

# Risk factors and clinical characteristics associated with a ruptured ectopic pregnancy

## A 19-year retrospective observational study

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### Abstract

Ectopic pregnancy is the most common cause of maternal mortality in the first trimester of pregnancy. The aim of this study was to find risk factors and clinical characteristics associated with ruptured ectopic pregnancies at a medical center in eastern Taiwan in a 19-year period. This was a retrospective observational study that included patients diagnosed with ectopic pregnancy between August 1999 and December 2018. Data about the demographic variables, initial presentation, pre-treatment beta-human chorionic gonadotropin levels, treatment routes (laparoscopy or laparotomy), surgical methods (salpingostomy or salpingectomy), operation time, blood loss amount, the status of ectopic pregnancy (ruptured or unruptured), the requirement for transfusion, and duration of hospital stay were collected. The categorical and continuous variables were analyzed using the correlation coefficients. This study included 225 women who were diagnosed as having an ectopic pregnancy. There were 49 and 176 women with unruptured and ruptured ectopic pregnancies, respectively. The beta-human chorionic gonadotropin levels, history of previous ectopic pregnancy, pelvic inflammatory disease, tubal surgery, abdominal history, and vaginal bleeding were not significantly different between the 2 groups. The ratio of women with abdominal pain was significantly higher in the ruptured ectopic pregnancy group than in the unruptured group (89.1% vs. 63.8%, respectively,  $P < .001$ ). Preoperative hemoglobin was lower in the ruptured group compared with the unruptured group ( $P < .001$ ). Blood loss, postoperative hemoglobin, and blood transfusion were significantly higher in the ruptured group than in the unruptured group ( $P = .000$  and  $P = .001$  for blood loss and blood transfusion, respectively). Multiple logistic regression analysis revealed that abdominal pain and blood loss were associated with ruptured tubal pregnancies (adjusted odds ratio [95% confidence intervals]: 3.42 [1.40, 8.40]; 1.01 [1.005, 1.014], respectively). In conclusion, early pregnancy with abdominal pain, more parity, and lower preoperative hemoglobin should be aware of the possibility of ruptured ectopic pregnancy. More blood loss, transfusion and lower postoperative hemoglobin were also noted with ruptured ectopic pregnancy.

**Abbreviations:**  $\beta$ -hCG = beta-human chorionic gonadotropin, CI = confidence interval, IP = interstitial pregnancy, MTX = methotrexate, OR = odds ratio.

**Keywords:** ectopic pregnancy, beta-human chorionic gonadotropin levels, blood loss, outcome, laparoscopy

### 1. Introduction

Ectopic pregnancies occur in 1% to 2% of all pregnancies, which can be a life-threatening emergency.<sup>[1]</sup> The various risk factors for ectopic pregnancy include fallopian tube injuries,<sup>[2,3]</sup> infertility,<sup>[4]</sup> contraceptive failure,<sup>[5]</sup> smoking,<sup>[6]</sup> age >35 years,<sup>[7,8]</sup> previous ectopic pregnancy,<sup>[9]</sup> and previous abortions.<sup>[10]</sup>

The most common extrauterine implantation site is the fallopian tube (over 95%). When a pregnant sac becomes larger

in the tube and the tubal lumen cannot accommodate, tubal rupture may occur. Some previous studies have suggested that higher beta-human chorionic gonadotropin ( $\beta$ -hCG) levels and gestational age seem to be significant risk factors for developing a ruptured ectopic pregnancy.<sup>[8,11]</sup> A ruptured ectopic pregnancy can cause major internal bleeding, accounting for approximately 4% to 6% of all maternal death.<sup>[12]</sup> Early diagnosis of an unruptured ectopic pregnancy is crucial.

P-CL and W-YL contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The management of ectopic pregnancies includes expectant management, pharmacological treatment with methotrexate (MTX), or surgery. However, MTX is relatively contraindicated in patients with initial  $\beta$ -hCG levels of  $>5000$  mIU/mL, a gestational sac size of  $>4$  cm, presence of fetal cardiac activity and hemoperitoneum, which indicate a high treatment failure rate.<sup>[12]</sup>

Thus, the aim of our study was to find the risk factors associated with ruptured ectopic pregnancies at a medical center in eastern Taiwan in a 19-year period.  $\beta$ -hCG levels, clinical presentation, demographic data, and risk factors were utilized for analysis to which patients may be beneficial from increased surveillance.

