

Ectopic pregnancies: Catch them early, treat them wisely!

Beena Kingsbury¹, Dibu Sam¹, Jeyasudha R¹, Elsy Thomas¹, Grace Rebekah², Jessie Lionel¹

¹Departments of Obstetrics and Gynaecology, ²Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India

ABSTRACT

Introduction: Ectopic pregnancy (EP) is a common condition encountered in Obstetrics and Gynecology. Different management protocols are currently available for haemodynamically stable patients but definitive recommendations is yet to be established, especially in developing countries with limited resources. **Aim:** To determine the outcome of EP in patients who are haemodynamically stable and to evaluate the factors that would predict success of specific management protocols in them. **Methodology:** Haemodynamically stable patients with HCG levels <1500 mIU/ml were recruited for expectant management, 1500-5000 mIU/ml were given MTX and those with >5000 mIU/ml were managed surgically. **Results:** The overall success rate for expectant management was 92.7% and that with MTX was 80%. Baseline HCG values was found to be the only significant factor for predictor of success of treatment in the expectant group (P 0.05). The size of mass seen on USG did not have a significant correlation with beta HCG values (P 0.257). **Conclusion:** Of all the predictors for success of treatment that have been studied, the initial HCG value alone remains of paramount importance. Women with initial values of HCG <1500 mIU/ml can be offered expectant management, with a much better assurance of success for those with values <1000 mIU/ml. Those with values <5000 mIU/ml can be given MTX, with single dose being sufficient most often for <3000 mIU/ml. The presence of fluid restricted to the pelvis on USG can be managed non-surgically. One should not opt for surgical management only on the basis of size of the adnexal mass on USG.

Keywords: Baseline Beta HCG, conservative management for ectopic pregnancy, expectant management, methotrexate therapy, unruptured ectopic pregnancy

Gone are the days when ectopic pregnancy (EP) was diagnosed only when women in the reproductive age group came with amenorrhea followed by abdominal pain and syncope, often in shock and had to be rushed into the operating room for a life saving laparotomy followed by salpingectomy. The clinical scenario has changed now with EP being diagnosed much earlier with the help of high resolution ultrasonography (USG) and highly sensitive beta HCG assays which have revolutionised the management of

unruptured EP.^[1,2] Different management protocols are currently available but definitive recommendations is yet to be established, especially in developing countries with limited resources.^[3]

Aim

This study was undertaken to determine the outcome of EP in patients who were haemodynamically stable and to evaluate the factors that would predict success of specific management protocols in such patients.

Methodology

This prospective cohort study was conducted in a large tertiary care centre in South India from September 2014 to June 2018.

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Address for correspondence: Dr. Elsy Thomas,
Department of Obstetrics and Gynaecology, Unit 1, Christian
Medical College, Ida Scudder Road, Vellore - 632 004,
Tamil Nadu, India.
E-mail: et@cmcvellore.ac.in

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The study was approved by the Institutional Review Board approval obtained (IRB number 9045 Dated 4.09.2014). Patient recruitment was done from the out patient clinics and emergency room admissions. The criteria for inclusion into the study was all pregnant women suspected to have an EP and were hemodynamically stable. Patients who had hemodynamic instability or who were partially treated elsewhere were excluded from the study. A patient was deemed to be hemodynamically unstable if any two of the following criteria were fulfilled 1) Pulse rate ≥ 110 /minute 2) Blood pressure $\leq 90/60$ mmHg 3) Hemoglobin < 10 gms/dl. Women with a diagnosis of EP and clinical signs of hemodynamic instability underwent laparotomy followed by total salpingectomy of the affected tube.

Haemodynamically stable women suspected to have EP underwent detailed trans-abdominal (TAS) and Trans-vaginal (TVS) ultrasonography (GE Voluson G8 and E8) by trained personnel with experience ranging from 7 to 14 years. Those patients with an empty uterine cavity were recruited into the study after obtaining informed consent. Each of them also had a serum beta HCG estimation. In addition to an empty uterine cavity the following USG features suggestive of EP were documented - a heterogenous adnexal mass, presence of gestational sac with/without a yolk sac in the adnexa, presence of fetal pole with or without cardiac activity in the sac and echogenic free fluid in pelvis or peritoneal cavity.

