Non-surgical Treatment of Ectopic Pregnancy: a Three-year Review

Edith OL CHENG MBChB, MRCOG
Department of Obstetrics and Gynaecology, United Christian Hospital, Hong Kong
William WK TO MBBS, M Phil, FRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, United Christian Hospital, Hong Kong
SW TSANG MBBS, FRCOG, FHKAM (O & G)
Department of Obstetrics and Gynaecology, Tseung Kwan O Hospital, Hong Kong
KM MOK MBBS, FRCOG, FHKAM (O & G)
Department of Obstetrics and Gynaecology, United Chrisitan Hospital, Hong Kong
CY SIT MBBS, FRCOG, FHKAM (O& G)
Department of Obstetrics and Gynaecology, Tseung Kwan O Hospital, Hong Kong

Objectives:
To evaluate the success rates of expectant and medical management of ectopic pregnancy in the Department of Obstetrics and Gynaecology in Tseung Kwan O Hospital, Hong Kong, and to look for any differences between the responders and non-responders.

Methods:
A retrospective study was conducted from December 2003 to December 2006. 121 women were identified by using a computer database to generate a list of patients with the diagnosis for ectopic pregnancy. Both in-patient and out-patient records were reviewed. The data of women who had received primary expectant management and medical treatment were analysed.

Results:
25 women who were treated with expectant management and 19 who received methotrexate were included in the analysis. The success rates of expectant and medical management were 63% and 73%, respectively. These figures were comparable to previous published results. There were no significant differences in the clinical characteristics such as the presence of abdominal pain, vaginal bleeding, size of adnexal mass, presence of free fluid in the pelvis, and pretreatment levels of serum beta-human chorionic gonadotropin between the responders and non-responders in the expectant and medical management groups.

Conclusion:
Both expectant and medical management are reasonable options in selected women with ectopic pregnancy who meet well-defined criteria. The non-surgical management options allow the use of more conservative treatment especially for those women who want to preserve their fertility or those who have high surgical risks.

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Introduction

According to the Hong Kong College of Obstetricians and Gynaecologists Territory-wide Audit Report in 2004[1], the rate of hospital admission for ectopic pregnancy increased from 2.1% in 1994 to 2.4% in 1999 and 2.9% in 2004. Also, the management of ectopic pregnancy has changed considerably over the past 10 years. In the past, the majority of ectopic pregnancies were treated surgically either by salpingectomy or salpingotomy. With the use of high-resolution

Correspondence to: Dr Edith OL Cheng, Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Kowloon, Hong Kong
Email: editholcheng@yahoo.com.hk

transvaginal sonography (TVS) and quantitative serum beta-human chorionic gonadotropin (hCG) assay, earlier diagnosis of ectopic pregnancy can be made which allows the use of more conservative management options that preserve the Fallopian tubes.

Methotrexate, a well-known chemotherapeutic agent, is particularly effective against trophoblastic tissue. It has been studied extensively and is the most widely used medical treatment for ectopic pregnancy. The recommended regimen for methotrexate is a single intra-muscular dose of methotrexate at 50 mg/m^2. Success rates of methotrexate in the treatment of ectopic pregnancy have been reported to be between 63% and 94%[2-4].

Early ectopic pregnancies can resolve spontaneously, and are therefore amendable to expectant management. Seven observational studies showed that the success rate of expectant management was 67%[5-11].

This study aimed to evaluate the success rates of expectant and medical management of ectopic pregnancy in the Department of Obstetrics and Gynaecology in Tseung Kwan O Hospital, Hong Kong, and to look for any differences between the responders and non-responders.

Methods

This is a retrospective study conducted from December 2003 to December 2006 in Tseung Kwan O Hospital. A total of 121 women were identified by using a computer to generate a list of women with the diagnosis of ectopic pregnancy. One woman received treatment in a private hospital after the diagnosis. 21 (17%) women received methotrexate as the primary intended treatment for ectopic pregnancy and 27 (22%) women received expectant management. The remaining 72 (60%) women were managed surgically. Both out-patient and in-patient records were reviewed.

The following criteria were used for the diagnosis of ectopic pregnancy in this study: (1) absence of an intra-uterine gestational sac on TVS with either a serum beta-hCG level greater than or equal to 2000 IU/L, or (2) an abnormally rising (<66% rise) or falling (<20% decline) of serum beta-hCG level in 48 hours in those having a serum beta-hCG levels of <2000 IU/L with an adnexal mass detected on TVS.