## 2. Methods

This was a retrospective observational study that included patients with ectopic pregnancy who were admitted to Hualien Tzu Chi Hospital between August 1999 and December 2018. The study protocol was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (IRB 109-130-B). The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institution. The requirement for informed written consent was waived because the research involved no more than minimal risk to the participants.

### 2.1. Inclusion criteria

We used the International Classification of Diseases-9 diagnosis code number “633” to search for patients from the electronic medical record system. Women aged 20 to 50 years diagnosed as having an ectopic pregnancy and requiring admission for surgery were included.

### 2.2. Exclusion criteria

Women with intrauterine pregnancies, those who received medical treatment with methotrexate, those who underwent diagnosed laparoscopy and lost to follow-up were excluded.

### 2.3. Patients' data collection

Data about the demographic variables, initial presentation, pre-treatment  $\beta$ -hCG levels, treatment routes (laparoscopy or laparotomy), surgical methods (salpingostomy or salpingectomy), operation time, the status of the ectopic pregnancy (ruptured or unruptured), blood loss amount, the requirement for transfusion, and duration of hospital stay were collected. We then divided the patients into 2 groups based on the outcome of the ectopic pregnancy: ruptured and unruptured.

### 2.4. Outcomes

The primary outcomes of the study were blood loss and the requirement for blood transfusion. The secondary outcomes included surgical routes, surgical methods, location of ectopic pregnancy, operation time, and duration of hospital stay.

### 2.5. Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation. Categorical variables were expressed as a number and percentage. Continuous variables were analyzed using the Student *t* test and the Mann–Whitney–Wilcoxon test. Categorical variables were evaluated using Pearson's Chi-Squared and Fisher exact tests. The receiver operating characteristic curve and area under the curve were analyzed for different variables. A logistic regression analysis was used to find the factors associated with tubal rupture. The analysis was performed using the statistical package for the Social Sciences version 25 (IBM, New York, NY).  $P < .05$  was considered statistically significant.

## 3. Results

In total 264 women were screened and 225 women were finally included in our study (Fig. 1). Among the 225 women diagnosed as having an ectopic pregnancy, there were 49 and 176 women with unruptured and ruptured ectopic pregnancies, respectively (Table 1). The  $\beta$ -hCG levels, history of previous ectopic

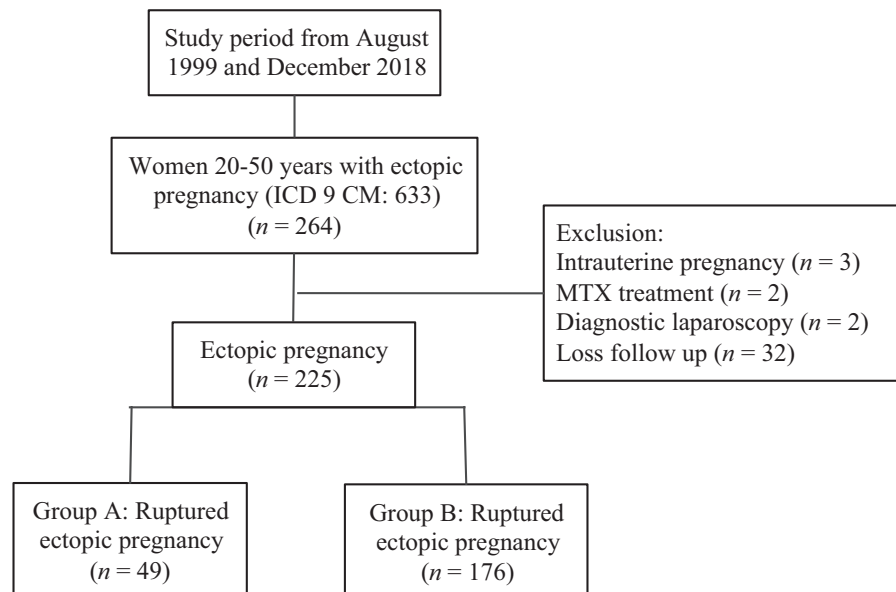


Figure 1. Flow chart of the study population.

