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ECTOPIC PREGNANCY AND ITS LONG-TERM RESULTS

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ABSTRACT

The aim: The purpose of this study was to assess the long-term outcomes of restoration of reproductive function after surgical and medical treatment of ectopic pregnancy, taking into consideration the patency of the fallopian tubes and the incidence of uterine pregnancy.

Materials and methods: A two-stage experimental approach was used to address research objectives. In the first stage, a retrospective analysis of 615 histories of patients with ectopic pregnancy has been performed. In a second stage – we examined 140 patients, which were divided into three groups, depending on the type of treatment. The first group consisted of patients with a disturbed ectopic pregnancy, who were treated with laparotomy and tubectomy. The second group included patients with exacerbated ectopic pregnancy, who were operated by laparoscopic access. Lastly, the third group comprised of women with ectopic pregnancy who were treated with methotrexate. The main source of information used for clinical and anamnestic analysis was “medical card-patient” (f. 003 / o).

Results: The number of patients diagnosed with ectopic pregnancy increased from 2005 to 2015. In 2005 and 2006, the laparotomy operations were 86.88% and 83.33%, but conservative management only 13.16% and 16.67%, respectively. In 2015, the number of patients treated with methotrexate was more than half (51.35%) compared with 2010 and 2005 increased to 16.97% and 38.19% respectively, and laparotomy operations decreased from 86.88% in year 2005 to 18.92% in year 2015.

Conclusions: The data showed that in women who underwent medical treatment with cytostatic, the patency of the fallopian tubes was significantly better than after surgical treatment. In cases of interrupted ectopic pregnancy for which laparotomy with the removal of the motor tube was applied, infertility of tubal peritoneal genesis developed in 60% of cases, which is consistent with the existing literature. Statistical analysis of the structure of ectopic pregnancy showed that in 2005 dominated interrupted ectopic pregnancy, due to late diagnostic and hospitalisation, that led to urgent laparotomy operations rather than conservative treatment.

KEY WORDS: ectopic pregnancy, methotrexate, infertility, removal of the fallopian tube, metrosalpingography

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INTRODUCTION

Ectopic pregnancy is one of the main causes of reproductive loss in women with the tubal factor being 39% of infertility structure. The risk for lethality from ectopic pregnancies is 10 times higher than that of childbirth and 50 times higher than that during an artificial abortion [1, 2]. Particularly relevant is the problem of the first ectopic pregnancy (EP), which results in 50-80% of the patients undergoing a reproductive function after its surgical treatment, and the frequency of repeated ectopic nidations is 7-17% [3, 4].

According to the literature, the conservative treatment of progressing EP by methotrexate under the control of chorionic gonadotrophin levels leads to complete degeneration of the fetal egg [5, 6]. Operative treatment of EP by laparoscopic access in comparison with laparotomy has a number of significant advantages, such as: small invasiveness, narcotic analgesics refusal, faster physical, sexual and social rehabilitation, cosmetic effect, reduction of purulent-septic complications. Indications and contraindications to the operative and conservative management of progressive ectopic pregnancy remain still current [7, 8].

Given the evidence presented, it is necessary to develop an advanced algorithm for progressive ectopic pregnancy and a method of operative technique that will provide an opportunity for optimal endosurgical intervention in the

case of interrupted ectopic pregnancy. Therefore, the purpose of this study was to elucidate the long-term outcomes of restoration of reproductive function after surgical and medical treatment of ectopic pregnancy, according to the patency of the fallopian tubes and the incidence of uterine pregnancy.

THE AIM

The purpose of this study was to assess the long-term outcomes of restoration of reproductive function after surgical and medical treatment of ectopic pregnancy, taking into consideration the patency of the fallopian tubes and the incidence of uterine pregnancy.