After reviewing the data collected, one woman treated with methotrexate was excluded because of cervical pregnancy. Four women did not fulfil the diagnostic criteria required in this study and were excluded. Among women with ectopic pregnancies (excluding the one with cervical pregnancy), adnexal masses were identified in 93%. All of the women were managed according to the protocol of Tseung Kwan O Hospital. Those who received methotrexate treatment should meet the following inclusion criteria: haemodynamically stable, size of adnexal mass is equal to or less than 3.5 cm, serum beta-hCG level is less than 5000 IU/L, absence of adnexal foetal heart, and minimal haemoperitoneum. For primary methotrexate treatment, it was given as a single intramuscular dose at 50 mg/m^2 body surface area in the hospital and the patients were subsequently discharged on the same day if there was no immediate problem. Serum beta-hCG level was checked on day 1, 4, 7 and then weekly afterwards. Women were followed up in the early pregnancy assessment clinic regularly and the call-back system was activated if they defaulted the appointments. Patients would receive additional doses of methotrexate if beta-hCG levels demonstrated either (1) less than 15% fall between days 4 and 7 or (2) a rise or plateau after day 7.

There is no formal protocol for the expectant management of ectopic pregnancy in Tseung Kwan O Hospital. In general, women who received expectant management should meet the following inclusion criteria: haemodynamically stable, size of adnexal mass is equal to or less than 3.5 cm, serum beta-hCG level is less than 3000 IU/L with a falling trend, absence of adnexal foetal heart, and minimal haemoperitoneum. For primary expectant management, the women were followed up with twice weekly serum beta-hCG and weekly TVS until serum beta-hCG level was less than 10 IU/L.

Treatment failures were defined as the need to undergo other modalities of interventions for any reason after the women had received primary intended treatment.

Data including women's demographics, presence or absence of risk factors for ectopic pregnancy such

