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Prediction of Location of a Symptomatic Early Gestation Based Solely on Clinical Presentation

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Abstract

Precis—Prediction of location of a symptomatic first-trimester pregnancy based on clinical symptoms and risk factors is possible, but must be used in conjunction with outpatient surveillance.

Objective—To evaluate three strategies for diagnosis of women at risk for ectopic pregnancy based on information collected at initial presentation.

Methods—Strength of association for risk factors, signs and symptoms obtained at initial presentation of women with pain, bleeding, or both in a first trimester pregnancy and a non-diagnostic ultrasound were calculated using a cohort of 2,026 women. Three models (logistic regression, a numeric scoring system and a Classification and Regression Tree) were created to predict final outcome and tested on a second cohort of 1,634 women. Accuracy was assessed using 2-by-2 tables evaluating the decision of send home vs. do not send home (combination of monitor or intervene) and intervene vs. do not intervene (monitor or send home). Sensitivity, specificity, and predictive values were calculated.

Results—The ultimate diagnosis of women in the test population was 304 (18.6%) patients with an ectopic pregnancy, 834 (51.0%) with miscarriage and 494 (30.2%) with an ongoing intrauterine pregnancy. A total of 95.9% of patients with ectopic pregnancy or miscarriage were correctly assigned to the strategy to monitor or intervene upon based on the scoring system, and 97.6% based on the Classification and Regression Tree. The specificity of the decision to send a patient home with a likely intrauterine pregnancy was greater than 95% for all three methods. The sensitivity of all strategies in the decision to intervene for an ectopic pregnancy was greater than 98%.

Conclusion—A simplified scoring system based on five factors (age, ectopic history, bleeding, prior miscarriage, and hCG level) was as effective as a Classification and Regression Tree or logistic regression modes in predicting outcome of women at risk for ectopic pregnancy. Prediction of location of a symptomatic first-trimester pregnancy based on clinical symptoms and risk factors is possible, but must be used in conjunction with outpatient surveillance.

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Introduction

Ectopic pregnancy (EP) is the leading pregnancy related cause of death in the first trimester of pregnancy and a major contributor to maternal morbidity (1,2). As a tubal pregnancy progresses, it erodes into blood vessels and can cause massive intra-abdominal bleeding. There are limitations in the strategies currently employed to diagnose EP. Even with the use of diagnostic algorithms that systematically evaluate all women at risk for an EP, only 50% of women with an EP can be diagnosed upon presentation. Diagnosis in the remaining 50% represents a clinical conundrum and can take up to 6 weeks (3). If the diagnosis of EP is delayed, rupture of the fallopian tube, resulting in greater risks of morbidity and mortality, can occur. Moreover, an EP of large size is not amenable to medical therapy and may require major surgery (laparotomy) instead of laparoscopy which can cause greater damage to the fallopian tube (and greater impairment of fertility), even if treated before rupture.

The presence of abdominal pain and vaginal bleeding in a woman known or suspected to be pregnant should be evaluated urgently in order to investigate the possibility of an EP or spontaneous abortion (SAB) (3-4). Ultrasound is the mainstay in the diagnosis of women at risk for ectopic pregnancy, but 8-25% of women at risk will have a non-diagnostic US at presentation (3-4) resulting in a pregnancy of unknown location (5-7). A solitary Human Chorionic Gonadotropin (HCG) value is not sufficient to definitively diagnose a woman at risk for EP (3,5,8). Thus, a combination of serial ultrasounds and hCG levels is the most efficient method for surveillance and ultimate diagnosis of women at risk (8-9). However, this diagnostic strategy is cumbersome and requires a high index of clinical suspicion (9-10). Additionally, up to 30% of all women with an EP present to an ED after rupture has occurred or, as we have demonstrated, rupture occurs during the lengthy diagnostic process, which can take weeks (3).