MATERIALS AND METHODS

This research was conducted in the gynecological department of Ternopil municipal communal hospital №2 affiliated with the Department of Obstetrics and Gynecology of I. Horbachevsky Ternopil National Medical University. The study was conducted in accordance with ethical principles of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and the relevant laws of Ukraine on conducting experimental and clinical

Table 1. Research design

Groups of patients	subgroups	Methods of treatment
I (n=20)		tubectomy viaa laparotomy access
II (n=40)	IIA (n=20)	removal of fertilized egg by laparoscopic access with preservation of the tube
	IIB (n=20)	tubecotomy vialaparoscopic access
III (n=80)	III A (n=20)	methotrexate
	IIIB (n=20)	methotrexate followed by removal of fetal egg vialaparoscopic access with preservation of the tube
	IIIC (n=20)	methotrexate followed by laparoscopic tubectomy
	IIID (n=20)	methotrexate followed by tubectomy via a laparotomy access

studies. The patients gave informed consent to participate in the study. The protocol of the study was approved by the Commission on Bioethics of I.Horbachevsky Ternopil National Medical University.

The source of information used for clinical and anamnestic analysis was «Patients' medical records» (p. 003 / o) of the patients undergoing ectopic pregnancy. Ectopic pregnancy was diagnosed as criteria for inclusion of patients in the study. The groups were selected in accordance with the aim and objectives of this study. The control group consisted of 30 women with the physiological course of pregnancy in the first trimester. At the second stage of the study, we examined 140 patients, which were divided into three groups, depending on the type of treatment (Table 1).

The first group consisted of patients with a disturbed ectopic pregnancy who were treated with laparotomy and tubectomy. The second group included patients with exacerbated ectopic pregnancy, who were operated by laparoscopic access, and the third group – comprised of women with EP, who were treated with methotrexate in a dose of 75-100 mg intramuscularly. If there was no effect of drug treatment, ectopic pregnancy continued to develop, patients were given prompt treatment. Depending on the type of treatment, groups were randomly divided into subgroups (Table 1) in order to adequately assess the results of the surveys.

The inclusion criteria for using methotrexate were as follows: the diameter of the fetal egg not more than 3.5 cm in the area of uterine application (according to ultrasound data), and the level of β -HCG of no more than 1500 IU / l as determined by the ECLIA analyzer Cobas 6000 (Roche Diagnostics, Rotkreuz, Switzerland).

The laparoscopic operation was performed using instruments made by "KarlStorz" firm (Germany). The ultrasound examination for the diagnosis of ectopic pregnancy was carried out transabdominally and transvaginally using the ultrasound device "Aloka SSD-1800" (Toshiba, Japan) with sensors from 3.5 to 10 MHz. Metrosalpingography (MSG) was performed in the radiological department and the department of vascular surgery of Ternopil communal city hospital №2 using the Siemens Axiom Artis 20 dBA_sm15724 angiograph with a digital flat-panel detec-

tor. Monitoring of the onset of pregnancy in the examined women was carried out within 6-24 months after treatment.

Statistical analysis of the data was performed on a personal computer using the STATISTICA-10 software for Windows®-6.0 package. Odds Ratio (OR) and its 95% confidence interval (95% Confidential Interval, 95% CI) were used to identify risk factors and predict complications. The reliability of the abolition of a pair of averages was calculated using the Student and Fisher test criteria.

RESULTS AND DISCUSSION

We conducted an analysis of various methods of ectopic pregnancy treatment during 2005 -2015 under conditions of one gynecological hospital. In 2015 the absolute number of ectopic pregnancies exceeded the indicators by 49.4% in 2005, and compared to 2010 – by 28.9% (Fig. 1).

There were significant changes in the structure of treatment methods from 2005 to 2015, as shown in Fig 2.

In years 2005 and 2006, the share of laparotomy operations was 86.88% and 83.33%, while medical treatment was only 13.16% and 16.67%, respectively (Fig. 2). In 2015, the number of patients treated with methotrexate was more than a half or 51.35%, which in comparison with years 2010 and 2005 increased by 16.97% and 38.19% respectively, whereas laparotomy operations decreased by 86.88% in 2005 to 18.92% in 2015; laparoscopic access was dominant over laparotomic access in 2015, almost twice compared to year 2005 (29.73% and 18.92%, respectively).