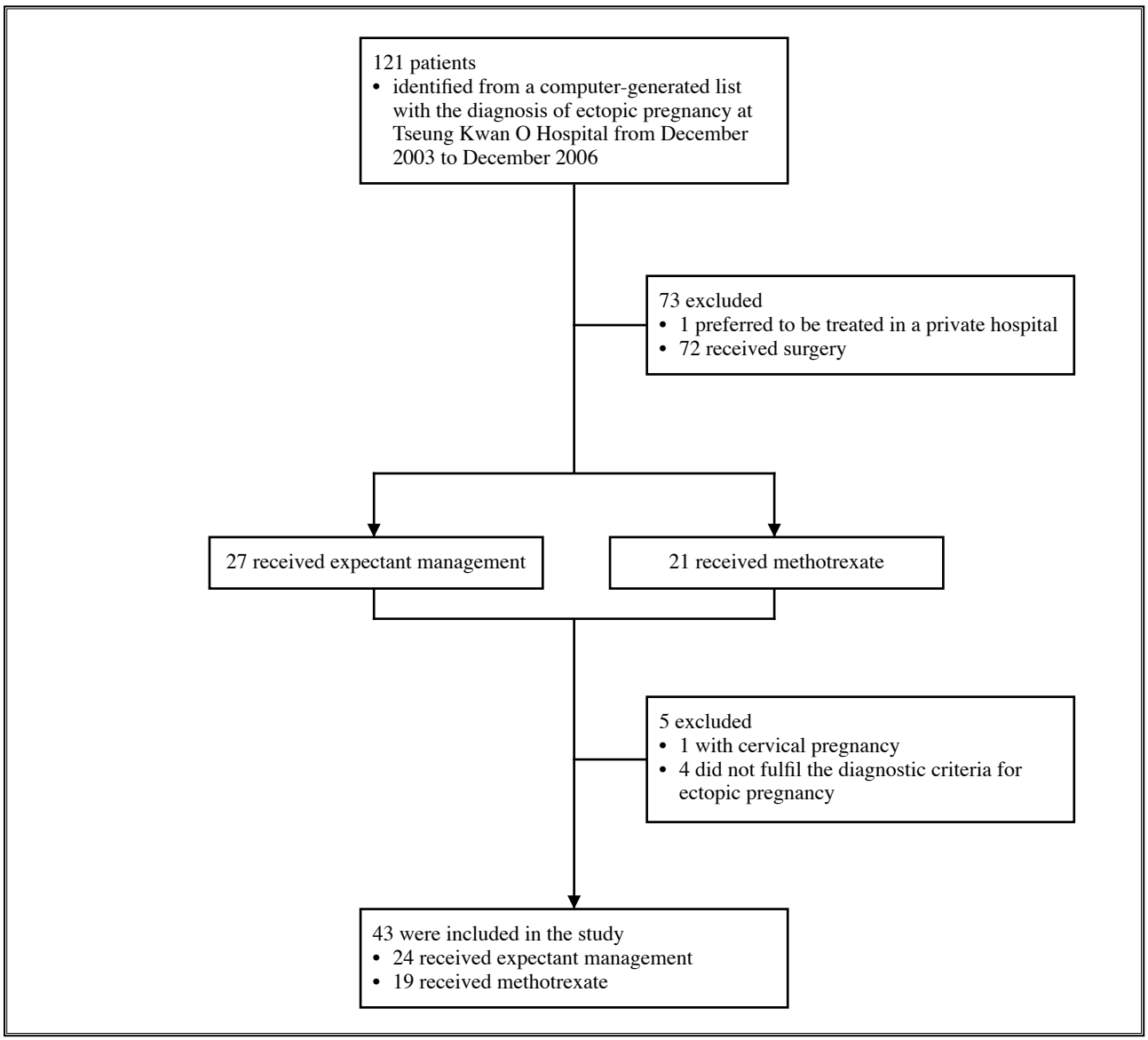

Figure. Flowchart

as a history of ectopic pregnancy, sexually transmitted disease, pelvic inflammatory disease and tubal surgery, clinical and ultrasonographic findings, pre-treatment serum beta-hCG levels, and the number of methotrexate doses administered were collected. Time to complete resolution was defined as the number of days from the initiation of treatment to a serum beta-hCG level of less than 10 IU/L. In women who required surgery, symptoms, procedure performed, and operative findings were also noted. This study was approved by the Hospital Research Ethics Committee.

Descriptive statistics, Mann Whitney *U* test and Fisher's exact test were performed for statistical analysis where appropriate. A p value of <0.05 was considered significant. The data were analysed using the Statistical Package for the Social Sciences version 15.0 (SPSS, Chicago, IL, US).

Results

43 women were included in the analysis (Figure) in which 24 received expectant management and 19 received methotrexate as primary intended treatment for ectopic pregnancy. In the expectant management group, the mean age of women with ectopic pregnancy was 30 years (range, 17-38 years). The estimated mean gestational age was 5 weeks (range, 4-9 weeks). Approximately 88% of women presented with abdominal pain and per-vaginal bleeding. In all women in this group, adnexal masses were found on ultrasound scan with a mean size of 24.5 mm. Pre-treatment serum beta-hCG levels ranged from 82 to 2994 IU/L with a mean of

Table 1. Comparison between clinical characteristics of women in expectant and methotrexate groups

	Expectant management group (n=24)*	Methotrexate group (n=19)*
Age (years)	30 ± 8	29 ± 5
Gravida		
Primigravida	5 (21%)	1 (5%)
Parity		
Nulliparity	11 (46%)	10 (53%)
Primiparity	6 (25%)	7 (37%)
Multiparity	7 (29%)	2 (11%)
Weeks of amenorrhoea	5 ± 3	6 ± 1
Presence of risk factors for ectopic pregnancy†	10 (42%)	13 (68%)
Symptoms		
Abdominal pain	21 (88%)	14 (74%)
Bleeding	21 (88%)	18 (95%)
Ultrasound findings at diagnosis		
Size of adnexal mass (mm)	24.5 ± 11.8	18.5 ± 6.91
Presence of free fluid in pelvis	11 (46%)	8 (42%)
Pre-treatment beta-hCG‡ level (IU/L)	591.3 ± 784.7	1086 ± 1033

* Data are shown in No. (%) or mean ± standard deviation

† Risk factors included a history of subfertility, tubal surgery, sexually transmitted disease, pelvic inflammatory disease, sterilisation or previous ectopic pregnancy, documented tubal abnormality, smoker, and use of intrauterine contraceptive device

‡ hCG denotes human chorionic gonadotropin

Table 2. The success rate of expectant and methotrexate management

	Success rate No. (%)	Failure rate No. (%)
Expectant (n=24)		
Expectant only	15 (63)	9 (38)
Expectant + methotrexate	18 (75)	6 (25)
Methotrexate (n=19)		
Single dose	13 (68)	6 (32)
>1 dose	14 (74)	5 (26)

591.3 IU/L (Table 1).

Of 24 women who received expectant management, three required subsequent medical treatment and six required surgical interventions. The success rate for women managed expectantly was 63% (Table 2). The mean resolution time was 29.2 days and the mean number of hCG assays required was 5.8. Three women required subsequent medical treatment because of rising serum hCG level and they were all treated successfully with single-dose intramuscular methotrexate. The overall success rate in the expectant management group was 75%. Six women required subsequent surgical treatment—two of them because of increasing abdominal pain, one with progressive fall in haemoglobin level, one due to suboptimal decline of beta-hCG and increased amount of free fluid on ultrasound scan, and two preferred to have early surgical interventions. All six women managed surgically had laparoscopic unilateral salpingectomy performed and histology confirmed tubal pregnancy. No major morbidity was noted in this group of women.