**Table 1**  
Basic characteristics.

	Unruptured group (n = 49)	Ruptured group (n = 176)	P value
Age (yr)	31.4 ± 5.8	30.2 ± 6.3	.2
Gestational age (wks)	7.1 ± 2.6	6.1 ± 2.4	.012
Parity	0.9 ± 1.2	1.4 ± 1.3	.028
HCG (mIU/mL)	10520 ± 11444	8073 ± 15398	.3
HCG level (mIU/mL)			.219
<100	2 (4.4%)	6 (3.8%)	
100–999	5 (11.1%)	34 (21.5%)	
1000–9999	24 (53.3%)	88 (55.7%)	
≥10000	14 (31.1%)	30 (19%)	
History of ectopic pregnancy			.1
yes	10 (20.4%)	21 (12%)	
no	39 (79.6%)	154 (88%)	
History of PID			.6
No	47 (95.9%)	171 (97.2%)	
Yes	2 (4.1%)	5 (2.8%)	
History of abdominal surgery			.16
No	29 (59.2%)	124 (70.5%)	
Yes	20 (40.8%)	52 (29.5%)	
History of tubal surgery			.057
No	40 (81.6%)	162 (92%)	
Yes	9 (18.4%)	14 (8%)	
Abdominal pain			.000
Yes	30 (63.8%)	156 (89.1%)	
No	17 (36.2%)	19 (10.9%)	
Vaginal bleeding			.2
Yes	17 (21.2%)	47 (26.9%)	
No	30 (63.8%)	128 (73.1%)	
Preoperative Hb (mg/dL)	12.3 ± 1.4	11.1 ± 1.7	.000

β-hCG = beta-human chorionic gonadotropin, Hb = hemoglobin, PID = pelvic inflammatory disease.  
Data was expressed mean ± standard deviation (SD) or n (%)

\*P value <.05 was considered statistically significant after the test

pregnancy, pelvic inflammatory disease, tubal surgery, and vaginal bleeding were not significantly different between the 2 groups. The ratio of women with abdominal pain was significantly different between the ruptured and unruptured ectopic pregnancy groups (89.1% vs 63.8%, respectively) (Table 1). The gestational age was significantly different between the 2 groups (7.1 ± 2.6 vs 6.1 ± 2.4 weeks in unruptured and ruptured ectopic pregnancy, respectively,  $P = .012$ ). The parity was significantly higher in the ruptured group than in the unruptured group (1.4 ± 1.3 vs 0.9 ± 1.2 weeks, respectively,  $P = .028$ ). The preoperative hemoglobin was significantly lower in the ruptured group than in the unruptured group (11.1 ± 1.7 vs 12.3 ± 1.4 mg/dL,  $P < .001$ )

Table 2 illustrates the surgical characteristics and outcomes in the 2 groups. Surgical routes (laparoscopy and laparotomy) and methods (salpingectomy and salpingostomy) used were not different between the 2 groups. The location of ectopic pregnancy was significantly different between the 2 groups ( $P = .03$ ). In the ruptured group, the proportion of tubal pregnancy (both the right and left sides) was more than that in the unruptured group. Blood loss and the requirement for blood transfusion were significantly more in the ruptured group than in the unruptured group ( $P = .000$  and  $P = .001$ , respectively). Operation time and the duration of hospital stay were not significantly different between the 2 groups.

Age and β-hCG levels could not predict the presence of a ruptured ectopic pregnancy (area under the curve: 0.451 and 0.376, respectively).

**Table 2**  
Surgical characteristics.

	Unruptured group (n = 49)	Ruptured group (n = 176)	P value
Surgical route			.2
Laparoscopy	44 (97.8%)	159 (93%)	
Laparotomy	1 (2.2%)	12 (7%)	
Surgical method			.4
Salpingectomy	28 (84.8%)	132 (89.8%)	
Salpingostomy	5 (15.2%)	15 (10.2%)	
Location			.03
Right tube	22 (44.9%)	82 (46.6%)	
Left tube	17 (34.7%)	78 (44.3%)	
Right cornua	1 (2%)	5 (2.8%)	
Right ovary	0	3 (1.7%)	
Left ovary	2 (4.1%)	2 (1.1%)	
Cul-de-sac	0	1 (0.6%)	
Abdomen	1 (2%)	0	
Cervix	0	1 (0.6%)	
Others	6 (12.2%)	4 (2.3%)	
Operation time (min)	73.9 ± 32.0	77.1 ± 30.2	.5
Blood loss	76.8 ± 111	587.4 ± 727.4	.000
Transfusion			.001
Yes	0	28 (16%)	
No	49 (100%)	147 (84%)	
Postoperative Hb	10.6 ± 1.1	9.0 ± 1.6	.01
Duration of hospital stay	2.7 ± 0.7	2.8 ± 0.9	.6

\*P value <.05 was considered statistically significant after the test.

