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Decision-Making in Pregnancy of Unknown Location Based on Clinical Presentation

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Abstract

Background: Management of pregnancy of unknown location (PUL) is still challenging. Early or inaccurate interventions may lead to termination of a normal intrauterine pregnancy, while an untreated ectopic pregnancy (EP) may lead to tubal rupture or even death. Objectives: To create a decision-making algorithm to determine probability of EP among PUL patients. Methods: In this cross-sectional study, we considered 522pregnant women with abdominal pain during their first trimester presenting to Imam Hossein Medical Center in Tehran between 2012 and 2018. The clinical signs, symptoms, medical histories, laboratory tests, and sonography of these patients were recorded in a questionnaire, and patients were divided in two groups of EP and non-EP. Finally, effective and significant factors were identified and entered into a decision-making tree for diagnosis of EP. Results: Patients divided into EP group including 188 women (36%) and Non-EP group of 334 women (64%). Of 92 variables measured for each patient, 41 variables had meaningful relationship with EP diagnosis (P-Value <0.05). Five Significant variables though six rules entered the decision-making tree including unilateral pain, tenderness, pelvic or abdominal free fluid, leukocytosis, and tachycardia. Conclusions: Clinicians can determine the probability of EP regarding to algorithm provided by the present study. In HCG positive and unilateral pain, EP probability is 95%, with logical consideration of laparoscopic intervention, and if positive HCG and bilateral pain is present along with abdominal tenderness, the probability of EP is 65%, and close observation of the patient might be considered. In bilateral pain, without abdominal tenderness, other characteristics including free fluid, leucocytosis, and tachycardia is used to determine probability of EP diagnosis.

Key words: Pregnancy of Unknown Location,(PUL) Ectopic Pregnancy (EP)HCG ,

Introduction

Ectopic pregnancy (EP) is a common and life-threatening problem (Creanga et al., 2017). Untreated or misdiagnosed EP can lead to catastrophic intra-abdominal hemorrhage, shock, and finally death. Based on a report by Centers for Disease Control and Prevention (CDC), EP accounts for almost 2% of pregnancies in the United States (CDC, 1995). Therefore, prompt diagnosis with diagnostic algorithms is critical for preventing adverse events (Barnhart et al., 1994; Hoover, Tao and Kent, 2010; Condous et al., 2007; Seeber et al., 2006; Barnhart et al., 2008).

Nowadays, combination of ultrasound and Human Chorionic Gonadotropin (HCG) is the most useful ways for EP diagnosis (Gracia and Barnhart, 2001; Seeber et al., 2006). However, 20% of women presenting with suspected EP in emergency department (ED) are classified as a pregnancy of unknown location (PUL) because their ultrasound is not diagnostic and shows no gestational sac in the uterus and adnexa (Barnhart, 2009; Barnhart et al., 2011; Condous et al., 2006). Thus, some practical strategies such as using patient medical history, physical examinations, and laboratory data could be beneficial to EP diagnoses among PUL patients (Barnhart et al., 2008).

The hallmark of EP is abdominal pain in first trimester of pregnancy with or without vaginal bleeding (Josie L. Tenore, 2000). In this paper, we propose a decision-making algorithm that could help clinicians to find EP among PUL patients presenting with abdominal pain. To this end, data from pregnant women with abdominal pain during their first trimester referred to Imam Hossein Medical Centre in Tehran between 2012 and 2018 were first reviewed and analysed. Then, characteristic signs of these patients such as clinical signs, symptoms, medical histories, laboratory tests, and sonography were recorded in a questionnaire, and then patients were divided in two groups of EP and non-EP. Finally, effective and meaningful factors were identified and entered a decision-making tree in the final

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detection of EP.