In the medical treatment group, the mean age of women was 29 years (range, 19-38 years). The estimated mean gestational age was 6 weeks (range, 4-10 weeks). Approximately 74% of women presented with abdominal pain and 95% of women presented with per-vaginal bleeding. Adnexal masses were found on ultrasound scan with a mean size of 18.5 mm in all

Table 3. Comparison of clinical characteristics of successes and failures in the expectant management group

	Success (n=15)*	Failure (n=9)*	p Value†
Age (years)	31 ± 5	29 ± 6	0.29
Gravida			
Primigravida	3 (20%)	3 (33%)	0.635
Parity			
Nulliparous	7 (47%)	4 (44%)	0.006
Primiparous	1 (6.7%)	5 (56%)	
Multiparous	7 (47%)	0%	
Presence of risk factors of ectopic pregnancy‡	6 (40%)	4 (44%)	1
Weeks of amenorrhoea	6.25 ± 2	6 ± 1	0.907
Symptoms			
Pain	14 (93%)	7 (77%)	0.533
Bleeding	14 (93%)	7 (77%)	0.464
Ultrasound findings			
Size of adnexal mass (mm)	27.7 ± 13.4	19.2 ± 6	0.055
Presence of free fluid	7 (47%)	4 (44%)	1
Pre-treatment beta-hCG§ level (IU/L)	561.7 ± 724.3	640 ± 920	0.64

* Data are shown in No. (%) or mean ± standard deviation

† Univariate analysis were tested by Mann Whitney *U* test and Fisher's exact test

‡ Risk factors included a history of subfertility, tubal surgery, sexually transmitted disease, pelvic inflammatory disease, sterilisation or ectopic pregnancy, documented tubal abnormality, smoker, and use of intrauterine contraceptive device

§ hCG denotes human chorionic gonadotropin

Table 4. Comparison of clinical characteristics of successes and failures in the methotrexate group

	Success (n=14)*	Failure (n=5)*	p Value†
Age (years)	30 ± 4	27 ± 5	0.219
Gravida			
Primigravida	0 (0%)	1 (20%)	0.263
Parity			
Nulliparous	7 (50%)	3 (60%)	
Primiparous	5 (36%)	2 (40%)	1
Multiparous	2 (14%)	0 (0%)	
Presence of risk factors of ectopic pregnancy‡	71%	60%	1
Weeks of amenorrhoea	7 ± 1	6 ± 1	0.444
Symptoms			
Pain	11 (79%)	3 (60%)	0.57
Bleeding	14 (100%)	4 (80%)	0.263
Ultrasound findings			
Size of adnexal mass (mm)	19.4 ± 7.22	16.1 ± 5.96	0.444
Presence of free fluid	9 (64%)	2 (40%)	0.603
Pre-treatment beta-hCG§ level (IU/L)	787 ± 586.4	1921 ± 1582	0.219

* Data are shown in No. (%) or mean ± standard deviation

† Univariate analysis were tested by Mann Whitney *U* test and Fisher's exact test

‡ Risk factors included a history of subfertility, tubal surgery, sexually transmitted disease, pelvic inflammatory disease, sterilisation or ectopic pregnancy, documented tubal abnormality, smoker, and use of intrauterine contraceptive device

§ hCG denotes human chorionic gonadotropin

women in this group. Pre-treatment serum beta-hCG levels ranged from 189 to 4509 IU/L with a mean of 1086 IU/L (Table 1).

Of the 19 women who received single-dose intramuscular methotrexate, one required second dose of intramuscular methotrexate and five required subsequent surgical interventions. The success rate for women managed with single-dose methotrexate was 68% and the overall success rate for methotrexate treatment was 74% (Table 2). The mean resolution time was 38.8 days and the mean number of hCG assays required was 8.1. Five women required subsequent surgical interventions—two of them because of increasing abdominal pain, one due to enlarging adnexal mass and increasing amount of free fluid on ultrasound scan, one showed a rising serum beta-hCG level despite two doses of methotrexate, and one requested to have early surgical intervention. All five women undergoing surgery had unilateral salpingectomy (2 laparotomies and 3 laparoscopies) performed and histology confirmed tubal pregnancy. Two women required blood transfusion in this group, but no other major morbidity was noted.