Hb = hemoglobin.

Multiple logistic regression analysis revealed that abdominal pain and blood loss were associated with ruptured tubal pregnancies (adjusted odds ratio 95% confidence intervals [CI]: 3.42 [1.40, 8.40]; 1.01 [1.005, 1.014], respectively) (Table 3).

#### 4. Discussion

This study included 225 women who were diagnosed as having ectopic pregnancies which included both unruptured and ruptured ectopic pregnancies. The β-hCG levels, history of a previous ectopic pregnancy, and vaginal bleeding were not significantly different between the ruptured and unruptured groups. Multiple logistic regression analysis revealed that abdominal pain and blood loss was associated with a ruptured tubal pregnancy.

The symptoms of ectopic pregnancy include missed menstruation, abdominal pain, and vaginal bleeding.<sup>[10]</sup> Therefore, pregnancy should be ruled out first in premenopausal women presenting with vaginal bleeding. If pregnancy is noted, ultrasonography is used for the diagnosis of intrauterine pregnancy. If there are no visible signs of an intrauterine pregnancy, ectopic pregnancy should be suspected. Serial serum β-hCG levels must be obtained to monitor the status of pregnancy.<sup>[13]</sup>

Abdominal pain is noted when there is tubal rupture. The pain may be unilateral diffuse pain or localized and may also be caused by hemoperitoneum.<sup>[10]</sup> However, these symptoms are not specific to ectopic pregnancy. In our case series, vaginal bleeding was present in nearly 21.2% and 26.9% of the unruptured and ruptured ectopic pregnancy patients, respectively. Abdominal pain was observed more frequently in the ruptured group than in the unruptured group. Multivariable analysis showed that abdominal pain was associated with a ruptured ectopic pregnancy.

**Table 3**  
**Factors associated with rupture (n = 225).**

Item	Crude		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.97 (0.92, 1.02)	.224	0.96 (0.90, 1.03)	.23
Gestational Age	0.84 (0.73, 0.97)	.014*	0.92 (0.77, 1.09)	.323
Parity	1.39 (1.03, 1.87)	.030*	1.23 (0.77, 1.97)	.395
History of abdominal surgery				
No	Ref.			
Yes	0.61 (0.32, 1.17)	.137		
History of tubal surgery				
No	Ref.			
Yes	0.38 (0.32, 1.17)	.038*		
History of PID				
No	Ref.			
Yes	0.69 (0.13, 3.66)	.660		
Location				
Right tube	Ref.			
Left tube	1.23 (0.61, 2.49)	.563		
Right cornua	1.34 (0.15, 12.08)	.793		
right ovary	4.33E8 (NA)	.999		
Left ovary	0.27 (0.04, 2.01)	.201		
Cul-de-sac	4.33E8 (NA)	1		
Abdomen	0.00 (NA)	1		
Cervix	4.33E8 (NA)	1		
Others	0.18 (0.05, 0.69)	.012*		
Abdominal pain				
No	Ref.		Ref.	
Yes	4.65 (2.17, 9.97)	<.001*	3.42 (1.40, 8.40)	.007*
Vaginal bleeding				
No	Ref.			
Yes	0.65 (0.33, 1.28)	.213		
β-hCG	1.00 (1.00, 1.00)	.34		
β-hCG level	0.67 (0.42, 1.07)	.096		
History of ectopic pregnancy				
No	Ref.			
Yes	0.53 (0.23, 1.22)	.136		
Preoperative Hb	0.58 (0.44, 0.77)	<.001*	0.91 (0.61, 1.37)	.658
Surgical route				
Laparoscopy	Ref.			
Laparotomy	3.32 (0.42, 26.24)	.255		
Surgical method				
salpingectomy	Ref.			
Salpingostomy	0.64 (0.21, 1.90)	.417		
Surgical time	1.00 (0.99, 1.02)	.548		
Blood loss	1.01 (1.005, 1.014)	<.001*	1.01 (1.005, 1.014)	<.001*
Postoperative Hb	0.46 (0.24, 0.87)	.016*		
Transfusion				
No	Ref.			
Yes	5.38 E8 (NA)	.998		
Duration of hospital stay	1.09 (0.77, 1.55)	.621		

β-hCG = beta-human chorionic gonadotropin, CI = confidence interval, Hb = hemoglobin, NA = not applicable, OR = odds ratio, PID = pelvic inflammatory disease.