Furthermore, it was found that EP is most common at the age of 26-30. The average age of patients was (25.29 ± 1.75) years (Fig. 3), and in the control group – (23.5 ± 0.62) years. EP diagnosis was established on the basis of clinical, ultrasound and laboratory methods in 65% of the surveyed patients during the period of 3-4 weeks of gestation, 20% – in 5-6 weeks of gestation, and 15% – in the term more than 6 weeks of gestation. The diagnosis of ectopic pregnancy was established by a transabdominal ultrasound sensor in 40.4% of women, and by transvaginal sensor – in 74.1% of women.

Determination of serum β -HCG level was performed in all patients with progressive ectopic pregnancy (EP).

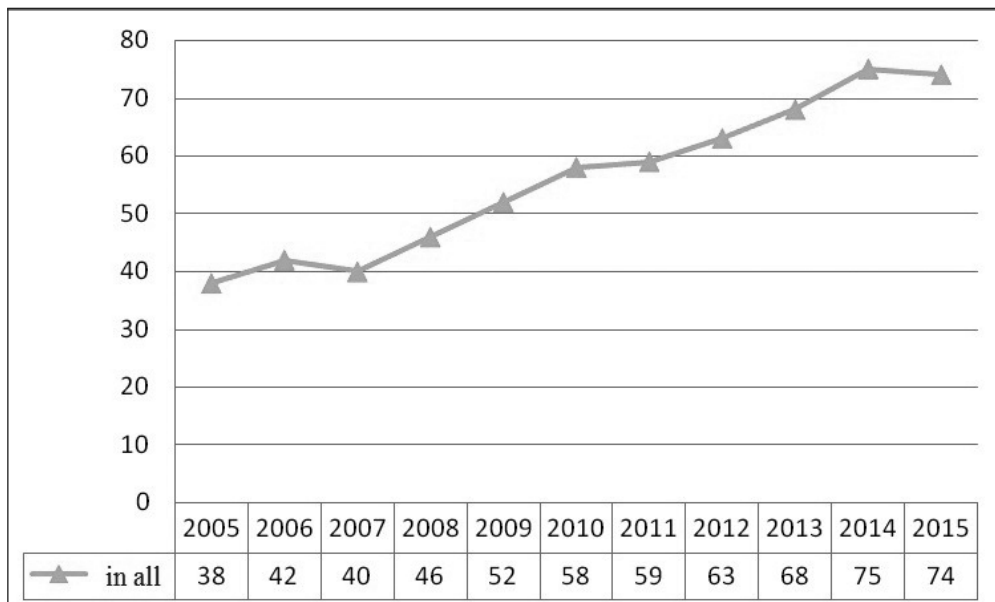


Fig. 1. Number of women with ectopic pregnancy hospitalized in the gynecological department of Ternopil municipal communal hospital №2

