MEDICAL VS. INTERVENTIONAL THERAPY FOR ECTOPIC PREGNANCY

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ABSTRACT:
ECTOPIC PREGNANCY REMAINS AN IMPORTANT CAUSE OF MATERNAL MORBIDITY AND MORTALITY. THE FREQUENCY OF ECTOPIC PREGNANCY VARIES BETWEEN 0.58 AND 1.3 %. CERVICAL ECTOPIC PREGNANCY IS VERY RARE (0.1% OF ALL EXTRA-UTERINE PREGNANCIES). MOST ECTOPIC PREGNANCIES ARE LOCATED IN THE FALLOPIAN TUBES, AND IN LESS THAN 5% OF ECTOPIC PREGNANCIES, THE IMPLANTATION IS IN THE CERVIX, OVARIES, OR THE ABDOMINAL CAVITY. THIS ARTICLE REVIEWS THE MODERN MEDICAL AND ENDOVASCULAR THERAPEUTIC APPROACH OF UNCOMPLICATED AND COMPLICATED ECTOPIC PREGNANCY.

KEY WORDS: ECTOPIC PREGNANCY, METHOTREXATE, ENDOVASCULAR THERAPY.

INTRODUCTION

An ectopic pregnancy is the condition in which the blastocyst implants anywhere other than the uterine cavity [1-4]. In Western countries the incidence of ectopic pregnancies varies between 1-2% [3,6]. The incidence of cervical pregnancy varies between 1 to 8600 and 1 to 12.400 pregnancies [5].

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Many patients with ectopic pregnancies have one or more risk factors, such as: age over 40, chronic smoking (more than 20 cigarettes/day) [7], previous history of salpingitis or unapparent or treated genital tuberculosis that can cause inflammatory stenosis, sequelae of tubal surgery, prior ectopic pregnancy, three or more prior spontaneous miscarriages, infertility >1 year, previous intrauterine device use [7-9,11].

The fallopian tube is by far the most common site of ectopic implantation, accounting for more than 95% of all ectopic pregnancies.

Tubal 95-96%
• Ampullary 70%
• Isthmic-12%
• Fimbrial 11%
• Cornual (interstitial) segment 2-3%
Cervical <1%
Ovarian 3%
Peritoneal (abdominal) 1%
Cesarean scar<1%

Table 1 - Various sites and frequency of ectopic pregnancies [12,13]

Specialists should consider the diagnosis of ectopic pregnancy in any woman with amenorrhea, abdominal or pelvic pain followed by vaginal bleeding [10]. Also nausea, breast tenderness and urinary disorders may be encounted. Other symptoms associated with ectopic pregnancies include shoulder pain (irritation of the diaphragm by blood in the peritoneal cavity), lightheadness and shock [14,15].

The diagnosis of ectopic pregnancy is established by dinamic dosage of serum beta human chorionic gonadotropin (β-hCG) and pelvic ultrasonography. The first developmental structure that can be visualized by transvaginal ultrasonography is the gestational sac, which appears at 4.5-5 weeks of gestation in the endometrial cavity (β-HCG =1000-1500 mIU/mL). Measurement of the mean sac diameter (MSD) is important for estimating the gestational age. The absence of an intrauterine gestational sac 38 days or more after onset of menses or 24 days after conception is an evidence for a nonviable pregnancy [17]. Some specialists observed that measurements of endometrial thickness have predictive value because the endometrium is thinner in women with ectopic pregnancy [18]. In a study involving 576 women who reffered to the emergency room for pain and/or vaginal bleeding, the mean endometrial thickness was 9.56±4.87 mm for women with ectopic pregnancies, 12.12 mm±6.0 mm for those with intrauterine pregnancies and 10.19 mm ± 6.10 mm for women with spontaneous abortions [19].

Human chorionic gonadotropin is a glycoprotein produced by syncitiotrophoblast and can be detected in serum within 9 days after ovulation in normal conception cycles. Levels of hCG can first be detected by a normal blood test approximately 11 days after conception and, in a healthy pregnancy, will typically double every 48 to 72 hours. A hCG level that is rising by less than 66% over 48 hours means it is likely, but not a certainty, that the pregnancy is ectopic [16].