These patients were then managed according to the protocol of the institution which was formulated by the department based on guidelines from professional bodies but with minor modifications to suit our population.^[4] The protocol is represented in Figure 1. Patients who had a gestational sac in the adnexa with a definite fetal pole with/without cardiac activity, or with beta HCG > 5000 mIU/ml—all pointers to failure of MTX therapy, underwent salpingectomy (laparoscopy/laparotomy). Other candidates for laparoscopic salpingectomy were patients desirous of sterilisation, patients with a tubal pregnancy after tubal ligation and those with significant fluid in the pelvis, defined as > 300 ml of echogenic fluid or the subjective USG finding of uterus floating in echogenic fluid.^[5]

Patients with initial beta HCG level < 1500 mIU/ml were recruited for expectant management. HCG levels were repeated for these patients after 48 hours. For those who did not have a satisfactory fall ($> 15\%$ from baseline value), one dose of Methotrexate (MTX) was given to hasten the process of resolution. All patients with levels of HCG > 500 mIU/ml were kept in hospital till a falling trend was observed, as we were cognisant of the fact that at this level of HCG, tubal rupture was a possibility.

Patients with initial HCG values between 1500 and 3000 mIU/ml received a single dose of MTX at 50/m² of body surface area. HCG values were repeated after one week from baseline and a drop in HCG $> 25\%$ was considered satisfactory;^[6] otherwise a repeat dose of MTX was given. MTX was administered to

all patients after appropriate lab investigations which ruled out contraindications to MTX therapy.

Patients with HCG values between 3000 and 5000 mIU/ml received the multidose regime. MTX was administered at 1 mg/kg body weight on days one, three, five, seven, and Tab Leucovorin at 0.1 mg/kg was given on days two, four, six, and eight. HCG value was assayed one week from the first (pretreatment) value with $> 25\%$ fall being counted as satisfactory. They were discharged 12 hrs/24 hrs after administration of first dose of Inj MTX or once symptom free. Subsequent dose was administered at the out patient clinic. Additionally, they were advised to stay within 15 minutes from hospital during the first seven days of treatment and were advised to report to the hospital in the event of increasing abdominal pain. Further monitoring of HCG values were done once weekly till it reached normal (< 5 mIU/ml) for all patients who were managed expectantly or with MTX.

All patients on conservative management were provided with a phone number for emergency contact and were advised to report to emergency department in the event of increasing abdominal pain or syncope.

Statistical analysis

Descriptive statistics was used for continuous variables. Frequency and percentage was reported for categorical variables. To test the association between the success of treatment and the variable assessed independent t test was used. P value ≤ 0.05 was considered as statistically significant. The analysis was carried out using SPSS 21.0 version.

Results

During the study period there were 262 haemodynamically stable patients with EP. The treatment offered to 53 patients was not in accordance with the study protocol, owing to physician preferences, one patient dropped out of the study and 118 patients needed surgical intervention, hence the remaining 90 patients were offered conservative management. The above patient selection process is depicted in the Figure 2. The descriptive characteristics of 208 patients consisting of the study population is noted in Table 1. Majority (77%) of the patients were multigravidae with most of them being in the age group of 21–30 years. Abdominal pain was the main presenting complaint (85%) in our patient population. Abdominal tenderness was elicited in about half of the patients (56%) and about 40% patients had a positive cervical excitation test. Risk factor assessment revealed previous LSCS (22%) to be a major predisposing condition for EP. The size of the adnexal mass on USG ranged from 0.9 cm to 8 cm.

Of the total 208 patients who were recruited for the study: 56 were in the expectant management group (with one drop out), 35 in the MTX group, and 118 in the surgical group.