Because current strategies of diagnosis and treatment of women at risk for EP have decreased morbidity, future strategies should focus on minimizing the potential for interrupting a desired viable intrauterine pregnancy and reducing the number of costly and invasive procedures used to confirm a diagnosis. A strategy assessing women at high and low risk for ectopic pregnancy, at initial presentation, would allow a more efficient use of resources and may improve accuracy of diagnosis. The goal of this manuscript was to assess three different strategies to develop a simple, accurate, non-invasive method of diagnosis of ectopic pregnancy based on information available at presentation for care in a woman whose initial ultrasound is non-diagnostic (does not demonstrate an intrauterine or extrauterine pregnancy) and who is in need of further outpatient surveillance to make a definitive diagnosis.

Materials and Methods

Study design

This analysis is based on two retrospective cohorts conducted at the University of Pennsylvania Medical Center. Information was obtained from a dataset, currently maintained at this Institution, of all women who present with complaints of bleeding and/or pain during the first trimester of pregnancy (by positive pregnancy test or a history of a missed period). The potential risk factors used in our analysis were obtained from the history, clinical presentation and diagnostic tests gathered by clinicians at initial presentation of a woman at risk for ectopic pregnancy. Approval to conduct the study was obtained from the Institutional Review Board of the University of Pennsylvania.

Risk factors included age, gravidity, number of live births, number of prior cesarean sections (CS), number of spontaneous abortions (NSAB), number of elective abortions (VIP), number of previous ectopic pregnancies (NEP), pelvic inflammatory disease (defined as inpatient

treatment), previous outpatient treatment of gonorrhea and/or chlamydia, history of pelvic surgery other than cesarean sections, history of intrauterine device use, and clinical findings on admission such as pain, HCG level, bleeding and current gonorrhea/chlamydia infection. Women were followed until a definite diagnosis was made of SAB, EP or IUP. A normal IUP was confirmed by current progression of the pregnancy by ultrasound with visualization of an intrauterine yolk sac, fetal pole or fetal heartbeat. EP was diagnosed by the presence of chorionic villi in the fallopian tube after surgical treatment, visualization of an extrauterine gestational sac (with yolk sac and/or embryonic cardiac activity) on ultrasound for those treated medically or by a rise or stall of the HCG level, after dilatation and evacuation (and no evidence of chorionic villi in the endometrial samples obtained). SAB was confirmed by either histopathological confirmation of the presence of products of conception from endometrial curetings obtained after dilatation and curettage or by spontaneous decline of HCG level to ≤ 5 mIU/ml. Pain and bleeding were both defined as present if self reported as presenting symptom for care.

Analysis

We have previously demonstrated that when using risk factors as predictors of EP it is optimal to divide the three potential outcomes (EP, SAB and ongoing IUP) into a dichotomous outcome of IUP vs. non viable gestation (SAB and EP) (11). This approach allows better classification (greater area under an ROC curve) than the dichotomization into extrauterine pregnancy vs. intrauterine pregnancy (EP vs. IUP + SAB) (11). Thus our initial step was to divide our sample between those subjects diagnosed with IUP vs. those diagnosed with other types of outcomes (SAB and EP).

Analyses were performed on the first cohort. Bivariable associations were evaluated using Student's t-test, for continuous variables, while categorical variables were evaluated by Pearson χ^2 test of association. Odds ratios and Wald statistics were constructed to estimate the associations and test for statistical significance between the categorical risk factors and diagnosis. Stratified analyses were then performed to look for effect modifiers and confounding variables. In the case of categorical values, one of the categories was chosen as the reference group. Three methods of creating a predictive model were explored with a focus on discrimination: 1) A logistic regression 2) a numeric scoring system, and 3) a Classification and Regression Tree (CART) algorithm.

A logistic regression model was created using backward selection methods. At each step the largest p-value variable was removed from the model and this process was repeated until all variables had a p-value ≤ 0.05 or were identified as a confounding variable. Potential confounders were kept in the model if they affected the coefficient estimates of the other variables by 15% or more, giving the final multivariable model.

