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Clinical characteristics of persistent ectopic pregnancy after salpingostomy and influence on ongoing pregnancy

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Abstract

Aim: The aim of this study was to assay the clinical characteristics of persistent ectopic pregnancy (PEP) and its influence on ongoing pregnancy.

Methods: We retrospectively reviewed 2498 patients who received salpingostomies as primary management for ectopic pregnancies from January 2004 to December 2009, using medical records and telephone inquiries. Clinical characteristics of the 52 patients (2.08%) who were diagnosed with PEP after salpingostomy were compared with those who received satisfactory treatment. The odds ratios and 95% confidential intervals were calculated for each variable by univariate and (for significantly different factors) multivariate analysis.

Results: Preoperatively, patients with PEP after salpingostomy significantly differed from the non-PEP patients in gestational age, mass size and pelvic adhesiolysis. Serum β-human chorionic gonadotropin levels in PEP patients were monitored after surgery, which had declined by 28.31% on postoperative day (POD) 4, 40.22% on POD 7, 51.46% on POD 10 and 53.43% on POD 21. Repeat ectopic pregnancy (REP) tended to occur more frequently in PEP patients (PEP: 5 cases, 10.20%; non-PEP: 4 cases, 2.80%; $P = 0.034$). Multivariate analysis showed that pelvic adhesions and PEP were the strongest independent predictors of REP.

Conclusion: Gestational age, mass size and pelvic adhesions were significantly correlated with PEP. PEP was an independent prognostic factor for REP. However, a multicenter study is needed to support and extend our findings.

Key words: ectopic pregnancy (EP), persistent ectopic pregnancy (PEP), salpingostomy, serum β-human chorionic gonadotropin (β-hCG).

Introduction

Ectopic pregnancy (EP), the implantation of a fertilized ovum outside the endometrial cavity, occurs in 1.5–2.0% of pregnancies.[1] Implantation in the fallopian tube accounts for more than 70% of all EPs.[2] There are four different management strategies for EP: expectant management (follow-up until a return to normal β-human chorionic gonadotropin [β-hCG] level), medical treatment, conservative surgery and radical surgery.[2]

The decision to perform a salpingostomy or salpingectomy is often made intraoperatively on the basis of the extent of damage to the affected and contralateral fallopian tubes, but also depends on the patient's history of EP and wish for future fertility, the availability of assisted reproductive technology and the skill of the surgeon.[3] Previously, surgery for tubal pregnancy included laparotomy incision of the fallopian tube, removal of the hematoma, and microsurgical end-to-end anastomosis.[4] Nowadays, salpingostomy laparoscopic conservative surgery is the most widely used.[5] Laparoscopic salpingostomy is a well-established procedure, and numerous studies have reported that EP can be treated completely by surgery alone.[6]

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The recently completed European Surgery in Ectopic Pregnancy study, an international multicenter randomized controlled trial, compared the effectiveness of salpingostomy with salpingectomy in tubal pregnancy. Significantly more women had persistent trophoblasts within 36 months after salpingostomy compared with women treated with salpingectomy.[7] PEP occurred as a complication, as the fallopian tube may result in the persistence of trophoblasts even after the hematoma is removed.[8]

Because PEP may require additional treatment and may result in intraperitoneal hemorrhage and shock if not detected at an early stage, a determination of the predictors of postoperative occurrence of PEP is urgently required.[9] In the present study, we have elucidated the nature of PEP by a retrospective survey of the medical records in our department over a six-year period.

Methods

This retrospective comparative study was based on data collected from the medical records of patients who were diagnosed with EP at the Shanghai First Maternity and Infant Hospital from January 1, 2004 to December 31, 2009. Inclusion criteria for this study were: hemodynamically stable women at least 18 years old, a desire for future pregnancy, laparoscopically diagnosed EP implanted in the interstitial or ampulla fallopian tube, a healthy contralateral tube (i.e. appearing macroscopically normal during surgery), salpingostomy had been performed, natural singleton conception, and no history of EP.

Experienced pathologists from our hospital performed all histopathologic evaluation. Patients' serum β-hCG levels were monitored after discharge on postoperative day 4. PEP was defined as a serum β-hCG level on POD 7 that was less than a 15% reduction of the POD 4 level, or an additional increase or no reduction over at least a week.

The Ethics Committee of the medical faculty at Shanghai First Maternity and Infant Hospital approved the study. All patients provided written informed consent during outpatient follow-up.