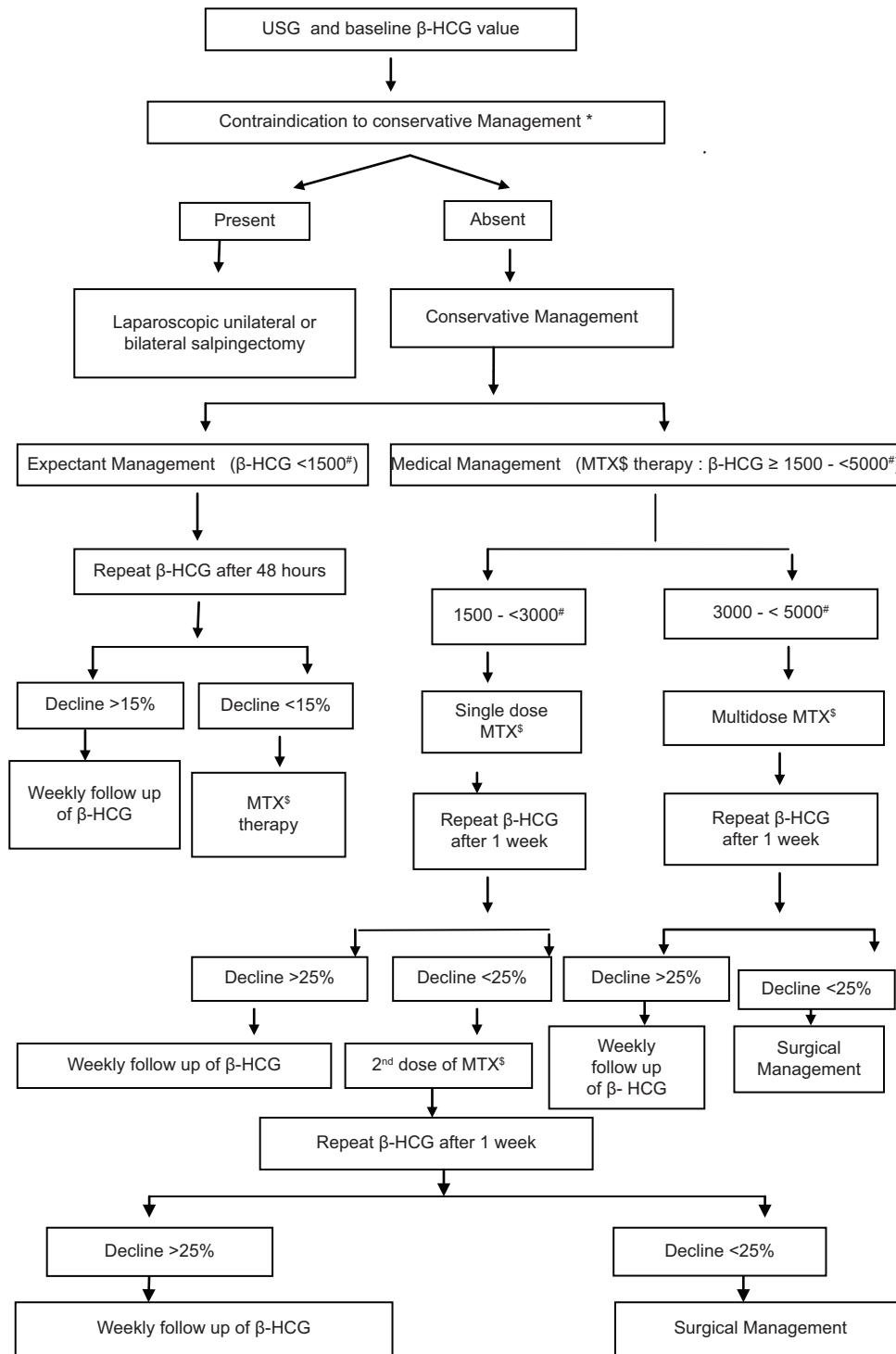
