Original Research

Clinical presentation, risk factors and management of ectopic pregnancy: a case-control study

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Summary

Purpose of Investigation: To evaluate risk factors in patients with ectopic pregnancy (EP), while emphasizing the clinical presentation and management. Materials and Methods: Eighty patients with EP were included in a retrospective case-control study between 2016-2017. Patient's socio-demographic features and pathological background were assessed in relation to 150 patients with live vaginal deliveries, in order to determine the main risk factors for EP. Results: Tubal (95%) was observed, with right side (60%) preponderance of EP, associated with vaginal bleeding (80%) and leukocytosis (61.25%). Main identified risk factors were previous EP (OR = 11.79), cesarean section (OR = 11.31), cigarette consumption (OR = 7.47), history of laparotomy (OR = 7.28), and tubal damage (OR = 7.09). Most patients underwent laparoscopy (87.5%) associated with a shorter hospital admission (p = 0.0011). Conclusion: Considering the risk factors, the physician could establish an accurate diagnosis in less time, avoiding complications by performing a suitable surgical intervention.

Key words: Ectopic pregnancy; Tubal; Cesarean; Laparotomy; Laparoscopy; Surgery.

Introduction

Ectopic pregnancy (EP), also known as extra-uterine, is defined as a condition in which the blastocyst is implanted outside the uterine cavity and about 95% having the fallopian tube as implantation site. As previous research showed, EPs account for 1-2% of reported pregnancies, being often an emergency diagnosis in women describing acute pelvic pain or abnormal vaginal bleeding [1, 2].

A certain etiology of EP remains unknown despite the many identified risk factors, but which vary depending on the demographic characteristics [3]. Among the identified risk factors for EP in previous studies, mentioned are age, smoking habits, abortion history, tubal pathologies, prior abdominal surgeries, history of EP, infertility, advanced reproductive technologies (ART), even endometriosis [4]. This study analyzes the main risk factors in women with EPs, together with demographic features, clinical and laboratory findings, and also surgical management of these implanted pregnancies.

Materials and Methods

A retrospective case-control study was conducted between January 2016 and December 2017 in the Department of Obstetrics and Gynecology, Târgu Mureş Emergency Clinical County Hospital (Romania). The research followed a study group (SG)

which included 80 patients with EP, confirmed by urine hCG testing and transvaginal ultrasonography, and the control group (CG) including 150 patients with live vaginal deliveries on term, randomly selected. Data was collected from medical, including socio-demographic data, obstetrical, gynecological and surgical history, previous tubal pathologies and advanced reproductive technologies, infertility history, and endometriosis. Risk factors for the two groups were qualitatively and quantitatively analyzed. Patients with ECs were also assessed with clinical and paraclinical findings, such as duration of amenorrhea, acute abdominal pain, presence of vaginal bleeding, hemoglobin, and white blood cell levels. Regarding the management of the EP, the surgical approach considered intraoperative lesions and types of performed procedures, placing also in attention to the amount of intraperitoneal hemorrhage, need of blood transfusion, and hospital stay. Collected data was processed in Microsoft Excel and statistical results were acquired using GraphPad InStat software by applying suitable statistical methods for each type of variables. Quantitative analysis was shown by mean or median of the two study groups, while the qualitative analysis was expressed by numbers and percent. The categorical variables were statistically analyzed using Fisher's exact test, and continuous variables by applying Mann-Whitney non-parametric test. The existing relationships between EP and risk factors was calculated by odds ratio (OR) and 95% confidence interval (95% CI) using logistic regression analysis. A p value < 0.05 was considered statistically significant.

Results

The retrospective study conducted during 2016-2017 followed 80 women with EPs considering the clinical presentation, laboratory exams, and surgical management of the case, whose risk factors were gathered from the medical records and were statistically analyzed in relation to a CG of 150 women with term vaginal deliveries.