In this study, we also tried to identify any predictive factors for the success of non-surgical treatments of ectopic pregnancy, Thus, a comparison of clinical characteristics including presence of abdominal pain, vaginal bleeding, size of adnexal mass, presence of pelvic fluid on ultrasound scan, and pre-treatment serum beta-hCG level between women who failed expectant management and those that required no further treatment was performed. However, no statistically significant differences between the two groups could be demonstrated (Table 3). The same analysis was performed in the methotrexate group, which again showed that the presence of abdominal pain and vaginal bleeding, size of adnexal mass, presence of free fluid on ultrasound scan and pre-treatment serum beta-hCG level were not associated with a significant risk of treatment failure (Table 4).

Discussion

Our success rates of expectant management and methotrexate treatment were 63% and 74% respectively. They were comparable to the quoted figures of 67%[5-11] and 63-94%[2-4] respectively in other published studies. The variable success rate in the previous studies probably reflected the differences in patient selection criteria and the number of patients involved. In well-selected patients, the success rate of non-surgical treatment of ectopic pregnancy could be up to 94%. There were no major morbidities associated with those who failed non-surgical treatments in our study except one woman who required immediate laparotomy for 1200 ml of haemoperitoneum and two women who required blood transfusion in the failed medical treatment group.

From the previous studies[8,10,12,13], the most commonly identified predictors of the success for methotrexate treatment of ectopic pregnancy are the size of adnexal mass, the presence of free fluid in the pelvis, and the pre-treatment serum beta-hCG level. Also, in a review of 350 women with tubal ectopic pregnancies who had been treated with single-dose methotrexate, logistic regression analysis showed that the serum beta-hCG level before treatment was the only factor that contributed significantly to the failure rate[14]. However, we are unable to demonstrate any significant association between the above clinical factors and the success rate. It may be due to our different selection criteria which only included those with adnexal masses equal to or less than 3.5 cm and serum beta-hCG level of less than 3000 IU/L for the expectant management group and less than 5000 IU/L in the methotrexate group.

All women included in the study had paired serum beta-hCG checked 48 hours apart and adnexal masses detected on TVS, but uterine curettage was not performed as a part of pre-treatment assessment. As the presence of chorionic villi in the uterine content would practically exclude the possibility of ectopic pregnancy in most cases, some studies would actually use uterine curettage as a part of diagnostic procedure to avoid the risk of unnecessary methotrexate administration. According to a systemic review[12], identification of any non-cystic adnexal mass on TVS had a sensitivity of 84.4% and a specificity of 98.9%, and had positive and negative predictive values of 96.3% and 94.8% respectively, in diagnosing ectopic pregnancy. In our study, all TVS performed for suspected ectopic pregnancy were done by senior gynaecologists who had attained specialist qualifications. In our series of 121 women, non-cystic adnexal masses were identified in 93% of ectopic pregnancy. On the other hand, dilatation and curettage are not without risks and need to be done under general

anaesthesia. Therefore dilatation and curettage were not included in our diagnostic algorithm.

Although the non-surgical treatment of ectopic pregnancy is widely accepted, these treatment modalities are underused in Hong Kong. Apart from one case report of expectant management of ectopic pregnancy[15], there are no other published data which are related to non-surgical treatment of ectopic pregnancy. The main benefit of non-surgical management of ectopic pregnancy is the avoidance of invasive surgical treatment, especially for those women who had previous salpingectomy and those at high risk of operation. The main drawback of non-surgical approach is the possible risk of rupturing of the ectopic pregnancy which can be a life-threatening condition. Also, the women need to be followed up closely with regular monitoring of serum beta-hCG level and transvaginal scanning. In our study, the mean resolution time for expectant and medical management was 29.2 days and 38.8 days respectively and was much longer than those treated surgically. Therefore, the risks and benefits of non-surgical treatment of ectopic pregnancy should be justified individually and fully explained to the women. Nonetheless, in well-selected patients, the non-surgical treatment should be offered as one of the management options.

The major limitation of this study is the small sample size. It would be more informative if we could also evaluate the cost-effectiveness, women's satisfaction and quality-of-life issues after receiving non-surgical treatments of ectopic pregnancy. Studies with larger sample sizes are needed for further evaluation.

Conclusion

Both expectant and medical management of ectopic pregnancy are reasonable options in well-selected women. In our study, success rates of expectant and medical management were 63% and 74% respectively and are comparable to other published studies. There was no significant clinical factor identified to predict the success of non-surgical treatment of ectopic pregnancy in our data.

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