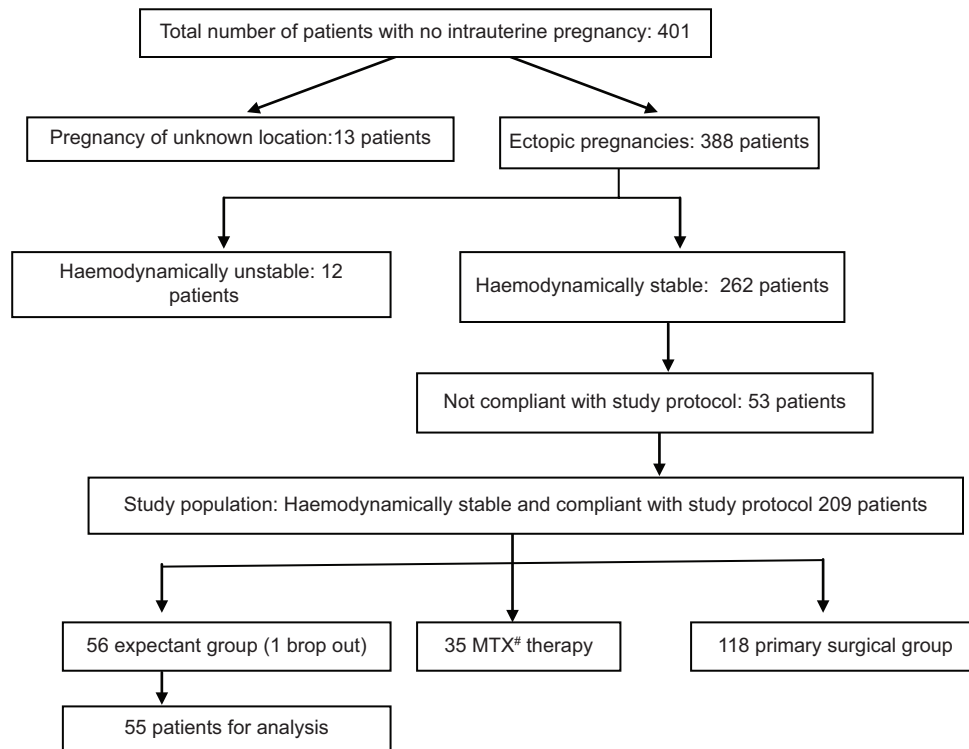


