Prediction of Outcome in Women with Symptomatic First-Trimester Pregnancy: Focus on Intrauterine Rather Than Ectopic Gestation

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Abstract

Objective: Symptoms of vaginal bleeding and abdominal pain are common in cases of ectopic pregnancy (EP), spontaneous abortions (SAB), and complications of an intrauterine pregnancy (IUP). It is important to determine if efforts should focus on differentiating EP from an IUP (IUP + SAB) or a viable IUP from a nonviable gestation (EP + SAB) in women at risk for EP.

Methods: This is a retrospective cohort study of women who presented with bleeding or pain or both during the first trimester of pregnancy. The cohort was divided into subjects diagnosed with IUP vs. (EP + SAB). The same cohort was then divided into subjects diagnosed with EP vs. (IUP + SAB). Logistic regression models based on risk factors for both outcomes (EP vs. [IUP + SAB] and IUP vs. [EP + SAB]) were obtained. ROC curves as well as Hosmer-Lemeshow goodness of fit and Akaike's information criterion (AIC) were used.

Results: Overall, 18.1% ($n = 367$) of the women were diagnosed with EP, 58.8% ($n = 1192$) were diagnosed with an SAB, and 23.1% ($n = 467$) had an ongoing IUP. The area under the ROC curve for the model IUP vs. (EP + SAB) was statistically greater than the model EP vs. (IUP + SAB), $p < 0.001$. AIC and Hosmer-Lemeshow goodness of fit confirmed the better accuracy of the model comparing IUP vs. (EP + SAB).

Conclusions: Information collected at initial presentation from women at risk for EP to be used for building prediction rules should focus on differentiating a viable from a nonviable pregnancy rather than attempting to distinguish an extrauterine from an intrauterine pregnancy. However, this distinction should not affect current clinical care.

Introduction

EACH YEAR, APPROXIMATELY 3 MILLION WOMEN are diagnosed with an ectopic pregnancy (EP), accounting for 2%–3% of all gestations. Furthermore, reports have shown that the prevalence of EP has been increasing.^{1–3} The diagnosis of EP can be difficult because the presenting symptoms are very similar to symptoms reported by women with spontaneous abortions (SAB) and complications of an ongoing intrauterine pregnancy (IUP). Two of the most common symptoms that overlap in these three conditions are vaginal bleeding and pelvic or abdominal pain.^{4,5} Accurate diagnosis for women with a symptomatic first trimester pregnancy is extremely important, as >40% of women with EP are misdiagnosed as having a less serious complication of early pregnancy or a non-pregnancy-related condition.^{6–8} The diagnostic strategies

currently used for EP are limited.^{9,10} Studies of the use of different markers to differentiate between an intrauterine and extrauterine pregnancy have not been optimal.^{8,11–16}

Follow-up care, treatment, and prognosis for a woman at risk for an EP depend on an accurate determination of both the location of a pregnancy (intrauterine or extrauterine) and the viability of a pregnancy. A fundamental issue in the diagnosis of symptomatic first-trimester pregnancies, not yet resolved, is whether efforts should be directed toward differentiating an EP from an IUP (either an IUP or an SAB) or instead toward differentiating a viable gestation (IUP) from a nonviable gestation (either an EP or an SAB). We evaluated the use of historical risk factors and presenting clinical symptoms to initially differentiate women with symptomatic first-trimester pregnancies and to aid in the development of a prediction model.

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Materials and Methods

Approval to conduct the study was obtained from the Institutional Review Board of the University of Pennsylvania. A retrospective cohort study was conducted at the University of Pennsylvania Medical Center. Risk factors and information on clinical presentation were obtained from a dataset

currently maintained at this institution of all women who come to the Emergency Department with complaints of bleeding or pain or both during the first trimester of pregnancy (by positive pregnancy test or missed period) in whom an IUP cannot be immediately confirmed. Variables used in our analysis were obtained from the history, clinical symptoms at presentation, and diagnostic tests obtained, all of

