is confirmed by the correlations obtained.

Thus, a correlation was detected between the AFC and a poor ovarian response in women under 35 years in the main and comparison groups. The study also found a correlation between the AMH concentration and a poor ovarian response in the main group in women under 35 years, which was not observed in patients over 35 years. In the comparison group, there was a moderate negative correlation between the AMH levels and a poor ovarian response only for women under 35 years, while for the subgroup of women over 35 years, the correlation was weak.

This research revealed that the FSH concentration was not associated with a poor ovarian response to stimulation in ART programs in women with a past surgical intervention on the ovaries, which is inconsistent with the previously published data. S. Salama et al. (2021) found that the basal FSH level in women under 35 years correlated more with the number of follicles and number of oocytes retrieved, which, in turn, determined the pregnancy rate [22]. G. Sahin et al. (2021) reported that at the concentration of $\text{FSH} \geq 10 \text{ IU/l}$, the frequency of pregnancy and live birth in younger women was higher despite elevated FSH levels [23].

Further research on the prediction of a poor ovarian response might explore the estradiol

concentration that also displays a correlation in the analysis of the data from the comparison group of women aged 35 years and older with infertility and potential hypergonadotropism.

CONCLUSION

The findings indicate that AFC and AMH were significant markers for women under 35 years in both examined groups. The FSH level is not the main predictor of a poor ovarian response. In the group of women aged 35 years and older with potential hypergonadotropism, the estradiol level can serve as a predictor of a poor ovarian response. Further research with a greater sample size should be carried out to establish the significance of known and potential markers of a poor ovarian response in women after ovarian surgeries and occult primary ovarian insufficiency. This will allow to develop a predictive mathematical model using logistic regression.

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Received 09.01.2023;
approved after peer review 17.04.2023;
accepted 25.05.2023