Figure 1: Protocol for management of haemodynamically stable patients with ectopic pregnancy, *USG – fetal pole +/- cardiac activity, significant hemoperitoneum >300ml, Desirous ofsterilisation, Sterilisation failure, Contraindications for administering Methotrexate #Serum β-hCG mIU/ml ^sMethotrexate

Expectant management

The overall success rate for expectant management in our study group was 92.7%. There were no instances of tubal rupture in those managed expectantly, although four patients (7.3%) needed MTX subsequently due to unsatisfactory fall in beta HCG values.

The success of expectant management declined as the beta HCG values increased. There was 72.7% success even for a hcg range from 1000 to 1500 mIU/ml as shown in Table 2. In the expectant group 29 patients (52.7%) had free fluid restricted to the pelvis on USG and of them 27 patients (93%) were successfully managed, without surgical intervention [Table 3]. Of all the

**Figure 2:** Patient selection process, #Methotrexate**Table 1: Descriptive characteristics**

	Mean±SD (range)/n (%)
Age	29.56±4.73 (19-41)
Gravidity	2.4±0.934 (1-5)
Gestational age in weeks	7.48±1.86 (1.4-13.2)
Risk factors	
Recanalisation	11 (5.29)
Sterilisation	36 (17.3)
Infertility	32 (15.38)
ART treatment	13 (6.25)
Previous EP	21 (10)
Previous LSCS	46 (22.11)
Symptoms	
Abdominal pain	177 (85)
Bleeding per vaginum	123 (59.1)
Giddiness	15 (7.2)
Signs	
Pulse rate (in min)	92.1±9.1 (66-122)
Systolic BP (mm/Hg)	108±9 (84-130)
Diastolic BP (mm/Hg)	69.55±8.23 (50-90)
Abdominal tenderness	117 (56.25)
CET positive	84 (40.4)
Scan findings (n 203)	
Presence of mass	171 (84.2)
Size of mass in cm	3.56±1.63 (0.9 - 8)
Gestation sac seen	80 (39.4)
Fetal pole seen	59 (29)
Presence of vascularity	42 (20.69)
Cardiac activity present	34 (16.75)
Presence of free fluid	113 (55.7)
Free fluid in pelvis	89
Free fluid in peritoneum	24

various predictors of success of treatment, baseline HCG was found to be the only factor with significant *P* value on univariate analysis (*P* 0.05) [Table 4]. Data regarding follow up of HCG levels (after the initial values) were absent in five patients (9%). It is still concluded that a ruptured EP was unlikely in these patients as in the event of such a complication our institution would invariably have been the first port of call for them. Only 23/55 patients (41.8%) had a follow up to document normal HCG levels. However, strict compliance with weekly HCG follow up was only 17/55 patients (31%) [Figure 3]. Time taken for HCG levels to normalise was about four weeks in all the 23 patients [Figure 4].

Medical management

The overall success rate with MTX was 80%. Of the 20% (7/35) patients who required surgical intervention only one patient had a ruptured EP. The other causes for surgical intervention were significant abdominal pain and rising or no significant fall in beta HCG. The success rates for MTX therapy was (23/26) 89% and (7/9) 78% for HCG levels between 1500 and 3000 mIU/ml and 3000-5000 mIU/ml, respectively [Table 2]. No patients with HCG in the range of 1500–3000 mIU/ml who received single dose MTX needed a second dose. Another important feature noted was that (12/35) 34% patients had a mass of size >3.5 cm and (10/12) 83% of them were managed successfully with MTX. About (13/35) 37% of patients had free fluid in the pelvis of which (9/13) 69% were managed successfully with MTX [Table 3]. Unlike as seen in expectant group of patients here the size of mass on scan was found to be statistically significant (*P* 0.05) [Table 4]. However it was also seen that there was no significant correlation between the

Table 2: Treatment success rate based on baseline HCG values

Baseline beta hCG (mIU/ml)	Number of Patients	Successful (percentage)	Treatment failure (percentage)
<500	19	100%	0%
500 to <1000	25	96%	4%
>1000 to <1500	11	72.7%	27.3%
>1500 to <3000 MTX	26	88.5%	11.5%
>3000 to < 5000 MTX	9	77.8%	22.2%

Table 3: Treatment success rate based on radiological parameters

	Expectant Management		Single dose MTX		Multi dose MTX	
	Successful treatment n (%)	Failed treatment n (%)	Successful treatment n (%)	Failed treatment n (%)	Successful treatment n (%)	Failed treatment n (%)
Size <3.5 cm	28 (93.3%)	2 (6.7%)	14 (93.3%)	1 (6.7%)	1 (25%)	3 (75%)
Size >3.5 cm	22 (91.7%)	2 (8.3%)	6 (75%)	2 (25%)	4 (100%)	0%
Free fluid Absent	24 (92.3%)	2 (7.7%)	13 (100%)	0%	4 (57.1%)	3 (42.9%)
Free fluid Present	27 (93.1%)	2 (6.9%)	8 (72.7%)	3 (27.3%)	1 (50%)	1 (50%)