TABLE 1. DESCRIPTION OF COHORTS

	<i>IUP vs. others</i>					<i>EP vs. others</i>				
	<i>IUP</i>		<i>EP + SAB</i>			<i>EP</i>		<i>IUP + SAB</i>		
	<i>n</i>	%	<i>n</i>	%	<i>p value</i>	<i>n</i>	%	<i>n</i>	%	<i>p value</i>
Age					<0.01					<0.01
<20	119	26.6	367	24.3		43	11.8	443	27.8	
20–24	156	34.9	433	28.7		87	23.8	502	31.5	
25–29	95	21.3	321	21.3		112	30.7	304	19.1	
30–34	52	11.6	242	16		84	23	210	13.2	
>35	25	5.6	147	9.7		39	10.7	133	8.4	
Race					0.15					0.69
African American	9	3.7	54	6		229	95.02	853	94.36	
Others	237	96.3	845	94		12	4.98	51	5.64	
Parity					0.35					<0.01
0	259	55.5	861	55.2		174	47.4	946	57	
1	91	19.5	322	20.7		94	25.6	319	19.2	
2	62	13.3	175	11.2		45	12.3	192	11.6	
3	39	8.3	118	7.6		29	7.9	128	7.7	
4 or more	16	3.4	83	5.3		25	6.8	74	4.5	
Prior VIP ^a					0.96					0.07
0	363	80.3	1199	80		294	82.4	1268	79.6	
1	58	12.8	191	12.7		33	9.2	216	13.6	
2 or more	31	6.9	109	7.3		30	8.4	110	6.9	
History of SAB					0.05					0.5
0	335	82.3	1166	85.7		269	83.8	1232	85.2	
1	59	14.5	139	10.2		36	11.2	162	11.2	
2 or more	13	3.2	55	4		16	5	52	3.6	
History of EP					0.42					<0.01
0	434	92.6	1442	92.9		306	83.4	1570	94.7	
1	31	6.3	99	6.6		48	13.1	82	5	
2 or more	2	1.1	17	0.4		13	3.5	6	0.4	
History of pelvic surgery	97	20.8	277	17.8	0.14	88	24	286	17.24	<0.01
History of prior CS					0.66					0.3
0	431	92.3	1456	93.5		342	93.2	1545	93.2	
1	28	6	77	4.9		16	4.4	89	5.4	
2 or more	8	1.7	25	1.6		9	2.4	24	1.4	
Past use of IUD	19	4.1	68	4.4	0.78	20	5.5	67	4	0.2
History of PID	106	22.7	311	20	0.2	90	24.5	327	19.7	0.04
History of outpatient treatment for GC/CT					0.17					0.11
0	366	78.4	1266	81.3		289	78.8	1343	81	
1	88	18.8	234	15		60	16.3	262	15.8	
2	11	2.4	53	3.4		18	4.9	46	2.8	
3 or more	2	0.4	5	0.3		0	0	7	0.4	
Vaginal bleeding	129	28.5	1246	83.6	<0.01	256	75.74	1119	69.72	0.03
HCG level					<0.01					<0.01
0–500	179	38.3	804	51.6		155	42.23	828	49.9	
501–2000	103	22.1	314	20.1		103	28.07	314	18.9	
2001–4000	59	12.6	148	9.5		40	10.9	167	10.1	
>4000	126	27	293	18.8		69	18.8	350	21.1	
Pain	324	69.4	966	62	<0.01	244	66.49	1046	63.05	0.2
GC/CT on presentation	39	10.4	134	10	0.82	22	6.9	151	10.8	0.03

^aVIP, voluntary interruption of pregnancy or termination; SAB, spontaneous abortion; EP, ectopic pregnancy; CS, cesarean section; IUD, intrauterine device; PID, pelvic inflammatory disease; GC/CT, gonorrhea/chlamydia.