Materials and Methods

In this cross-sectional study, first trimester HCG positive women presenting with lower abdominal pain at the Imam Hossein Medical Center during 2012-2018 entered to our descriptive study. All cases with complete record of study variables were included in this study. Clinical symptoms, sings, past medical history, laboratory tests, and sonographic data were recorded in a questionnaire. Questions consist of main related data including demographic, past medical and surgical history, obstetrical and gynecological history, contraception, pain and tenderness characteristics, nausea and vomiting, bleeding pattern, vital signs, CBC & Diff., HCG titre, and sonographic findings. Comparative analyses in two groups of EP and non-EP was performed. Cases with incomplete documents excluded from our study.

Statistical analysis

Quantitative data are represented as mean and standard deviation or median and inter quartile range and qualitative data are represented as frequency and percent. For comparison of qualitative data between the two groups, chi-squared test, Fisher exact test, and Kendal tau coefficient were applied whenever needed. Quantitative data were compared using independent sample t-test and Mann-Whitney test. All significant quantitative variables were converted into qualitative variables by defining cut-off value based on Youden Index. Diagnostic values were calculated for statistically significant variables, considering differences between the two groups. All statistically significant variables were included in a decision tree algorithm. Classification and regression tree (CART) were used to partition data into homogeneous groups in order to develop a prediction rule for EP diagnosis (Breiman et al., 1984). CART creates a tree-based classification. At each parent node of a tree, CART algorithm selects the independent variable that has the highest association with the binary dependent variable according to specific criteria. Gini index was used as splitting criteria for each parent nodes. A 10-fold cross-validation procedure was used to suggest the optimal number of leaves on the tree (Clark and Pregibon, 1993). The minimum numbers of observations in parent and child nodes were 50 and 20, respectively. The accuracy of the final tree was assessed calculating area under receiver operating characteristics (ROC) curve. All statistical analysis was performed with 0.05 significance level. Statistical package R 3.2.1 was used for all analysis (Core Team, 2015).

Results

In this study, 522 out of 574 cases were included, 52 cases were excluded from the study due to incomplete data recording. EP was diagnosed among 188 cases (36%). On 137 cases (72.9%) laparotomy, 3 cases (1.6%) laparoscopy, and 48 cases (25.5%) observation or medical treatment was performed. Of the study subjects, 334 cases (64%) were categorized as the non-EP group (abortion, normal pregnancy and luteal cysts), consist of 15 cases(47.6%) curettage, 135cases (40%) spontaneous abortion, 31 cases (9%) normal pregnancy without complication, 10cases(3%) surgery for luteal cysts complications. Mean age of EP cases was 30.45±5.61 (range: 17-43) and mean age of non-EP cases was 30.30±6.31 (range: 16-46).

Studied variables include70 qualitative data and 22 quantitative data. Statistical significant association was observed between 41 variables and EP (P-value <0.05, Table 1 and 2). Sensitivity, specificity, positive and negative predictive value, + LR, and -LR, were determined for significant variables as shown in Table 3 and Table 4. Finally, significant variables entered the decision tree (Fig. 1). Five rules were derived from decision tree algorithm:

In patients with a positive HCG and lower abdominal pain, if the pain was unilateral, EP probability was 95.6%. While in bilateral pain, EP was diagnosed in 9.7% of cases.
In patients with positive HCG who present with lower abdominal pain, if the pain was bilateral and accompanied by deep, superficial or generalized tenderness, the probability of EP was 65.1%. And if tenderness was not present, the likelihood of EP was 2.2%.
In patients with positive HCG and lower abdominal pain, if there is bilateral pain and no tenderness, in the presence of free fluid in the abdomen or pelvis, the probability of EP increases to 10.8%(vs. 1.1% if no free fluid was present).
In patients with positive HCG and lower abdominal pain, if the pain is bilateral and without tenderness and without free fluid, in the case of leukocytosis (more than 11950 /ml), the probability of EP increases to 10% (vs. 0.4% if leukocytosis was not present).
In patients with no leukocytosis, in the case of tachycardia (PR> 99/min), the probability of EPwas 4.3% (versus 0% in the case of PR<99 /min).

It should be noted that the surface under the ROC curve for decision making tree was 0.979 (95%CI(0.968-0.990))as shown in Fig. 2.

