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Efficacy and safety of laparoscopy versus local injection with absolute ethanol in the management of tubal ectopic pregnancy



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ABSTRACT

Objective: To compare the efficacy and safety between laparoscopy and local injection with absolute ethanol (AE) for treating tubal ectopic pregnancy (EP).

Study design: Retrospective cohort study of ectopic pregnancies in the fallopian tube from two tertiary hospitals between January 2015 and December 2017. Clinical information such as presenting symptoms, reproductive history, possible risk factors, initial diagnosis, serum beta-human chorionic gonadotropin (β -HCG) level, transvaginal ultrasonography findings, methods of treatment and outcomes were reviewed and analyzed.

Results: A total of 119 patients were identified for this study. The diagnosis was based on clinical manifestations, ultrasonography scan and dynamic serum β -HCG. 71.4% of women (85/119) had at least one risk factor for ectopic pregnancy, with the most common risk factors being a history of induced labor, uterine curettage, spontaneous abortion or tubal pregnancy. 64 patients were managed by laparoscopic surgery (Group A) and 2 subjects were failure and followed by a systemic methotrexate (MTX) prescription. The other 55 patients had local injection with absolute ethanol, of which 9 cases failed, followed by a second local injection and intramuscular MTX. The HCG decrease rate post absolute ethanol injection was a value predictive factor for prognosis. Moreover, the pregnancy rate one-year post treatment in local injection subjects (10/55, 18.2%) was higher than that of surgical subjects (5/64, 7.8%).

Conclusion: Local injection of absolute ethanol and laparoscopic surgery for tubal ectopic pregnancy are both effective and relatively safe, but laparoscopic surgery has better efficacy and shorten hospitalization day. Local injection may be less invasiveness and thus beneficial to fertility preservation.

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1. Introduction

Ectopic pregnancy (EP) is the implantation of a blastocyst outside of the uterus body, which occurs in 1–2% of pregnant women; However, it may seriously compromise health and future fertility of the patients [1,2]. EPs may present in cervix, cornual region, ovary, splenic flexure, and the most common location is the fallopian tube, which accounts for more than 90% of cases [3]. The routine use of transvaginal ultrasound scanning and dynamic monitoring human chorionic gonadotropin (HCG) and

progesterone (P4) levels during early pregnancy leads to a better diagnosis of EPs [4]. Prompt diagnosis allows considering the full range of treatment options, which include expectant management (follow-up until a decrease in β -HCG), medical treatment (including ultrasound-guided adnexal aspiration and/or local injection), conservative surgery, and radical surgery. The treatment options are dependent on the locations of EP and other clinical features. Generally, surgery is the first line treatment method, and laparoscopy (salpingostomy or salpingectomy) is the accepted approach for hemodynamically stable patients, while laparotomy is more suitable for a ruptured EP with hemodynamic instability. However, conservative management of EPs using adnexal aspiration with instillation of hyperosmolar glucose/methotrexate/Potassium chloride (KCl) has attracted a great deal of attention recently since there were less invasiveness [5–8]. Local injection may be an ideal therapeutic option for patients who clearly

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demonstrate an unruptured extrauterine pregnancy through ultrasonography, because this procedure is simple and the patient tolerates well.

It should be noted that the prognosis of hyperosmolar glucose/methotrexate/KCl injection is usually not encouraging due to the long HCG clearance duration and/or side effects [9]. Thus, our hospital sought absolute ethanol (AE) for local injection in treating live tubal ectopic pregnancies and got promising results. The purposes of this retrospective cohort study were: (1) To assess the safety and efficacy of the local AE instillation for tubal pregnancies; (2) To compare the effectiveness of laparoscopic management and local instillation, in terms of treatment success (i.e. complete elimination of trophoblast tissue), hospitalization durations and future fertility.

2. Material and methods

Data were collected from the medical history of patients at both the Gynecological department of the first affiliated hospital of Guangxi Medical University and the Gynecological department of the affiliated hospital of Guilin Medical University. All clinical information was obtained under protocols approved by the Clinical Research Ethics Committee, and private information of the patients was highly protected.