TABLE 2. FINAL MODEL PREDICTING IUP vs. (EP + SAB)

<i>Variable</i>	<i>Value</i>	<i>OR</i>	<i>95%CI</i>	<i>p value</i>
Age (years)				0.01
	<20	1.20	0.79–1.82	0.40
	20–24	1.09	0.74–1.63	0.65
	25–29	Referent		
	30–34	0.62	0.38–1.02	0.06
No. of prior ectopic pregnancies	<35	0.50	0.27–0.94	0.03
				0.18
	1	0.70	0.39–1.25	0.23
	≥2	0.31	0.06–1.53	0.15
				0.46
Parity				
	1	2.02	0.51–7.96	0.32
	2	2.87	0.71–11.65	0.14
	3	2.75	0.65–11.55	0.17
	<4	2.11	0.46–9.73	0.34
Vaginal bleeding	Yes/no	0.06	0.05–0.09	<0.01
Previous Live Births	Yes/no	0.43	0.11–0.66	0.22
No. of prior SAB ^a				0.02
	1	1.82	1.19–2.79	<0.01
	≥2	0.88	0.42–1.84	0.73
				<0.01
HCG level				
	0–500	Ref		
	501–2000	1.52	1.05–2.21	<0.03
	2001–4000	2.11	1.33–3.34	<0.01
	>4000	2.20	1.54–3.14	<0.01

^aSAB, spontaneous abortion.

which were included in the dataset. Data were entered by the medical staff as part of routine patient care.

Risk factors incorporated into our analysis included age, gravity, number of live births, number of prior cesarean sec-

tions (CS), number of SAB, number of elective abortions (VIP), number of previous EP, pelvic inflammatory disease (PID) (defined as inpatient treatment), outpatient treatment of gonorrhea or chlamydia or both, history of pelvic surgery

TABLE 3. FINAL MODEL PREDICTING EP vs. (IUP + SAB)

<i>Variable</i>	<i>Value</i>	<i>OR</i>	<i>95%CI</i>	<i>p value</i>
Age (years)				0.01
	<20	0.33	0.22–0.50	<0.01
	20–24	0.59	0.42–0.83	<0.01
	25–29	Ref		
	30–34	1.11	0.76–1.60	0.60
No. of prior VIPs ^a	>35	0.87	0.55–1.38	0.56
				0.07
	1	0.61	0.40–0.92	0.02
	≥2	0.98	0.62–1.56	0.93
				<0.01
No. of prior EPs				
	1	2.72	1.79–4.13	<0.01
	≥2	11.01	4.01–30.24	<0.01
History of PID	Yes/no	1.44	1.07–1.92	0.02
Parity				0.04
	1	1.57	1.15–2.15	<0.01
	2	1.08	0.71–1.63	0.72
	3	0.85	0.52–1.39	0.52
	>4	1.18	0.67–2.08	0.58
Vaginal bleeding	Yes/no	1.44	1.08–1.92	0.01
HCG level				<0.01
	0–500	Referent		
	501–2000	1.82	1.34–2.48	<0.01
	2001–4000	1.40	0.92–2.14	0.12
	>4000	1.01	0.71–1.42	0.97

^aVIP, voluntary interruption of pregnancy or termination; EP, ectopic pregnancy; PID, pelvic inflammatory disease.

FIG. 1. ROC curve. Final model IUP vs. (EP + SAB).

other than CS, history of intrauterine device (IUD) use, clinical findings on admission, human chorionic gonadotropin (HCG) level at presentation, presence of vaginal bleeding, and current gonorrhea/chlamydia infection. Variables, such as history of prior SAB, VIP, EP, CS, and pelvic surgery were examined as both continuous and dichotomous variables. Women were followed until a definite diagnosis of SAB, EP, or IUP was made. A normal IUP was confirmed by ultrasound visualization of an intrauterine yolk sac, fetal pole, or fetal heartbeat. EP was diagnosed by the presence of chorionic villi in the fallopian tube when the EP was treated surgically, by visualization of an extrauterine gestational sac with a yolk sac or embryonic cardiac activity for those treated medically, or by a rise or a plateau of the HCG level after dilatation and evacuation with absent chorionic villi in the uterine curettings. SAB was confirmed by either histopathological identification of chorionic villi in the uterine curettings obtained after dilatation and curettage or by spontaneous decline of HCG level to ≤ 5 mIU/mL postoperatively. Pain and the presence of vaginal bleeding were defined as present/absent based on patient self-report at presentation.