Gestational age (weeks of amenorrhea)	Embryo size (mm) at ultrasound	Values of B-HCG mIU/ml
4	0.5	28
5	1.5-3	300
6	4-8	3000
7	9-16	50000

Table 2 - The relation between the size of the embryo, B-HCG and gestational age in a normal pregnancy [20]

Determination of seric progesterone concentration is used to diagnose ectopic pregnancy when serum b-hcg levels and sonographic findings are inconclusive [21]. The levels are lower in ectopic pregnancies than in intrauterine pregnancies [22-25]. Levels greater than 20ng/mL indicate a normal pregnancy. Concentrations less than 5ng/mL always indicate a nonviable pregnancy, which may be either ectopic or intrauterine [21, 26].

Recent studies have shown that 50% of ectopic pregnancies, nearly 20% of spontaneous abortions and almost 70% of viable intrauterine pregnancies are associated with serum progesterone concentrations between 5 and 20 ng/mL [27,28].

Conservative treatment is indicated in patients with uncomplicated ectopic pregnancy. Choosing this modality of treatment should be determined by the score Fernandez.

FERNANDEZ SCORE			
Criterion	**1 point**	**2 points**	**3 ppoints**
Gestational age (weeks of amenorheea)	**>/= 8**	**6-7**	**</=6**
β-HCG (UI/l)	**<1000**	**1000-5000**	**>5000**
Progesterone ng/ml	**<5**	**5-10**	**>10**
Abdominal pain	**absent**	**induced**	**spontaneous**
Hematosalpinx(cm)	**<1**	**1-3**	**>3**
Hemoperitoneum(ml)	**0**	**1-100**	**>100**
Scord < 12 success with various nonsurgical treatments, including expectant management.			
Scor ≥ 13 less than 50 % success rate of medical management			

Table 3 - Predictive score for successful treatment of ectopic pregnancy [29]

Ectopic pregnancy may be managed surgically, medically or by expectative. The usual drugs used are: methotrexate, potassium chloride, hyperosmolar glucose, actinomycin-D and prostaglandins [30-36]. Methotrexate is a folic acid antagonist that targets rapidly dividing cells and arrests mitosis [37,38]. The most common side effects of methotrexate

include dizziness, drowsiness, headache, tender gums, decreased appetite, reddened eyes, blood in the urine or stools ,bloody vomit and hair loss [39]. The requirments for medical treatment of ectopic pregnancy are hemodynamic stability, minimal symptoms and a low volume of free intraperitoneal fluid on ultrasound scan, no contraindications to methotrexate treatment, serum b-hcg levels less than 5000IU/L, absent embryonic heart activity, ectopic mass measuring less than 4 cm in diameter [40-42]. Contraindications of methotrexate treatment are: active peptic ulcer disease, imunodeficienty states, advanced renal failure, leukopenia, thrombocytopenia, pleural effusion, ascites, pregnancy, breast-feeding, alcoholism [39]. Before starting methotrexate therapy, pre-treatment evaluation should include the following-complete blood count, blood type and Rh, serum creatinine, lever function tests and transvaginal ecography[43, 44]. The commonly used single-dose methotrexate treatment regimen involves a deep intramuscular injection at a dose of 50 mg/m^2 of the calculated body surface area [45]. Methotrexate treatment is very successful for small stable ectopic pregnancies. Ths meta-analysis of non-randomised studies showed success rates of 93% (95% CI 89–96%) for multi-dose protocols and 88% (95% CI 86–90%) for single dose therapy [46]. Uterine and ovarian artery embolization are minimally invasive techniques. It represents a treatment option for cervical ectopic pregnancies by means of devascularization and resorbtion [47-50].

MATERIALS AND METHODS

We retrospectively analysed the charts of all the patients diagnosed with ectopic pregnancy, who were hospitalized in the Department of Obstetrics and Gynecology of the University Emergency Hospital Bucharest between 1st January 2013 and 31 December 2014.

We evaluated the risk factors for ectopic preganancy of each patient enrolled in the study and the diagnostic and curative methods used. We analysed and compared the different types of treatment, in order to determine the profile of the patient who can be cured with Methotrexate, can undergo embolisation, or who requires surgical management.