Table 1 presents the clinical and paraclinical assessment of the study group, including laboratory exams, aspects regarding the side and location of the EP detected through transvaginal ultrasonography. Most included subjects (98.75%) had amenorrhea < 14 weeks, abdominal pain was present in 66.25% of cases, a minimum of vaginal bleeding was found in more than a half of patients (66.25%), although the ratio of patients who presented any amount of vaginal bleeding was significantly higher (80%). A higher percentage of EPs on the right side of the body (60%) were observed, with tubal locations found in 95% of patients. Concerning the laboratory exams, low hemoglobin levels were observed in more than one-third (37.5%) of patients, with more than half patients (61.25%) presenting leukocytosis.

Table 2 shows the statistical analysis of some demographic features in relation to EP occurrence. As presented, age below 20 years had the role of a protective factor (OR = 0.18, p = 0.0029), the risk of EP increased with aging, but the numbers showed no statistical significance of this demographic feature in relation with EP incidence. The main habit involved in the development of the EP was cigarette smoking, the risk in smokers being significantly higher (OR = 7.47).

Aspects on obstetrical, gynecological and surgical history can be seen in Table 3, including the main risk factors on EP also cited in gynecologic literature. The obstetrical background for each patient in both study and CGs was first analyzed, and it was observed that gravidity had no significant impact on EP occurrence, but on the other hand, parity proved to be a statistically significant protective factor for EP (OR = 0.31 for primiparas, OR = 0.42 for multiparas, p value < 0.05). Abortion history constituted an important risk factor, patients with prior spontaneous, drug-induced or classic surgical abortions presented a statistically higher chance of EP (OR = 2.53, p = 0.014); previous EP was found to be the main risk factor belonging to obstetrical antecedents of the patients, calculated OR = 11.79, p = 0.0002.

Among the risk factors belonging to gynecological history, tubal damage presented the highest statistical significant risk for EP with OR = 7.09, followed by infertility (OR = 6.00). Also risk factors due to an ART history (OR = 5.81) was found and endometriosis background (OR = 9.59), but both proved to be not statistically significant.

Abdominal surgical interventions, conventional or laparoscopic, determined an important impact on EC inci-

Table 1. — *Clinical evaluation*.

Variable	Number of cases (%)		
Symptoms:			
A 1	< 14 weeks:	> 14 weeks:	
Amenorrhea	79 (98.75)	1 (1.25)	
Abdominal pain		53 (66.25)	
		Moderate: 11 (13.75)	
Vaginal bleeding		Minimum: 56 (66.25)	
		Absent: 16 (20)	
EP side:			
Right side		48 (60)	
Left side		31 (38.75)	
NA*		1 (1.25)	
EP location:			
Tubal		76 (95)	
Extratubal		4 (5)	
Laboratory exams:			
Low Hb level (< 12 g	/dL)	30 (37.5)	
Leukocytosis (> 10.0	mil/μL)	49 (61.25)	

dence. In relation to CG, laparoscopic surgery history presented the smallest risk for EP(OR = 4.23), while after laparotomies, the risk dramatically increased (OR = 7.28). Among all types of performed general surgery interventions on abdominal level found in the medical records of all patients, appendectomy had the highest frequency in both groups, making it a significant risk factor for EP (OR = 4.55). From all types of gynecologic abdominal procedures, a cesarean section was performed most often in study and CGs, calculated as a major risk factor for EP (OR = 11.31, p < 0.0001).

In addition categorical variables represented by the main risk factors were found among the studied subjects, with an important statistical analysis of the continuous variables involving the risk factors for EP, that can be observed in Table 4. A significantly smaller average age for CG (p = 0.0005) was found and the smoking quantity was remarkably higher for SG (p < 0.0001).

Aspects regarding the obstetrical history also had interesting variances: a higher gravidity and abortion average in SG (p = 0.0097, p = 0.0021) were observed, while the parity average was significantly higher in CG (P < 0.0001). Regarding the abdominal surgical procedures, in SG there were more performed cesarean sections (p = 0.0253) and also a higher number of abdominal surgeries in pathological antecedents (p < 0.0001).

