CEOG Clinical and Experimental Obstetrics & Gynecology

Meaningful clinical information for impending rupture in tubal pregnancy

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Summary

Purpose of investigation: This study provides valuable information to help clinician's decision for treatment modality that patients with tubal pregnancy are at risk for impending rupture. *Materials and Methods:* This was a retrospective study of patients diagnosed with tubal pregnancy between January 2001 and September 2010. The definite diagnosis of tubal pregnancy was confirmed intraoperatively. *Results:* This study recruited 495 women with tubal pregnancy. Of these, 162 (33.7%) had ruptured tubal pregnancies and 333 (67.3%) had unruptured tubal pregnancies. Multivariate logistic regression analysis revealed that gestational age > 8 weeks (odds ratio (OR): 4.69), beta-subunit human chorionic gonadotropin (ß-hCG, > 5,000 mIU/ml, OR: 2.43), and tubal mass size > 30 mm (OR: 12.09) were significant increased incidence for rupture of tubal pregnancy. *Conclusion*: The advanced gestational age is important factor, but the tubal mass size with elevated ß-hCG level were the more meaningful risk factors for rupture of tubal pregnancy.

Key words: Measurable information; Rupture; Serum ß-hCG; Tubal mass size; Tubal pregnancy.

Introduction

Ectopic pregnancy is the implantation of a pregnancy at an extrauterine site, with an estimated incidence of eight to ten per 1,000 pregnancies [1]. More than 95% of ectopic pregnancies occur in the fallopian tubes [2-4]. The case-fatality rate for ectopic pregnancy has decreased primarily due to earlier detection using sensitive assays for serum beta-subunit human chorionic gonadotropin (ß-hCG) and improved imaging with transvaginal ultrasonography [4, 5].

The absence of a gestational sac on transabdominal ultrasonography with serum ß-hCG > 6,500 mIU/mL or the absence of a sac on transvaginal ultrasonography with ß-hCG > 1,500 mIU/mL indicates ectopic pregnancy in 87% of cases [6].

Ectopic pregnancy is an important cause of maternal morbidity and mortality, especially in developing countries where the majority of patients present late with rupture and hemodynamic compromise [7]. Despite the widespread use of these diagnostic methods included ultrasonography and serum ß-hCG, ruptured ectopic pregnancy is a true medical emergency. It is the leading cause of maternal mortality in the first trimester and accounts for 10–15% of all maternal deaths [2, 8-10]. However, both morbidity and mortality associated with ectopic pregnancy have declined concurrently, largely due to early diagnosis and improved treatment modalities.

Assessing risk factors associated with ectopic pregnancy rupture would be valuable for identifying women at risk for this life-threatening condition. Prevention of tubal rupture would have a strong impact on gynecologic morbidity and mortality and would decrease surgery and hospitalization costs. Ectopic pregnancies could be asymptomatic, especially before rupture. When ruptured, symptoms could be acute or subacute [4]. Although ectopic pregnancies that rupture are associated with higher serum ß-hCG, no cutoff level has been established that predicts or excludes rupture [11-17]. In addition, currently used indicators of ectopic pregnancy, such as tubal mass on ultrasound examination, heart rate, blood pressure, ß-hCG, and hemoglobin levels, do not adequately predict ectopic pregnancy rupture [11, 14, 15].

This study assessed patient characteristics, serum ß-hCG, and ultrasonography findings to identify patients at greatest risk for tubal rupture. The purpose of this study was to assess valuable information to help clinician's decision for treatment modality that patients with tubal pregnancy are at risk for impending rupture based on diagnostic and laboratory tests.

Materials and Methods

This retrospective review of medical records was approved by the Institutional Review Board of the Catholic University of Korea. The study sample was drawn from tubal pregnancy cases diagnosed in the Department of Obstetrics and Gynecology at the university's two teaching hospitals (Seoul and Incheon St. Mary's

Revised manuscript accepted for publication November 15, 2017

Hospital) between January 2001 and September 2010.

The authors conducted a retrospective analysis of age; parity, gestational age, number of miscarriages, ruptured or unruptured status, previous risk factors for tubal pregnancy, including history of ectopic pregnancy, pelvic inflammatory disease (PID), use of an intrauterine contraceptive device (IUD), use of oral contraceptives (OCs), smoking, ultrasonography and operative findings, and quantitative serum ß-hCG concentration. Gestational age was calculated according to the last menstrual period (LMP) at the time of presentation. In addition, the authors obtained data from operative reports, including site, size (diameter of the most dilated part of the tube), and tube status (ruptured or unruptured) of the ectopic pregnancies. Final diagnosis of a tubal pregnancy and status for salpinx were confirmed at the time of laparotomy or laparoscopy. The authors excluded patients who were surgically diagnosed with angular, or other non-tubal ectopic pregnancy, abortive type of tubal pregnancy, and those at high risk for complications from general anesthesia. The resulting study group of 495 patients with tubal pregnancy was divided into two subgroups: ruptured and unruptured tubal pregnancy.

