

## ENGLISH VERSION: CLINICAL FINDINGS ON TREATMENT AND REHABILITATION OF PATIENTS WITH INFERTILITY CAUSED BY INFLAMMATORY DISEASES OF THE UTERINE APPENDAGES\*

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*The aim of the clinical study was to develop a complex of treatment and rehabilitation of the reproductive function in women with tubal-peritoneal infertility using radiowaves energy during laparoscopic treatment, intraoperative prevention of adhesion with the use of an antiadhesion gel of derivative carbomethylcellulose and a complex of physiotherapy in the postoperative period. Materials and methods: the clinical study was performed in 96 women with tubal-peritoneal infertility of inflammatory genesis, which included laparoscopic treatment and rehabilitation in the postoperative period. The results of our proposed clinical study allowed us to reduce the average blood loss during the operation, the duration of the postoperative bed day, the need for the prescription of analgesic and antibacterial drugs. The proposed method of treatment and rehabilitation of women with tubal-peritoneal infertility allowed us to increase the percentage of restoration of uterine tubes patency, the onset of uterine pregnancy, to reduce the risk of an ectopic pregnancy and reocclusion of the fallopian tubes.*

**Key words:** tubal-peritoneal infertility of inflammatory genesis, adhesive process, radio-wave energy, antiadhesion barrier, rehabilitation in the postoperative period.

### Introduction

An important and socially significant problem in Ukraine is the problem of infertility in marriage, which afflicts more than 1 million couples, which affects the birth rate and natural population growth. In the structure of female infertility, the main role belongs to the tubal-peritoneal infertility (TPI) which fluctuates within 30-75% [7]. In primary infertility, the incidence of fallopian tubes lesion is 29.5-70%, in secondary infertility – 42-83% [1]. The main cause of the tubal-peritoneal infertility is the transient inflammatory diseases of the pelvic organs due to various infections that lead to complete or partial obstruction of tubes due to irreversible damage to the cylindrical epithelium of the fallopian tubes, obliteration of the walls, infiltration, inflammation caused by peritubal and ovary fusion [4, 13]. After a single episode of salpingitis, uterine tube obstruction occurs in 11-13%, after a double – in 23-36%, with three or more exacerbations – in 54-75% of cases [9]. In 27% of patients with TPI in laparoscopy revealed adhesive process II-III degree of prevalence [2]. In 43% of women who have suffered from inflammatory diseases of the uterine appendages, complete obstruction of the fallopian tubes is observed, and in 49% of cases it is partial [10]. The irregularities that occur after the primary inflammatory lesion of the fallopian tubes disrupt the mechanisms of the ovum pick-up and transport.

### Substantiation for the study

Taking into account the statistical data on the efficacy of tubal-peritoneal infertility surgical treatment [11, 12] with the use of drugs for prevention of adhesive disease [6] further research and a selective approach to the use of the most effective drugs with anti-adhesive properties are needed to improve the results of prevention of adhesion and rehabilitation of reproductive function of women. The aim of the research is development of comprehensive treatment and rehabilitation of reproductive function in women with tubal-peritoneal infertility, using radio-waves energy in the laparoscopic treatment, intraoperative prophylaxis with antiadhesion gel, derivatives of car-

bomethylcellulose and a complex of physiotherapy in the postoperative period.

### Materials and methods

Clinical material for the study was data elicited during examination and treatment, data from catamnesis of 96 patients with tubal-peritoneal infertility of inflammatory genesis of the uterus and 30 gynecological and somatically healthy non-pregnant women of childbearing age taken for monitoring. All patients who took part in the study were treated at the clinical basis of the department of obstetrics and gynecology No.2 of Kharkiv Medical Academy of Postgraduate Education in the hospital "M. H. Gelferikh City Clinical Maternity Hospital No.2 of Kharkiv". All women signed the informed consent to participate in the study.