Table 5 presents the major aspects regarding the surgical findings and management in cases of EPs. Concerning the surgical approach, it was found that laparoscopic procedure was preferred (87.5%) in detriment of the conventional open procedure. Intraoperatively tubal lesions were seen mostly in patients presenting dilatation of the fallopian tube (65%) and rupture in a smaller percentage (24%), while the tube was found to be normal in cases of extratubal EP. In most

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	Study group $n = 80 (\%)$	Control group $n = 150$ (%)	Odds ratio (OR)	95% CI	p value
Age (years):					
≤ 20	3 (3.75)	26 (17.3)	0.18	0.05-0.63	0.0029
21 - 30	37 (46.25)	74 (49.3)	1*	0.51-1.52	
31 - 40	35 (43.75)	47 (31.4)	1.70	0.97-2.99	NS
> 40	5 (6.25)	3 (2)	3.27	0.75-14.04	NS
Smoking habits					
Smokers	46 (57.5)	23 (15.3)	7.47	3.99-13.99	< 0.0001
Non-smokers	34 (42.5)	127 (84.7)	0.13	0.07-0.25	< 0.0001

CI = confidence interval; NS = not significant p value (> 0.05); 1* = odds ratio close to 1.

cases, the EP was ampullary (72.5%), followed by fimbrial (15%), and isthmic (7.5%). Due to the preponderant tubal localization of EP, the most frequently performed surgical procedure was salpingectomy (90%), adhesiolysis being the main associated surgical procedure (34%) as a result to the high number of surgical abdominal interventions found in the antecedents of the patients. Regarding EP complications, it was found that 68.75% of cases were complicated with intraperitoneal hemorrhage (hemoperitoneum), but only 18.75% of patients required intraoperative or postoperative blood transfusions. Most patients with EP had a hospital admission of 3-5 (78.75%) days, and only a smaller proportion (21.25%) required hospitalization prolonged to 6-9 days.

Discussion

EP is one of the most frequent causes of gynecologic acute abdomen in women of childbearing age. An efficient diagnosis requires a complete assessment of the personal and pathological history, clinical examination, and appropriate investigations [5, 6]. Regarding the clinical presentation, vaginal bleeding in different amounts is the main reason for searching a gynecological emergency consult, in many cases being accompanied by abdominal pain, but there exists no association of symptoms that secures an EP diagnosis [7]. The fraction of women from the present study accusing abdominal pain was similar with other authors' findings, while the number of patients with minimum irregular vaginal bleedings was significantly higher. Other studies reporting high percentages for moderate or severe vaginal bleeding. Regarding the location of the EP, other studies reported similar results for tubal and extratubal distribution, though non-tubal incidence of the EP has been increasing recently [8].

Maternal age was the first demographic risk factor analyzed during this study; the average for SG (30.78 years old) being significantly higher than for CG (27.3 years old). For young women under 20 years old, age has proven to be a statistically significant protective factor, same results being reported by a study conducted in Pennsylvania (OR = 0.3, p < 0.0001). In addition, aging increased the risk of EP as shown in Table 2. The maximum incidence was ob-

served in women over 40-years-old (OR = 3.27), but these findings were not statistically significant [9]. Other authors reported that youth had no influence on the incidence of EP; a lack of statistical significance of maternal aging as a risk factor and the exact pathophysiological impact of age remain unclear [10]. Studies reported a high improbability for an increase of chromosomal abnormalities in the trophoblastic tissue due to aging, but also that changes in tubal function could delay ovum transportation, resulting in a vicious implantation [11].

Related to cigarettes consumption, according to the present study, smokers presented a risk of 7.47-fold higher for EP. An Iranian study observed a risk of 4.21-fold higher [12]. Another study conducted in Turkey reporting a risk of only 1.9-fold higher for current smokers, but without statistical significance [13]. Studies have shown that smoking could cause tubal dysfunctions as deciliation, also alterations of the paracrine signals for coordinating the transport and development of the embryo [14].