Discussion

In various studies different items have been used for diagnosis of EP. In a study carried out by C. Mimoun et al. (2016), a self-assessed questionnaire for the diagnosis of EP was designed for women presenting with abdominal pain. In their study, five variables had significant association with EP including vaginal bleeding more than 24 hours, cough sign, one-sided pelvic pain, brown discharge, and no frequent need to change sanitary towels. Patients received scores due to these five variables ranging 0 to 100 and divided to low-risk ad high-risk groups for EP with score of less than 25 and more than 70, respectively.

In another study by J. Bouyer et al. (2003), different risk factors associated with EP was analysed, and the major and meaningful risk factors were infectious history and smoking. Other variables were age, previous spontaneous abortion, IUD, and infertility.

In a follow-up study by M. Malek-mellouli et al. (2013), in PUL patients, three items had meaningful relationship with diagnosis of EP, including vaginal bleeding with pain, free fluid, and progesterone level (sensitivity 79% and specificity 59%).

In another study by Makhijani R. et al. (2017) for prediction of EP, initial BHCG and BHCG ratio had a significant relationship for prediction of EP among PUL patients (the area under the ROC curve was 0.863).

In a study performed by RG Buckley et al (2000), a clinical model was designed for EP prediction. Patients were divided in three groups of high, intermediate, and low-risk. The high-risk group consisted of women presenting with cervical-motion tenderness or abdominal tenderness.

In the present study, 5 items are strong predictors of EP, including unilateral pain, tenderness, pelvic or abdominal free fluid, leukocytosis, and tachycardia (with AUC of ROC equal to 94%). Predictors of the EP in the present study regarding the unilateral pain, abdominal tenderness, and free fluid are consistent with Mimoun study (2016), RG Buckley study (2000), and Malek-Mellouli (2013), respectively.

In our study, positive BHCG test was necessary along with abdominal pain as inclusion criteria. Since HCG test and its titer are available at the most medical centers – and even at the emergency rooms – we have excluded patients with negative or undermined HCG. That is, patients with final diagnosis of ovarian torsion, tumor, and appendicitis, if were not pregnant, have been excluded from the present study.

As a limitation, the present study examined patients with PUL and abdominal pain. Future studies might focus on all PUL cases with or without abdominal pain.

In future studies, 41 out of 92 studied variables which had a meaningful relationship with EP might be studied. Undoubtedly, these variables help clinicians to recognize EP. On he other hand, another study can be carried out in the future for validating the present study using our algorithm for PUL patients with abdominal pain in a separate population.

In conclusion, patients whose ultrasound is equivocal, and HCG has not reached to the discriminatory zone of the intrauterine pregnancy, using the decision-making tree of the present study can determine the probability of EP diagnosis. HCG positive women with lower abdominal pain might enter in this algorithm based on the bilateral or unilateral pain, as the first step. If the pain is bilateral based on the abdominal tenderness, free fluid, leucocytosis, and tachycardia, EP probability is defined. For instance, in the case of HCG positive and unilateral pain, the EP probability is 95%, with logical consideration of laparoscopic intervention; and if positive HCG and bilateral pain is present along with abdominal tenderness, the probability of EP is 65%, and close observation of the patient might be considered.

Table 1. Comparison of qualitative variables in EP and Non-EP groups

Variable		EP	Non-EP	P value
		frequency (percent)	frequency (percent)	
Abortion		51 (27.1%)	89 (26.6%)	0.905
Contraception	non	97 (51.6%)	165 (49.4%)	
	IUD[a]or TL[b] Use	18 (9.6%)	8 (2.4%)	0.001
	Other methods*	73 (38.8%)	161 (48.2%)	
Infertility		25 (13.3%)	19 (5.7%)	0.003
ART history	non	4 (21.1)	7 (30.4)	
	IVF[c]	4 (21.1)	2 (8.7)	0.435