To address our goals and objectives, we examined 126 patients. All 96 patients with of tubal-peritoneal infertility of inflammatory genesis before the operative treatment were standardized in outpatient settings in accordance with the Order of the Ministry of Public Health of Ukraine No. 417 as of July 15, 2011 (clinical, biochemical analyses, coagulogram, blood group, RW, VID (by consent), vaginal discharge analysis, sexually transmitted infections, colposcopy, ECG, ultrasound, doppler method, MSG, hormonal background study, blood serum test for IL-1, IL-6, TGF- $\beta$ , fibronectin, consultation of a therapist, etc.) [8]. From the group of women with tubal-peritoneal infertility we excluded patients with other forms of infertility, exacerbation of the inflammatory process, severe extragenital pathology, and also excluded the male factor infertility. Women were divided into three groups: comparison group – 30 gynecological and somatically healthy non-pregnant women of reproductive age;

1 – study group – 48 patients with tubal-peritoneal infertility of inflammatory genesis, who underwent usual methods of treatment and rehabilitation, which included: laparoscopy with the use of diathermic energy, with washing of the abdominal cavity heated to 37° C with 0.9% sodium chloride solution in volume 200-300 ml,

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dexamethasone solution 4 mg, artificial ascites creation with sodium chloride solution 0.9% in volume 200-300 ml; active mode of behavior from the first day of the postoperative period.

2 – study group – 48 patients with tubal-peritoneal infertility of inflammatory genesis, who underwent our program of treatment and rehabilitation, which included: laparoscopy with the use of radiowaves energy, intraoperative introduction of the antiadhesion barrier derivative of carboxymethylcellulose, and developed program of rehabilitation. Later on, from the second day, women of the 2nd study group were prescribed rectal suppositories for 9 days – a combination of streptokinase and streptodornase according to the scheme: days 1-3 – 1 suppository 3 times a day, days 4-6 – 1 suppository 2 times a day, days 7-9 – 1 suppository 1 time a day. In addition, the complex of physiotherapy suggested by us was carried out: ultrasound in pulsed mode on the lower abdomen with a power of 0.5 W / cm<sup>2</sup> for 10 minutes duration followed by intrauterine electrophoresis of the hyaluronidase enzyme № 10 on dermatoparabic technique by force of current m 10-15 mA for 20 minutes, one day from the second day of the postoperative period. The procedures were supplemented by uterine tube stimulation sessions using V.M. Strugatsky's (2005) technique for 20 days for 5 minutes using the Endoton-01B apparatus (Bulgaria) in the vaginal and sacral technique from the sixth day of the postoperative period.

### Results and discussion

The average age of women in the 1st study group was 32.5 ± 3.9 years, in the second study group – 32 ± 4.8 years, in the comparison group – 30.4 ± 6.3 years. All women with tubal-peritoneal infertility complained of infertility. 7 (14.6%) women suffered from primary infertility, 9 (18.7%) with primary infertility for more than 5 years, 12 (25.0%) with secondary infertility for 5 years, 25 (5%) with secondary infertility, 20 (41.7%) patients for more than 5 years. That is, the indicator of primary infertility of more than 5 years of duration, and secondary infertility of more than 5 years, is determined to be by 1.5 times higher than that of primary infertility and secondary duration of up to 5 years. All women with of tubal-peritoneal infertility of inflammatory genesis had in history the inflammatory

diseases of the uterus – 96 (100%), of which up to 5 years – 24 (25%), and more than 5 years – 72 (75%).

In the clinical and laboratory examination of 96 women with TPI of inflammatory genesis, no changes were found. During ultrasound examination and in determining the average size of the uterus and appendages, no probable changes in comparison group were detected. In women with TPI, we revealed a number of structural changes in reproductive organs: in 18 (18.75%) hydrosalpinges with the thickness of the fallopian tube not more than 5 mm, the presence of follicular ovarian cysts in 2 (2.1%) women. In the majority of women with TPI – 27 (28.1%) – ultrasound signs of adhesive process in the form of hyperechoic linear formations and in 43 (44.8%) women in the form of restriction in case of ovarian displacement were revealed [3]. On dopplerometry, the decrease of blood supply to the walls of the fallopian tubes was observed, while the index of resistance in the uterine arteries exceeded 0.62 ± 0.06 (as contrasted with the comparison group 0.46 ± 0.02) at p < 0.05.

In order to determine the state of the cavity of the uterus and fallopian tubes, 96 patients with TPI underwent metrosalpingography (MSG) using contrasting water-soluble drugs (triombrast – 76%) on 7-11 days of the menstrual cycle, as well as the comparison of the effectiveness of MSG to chromosalpingography (CSG) at the beginning of the laparoscopic surgery. The obstruction of both (or single) fallopian tubes was detected on MSG in 77 and 79.2%, respectively, in women of the 1st and 2nd clinical groups, and obstruction of CSG 62.5% and 64.6% respectively. Also, during laparoscopic examination, patients from the 1st and 2nd clinical groups presented coarse peritubal adhesions, loop-shaped edema of the fallopian tubes, retraction of the terminal regions of the fallopian tubes, partial penetration of the contrast medium into the limited cavities of the one (single) with the obstruction of the second uterine tube, which they deformed, and possibly disrupted their transport function. These parameters indicate a greater diagnostic informativeness of laparoscopy than MSG.