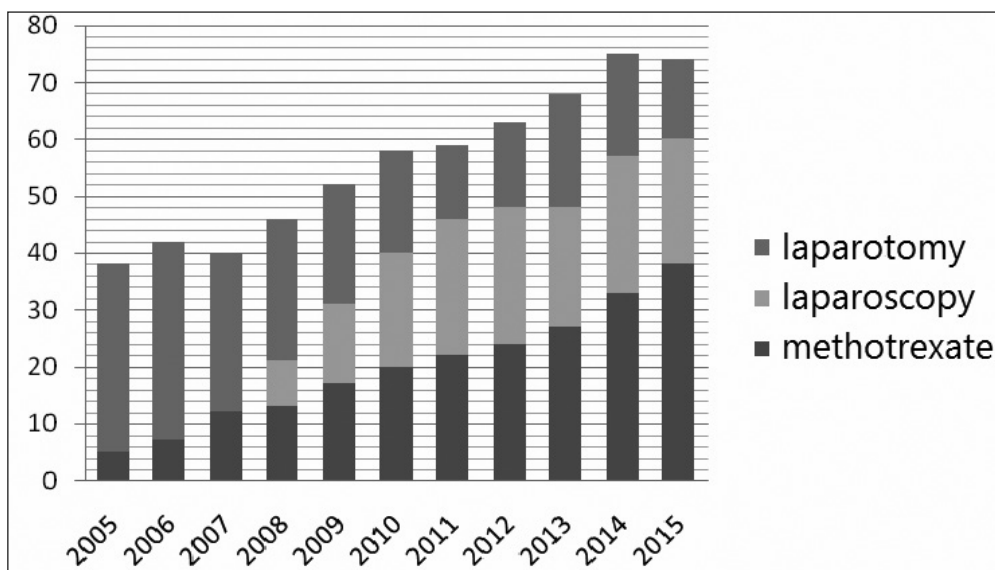


Fig. 2. The number of patients with ectopic pregnancy who were treated with operative (laparotomy, laparoscopic) and medication method.

At 3-4 weeks of pregnancy, the concentration of β -HCG hormone was 476.25 ± 11.86 IU / L, and 2736.14 ± 142.67 IU / L in patients with ectopic pregnancy in the period of 5-6 weeks, that did not correspond to the reference value of β -HCG hormone during the physiological course of uterine pregnancy in the appropriate period.

For the purpose of differential diagnosis of ectopic pregnancy and uterine pregnancy, the growth of β -HCG was studied in the early stages. After a 48-hour re-analysis, the increase in β -HCG levels was less than 1.6-fold compared to the physiological course of uterine pregnancy; a lack of growth or drop of β -HCG testified in favor of ectopic pregnancy.

Patient complaints upon arrival to the clinic were as follows: delayed menstruation – 100%, pain in the lower abdomen 98.68%, vertigo – 48.35%, loss of consciousness – 31.29%, general weakness – 78.40%, and nausea – 8.30%.

The analysis of gynecological history revealed that menstrual cycle was regular in 84.45% of women. In 78.93%

of women, the cycle lasted from 21 to 28 days, it was more than 29 days in 15.76%, and – 20 or less days in 5.31% of women, as presented in Fig. 2. The duration of menstruation was on average 3-7 days in 69.40% of women, it was up to 3 days in 25.89% of women, and – over 1 week in 4.71% of women (Fig. 4).

Menstrual dysfunction in women with ectopic pregnancy was found in 53.00% of patients and was manifested mainly by algomenorrhea in 24% of women, dysmenorrhea in 18.75%, and hypertension in 9.37%, which was 7.3 times that of control group (OR = 7.3; 95% CI: (2.51-21.25); $p < 0.05$) (Fig. 5).

Among the risk factors found during the analysis of anamnestic data of patients, it was found that 40.2% of patients had early puberty (OR = 4.36; 95% CI: (1.50-12.69); $p < 0.05$), and among different contraceptive methods, intrauterine helix prevailed in 43.4% of cases (OR = 6.9; 95% CI: (2.07-22.00); $p < 0.05$). In 32.76% of women this pregnancy was the first, in 38.31% – the second, in 20.85% – the