We obtained complete data, including age at diagnosis, gravidity, parity, gestational age, mass size, location, rupture, β-hCG levels, fetal cardiac activity, sensation of rectal tenesmus and positive puncture of the posterior vaginal fornix, from the medical records of the 2498 patients who received salpingostomy, of whom 52 (2.08%) were postoperatively diagnosed with PEP. We matched a 1:3 cohort of non-PEP patients by age, gravidity and parity as a control group. We also collected the clinical characteristics of the PEP group after methotrexate (MTX) therapy, including ongoing pregnancies, term pregnancies and repeat ectopic pregnancy (REP).

All of the patients underwent thorough follow-up examinations consisting of clinical check-ups, including pelvic examinations, β-hCG evaluation and ultrasound (US) scans. Follow-up data regarding ongoing pregnancy outcomes were obtained from outpatient medical records and telephone inquiries and were updated until December 31, 2014. If an ongoing pregnancy did not occur, follow-up ceased at the last date of contact.

We used SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) for all analyses. Distributions of clinicopathologic events were evaluated by Student's t -test (continuous data) and the $\chi 2$ test (categorical data). Multivariate analysis was performed using the Cox proportional hazards model. Because the variables that reflected the baseline cohort characteristics were compared with the number of endpoints, we used univariate analysis to screen for variables. Variables for which $P < 0.05$ were included in multivariate analysis. $P < 0.05$ (two-sided) was considered significant.

Results

During the six-year study period, 2498 patients underwent salpingostomies, 52 of which were postoperatively diagnosed with PEP. All patients were identified by postoperative histology.

The average age at the time of diagnosis was 31 years (range: 19–42) in the PEP group and 32.6 years (range: 19–44) in the control and did not significantly differ ($P = 0.767$). In the PEP group, 40 (76.92%) patients were aged under 35. Clinical characteristics did not significantly differ between the two groups. Details regarding gravidity, parity, history of pelvic inflammatory disease, intrauterine device in situ, duration of lower abdominal pain, pelvic pain, β-hCG level, location of tube pregnancy, sensation of rectal tenesmus and positive embryonic cardiac motion are summarized in Tables 1 and 2.

In the PEP group, 41 patients had been pregnant more than twice, and there were 36 cases of parity of twice or more. The median mass diameter was 2.6 cm (range: 1.7–4.7) and 33 (63.46%) were smaller than 3 cm, which was significantly different from the control group (3.8 cm, range: 2.4–5.2; $P = 0.023$) (Table 3).

Table 1 Biodemographic characteristics of patients with PEP

Patient characteristics	PEP (n = 52)	Treated satisfactorily (n = 156)	P
Mean age (years)	31 (19–42)	32.6 (19–44)	0.767
< 35	40 (76.92%)	102 (65.38%)	0.121
≥ 35	12 (23.08%)	54 (34.62%)	
Gravidity			0.637
0–1	11 (21.15%)	38 (24.35%)	
≥ 2	41 (78.84%)	118 (77.63%)	
Parity			0.611
0–1	16 (30.77%)	54 (34.62%)	
≥ 2	36 (69.23%)	102 (65.38%)	
Marital status			0.805
Married	21 (40.39%)	60 (38.46%)	
Single	31 (59.61%)	96 (61.53%)	

Values are given as median, mean ± standard deviation or number (percentage), unless indicated otherwise. PEP, persistent ectopic pregnancy.

In the PEP group, the median duration from the patient presenting with lower abdominal pain to undergoing surgery was 5.16 days (3–21). Eight women presented with slight pain, 44 with obvious pain and 12 with rectal tenesmus. Physical examination generally revealed tenderness in the hypogastrium, uterus and bilateral accessory, with swing cervical lifting pain. Twelve PEP patients experienced a blood puncture through the vaginal fornix compared with 38 in the non-PEP group (P = 0.851). No patients displayed peritoneal irritation or shifting dullness (Table 3).

Patients were diagnosed with PEP when their postoperative serum β-hCG levels increased again or did not decrease for at least a week, or the level on POD 7 decreased less than 15% of the POD 4 level. Serum β-hCG levels of PEP patients were monitored on PODs 4, 7, 10, 14 and 21. Serum β-hCG levels reduced 28.31% on POD 4, 40.22% on POD 7, 51.46% on POD 10, 53.43% on POD 14 and 53.51% on POD 21.