RESULTS AND DISCUSSIONS

Between 1st January 2013 and 31 December 2014, in the Department of Obstetrics and Gynecology of the University Emergency Hospital Bucharest, 387 patients were diagnosed with ectopic pregnancy, 189 in 2013 and 198 in 2014.

Analysing the type of treatment performed we observed that 94 patients underwent surgery, in 15 cases interventional therapy was preferred and medical management using MTX protocol was applied in 283 patients.

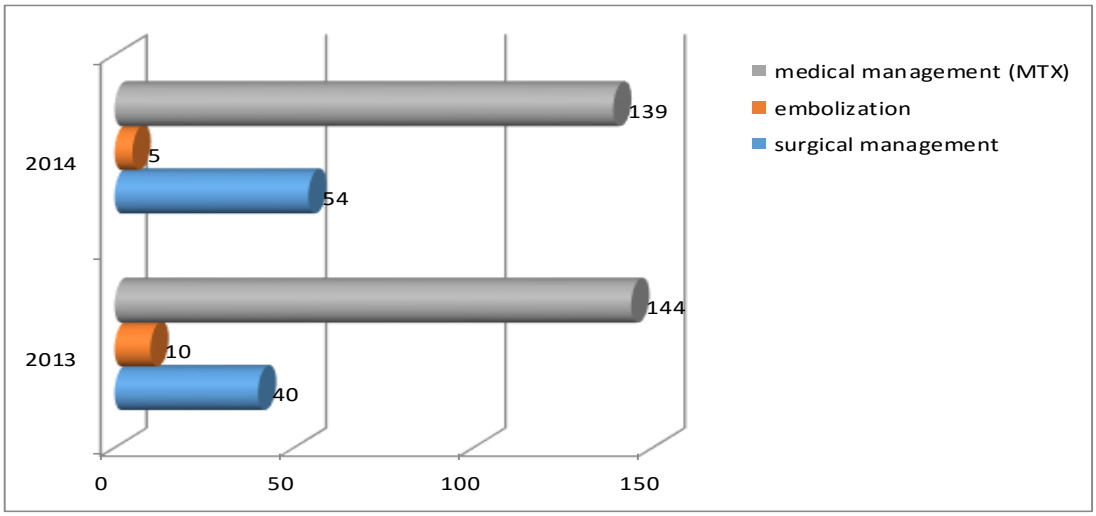

Figure 1 – The distribution of patients diagnosed with ectopic pregnancy accroding to the therapeutic management

94 patients diagnosed with ectopic preganancy underwent surgical treatment (classic or laparoscopic) – see Figure 1 and Figure 2.

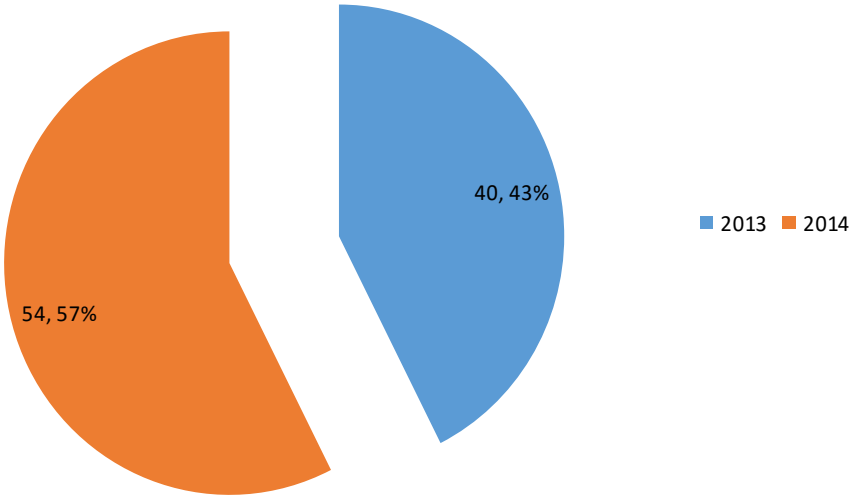

Figure 2 – The distribution of patients who underwent surgical treatment between 1st January 2013 and 31 December 2014