	IUI[d]	5 (26.3)	5 (21.7)	
	Clomiphene	5 (26.3)	4 (17.4)	
	Lethrozol	1 (5.3)	5 (21.7)	
EP history		4 (2.1%)	4 (1.2%)	0.647
Previous EP treatment (surgery)		3 (75%)	1 (25%)	0.486
Diabetes		2 (1.1%)	7 (2.1%)	0.500
Thyroid disease		14 (7.4%)	37 (11.1%)	0.180
Uterine abnormality		3 (1.6%)	3 (0.9%)	0.672
PCO[e]		10 (5.3%)	9 (2.7%)	0.124
Immune abnormality		1 (0.5%)	7 (2.1%)	0.269
Surgery history		68 (36.2%)	100 (29.9%)	0.144
Adhesiolysis		4 (2.1%)	0 (0%)	0.016
Cystectomy		0 (0%)	5 (1.5%)	0.165
Salpingectomy		3 (1.6%)	3 (0.9%)	0.672
Appendectomy		6 (3.2%)	13 (3.9%)	0.810
Other surgeries		59 (31.4%)	93 (27.8%)	0.393
Surgical incision	Pfannenstiel incision	58 (100%)	89 (95.7%)	0.161
	Vertical incision	0 (0%)	4 (4.3%)	
Chronic pelvic pain		0 (0%)	1 (0.3%)	0.999
Vaginal discharge history		6 (3.2%)	9 (2.7%)	0.744

Pain Start	Gradually	45 (23.9)	170 (50.9)	<0.001
	Sudden or post-coital	143 (76.1)	164 (49.1%)	
Pain Quality	Continuous pain	98 (52.1%)	16 (4.8%)	<0.001
	Intermittent pain	44 (23.4%)	260 (77.8%)	
	Radiating pain	15 (8%)	4 (1.2%)	
	Shifting or vague pain	31 (16.5%)	54 (16.2%)	
Pain fluctuation	Increasing pain	142 (75.5%)	88 (26.3%)	<0.001
	Decreasing pain	24 (12.8%)	104 (31.1%)	
	Fluctuating pain	22 (11.7%)	142 (42.5%)	
Primary pain	One-sided pain	153 (95.6%)	7 (4.4%)	<0.001
	Two-sided pain	35 (9.7%)	327 (90.3%)	
Nausea and vomiting		77 (41%)	35 (10.5%)	<0.001
Vaginal bleeding		136 (72.3%)	223 (66.8%)	0.187
Severity of vaginal bleeding	sever	18 (13.2%)	33 (14.8%)	0.681
	spotted	118 (86.8)	190 (85.2)	
		118 (86.8%)	190 (85.2%)	0.681
Urinary symptoms		15 (8%)	11 (3.3%)	0.018
Tilt sign		43 (22.9%)	8 (2.4%)	<0.001
Tenderness	no	65 (34.6)	317 (94.9)	<0.001
	Tenderness with deep palpation	67 (35.6%)	12 (3.6%)	
	Tenderness with superficial palpation	29 (15.4%)	3 (0.9%)	
	Generalized tenderness	27 (14.4%)	2 (0.6%)	
Tenderness Site	RLQ	58 (47.2%)	9 (52.9%)	0.003
	LLQ	49 (39.8%)	1 (5.9%)	

	Two-sided	16 (13%)	7 (41.2%)	
Rebound tenderness		52 (27.8%)	2 (0.6%)	<0.001
Cough sign		2 (1.1%)	2 (0.6%)	<0.001
Mass palpation		3 (1.6%)	0 (0%)	0.046
CMT		2 (1.1%)	0 (0%)	0.129
Uterosacral nodule		2 (1.1%)	0 (0%)	0.129
Normal sonography		1 (0.6%)	31 (9.3%)	<0.001
Free fluid		152 (77.6%)	44 (22.4%)	<0.001
Myoma		14 (7.4)	12 (3.6)	0.052
Hemoperitoneum		114 (85.1%)	6 (60.1)	0.355

a: intra uterine device, b: tubal ligation, c: invitro fertilization, d: intra uterine insemination, e: poly cystic ovary