In the PEP group, 23 patients had fallopian pregnancies on the left side, and 29 on the right. Thirty-seven patients had tubal ampullary pregnancies and 15 had interstitial tubal pregnancies. Postoperative histology identified clinical diagnoses. All PEP patients were treated with MTX as soon as they were diagnosed. Twelve patients received second doses when their serum β-hCG levels did not fall more than 15% between days 4 and 7 after injection with a dose of 50 mg/m^2 surface

Table 2 Clinical presentation of patients with PEP

Patient characteristics	PEP(n = 52)	Treated satisfactorily(n = 156)	P
History of pelvic inflammatory disease	15 (28.85%)	29 (18.59%)	0.117
Intrauterine device in situ	6 (11.54%)	17 (10.89%)	0.898
Gestational age (days)†	47.2 (36–80)	53.6 (38–95)	**0.016**
β-hCG (mIU/ml)	2415 (1219–3254)	2598 (989–4239)	0.319
Duration of lower abdominal pain (days)	5.16	4.95	0.592
Pelvic pain			0.748
Slightly	8 (15.38%)	27 (17.31%)	
Obviously	44 (86.52%)	129 (82.69%)	

Values are given as median, mean ± standard deviation or number (percentage), unless indicated otherwise. †Gestational age was calculated as the period from the date of last menstrual period to the date of surgery. Bold text emphasizes the result which P-value is less than 0.05. β-hCG, β-human chorionic gonadotropin; PEP, persistent ectopic pregnancy.

Table 3 Characteristic physical signs of PEP

Patient characteristics	PEP(n = 52)	Treated satisfactorily(n = 156)	P
Sensation of rectal tenesmus	12 (23.07%)	39 (25.00%)	0.780
Puncture of posterior of fornix of vagina	12 (23.08%)	38 (24.36%)	0.851
Median mass diameter (cm)	2.6 (1.7–4.7)	3.8 (2.4–5.2)	**0.023**
Positive embryonic cardiac motion	5 (9.61%)	10 (6.41%)	0.439
Location of tube pregnancy			0.584
Interstitial	15 (28.8%)	39 (25.9%)	
Ampulla	37 (71.2%)	117 (75.0%)	
Rupture†	22 (42.31%)	80 (51.28%)	0.262
Pelvic adhesiolysis	27 (51.92%)	51 (32.69%)	**0.013**

Values are given as median, mean ± standard deviation or number (percentage), unless indicated otherwise. †Massive hemoperitoneum was noted on transvaginal sonography, and we could not preoperatively exclude tubal rupture with active bleeding. Bold text emphasizes the result which P-value is less than 0.05. PEP, persistent ectopic pregnancy.

Table 4 Univariate analysis of predictors for second dose of methotrexate

Patient characteristics	PEP(n = 52)	One dose(n = 40)	Need for second dose(n = 12)	P
Mean age (years)	31 (19–42)	32.1 (19–40)	34.6 (21–42)	0.678
< 35	40 (76.92%)	32 (61.54%)	8 (15.38%)	0.336
≥ 35	12 (23.08%)	8 (15.38%)	4 (7.70%)	
Gravidity				0.244
0–1	27 (51.92%)	19 (36.54%)	8 (15.38%)	
≥ 2	25 (48.08%)	21 (40.38%)	4 (7.70%)	
Parity				0.710
0–1	11 (21.15%)	8 (15.38%)	3 (5.77%)	
≥ 2	41 (78.85%)	32 (61.54%)	9 (17.31%)	
Marital status				0.646
Married	23 (44.23%)	17 (32.69%)	6 (11.54%)	
Single	29 (55.77%)	23 (44.23%)	6 (11.54%)	
β-hCG (mIU/ml)	2415 (1219–3254)	1904 (1219–2798)	1704 (1579–3254)	0.102
Median of mass diameter (cm)	2.6 (1.7–4.7)	2.9 (2.0–4.7)	2.1 (1.7–3.2)	**0.032**

Values are given as median, mean ± standard deviation or number (percentage), unless indicated otherwise. Bold text emphasizes the result which P-value is less than 0.05. β-hCG, β-human chorionic gonadotropin; PEP, persistent ectopic pregnancy.

area. The subgroup that received two doses of MTX had a significantly smaller median mass diameter than that of the one MTX dose subgroup (P = 0.032) (Table 4). The median time before serum β-hCG levels returned to normal was 26.18 days (range: 19–31).

Three women in the PEP group (5.77%) and 13 women (8.33%) in the control were lost to follow-up. The two groups did not significantly differ in fertility follow-up, for either ongoing pregnancy (P = 0.129) or ongoing term pregnancy (P = 0.393). The PEP group had a significantly higher rate of REP (PEP: 5 cases, 10.20%; control: 4 cases, 2.80%; P = 0.034) (Table 5).