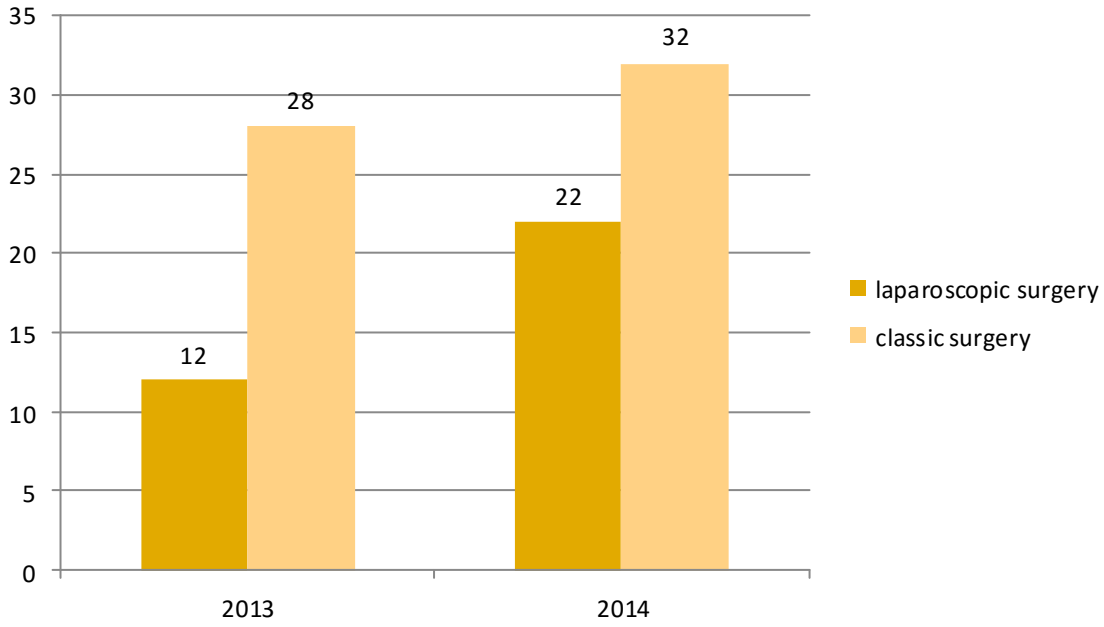

Figure 3 – The distribution of patients who underwent surgical treatment between 1st January 2013 and 31 December 2014, according to the operative management

Analysing Figure 3, one can observe that in 2014 the number of laparoscopic surgeries increased with 10.74%.

15 patients with cervical ectopic pregnancy were hospitalized complaining of abnormal vaginal bleeding. These patients underwent uterine artery embolization. The procedure was performed under local anesthesia, by radial or femoral approach. A guiding

catheter was used and placed into the uterine artery under x-ray fluoroscopy guidance in order to select the uterine vessels for embolization. An angiogram with contrast was performed to confirm placement of the catheter. Afterwards an embolizing agent with rapid resorption (complete reperfusion within a few days) was released.