Data are presented as odds ratio (95% confidence interval).

\* P value <.05 was considered statistically significant after the test.

The various risk factors for ectopic pregnancy include fallopian tube injuries,<sup>[2,3]</sup> infertility,<sup>[4]</sup> contraceptive failure,<sup>[5]</sup> smoking,<sup>[6]</sup> age >35 years,<sup>[7,8]</sup> previous ectopic pregnancy,<sup>[9]</sup> and previous abortions.<sup>[10]</sup> However, in our analysis, age and a previous history of ectopic pregnancy were not found to be risk factors for ruptured tubal pregnancy.

The previous retrospective study including 693 ectopic pregnancy patients, the gestational age was  $6.9 \pm 1.9$  weeks and  $7.2 \pm 2.2$  weeks in the unruptured and ruptured groups,

respectively.<sup>[14]</sup> In another study including 269 patients, the gestational age was 7 weeks and 6.5 weeks in the ruptured and unruptured groups. However, the comparison did not reach statistical significance ( $P = .31$ ).<sup>[15]</sup> The previous study, which included 99 patients, the gestational age was  $7.3 \pm 1.0$  and  $8.0 \pm 0.9$  in the unruptured and ruptured ectopic pregnancy, respectively.<sup>[16]</sup> Above all, the gestational age is older in the ruptured group than in the unruptured group. However, in our study, a converse result was noted ( $7.1 \pm 2.6$  vs  $6.1 \pm 2.4$  weeks in

unruptured and ruptured ectopic pregnancy, respectively). We speculated that unruptured ectopic pregnancy could maintain for a longer time till diagnosis than ruptured ectopic pregnancy.

Previous study included 223 patients with ectopic pregnancies, 23% of patients were with ruptured ectopic pregnancies.<sup>[17]</sup> They found a significant positive association between rupture and parity ( $1.19 \pm 1.02$  for ruptured cases vs  $0.85 \pm 0.89$  for unruptured cases;  $P = .015$ ).<sup>[17]</sup> Higher parity was associated with a risk of ruptured ectopic pregnancy.<sup>[17]</sup> Another study including 199 women with ectopic pregnancy, 93.5% of patients were with ruptured ectopic pregnancy.<sup>[18]</sup> Higher parity was also associated with ruptured ectopic pregnancy ( $5.1 \pm 2.6$  vs  $2.8 \pm 2.3$  in ruptured and unruptured ectopic pregnancies, respectively;  $P = .003$ ).<sup>[18]</sup> In our study, higher parity was also associated with ruptured ectopic pregnancy ( $1.4 \pm 1.3$  vs  $0.9 \pm 1.2$  weeks in ruptured and unruptured ectopic pregnancy, respectively,  $P = .028$ ).

Previous research has revealed that  $\beta$ -hCG levels  $>1750$  mIU/mL was associated with a higher odds ratio (OR) for ruptured ectopic pregnancy (OR: 1.41; 95% CI: 1.18–1.68).<sup>[8]</sup> Another report showed that  $\beta$ -hCG levels  $>5000$  mIU/mL was associated with an increased risk of ruptured ectopic pregnancy (OR 1.85; 95%, CI: 1.12–3.06).<sup>[19]</sup> However, in our report,  $\beta$ -hCG levels failed to predict the risk of ruptured ectopic pregnancies.

In a ruptured ectopic pregnancy, the amount of blood loss is more than that in an unruptured ectopic pregnancy. Therefore, the requirement for blood transfusions is increased. A previous study has shown that the amount of blood loss was increased in ruptured ectopic pregnancies (OR: 13.1).<sup>[20]</sup> Similarly, in our report too, we found that the amount of blood loss was associated with ruptured ectopic pregnancy. The probability of blood transfusion was also higher in ruptured ectopic pregnancy than in unruptured ectopic pregnancy. Thus, preoperative estimation of the amount of intra-abdominal blood loss using the ultrasound scan might be useful in predicting tubal ruptures.

The preferred surgical route for treating ectopic pregnancy is laparoscopy. Our previous report on ectopic pregnancy conducted between 2005 and 2007 in 49 patients established that laparoscopy was performed in 77.5% of the patients.<sup>[21]</sup> Another report revealed that 57% of patients underwent laparoscopic management of ectopic pregnancy.<sup>[22]</sup> In our study, laparoscopy was performed in 97.8% and 93% of patients in the unruptured and ruptured groups, respectively.