Table 4: Comparison of various prognostic features for success in management

	Expectant management		Single dose MTX		Multi dose MTX	
	Mean±SD	P (95% CI)	Mean±SD	P (95% CI)	Mean±SD	P (95% CI)
Gestational age (weeks)	6.9±1.84	0.879 (-2.8, 2.5)	7.7±1.51	0.481 (-1.0, 1.8)	9.4±2.2	0.036 (0.22, 5.13)
Baseline HCG	625.41±351.33	0.05 (-670.6, 10.47)	2177.63±482.9	0.326 (-1344.7, 649.98)	3932±695.42	0.487 (-662.72, 1263.72)
Size of Mass on scan	3.42±1.54	0.612 (-4.92, 3.4)	2.7±1.5	0.05 (-2.9, 0.03)	3.86±0.54	0.034 (0.29, 3.73)

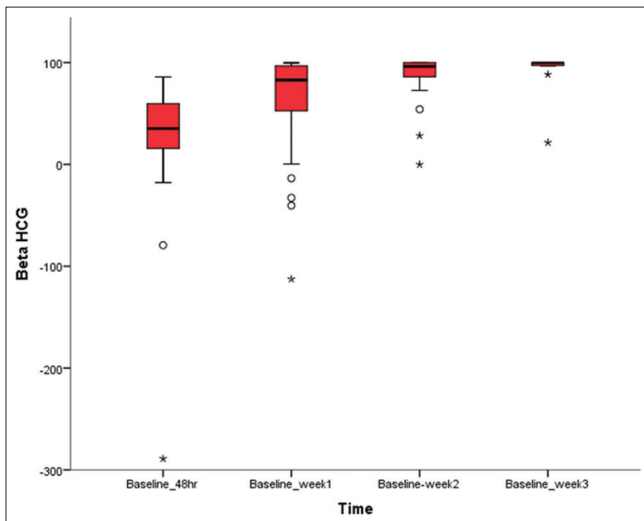


Figure 3: Poor compliance in follow up of weekly beta HCG levels following expectant management

size of mass and baseline HCG. Only 13/35 patients (37%) had a follow up to document normal HCG levels and 11/13 patients (85%) normalized in 3–4 weeks [Figure 4]. However, strict compliance with weekly HCG follow up was in only 6/35 patients (17%) [Figure 5].

Surgical management

Of the total 118 patients who underwent surgical

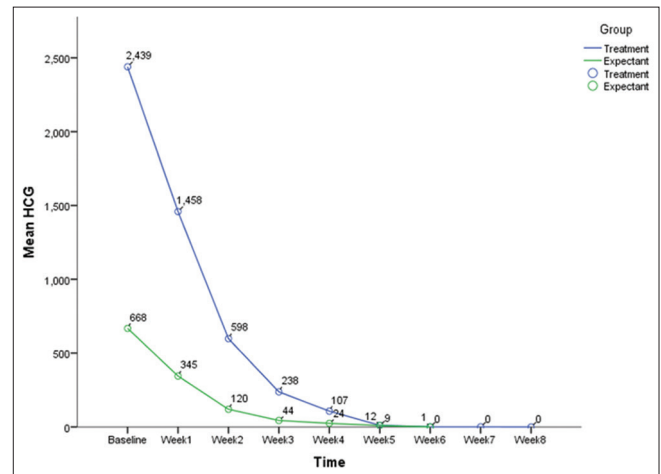


Figure 4: Pattern of fall in mean HCG levels for expectant and MTX management

intervention, (86/118) 73% were managed laparoscopically and the rest needed a laparotomy. The indications for surgical intervention are presented in Table 5.

Discussion

The treatment options for management of unruptured EP include expectant, medical, and surgical modalities. Surgical treatment is required for all patients with suspected ruptured EP