For the statistical analyses, the Student's *t*-test and the Mann-Whitney-Wilcoxon test were used for intergroup comparisons of continuous variables, and the Pearson's chi-square or Fisher's exact test was used for intergroup comparisons of categorical variables. Multivariate logistic regression analysis was used to identify predictors of tubal pregnancy outcomes. Variables with a p-value < 0.05 by univariate analysis were used for the multivariate analysis. A p-value < 0.05 indicated statistical significance. The Statistical Package for Social Science Software (SPSS, version 18.0) was used for statistical analysis.

Results

This study examined 495 patients with tubal pregnancy. Among these patients, there were 333 (67.3%) cases of unruptured tubal pregnancy and 162 (33.7%) cases of ruptured tubal pregnancy. The mean age was 31.16 ± 5.56 years for patients with ruptured tubal pregnancy and 30.77 ± 4.98 years for patients with unruptured tubal pregnancy ($p = 0.452$).

The characteristics of the patient groups are shown in Table 1. The groups were similar in terms of number of miscarriages, use of an IUD or OCs, history of ectopic pregnancy or abdominal surgery, history of PID or endometriosis, and smoking. There were no significant intergroup differences in patient characteristics.

Table 2 shows the measurable clinical data from both groups stratified by preoperative hematocrit, gestational age, serum ß-hCG, fetal cardiac activity, and tubal mass size. Compared to the unruptured group, hematocrit levels were significantly lower in the ruptured group ($p < 0.001$). The mean gestational age and mean level of ß-hCG at presentation were 52.35 ± 14.31 days and 9,897.1 ± 15,921.9 mIU/ml, respectively, for the ruptured tubal pregnancy group, and 45.02 ± 13.85 days and 4,464.8 ± 5,692.1 mIU/ml for the unruptured group. These values were significantly higher in the ruptured group than in the unruptured group ($p < 0.001$). Mean tubal mass size was significantly larger in the ruptured group than in the unruptured group (33.40 ± 14.43 *vs*. 21.69 ± 10.72, $p < 0.001$). However, there were no significant intergroup differences in preoperative fetal cardiac activity on ultrasound.

Patients with ruptured tubal pregnancy most frequently had a gestational age of 42–56 days (6–8 weeks, 37.7%) or > 56 days (> 8 weeks, 43.8%), and only 18.5% had a gestational age < 42 days (< 6 weeks). Patients with ruptured tubal pregnancies were more likely to have ß-hCG levels of 1,501–5,000 mIU/ml (32.7%) or > 5,000 mIU/ml (46.9%); 20.4% of these patients had ß-hCG levels of 0–1,500 mIU/ml. Patients with ruptured tubal pregnancy were also more likely to have a tubal mass size of 16–30 mm (46.9%) or > 30 mm (44.4%) than a size of 0–15 mm (8.7%).

Univariate and multivariate logistic regression analyses were performed introducing all variables were included in univariate analysis, and that those found to be significant were then included in multivariate analysis. Univariate logistic regression analysis revealed that gestational age, ß-hCG level, and tubal mass size were significant risk factors for tubal rupture ($p < 0.001$, respectively) (Table 3). The number of miscarriages was not used in multivariate analysis because it was not significant in univariate analysis.

Multivariate logistic regression analysis revealed that the significant risk factors for tubal rupture were gestational ages of 42–56 days (6–8 weeks) (OR: 2.48; 95% CI: 1.45–4.24) and > 8 weeks (OR: 4.69; 95% CI: 2.55–8.61). In addition, ß-hCG levels of 1,501–5,000 mIU/ml (OR: 2.60; 95% CI: 1.51–4.50) and > 5,000 mIU/ml (OR: 2.43; 95% CI: 1.39–4.27) were significant risk factors for tubal rupture, as were tubal mass sizes of 16–30 mm (OR: 3.52; 95% CI: 1.98–6.28) and > 30 mm (OR: 12.09; 95% CI: 6.10–23.96) (Table 4).