Univariate analysis associated gestational age, mass size, pelvic adhesion and PEP with REP. Cox multivariate regression of gestational age, mass size, pelvic adhesion and PEP, with REP as the endpoint, showed that the strongest independent predictors were pelvic adhesions and PEP ($P < 0.05$) (Table 6).

Ongoing pregnancies were defined as intrauterine pregnancies, visible on US at a gestational age of 12 weeks or later with fetal cardiac activity or pregnancies that resulted in live births. If an ongoing pregnancy did not occur, follow-up ceased at the last date of contact. REP was defined as any EP or a persistent pregnancy of unknown location for which surgery or medical treatment of MTX was necessary.

Discussion

Patients with EPs were considered to have PEP if their hCG levels increased or did not decrease after being treated for EP.[3] Decidual tissue develops imperfectly in fallopian EP patients, with trophoblasts infiltrating into the oviduct muscular layer after conservative surgery. The infiltrated trophoblasts may stay in the fallopian tube, muscular layer or placenta accreta or scatter into the blastocoel and then continue to grow. Postoperative serum hCG levels that do not decline or that increase again are characteristic of persistent trophoblasts, which

Table 5 Infertility follow-up after ectopic therapy

Patient characteristics	PEP(n = 49)	Treated satisfactorily(n = 143)	P
Ongoing pregnancy	27 (55.10%)	96 (67.13%)	0.129
Spontaneous pregnancy	5 (10.20%)	18 (12.59%)	0.657
Assisted reproduction	24 (48.98%)	79 (55.24%)	0.448
Ongoing term pregnancy	25 (51.02%)	83 (58.04%)	0.393
Natural labor	31 (63.27%)	101 (70.63%)	0.337
Cesarean section	18 (36.73%)	42 (29.37%)	
Repeat ectopic pregnancy	5 (10.20%)	4 (2.80%)	**0.034**

Values are given as median, mean ± standard deviation or number (percentage), unless indicated otherwise. Bold text emphasizes the result which P-value is less than 0.05.

Table 6 Univariate and multivariate survival analyses evaluating the factors influencing repeat ectopic pregnancy†

Variable	Univariate analysis	Multivariate analysis		
		P	HR	95% CI
Age	0.612	-	-	-
Gravidity	0.258	-	-	-
Parity	0.517	-	-	-
Pelvic adhesiolysis	0.003	**0.005**	1.903	1.312–3.208
Median of mass diameter (cm)	0.023	0.437	1.103	0.781–3.630
Gestational age (days)†	0.012	0.521	1.075	0.852–2.329
PEP	0.009	**0.002**	1.875	1.214–4.132

†Gestational age was calculated as the period from the date of last menstrual period to the date of surgery. Bold text emphasizes the result which *P*-value is less than 0.05. CI, confidence interval; HR, hazard ratio.

should be treated with particular caution and close postoperative surveillance.[10]

The incidence of postoperative PEP is 5.4%, but its reported occurrence is inconsistent.[3] In this study, the incidence of PEP was 2.08%, lower than reported, possibly because earlier studies reflect an initial stage, and perhaps a less-refined stage of laparoscopic use for EP.

Seifer *et al*. reported that EP treated at an earlier stage ($<$ 42 days' amenorrhea) or smaller EP masses ($\leq$ 2 cm in diameter) predicted PEP.[11] Another retrospective study including 206 cases reported 14 cases of PEP with an ectopic mass 8 mm in diameter and 13 cases smaller than 8 mm.[12]

In our study, gestational age in the PEP group was $<$ 45 days in 18 cases (34.62%), 45–50 days in 17 cases (32.69%) and $<$ 50 days in 35 cases (67.31%). In the PEP group, 34 (65.38%) patients had mass diameters $<$ 3 cm, similar to Larrain *et al*.'s results.[13] Median gestational age at diagnosis was 47.2 days, which implies that gestational age or smaller mass diameter is a risk factor for PEP. Earlier EP stage could be a risk factor for PEP and was more likely because of the incomplete removal of trophoblastic tissue during initial surgery, which resulted in the poorly defined cleavage planes between the implantation and trophoblastic material as a result of reduced hemorrhaging surrounding the eccyesis.[11]

Pelvic adhesion is sometimes associated with infected lesions, which should be excised, followed by postoperative anti-inflammatory therapy. Damage to the fallopian tubes from pelvic inflammatory disease, previous tubal surgery or a previous EP is strongly associated with an increased risk of EP.[14] In our study, 51.9% PEP patients received lysis for adhesions. Adhesiolysis appears to be critical to satisfactory EP treatment.