Indicators that we used to assess the presence of the adhesive process in women in the comparison group, 1st and 2nd clinical groups prior to surgery are presented in Table 1.

Table 1  
Indicators of the level of fibronectin, TGF-β, IL-1, IL-6 in women of comparison group, 1st and 2nd clinical groups prior to surgery

Indicator	Comparison group (n=30)	1st clinical group (n=48)	2nd clinical group (n=48)
		before surgery	before surgery
fibronectin, mcg/ml	324±8.5	461.7±7.8 p<0.05	461.4±7.7 p<0.05
TGF-β mcg/ml	10.79±1.56	23.5±2.42 p<0.05	26.98±2.2 p<0.05
IL-1b pg/ml	15.81±2.08	44.35±2.4 p<0.05	50.88±2.59 p<0.05
IL-6 pg/ml	17.62±1.5	60.99±3.29 p<0.05	65.42±3.43 p<0.05

Note: p – probability of difference of indicators as contrasted with the comparison group.

As it can be seen from Table 1, the level of incidence of fibronectin, TGF – β, IL – 1, IL – 6 in the serum of women of the 1st and 2nd clinical groups before surgery as contrasted with the comparison group women was increased by almost 3 times, which was statistically significant (p < 0.05).

During the laparoscopic intervention, the degree of adhesive process according to the classification of the American Society for Fertility (1988) [2] was assessed.

Patients of the 1st clinical group during the laparoscopy revealed the following results: I. – 17 (35.4%), II. – 10 (20.8%), III. – 7 (14.6%), IV. – 14 (29.2%). In patients of the 2nd clinical group during laparoscopy, the following was revealed: I. – 9 (18.75%), II. – 14 (29.1%), III. – 8 (16.6%), IV. – 17 (35.4%).

All 96 women with tubal-peritoneal infertility of inflammatory genesis underwent operative treatment, which included (Table 2):

Table 2  
Types of surgical intervention during laparoscopy

	1 <sup>st</sup> clinical group (n=48)	2 <sup>nd</sup> clinical group (n=48)
Salpingolysis	12 (25%)	6 (12.5%)
Salpingolysis, ovariolysis	14 (29.2%)	15 (31.2%)
Salpingolysis, fimbrioplastic of either uterine tube	3 (6.3%)	8 (16.7%)
Salpingolysis, ovariolysis with salpingotomy of both or one uterine tube	19 (39.6%)	19 (39.6%)
Total	48 (100%)	48 (100%)

In the postoperative period, we compared the duration of antibiotic therapy, the need for pain relievers,

postoperative bed / day and average blood loss during surgical intervention. Data are presented in Table 3

Table 3  
Comparison of duration of antibiotic therapy, prescription of analgesic therapy, postoperative bed-days and average blood loss in women in the 1st and 2nd clinical groups

Indicator	1 <sup>st</sup> clinical group (n=48)	2 <sup>nd</sup> clinical group (n=48)
Duration of antibiotic therapy (days)	4.94±1.04	4.08±1.3 p<0.05
Duration of anesthetic prescription (days)	2.56±0.74	1.25±0.48 p<0.05
Duration of postoperative bed-days	4.94±1.04	3.88±1.09 p<0.05
Average blood loss during surgery (ml)	42.29±26.36	31.88±17.09 p<0.05

Note: p – the probability of differences in the rates of women in the 2nd clinical as compared with women in the 1st clinical group.

When applying the minimum power of radiowaves, reducing the area of influence of tissue damage – the optimal coagulation effect is maintained, which reduces the average blood loss during the operation by almost 1.3 times. In the postoperative period, the average duration of antibiotic therapy in women of the 2nd clinical group was 4.08 ± 1.3 days, the need for anesthetic preparations was 1.25 ± 0.48 days, and the duration of postoperative bed-days was 3.88 ± 1.09 days (p <0.05) as compared

with the 1st clinical group in patients of the 2nd clinical group, the duration of antibiotic therapy has been statistically significantly reduced, the need for anesthetic preparations and the duration of the postoperative bed-days decreased, which in our opinion are the advantages of using radiowaves during surgical intervention.