Analysis

Two distinct approaches were used to evaluate our cohort. We first divided our sample into those diagnosed with IUP vs. those diagnosed with the other outcomes (SAB and EP). Second, the same sample was divided into those patients diagnosed with EP vs. those with other outcomes (IUP and SAB). In both instances, statistical analyses were performed using the following steps. First, descriptive analyses were performed. Bivariate associations were evaluated using Student's *t* test for continuous variables, and categorical variables were evaluated by Pearson chi-square test of association. Wald statistics were constructed to test for an overall association between the categorical risk factor and diagnosis. Stratified analyses were performed for both groups (IUP vs. others; EP vs. others) to identify potential effect modifiers and confounding variables. In the case of categorical values, one of the categories was chosen as the reference group. Two separate logistic regression models were then developed using a backward, stepwise method for variable selection. Independent risk factors for the outcome were re-

tained if the $p \leq 0.05$. Potential confounders were kept in the model if they affected the coefficient estimates of the other variables by $\geq 15\%$. The goodness of fit of the logistic regression models was confirmed using a Hosmer-Lemeshow test. The area under the ROC curves were then generated for both—IUP vs. others and EP vs. others—scenarios. Finally, we used Akaike's information criterion (AIC), which is a statistical model of fit measure, to compare these two nonnested models. A lower AIC value is indicative of a better fitting model. All statistical analyses were performed using STATA software (College Station, TX).

Results

The database contained information on 2026 patients who came to the Emergency Department with complaints of pain or bleeding or both in the first trimester of pregnancy. The mean gravity of our total population was 2.15 gestations, and the mean parity was 0.83. Three hundred sixty-seven (18.1%) patients were diagnosed with EP, 1192 (58.8%) patients were diagnosed with an SAB, and 467 (23.05%) had an ongoing IUP. The mean serum HCG level found in our complete cohort was 4269.7 mIU/mL. Our cohort was then subdivided into EP vs. others (IUP + SAB) and IUP vs. others (EP + SAB). A comparison of these groups is presented in Table 1. In the EP vs. others (IUP + SAB) group, we found that the mean gravity of women with an EP was 2.7, with a mean parity of 1.0 and a mean serum HCG level of 3404.7 mIU/mL; in the (IUP + SAB) group, we found a mean gravity of 2.3, mean parity of 0.87, and HCG of 4547.1 mIU/mL. In the analysis of IUP vs. others (EP + SAB), the mean gravity for IUP was 2.3, mean parity was 0.86, and mean HCG was 6488.9 mIU/mL. In the EP + SAB group, a mean gravity of 2.40, mean parity of 0.91, and mean HCG of 3697 mIU/mL were obtained. The results of the final logistic regression model comparing IUP vs. others (EP + SAB) are presented in Table 2. The results from the final logistic model comparing EP vs. others (IUP + SAB) are presented in Table 3.

The area under the ROC curve for the first model (IUP vs. others) was 0.83 (CI = 0.81-0.86) (Fig. 1). The Hosmer-Lemeshow goodness of fit for the first model (IUP vs. others) showed a chi-square of 9.68 (8 degrees of freedom [df] $p = 0.29$). The area under the ROC curve for the second

FIG. 2. ROC curve. Final model EP vs. (IUP + SAB).

model (EP vs. others) was 0.70 (CI = 0.67-0.73) (Fig. 2). The Hosmer-Lemeshow goodness of fit for this model (EP vs. others) showed a chi-square of 3.58 (8 df, $p = 0.89$). Model fit was also evaluated using AIC. The model IUP vs. others had an AIC value of 1327.4, and the model EP vs. others had an AIC value of 1436.4.