The predictive effect of preoperative β-hCG level for PEP is contradictory. Seifer *et al*. reported that higher hCG and progesterone levels before surgery indicated trophoblast viability and were risk factors for PEP.[11] Rabischong *et al*. determined that a hCG level $\geq$ 1960 IU/L was the only risk factor related to treatment failure.[15] Tews *et al*. found that presurgical hCG and progesterone levels were irrelevant to EP surgery outcomes.[16] In our study, the median presurgical hCG level did not significantly differ between the groups.

Postoperative serial monitoring of hCG values is required after salpingostomy because trophoblastic cells remain in the fallopian tube in 5–20% of women.[3] As there is no specific clinical manifestation of PEP in general, besides non-specific pelvic or hypogastrium pain and vaginal bleeding, continuous monitoring of hCG levels may be helpful.[17,18]

A recent study assayed sequential postoperative hCG samplings at early (POD 0–2) and late (POD 2–7) stages. Serum hCG levels increase or decrease over one to four weeks after surgery. hCG levels declined more quickly during POD 0–2 (half-life: 29.6 $\pm$ 3.6 hours) than during POD 2–7 (half-life: 64.3 $\pm$ 7.7).[19]

Seifer *et al*. reported that if the serum hCG level had declined more than 55% by POD 3 after conservative EP surgery, no PEP appeared, but PEP was a possibility if the serum hCG level declined by less than 55%.[3] Tews *et al*. divided the monitor time into four parts, 1–2, 3–4, 5–6 and 7–9 days after surgery and determined that a decline in the hCG level 5–6 days was significant for PEP, and less than 14% had a risk of PEP.[16] Early-stage hCG level is affected by preoperative hCG level, whereas late-stage hCG changes may reflect a risk of PEP.[16]

Scholars have different views. Billieux *et al*. carried out a prospective study of conservative surgery in EP in early (0–2 days) and late stage (2–7 days) and diagnosed two and nine cases of PEP, respectively.[20] In the late stage, two patients were diagnosed with false positive and one case exhibited an increased hCG level (false

negative) on POD 7. Early or late stage monitoring of hCG level is not effective in all patients, but that the hCG level should be monitored until it returns to normal in order to diagnose PEP.

In our study, serum hCG levels declined less than 30% by POD 3, consistent with Seifer *et al.*'s findings.[3] The decrease of 15.93% at POD 7 in our study was a little higher than Tews *et al.*'s result.[16] No current consolidated PEP diagnosis criteria exist. Patients sometimes present with plateaued β-hCG levels but no obvious pelvic mass. Expectant treatment is advised, and may be self-healing.

When a persistent EP is identified, it may be managed with surgical removal or with adjuvant MTX.[3] MTX is the most common treatment for PEP, as it usually only requires a single dose by intramuscular injection. Patients whose β-hCG levels are below 1375 I/IU are good candidates for medical treatment, and MTX treatment of EP has a 71% success rate.[21,22] Secondary surgery is an option for patients who suffer from abdominal pain, when MTX is ineffective or when a patient suffers from high-volume intraperitoneal hemorrhage. Locally injected MTX in the area suspected of harboring residual trophoblast tissue is also advised. If the tube cannot be saved, salpingectomy is recommended.

In general, MTX works better for EP in patients with lower hCG levels.[21] The main predictor of MTX failure was an initial β-hCG value ≥ 1790 mIU/ml; however, the success of MTX treatment does not depend solely on the hCG level.[23] In our study, the hCG levels in the one and two dose MTX groups were close to 2000 mIU/mL with no significant difference, which demonstrated the complexity of the phenomenon, and serum β-hCG may not have been the main reason for the second injection.

In our study, PEP was definitely diagnosed by US identification of an accessory mass, and MTX was used. However, PEP diagnosis based on hCG decline can sometimes be performed before a US diagnosis, and increases the chance of timely medical treatment.

Previous case series suggest that approximately 60% of women diagnosed with EPs are subsequently able to have intrauterine pregnancies.[24–26] This trial showed a non-significant higher rate of ongoing pregnancy within 60 months after salpingostomy when the PEP group was compared with controls. However, the PEP group had a significantly higher rate of persistent trophoblast and a slightly higher REP rate after salpingotomy. Although the lesions were removed by surgery in these cases, the tubal function may not have been restored, resulting in secondary infertility and REP.[27,28]

Disclosure

None declared.

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