

# The Study of Clinical, Anamnestic, and Hormonal Parameters in Patients with Infertility Prior to Assisted Reproductive Technology (ART) Protocols

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**Abstract** Consequently, infertility treatments should be seen as a means to ensure the birth of desired children and to increase the overall reproductive capacity of the population. The most significant and essential stage in the management of infertility is the development and implementation of assisted reproductive technologies (ART) in clinical practice. These techniques enable the realization of childbearing in forms of infertility that previously were considered absolutely intractable: the absence or complete blockage of the fallopian tubes, and the absence or premature depletion of ovaries.

**Keywords** Assisted reproductive technologies, In vitro fertilization, Ovarian stimulation protocols, Recombinant gonadotropins, Gonadoliberein agonists or antagonists

## 1. Introduction

The problems of preserving and restoring reproductive health are far from being completely solved and are a major medical concern of national significance [1,2]. Currently, approximately 10% of married couples in Europe, 8-15% in the United States, and around 17% in Canada are unable to conceive [7,9]. In our country, the prevalence of infertility ranges from 8% to 17.8%, with some regions exceeding the critical threshold of 15%, as defined by the World Health Organization (WHO), where infertility can significantly impact demographic indicators and represent a significant public health concern [8]. Consequently, infertility treatments should be seen as a means to ensure the birth of desired children and to increase the overall reproductive capacity of the population.

The most significant and essential stage in the management of infertility is the development and implementation of assisted reproductive technologies (ART) in clinical practice. These techniques enable the realization of childbearing in forms of infertility that previously were considered absolutely intractable: the absence or complete blockage of the fallopian tubes, and the absence or premature depletion of ovaries.

Today, ART encompasses all types of treatment for infertility based on in vitro fertilization (IVF), including the use of donor gametes and embryos, surrogacy, freezing of gametes and embryos, and micromanipulation techniques such as intracytoplasmic sperm injection (ICSI), preimplantation

genetic diagnosis (PGD), and assisted hatching [6,9].

Ovarian function stimulation forms the basis of assisted reproductive programs, as it determines the ovarian response to ovulation induction: the number of follicles that grow, the quantity and quality of eggs produced, and the cultured embryos.

The use of exogenous luteinizing hormone (LH) and the choice between urinary and recombinant LH-containing gonadotropin during the stimulated cycle are important aspects of modern reproductive medicine, which have been the focus of our research.

**The purpose of the study** – optimize ovarian stimulation protocols in ART programs using recombinant gonadotropins in patients with a history of unsuccessful IVF attempts.

## 2. Materials and Methods

257 women receiving infertility treatment in IVF programs at the Department of Assisted Reproductive Technologies at the Eramed Clinic from May 2021 to May 2023 were examined.

The criteria for inclusion in the study were:

reproductive age  $\geq 30$  and  $\leq 45$  years at the time of inclusion in the study;

absence of severe somatic pathology;

ineffectiveness of previously performed infertility therapy: assisted reproductive technologies, reconstructive plastic surgery on the ovaries and fallopian tubes, hormone therapy;

The concentration of functional spermatozoa (CFS) is more than 30%.

All patients were comparable in age and diagnosis; all had no contraindications for ovulation stimulation in IVF programs or for pregnancy. All patients gave voluntary informed consent to participate in the study.

The assessment of clinical and anamnestic data, clinical and laboratory parameters, indicators of the embryological stage, and the results of instrumental research methods was carried out in the compared groups. The groups were formed in 2 stages. At the first stage, depending on the inducer used during stimulation, at the second stage, depending on the addition of gonadoliberein agonists or antagonists.

The examination of patients from all groups was carried out in several stages. At the first stage, the compared groups were formed depending on the ovulation stimulation protocol used to assess the initial clinical and anamnestic, clinical and laboratory data, and the outcomes of previous infertility treatment methods. At the second stage, a comparative analysis of the indicators of the induced cycle and its effectiveness was carried out, depending on the applied stimulation protocol. At the third stage, the hormonal profile of follicular fluid and peripheral blood was analyzed, the correlation between them and with indicators of follicular and oogenesis. At the fourth stage, recommendations were developed on the choice of an individual ovulation stimulation protocol, which helps to increase the effectiveness of IVF.

The study protocols carefully evaluated obstetric and gynecological and andrological anamnesis, objective examination data (general somatic and gynecological), laboratory and instrumental (ultrasound) examination methods. Endometriosis, uterine fibroids with a node size of more than 2 cm in diameter, neoplasms of the reproductive system, pituitary gland, large ovarian cysts, malformations of the uterus, and the male factor were excluded in all examined patients.

During the induced cycle, stimulation patterns, average initial and course doses of gonadotropins, duration of stimulation, hormonal and ultrasound dynamic monitoring of follicle and endometrial growth were taken into account.

The concentration of hormones in the blood serum was determined using immunochemiluminescent test systems from Siemens Healthcare Diagnostics Inc. (USA) on an automatic Immulite 2000 analyzer from the same company. AMH analysis was performed using enzyme-linked solid-phase immunoassay (Beckman Coulter MIS/AMH ELISA, USA) based on the principle of enzyme-enhanced "two-stage" sandwich immunoassay.

The basal serum concentrations of FSH, LH, E2, and AMH in all the studied patients were determined by sampling blood from the ulnar vein on day 2-3 of the menstrual cycle. The basal values of blood progesterone were evaluated in the second phase of the previous natural cycle.