Although gravidity is not cited as a major risk factor for EP, in the present study it was seen that even if the first pregnancy has no statistical influence, the risk increases slightly in multigravidas; other studies reporting similar results and in addition reported an average of total pregnancies that were significantly higher in SG compared to CG (p = 0.0097). On the other hand, parity was observed to be a protective factor for EP, an assertion approved by the higher average of births found in CG, even by other authors' findings reporting a minimum parity influence on EP incidence [15, 16]. Prior abortion's role as a risk factor presented variable findings in previous studies and it is still debatable, depending on the type of abortion - spontaneous or induced. The present study found a significant risk of EP in case of existing abortion history, this being in accordance with some published reports [17]. History of EP presented the highest risk for EP, other studies described the same results [18].

According to the present study, previous fallopian tube damage proved to be strongly associated with EP occurrence, with patients presenting a risk of 7.09-fold higher. Published studies also reported an association between tubal lesions and extrauterine pregnancy, being still uncertain if these are due to a surgical procedure or

Table 3. — *Obstetrical, gynecological, and surgical history.*

	Study group $n = 80 (\%)$	Control group $n = 150 (\%)$	Odds ratio (OR)	95% CI	p value
Gravidity:					
Primigravida	20 (25)	54 (36)	1*	0.32-1.08	NS
Multigravida	60 (75)	96 (64)	1.68	0.92-3.09	NS
Parity:					
Nullipara	37 (46.25)				
Primipara	17 (21.25)	70 (46.7)	0.31	0.16-0.57	0.0002
Multipara	26 (32.5)	80 (53.3)	0.42	0.24-0.74	0.0034
Abortion history:					
Present	39 (48.75)	41 (27.3)	2.53	1.43-4.46	0.0014
Absent	41 (51.25)	109 (72.7)	1*		
Previous EP:					
Yes	11 (13.75)	2 (1.3)	11.79	2.54-54.7	0.0002
No	69 (86.25)	148 (98.7)	0.08	0.02-0.39	
Tubal damage:					
Yes	7 (8.75)	2 (1.3)	7.09	1.437-35.03	0.0095
No	73 (91.25)	148 (98.7)	0.14	0.03-0.69	
Infertility history:					
Yes	6 (7.5)	2 (1.3)	6.00	1.18-30.47	0.0225
No	74 (92.5)	148 (98.7)	0.17	0.03-0.84	
ART history:					
Yes	3 (3.75)	1 (0.7)	5.81	0.59-56.78	NS
No	77 (96.25)	149 (99.3)	0.17	0.02-1.68	
Endometriosis history:					
Present	2 (2.5)	0 (0)	9.59	0.45-202.28	NS
Absent	78 (97.5)	150 (100)	0.10	0.005-2.20	
Surgical interventions					
Laparoscopy	12 (15)	6 (4)	4.23	1.52-11.77	0.0045
Laparotomy	31 (38.75)	12 (8)	7.28	3.46-15.28	< 0.0001
Appendectomy	18 (22.5)	9 (6)	4.55	1.94-10.69	0.0004
Cesarean section	15 (18.75)	3 (2)	11.31	3.16-40.42	< 0.0001

CI = confidence interval; NS = not significant p value (> 0.05); EP = ectopic pregnancy; ART = advanced reproductive technology.

an existing latent problem [19]. Also, an infertility history was observed to be associated with a higher risk of EP, and other authors reporting similar results. ART and endometriosis background analysis showed no statistical relevance in the present study due to the lack of specific cases, and published research affirmed a strong association with EP [20, 21].

Abdominal surgeries, especially those performed in the pelvis, were proven as significant risk factors for EP in previous researches, due to the possibility of abdominal and pelvic adhesions that may affect the normal anatomy of the Fallopian tube [22]. Present study found that CG presented a higher average of surgical interventions in relation to SG (p < 0.0001) and the impact of the risk factor depended on the surgical approach, performed laparotomy increasing significantly the risk of EP compared to laparoscopic procedures, but no published results were found in literature. Appendectomy was the most frequent abdominal procedure in the medical records of patients and showed a significant risk for EP occurrence (OR = 4.55),

and some authors reporting similar results [23], while others describing increased odds ratios but without statistical significance [24]. In addition, the present authors found a remarkably high risk of EP in case of previous cesarean section, also statistically relevant, and these findings are in contradiction to other authors' results, who affirmed an increased risk for EP in women with at least two cesarean deliveries [25].