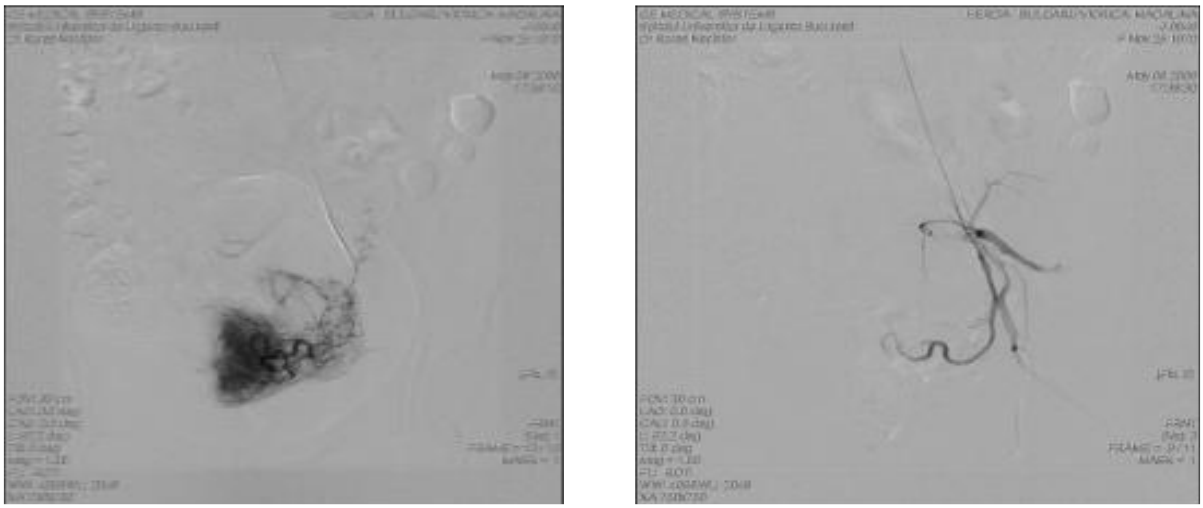

Figure 4 – Left tubal pregnancy – ovarian and uterine artery embolization (intraprocedural aspect)

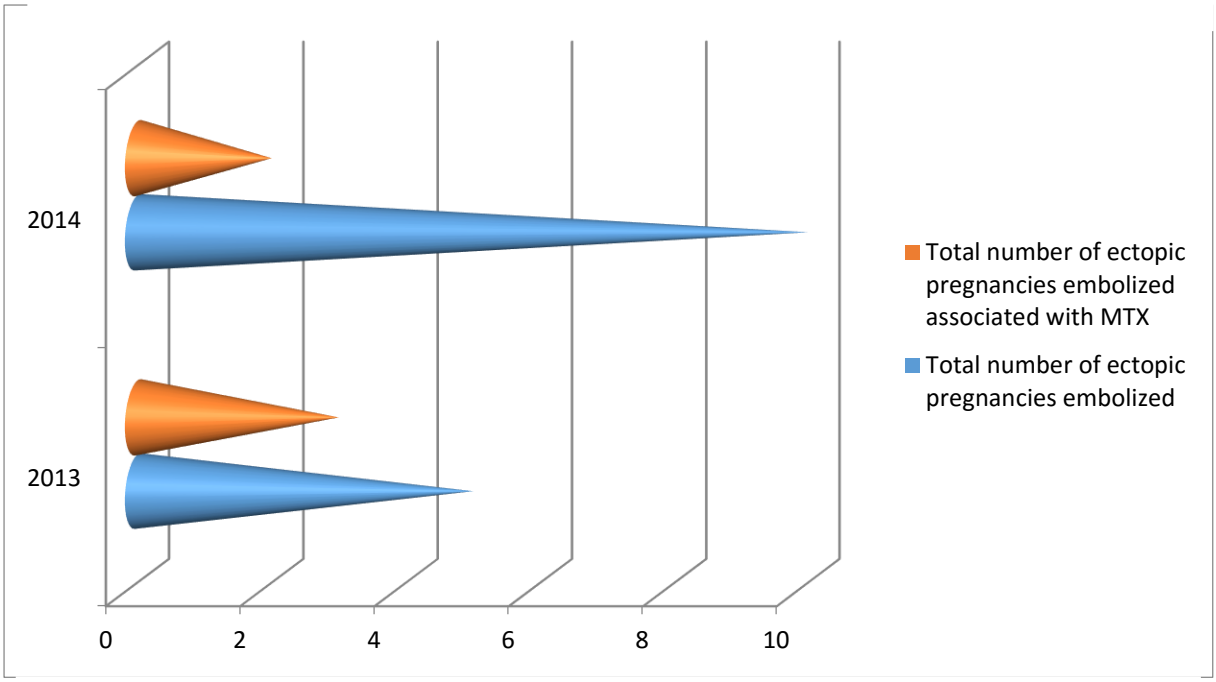

Figure 5 – The distribution of patients who underwent combined therapy – embolization and MTX protocol

A single-dose MTX protocol before endovascular therapy was administered to 3 patients in 2013 and 2 patients in 2014.

There are significant differences considering the response to a different type of treatment, considering the ages of patients enrolled in the study (see Figure 6) - in 2013 the mean age of patients cured using uterine and ovarian artery embolization was 30.2, while in

2014 the mean age of patients was 31.1. Regarding conservative treatment with Methotrexate, patients with a good response to therapy were younger - the mean age of patients was 25.4 in 2013 and 23.5 years in 2014.