For the purpose of dynamic hormonal monitoring of the induced cycle, serum concentrations of FSH, LH, E2, P and AMH were determined in 55 patients in groups 1 and 2 by blood collection on the 5th-7th day of stimulation when the leading follicle reached 14 mm (on the day of the GnRH antagonist start) and on the day of transvaginal puncture. In the same patients, concentrations of FSH, LH, E2, P and

AMH in the follicular fluid were determined on the day of oocyte collection.

Ultrasound examination of the pelvic organs was performed on the 2nd-3rd day of spontaneous menstruation or a menstrual-like reaction (on the first day of ovulation stimulation) on a Sonoline Sienna device (Siemens, Germany) using a transvaginal sensor with a frequency of 6.5 MHz.

When 3 or more follicles with a diameter of > 17 mm were reached, the ovulation trigger chorionic gonadotropin was administered, the dose of which was 5,000-10,000 units. After 35-36 hours, a transvaginal puncture of the follicles was performed under aseptic conditions under intravenous anesthesia under ultrasound control, followed by an embryological stage.

Follicular fluid was collected, and after determining the presence or absence of an oocyte in it, it was centrifuged for 10 minutes at 1,000 rpm in order to purify it from blood elements. Subsequently, concentrations of FSH, LH, E2, P, and AMH were determined in the VF.

Statistical data processing was performed on an individual computer using Microsoft Excel spreadsheets and the Statistica for Windows v.6.1 application software package, StatSoft Inc. (USA).

### 3. Results and Discussion

257 patients with tubo-peritoneal infertility undergoing IVF treatment were examined, of which 81 (31.5%) had primary infertility, 176 (68.5%) had secondary infertility. The average duration of infertility was  $8.4 \pm 4.7$  years. All patients were shown an IVF program.

The age of the patients ranged from 30 to 45 years, which averaged  $35.7 \pm 3.8$  years and corresponded to the late reproductive age (35 years and older).

The average age of menarche was  $13.3 \pm 1.3$  years (from 10 to 17 years), the average duration of the menstrual cycle was  $28.6 \pm 5.5$  days (from 21 to 45 days), which corresponded to these indicators in the general population.

The most common types of menstrual disorders in the studied patients were menorrhagia and algomenorrhea (17.3% and 25.0%, respectively), which characterize the clinical picture of pelvic inflammatory diseases.

At the time of joining the IVF program, the patients' physical health was considered normal. In the presence of chronic extragenital pathology, stable remission or a compensated condition was noted, hemostasis, clinical and biochemical blood tests were within the normal range.

Analysis of the structure of extragenital pathology of the studied patients showed that every 5th of the studied patients had thyroid pathology - 15.4%. The main diagnosis was endemic goiter (90%), which was explained by iodine deficiency in our country.

Gynecological diseases in the study group of patients were cured, did not violate the health status of women, or required only follow-up.

Pelvic inflammatory diseases prevailed in the structure of gynecological diseases, which determined the presence of

tubo-peritoneal infertility in the studied patients.

Surgical interventions on the ovaries were performed in 48 patients (14.8%), of them for cysts in 34 (70.8%), for apoplexy in 14 (29.2%) cases. Reconstructive plastic surgery on the tubes was performed in 156 patients (48.1%), of which 118 (75.6%) had ectopic pregnancies, and 38 (24.4%) had pio-, sacto-, and hydrosalpinxes. The adhesive process of the small pelvis during surgical interventions was registered in 155 patients (47.8%). It should be noted that spontaneous pregnancy after reconstructive plastic surgery was observed in only 5 patients (1.5%).

Based on the presented data, it can be concluded that previous reconstructive plastic surgery on the pelvic organs has little prospect for the spontaneous realization of reproductive function. An analysis of the reproductive function of the patients included in the study group showed that 220 women (67.9%) had a history of independent pregnancies, and 16 patients (4.9%) after IVF. 85 patients (26.2%) became pregnant with an emergency delivery, and 12 (3.7%) became pregnant prematurely. Early spontaneous miscarriage (before 12 weeks) occurred in 54 women (16.7%). 110 patients (34.0%) had a history of induced abortions. Ectopic pregnancy was diagnosed in 118 cases (36.4%). The average basal level of blood hormones in the studied patients ( $n=324$ ) was within the standard values. The average values of FSH and AMH were within the normal range and fit into the parameters of fertile women, the average number of antral follicles corresponded to a low ovarian reserve ( $6.3 \pm 3.3$ ), less than 5-7 follicles in both ovaries.

## 4. Conclusions

The analysis of clinical and anamnestic data, hormonal and ultrasound examinations showed that the patients of the study group were more likely to be of late reproductive age, with tubo-peritoneal infertility factor, low ovarian reserve, with a predominance of pelvic inflammatory diseases and unsuccessful IVF attempts in the anamnesis.

It was found that in tubal infertility, the largest number of mature oocytes ( $13.3 \pm 1.2$ ) was obtained by superovulation induction according to the protocol using a gonadotropin-releasing hormone antagonist. In the control group with male infertility factor, the number of mature oocytes in patients

who received pregnancy was higher ( $10.9 \pm 1.9$ ) compared with the group with tubal infertility ( $6.7 \pm 0.6$ ).

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