From January 2015 to December 2017, there were 158 cases of ectopic pregnancies in these two tertiary hospitals, of which 119 patients were enrolled to our study. Data were collected using a specially designed chart and the following parameters were collected: age, reproductive history, risk factors, symptoms, quantitative serum HCG, transvaginal ultrasonography, treatment method, perioperative findings, and the subsequent outcome. All patients whose medical records were incomplete or missing were excluded from this study. According to the treatment methods, patients were classified into two groups:

Group A - Surgical treatment: 39 patients underwent conservative salpingostomy and 25 underwent radical salpingectomy.

Group B - Local injection: 55 patients underwent ultrasound-guided transvaginal injection of absolute ethanol.

Statistical analysis was performed on SPSS version 15.0 for Windows (IBM, Armonk, NY, USA), and the process involved descriptive statistics. All data were expressed as the mean \pm SD. One-way analysis of variance (ANOVA) was used for the comparison of multiple sample means, and the least significance difference test (LSD) was used for comparison between different groups. Chi-square (X^2) test or Fischer's exact test were performed to crude calculate odds ratio (OR) and the corresponding 95% confidence interval (CI). P values <0.05 were considered statistically significant.

3. Results

3.1. General characteristics and risk factors

The patients were 30.18 ± 6.20 (19–46) years old, and the mean gestational age at the time of diagnosis was 48.04 ± 11.24 (23–88) days. 23 women (19.3%) had experienced at least once ectopic pregnancy.

Detailed information on the clinical characteristics of all patients is summarized in Table 1. A total of 85 (71.4%) subjects had at least one risk factor for EP. The most common factors included induced labor, uterine curettage, or a spontaneous abortion; 32 (26.9%) patients had two or more of these risk factors. However, there were still 34 patients who had none of the above common risk factors (Table 2).

3.2. Diagnosis of ectopic pregnancy

The diagnosis of an EP in our study was mainly based on clinical manifestations and carefully transvaginal ultrasound scanning. In the current study, 47(39.5%) subjects had both abdominal pain and vaginal bleeding, while 3(2.5%) subjects were asymptomatic, and the diagnosis for these subjects were based on their routine follow-up through a transvaginal ultrasound scan (Table 1).

3.3. Treatment methods and outcomes

Treatment options were recommended based on the patient's clinical presentations and fertility desire. In group A, 39 patients underwent conservative salpingostomy, 25 underwent radical salpingectomy, two subjects (3.125%) in this group were failure with a persistent ectopic pregnancy and needed a systemic MTX administration. 9 subjects (16.4%) in group B with local AE injection were failure and needed another local injection and a systemic MTX administration. The persistent EP rate in surgical group was significantly lower than that in the local injection group (OR: 0.165, 95%CI:0.034–0.800). The average duration of hospitalization was shorter in surgical treatment subjects than that in local injection subjects (Table 3).

We then analyzed HCG level between the salpingotomy subjects and the salpingectomy subjects by using Least-significant differences (LSD) (Table 4) and found that there was no statistic difference before/after treatment and also the HCG clearance duration. On the other hand, the HCG decreasing rate in local injection subjects was significantly lower than that in the salpingotomy subjects or salpingectomy subjects respectively, from the first day to the first week posttreatment, but there was no significant difference on HCG clearance days (Table 4).

Table 1
Main clinical characteristics of ectopic pregnancy patients (n = 119).

Parameter		Number	Percentage
Maternal age (years)		30.18 ± 6.20 (19–46)	–
Gestational age (days)		48.04 ± 11.24 (23–88)	–
Reproductive history	G1P0A0	22	0.18487395
	G _n P _n A _n	97	0.81512605
EP history	0	96	0.806722689
	1	20	0.168067227
	2	3	0.025210084
Symptoms	Vaginal Bleeding	47	0.395
	Abdominal Pain	22	0.185
	Abdominal Pain and vaginal Bleeding	47	0.395
	None	3	0.025
Serum HCG (mIU/L)		3514.44 ± 5611.87	–

Table 2

Risk factors found in patients with ectopic pregnancy.

Risk factor	case(s)	percentage
Induced labor, Uterine curettage, Drug abortion or spontaneous abortion	78	0.6555
Former tubal pregnancy	23	0.1933
Previous Laparotomy or Cesarean	17	0.1429
Intrauterine device, emergency OC	6	0.0504
tubal ligation or reversal	2	0.0168
Congenital abnormality of fallopian tube	1	0.0084
None	34	0.2857
At least two risks	32	0.2689

Table 3

Serum HCG level decreased in each group posttreatment.