Indicators for the level of fibronectin, TGF-β, IL-1, IL-6 in women in the comparison group, 1st and 2nd clinical groups before and after surgery are presented in Table 4.

Table 4  
Indicators of fibronectin, TGF-β, IL-1 and IL-6 levels in women of the comparison, 1st and 2nd clinical groups before and after 7 days of surgery

Indicator	Comparison group (n=30)	1st clinical group (n=48)		2nd clinical group (n=48)	
		before surgery	after surgery	before surgery	after surgery
fibronectin, mcg/ml	324±8.5	461.7±7.8 p<0.05	427.3±18.8 p<0.05 p1<0.05	461.4±7.7 p<0.05	397.9±22.4 p<0.05 p1<0.05
TGF-β mcg/ml	10.79±1.56	23.5±2.42 p<0.05	19.04±1.92 p<0.05 p1<0.05	26.98±2.2 p<0.05	17±1.56 p<0.05 p1<0.05
IL-1b pg/ml	15.81±2.08	44.35±2.4 p<0.05	27.14±3.96 p<0.05 p1<0.05	50.88±2.59 p<0.05	21.38±3.91 p>0.05 p1<0.05
IL-6 pg/ml	17.62±1.5	60.99±3.29 p<0.05	38.47±5.67 p<0.05 p1<0.05	65.42±3.43 p<0.05	31.29±4.71 p<0.05 p1<0.05

As can be seen from the data in Table 4, the rates for surgical treatment were elevated (p <0.05) almost by 3 times in women of the 1st and 2nd clinical groups as contrasted with the comparison group of women. After conducting the operative treatment, the indicators of TGF, IL-1, IL-6, fibronectin in comparison with preoperative data statistically showed a significant decrease (p <0.05) by 2 times. However, all indicators were somewhat elevated (statistically significant) as contrasted with the comparison group, that is, healthy women. Comparison of women in the 1st and 2nd clinical groups revealed a more significant decrease in these parameters in women of the 2nd clinical group.

The catamnesis of 31 patients of the 1st clinical group and 38 patients of the 2nd clinical group was studied 1 year after the end of rehabilitation therapy. The criteria for the effectiveness of treatment of infertility were indicators of ultrasound, doppler method, MSG, and pregnancy.

Discussion of results. When comparing the results of MSG after 3 months after the operation with the data of CSG at the end of the operation, it was found that the fallopian tubes recovered during the operation remained passable in almost all women from 25 to 96.1% of the 2nd clinical group, except for 1 woman. At the same time, in women of the 1st clinical group, in only 12 women (38.7%) fallopian tubes remained passable.

Indicators of the onset of uterine and tubal pregnancy in patients of the 2nd clinical group were compared with the fertility indices of 30 healthy women in the comparison and 1st clinical group: pregnancy occurred in 18 (47.4%) patients of the 2nd clinical group, including the uterine – in 15 women (39.5%), and tubal in 3 (7.9%) patients from 38 women who were taken for further treatment. According to the literature, the incidence of pregnancy after reconstructive and plastic operations performed even by laparoscopic access does not exceed 21-28%. When comparing the rates in women of the 1st clinical group and the 2nd clinical group, the onset of

pregnancy in patients of the 2nd clinical group was by 1.6 times higher than in patients of the 1st clinical group. Furthermore, in women of the 1st the clinical group the onset of ectopic pregnancy reduced by 1.6 times, as well as the restoration of fallopian tubes was by 2.5 times higher in patients of the 2nd clinical group than in women of the 1st clinical group, as confirmed by the data of metrorrhagia 3 months after the operation.

Conclusions. The application of the proposed method of surgical treatment using radiowaves, intraoperative prevention of adhesion using an antiadhesive gel of derivative carbomethylcellulose and a complex of early phased rehabilitation led to a decrease in the markers of adhesive process (fibronectin, IL-1b, IL-6, TFR-β) almost 2-fold, decrease postoperative bed / day by 1.3 times, reduction of the necessity of the duration of analgesic and antibacterial preparations in the early postoperative period by almost 1.5 times, increased the percentage of FT permeability, reduced the risk of an ectopic pregnancy by 1.6 times, and increased the incidence of uterine pregnancy by 1.6 times as compared with the use of conventional methods of laparoscopic treatment and prevention of the adhesive process, despite the fact that women of the 2nd clinical group had adhesive process of III-IV degrees, and the clinical manifestations of the adhesive process were more pronounced.

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