The present authors observed the highest fraction of cases resolved through laparoscopic, minimally invasive approach, being preferable to a conventional approach in hemodynamically stable patients and associated in scientific literature with a more rapid access to the abdominal cavity, shorter operating time, less intraoperative blood loss, shorter hospital admissions, less postoperative pain and adhesion formation, while other authors reported variable results [26, 27].

According to the present study, the most frequent performed procedure was salpingectomy, followed by salpingostomy; these findings are confirmed by some researchers

Table 4. — *Ectopic pregnancy vs. vaginal deliveries at term.*

	SG Mean	SG Median	CG Mean	CG Median	p value
Age (years)	30.78	30.5	27.3	28	0.0005
Smoking quantity (cigarettes/day)	4.98	1	3	0	< 0.0001
Gravidity (total of pregnancies)	3.16	3	2.43	2	0.0097
Parity (total of births)	1.15	1	2.02	2	< 0.0001
Abortions	0.87	0	0.4	0	0.0021
Cesarean sections	0.26	0	0.02	0	0.0253
Surgical interventions	0.86	1	0.13	0	< 0.0001

 $SG = study \ group; \ CG = control \ group; \ NS = not \ significant \ p \ value \ (> 0.05).$

Table 5. — *Management of ectopic pregnancy*.

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Variable	Number of cases (%)
Surgical approach:	
Laparoscopic	70 (87.5)
Open	10 (12.5)
Tubal status:	
Dilatation	52 (65)
Rupture	24 (30)
Normal	4 (5)
EP sites:	
Fimbrial	12 (15)
Ampullary	58 (72.5)
Isthmic	6 (7.5)
Tubal stump	1 (1.25)
Cornual (interstitial)	1 (1.25)
Ovarian	1 (1.25)
Cervical	1 (1.25)
Surgical procedure:	
Salpingectomy	72 (90)
Partial salpingectomy	1 (1.25)
Salpingostomy	3 (3.75)
Partial ovariotomy	1 (1.25)
Hysterectomy	1 (1.25)
Tubal stump removal	1 (1.25)
Suction	1 (1.25)
Other performed procedures:	· · · ·
Adhesiolysis	34 (42.5)
Surgical sterilization on demand	6 (7.5)
Contralateral salpingectomy	9 (11.25)
Endometriosis patches	
Electrocoagulation	2 (2.5)
Hemostatic hysterectomy	1 (1.25)
Hemoperitoneum	55 (68.75)
Blood transfusion	15 (18.75)
Hospital admission	
3-5 days	63 (78.75)
6-9 days	17 (21.25)
Laparoscopic approach	Mean: 4.51 days
Open approach	Mean: 6.4 days
Laparoscopic vs. open approach	p = 0.0011
Zaparoscopie vs. open approuch	P 0.0011

 $EP = ectopic \ pregnancy; \ NA* = not \ available.$

[28], while other authors referred salpingectomy only in cases of seriously damaged fallopian tubes, complicated EP, or in patients without the desire of further pregnancies [29, 30].

Length of hospital stay was variable and most patients required 3-5 days of hospitalization. Hospital admission depended on the surgical approach, observing that patients who benefited from a laparoscopic surgery required less time for postoperative recovery in relation to those who underwent a conventional surgery (p = 0.0011) and previous studies reporting similar results [31-33].

Conclusion

EP is one of the most frequent causes of emergency interventions in gynecology, this study identifying the clinical and paraclinical features in patients with this medical condition, the physician's role being essential for a prompt diagnosis and an appropriate surgical treatment. Furthermore, the present paper emphasizes the main risk factors involved in extrauterine pregnancy occurrence, including eigarette consumption, previous EP, tubal lesions or infertility, also a history of cesarean section and laparotomy. Considering the attested risk factors, can be established a more accurate diagnosis in less time, in order to perform suitable a surgical intervention which could avoid complications, such as intraperitoneal massive hemorrhage, or prolonged hospital admissions.

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