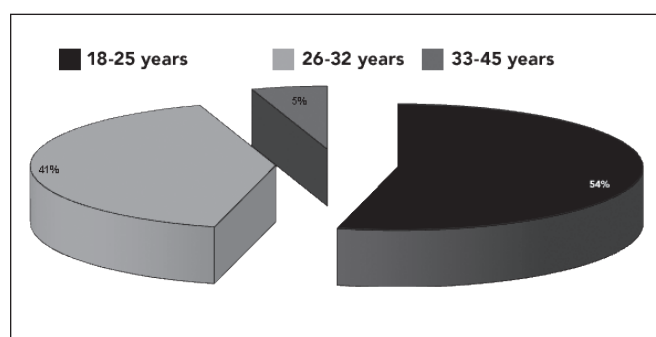


Fig. 3. Distribution of patients by age

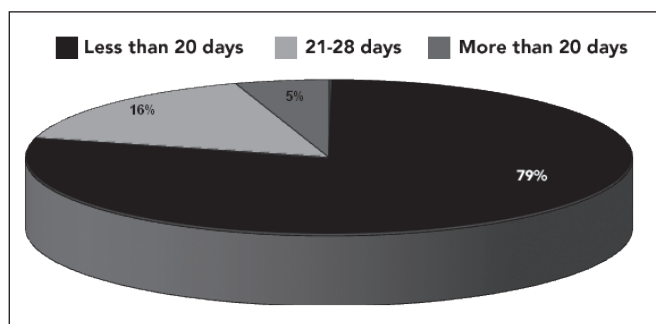


Fig. 4. Duration of the menstrual cycle

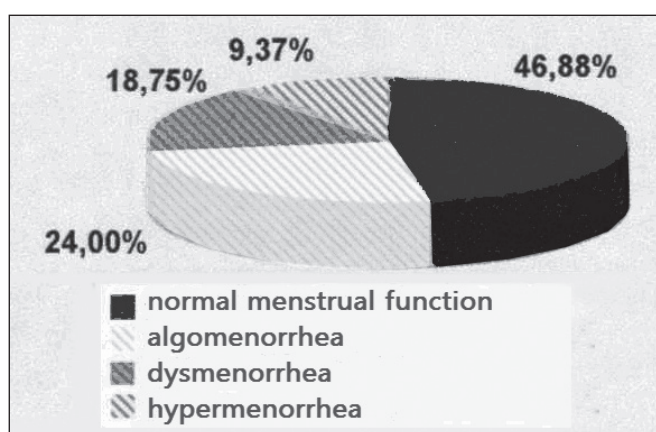


Fig. 5. Characteristics of menstrual function in the surveyed patients

third, in 8.08% – the fourth or more. 48.74% of women had birth in history. Out of 56.25% total complications from the previous labor and the postpartum period, 28.12% of women had a subinvolution of the uterus, 15.63% – hematometry, and 12.5% – the weakness of labor. Medical abortions were registered in 19.2% of patients (OR = 2.13; 95% CI: (0.63-7.16); $p < 0.05$). Among this population, one abortion was reported in 24.4% of women, two – 8.9%, and three of 1.67%. Unauthorized abortions were registered in 6.5% of the total number of women with ectopic pregnancy.

According to the anamnesis, 24.9% of the surveyed women had bad habits, namely smoking (OR = 2.98; 95% CI: (0.89-9.96); $p < 0.05$). The extragenital diseases were found out in 84.4% of patients with ectopic pregnancy, pediatric infections – in 66.3% (OR = 6.81; 95% CI: (2.05-22.65); $p < 0.05$). Moreover, 65.6% of women with ectopic pregnancy had gynecologic diseases such as inflammatory diseases of

the uterus and appendages, and benign tumors occurred in 40.7% of patients.

Further analysis of the data derived from 140 patients (the second stage of the study) revealed that in women of group I the restoration of menstruation after surgery occurred in $31,56 \pm 2,09$ days, in women of group II – in $30,64 \pm 1,72$ days or less than 3.54% compared to group I, although it was not statistically significant ($p > 0.05$). Patients in the third group receiving methotrexate noted a later onset of the next menstrual period ($40,78 \pm 2,13$), which grew by 29.2% ($p < 0.05$) compared with group I, and by group II by 33, 9% ($p < 0.05$).

Table 2 shows the absolute numbers of women with passable, partially passable and obstructed uterine tubes based on the results of MSG. In group II A, where the laparoscopic operation with conservative removal of the fetal egg was performed, the number of women with the passage of the fallopian tubes was 11 or 55%. In group IIIA, where methotrexate was used, this number was 17 (85%), which indicates the best result in 30% of women ($p < 0.05$).