A second method to predict outcome was then generated in the form of a numeric scoring system. For this system a numeric values (ranging from a possible -2 to +14) was assigned to each risk factor that was in the final model based on its strength of associations estimated from the logistic regression model. For example an odds ratio (OR) of approximately 1.3 - 1.5 was given a score of 1, an OR of 1.5 - 2.0 was given a score of 2, and OR of ≥ 3.0 was given a score of 3 and an OR of 0.5 was given a score of -1. A total score of -2 to -1 was correlated with a low risk for nonviable gestation (EP or SAB); a total score of 0 - 4 corresponded to an intermediate risk for nonviable gestation, while a total score ≥ 5 showed a high risk for a nonviable gestation.

The third method used was a Classification and Regression Tree (CART), which was also created based on the variables identified by screening them with logistic regression. CART was employed to allow for further consideration of combinations of patient characteristics that

may further discriminate a potentially viable vs nonviable gestation. CART uses a computer-based technique of cross validation, CART dividing the sample into 10 roughly equal parts, each containing a similar distribution for the dependent variable. CART takes the first 9 parts of the data, and uses the remaining 1/10 of the data to obtain initial estimates of the error rate of selected trees. The results of the 10 mini-test samples are then combined to form error rates for trees of each possible size; these error rates are applied to the tree based on the entire sample. Decision tables were then generated for the scoring system and CART and each of them applied independently to our cohort. Different alternatives of management were then used based on the prediction from each of the modeling strategies for the diagnosis of a potentially viable vs nonviable gestation.

The developed models were then applied to a second, or test, cohort using logistic regress to assess accuracy of classification. A three tiered clinical action plan or decision rule was developed based on the outcome from these clinical prediction rules. The three possible action plans were to a) "Send home", b) "Intervene" or c) "Monitor". The three clinical prediction strategies (described above) were applied to the dataset retrospectively. Each model was applied to these data to obtain recommendations. In the case of the scoring system, patients with a total score compatible with a low risk (-2 to -1) for EP/SAB (or likely viable IUP) were assigned the treatment "send home" with less intensive evaluation. Patients at intermediate risk (0-4) were assigned standard clinical evaluation with serial outpatient surveillance, while women at high risk for EP/SAB (≥ 5) were recommended for intervention to distinguish a miscarriage from an EP. The recommendations for each of these methods were then compared to the actual definitive diagnosis to assess accuracy. Thus we were able to calculate and compare the sensitivity, specificity and predictive value for each model.

For the calculation of test characteristic the three outcomes and the three decision rules were collapsed to 2 by 2 tables evaluating the decision of send home vs. do not sent home (combination of monitor or intervene) and intervene vs. do not intervene (monitor or send home). Importantly we focused on each of the three methods' specificity to send home only patients with a high suspicion of an IUP, and their predictive value for intervening only on those patients with a low suspicion for an IUP. All the statistical analysis were performed using SAS, version 9.1 (SAS Institute Inc., Cary, NC), STATA version 9 (Stata Corp. College Station, TX) and CART (Salford Systems, San Diego, CA).

Results

The original cohort consisted of 2026 patients, whose initial ultrasound was non-diagnostic and needed outpatient surveillance to obtain a definitive diagnosis, were used in this analysis. These patients presented to the University of Pennsylvania Medical Center with complaints of pain and/or bleeding in the first trimester collected over a nine year period (1/90 - 7/99). A total of 367 (18.11%) patients were diagnosed with EP, 1192 (58.84%) patients were diagnosed with an SAB and 467 (23.05%) had an ongoing IUP. Overall, the median gravity of our total population was 2 gestations and the median parity 1, while the mean serum HCG level found was 4269.7mIU/ml. For women ultimately diagnosed with an IUP, mean gravity was 2.3, mean parity of 0.86 and mean HCG of 6488.9mIU/ml. In the EP+SAB group mean gravity of 2.40, mean parity of 0.91 and mean HCG of 3697mIU/ml, were found. A description of our cohort is presented in table I.

Each prediction model was then tested on a new cohort of women (1634) collected at the same institution under the same circumstances for 5 years (7/99 - 7/04). The final diagnosis of this cohort was IUP 494 (30.2%), SAB 834 (51.0%) and EP 304 (18.6%).