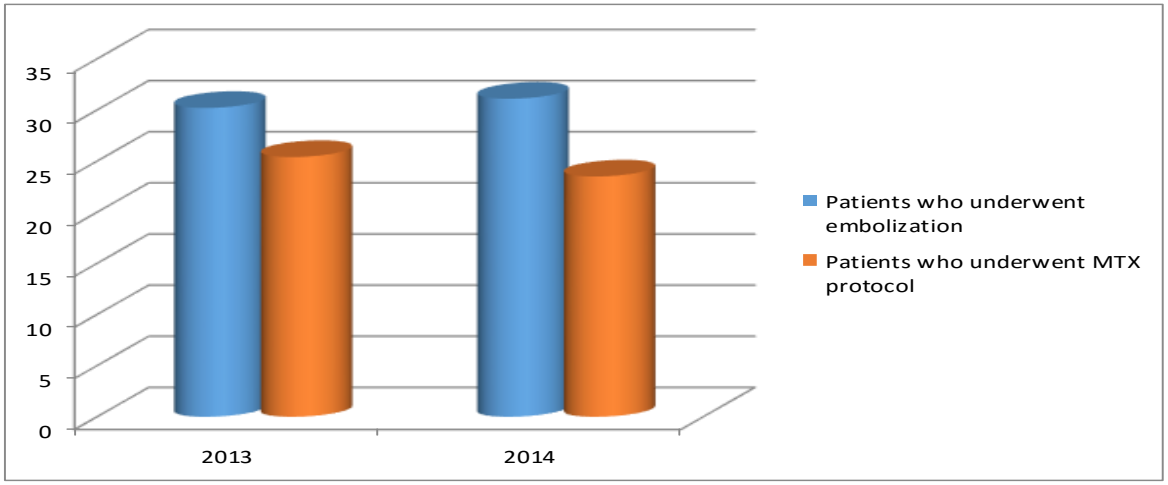

Figure 6 – The differences between the mean ages of patients with a good response considering different types of treatment

The patients included in this study who received the single-dose regimen that uses an intramuscular injection dose of 50 mg/m2 of Methotrexate without Leucovorin meet the following criteria: uncomplicated ectopic pregnancy, hemodynamically stable, gestational sac <3.5 cm, β-hCG <5000 mIU/mL and no fetal cardiac activity. It had a success rate of 76.38% in 2013, and 69.78% success rate in 2014. β-hCG levels were measured after 4 and 7 days. If the β-hcg levels decreased by less than 15% between days 4 and 7, the patients received another dose of Methotrexate. This regimen was performed to 20.13% of women in 2013 and 23.74% of patients in 2014 (see Figure 7). Under ultrasound guide, Methotrexate was administrated directly into the amniotic sac in 14 patients (5 in 2014 and 9 in 2014). In these case the efficacy was 100%.

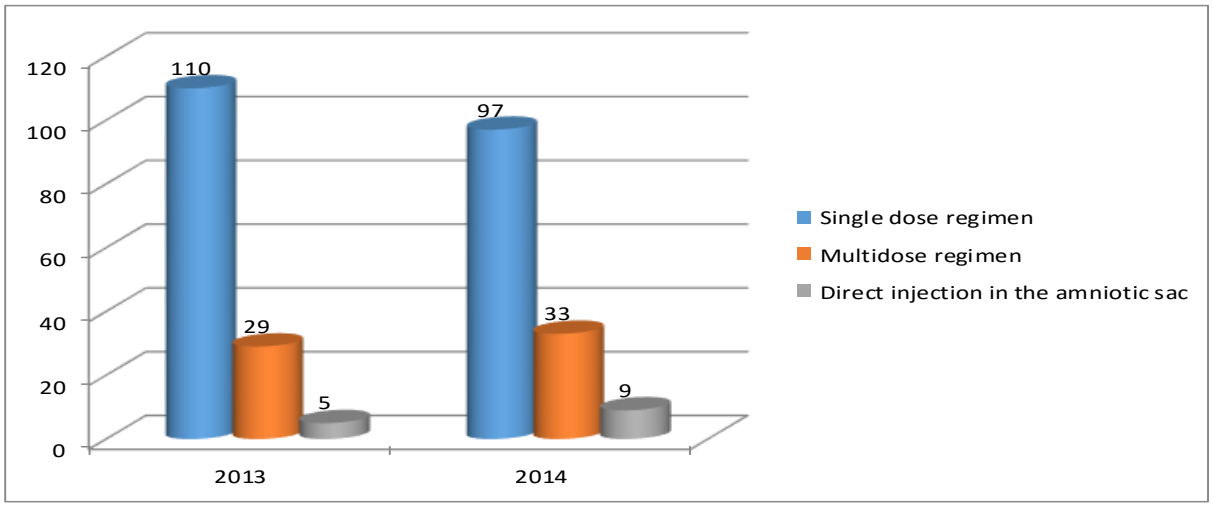

Figure 7 – The distribution of patients according to the type of regimen with Methotrexate received