In group IIIB (patients were administered methotrexate, and then laparoscopic intervention, conservative removal of the fetal egg was performed), women with passable fallopian tubes accounted for 70% (14 patients), which compared to group IIIA (only methotrexate) was 15% less ($p < 0.05$), but compared with group IIA (nocytostatic) it was better by 15% ($p < 0.05$). Partially passable tubes were found in 4 patients (20%) of group IIA, 3 (15%) patients of group IIIA, and 4 (20%) patients of group IIIB, however the difference between these indicators were statistically significant ($p > 0.05$). Moreover, women with obstructed uterine tubes were – 3 (15%) in group IIA and 2 (10%) in group IIB, whereas the fallopian tubes obstruction was not detected in women of group IIIA.

Patency was evaluated in women who have undergone tubectomy and had a single uterine tube that was not operated. In group I, the passable tube was in 4 women (20%), whereas in group IIB, when performing tubectomy with laparoscopic access, the patency of the single fallopian tube was diagnosed in 12 women (60%), which increased by 40% compared to the laparotomic method ($p < 0.05$). Following the use of methotrexate and laparoscopic tubectomy (group IIIB), the patency of the fallopian tubes was found in 13 (65%) of women, and in 7 (35%) of group III C, which is less in comparison with group III B by 30% ($p < 0.05$). The patency of fallopian tubes after laparotomy tubectomy (group I) was 20%, which is 15% less ($p < 0,05$) than in the group IIIC with the previous use of cytostatics (35%). In the case of laparoscopic access without using cytostatics (group II B), 12 (60%) of the passable fallopian tubes, and after using methotrexate (group III C) – 13 (65%), ($p > 0,05$). Partially passable fallopian tubes were observed in 35% of women in groups I and III B, however it was independent of the use of methotrexate. In the group II B, the fallopian tube, that was not used, preserved partially passable in 4 women (20%), and it was in 6 patients (30%) in group IIIC.

There were 9 (45%) women who were subsequently diagnosed with a tubal peritoneal infertility based on MSG after

Table 2. Fallopian tubes passages in women with an ectopic pregnancy in anamnesis based on the results of digital and analogue metrosealingography

	Group I n=20	Group II n=40		Group III n=80			
		II A n=20	II B n=20	III A n=20	III B n=20	III C n=20	III D n=20
Passable	4 (20%)	11 (55%)	12 (60%)	17 (85%)*	14 (70%)*	13 (65%)	7 (35%)
Partially passable	7 (35%)	4 (20%)	4 (20%)	3 (15%)	4 (20%)	6 (30%)	7 (35%)
Obstructed	9 (45%)	3 (15%)	2 (10%)	0 (0%)	2 (10%)	1 (5%)	6 (30%)

* – significant difference between the groups ($p < 0,05$)

Table 3. Reproductive function of women in 2-24 months after the EP episode

	Group I n=20	Group II n=40		Group III n=80			
		II A n=20	II B n=20	III A n=20	III B n=20	III C n=20	III D n=20
Maternal pregnancy	2 (10%)	12 (60%)	6 (30%)	15 (75%)	14 (70%)	5 (25%)	1 (5%)
Reproductive technologies	3 (15%)	2 (10%)	3 (15%)	1 (5%)	2 (10%)	2 (10%)	3 (15%)

laparotomy tubectomy (Group I), which was the highest indicator in comparison with the whole population. In the group III C (laparotomy with tubectomy after methotrexate therapy), tubal peritoneal infertility was observed in 6 (30%) of women, which is 15% lower than in the group I ($p < 0,05$). In groups II B and III B there was a decrease in the number of tubal obstruction down to 10% and 5% compared to group III C, respectively.

Analysis of the data presented in Table 3 revealed that spontaneous pregnancy occurred in 2 women (10%) with laparotomy tubectomy (Group I) and in 1 (5%) woman who was performed laparotomy tubectomy and previously used methotrexate (Group III C), however there was no significant difference between these groups.