Items	Treatment method			F ^a	P
	Salpingectomy (25)	Salpingotomy (39)	Injection (55)		
HCG before	4780.66 ± 5276.60	5343.50 ± 8035.49	1641.92 ± 2068.00	6.108	0.003
HCG 1-day decrease	57.95 ± 19.75	56.47 ± 20.65	41.08 ± 28.01	6.111	0.003
HCG 1 week decrease	94.26 ± 6.84	94.63 ± 4.87	83.61 ± 23.22	6.188	0.003
HCG clearance days	24.4 ± 7.65	26.33 ± 10.11	26.98 ± 13.02	0.325	0.723
Hospitalization days	4.84 ± 1.25	5.46 ± 2.48	7.55 ± 3.102	11.510	<0.001
Persistent EP	0	2(5.13%)	9(16.36%)	—	0.018
Spontaneous pregnancy	2	3	10	—	0.089

^a F is the ratio of mean square between groups and mean square within groups.**Table 4**

Multiple comparison of serum HCG levels between treatment groups.

HCG level	Treatment Groups		Significance(P)	95%CI
before	Injection	Salpingotomy	0.002	(-5930.10, -1435.71)
		Salpingectomy	0.019	(-5706.95, -533.19)
	Salpingotomy	Salpingectomy	0.685	(-2176.95, 3302.62)
1day decrease	Injection	Salpingotomy	0.004	(-0.251386, -0.049565)
		Salpingectomy	0.006	(-0.281402, -0.049075)
	Salpingotomy	Salpingectomy	0.813	(-0.137793, 0.108267)
I week decrease	Injection	Salpingotomy	0.002	(-0.176513, -0.039815)
		Salpingectomy	0.010	(-0.183117, -0.025756)
	Salpingotomy	Salpingectomy	0.930	(-0.079603, 0.087059)
Negative day	Injection	Salpingotomy	0.987	(-4.45, 4.52)
		Salpingectomy	0.451	(-3.19, 7.13)
	Salpingotomy	Salpingectomy	0.485	(-3.53, 7.40)

Among all the subjects, only 5 women (5/64, 7.8%) in surgical treatment group and 10 women (10/55, 18.2%) in local injection group reported spontaneous intrauterine pregnancies after 1 year of follow-up.

4. Comments

Ectopic pregnancy refers to the implantation of a blastocyst outside of the uterine cavity, which is a common acute abdomen complication in gynecology department and also the most common cause of maternal morbidity and mortality in the first trimester of pregnancy [10]. In recent years, the early diagnosis and treatment of EPs have significantly improved survival rate and fertility retention of patients.

4.1. Risk factors of tubal ectopic pregnancies

The risk factors of EPs include laparoscopic surgery, cesarean section, abortion and curettage, smoking and previous use of an intrauterine device [11]. Although the pathogenesis of EPs is

varied, the partial obstruction of fallopian tubes and defective ciliary movement are the main causes [12]. Recently, the incidence of tubal pregnancies increased due to the booming of assisted reproductive technology (ART) and transferred more embryos. In addition, ART also increased the risk of ipsilateral or bilateral multiple pregnancies [13,14]. Therefore, reducing risk factors may effectively reduce the incidence of ectopic pregnancies.

4.2. Diagnosis of a tubal ectopic pregnancy

The typical symptoms of tubal pregnancy are postmenopausal abdominal pain and vaginal bleeding. The auxiliary diagnosis includes serum HCG, progesterone, vaginal ultrasonography and laparoscopy [15]. Among them, laparoscopy is the golden standard of diagnosis, which can be used for diagnosed as well as endoscopic surgery [16]. When the patient is under the following circumstances, a tubal pregnancy should be suspected: (1) a history of tubal pregnancies or operations; (2) assisted reproductive technology and ovulation-stimulation pregnancies; (3) presentation with postmenopausal abdominal pain and vaginal bleeding;

(4) serum HCG level greater than 2000IU/L, and progesterone level less than 5 ng/ml; (5) vaginal ultrasonography showing that no gestational sac is detected in the uterine cavity, but the germ and the fetal heart beat is visible near the uterus [17].

4.3. Management of tubal ectopic pregnancies

The treatment strategies of an ectopic pregnancy include surgical treatment, local injection, drug therapy and expectant. The decision-making is dependent on patient's medical presentations, examination findings and their desire for future fertility [18]. Emergency surgeries including salpingectomy and salpingostomy should be performed when the patient has an acute abdomen pain or EP rupture. Radical surgery can be performed if the contralateral fallopian tube is infected and when the patient has no fertility requirement; Otherwise, conservative surgery or local injection or expectant may be also the choices.