We detected that 46 patients who received the Methotrexate protocol, consecutively underwent surgery – therefore the mean failure rate of medical therapy in this study is 16.25%.

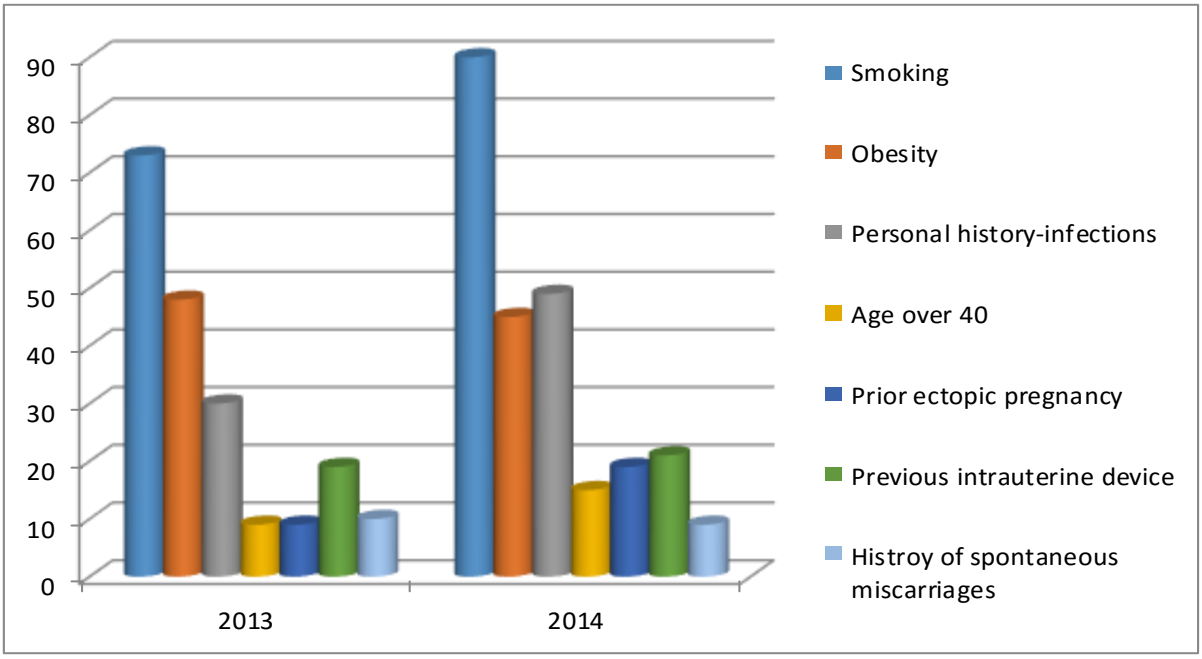

Figure 8 – The distribution of patients enrolled in the study according to the risk factors for ectopic pregnancy

Smoking and obesity are the most important risk factors for ectopic pregnancy. We detected that from a total of 387 patients diagnosed with ectopic pregnancies, 163 were chronic smokers, 93 were obese (BMI>30), 79 had sexually transmitted diseases, 24 patients were over 40 years, 29 had a prior ectopic pregnancy, 40 used an intrauterine device as a method of contraception and 19 had at least two spontaneous miscarriages.

CONCLUSIONS

Ectopic pregnancy remains an important public health issue due to increased maternal morbidity. Every patient diagnosed with this condition requires a strictly individualised management. Medical and interventional therapy play an essential role in the treatment of patients with ectopic pregnancy in incipient stages, therefore it this mandatory to establish the diagnose rapidly and correctly.

DISCLOSURE: All authors contributed equally in developing this study.

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