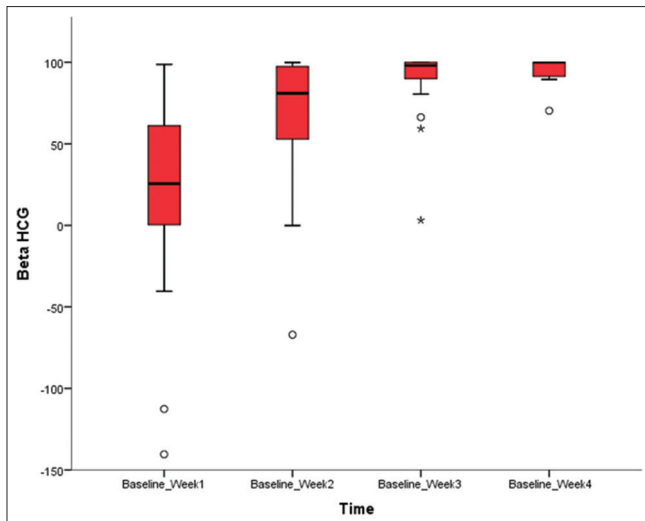


Figure 5: Poor compliance in follow up of weekly HCG levels following MTX management

Table 5: Indications for surgical intervention

Indication for surgery (n=118)	Number of patients n (%)
Completed family	8 (6.8)
Sterilization failure	22 (18.6)
Rupture of sac	38 (32.2)
Persistent or increase in abdominal pain	1 (0.8)
Presence of cardiac activity	28 (23.7)
High beta HCG	15 (12.7)
Others	
High liver enzymes	1 (0.8)
Persistent tachycardia	1 (0.8)
Recurrent ectopic pregnancy	3 (2.5)
Chronic EP	10 (8.5)

or patients not eligible for medical or expectant management. Medical management with MTX is an option available for select group of patients with unruptured EP who fulfil certain criteria. Expectant management involving watchful observation is a choice for managing highly selected patients with unruptured EP.

Expectant management

Expectant management is increasingly possible now with the availability of highly sensitive beta HCG assays, high resolution TVS scans, increasing awareness and changing trends of early antenatal checkup. The main parameter to be considered for expectant management is the initial beta HCG value, with American College Of Obstetrics And Gynaecology stating a 88% success rate for resolution of EP with initial beta HCG values <200 mIU/ml.^[7] However, there have been other studies that have investigated higher levels of beta HCG for success with this modality of treatment. In 2016 Elson *et al.* reported 77% success in those with HCG values <1500 mIU/ml.^[4] Our finding of 92.7% success is similar to another study by Ramakrishnan and Scheid DC published in 2006.^[8] We found 100% success in resolution of EP for HCG values <500 mIU/ml and 96% for those with values ranging from 500 to 1000 mIU/ml. Of those

patients who had a failure of expectant management (3/4) 75% had an initial HCG values ranging from 1000 to 1500 mIU/ml. We therefore conclude that expectant management can be safely offered to those with beta HCG values <1000 mIU/ml. The subset of patients with HCG values ranging from 1000 to 1500 mIU/ml can be offered expectant management but should be counselled regarding a higher chance of failure and conversion to MTX therapy. This is in accordance with the NICE guidelines which states that expectant management should be offered to patients with values <1000 mIU/ml and be considered for patients with values between 1000 and 1500 mIU/ml.^[9]

In our study 98% of patients managed expectantly had an adnexal mass seen on USG and 44% of them had a mass of size ≥ 3.5 cm. Contrary to findings in some studies stating better success in expectant management with mass size <3 cm, we found that 92% of our patients who had an adnexal mass ≥ 3.5 cm were managed successfully by expectant management.^[8] This is probably because the mass that is measured includes the haematoma formed around the ectopic gestation and is therefore not a true depiction of the trophoblastic activity in the site. This is supported by the analytical finding of no significant correlation between the size of the mass and baseline HCG levels ($r = 0.19$ and $P = 0.257$). In addition, we also noted that 93% of patients with free fluid in the pelvis were successfully managed expectantly. Therefore, we opine that, size of adnexal mass and free fluid restricted to the pelvis should not be a deterrent to expectant management, if initial HCG level is low. The criterion for considering expectant management is to be limited to initial HCG levels. This is in agreement with the opinion by authors Craig LB and Khan S who stated that 'initial HCG level is the single best marker that predicts success with expectant management, but is far from perfect'.^[10] Analytical results of our study also echoes the same as baseline HCG was found to be the only statistically significant variable to predict success of treatment.