Table 2. Comparison of quantitative variables in EP and Non-EP groups

		EP	Non-EP	
Variable	Unit	Mean ±SD	Mean ±SD	P value
Age	yrs	30.45±5.61	30.30±6.68	0.802
Gestational age	days	55.62	68.21	<0.001
Gravid	No.	2 (2)	2 (2)	0.066
NVD	No.	0 (1)	0 (1)	0.082
C/S	No.	0 (1)	0 (1)	0.319
Temperature	°c	36.99±0.341	36.99±0.231	0.914
Pulse rate	/min	94.57±12.68	89.67±8.01	<0.001
Respiratory rate	/min	17.5 (1.5)	17 (2)	0.100
Systolic blood pressure	mm.Hg	104.65±12.86	106.18±8.91	0.110
Diastolic blood pressure	mm.Hg	64.41±17.29	71.13±8.73	<0.001
Pain duration	hours	5 (4)	13 (15)	<0.001
Pain interval	min	17.5 (27.5)	10 (5)	0.032
Hemoglobin 1	g/dl	11.21±1.65	11.85±1.24	<0.001
Post-op Hemoglobin	g/dl	9.67±1.59	10.38±0.905	0.004
Leucocyte	/ml	9507±3674	8500±3531	0.004
Neutrophil	%	73.36±9.39	71.52±8.68	0.039
HCG 1	mIU/ml	1611±2767	4450±18167	0.073
HCG 2	mIU/ml	1512±1834	5839±20685	0.138
HCG 3	mIU/ml	1684±2959	7619±34764	0.393
Myoma size	cm	3 (3.5)	2 (0.80)	0.145

Table 3. Sensitivity, specificity, + LR, -LR, PPV and NPV in meaningful qualititative variables for EP

Variable	Sensitivity	Specificity	+LR	-LR	PPV	NPV
Tilt	22.87%	97.60%	9.55	0.79	84.31%	69.21%
Tenderness	65.43%	94.91%	12.85	0.36	87.86%	82.98%
One-sided Tenderness	86.99%	41.18%	1.48	0.32	91.45%	30.43%
Rebound Tenderness	27.66%	99.40%	46.19	0.71	96.30%	70.94%
Cough sign	1.17%	99.39%	1.91	0.99	50%	65.79%
Mass palpation	1.60%	100.00%		0.98	100%	64.35%
Pain start (gradually vs others)	76.06%	50.90%	1.55	0.47	46.58%	79.07%

Pain quality (continuous vs. others)	52.13%	95.21%	10.88	0.5	85.96%	77.94%
Pain fluctuation (increasing vs. others)	75.53%	73.65%	2.87	0.33	61.47%	84.25%
Recent pain location (one-sided vs. two-sided)	95.21%	97.60%	39.75	0.05	95.72%	97.31%
Nausea and vomiting	40.96%	89.52%	3.91	0.66	68.75%	72.93%
Urinary symptoms	7.98%	96.71%	2.42	0.95	57.69%	65.12%
No gestational Sac in sonography	100.00%	9.28%	1.1	0	35.81%	100%
Myoma	8.24%	96.40%	2.29	0.95	53.85%	67.30%
Free fluid (severe and moderate vs. non)	67.59%	80.00%	3.38	0.41	93.59%	36.36%
Free fluid (yes vs. non)	80.85%	86.83%	6.14	0.22	75.55%	88.96%
Contraception (TL&IUD vs. others)	9.57%	97.60%	4	0.93	69.23%	65.73%
Contraception (yes vs. non except TL&IUD)	42.94%	50.61%	0.87	1.13	31.20%	62.98%
Infertility history	13.30%	94.31%	2.34	0.92	56.82%	65.90%
Adhesiolysis	2.13%	100.00%		0.98	100.00%	64.48%

Table 4. Sensitivity, specificity, + LR, -LR, PPV and NPV in meaningful quantitative variables for EP