Discussion

Ruptured tubal pregnancy is a serious complication that can result in life-threatening consequences for the patient. The prevalence of ruptured tubal pregnancy in all ectopic pregnancy ranges from 18.0% to 64.5% in large, population-based studies [14-18,19].

We found a lower preoperative hematocrit value in women with ruptured tubal pregnancies, which might have resulted from blood loss from the tubal rupture. In the present results, none of the known risk factors for ectopic pregnancy (Table 1) occurred more frequently in women with tubal rupture. Women with a history of ectopic pregnancy have an increased risk of ectopic pregnancy rupture [12, 16, 20]. In the present study, tubal rupture was encountered more often among women with a history of ectopic pregnancy than in women without this history, but the difference was not significant. The authors found that higher gestational age, higher levels of ß-hCG, and larger tubal mass were important risk factors for tubal rupture. Gestational age has been reported as a risk factor for tubal rupture, although results are conflicting [17, 21]. In this study,

Table 1. — *Comparison of patient characteristics between the ruptured and unruptured ectopic pregnancy groups.*

	Ruptured group (n = 162)	Unruptured group (n = 333)	*p-value*
Age (mean ± SD)	31.16 ± 5.56	30.77 ± 4.98	0.452
Parity (mean ± SD)	1.67 ± 1.68	1.74 ± 1.69	0.687
Number of miscarriages			
Mean ± SD	1.08 ± 1.32	1.08 ± 1.28	0.986
0-1	118 (72.8%)	230 (69.1%)	0.710
2-3	35 (21.6%)	82 (24.6%)	
> 4	9 (5.6%)	21 (6.3%)	
Use of an IUD	7 (4.3%)	19 (5.7%)	0.650
Use of OCs	8 (4.9%)	21 (6.3%)	0.669
Previous ectopic pregnancy	15 (9.3%)	27 (8.1%)	0.731
History of abdominal surgery	35 (21.6%)	68 (20.4%)	0.816
History of PID	12 (7.4%)	33 (9.3%)	0.478
Endometriosis	4 (2.4%)	0	0.578
Smoking	13 (8.1%)	16 (4.8%)	0.262

N: numbers; SD: standard deviation; IUD: intrauterine contraceptive device; OCs: oral contraceptives; PID: pelvic inflammatory disease.

Table 2. — *Comparison of clinical features of the unruptured and ruptured ectopic pregnancy groups.*

	Ruptured group (n = 162)	Unruptured group (n = 333)	*p-value*
Preoperative hematocrit (%)			
Mean ± SD	34.02 ± 4.03	36.59 ± 7.84	<0.001
Gestational age (days)			
Mean ± SD	52.35 ± 14.31	45.02 ± 13.85	<0.001
<42	30 (18.5%)	148 (44.4%)	<0.001
42–56	61 (37.7%)	121 (36.3%)	
>56	71 (43.8%)	64 (19.2%)	
Initial ß-hCG (mIU/ml)			
Mean ± SD	9,897.1 ± 15,921.9	4,464.8 ± 5,692.1	<0.001
0-1,500	33 (20.4%)	150 (45.1%)	<0.001
1,501-5000	53 (32.7%)	86 (25.8%)	
>5,000	76 (46.9%)	97 (29.1%)	
Positive findings of adnexal cardiac activity	8 (4.9%)	12 (3.6%) 0.687	
Tubal mass size (mm)			
Mean ± SD	33.40 ± 14.43	21.69 ± 10.72	<0.001
0-15	14 (8.7%)	96 (28.9%)	<0.001
16-30	76 (46.9%)	181 (54.3%)	
>30	72 (44.4%)	56 (16.8%)	

N: numbers; SD: standard deviation; ß-hCG: beta-subunit human chorionic gonadotropin.

Table 3. — *Univariate analysis of potential risk factors for tubal rupture.*

	OR	95% CI	*p-value*
Gestational age (weeks)			
<6	1		
6–8	2.50	1.58 – 3.96	<0.001
>8	5.59	3.34 – 9.38	<0.001
Initial ß-hCG (mIU/ml)			
0-1,500	1		
1,501-5,000	2.79	1.71 – 4.53	<0.001
>5,000	3.56	2.24 - 5.67	<0.001
Tubal mass size (mm)			
0-15	1		
16-30	2.99	1.75 – 5.12	<0.001
>30	9.20	4.94 – 17.14	<0.001
Number of miscarriages			
0-1	1		
2-3	0.83	0.53 – 1.30	0.423
>4	0.88	0.39 – 1.95	0.752

OR: odd ratio; CI: confidence interval; ß-hCG: beta-subunit human chorionic gonadotropin.