The final multivariable logistic regression model differentiating IUP from non viable gestation included the following variables: age, number of ectopic pregnancies, parity, vaginal bleeding on presentation, previous live births, spontaneous abortions and serum HCG level (See Table II). A scoring system was then developed based on the values of odds ratios obtained from the logistic regression model. This scoring system is presented in Table III. A CART tree was also developed as the third method of evaluation. After testing several configurations of CART options, it was found that CART with a node size of 40, under which no more partitions were to be made, brought the best results. The optimal CART tree obtained is presented in figure I.

Information regarding three different treatment options for *Sending the patient home*, *Continue monitoring* or *Intervene*, for both CART and the scoring system, are presented in table IV. We found that 95.9% of patients with EP or SAB were correctly monitored or intervened based on the scoring system, while the same number was 97.6% based on CART.

A summary of the collapsed 2 by 2 decision tables (send home/do not send home), (intervene/do not intervene) for the three methods under evaluation are presented in tables V and VI. In these two tables sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV) were presented for each of the methods under evaluation.

Discussion

The current standard of care when evaluating a woman with a potentially complicated first trimester pregnancy is to take a detailed history of risk factors and ascertain the clinical course. The classic risk factors for ectopic pregnancy and miscarriage have been well characterized in a normal population (12) as well as in the population presenting with pain and bleeding (13-14). Knowledge of risk factors is particularly valuable if they can inform clinical care. The use of risk factors and presenting information as part of a clinical decision rule can be helpful for clinicians in cases when diagnosis is not definitive upon initial presentation for care. A clinical prediction rule enables clinicians to use information based risk factors to assess the probability of developing it in the future (15). This type of strategy has been used to predict children at risk for dehydration (16), interpretation of testing to assess for pulmonary embolism (17), management of cytology for women with abnormal pap smears (18) and in the prediction of iron deficiency anemia in pregnant women (19). In the situation of women at risk for an ectopic pregnancy, a potential clinical decision rule would be used for a woman with a “pregnancy of unknown location” or when the initial ultrasound was non-diagnostic, and further tests are required to confirm a diagnosis.

In this study we used three different methods to assess the predictive ability of signs and symptoms at presentation to discriminate an IUP from the presence of a nonviable gestation in a first trimester pregnancy, each with its own advantages and disadvantages. Logistic regression is a generalized linear statistical model used to predict a specific outcome and is widely used in medical statistics today. This method is very precise, but requires the use of a computer to estimate risk. The second method, a scoring system, uses the variables included in the final logistic model, in a simplified form by assigning scores to each based on the weight of the odds ratios (OR). This method is very easy to use, and it does not require a computer system. However it may not be as precise as a full logistic regression model as risk was “rounded” to obtain a numeric score. We also considered CART, an automated data-analysis tool that searches for important patterns and relationships to generate accurate and reliable predictive models (20). CART uses tree-building algorithm to determine a set of *if-then* logical (split) conditions that permit accurate prediction of a specific outcome. The advantages of using CART are, the simplicity of the results and that there is no implicit assumption that the underlying relationships between the predictor variables and the dependent variable.

The diagnosis of women at risk for EP is complicated by the fact that there are three possible outcomes.(EP, SAB and ongoing IUP) that dictate very different treatment strategies and consequences of missed diagnosis. Our three tiered decision model was designed to mimic potential clinical care. “Send home” suggested a strategy of discharging the patient from the hospital with minimal further evaluation planned other than referral for potential care as there was high suspicion of IUP. “Intervene” suggested a strategy for a patient with a nonviable pregnancy at high risk for EP. “Intervention”, does not indicate the need for surgical procedure, rather the need for increases level of care or counseling. The “increased care” recommended further urgent evaluation is suggested to diagnose or treat (such as laparoscopy, uterine curettage, expectant management with heightened suspicion and/or surveillance). “Monitor” suggests a strategy when there is insufficient information to distinguish among EP, SAB and IUP. In this instance the clinical prediction rule was not informative and current standard care of serial hCG values and ultrasound should be used to make the ultimate definitive diagnosis in a woman at risk for EP.