Variable	Cut-point	Sensitivity	Specificity	+LR	-LR	PPV	NPV
Pain duration	≤ 9 hours	80.85%	62.87%	2.18	0.30	55.70%	85.64%
Gestational age	≤ 65 days	85.11%	50.00%	1.7	0.30	48.93%	85.64%
Pulse rate	> 95 /min	44.68%	79.34%	2.16	0.70	54.90%	71.82%
Diastolic blood pressure	≤ 60 mm.Hg	43.62%	78.74%	2.05	0.72	53.59%	71.27%
Hemoglobin	≤ 10.9 g/dl	39.89%	82.04%	2.22	0.73	55.56%	70.80%
Leucocyte	> 8600 /ml	60.11%	74.25%	2.33	0.54	56.78%	76.78%
Neutrophil	> 69.4%	69.15%	35.33%	1.07	0.87	37.57%	67.05%

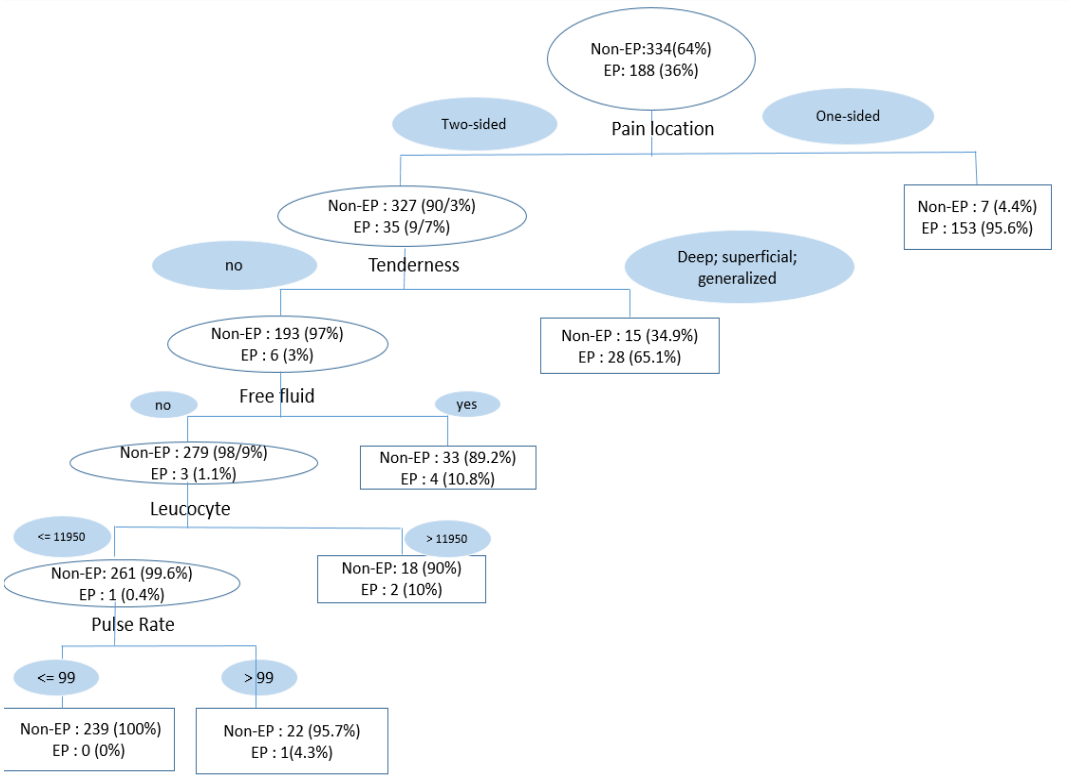

Figure 1. Decision-making tree for EP probability

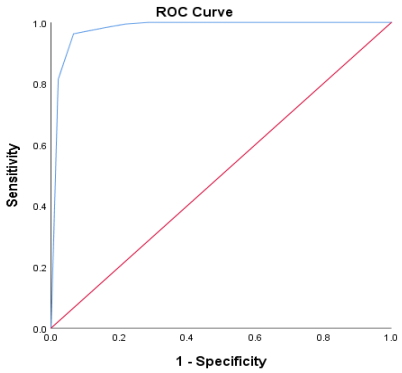

Figure 2. ROC curve for decision-making tree.

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