Salpingectomy or salpingostomy was the preferred surgical method. A radical surgery like salpingectomy could help avoid a recurrence of ectopic pregnancy at the same site. However, it is considered to decrease the chances of becoming pregnant. In a randomized control trial, the pregnancy rate among patients in the salpingostomy group was not better than that among those in the salpingectomy group when the contralateral tube was healthy.<sup>[23]</sup> Another retrospective study revealed that the pregnancy rates in patients who underwent salpingectomy and salpingostomy were similar.<sup>[24]</sup> A systematic review also showed that there was no significant difference between subsequent intrauterine pregnancies and the recurrence of ectopic pregnancy.<sup>[25]</sup> In our study, the percentage of salpingectomy and salpingostomy was almost the same in the 2 groups. The effect of these surgeries on future fertility or recurrent ectopic pregnancies needs to be evaluated.

Ruptured ectopic pregnancy is a surgical emergency. In most case series, the percentage of cases with ruptured ectopic pregnancy was observed to be less than in cases with unruptured ectopic pregnancy.<sup>[8]</sup> In a study by Darkhaneh et al, ruptured

ectopic pregnancy cases accounted for 20.2% of the total ectopic pregnancy cases. In contrast, another study showed a higher proportion of rupture in those with ectopic pregnancies (59%).<sup>[19]</sup> Similarly, in our study, ruptured ectopic pregnancy cases accounted for 79% of the total ectopic pregnancy cases. We speculate that this increase in ruptured ectopic pregnancy cases might be due to women being unaware of being pregnant.

The location of ectopic pregnancy may be associated with a higher incidence of ruptured ectopic pregnancies. A previous study showed that ectopic pregnancies located at the cornua and isthmus were associated with a high incidence of ruptures.<sup>[16]</sup> Interstitial and angular pregnancies are relatively different in the treatment and outcomes. Angular pregnancy can be considered a viable intrauterine pregnancy. However, there is an increasing risk of ruptured uterus when expectant management is performed. If uterine rupture happens, severe bleeding and high mortality rate (5%) will be expected.<sup>[26]</sup> The management includes hysteroscopic resection, dilation and curettage, or MTX injection.<sup>[26]</sup> Interstitial pregnancy (IP) occupied 2% to 4% of ectopic pregnancies.<sup>[27]</sup> Usually IP is considered a nonviable pregnancy, and has a 2.5% mortality rate due to uterine ruptured and severe bleeding.<sup>[27]</sup> The treatment is also the same with angular pregnancy including hysteroscopic resection and systemic MTX injection.<sup>[27]</sup> Other surgical treatments for IP include cornuostomy, cornual resection, and hysterectomy.<sup>[27]</sup> However, in our study, the most common site of ectopic pregnancy was tube (bilaterally), which accounted for 78% and 90% in the unruptured and ruptured groups, respectively. Therefore, tubal ectopic pregnancies had an increased risk of rupture.

This study has a strength. We collected the cases for a 19-year period from our hospital. Among 225 patients, the data were completely collected. This study also has some limitations. First, this is a retrospective observational study. The power of these results is lower than that obtained from randomized controlled trials. Second, the patients were only recruited from one hospital and a selection bias might have existed. A multicenter data or population study will be needed for confirming our results. Third, the case number is small, necessitating a study with a large sample size for better generalizability.

## 5. Conclusion

In conclusion, early pregnancy with abdominal pain, more parity, and lower preoperative hemoglobin should be aware of the possibility of ruptured ectopic pregnancy. More blood loss, transfusion and lower postoperative hemoglobin were also noted with ruptured ectopic pregnancy. The  $\beta$ -hCG levels, history of ectopic pregnancy, pelvic inflammatory disease, abdominal surgery, and tubal surgery failed to predict ruptured ectopic pregnancies.

## Author contributions

**Conceptualization:** Dah-Ching Ding.

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**Software:** Dah-Ching Ding.

**Supervision:** Dah-Ching Ding.

**Visualization:** Dah-Ching Ding.

**Writing – original draft:** Dah-Ching Ding, Pei-Chen Li.

**Writing – review & editing:** Dah-Ching Ding, Pei-Chen Li, Wen-Yu Lin.

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