Our strategy was to assess the capacity of each method to identify patients with an IUP, for which no further treatment was necessary (send home/do not send home) and also to identify patients with a potential EP who require immediate treatment (intervene/do not intervene). The advantage of our tiered treatment/surveillance strategy was that sensitivity and specificity could be maximized at different decisions points in an effort to minimize false positive and false negative diagnoses. For example, we attempted to maximize specificity (at the expense of sensitivity) when confronted with the decision to send home, reducing the possibility of sending women with an EP home with no follow up. Conversely, we maximized sensitivity and negative predictive value (at the expense of specificity) when confronted with the decision to intervene. In this instance intervention (to distinguish a miscarriage from an ectopic pregnancy) was only entertained when non viable gestation was confirmed, thus the chance of interrupting a viable pregnancy was low.

The test characteristics of each of our three strategies, in these two clinical situations, demonstrated a remarkable equivalence. The specificity of diagnosis in the decision to send home was greater than 95% for all three methods, with negative predictive value about 81%. In the case of the decision to intervene, all strategies had a sensitivity greater than 98% with all three having a negative predictive value of greater than 93%. Based on these data we concluded that the use of a simple numeric scoring system can be as accurate as a more complicated computer model derived using logistic regression or CART. Therefore, data obtained on the initial presentation of a woman at risk for EP can be used to inform a clinician as to risk of EP, and possibly aid in the decision of the frequency of follow up. Of note, race was not part of our models as it was unavailable in the majority of cases in our dataset.

There are two important limitations of the diagnostic strategy described. The decision to send home or intervene based on risk factors is only made in a small subset of the population. In the case of the scoring system, 70% of those ultimately diagnosed with an IUP, and 81% of those diagnosed with a nonviable gestation are recommended to be treated with the usual standard of care including surveillance with serial HCG values and/or ultrasound (9-10,21-23). Moreover, the accuracy of the rule is not 100%. Of the approximately 30% of women with an IUP, 1.8% would have been falsely diagnosed as a nonviable gestation. Therefore this classification system cannot be used in isolation without continued outpatient surveillance.

In summary, the strategy of surveillance of a woman who presents with pain and bleeding in the first trimester, in those not initially definitely diagnosed with an ongoing IUP, SAB or EP is cumbersome. Others have attempted to simply follow up looking at hCG values (24-26). However, we have demonstrated that a simple clinical decision rule can be used to assess the chance of a woman having an ongoing intrauterine pregnancy despite the presence of vaginal

bleeding/pain. This allows clinicians to potentially individualize a patient to out-patient follow up or to intervention to distinguish an ongoing IUP from a miscarriage and ectopic pregnancy. The simple rule based on five factors has good diagnostic accuracy, and distinguishes about 30% of the population as high or low risk. Like other clinical decision rules, this simple scoring system should not be used solely, but in combination with current strategies to definitively diagnose women at risk for ectopic pregnancy.

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Figure 1. Classification and Regression Tree system predicting ectopic pregnancy and spontaneous abortions *

*Minimum size below which a node will not be split is 30

Class 0 = Intrauterine pregnancy

Class 1 = Ectopic pregnancy and spontaneous abortions

Table 1

Description of the cohort

		IUP vs. (EP+SAB)			p-value <0.01
		IUP		EP + SAB	
Age	n		%	N	%
<20	119		26.6	367	24.3
20-24	156		34.9	433	28.7
25-29	95		21.3	321	21.3
30-34	52		11.6	242	16
>35	25		5.6	147	9.7
Race					0.15
African American	9		3.7	54	6
Others	237		96.3	845	94
Parity					0.35
0	259		55.5	861	55.2
1	91		19.5	322	20.7
2	62		13.3	175	11.2
3	39		8.3	118	7.6
4 or more	16		3.4	83	5.3
Prior VIP					0.96
0	363		80.3	1199	80
1	58		12.8	191	12.7
2 or more	31		6.9	109	7.3
H/o SAB (¹)					0.05
0	335		82.3	1166	85.7
1	59		14.5	139	10.2
2 or more	13		3.2	55	4