Table 4. — *Multivariate analysis of risk factors for tubal rupture.*

	OR	95% CI	*p-value*
Gestational age (weeks)			
<6	1		
6–8	2.48	1.45 – 4.24	<0.001
>8	4.69	2.55 – 8.61	<0.001
Initial ß-hCG (mIU/ml)			
0-1,500	1		
1,501-5,000	2.60	1.51 – 4.50	<0.001
>5,000	2.43	1.39 – 4.27	<0.001
Tubal mass size (mm)			
0-15	1		
16-30	3.52	1.98 – 6.28	<0.001
>30	12.09	6.10 – 23.96	<0.001

OR: odd ratio; CI: confidence interval; ß-hCG: beta-subunit human chorionic gonadotropin.

higher mean gestational age was a significant risk factor for rupture when compared with unruptured ectopic pregnancies. Compared to women with < 6 weeks of amenorrhea, women with 6–8 weeks of amenorrhea, and those with > 8 weeks of amenorrhea were 2.4 and 4.6 times more likely, respectively, to experience tubal rupture.

The present data also showed higher ß-hCG levels in patients with ruptured tubal pregnancy compared to patients without rupture. Stratifying by ß-hCG level showed that patients with ß-hCG > 1,500 mIU/ml as well as patients with ß-hCG > 5,000 mIU/ml were considerably more likely to experience rupture (OR: 2.60; 95% CI: 1.51–4.50 for > 1,500 mIU/ml and OR: 2.43; 95% CI: 1.39–4.27 for > 5,000 mIU/ml). However, a recent study showed that serum ß-hCG does not predict the likelihood of tubal ectopic pregnancy rupture. This study found that no ß-hCG titer predicts ruptured ectopic pregnancy and the range of serum ß-hCG levels in that study was broad for both the ruptured and unruptured groups [21].

Although the present study population showed a positive association between risk of tubal rupture and gestational age and ß-hCG level, the authors did not find a significant association between risk of tubal rupture and number of miscarriages, history of PID or endometriosis, use of an IUD or OCs, or cigarette smoking. The association with gestational age could be explained by the increase in ectopic pregnancy mass during gestation. The present authors found that tubal mass sizes of 16–30 mm and > 30 mm were significantly increased risk for tubal rupture, confirming that larger tubal mass increases risk of rupture.

Other studies have reported that serum ß-hCG correlates well with adnexal mass size. However, no differences have been reported in serum ß-hCG levels between hemodynamically stable and unstable patients because high ß-hCG suggests a larger adnexal mass in women with uncomplicated tubal pregnancies [22].

This study has several limitations. The study is susceptible to all limitations and biases inherent to retrospective studies. Since the present authors sought to identify meaningful risk factors for rupture of tubal pregnancy, they were limited to using inclusion criteria that restricted the study sample to cases of tubal ectopic pregnancy. Future studies with longer study periods and varied, larger patient samples may enable better comparisons.

If the study were included for the patients who were therapeutic failure of medical treatment, the quality of study would be better. However, the authors thought the following reason why excluded the medical treatment with methotrexate. First, when the patients were treated with methotrexate, they were very difficult to measure the exact concentration of ß-hCG at the time of the tubal pregnancy rupture. Because the concentration of ß-hCG was fluctuating with medical treatment with methotrexate, the authors could not measure the exact level of ß-hCG at the time of tubal pregnancy rupture in compare with natural course of disease. Second, in this study, the prevalence of tubal rupture was sometimes high and there are several potential explanations for this difference. The university's hospitals are general hospitals that provide emergency surgery. In addition, the present hospital is a tertiary referral center for the Korean national healthcare system. Therefore, the authors may have experienced relatively many cases of rupture because they are more likely to be transferred from private clinics or primary healthcare centers that do not have the capability to perform emergency surgery and provide postoperative care for patients with ruptured ectopic pregnancies.

In conclusion, although the exact risk factors for rupture in tubal pregnancy remain poorly defined, higher gestational age, higher ß-hCG levels (especially > 5,000 mIU/ml), and larger tubal mass size were associated with significantly increased risk of tubal rupture in tubal ectopic pregnancy in this study. In addition to history taking from patients, using a combination of measurable information such as serum ß-hCG, and tubal mass size determined by ultrasonography might identify patients at greatest risk of impending tubal rupture and allow to improved decision-making in case management by surgical or medical treatment. It is essential to perform early ultrasonography in cases of suspected ectopic pregnancy in order to identify patients at high risk of rupture and to potentially prevent this serious complication.

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