4.3.1. Laparoscopic surgery (including salpingectomy and salpingostomy)

Two surgical options are available for EPs: salpingotomy and salpingectomy. It is obvious that the persistence of trophoblast material is an important reason for the failure of salpingotomy (Table 3). The success of treatment is not only related with the permeability of the concerned tube, but also with the health status of the contra tube. It has been shown that the fertility rate after salpingectomy in patients without a history of infertility and with a normal contra lateral tube is comparable to those treated with salpingotomy in patients under 30 years old. If an ipsilateral ectopic pregnancy recurs, salpingectomy is usually required [6]. It is suggested that, in cases without adhesions, the remaining healthy tube will be capable of catching the ovule coming from the contralateral ovary. In some rare or complex cases, bilateral salpingectomy should be considered. In addition, Chen et al. [19] and Cheng et al. [20] showed that there is no statistical difference in long-term reproductive outcomes between the two surgical options. After surgical treatment of the tube, a serum β -HCG based control is necessary. Hajenius et al. [21] also supposed that HCG levels should be mandatory monitored after treatment. In our study, nearly all the surgical subjects were successful except for only two cases were required for additional MTX administration.

4.3.2. Local injection of anhydrous ethanol

The function of the AE injection is to dehydrate and destroy chorionic villi. Kaijima et al. [22] pointed out that AE and MTX are equally effective, and Osada et al. [23] also suggested AE is effective in treating ectopic pregnancy. The advantages of AE local injection may refer to: 1) the response is quickly and the evaluation can access just after the injection; 2) a low dose of AE has little impact on the body; 3) because of its antiseptic effect, it is less likely to cause local infection during therapy; 4) the flow of ethanol during the injection can be clear demonstrated as high-intensity signal under ultrasound scanning [22]; 5) AE is less toxic and allows for repeat administrations if needed. However, the biggest disadvantage of local injection is that it can only produce local effects. Moreover, the leakage of AE into the abdominal cavity can cause peritoneal irritation, which may in turn cause severe pain and adhesions to patient.

In case of failure after AE local injection, it was generally suggested another dose of MTX systemic administration. However, the dosage of MTX needed to carefully calculate due to its various side effects [24,25]. In our study, 9 subjects (16.4%) with local AE injection were failure and needed another local injection and a systemic MTX administration.

4.3.3. Comparisons between two treatment strategies

HCG monitoring is crucial for therapy effect evaluation. The serum HCG level in these two groups was statistically significant difference before and after treatments. HCG decrease rate between the two groups were also significant difference at one day posttreatment and one week later, but the HCG clearance duration was the similar between two groups (Table 4).

The HCG decrease rate on the first day post treatment was probably correlated with prognosis and could be used as a predictive marker. In our study, the HCG decrease rate did not clearly present predictive value in the surgical treatment subjects. However, for the local injection subjects, HCG increased post treatment indicated the failure of this treatment: if HCG decreases by less than 10%, the rate of persistent EP probability will increase, and another injection should be subsequently given (Table S1).

In addition, the hospitalization duration in surgical subjects was much shorter than that of the local injection subjects, which means less of financial burden. However, local injection was less invasiveness and well-tolerant for patients, also cheaper compared to surgical methods. Moreover, the pregnancy rate one-year post treatment in local injection subjects was trendy higher than that of surgical subjects, although without statistical difference which is more likely due to small sample size, suggesting local injection might be more benefit for fertility preservation.

5. Conclusion

In this study, local injection of absolute ethanol and laparoscopic surgery are both effective and relatively safe, but laparoscopic surgery has better efficacy, lower hospitalization duration and lower persistent EP rate. Local AE injection is economic, less invasiveness and easy to perform but relatively higher persistent EP rate. Furthermore, Local AE injection is more beneficial to fertility preservation. Our data provides a piece of reliable information for treatment of tubal pregnancy with absolute ethanol. However, the current study also had several limitations. Firstly, this was a retrospective evaluation based on limited data resources from two hospitals. A prospective, randomized, multi-center study is needed to confirm the effectiveness and safety of the AE local injection. Secondly, it remains to be investigated whether our findings can be applied to other types of ectopic pregnancy.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eurox.2019.100032>.

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