Pregnancies occurred in 6 (30%) women of group IIB and in 5 (25%) women of group IIIB, which was 20% more than in the case of laparotomy surgery (group I). If the uterine tube is maintained, the percentage of pregnancy in the natural way was almost 2 times higher. The pregnancy occurred in 12 (60%) women in the group IIA, which was 2 times higher than in the group II B and 6 times higher than in the group I. Patients of group III A showed the best result: 15 women (75%) became pregnant independently, which is 15% higher than in the group IIA. In the group III B, when using methotrexate and laparoscopic removal of a fertilized egg with preservation of the fallopian tube, this figure was 70% (14 women), or 5% lower than when using only methotrexate (group III A), but – 10% higher than after conservative removal of a fertilized egg by a laparoscopic method without the use of methotrexate (group II A). 16 (11.4%) of women out of total 140 were pregnant with the help of auxiliary reproductive technologies, but differences in groups were not statistically significant,

indicating the independence of this factor from the type of treatment of ectopic pregnancy in the history (Table 3).

A new ectopic pregnancy occurred in one woman of group IIA (after the conservative removal of the fetal egg) after 1.5 years. This pregnancy was localized in the opposite tube from the operated one. Two women (10%) in the group I were readmitted with an ectopic pregnancy in a single uterine tube.

An increase in the proportion of ectopic pregnancy in the gynecological hospital was established on based on the conducted clinical and statistical analyses of the structure of gynecological diseases from years 2005 to 2015.

The risk factors for developing ectopic pregnancy are as follows: early sexual life (OR = 4.36; 95% CI: (1.50-12.69); $p < 0.05$), use of intrauterine helix as a contraception (OR = 6.9, 95% CI: (2.07-22.00), $p < 0.05$), abortions and inflammatory diseases of the uterus and appendages in the history (OR = 2.13; 95% CI: (0.63 - 7.16); ($p < 0.05$).

The markers of EP diagnosis and the effectiveness of the drug treatment of this pathology are the dynamic determination of serum β -HCG levels, ultrasound examination of ectopic pregnancy with a transvaginal probe.

It has been established that significant changes have taken place in the approaches to the management and surgical treatment of ectopic pregnancy in the last decade. Thus, in 2005, the cases of laparotomy operations was 86.88%, and medical treatment was only 13.16%. In 2015, the number of patients treated with methotrexate was already more than a half (51.35%) the percentage of laparotomy operations decreased to 18.92%, and the number of laparoscopic interventions with the preservation of the fallopian tube almost doubled. It was also found that restoration of menstrual function in patients receiving methotrexate was later compared to mechanically isolated ectopically placed fatal eggs.

The use of methotrexate before surgery in patients with progressive ectopic pregnancy with high levels of β -HCG (> 1500 IU / L) and a fetal egg of more than 3.5 cm, followed by the conservative removal of a fertilized egg by laparoscopic access, helps to maintain the patency of fallopian tubes in 70% of cases, due to, in our opinion, medication apoptosis of trophoblast cells, separation of trophoblast from the walls of the uterine tube and thrombosis of the attachment site, that may limit massive coagulation during surgery.

When comparing the results of the patency of the uterine tubes after the use of laparotomic access with laparoscopic access, there was a decrease in the number of tubal obstruction to 10% and 5% respectively. The effectiveness of medical treatment of ectopic pregnancy by methotrexate, which was manifested in the survival of fallopian tubes compared with surgical intervention, was established. If the uterine tube is maintained, the percentage of pregnancy in the natural way was shown to be almost two times higher. The best long-term outcome was shown in patients treated with methotrexate.

CONCLUSIONS

1. Women diagnosed with progressive ectopic pregnancy should be offered conservative medical treatment that may help preserve their reproductive function in the future.
2. Treatment of women with progressive ectopic pregnancy, with an uterine tube size even more than 3.5 cm and unfulfilled reproductive plans, should include the introduction of methotrexate for 6-24 hours prior to surgery, followed by the conservative removal of the fertilized egg via a laparoscopic access. This approach was shown to maintain the patency of fallopian tubes in 70% of cases.

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Conflict of interest:

The Authors declare no conflict of interest

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