IUP vs. (EP+SAB)						
	IUP			EP + SAB		
	n	%		N	%	p-value
H/oEP						0.42
0	434	92.6		1442	92.9	
1	31	6.3		99	6.6	
2 or more	2	1.1		17	0.4	
H/o pelvic surgery	97	20.8		277	17.8	0.14
H/o prior c-section						0.66
0	431	92.3		1456	93.5	
1	28	6		77	4.9	
2 or more	8	1.7		25	1.6	
Past use of IUD	19	4.1		68	4.4	0.78
H/o PID	106	22.7		311	20	0.2
H/o outpt tx for GC/CT⁽²⁾						0.17
0	366	78.4		1266	81.3	
1	88	18.8		234	15	
2	11	2.4		53	3.4	
3 or more	2	0.4		5	0.3	
Bleeding	129	28.5		1246	83.6	<0.01
HCG level						<0.01
0 - 500	179	38.3		804	51.6	
501 - 2000	103	22.1		314	20.1	
2001 - 4000	59	12.6		148	9.5	
>4000	126	27		293	18.8	

IUP vs. (EP+SAB)					
IUP			EP + SAB		
	n	%	N	%	p-value
Pain	324	69.4	966	62	<0.01
GC/CTon presentation	39	10.4	134	10	0.82

(1) h/o= history of

(2) tx= Treatment, outpt=outpatient, GC/CT= Gonorrhea/Chlamydia

Table II

Final logistic model predicting (EP+SAB)

Variables	Value	OR	95%CI
Age	<18	1.32	0.86-2.01
	18-38	ref	
	>38	6.26	2.08-18.82
NEP	1	1.7	0.95 - 3.05
	>=2	3.74	0.75-18.53
Parity	>=2	0.58	0.29-1.16
Bleeding	yes/no	15.6	11.74-20.74
Previous Live Births	yes/no	1.22	0.94-1.59
NSAB	1	0.56	0.37 - 0.86
	>=2	1.05	0.50-2.21
HCG	0-500	ref	
	501 - 2000	0.67	0.46 - 0.98
	>2000	0.46	0.34 - 0.63

NEP: Number of ectopic pregnancies

NSAB: Number of spontaneous abortions

HCG: Human Chorionic Gonadotropin

Table III

Prediction of nonviable gestation via scoring system

Variable	Numeric value used in decision rule
Age	
• Age<18yo	+1
• Age > 38yo	+3
Ectopic Pregnancy	
• 1 prior EP	+2
• >=2 prior EP	+3
Bleeding	
	+4
Prior miscarriage	
• 1 prior SAB	-1
HCG^I > 2000mIU/ml	-1

A score of -1 or -2 is Low risk for nonviable gestation
(EP+SAB)

A score of 0 - 4 is Intermediate risk for nonviable gestation

A score of >=5 is High risk for nonviable gestation

^I HCG: Human Chorionic Gonadotropin

Table IV

Decision table comparing Scoring system and CART

	IUP		nonviable gestation (EP+SAB)	
Scoring system	N	%	N	%
• Send Home	105	27.7	52	4.15
• Monitor	267	70.45	1021	81.35
• Intervene	7	1.85	182	14.5
CART				
• Send Home	93	24.54	30	2.39
• Monitor	283	74.67	1060	84.46
• Intervene	3	0.79	165	13.15

Table V

Send home / do not send home

Method used	Sensitivity	Specificity	NPV	PPV
Logistic regression model	27.70%	95.86%	81.45%	66.86%
Scoring system	25.33%	96.25%	81.02%	67.13%
CART	24.54%	97.61%	81.02%	75.61%

Table VI

Intervene / do not intervene

Method used	Sensitivity	Specificity	NPV	PPV
Logistic regression model	98.15%	14.50%	96.30%	25.74%
Scoring system	98.42%	6.45%	93.10%	24.11%
CART	99.21%	13.15%	98.21%	25.65%