Medical management

In our study the overall success rate for medical management with MTX was 80% which is in accordance with a study published in 2016 by Mergenthal MC and Senapati S, *et al.* where success rate reported is approximately 90%.^[11] It is known that as HCG values increase the success for medical treatment decreases as shown in studies published by Bonin L, *et al.* in 2016 and Bachman EA, *et al.* in 2012.^[12,13] Initial HCG levels >5000 mIU/ml, presence of cardiac activity and moderate amount of free fluid on scan are shown to be predictors of higher failure rates with MTX in a study by Menon *et al.*^[14] Based on these findings we excluded women who had such features and on strict individualised selection of candidates our success rate with medical management was 89% for single dose Methotrexate (HCG values of 1500–3000 mIU/ml) and 78% with multidose regimen (HCG values of >3000–<5000 mIU/ml). This is in accordance with several studies and guidelines which suggest that patients with HCG <5000 mIU/ml can be offered medical Management.^[15,9]

Studies have shown that presence of a mass of size >3.5 cm is associated with higher chances of failure,^[13] but we noticed no statistical correlation between the mass size and beta HCG levels. The success rate with Methotrexate in our women having a mass of size >3.5 cm was 83%. Our study also emphasizes the fact that presence of free fluid restricted to the pelvis need not be taken as a contradiction for offering MTX, as 69% of women in our study who had free fluid on scan were managed successfully with MTX.

One drawback of non surgical management modality for treatment of patients with EP is the need for regular weekly follow up of HCG levels till normal (<5 mIU/ml). In our study “appropriate” follow up was seen in only 31% and 17% of patients with expectant and medical management, respectively. The reason for such poor compliance with regards to follow up can be two-fold—first, the inconvenience of frequent hospital visits and second, financial constraints; as in our clinical practice patients are not covered by medical insurance. This type of poor compliance is also documented in literature by Jaspan D, *et al.*^[16] Kirk *et al.* opined that the ratio of decline of HCG levels over a 48-hour period was the best predictor of success for expectant management.^[17] Hence, it is reasonable to tailor the follow up visits depending on the fall in HCG levels for patients offered non surgical management, especially in low resource settings. Such a recommendation can be made only if a patient is appropriately counselled regarding the need for seeking health care in the event of increasing abdominal pain and if such health care is easily accessible.

Conclusion

Since ectopic pregnancy is the most common cause for pregnancy related death in the first trimester, a treating physician even in a primary health care facility will benefit with a basic understanding of its pathophysiology and safe management.^[18] With the increased use of high resolution USG and highly sensitive beta HCG assays more and more patients with EP are being diagnosed in the early stages; therefore, a clearer understanding of the rationale and the selection of patients for conservative management will help the patients especially on a long-term basis, for their future fertility.^[2] Management for haemodynamically stable patients with unruptured EP should be individualized and a select group of patients can be safely managed even in a primary health care facility. Of all the predictors for success of treatment that have been studied, the initial beta HCG value still remains of paramount importance. Women with initial values of <1500 mIU/ml can be offered expectant management, with a much better assurance of success for those with values <1000 mIU/ml. Since the chance of rupture in those patients with HCG <1000 mIU/ml is less likely, they can be managed by a primary health care physician. Those with values <5000 mIU/ml can be given MTX therapy with single dose being sufficient mostly for women with values <3000 mIU/ml. The presence of free fluid restricted to the pelvis on USG can still be managed non-surgically. The size

of adnexal mass should not be a deterrent to offering non-surgical management. Since compliance with “appropriate” follow up for patients managed non surgically has always been a challenge, we opine that follow up should be tailored/spaced out according to the trend of drop in Beta HCG levels.

Limitation of study

Larger numbers need to be studied in order to comment on the correlation between various factors and success of treatment with MTX.

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Conflicts of interest

There are no conflicts of interest.

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