Discussion

Available methods for diagnosis of ectopic pregnancy can be problematic, complex, and prolonged.^{14,17-19} Optimizing the diagnosis without sacrificing accuracy is of tremendous public health value. The main objective of this study was to address the initial question for the development of a clinical prediction rule. Given that there are three possible outcomes for women with a symptomatic early gestation, we need to establish if it is more accurate to focus on the prediction of an EP or an IUP. We restricted our cohort to women who sought evaluation of pain or bleeding or both during the first trimester of pregnancy and without a definite diagnosis. This study design limits selection bias and information bias, as information about exposures was collected before a definite diagnosis was obtained. Logistic regression analysis demonstrated that only seven variables (age, number of previous pregnancy terminations, number of previous EP, PID, parity, vaginal bleeding on presentation, and HCG level on presentation) were significantly associated with EP when compared with IUP and SAB combined. Of these seven variables present in our final model, a history of previous EP carried the highest risk for a new episode of EP. This risk increased dramatically, from almost three times the risk with a history of one previous EP to more than 11 times the risk of a new EP when a history of two or more previous EP was reported. These numbers most likely reflect the presence of persistent tubal pathology, which can lead to a higher risk of subsequent EP in the same patient. This is in agreement with previous studies that reported the number of previous EP as a major risk factor for a new episode of EP.^{18,20-24}

Logistic regression showed that seven variables were significantly associated with IUP when compared with EP and SAB combined (age, number of previous EP, parity, a complaint of vaginal bleeding on presentation, number of live births, SAB, and HCG level on presentation). The most significant risk factor found for IUP was parity. The odds of an IUP were increased for women with a history of two or three previous pregnancies. It is important to note that the presence of vaginal bleeding significantly decreased the odds of an IUP.²⁵ Furthermore, an HCG level >500 mIU/mL was statistically significantly associated with the presence of an IUP when compared with levels <500 mIU/mL. As expected, the odds of IUP increased as HCG level increased.

Age was also a significant factor associated with IUP, as we found that women older than 30 had lower odds of being diagnosed with an IUP compared with women aged 25-29. Interestingly, a history of one previous SAB carried a significant increase in the odds of having an IUP (as opposed to having an EP or SAB). Nonetheless, when a history of two or more SAB was present, this significance was lost.

When we compared the ROC curves designed for each of these two models, we found that the area under the ROC curve (sensitivity and 1-specificity) for IUP vs. (EP and SAB) was larger than that of EP vs. (IUP and SAB), indicating a

better prediction for IUP than for EP. When we obtained the Hosmer-Lemeshow goodness of fit as well as the AIC for both models, we confirmed using both methods that predicting an IUP (vs. EP and SAB) is a better fit than predicting EP (vs. IUP and SAB). This information demonstrates that the prediction of an IUP in women with complaints of vaginal bleeding or pain or both is more accurate than the prediction of EP in women with the same symptoms. It is difficult to explain why it is more accurate to predict a viable IUP than an EP. We may speculate that some risk factors (or the absence of them) may be more predictive of a nonviable gestation (EP and SAB combined) than an ectopically implanted gestation. It is also possible that not all EP have any well-known or identifiable risk factors.^{12,13,18}

Our model can help increase the accuracy of clinicians differentiating IUP vs. EP in patients seeking care with symptoms similar to those of both conditions. However, the use of this logistic regression model to predict IUP may not be practical in a clinical setting. There is a need for a simpler scoring system, such as a clinical prediction rule, that will allow clinicians to use this information in their daily practice. A clinical prediction rule is a decision-making tool for clinicians and is created by identifying the best combination of variables from the history, physical examination, or diagnostic tests to predict the probability of a certain disease or outcome.²⁶ The rules are based on the strength of associations (calculated via logistic regression) and the prevalence of the risk factor. Prediction rules have been proven to work in other diseases or clinical outcomes. For example, a well-known prediction rule widely used in obstetrics today to predict the success of induction of labor in patients with unfavorable cervix is the Bishop Score.²⁷ A clinical prediction rule for the diagnosis of EP in women experiencing pain or bleeding or both in early pregnancy would be very useful. This study identifies which variables are important to help predict the final diagnosis of a symptomatic first-trimester pregnancy.

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